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SYNDROMES AND SEIZURES:
CASE STUDIES IN COGNITION AND MENTAL
DISORDERS OF ADULTS WITH EPILEPSY

Thesis submitted by
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June, 2013

For the degree of Master of Philosophy
in the School of Arts and Social Sciences
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The research presented and reported in this thesis was conducted within the guidelines for research ethics outlined in the *National Statement on Ethical Conduct in Research Involving Humans (1999)*; the Joint NHMRC/AVCC *Statement and Guidelines on Research Practice (1997)*; the James Cook University *Policy on Experimentation Ethics, Standard Practices and Guidelines (2001)*; and the James Cook University *Statement and Guidelines on Research Practice (2001)*.

The proposed research methodology received clearance from the James Cook University Experimentation Ethics Review Committee.

Approval Number: H 1949, Category 2.

Approval Date: 13 November, 2004.

The Cairns Base Hospital Ethics Committee granted permission to conduct the study at CBH and approved the proposed research methodology.

Reference: Study Number 331

Approval Dates: 28th June, 2004; 15th December, 2004.

Copies of JCU Ethics approval and letters of CBH Ethics approval can be found in Appendix F.

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ABSTRACT

The **study's general purpose was to examine** cognitive functioning and mental disorders associated with syndromes or seizures of individuals with different epilepsies. More specifically, the aim was to investigate the cognitive and psychosocial profile of individuals with a history of prolonged seizures (status epilepticus). Neuropsychological assessment included cognitive tasks, test batteries and three self-rated questionnaires on psychopathology. Case studies included absence status (ASE), complex partial status (CPSE), generalized convulsive status (GCSE) temporal lobe epilepsy (TLE), and idiopathic generalized epilepsy (IGE). Most of the 24 adults, 18 to 65 years, had epilepsy of a cryptogenic or genetic aetiology. Individuals were compared to an IGE comparison group utilizing computational techniques designed for single case analyses.

Overall, the findings from the series of case studies in IGE concurred with the traditional view that IGE does not generally impact on cognitive function. Against this background, two photosensitive cases with perioral myoclonia and eyelid myoclonia with absences had severe impairments of attentional control and memory systems. Those IGE individuals with single or no reflex components had very mild dysfunction (if any at all).

At best, the assumption that TLE impacts on localized memory deficits which lateralize according to material-specificity principles was only partially upheld. An organization into three classes of deficits and strengths emerged from the assessment results, based loosely on seizure-types and the presence of structural abnormalities. Adaptability of cognitive skills to alleviate possible memory problems seems to have been possible through **an individual's reserve strengths**; less possible when attention responses and fluency errors reflected a quality of rigidity (those cases with secondarily generalized seizures); or when generalized impairment (executive functions, language and verbal memory) was

associated with compromised brain reserve such as hippocampal sclerosis. It was concluded that these three classes might be interpreted as cognitive phenotypes of TLE.

The SE results showed that not *all* prolonged seizures are associated with long-standing cognitive deficits and a poor prognosis. Overall, the GCSE participants did not demonstrate the most severe cognitive impairments as predicted, most having transient cognitive impairment which resolved over time. More widespread and longer-lasting deficits were reported in the two CPSE cases with secondarily generalized seizures and histories of polysubstance abuse.

Attentional impairments were ubiquitous throughout the SE performance scores (particularly divided attention and vigilance) in the SE participants, followed by verbal executive abilities, then language and memory. Four SE cases showed a decline from pre-morbid levels of intelligence which might have been associated with the duration of their prolonged seizures (> 45 minutes). The number of GCSE seizures was negatively associated with current estimated I.Q. and delayed verbal memory. The presence of severe deficits and higher seizure numbers seemed associated with SE **participants' healthy or** unhealthy life-styles pre- and post-onset of prolonged seizures, rather than attributable directly to SE seizure-type impact. The study results concur with the view that SE seizures are more likely to occur in an abnormal brain with little neuroprotection.

The GCSE and TLE participants differed in the co-morbid relations underlying their psychopathology and epilepsy condition. The TLE **participants' epilepsy and mood** disorders may have been linked by their common origins in the temporal lobes, a product of disrupted activity in the limbic **system**. **In contrast, the GCSE participants' lack of awareness** of depression and emotional-social dysfunction was probably a component of their epilepsy syndrome and also a complication of prolonged seizures.

All three questionnaires used in this study (ESDQ, EFQ and DASS) involved self-rated responses. Self-rating scores for everyday memory and concentration difficulties were compared to formal tests of attention and memory, perceived abnormality was compared to the participants' descriptions of their actual life circumstances and these were then corroborated (or not) by their partners. Results were interpreted as indicating *how* participants arrived at their perceptions of abnormality rather than giving an accurate estimate of emotional status. The most interesting finding for the psychopathology investigation was the contrast (found across several analyses) between a lack of understanding or insight (TLE cases) and a lack of self-awareness (GCSE cases).

This study was carried out in the theoretical **context of the ILAE's** previous classification and diagnostic systems, which have recently been up-dated to encompass the influx of new knowledge from neuroimaging and genetics research. Their adequacy for atypical, sometimes rare, single cases was considered, and whether each profile contradicted or conformed to traditional assumptions about functioning in epilepsy. Some cases did not uphold predictions about cognition in IGE, TLE and SE, highlighting exceptions to the old black-or-white classification dichotomies.

Participants' disorders might be better conceptualized as "system epilepsies" rather than the syndromes of signs and symptoms which constituted the 1989 ILAE classification systems.

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CHAPTER 1

INTRODUCTION

1.0 CHAPTER OVERVIEW

The thesis begins with a brief history of ancient and medieval beliefs about epilepsy. Early psychiatric interpretations of epilepsy symptoms and their consequences for people with epilepsy, both in **medical treatments and society’s “solutions”**, are discussed. Next, crucial early investigations by neurologists are described, together with an up-date on areas of progress: conceptualization of epilepsy as a neurological condition rather than a psychiatric disorder, an international classification system for the epilepsies, and the development of neuroimaging tools and techniques. The chapter ends with a rationale for carrying out the study, its purpose and planned approach, and general investigative aims.

1.1 HISTORICAL BACKGROUND

Today, the majority of Western societies know that epilepsy is a medical condition, though few people understand that it consists of many underlying disorders and has varied clinical symptoms. Medical **practitioners know that the allocation of the patient’s particular** configuration of signs and symptoms to a particular epilepsy syndrome is part of making a diagnosis, and are aware that predicted outcomes also need to be based on scientific knowledge about the underlying condition. This was not always so.

People with epilepsy and their seizures have always provoked strong emotions and sometimes violent reactions. The dramatic convulsions of idiopathic generalized epilepsy (IGE) or the mysterious

auras and altered consciousness of temporal lobe epilepsy (TLE) made observers search for explanations, usually based on their cultural belief systems. Some of the concepts were even adopted by people with epilepsy (PWE) in an effort to understand their own condition.

Certainly, some people with epilepsy have to deal not only with the unpredictability of seizures but also with societal perceptions of the disorder. Epilepsy has a pervasive interference in all aspects of life.

1.1.1 RELIGIOUS BELIEFS

According to the World Health Organization, the earliest record of epilepsy dates back to 2000 B.C. and was found on an ancient Babylonian stone tablet describing different seizure-types but attributing them to an evil spirit or god. One record dated about 400 **B.C. refers to “loss of consciousness” and uses objective concepts such** as symptomatology, aetiology, diagnosis and treatment. In a 500 B.C. treatise, Hippocrates described epilepsy as a disorder of the brain (rather than a sacred disease which was the contemporary Greek view), and recommended physical treatments instead of spiritual ones (World Health Organization, 2001a). A comprehensive account of epilepsy in the times of the Assyrians, Babylonians, Ancient Greeks and Romans (Magiorkinis, Sidiropoulou, & Diamantis, 2010) describes connections made between magic and epilepsy together with some of the more harrowing treatments for a divine disease.

The supernatural view continued for another 2000 years. Medieval Europe’s beliefs about epilepsy included possession of a person by an evil spirit or demon, witchcraft, magic, and hysteria. **Seizures were then “treated” accordingly** (Devinsky, 2003; Temkin, 1971). Just one example occurred in 1494, when two Dominicans (with papal authority) wrote *Malleus Maleficarium* stating that seizures were one characteristic of witches, thus triggering another wave of persecution (Devinsky, 2003). Less violent medieval practices included

pilgrimages as a successful cure for epilepsy (Wolf, Trinkka, & Bauer, 2007). A recent review (Devinsky & Lai, 2008, p. 637) has provided a comprehensive account of spirituality and religion in epilepsy which includes not only some of the historical superstitions and famous religious figures through the ages, but also neurological studies of religious experience in people with epilepsy, right TLE in particular. Also of interest is a neuroanatomical distinction made between two **varieties of religious experience: an ordinary person's faith associated** with the right frontal lobe and a more ecstatic variation originating in the right temporal lobe.

1.1.2 PSYCHIATRIC INTERPRETATIONS

Epilepsy was not considered to be a neurological disorder until the late 19th century when it became the subject of scientific research. Even so, whilst the observations were accurate and scientific methods rigorous, the theories used to interpret them were embedded in the perspectives of their time (Chio, Spreafico, Avanzini, Ghiglione, & Vercellino, 2003). They **include Lombroso's theory of criminality, Charcot's ideas of hysteria in women, and the eugenics movement** with its seemingly laudable intentions. A historical review of epilepsy, psychiatry and neurology (E. H. Reynolds & Trimble, 2009) describes other mistaken interpretations including hereditary degeneration made by Morel in France in 1857 and Neumann in Germany in 1859.

A particularly illustrative study is provided in the writings of Cesare Lombroso (1894; 1897) an Italian anthropologist and neuropsychiatrist who, together with his adherents, used scientific methods of enquiry and formal reasoning, but whose pre-conceived theories led to claims of inter-relationships among epilepsy, criminality and genius. All three were expressions of *atavism*, a regression to more immature forms of evolution going back to primitive peoples and monkeys (Chio, et al., 2003). Unfortunately, **Lombroso's** ideas

influenced lawyers as well as doctors for many years (Hermann & Whitman, 1992). Even after his death and as late as 1931, atavistic defining features of criminality were distorting the Italian Criminal Code (Chio, et al., 2003).

Not until the early to mid-19th century were neurological and psychiatric disorders recognized as separate entities. In the late 19th century, the neurologist Charcot and his colleagues at the Salpêtrière Hospital in Paris made valuable contributions through their extensive studies on how to differentiate between psychiatric and neurological disorders. For some cases, however, Charcot could not quite let go the idea of genuine epilepsy arising from hysteria. He coined the term *hystero-epilepsie* as a psychiatric problem of repressed sexuality, **attributing some patients' non-convulsive epilepsy** to features of hysteria such as anaesthesia or contracture (D'Olier, 1882; Devinsky, 2003).

Another psychiatric interpretation linked patterns of genetic inheritance to various forms of “madness” **and “intellectual degeneracy”** (Hermann, 2010). Eugenic principles advocated manipulation and control of genetic inheritance by the state, the aim being to eliminate genetic impurities by enforced sterilization. Extreme legislations affecting people with epilepsy often used theories of eugenics as a justification for their disregard of human rights (Hermann, 2010). In Germany during the Nazi period, some doctors falsely diagnosed a symptomatic origin to let their patients escape the sterilization enforced **on those with a genetic “degeneracy” such as epilepsy** (Wolf, 2005).

The World Health Organization (2001b) has listed more recent examples. Eighteen states in the U.S.A. continued to provide eugenic sterilisation of people with epilepsy until 1956; while in some States, laws forbidding people with epilepsy to marry continued until 1980. The United Kingdom did not repeal its law forbidding people with

epilepsy to marry until 1970. Similar laws still exist and are being enforced in both India and China (World Health Organization, 2001b).

1.1.3 NEUROLOGICAL INVESTIGATIONS

In the late-19th century, neurology emerged as a discipline separate from psychiatry, treating epilepsy as a brain disorder rather than a mental illness (E. H. Reynolds & Trimble, 2009). The London neurologist Hughlings Jackson (1870) is credited with the discovery that seizures were the result of sudden brief electro-chemical discharges in the cerebral cortex, and that the character of the seizures depended on the location and function of the site of the discharges. In his critical review of early neurological research at Guy's Hospital, London, Eadie (2007) also considers the contributions of predecessors such as Bright (1831), Wilkes (1866), and Dickson (1873). A few years later, the electrical excitability of the brain was confirmed by David Ferrier in London, and Gustav Theodor Fritsch and Eduard Kitzig in Germany. In 1920s Germany, the psychiatrist Hans Berger developed the electroencephalogram (EEG) which showed different patterns of neurophysiological activity associated with different seizure types (World Health Organization, 2001c). Thus an enlightened conceptualization of epilepsy began to emerge, followed by more efficacious treatments. For example, neurosurgical treatments became more available from the 1950s onwards in London, Montreal and Paris (World Health Organization, 2001c).

Treatment with anti-epileptic drugs (AED) was not widely practised until the mid-20th century (Kwan & Brodie, 2001). The **world's first effective AED is claimed to be potassium bromide**, introduced in 1857 (Locock, 1857), but this has been disputed by Eadie (2004). He recounts a 1592 report by Fabio Colonna of Naples in his botanical classic *Phytobasanos*, describing use of powdered valerian root to cure his own epilepsy (see Tissot, 1840). Drugs specific to

epilepsy were not developed until the first half of the 20th century: phenobarbitone was first used in 1912, and phenytoin in 1938. The 1960s saw the beginnings of active AED research based on a greater understanding of the electrochemical activities of the brain, especially the excitatory and inhibitory neurotransmitters (Eadie, 2004). Since the 1990s, new drugs have been developed which can control seizures in 70% to 80% of newly diagnosed children and adults, and research for yet more effective AEDs is on-going (Reijs, Aldenkamp, & De Krom, 2004; World Health Organization, 2001c).

Recently, the International League Against Epilepsy (ILAE) celebrated a century of epilepsy research (1909 – 2009) (Hermann, 2010). One area where it has played an important role is in the research on status epilepticus, and publication of findings in *Epilepsia* (Meldrum, 2007). See Neligan and Shorvon (2009) for a comprehensive history of SE and its treatment.

Finally, a family history taken from the epilepsy literature illustrates the contrast between medieval beliefs and the progress of modern genetics (Wolf, et al., 2007). There is a 1501 painting and written record in Gmund, Austria, which gives thanks to the Virgin Mary for successful recovery of the son of Oswald. His father had gone on pilgrimage to the city of old Otterling after the family had lost all **hope for the boy's life**. It is difficult to tell from the old description **whether Oswald's son was in a three-day stupor following convulsive SE, or a post-convulsive stupor after IGE, or whether in absence status (NCSE)**. Five hundred years later, a father and daughter contacted one **of the writers (Dr. Bauer) with evidence of being Oswald's descendents**. Medical histories and EEG evidence showed they both had early absence seizures, followed by generalized tonic-clonic seizures later in life. The writers conclude that this case provides evidence of strong genetic preservation of the syndrome category over generations without deterioration (Wolf, et al., 2007).

1.1.4 STORE OF SCIENTIFIC KNOWLEDGE

In the past 30 years, two steps have brought many researchers across disciplines (including psychology) closer to an understanding of epilepsy (Aldenkamp, Baker, & Meador, 2004; Barr, 2007). The first organized classification systems together with an internationally-based terminology. The second step involved rapid development of neuroimaging techniques and neuropsychological knowledge, allowing theories of brain function, cognition and behaviour to be rigorously explored.

ILAE Classification Systems

In 1981 and 1989, the criteria for two classification systems (seizure-types and epilepsy syndromes) were compiled through a series of scientific discussions and debates by leading experts from countries across the world and presided over by the ILAE. The resulting consensus on definitions, together with establishment of classification systems, facilitated exchanges of scientific findings across nations; a rapid increase in the store of scientific knowledge about the condition itself; and evidence-based treatments for individuals. Abbreviated versions of the 1981 seizure classification system and of the 1989 syndrome classes (G. P. Lee, 2004) are provided in Appendix Tables 1 and 2 in Appendix A.

These original ILAE classification systems were based on a purely descriptive approach, using careful observation of behavioural and electrophysiological patterns of seizures. By 2001, four areas of the original systems had been identified as needing re-appraisal, and the ILAE has undertaken modifications based on scientifically rigorous criteria, rather than the original descriptive phenomena. The most recent (2010) ILAE proposed organization of seizures and syndromes can be found in Appendix Tables 3 and 4, Appendix A.

The distinction between the terms *seizure type* and *epilepsy syndrome* is important because they play different roles in the conceptualization of epilepsy as a neurological disorder. *Epilepsy syndromes* are defined by a constellation of signs and symptoms that include characteristic seizure-types and their aetiologies, other clinical features, and family history (Engel, 1995). *Epileptic seizures* are defined as an ictal episode of abnormal brain activity representing unique pathophysiological mechanisms and anatomical substrate (Engel, 1995). Whereas treatment is based on the type of seizure, identification of a specific syndrome often provides additional insights into management and prognosis, as well as knowledge of its aetiology (Engel, 1995). Further, symptoms alone cannot differentiate between syndromes: two people might have the same collection of symptoms yet have different underlying causes such as genetic origin or acquired disorder (Wolf, 2005). Revisions to the 1989 classification systems have included modifications to key terms in epilepsy terminology (Engel, 2006). A list of amended terms can be found in Appendix A.

Neuroimaging Methods and Psychological Theories

Neurodiagnostic tools and techniques include magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT) and use of combined video and computerized EEG recordings (Duncan & Thompson, 2003). These modes of investigation have facilitated knowledge about the fundamental neuronal mechanisms underlying epileptic seizures and an understanding of syndromes as system disorders of the brain with associated pathophysiology (Engel, 1995). Consequently, our conceptualization of the relationship between syndrome classes and the cognitive patterns associated with them has changed (Duncan & Thompson, 2003). In addition, research on the co-morbidity of interictal epileptiform activity and interictal mental illness such as

dysphoric disorder has opened a new field of study in the neuropsychiatric aspects of epilepsy (Aldenkamp & Arends, 2004; Marsh & Rao, 2002).

In 2006, the journal *Cortex* held a forum which debated the question “**what has functional MRI told us about the evaluation of theories that are expressed *solely at the psychological level?*”** (Coltheart, 2006a). One eminent cognitive scientist (Coltheart, 2006a, 2006b) has come to the conclusion that neuroimaging can give localization of mental functions, but not distinguish between psychological theories (but see Umilta, 2006). Cappa (2006) has discussed useful neuroimaging data on deductive versus probabilistic inferences, as a surrogate behavioural marker and as showing language in action. Nonetheless, with regard to functional MRI and psychological theories, one crucial experiment which proves unequivocal evidence refuting a theory is unlikely. A more fruitful approach would be a collection of relevant results which all favour one theory and are inconsistent with the predictions of another (Coltheart, 2006b; Rastle & Coltheart, 2006).

Most forum participants provided examples where they believed functional neuroimaging provided support for one cognitive theory and/or was inconsistent with predictions made by its competitor (but see Page, 2006). Their examples of competing theories included those for visual attention (Umilta, 2006); visual and verbal working memories; attention interference versus conflict resolution of attention responses; adapted-item and verb-generation tasks; perception versus visual imagery (Jonides, Nee, & Berman, 2006); rehearsal processes versus speech production (Vallar, 2006); sentence comprehension theories (Caplan, 2006); and remember/know theories of recall and familiarity (Henson, 2006). One interesting example revealed which mechanisms best accounted for inefficient visual search: parallel versus serial search processes (Jack, Sylvester, & Corbetta, 2006).

Coltheart (2006b) argued against all these examples, saying neuroimaging might provide relevant information about cognitive theories in the future, but not now. Summed up, he said that the participants were assuming that the key brain region associated with a cognitive process has only this cognitive function and no other (see Fodor, 2000 for uses of facts about localisation; 2005). Coltheart described localisation of visual attention shift in the right parietal region. This same region, however, might be activated by other cognitive tasks (e.g. orientation of attention, and location detection tasks which do not require visual shift) (Coltheart, 2006b).

1.2 CASE-BASED STUDY

Studying *patients* with epilepsy does not necessarily inform us about *people* with epilepsy

(Hermann & Whitman, 1992, p. 1135)

1.2.1 RATIONALE FOR THE STUDY

As seen in the previous section, biological research has built a large store of scientific knowledge about epilepsy, its causes and the constant improvement in medical treatments available. Cognitive neuropsychology and neuropsychiatry have not produced as large a body of research (Barr, 2007). Early researchers confined their studies **to the cognition of TLE surgery patients and/or their “epileptic personality”, which is a narrow focus** at best and probably added to the social stigma already associated with the illness (E. H. Reynolds & Trimble, 2009). Research and experience with a wider range of patients and their abilities/deficits can only improve neuropsychological accuracy of interpretations and psychiatric reports.

The focus of medical research on seriously ill people with epilepsy has had a beneficial effect in ameliorating their condition.

Psychological research is also concerned with the more dysfunctional end of the spectrum for cognitive deficits and epilepsy. It is possible that this focus on studying and reporting the deleterious impact of some epilepsy disorders on human functioning has led to a societal view which associates all epilepsies with severe cognitive dysfunction and psychiatric illness.

What is needed is a balanced appraisal of the cognitive and emotional status of people whose epilepsy is not severe or debilitating, e.g. has not required surgery. For example, the deterioration of intellectual abilities is not always present with an epilepsy condition. Equally important, such knowledge enables people with epilepsy and their significant others to gain greater understanding of their illness: the first step towards self-management and perceived control over the condition. In addition, such knowledge needs to become available to **the wider public before society's attitudes** can become more enlightened.

1.2.2 PURPOSE AND PLAN

The general purpose of the current study is to investigate any association between syndromes or seizures and the cognitive and emotional-social functioning of adults with epilepsy. There is already a substantial body of literature, and relatively well understood cognitive and psychosocial profiles for epilepsies with self-terminating seizures. **The current study's** core purpose is to examine the cognitive and psychosocial profile of individuals with a history of prolonged seizures (status epilepticus).

To achieve these objectives, it is planned to carry out comprehensive neuropsychological assessment of four groups of individuals.

1. Generalized Convulsive Status Epilepticus (GCSE);

2. Nonconvulsive Status Epilepticus (NCSE) comprising Absence Status (ASE) and Complex Partial Status (CPSE);
3. Idiopathic Generalized Epilepsy (IGE); and
4. Temporal Lobe Epilepsy (TLE).

The planned data-analyses will be in two steps: comparisons across groups using a methodology of comparing single cases with a small epilepsy group acting as controls; and a search for within-group patterns emerging from multiple cases with the same type of epilepsy disorder, using dissociation tests and correlations.

IGE participants will be used as a comparison group for the individuals with prolonged seizures and the TLE participants. Associations between seizure-property variables and cognitive tasks or psychosocial measures will also be explored. In-depth investigations will also be undertaken of individual and multiple cases within each epilepsy group, with a view to identifying potential shared characteristics and specific cognitive/emotional profiles.

While large studies have the advantage of higher statistical power, case study approaches enable a more thorough exploration of the interaction between an individual and his/her reaction to the illness. Further, placing the study in the context of classification dichotomies and their related assumptions about cognition in epilepsy, **means that the study's findings might** serve as a catalyst for larger group-based research and thereby contribute to the knowledge pool about epilepsy.

1.2.3 AIMS OF STUDY

The general aim of the thesis is to assess and investigate cognitive abilities and emotional functioning in adults with different types of epilepsy. The specific aims are as follows.

1. Assess and compare the cognitive profiles associated with four types of epilepsy: Non-Convulsive Status Epilepticus (NCSE), Generalized Convulsive Status Epilepticus (GCSE), Temporal Lobe Epilepsy (TLE) and Idiopathic Generalized Epilepsy (IGE).
2. Identify the patterns of cognitive dysfunction associated with SE and those seen in TLE and IGE.
3. Examine associations (if any) between chronic epilepsy and increasing cognitive dysfunction.
4. Investigate the association (if any) of epilepsy with psychopathology.
5. Determine whether there is a relationship between psychopathology and severity of SE (as measured by one or multiple episodes).

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CHAPTER 2 LITERATURE REVIEW

2.0 CHAPTER OVERVIEW

This chapter begins with the ILAE classification dichotomies used **by clinicians as “rules-of-thumb” for diagnoses; and by researchers as a common language**, followed by a rationale for a case-based approach to this study. Each of the sections addressing the different epilepsy syndromes and psychopathology begins with a universal statement about birds. These analogies represent the all-or-none nature of the ILAE **classification criteria and focus attention on the ILAE system’s** assumptions about the epilepsy classes and their impact on psychological functioning (e.g. benign or severe).

The bulk of Chapter Two contains research background for the case study chapters which follow it. Each section describes research findings from single cases and large group studies in relation to cognitive and emotional-social dysfunctions associated with particular epilepsy disorders. Each section concludes with a statement of very general assumptions which provide the background upon which specific predictions will be examined in subsequent chapters. The final section reports relevant research studies on epilepsy-specific mental disorders.

2.1 CLASSIFICATION DICHOTOMIES

Botanists and Gardeners

There are two ways of investigating diseases, and two kinds of classification corresponding thereto, the empirical and the scientific...

(Jackson, 1873).

The different kinds of knowledge used by botanists and gardeners form a useful metaphor for understanding the two complementary approaches to understanding epilepsy disorders. Jackson used plants to illustrate how a disease can be understood on the basis of two different **knowledge organizations: the botanist's hierarchical taxonomy and the gardener's arranged lists** for daily use. The Botanist uses existing scientific knowledge both as a basis for plant classification and for developing hypotheses for further investigations. The Gardener lists plants for everyday practical use, for example, a list of trees, shrubs and flowers which can be used as ornamental plants (Wolf, 2003).

Both kinds of knowledge organization are needed in epileptology, while the separate but complementary roles avoid the confusion of utilitarian purposes with scientific criteria i.e. **“cabbages with kings”**. Beginning with a series of debate articles in the ILAE journal *Epilepsia*, these two approaches to understanding disease have been the basis for modifying the ILAE epilepsy classification systems first devised in 1981 and 1989 (Avanzini, 2003; Berg & Blackstone, 2003; Engel, 2003; Fisher, 2003; H. O. Luders, Najm, & Wyllie, 2003; Wolf, 2003).

One suggestion during the “cabbages and kings” debate was that the term *classification* should be reserved for categorization based on scientific knowledge about epilepsy syndromes; while the term *diagnostic scheme* would encapsulate the signs and symptoms underlying identification of seizure types (Wolf, 2003). Also agreed was that the either-or nature of criteria for seizure diagnosis (Commission on Classification and Terminology of the International League Against Epilepsy, 1981) and syndrome classification (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) could not cover the grey areas adequately. In Chapters Four to Seven, atypical and/or rare cases are reported which do not fit neatly into the either-or dichotomies.

The two ILAE dichotomies underlying classification and diagnosis propose that decisions involve either-or choices.

- Diagnosis of seizure-type: Is spread of abnormal brain-wave activity generalized or localized?
- Classification as a syndrome: Is the aetiology symptomatic or idiopathic (i.e. familial, genetic)? A third possibility is cryptogenic (i.e. unknown aetiology).

Any decision carries certain expectations about the cognitive profiles for the different epilepsy disorders. The literature shows that in the subsequent debates held over several years, many exceptions to the predicted profiles were cited from clinical practice and neuroimaging studies. Such exceptions undermine the utility of the ILAE dichotomies, thus demonstrating a need for adjustments to the 1981 and 1989 ILAE classification systems.

2.1.1 FALSIFICATION AND CASE-BASED STUDIES

Investigation of these cases will employ a *falsification* method for testing universal statements generated by simple dichotomies (Buck, 1975; Flyvbjerg, 2006; Popper, 1959). Popper wrote about two contexts for the research process: discovery and justification, with falsification somewhere in the middle. Case studies take place in the *discovery* context but must be put through a *falsification* process which includes searching for exceptions. The case study approach might fall short in the *justification* process which needs a rigorous method of refutation (Edwards, Dattilio, & Bromley, 2004). In this study, statistical analyses of single cases compared to a control group support interpretations.

Rationale for a case-based approach

Because of its use of atypical and/or rare cases, a case-based approach for a study of forms of epilepsy was deemed to be suitable for this project. Case studies are more useful for a clinician because they investigate a phenomenon within its real-life context, can include quantitative evidence, rely on multiple sources of evidence, and benefit from using theoretical propositions as a starting-point (Flyvbjerg, 2006; Yin, 2009). For the current project, specific benefits of a case-based approach include the following.

1. *Rarity of cases (SE)* An abnormality might be rare. Single or small numbers can be less misleading than group data and more informative, particularly when the object of study is the neurological and functional architecture of mental processes (Crawford, 2007). Using models based on large statistical studies to explain exceptional cases seems to be a self-contradictory or inconsistent method (Doidge, 2008).
2. *Heterogeneity of groups (TLE)* **The brain's potential for functional re-organization means individuals do not always conform to theoretical models about the brain's cognitive architecture** (Doidge, 2008). This means people can produce a wide range in performance abilities. Group studies cannot provide information about the variability from person to person (e.g. individual treatment response, outcome or task performances) yet these details can be of great clinical significance leading to new knowledge (Jacobson, Roberts, Berns, & McGlinchey, 1999).
3. *Loss of experiential knowledge (IGE)* **A practitioner's valuable experiential knowledge is lost in large group studies. Case studies'** focus on the individual, their replicability and aggregation of findings can form the basis for further large number research. Kazdin (2008) argues for both research and practice, saying they

can contribute to a knowledge base which deepens understanding and improves interventions.

2.2 IDIOPATHIC GENERALIZED EPILEPSY

All swans are white

Popper himself used the now famous example “all swans are white” and proposed that just one observation of a single black swan would falsify this proposition..... The case study is well-suited for identifying black swans because of its in-depth approach. What appears to be *white* often turns out on closer examination to be *black*

(Flyvbjerg, 2006, p. 228).

The research articles in this section question whether all IGE disorders have a benign impact on cognition.

2.2.1 DEFINITION

Clinical observations and evidence from neurobiological and genetic studies contradict the current definition of IGE which implies that all IGE syndromes are the same.

.... idiopathic really is the opposite of symptomatic and means that a disease is a primary disorder with an independent etiology, pathogenesis, and pathology, not caused or occasioned by, or secondary to, another disorder

(Wolf, 2005, p. 7).

To have any clinical utility, the all-inclusive definition of IGE should be varied to allow differentiation of the IGE genotypes (Avanzini, 2003; Wolf, 2005). Figure 2.1 consists of two tree structures which represent the natural classes of epilepsy disorders, but are also representing different classification systems (Berg & Blackstone, 2003).

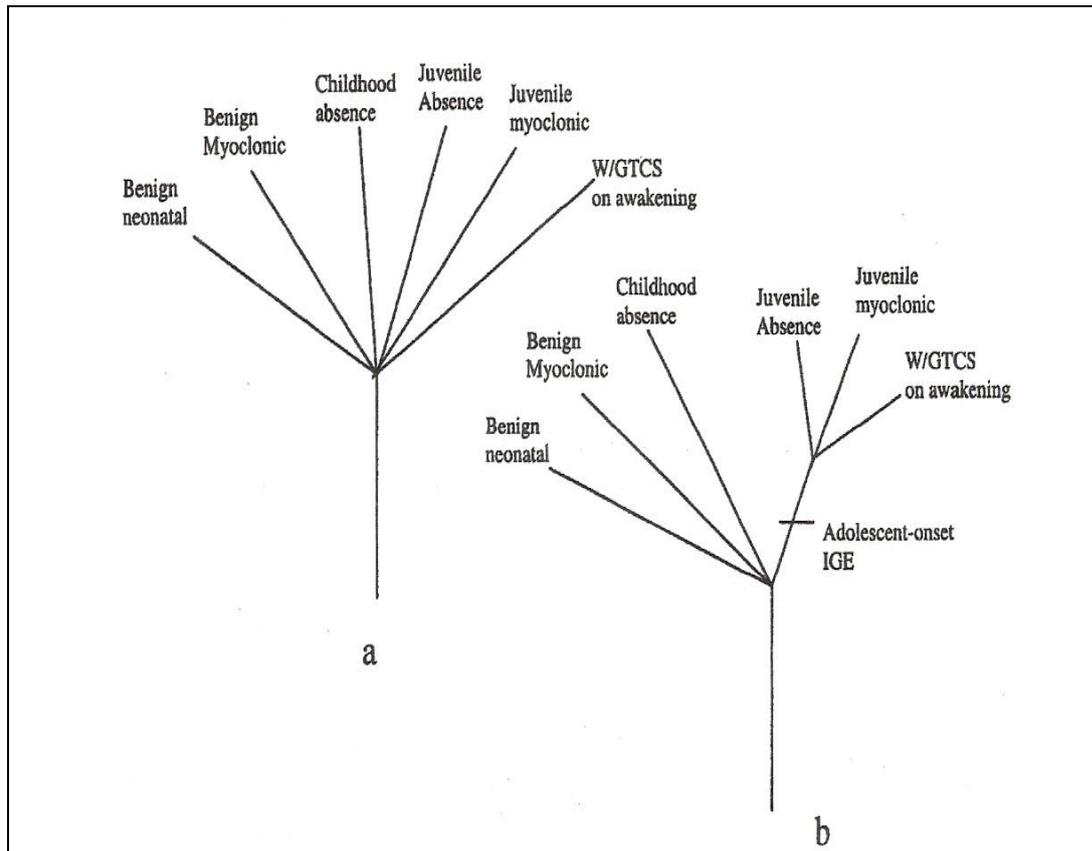


Figure 2.1 Genetically-based relations of IGE sub-syndromes.

(Source: Berg & Blackstone, 2003, p.11).

Berg and Blackstone (2003) describe Tree (a) as the undifferentiated IGE syndromes constructed from expert opinions and descriptions which generated the early ILAE classes. Tree (b) represents IGE classes also, but this structure is based on evidence from genetic studies. Here, the adolescent-onset epilepsies share one or more derived characteristics that make them more similar to each other than they are to syndromes outside their cluster. The more differentiated branches of Tree (b) mean this method of classification is likely to be more useful for research and diagnosis.

Genetic origins of idiopathic generalized epilepsies

Idiopathic generalised epilepsies are a heterogeneous group of conditions characterized by different types of seizures, ages of onset and EEG features (Stefan, Halasz, Gil-Nagel, & Shorvon, 2001). The past two decades of research have shown that IGE disorders are genetic in origin and their seizures are due to dysfunction of neuronal ion channels responsible for generating and controlling neuronal excitability. Genes have been found to encode neuronal ion channels with altered neuronal properties causing subtle alterations in neuronal excitability and response characteristics (Stefan, et al., 2001; Tan, Mulley, & Berkovic, 2004). For a review on the genetics of human epilepsy which describes the central role of ion channels in the pathophysiology of IGE, see Scheffer and Berkovic (2003).

On-going genetic studies have identified several different genotypes of IGE, meaning that they share only some, not all, common traits (Sisodiya, Cross, Blumcke, Chadwick, & Craig, 2007). Instead, several different genetic modifiers of ion channel physiology have been found, uncovering sub-syndromes. Gene mutations which modify ion channels by various processes have already been linked to various forms of idiopathic epilepsy (Mazzuca, Lesage, & Lazdunski, 2006), thus providing a natural order or phylogenetic system which can differentiate among the IGE sub-syndromes (Steinlein, 2004).

The rare forms of IGE involve Mendelian or monogenic epilepsies, while the more common varieties are familial but manifest as complex, non-Mendelian traits (Gardiner, 2005). Rare or infrequent varieties of IGE include (among others) severe and benign myoclonic epilepsies of early childhood, myoclonic absence epilepsy, and – relevant for this study – epilepsy with reflex seizure components (Duron et al., 2005).

The more common idiopathic syndromes have a complex mode of inheritance rather than monogenic, with a range of gene mutations that add to produce an increase in neuronal excitability and hence seizure excitability. Thus, common forms of idiopathic epilepsy such as juvenile myoclonic epilepsy (JME), childhood absence epilepsy (CAE), and pure grand mal-on-awakening seem to be caused by either oligogenic or polygenic inheritance. Polygenic inheritance involves several or many genes and the phenotype might be further modified by environmental factors (Stefan, et al., 2001). CAE and juvenile absence epilepsy (JAE) have been found to share a close genetic relationship, while JME is a more distinct entity (Marini, Scheffer, & Crossland, 2004; Winawer, Rabinowitz, Pedley, Hauser, & Ottman, 2003; Winawer & Shinnar, 2005). Advances in recent research have established mutations in genes EFHC1 and in CLCN2, which establish JME as a clinical entity (Gardiner, 2005; Suzuki et al., 2004).

Classification

In actual practice, an IGE seizure diagnosis probably involves a more complex decision than the current dichotomous choice presented by the original 1981 system (generalized spread versus localisation-related seizure onset). The problem with the current IGE classification rule is that if an all-inclusive definition is adopted then its sub-syndromes should all have the same benign prognosis, at least as far as cognitive functioning is concerned.

Until recently, the general assumption was that an idiopathic aetiology did not have an adverse impact on cognition or mental health. Before improved imaging techniques became available, structural or functional abnormalities in IGE disorders were not detectable. Based on diffuse EEG patterns, IGE was believed to involve generalized activity with bilateral onset only, excluding the possibility that any partial location in the brain might be the focus of abnormal activity (Stefan & Snead, 1997).

2.2.2 REGIONAL PRE-DOMINANCE OF BRAIN PATHOLOGIES

The question whether microscopic neuropathologies exist in IGE has sparked numerous studies using a variety of improved investigative tools and techniques. The results have provided solid evidence for subtle abnormalities of cerebral structure which may either contribute to the pathophysiology of IGE or be a consequence of seizure activity (Duncan, 2005a).

Magnetic resonance imaging (MRI) – the structure of the brain

MRI morphometry revealed structural distortions in patients with primary generalized tonic-clonic seizures (Savic, Seitz, & Pauli, 1998). Another study used an anatomical MRI segmentation technique to find that patients with IGE had a significantly larger proportion of grey matter than control subjects. In addition, 5 out of 20 JME patients had significant abnormalities of cerebral structure, and showed an increase in cortical grey matter in the medial frontal lobes. The investigators concluded that these abnormalities in frontomesial and subcortical structures of JME patients may play a role in epileptogenesis (Woermann, Free, Koepp, Sisodiya, & Duncan, 1999). Quantitative analysis of volumes of cerebral grey and white matter indicated a relative increase in IGE grey matter compared to controls. Significant abnormalities of the distribution of cerebral grey and subcortical matter were found in 8 of 20 patients with JME, 4 of 10 with JAE, and 2 of 5 with GTCS on awakening, but in none of the 30 controls (Duncan, 2005a; Woermann, et al., 1999).

Magnetic resonance spectroscopy (MRS)

Savic, Lekvall, Greitz, and Helms (2000) went on to investigate whether an underlying mechanism could involve regional neuronal damage not visible with structural magnetic resonance, but detectable with magnetic resonance spectroscopy. Their results supported the view

that prefrontal cerebral changes exist in JME, which are neuronal in origin. JME patients had reduced frontal lobe concentrations of *N*-Acetyl Aspartate (NAA), but other brain regions showed normal levels and other metabolites were also normal. In contrast, patients with generalized tonic-clonic seizures had significantly lower thalamic NAA values than controls. Both patient groups had reduced thalamic choline and myo-inositol. The researchers concluded that the aetiology of such damage might be associated with regional cortical dysplasia. Of particular interest is that these data suggested differences in the neurobiological substrate of IGE sub-syndromes (Duncan, 2005a; Savic, Osterman, & Helms, 2004).

Electroencephalogram (EEG) recordings

EEG recordings have shown that the amplitude of the generalized spike-waves is usually greatest over the frontal lobe region in adults, which is suggestive of an increased involvement of this area (Rodin & Ancheta, 1987). Further studies have pointed to the additional involvement of a thalamic-cortical loop (Hommet, Sauerwein, De Toffol, & Lassonde, 2006; Marescaux & Vergnes, 1995; Marescaux et al., 1984; Niedermeyer, 1996). See also studies of GAERS rats with absence epilepsy showing spike and wave onset in pericentral neurons which spread to the thalamus then in a thalamic-cortical loop (Powell, Cain, Ng, Sirdesai, David et al., 2009).

Isotope imaging of cerebral glucose metabolism

Swartz, Simpkins, Halgren, et al. (1996) used 18-fluorodeoxy-glucose positron emission tomography (18FDG-PET) to study regional glucose metabolism during a visual working memory task and a control task. They found a relative reduction in glucose metabolism in the dorsolateral pre-frontal cortex during rest in JME, as compared to controls; and absence of an increase in glucose uptake in dorsolateral pre-frontal cortex, pre-motor cortex and basal frontal cortex during the mental

task, which points to a disorganization of these regions. Only the JME patients showed an increased uptake in the medial temporal structures (Gershengorn, Perrine, Luciano, Vazquez, & Devinsky, 1992; Swartz, et al., 1996). People with JME may suffer from cortical disorganization which influences both epileptogenic potential and frontal lobe cognitive functioning (Gershengorn, et al., 1992; Swartz, et al., 1996).

Functional MRI (fMRI)

Continuous EEG-correlated fMRI has been used to study neural correlates of spontaneous generalized spike and slow-wave discharges (Duncan, 2005a; Salek-Haddadi et al., 2003). One study used fMRI to record BOLD activity associated with spontaneous generalized spike and slow-wave discharges (GSW) (Archer, Abbott, Waites, & Jackson, 2003). They found reduced neural and synaptic activity in the posterior cingulate in four of five IGE individuals; and suggested that cingulate activity might be a marker of altered thalamic-cortical activity (Duncan, 2005a).

Another study found symmetrical deactivation of the cortex of both hemispheres involving the anterior as much as posterior regions (Aghakhani et al., 2004). An fMRI measure of BOLD activity in 15 patients found 14 (93%) produced cortical changes as a result of GSW activity. Activation predominated over deactivation in the thalamus whereas the opposite occurred in the cerebral cortex leading researchers to claim this was human evidence confirming thalamic involvement during GSW burst firing. These studies support the concept of thalamic-cortical circuit abnormalities as the underlying pathophysiological substrate of IGE (Duncan, 2005a).

In conclusion, research studies using a variety of investigative techniques found microscopic neuropathologies: some in the frontal lobes and some in the thalamus, while MRI evidence suggests that dysfunction

occurs along thalamo-cortical circuits (for a review, see Duncan, 2005a; Hommet, et al., 2006).

The next sections contain background information on two contexts where IGE sub-syndromes might be associated with cognitive deficits: IGE co-morbid with another disorder, and the reflex seizures manifested in some IGE sub-syndromes.

2.2.3 CO-MORBID DISORDERS

In a patient with a particular index disease, the term co-morbidity refers to any additional co-existing ailment

(Feinstein, 1970, p. 467).

In their review on co-morbidities found within psychopathologic disorders, Krueger and Markon (2006) pointed out that co-morbidity can encompass the co-occurrence of two separate disorders within the same individual or possibly refer to two disorders sharing the same underlying aetiology.

Diffuse axonal shearing (DAS)

Neuronal shearing, stretching and tearing most often results from rapid acceleration and deceleration of the brain caused by the brain being shaken within the cranial cavity as in the case of closed head injury....

(Selby. 2000, p.54).

Diffuse axonal injury, which includes axonal strain and shearing, is the result of concussion. Diffuse axonal shearing (DAS) is a characteristic of mild traumatic brain injury (TBI) (Lezak, Howieson, & Loring, 2004). Post-concussion syndrome occurs when axonal injury results in a period of amnesia, followed by neurophysiological symptoms (headache and fatigue); and neuropsychological deficits including attention dysfunction,

slowed information-processing, verbal retrieval problems and emotionality disorders (Andrewes, 2001; Lezak, et al., 2004). For example, moderately severe TBI can be accompanied by emotionality expressed as either apathy or disinhibition (Andrewes, 2001). Lezak et al. (2004, p. 182) have also discussed the impact of TBI on emotional and social functioning.

Autism (ASD)

The association of autism with clinical or subclinical epilepsy might denote common genetic factors in some cases.... The prevalence of epilepsy among all children is estimated at 2-3%, compared with some 30% in autism. This high proportion rules out a mere coincidence and indicates that autism and epilepsy frequently share a common basis

(Tuchman & Rapin, 2002, pp. 352-353).

Research evidence suggests that autism and epilepsy have pathophysiological mechanisms in common, with one investigatory method being EEG abnormalities. For example, observation of frequent epileptiform activity, whether the patient has been diagnosed with epilepsy or not, suggests that the abnormal epileptiform activity might be aetiological and causal, not just correlational (Levisohn, 2007). The incidence of epilepsy in autism varies according to the particular sub-type: **autistic disorder, Asperger's syndrome, Disintegrative disorder** or **Rett's syndrome**. What these disorders have in common is impairment in sociability; language, communicative skills, and imagination; and a lack of intellectual and behavioural flexibility (Tuchman & Rapin, 2002).

2.2.4 REFLEXIVITY

At least some understanding of how the brain works in the useful yet somewhat artificial construct of generalized epilepsy has come from the study of reflex seizures

(Zifkin & Inoue, 2004, p. 44).

The question raised in several research studies is how focal motor seizures (e.g. photosensitive, eyelid or perioral myoclonia) can fit into a **“generalized” syndrome such as IGE** (Covanis, 2005; I. Taylor, Scheffer, & Berkovic, 2003; Zifkin & Inoue, 2004). The distinction between focal and generalized epileptic ictogenesis is probably less clear-cut than might be expected (Mayer, Schroeder, May, & Wolf, 2006).

Idiopathic occipital lobe epilepsies?

Occipital epilepsies often elude diagnosis as they frequently masquerade as other seizure syndromes. Visual hallucinations are the key clinical symptoms indicating an occipital focus

(I. Taylor, et al., 2003, p. 753).

Researchers disagree as to the nature of the association between epilepsy and migraine (Marks & Ehrenberg, 1993; Ottman & Lipton, 1994). Some claim migraine and epilepsy are distinct disorders, both in underlying pathophysiological mechanisms and symptomatology (Andermann & Zifkin, 1998) or that headaches can cause seizures (see Milligan & Bromfield, 2005 for a case of "migralepsy"). Others claim the presence of one disorder increases the likelihood that the other is also present (Bigal, Lipton, Cohen, & Silberstein, 2003). Clinically similar symptom profiles between the two disorders can lead to misdiagnoses where migraine can be confused with epilepsy (Bigal, et al., 2003; Gilliam, Mendiratta, Pack, & Bazil, 2005). In their review of research into epilepsy and migraine, Bigal et al. note one notable difference is duration of an aura: 15-60 minutes for migraine and brief, often not more than 1 minute for epilepsy (see Table 2 for differentiating features in Bigal, et al., 2003, p. S15).

Many of the manifestations of classical migraine emanate from the occipital lobes, so that differential diagnosis might depend on comparisons of visual hallucinations (I. Taylor, et al., 2003). The elementary visual

hallucinations of occipital seizures are mainly coloured and circular, develop within seconds and are very brief (2-3 minutes). They appear in the periphery of a temporal visual hemifield, become larger and sometimes move horizontally to the other side. In migraine, the visual aura starts as a flickering, uncoloured, zigzag line/s in the centre of the visual field, affecting central vision, then sometimes progress towards the periphery of one hemifield. Duration can be up to 60 minutes (Panayiotopoulos, 2006; I. Taylor, et al., 2003).

Photosensitivity

Photosensitivity is an abnormal visual sensitivity of the brain in reaction to flickering light sources or patterns expressed in the EEG as generalized spike-and-wave discharge or photo-paroxysmal response (PPR), and in more susceptible individuals as clinical seizures

(Covanis, 2005, p. 67).

Photosensitivity covers a number of triggers which include television, video and computer games, natural light (sunlight reflection); and environmental light (fluorescent, disco strobes) (Covanis, 2005; Szabo, 2010; Yalcin, Kaymaz, & Forta, 2000). Occipital epilepsies and the PPR of photosensitivity both begin in the occipital-visual cortex regions (Covanis, 2005). One study has described two types: *purely photosensitive epilepsy* and *epilepsy with photosensitivity*. **The former's seizures are triggered only by lights; whilst the latter is an epileptic trait, one of several seizure-types in a person** (Zifkin & Kasteleijn-Noist Trenite, 2000).

Either type of photosensitivity is not an epilepsy syndrome in its own right, but is most prevalent in idiopathic epilepsies such as IGE, JME and less commonly in localization-related occipital epilepsies (Covanis, 2005; I. Taylor et al., 2004). A single gene for photosensitivity has not been identified yet, but photosensitivity can occur in several family members suggesting a genetic base (I. Taylor, et al., 2003; Zifkin & Kasteleijn-Noist Trenite, 2000).

Eyelid myoclonia with absences

Eyelid myoclonia is the feature characteristic of Jeavons Syndrome, and consists of marked jerking of the eyelids often associated with jerky upward deviation of the eyeballs and retropulsion of the head. Seizures are brief (3 to 6 seconds) and occur mainly after eye closure

(Panayiotopoulos, 2005a, p. 62).

In eyelid myoclonia with absences (EMA) the combination of clinical and EEG phenomena is pathognomonic of Jeavons Syndrome, which the ILAE Commission has recently recognized as a new seizure-type: eyelid myoclonia with and without absences (Striano et al., 2009). Patients with EMA are all photosensitive, but as well as the flickering lights which evoke seizures in other epilepsies, these patients are sensitive to bright uninterrupted light (Covanis, 2005). Generalized tonic-clonic seizures occur immediately after closing the eyes against the light, while EMA can be controlled by eye-opening in some cases (Panayiotopoulos, 2005a; Striano, et al., 2009). Notably, prolonged eyelid myoclonic seizures have been observed, but rather than continuous nonconvulsive SE, EMA status consists of repetitive and discontinuous episodes of eyelid myoclonia with mild absences, with no recovery of full awareness between episodes (Panayiotopoulos, 2005a).

Video EEG recordings will rarely be normal, but rather will document irregular and frequent high-amplitude generalized discharges of 3-6 Hz spike, usually polyspike waves (Panayiotopoulos, 2005a). This pattern is related to eye closure and invariably evoked by IPS, but vanishes in total darkness (Covanis, 2005).

Perioral Myoclonia with absences

Perioral reflex myoclonia (PORM) are short, sometimes repetitive, abrupt myoclonia around the mouth, which will clearly be noticed by the patients, sometimes with interruption of reading and speaking. Most of these jerks appear strongly localized and do not change the side in individual patients. In some cases, PORM are bilateral

(Mayer, et al., 2006, p. 1059).

Other studies have described rhythmic contractions of the facial and mastication muscles, which result in protrusion of the lips, twitching at the corners of the mouth, or more rarely widespread chewing and jaw jerking. Impairment of consciousness ranges from mild to severe, duration is about 4 seconds. The semiology does not fundamentally differ across epileptic syndromes (Mayer, et al., 2006; Panayiotopoulos, 2005a). Perioral myoclonia occur in conjunction with generalized convulsive seizures, and have been found most often in conjunction with JME (Mayer, et al., 2006). As noted above, absence SE is known to occur in EMA, but it is more common in perioral myoclonia with absences (PMA) than in any other IGE sub-syndrome (57%), and frequently ends with generalized tonic-clonic seizures. PMA are rare in the complex partial seizures of TLE, but are more likely to occur during secondarily generalized tonic-clonic seizures (Shorvon & Walker, 2005).

Brain scans are normal but interictal EEG shows generalized discharges of spikes or multiple (3-4) spikes, and slow waves (4-7 Hz), usually asymmetrical, giving impression of a localized focus (Panayiotopoulos, 2005a, 2005b). First-degree relatives or family members might also have IGE with absences, suggesting a common genetic aetiology. The research literature contains a growing number of case reports where PMA has been diagnosed as focal seizures characterized by oral automatisms (Baykan & Noachtar, 2005; Bilgic, Baykan, Gurses, & Gokyigit, 2001) resulting in ineffective treatment with carbamazepine which in turn leads to worsening of seizures.

2.2.5 GENERAL ASSUMPTIONS ABOUT IDIOPATHIC GENERALIZED EPILEPSY

The seizures in individuals with IGE syndromes appear to have a diffuse, distributed onset attributed to disorders of ion channel function inherited in a polygenic fashion. Recent detection of regional brain pathologies, however, implies the existence of cognitive deficits.

- With a few known exceptions, because IGE aetiology is genetic (rather than symptomatic), any cognitive impairment will take the form of a very mild lowering of overall intellectual abilities.
- Because IGE seizures are known to involve generalized abnormal brain activity, an absence of localized deficits can be expected.

Specific clinical and cognitive predictions based on these general assumptions will be further investigated in Chapter Four (IGE case studies).

2.3 TEMPORAL LOBE EPILEPSY

All finches are the same.

When Darwin returned from his legendary voyage to the Galapagos Islands on the *Beagle*, he brought with him many specimens including various birds of different appearance which he could not identify. After consulting John Gould, an expert ornithologist, they observed the birds differed systematically in their beak features: those with large beaks lived on islands with hard food including nuts; while those with thin-shaped beaks had berries and soft foods on their home islands. Darwin and his colleague concluded that despite their dissimilar appearances, the birds had evolved into different species of finch that had adapted successfully to the necessities of their different island environments.

The research articles in this section question whether all temporal lobe epilepsies have the same cognitive deficit (memory), varying only according to locus of onset in the left or right temporal lobe.

2.3.1 DEFINITIONS

Episodic memory contains time- and context-dependent information and recall is enhanced by the presence of matching contextual or time cues. For example, it might include personal details about a pet (e.g. the colour of a cat). *Semantic memory* is independent of time or context cues, and consists of world knowledge such as general facts about animals and pets (Hart et al., 2007; Saumier & Chertkow, 2002).

Two studies suggest that episodic memory is separate from semantic memory, both structurally and functionally. Tulving and Markowitsch (1998) suggest a separation of declarative memory in which acquisition of factual knowledge (semantic memory) can occur independently of episodic memory (everyday experience), and where episodic memory can be more severely impaired than semantic memory (Knowlton & Squire, 1995). This means that the hippocampus is necessary for remembering ongoing life experiences but not necessarily for the acquisition of factual information, such as school or academic knowledge (Vargha-Khadem et al., 1997).

The cognitive distinction between episodic and semantic memory is matched by the anatomic distinction between *medial* and *lateral* (or neocortical) temporal lobes. There is general consensus that medial temporal lobe structures (including the hippocampus) are critical for episodic memory. Semantic memory findings are less conclusive, but impairment does not seem to be related to medial hippocampal damage.

Garrard and Hodges (2000) review some evidence from TLE patient studies that long-term consolidation and retrieval of semantic memory depends on perihippocampal cortical regions of the lateral temporal lobe. Lateral TLE patients do seem to have problems with semantic memory processing, but it is unclear if they are due to disruption of the relational structure of the semantic knowledge network or to impaired retrieval processes (see Helmstaedter, 2002 for a review). Evidence from neuroimaging studies shows semantic search mechanisms situated in the frontal lobes which interact with semantic knowledge stores localized in the posterior region of the left temporal lobe (for a review, see Saumier & Chertkow, 2002).

Classification

The recent classification debate has questioned the adequacy of the **ILAE system's diagnostic choice between *partial focal* versus *generalized*** (Avanzini, 2003; H. O. Luders, et al., 2003; Wolf, 2003). Whilst complex partial seizures might begin with unilateral abnormal brain activity, over time they have been known to evolve bilaterally into convulsions and total loss of consciousness (for a review, see Hwang & Golby, 2006). To include the possibility of secondary generalization of seizures to extra-temporal structures, the ILAE has improved the diagnostic choice to *localization-related* versus *generalization* (Wolf, 2005).

2.3.2 MODULARITY OF MIND

Modularity of mind is one way to describe different types of memory (e.g. verbal or visual): separate entities located in neatly separated neuroanatomical locations e.g. left temporal and right temporal respectively (Fodor, 1983, 2000, 2005). The term *module* means a processor within the cognitive system which functions in an independent or separate fashion. Modules are domain-specific, that is, responses are

elicited only by stimuli of a particular class and not by others (Coltheart, 1999; Eysenck & Keane, 2005).

The weakness of purely anatomical or spatial modularity models is that they equate cognitive architecture with brain structure in an isomorphic, or one-to-one, relationship (Barrett & Kurzban, 2006; Marr, 1982). This connection limits spatial plasticity and cannot account for impaired cognitive functions in a damaged area of the brain being re-organized and carried out by a (usually neighbouring) healthy area (Quartz & Sejnowski, 2002; Ramachandran & Blakeslee, 1998).

Material-specific models of memory are in accord with Fodor's (1983) modularity of mind principles, and were developed to explain research findings into surgery patients with TLE. More recent modularity models conceptualize memory as involving specialized mechanisms of information-processing rather than material-content (Barrett, 2005; for a review, see Barrett & Kurzban, 2006; Pinker, 1997, 2005; Sperber, 2005). One example is HERA (hemispheric encoding-retrieval asymmetry), a process-specific model which was developed on the basis of PET findings. Learning is associated with left dorsolateral prefrontal activation and encoding of novel events in episodic memory (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Retrieval of episodic information is mediated bilaterally, but with a right hemispheric bias (LePage, Ghaffar, Nyberg, & Tulving, 2000). Visual recognition is associated with the right inferotemporal cortex (Kapur et al., 1994).

A general function which can evaluate and process more-than-one type of input information (e.g. auditory, visual or verbal cues) has not been included in either material-specific or process-specific modular theories (Eysenck & Keane, 2005; Miller & Cohen, 2001). Thus, because cognitive domains including memory are assumed to be dissociated from one another, a modular view of memory cannot account for any cognitive deficits of TLE other than episodic memory (Barr & Goldberg, 2003). The

same goes for the left and right hemispheres: cognitive functions associated with the right hemisphere are tied to their neuroanatomical site and so theoretically cannot interact with those of the left hemisphere.

2.3.3 MATERIAL-SPECIFIC MODULAR MODELS

A material-specificity model supports the view that laterality of seizure onset impacts memory performance along a verbal or nonverbal division, or an auditory versus visual difference. Early studies show that left temporal lobectomy patients had superior nonverbal memory abilities compared with their verbal memory, whilst right temporal lobectomy patients show better ability to learn and recall verbal rather than nonverbal material (Jones-Gotman & Milner, 1978). In his review, Saling (2009) describes two features (localization and lateralization) inherent in material-specificity, then goes on to provide evidence which undermines **this model's construct validity**.

Fractionation of memory

- Verbal and nonverbal memory systems are unitary and internally homogenous constructs (Saling, 2009).

Neurologically healthy people produce correlations across a range of memory tasks but this is not the case in people with symptomatic TLE (Saling, 2009; Saling, Berkovic, O'Shea, & Kanins, 1993). Less is known about cognition in idiopathic TLE, but findings indicate either minimal memory impairment (Loring, Lee, Martin, Meador, & Kimford, 1988); or none at all (Barr et al., 1997; Naugle, Chelune, Cheek, Luders, & Awad, 1993).

Most of Saling's (2009) review of evidence against the construct validity of material-specificity comes from fractionation of memory studies which have found that neither the verbal nor the nonverbal memory

domains are affected as a whole. Rather, components of verbal (e.g. episodic or semantic) or nonverbal (e.g. visual or spatial) memory are affected (Saling, 2009). Because an impaired component is usually associated with seizure onset in a particular area of the temporal lobe, Saling describes these cognitive deficits as “**neurocognitive markers for epileptogenesis**” (2009, p. 6).

Hemispheric interaction during memory functions

- Left and right memory systems are independent and self-contained (Saling, 2009).

With the advent of modern imaging techniques, strictly separate functions have not been found to be the case either for neurologically healthy people or those with epilepsy (Barrett & Kurzban, 2006; Golby et al., 2001). Rather, verbal and nonverbal memory functions seem to operate in an asymmetric fashion (Golby, et al., 2001). Nevertheless, the material-specificity model describes a double dissociation of verbal and nonverbal deficits according to left or right seizure onset in TLE. It predicts that people with dominant hemisphere TLE will have verbal impairments but normal nonverbal functions; while those with nondominant hemisphere TLE will show nonverbal impairments but normal verbal functioning (Delaney, Rosen, Mattson, & Novelly, 1980; Kim, Yi, Son, & Kim, 2003). A theory positing a single dissociation might be more accurate (at least for surgery patients), since the majority of studies support the former claim, but evidence for spatial and nonverbal memory deficits is sparse, and most comes from animal studies (Majak & Pitkanen, 2004). In his review, Saling (2009) concludes the material-specificity principle has restricted explanatory power for how memory works.

2.3.4 ASSOCIATIVE NETWORK MODELS

Description

The long-held view of seizures confined within the temporal lobes affecting only the hippocampus and nearby structures has not been supported by results from studies using modern brain mapping techniques (for a review, see Hwang & Golby, 2006). Recent findings are best accounted for by associative network models of memory which describe memory as a collection of systems functioning across neuroanatomical structures, with memory processes which acquire, store, consolidate and retrieve information utilizing neocortical and subcortical circuits in the brain (Eysenck & Keane, 2005).

The role of the Hippocampus as mediator

The hippocampus is viewed as the mediator of these large-scale associative networks involving other brain regions (Eichenbaum & Bunsey, 1995; Gluck & Myers, 1995). The hippocampus has dense connections with the prefrontal cortex (Barr & Goldberg, 2003; Hermann & Seidenberg, 1995), and also diffuse connections to the diencephalon, including the mamillary bodies and anterior thalamus (for discussion and peer commentary, see Aggleton & Brown, 1999). Thus, affected extra-temporal lobe structures in medial TLE can include the anterior thalamus (Kimiwada et al., 2006), and the pre-frontal cortex (Knowlton, 1999).

Hippocampal connections with cortical zones, including the frontal lobes, have been described as reciprocal (see schematic view of multiple memory circuits in Squire & Zola, 1998). Hence, damage or structural abnormalities to these areas outside the temporal lobe could account for the cognitive impairments (other than episodic memory) sometimes seen in TLE patients (Seidenberg et al., 2008). Also, multiple brain circuits

might explain the widespread cognitive deficits thought to follow from repeated secondarily generalized complex partial seizures and/or from hippocampal sclerosis (Barr & Goldberg, 2003). When TLE involves seizures-types which extend across brain structures and cognitive domains, then material-specific modular models can no longer fully account for the nature of cognitive impairment in TLE.

Asymmetry not lateralization

Wagner, Poldrack, Eldridge, Desmond, et al. (1998) used fMRI of nine healthy volunteers to compare pre-frontal activation elicited by two material-types (abstract words versus visual textures difficult to label verbally) during encoding and retrieval tasks. Regardless of whether the task elicited encoding or retrieval processes, inferior pre-frontal activation lateralized according to stimulus material. Verbal encoding and retrieval resulted in greater left inferior prefrontal activation, whereas non-verbal encoding and retrieval resulted in greater right inferior prefrontal activation (Wagner, et al., 1998).

The investigators concluded that both encoding and retrieval processes of episodic memory depend on shared processes mediated by the left and right pre-frontal cortices e.g. evaluation and inference processes (Leboe & Whittlesea, 2002; Wagner, et al., 1998). This model is similar to the process-specificity model (Tulving, et al., 1994) insofar that they both propose an asymmetry of processes governed by the pre-frontal cortex. **Wagner et al.'s** (1998) construct also includes evaluation which allows more conceptual control over memory than process-specificity which is based on automaticity of memory processes (Schacter & Wagner, 1999).

To conclude, associative network models describe how executive functions associated with the pre-frontal cortex evaluate stimulus materials, thus mediating learning and retrieval from memory. They

predict that right-handed people with dominant TLE (usually left temporal lobe) will show dysfunction of both learning and retrieval of verbal information associated with the left pre-frontal cortex and left temporal lobe, while people with non-dominant (usually right) TLE will show both learning and retrieval deficits of non-verbal information associated with the right pre-frontal cortex and right temporal lobe (Schacter & Wagner, 1999; Wagner, et al., 1998) .

2.3.5 THE RIDDLE OF ADAPTABILITY

Adaptability is not just a property of the frontal lobes, it is the fluid recruitment of different processes anywhere in the **brain as required by the current task ... What is perhaps** most relevant is the considerable complexity of this adaptability

(Stuss, 2006, p. 268).

The focus of Stuss's review (2006) is summed-up in a riddle about modularity of mind: do the frontal lobes function in a general adaptability mode, or do they consist of a series of distinct processes?

Adaptability takes different forms, apparently separate. First, *general* adaptability becomes apparent during lesion studies of the anterior cingulate, when the importance of larger areas of the superior medial frontal cortex to tasks of increasing complexity is revealed (Stuss, 2006). Second, evidence for a more specific and *regional* adaptability to task demands is found in the research literature, and involves the flexible recruitment of additional processes depending on task context (Duncan & Owen, 2000).

Neither alternative can fully explain frontal lobe functions. First, as a general computational resource, the functional complexity of the frontal lobes has not been recognized (Stuss, 2006). Complexity can be seen in the categories of frontal lobe functions: behavioural and emotional self-

regulation, meta-cognition (Stuss, 2006; Stuss & Levine, 2002); self-awareness (Stuss, 1991); and executive abilities such as task-setting, problem solving, monitoring and shifting (Stuss, 2006). Second, regional specificity of functions needs to explain integration of processes during goal-directed activity, that is, “**how**” the pre-frontal region selects and discards information for solving the sometimes quite different cognitive problems (see Duncan & Owen, 2000 for a review).

Stuss (2006) concludes the controversy (i.e. regional fractionation versus general adaptability roles) can be resolved by proposing an interaction between specific functions and a global adaptability. Further study is needed on how specific regions work together under different task conditions such as context, complexity and different task-types (e.g. reaction times versus memory accuracy, visual versus verbal, spatial versus non-spatial) (Stuss, 2006).

2.3.6 GENERAL ASSUMPTIONS ABOUT TEMPORAL LOBE EPILEPSY

The seizures in patients with TLE syndromes are believed to have a localized onset and commonly are associated with focal structural brain damage, such as hippocampal sclerosis in the left or right temporal lobe. Thus, memory deficits are expected to be localized and with clear material-specific laterality dissociations. If there is structural damage (either as cause or consequence) then cognitive deficits will ensue, but still largely be confined to memory functions.

- Because TLE aetiology involves the temporal lobes and is symptomatic in the vast majority of clinical cases, it is assumed that people with TLE will have localized memory deficits only.
- The material-specificity model is based on the theory of clearly lateralized memory impairment: people with dominant hemisphere (usually left) TLE will have verbal memory deficits, while those with

nondominant (usually right) TLE will have visuo-spatial memory deficits.

Specific clinical and cognitive predictions based on these general assumptions will be further investigated in Chapter Five (TLE case studies).

2.4 STATUS EPILEPTICUS

All ravens are black

Thus, to falsify the statement *all ravens are black* the testable statement that there is a family of white ravens in the zoo at New York would suffice. All this shows the urgency of replacing a falsified hypothesis by a better one

(Popper, 1992, p. 87).

Popper was asked how often falsification had to be actually shown in order to be a *reproducible effect*, and answered that in some cases, not even once: one white raven would be sufficient to disprove the universal statement (Buck, 1975). The SE research in this section questions whether all prolonged seizures produce long-lasting cognitive deficits.

2.4.1 DEFINITIONS

One notable fact of status epilepticus seizures is their clinical heterogeneity. *Status Epilepticus* is a general term applied to types of prolonged seizures: generalized convulsive status (GCSE), nonconvulsive status (NCSE), complex partial status (CPSE) and absence status (ASE). Each has a different presentation, distinct pathophysiology, EEG patterns, treatment requirements and potential outcomes so the various seizure-types need to be differentiated accurately (for a review, see Gaitanis & Drislane, 2003; Thomas, Zifkin, & Andermann, 2006a; Treiman, 2006). The basic division is between convulsive and nonconvulsive status on the

presence/absence of a predominant motor component (Tomson, Lindbom, & Nilsson, 1992). Clear-cut distinctions are the exception in NCSE, where various sub-types with overlapping clinical features can make diagnosis particularly challenging, for example generalized ASE and focal CPSE (Riggio, 2005; Thomas, Zifkin, & Andermann, 2006b).

The general rule for GCSE used in clinical practice is **“whether a seizure persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur”** (Chen & Wasterlain, 2006, p. 247). **A working definition of NCSE could be “a range of conditions with a prolonged state of impaired consciousness or altered sensorium associated with continuous paroxysmal activity or EEG discharges of abnormal brain activity” with associated changes in behaviour and mental status** (Maganti, Gerber, Drees, & Chung, 2008, p. 573). Shorvon (2007) has deliberately given a loose definition for NCSE as denoting a range of conditions in which electrographic seizure activity is prolonged, thus resulting in nonconvulsive clinical symptoms.

2.4.2 CLASSIFICATION

Traditionally, SE has been conceptualized as a prolonged version of brief seizures and classified accordingly as a seizure-type forming part of an epilepsy syndrome. Since then, dissatisfaction with the adequacy of the current ILAE scheme has led to a few revisions (Leppik, 1990) and an entirely new semiologically-based scheme has been proposed (H. O. Luders, Rona, Rosenow, Arnold, & Carreno, 2005; Rona et al., 2005). Others have put forward categorization schemes based on age and epilepsy syndrome for GCSE seizure-types (Shorvon, 1994, 2005b, 2007; Shorvon, Trinka, & Walker, 2007) and more recently, NCSE sub-types based on age and presence or absence of encephalopathy (Shorvon, 2005b). (For types of prolonged seizures occurring in adult life and childhood, see Shorvon, 2001, p. ii22).

As it stands, the present ILAE scheme depends on duration criteria by which to differentiate prolonged from brief seizures, but precise duration remains controversial (see Dupont & Crespel, 2009 for a discussion). Clinical GCSE diagnosis has used 30 minutes duration, derived from animal and human evidence that this is the time interval at which reversible brain injury begins, and irreversible brain injury after 60 minutes (Lowenstein, Bleck, & Macdonald, 1999; Meldrum, 1999, 2002). More recently, to enable speedier treatment, necessary duration has been reduced to 10 minutes (Rona, et al., 2005; Treiman, Meyers, & Walton, 1998), or even five minutes (Lowenstein & Alldredge, 1998; Lowenstein, et al., 1999). Diagnosis as NCSE has a longer duration of 30 to 60 minutes, which might reflect a belief that less risk of neuronal injury and cognitive impairment is expected (Kaplan, 1996a, 1996b; Tomson, et al., 1992).

In short, duration criteria work in the clinical setting, but such a one-dimensional construct fails to incorporate whole areas of epilepsy phenomenology (Shorvon, 2007). Information to be considered should include pre-existing epilepsy syndrome (if any), age at onset of SE, possible co-morbidities, and underlying aetiology to name but a few (Shorvon, et al., 2007). Of particular interest, individuals with an SE condition might not reveal the same patterns of cognitive dysfunction as found in people with brief seizures (Shorvon & Walker, 2005).

2.4.3 EPIDEMIOLOGY

Cross-cultural Incidence and Ethnic Background

Incidence and mortality rates might be under-estimated due to methodological difficulties such as differing definitions of NCSE or inaccurate diagnoses due to unavailability of EEGs outside of hospitals (Maganti, et al., 2008; Rosenow, Hamer, & Knake, 2007). The annual incidence of SE ranges from 10.3 to 41 for 100,000 inhabitants (Dupont & Crespel, 2009), and 18-28 per 100,000 persons for GCSE (Shorvon, 2001).

Incidence of SE rates reported in epidemiological studies vary according to ethnic background, age and possibly gender (see Rosenow, et al., 2007 for a review).

Ethnic Background. The minimal incidence of SE in the Caucasian population of industrialized countries is about 20 per 100,000 per year in adults (Rosenow, et al., 2007). Maganti et al. (2008) also have reviewed epidemiological studies of SE in various countries including the United States (Rochester and Richmond), French-speaking cantons of Switzerland, Italy (Bologna), Finland and Germany. The incidence of SE in the Afro-American population of Richmond, Virginia, was three times as high as in the Caucasian population (DeLorenzo, 2006; DeLorenzo, Hauser, & Towne, 1996; Rosenow, et al., 2007). Another retrospective study of GCSE in California reported relative risk as compared to Caucasians for Afro-Americans to be 1.92, Hispanics 0.5, and Asians 0.4 (Wu, Shek, Garcia, Zhao, & Johnston, 2002). A London-based study found Indian children to have a relative risk to develop SE of 6.5 (Chin et al., 2006), and this was attributed to a higher frequency of prolonged febrile seizures in children, indicating a different susceptibility, perhaps genetic (Rosenow, et al., 2007).

A retrospective, cross-sectional study on epilepsy patients in a regional hospital in Far North Queensland included data-analysis of 359 patients (Archer & Bunby, 2006). The researchers found that whilst indigenous Australians had similar epilepsy disorders to the non-indigenous patients, the former group had a greater incidence of SE seizures. Indigenous patients constituted 11% of attendees at the epilepsy clinic, but they made up 44% of admissions for SE seizures. The researchers did not attribute this discrepancy to greater consumption of alcohol or more cases of head trauma since both groups had roughly similar percentages. Less use of health care (geographical isolation, cultural issues and mistrust of the public hospital system) and *learned*

helplessness tied to low socioeconomic status, were suggested as possible explanations (Archer & Bunby, 2006).

Gender and Age Incidence of SE is higher in males (DeLorenzo, 2006; Knake et al., 2001) with the exception of Italy (Vignatelli, Rinaldi, Galeotti, de Carolis, & D'Alessandro, 2005; Vignatelli, Tonon, & D'Alessandro, 2003). Age of SE has a bimodal distribution, with the highest incidence in children less than 1 year of age and in the elderly of 60 and over (DeLorenzo, et al., 1996; Drislane, 2005; Hesdorffer, Logroscino, Cascino, Annegers, & Hauser, 1998).

There is some controversy over the rarity (or not) of ASE and CPSE cases (Thomas, et al., 2006a). Originally, knowledge of ASE was limited but Koutroumanidis (2005) claims recent research finds ASE to be the commonest form of NCSE, reports ranging from 53% to 94% of all SE in different studies. Discrepancies have been attributed to ASE being completely ignored or misdiagnosed (e.g. CPSE, dementia, psychogenic or other behavioural disorders, depression, postictal confusion) before the development of more exact neuroimaging tools (Agathonikou, Panayiotopoulos, Giannakodimos, & Koutroumanidis, 1998; Andermann & Robb, 1972; Berkovic & Bladin, 1983). Similarly, CPSE was once considered rare, but with the advent of CCTV/EEG epilepsy monitoring, more than 200 cases had been reported by 1990 (Delgado-Escueta & Treiman, 1987; but see Knake, et al., 2001; Treiman, 2005).

Mortality and Status Aetiology

Longitudinal data indicate SE incidence and mortality is increasing and attributable to an aging population living longer (Hitiris, Mohanraj, Norrie, & Brodie, 2007; Logroscino et al., 2002). The three leading aetiologies for SE are low-dose AED, non-acute brain lesions and acute stroke (Dupont & Crespel, 2009). For uncommon causes, see Shorvon and Tan (2009).

GCSE Mortality rates vary according to age, aetiology, seizure duration and also across countries (for reviews, see Maganti, et al., 2008; Rosenow, et al., 2007). Case fatality ranges from 1.9% to 40% depending on age (over 65 years and under 20 years have a higher rate of mortality). Some 80% of fatalities can be accounted for by SE aetiologies such as hypoxia, stroke, CNS infections and metabolic disorders (Simon, Pellock, & DeLorenzo, 1997), whereas lower rates of mortality are associated with low antiepileptic drug levels, fever, alcohol-related mortality and trauma (DeLorenzo, Pellock, Towne, & Boggs, 1995; Towne, Pellock, Ko, & DeLorenzo, 1994).

NCSE Routine clinical experience would suggest that NCSE (whether ASE or CPSE) is rarely fatal. There have been just a few case studies reported of adult mortality in CPSE (Fugikawa, 2005; Labar, Barrera, Solomon, & Harden, 1998; Shorvon, 2002). One study by Logroscino et al. (2002) assessed increased risk for long-term mortality (within 10 years after the first SE episode). Symptomatic aetiologies (myoclonic status, longer duration of SE e.g. 24 hours, and acute symptomatic SE) increased the mortality rate to three times that of the general population, while idiopathic or cryptogenic aetiologies resulted in the same mortality rate as the general population (Logroscino, et al., 2002). Berg (2002) **claims this is evidence that the “one size fits all”** approach to prognosis for SE is too simplistic, including predictions about the possibility of mental decline.

2.4.4 COGNITION

Animal Studies of SE seizures

For logistical reasons, GCSE studies with humans are limited in design and numbers of participants available. Due to ethical

considerations, knowledge about the impact of prolonged seizures on the brain has had to come from animal studies.

Pathological changes in rats and felines show that convulsive SE can result in neuronal injury caused directly by the neuronal epileptic activity, including damage to the hippocampus, cerebral neocortex, specific nuclei of the thalamus and cerebellum (Shorvon, 1994). More recently, animal studies have found that duration of the status activity determines distribution of the damage in rats, with widespread damage recorded after one hour of untreated status (Lukasiuk & Pitkanen, 1998; Pitkanen, Nissinen, & Nairismagi, 2002). Some rat studies have found long-term motor deficits and disturbed social interactions associated with nonconvulsive status epilepticus (Brandt, Glien, Potschka, Volk, & Loscher, 2003; Krsek et al., 2004). Others have found memory impairment after induced status epilepticus (Holmes et al., 2002; Mikati, Tarif, Lteif, & Jawad, 2001).

Majak and Pitkanen (2004) reviewed 16 studies investigating whether convulsive SE seizures cause irreversible cognitive damage in **rats. The reviewers report “unequivocal” evidence that induced-SE** results in impaired spatial and emotional learning and memory, with memory decline correlating with severity of hippocampal damage. However, the minimal duration and severity of SE that causes irreversibly impaired behaviour remained unclear. Genetic background was found to influence both susceptibility to seizure-induced damage and the gene expression induced by seizures. Increased seizure number was associated with decline in spatial learning; while brain reserve had no effect either way. Most notably, Majak and Pitkanen (2004) argued that as in humans, the interval between the last seizure and the beginning of behavioural testing can influence task performance and results.

Human prospective studies

Cognitive impairment in adult humans has been reported in isolated cases in convulsive status, and to lesser degree also in complex partial status and absence status (Thomas, et al., 2006a; Thomas, et al., 2006b). However, most studies are retrospective, cross-sectional and few are larger than fifteen cases, with even fewer in GCSE studies. Most of the available research involves lesions or neurodegenerative disease and does not always include formal neuropsychological testing (C. Dodrill, 1986; Shinnar & Babb, 1997). Consequently, little is certain about cognitive impairment in SE, even less when the SE has a non-symptomatic aetiology. Longitudinal designs enable differentiation between impact of prolonged seizures versus underlying aetiology and also questions about reversibility of deficits over time. Descriptions of some studies follow.

Absence Status

Guberman, Cantu-Reyna, Stuss, and Broughton (1986) studied 10 people with what they described as nonconvulsive generalized status and which today is termed absence SE. **The study's design included a five to six year formal neuropsychological review of eight of the original 10 patients and included examination of speed of response, cognitive set, humour, attention and information, language, memory, and drawing.** In spite of multiple recurrences of absence status no evidence was found of long-term intellectual, memory or behavioural deterioration.

Agathoniku, Panayiotopoulos, Giannakodimos, and Koutroumanidis (1998) looked at the incidence of typical absence status in 21 adult patients with IGE. Diagnosis was based either on EEG clinical features or pathognomonic signs such as prolonged episodes of altered consciousness and eyelid, perioral or limb jerks, often terminating in a generalized tonic-clonic seizure. No permanent after-effects were found, all had normal mental and neurological status, 17 cases also had brain imaging found to

be normal. The most prominent clinical feature had been a mild to moderate clouding of consciousness. They itemized the following distinguishing features.

1. Frequent termination of absence status with a tonic-clonic seizure;
2. moderate to no amnesia of the episode, in contrast to CPSE;
3. relative preservation of verbal functioning, in contrast to CPSE;
4. recovery without post-ictal confusion, in contrast to CPSE; and
5. absence of cycling between unresponsiveness and partial responsiveness which tends to occur in CPSE seizures.

Complex Partial Status

Adachi, Kanemoto, Muramatsu, Kato, et al., (2005) excluded participants with a neurodegenerative disease or brain lesions. They investigated and evaluated intellectual function prospectively in adult epilepsy patients with and without SE. Fifteen SE patients who experienced an SE episode undertook a second neuropsychological evaluation. Mean interval between exam 1 (before SE) and exam 2 (after SE) was 4.4 years (range 2-10 years). Performance of the 15 SE patients was compared with 40 clinically matched epilepsy controls (FLE or TLE but no SE) on I.Q. and WAIS-R subtests. When patients with SE were compared to those without SE, the former failed to show any significant post-SE intellectual decline, suggesting CPSE does not necessarily lead to a significant intellectual decline in adult patients receiving treatment for epilepsy. The study had some shortcomings (e.g. inclusion criteria for people with SE required that only one SE episode occurred *after* Exam 1 but some controls had an SE episode *before* Exam 1).

Profitlich, Hoppe, Reuber, Helmstaedter, and Bauer (2008) conducted neuropsychological testing of six impaired patients with focal

complex partial status, four of whom had marked deficits and two had discrete deficits. Most patients had selective rather than global neuropsychological deficits which encompassed the domains of:

- consciousness (reduced vigilance, reactivity and orientation);
- language (expressive aphasia and severe language deficits associated with reduced vigilance);
- cognition (memory disturbance, apraxia, acalculia, alexia); and
- affect (depressive ideation, withdrawal and severe anhedonia, panic attacks, no self-initiated directed behaviour, and emotional instability overall).

Profitlich et al.'s (2008) findings contrast with **Adachi et al.'s** (2005) lack of deficits, probably due to the former study involving participants with an underlying pathology. Few studies have included formal tests of **mental health so Profitlich et al.'s findings of overall emotional instability** are interesting.

Generalized Convulsive Status

There is a lack of consensus in the literature about specific cognitive deficits associated with a GCSE disorder. **Dodrill (1986)** examined relationships among generalized tonic-clonic seizures and indicators of intellectual, neuropsychological, emotional, and social function. Epilepsy patients were divided according to numbers of lifetime attacks and the presence or absence of a history of major motor status epilepticus. Cognitive abilities were most affected in the group with convulsive status, whereas emotional and psychosocial adjustment was worse in persons having large numbers of single brief convulsions.

Often cited in the literature, Dodrill and Wilensky (1990) conducted a prospective longitudinal study where adult participants had SE with no known etiology: four with tonic-clonic SE and five with complex partial SE. A comprehensive neuropsychological evaluation was administered to 143 epilepsy patients on two occasions five years apart. On the second occasion, nine adults were found to have had at least one episode of continuous or recurrent seizures lasting for at least 30 minutes without regaining consciousness. Each SE patient was closely matched (on gender, age and years of education) with one of the remaining epilepsy patients.

Those who had had SE tended to have lower IQs at baseline than those who did not experience SE during the five year period, which “**raises the possibility that persons with lowered mental ability and a greater compromise in brain functions generally are more likely to experience SE**” (C. Dodrill & Wilensky, 1990, p. 25). After five years, the follow-up assessments showed that controls had improved in performance on the WAIS indices, but that SE participants had deteriorated in I.Q. scores, (most obvious in Verbal I.Q.), as well as other cognitive measures. However, these differences (already evident at baseline testing) failed to attain statistical significance.

Dodrill and Wilensky concluded that overall status epilepticus has “a slight adverse effect on mental abilities apart from underlying neurological disease, and that in many individuals no effects are **discernible**” (1990, p. 26). They suggest future research should include a study of the characteristics of SE itself in those cases where there are some cognitive deficits but no underlying brain disease. The participants in this present study fit that description.

Shorvon (2002) points out some confounding variables in the Dodrill et al. (1990) study. The SE group was slightly younger at seizure onset, and on a larger number of medications. The appropriate tests were

seldom chosen, there were few prospective data, and serial data on the immediate aftermath of SE episodes was not gathered. **Shorvon's** interpretation of their results is not so reassuring, and emphasizes that mild to moderate intellectual impairment was present already at baseline. While this reduces the significance of their deterioration during the intervening five years, it does provide support for epidemiologic data that SE is more common among those who are neurologically abnormal (W. A. Hauser, 1990).

Finally, an absence of cognitive deficits associated with SE might simply be reflecting the availability of prompt treatment during a **prolonged seizure**. See **Appendix E** for **Dr. John S. Archer's** presentation of four indigenous SE cases in remote Far North Queensland. In three cases, treatment was delayed due to transporting patients over great geographical distances from remote areas with no medical services. Their MRI scans show the impact of prolonged seizures not promptly treated.

2.4.5 AETIOLOGY

As for status epilepticus and subsequent cognitive decline, it often remains open whether the epileptic condition itself or the underlying clinical condition is causative for the aftermath

(Helmstaedter, 2007, p. 85).

Promptly treated SE seizures alone are unlikely to cause severe cognitive deficits, since not all SE conditions are associated with long-lasting mental impairment and most post-ictal cognitive deficits are fully reversible over weeks or months (Berg, 2002; Besag, 2005; Helmstaedter, 2007). Aetiology is agreed to be the main factor for morbidity in SE in most large-scale studies (C. Dodrill & Wilensky, 1990; Drislane, 2000; Shinnar & Babb, 1997). Aetiology appears to be the key variable not only for (a) occurrence of SE, but also for (b) predicting recovery/decline in the SE condition over time (Helmstaedter, 2007).

Cognitive impairment and occurrence of SE

Researchers in one small study observed a series of 10 patients with CPSE over 36 hours or more and tested their cognition at 3, 6 and 24 months (Krumholz, Sung, Fisher, Barry, & Grattan, 1995). All had memory deficits, several also had attention and concentration difficulties, but those with CPSE unrelated to acute focal lesions or neurologic precipitants improved after three months. Medical histories indicated that the severe cognitive problems did not seem to pre-date the SE (Drislane, 1999; Krumholz, et al., 1995). Those with lasting neurological damage still showed impaired cognition at six months and 24 months in some cases. The researchers concluded that non-convulsive CPSE is associated with memory loss which might not be permanent. When GCSE and convulsive CPSE interact with acute neurological disorders that precipitate the SE, however, the cognitive deficits which follow might not be reversible even with early AED treatment (Krumholz, et al., 1995).

Kaplan (2000) argues this paper clearly delineates the problems in separating co-morbidity from cause and effect. Most of Krumholz et al.'s (1995) participants had lasting neurological injuries (strokes, encephalitis or multiple co-morbidities) which probably contributed towards the severity of the cognitive sequelae of CPSE or even independently account for them (Drislane, 1999; Helmstaedter, 2007; Kaplan, 2000; Tatum, French, Benbadis, & Kaplan, 2001). The immediate causes of CPSE could in themselves be reflecting an apparent permanent sequelae (Tatum, et al., 2001). In cases where SE occurs in the context of lasting brain damage, distinguishing cognitive deficits due to prolonged seizures from those caused by the acute brain injury itself is difficult, if not impossible (Shinnar & Babb, 1997).

Cognitive recovery or decline over time

Linked to the kind of aetiology is the course of the SE condition: recovery or decline of cognitive abilities (see descriptions of the prospective studies in previous section). Thus, long-standing cognitive deficits act as markers for a worsening course of the underlying illness, also manifested in an increasing frequency and duration of seizures and degenerative changes in seizure-type (Drislane, 2000; Shinnar & Babb, 1997). In ASE and CPSE, mental impairment is usually the product of the underlying illness which causes the SE (e.g. drug or alcohol withdrawal) and conceivably, cognitive impairment is more likely to be transient with such underlying aetiologies (Shinnar & Babb, 1997).

Fujikawa (2005) describes two NCSE cases illustrative of a differing outcome of SE illness and cognitive functioning. For an ambulatory patient with ASE, over nine years there was a gradual decrease in duration of subsequent ASE episodes (spike and slow-wave discharges recorded on the EEG). Over the same period, his full-scale IQ improved from 102 to 125 and deficits of frontal executive function normalized. **The second case was “ictally comatose” after an episode of prolonged and untreated CPSE.** MRI scans at one year follow-up showed mild cortical atrophy, but neuropsychological testing done 1.3 years after the untreated episode revealed significant cognitive impairment: attention and concentration were fair-to-poor, memory tasks were variably impaired, visuospatial skills and frontal lobe functioning were poor, Full-scale I.Q. was 88 (Fugikawa, 2005; Licht & Fujikawa, 2002).

The researcher argues that prognoses for cases can be differentiated according to

- those whose cognitive dysfunction arises from the discharges themselves and so are likely to be reversible over time; and

- those in whom the status is due to an underlying neurological abnormality, in which the discharges are an epiphenomenon and cognitive deficits are longer-lasting.

2.4.6 GENERAL ASSUMPTIONS ABOUT STATUS EPILEPTICUS

Status epilepticus is a prolonged seizure of longer duration and more intense abnormal brain activity than brief seizures. Most clinicians view the SE seizure-types as prolonged versions of their brief seizure counter-parts, but with potentially worse outcomes. Thus, the cognitive deficits expected with SE would be the same as those associated with brief seizures, but perhaps at a more severe level of impairment.

- Because SE is commonly viewed by the ILAE and most clinicians as another version of brief seizure syndromes, it is assumed that SE participants will show similar deficits in the same cognitive domains as those known to be associated with their counter-part brief seizure syndromes.
- Because SE seizures are prolonged when compared to brief seizures, **it is assumed that SE participants' cognitive dysfunction** will be at more severe levels of impairment and show progressively faster deterioration of cognitive abilities.

Specific clinical and cognitive predictions based on these general assumptions will be further investigated in Chapter Six (SE case studies).

2.5 EPILEPSY AND PSYCHOPATHOLOGY

Birds of a feather flock together.

The notion that people with shared characteristics group together has been attributed to the ancient Greek philosopher Democritus (circa

460BC). **This section's research findings** indicate that epilepsies and psychopathology are linked by a shared characteristic. In other words, they do not simply coincide.

The term *psychopathology* has been used in the literature to cover numerous types of psychiatric problems including maladaptive emotional disorders, psychosocial adjustment difficulties, behavioural and personality characteristics (Swinkels, Kuyk, van Dyck, & Spinhoven, 2005). In this thesis, the term has been adopted as a general descriptor.

2.5.1 EPILEPSY CO-MORBID WITH PSYCHOPATHOLOGY

Some researchers hypothesize that epilepsy causes psychological changes through direct neural effects while others implicate difficulties adapting to a chronic illness. Other investigators emphasize antiepileptic medications in the genesis of psychopathology, and some argue that epilepsy and psychopathology simply co-occur with no causal relationship between them

(G. P. Lee, 2004, pp. 131-132).

Definition of the term *co-morbidity* has generated some controversy in the literature (for a detailed discussion, see Drake & Wallach, 2007; Meuser & Drake, 2007; Piotrowski, 2007; Rutter, 1994). It could be defined as co-occurrence of two diagnostic entities which are not causally connected, but might share a common underlying mechanism (Rutter, 1994). In such cases, conventional criteria as listed in the ICD-10 or DSM-IV manuals will suffice for diagnoses (Krishnamoorthy, 2000; Krishnamoorthy, Trimble, & Blumer, 2007; Onuma, 2000).

However, neither of these manuals make allowance for psychiatric disorders *specific to epilepsy* (which they define as an **“organic” condition** only) thus limiting their flexibility of application (Krishnamoorthy, 2002). If the epilepsy disorder itself, either directly or indirectly, contributes to

the psychopathology, symptoms not listed in the manuals are manifested. The result is under-recognition, due mainly to the instruments used for diagnosis (Swinkels, et al., 2005). During a debate (Kanner & Barry, 2001), Barry argued that patients with and without epilepsy were not that dissimilar, while Kanner examined features of various disorders specific to epilepsy, which he summarized as follows.

1. Both depression and psychosis present with unique features in people with epilepsy. These are especially frequent in the perictal and interictal forms (Kanner & Barry, 2001).
2. Identification of unique clinical features is not possible with the existing diagnostic instruments. Further, the available tools for measuring depression and some psychoses in epilepsy cannot differentiate amongst symptoms deriving from interictal, perictal or both types of events (Kanner & Balabanov, 2002; Kanner & Barry, 2001).
3. Amendments and additions to the criteria in current diagnostic manuals are insufficient to cover all forms of some co-morbid disorders. As an example, Kanner argues that diagnostic criteria for postictal psychosis are essential given the unique clinical presentation, course and response to therapy (Kanner & Barry, 2001; Kanner & Palac, 2002).

Krishnamoorthy (2000, 2002; Krishnamoorthy, et al., 2007) has argued that the advantages of a classification system for epilepsy-specific psychopathology and distinct from the DSM-IV and ICD-10 would:

- ensure that mental illness in people with epilepsy is more accurately diagnosed and treated;
- enable phenomenological descriptions of psychiatric disorders in epilepsy;

- enable characteristics of such disorders in epilepsy to be discriminated from those of DSM-IV; and
- provide an accurate construct for empirical testing (Krishnamoorthy, 2000, 2002; Krishnamoorthy, et al., 2007).

2.5.2 EPILEPSY-SPECIFIC MENTAL DISORDERS

A number of epilepsy-specific psychiatric disorders have been causally linked to seizures (preictal, postictal, interictal and perhaps perictal), their relationship to the EEG (Krishnamoorthy & Trimble, 1999), and/or their relationship to antiepileptic drug therapy (Trimble & Schmitz, 1998). The disorders come from different classes and some are listed below, though they are still the subject of debate by the ILAE Commission on Neuropsychiatric Aspects of Epilepsy (see Krishnamoorthy, 2000).

- Organic disorders such as postictal confusional states and complex partial status with psychopathological manifestations (Blumer, Montouris, & Hermann, 1995; Blumer, Wakhulu, & Montouris, 2000).
- Personality changes (the Gastaut-Geschwind syndrome of TLE, and the labile personality of JME).
- A spectrum of psychoses with varying intensity, features and manifestations depending on the temporal relationship with seizures (Trimble, 1992).
- A spectrum of neuroses with predominantly affective features (Krishnamoorthy, et al., 2007) such as major depression (Blumer, et al., 2000; Briellmann, Hopwood, & Jackson, 2007; Hermann, Seidenberg, & Bell, 2000; Kanner & Balabanov, 2002; Kanner & Palac, 2002).

- Mood disorders such as interictal dysphoric disorder (ISS), most common in TLE (Blumer & Altshuler, 1998; Blumer, et al., 1995; Blumer, et al., 2000).

A suggested scheme for classification of mental disorders in epilepsy has been drawn up (Krishnamoorthy, et al., 2007). Selected items from Krishnamoorthy et al., (2007) are presented in an abbreviated form in Table 2.1.

Table 2.1
ILAE Classifications of Mental Disorders: key categories, clinical features and conclusions

<u>Clinical Features</u>	<u>Key Conclusions (draft proposal)</u>
<p>Key: Co-morbidity</p> <ul style="list-style-type: none"> • Anxiety and phobic disorders • Minor and major depression • Obsessive-compulsive disorder • Other somatoform, dissociative and neurotic disorders 	<p>No different from the range of common mental disorders prevalent in the community and clinic/hospital populations. Classification should be as per ICD-10 and DSM-IV.</p>
<p>Key: Psychopathology as presenting symptoms of epileptic seizures Altered awareness, confusion, memory disturbances, disorientation, anxiety, dysphoria, hallucinations and paranoid syndromes</p>	<p>Complex partial, simple partial and absence status and other epilepsy syndromes can be diagnosed; clinically supported by EEG.</p>
<p>Key: Interictal psychiatric disorders that are specific to epilepsy</p> <ul style="list-style-type: none"> • Cognitive dysfunction • Memory complaints 	<p>Maybe general or specific; diagnosed by standard neuropsychological tests.</p>
<ul style="list-style-type: none"> • Psychoses of epilepsy 	<p>To be classified based on relationship to seizure: prodromal, interictal, postictal.</p>
<ul style="list-style-type: none"> • Affective - somatoform disorders • Personality disorders 	<p>Hyperethical, viscous, labile, mixed. Both trait accentuation and disorder to be coded.</p>
<ul style="list-style-type: none"> • Anxiety and phobias that are specific to epilepsy 	<p>Fear of seizures recognised as a distinct and disabling entity.</p>
<p>Key: Other information of relevance</p> <ul style="list-style-type: none"> • Relationship to AED therapy • Relationship to EEG change 	<p>Both induction and/or withdrawal from AED with specified time periods for both. Presence or absence of associated EEG change documented.</p>

Source: based on (Krishnamoorthy, et al., 2007, p. 352)

Research into mental illness in epilepsy has focused mainly on two classes differentiated in the DSM-IV: clinical psychopathology (Axis I); and to a lesser extent, Personality and Behavioural disorders (Axis II).

2.5.3 CLINICAL DISORDERS AXIS I

Studies in this area conceptualize symptoms according to their temporal relationship with seizure occurrence: periictal and ictal clinical manifestations (preceding and during the seizure itself); postictal (immediately following the seizure) and interictal (independent of the seizure) (for a review, see Kanner & Palac, 2002). Marsh and Rao (2002) evaluated psychiatric phenomena during these states. The following sections have been selected and summarized from their review article and also the review by Swinkels et al. (2005).

Ictal disturbances in Status Epilepticus

A prolonged epileptic seizure can be mistaken for a primary psychiatric condition, especially if the patient has co-morbid interictal psychopathology (Yoshino et al., 1997). Nonconvulsive partial status can manifest as prolonged states of fear, mood changes, automatisms or psychosis (delusions or hallucinations) that resemble an acute schizophrenic or manic episode (Marsh & Rao, 2002; Trimble, 1991). Absence status is associated with fluctuating states of arousal, blinking, staring and myoclonic jerks which can be attributed to an attention deficit disorder (Marsh & Rao, 2002).

Ictal and postictal anxiety and depression

Anxiety is a common affective state during complex partial seizures and is associated with right temporal foci (Alemaheyu et al., 1995; Hermann, Whitman, & Anton, 1992). Ictal dysphoria is less common, tends to happen suddenly without outside triggers and can extend into a

postictal state lasting hours, sometimes weeks (Marsh & Rao, 2002). Ictal sadness includes feelings of pathological guilt, hopelessness, worthlessness, profound despair, and suicidal ideation (Jobe, 2003). Some patients do not recognize these states as being out-of-context during the seizure so that ictal dysphoria can result in aggression or self-harm including suicide attempts (Kanemoto, Kawasaki, & Kawai, 1996; Kanemoto, Kawasaki, & Mori, 1999; Kanemoto, Tsuji, & Kawasaki, 2001). Finally, there is no evidence that postictal affective changes are emotional reactions to the recent seizure, though patients and families might make that interpretation (Marsh & Rao, 2002).

Interictal clinical disorders

Interictal mood disorders such as major depression, dysthymic disorder and atypical depressive syndromes, bipolar disorder and adjustment disorders with depressed mood, are common in epilepsy co-morbid with psychopathology (Blumer & Altshuler, 1998). Interictal dysphoric disorder (IDD), a term coined by Blumer et al. (1995), is specific to people with epilepsy (PWE). They describe affective changes secondary to epilepsy, which include labile depressive symptoms (flat affect, anergia, pain and insomnia), labile affective symptoms (fear, generalized anxiety), and distinctive symptoms (paroxysmal irritability, euphoric mood). One study by Kanner (2003) has compared IDD with depression and concludes that there is a spectrum with a chronic dysthymic state characterized by the features of IDD that may intermittently exacerbate and at that time meet the criteria for major depressive disorder.

Interictal anxiety disorders also occur with primary IGE (Devinsky & Vazquez, 1993; Vazquez & Devinsky, 2003). They include generalized anxiety disorder, phobias, panic disorder, and obsessive-compulsive disorder.

Psychotic disorders of an interictal nature typically involve delusions, usually paranoid or religious in nature, visual and auditory hallucinations (Slater, Beard, & Glithero, 1963). Chronic schizophrenia-like psychosis has symptoms similar to schizophrenia, and is six to twelve times more likely to occur in epileptic patients than in the general population (P. Sachdev, 1998). *Schizophrenia-like psychosis* was first described by Slater, Beard, and Glithero (1963). It has atypical features, including lack of negative symptoms (i.e. preservation of warm affect) and adequate or even well-preserved personalities and interpersonal relations (P. Sachdev, 1998).

2.5.4 PERSONALITY DISORDERS AXIS II

Defined by the DSM-IV, **an axis II personality disorder (PD)** is “an enduring pattern of inner experience and behaviour that deviates **markedly from the expectations of the individual’s culture, is pervasive** and inflexible, has an onset in adolescence or early adulthood, is stable **over time, and leads to distress or impairment**” (American Psychiatric Association, 2000, p. 685). The consensus among researchers is that the higher co-morbidity of personality disorders in epilepsy is not a consequence of the chronic epilepsy condition (e.g. antiepileptic drugs, psychosocial problems), but is possibly related to a shared aetiology (e.g. structural brain lesions) (Swinkels, Duijsens, & Spinhoven, 2003).

Epileptic personality or interictal behavioural syndrome has been described as a cluster of personality characteristics associated with TLE patients: deepened emotionality, circumstantiality, disrupted religious and sexual concerns, and hypergraphia (Bear & Fedio, 1977). Unlike these researchers, Waxman and Geschwind (1975) suggested the characteristics are not maladaptive, but should be seen as behavioral change rather than psychopathology.

None of the interictal traits in epilepsy have ever proven to be unique to epilepsy (Swinkels, et al., 2005). Nonetheless, studies have **continued to investigate the “epileptic personality” and have found many** negative traits, such as dependent and avoidant personalities (Lopez-Rodriguez et al., 1999), personality disorder not otherwise specified (Victoroff, 1994), dependent and avoidant personality disorders (Manchanda, Schaefer, McLachlan, & Blume, 1992), and avoidant personality disorder (Arnold & Privitera, 1996).

In 2003, Swinkels and colleagues carried out a personality study of Dutch patients with epilepsy. They found their patients exhibited more disorders of personality compared with a control group from the general population. Their findings corresponded with the clinical impression that patients with epilepsy are frequently seen as unstable, introverted and anxious people, who avoid personal contact for reasons of uncertainty (Swinkels, et al., 2003). Another study found that JME patients with personality disorders demonstrate a prevalence of Cluster B traits, which include emotional instability, immaturity, unsteadiness, lack of discipline, and rapid mood changes (de Araujo Filho et al., 2009).

2.5.5 THE PSYCHOSOCIAL CONTEXT FOR EPILEPSY

Epilepsy can include a very wide range of difficulties in cognition, psychiatric status and social adaptive functioning. Although neurobiological factors may prove important, they operate in a social setting and therefore, a full accounting of the aetiology, treatment and prevention of psychosocial problems in epilepsy will require an integrated biopsychosocial model and life span perspective

(Hermann & Jacoby, 2009, p. S11).

One review of predictor studies of depression in epilepsy examined some 60 different predictor variables. Of these, most studies involved brain-related variables, with fewer psychological, social, and medication

variables included in the investigations. The brain-related variables provided the fewest positive findings (6%) whereas psychosocial variables were associated most frequently with depression (79%). Variables such as seizure frequency, age at onset, and duration of epilepsy had minimal association with depression (Hermann, et al., 2000; Hermann, et al., 1992). Adverse psychosocial factors contribute to both clinical psychopathology and personality disorders. Some examples follow.

Depression and anxiety can develop or worsen with low quality of social support, low self-esteem, epilepsy stigma, or a perceived lack of **control over one's life because of random seizure episodes**. **Learned helplessness** is a maladaptive behaviour and refers to a pattern of emotional, cognitive and adjustment difficulties. The unpredictable nature of seizures may contribute to a tendency to give up, become helpless and lose motivation (DeVellis, DeVellis, & Wallston, 1980; Hermann, Trenerry, & Colligan, 1996; Seligman, 1975). In 1996, Hermann and colleagues examined the association of depression and attributional style as defined by the Optimism/Pessimism Scale in 143 patients with unilateral TLE. The researchers concluded that the concept of learned helplessness, specifically attributional style, is related to the origins of depression in epilepsy (Hermann, et al., 1996).

Demoralization is a normal response to adversity, like a grief reaction (Slavney, 1999). Stressors include employment and scholastic difficulties, financial constraints, social isolation, increased dependency on others, and adverse medication side-effects such as weight-gain and cognitive impairment (Bishop & Slevin, 2004; Jacoby, Gorry, & Baker, 2005; Marsh & Rao, 2002; Thapar, Stott, Richens, & Kerr, 1998).

Of all the factors mentioned above, social and family stigma is a significant psychosocial risk factor for depressed mood in epilepsy patients (Austin, Shafer, & Deering, 2007; Jacoby, 1994; Scambler, 1989; Scambler & Hopkins, 1986). Jacoby (1994) distinguished between perceived and enacted stigma, with the former being a serious risk for

dysphoria, anxiety, low self-esteem, helplessness and somatic symptoms (Arnston, 1986).

See Appendix B for brief summaries of some research studies addressing the cultural and psychosocial aspects of living with the disorder. Epilepsy has a pervasive influence on all aspects of life, and Appendix B looks at such areas as western stereotypes maintained through art, film and television, family relations and expressed emotions, professional attitudes and misconceptions (teachers, general medical practitioners), unemployment, stigma, and mental illness.

A schematic representation of how the familial environment (support versus shame) can provide a solid foundation or undermine the best medical and surgical treatments is outlined in Figure 2.2.

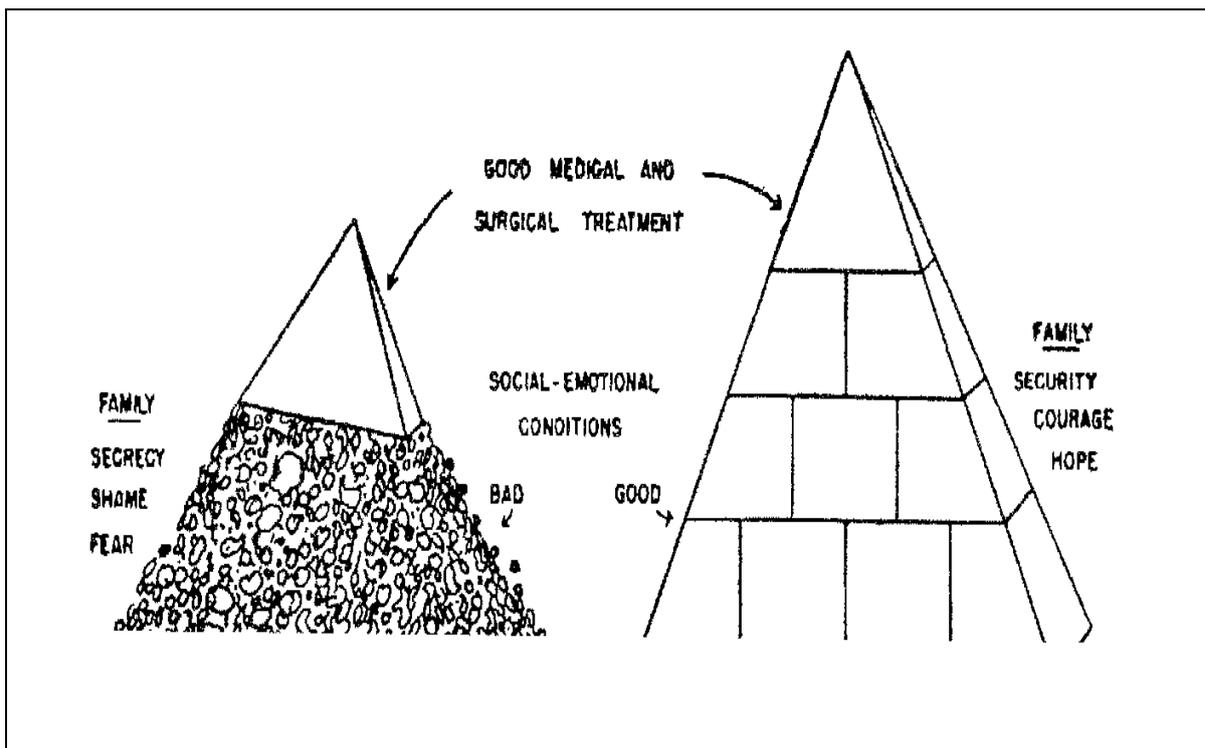


Figure 2.2 Psychosocial factors associated with epilepsy.

Source: Hermann and Jacoby (2009, p.S12); originally in Lennox (1960).

2.5.6 GENERAL ASSUMPTIONS ABOUT CO-MORBIDITY

Current diagnostic manuals (ICD-10 and DSM-IV) as well as the **ILAE's classification system** have not recognized epilepsy-specific psychopathology, and define mental disorders in people with epilepsy as in no way different to those without epilepsy. In contrast, many clinicians working in the area have long recognized that mental illness in people with epilepsy is more common than is found in the general population. Helmstaedter (2007) has outlined possible links underlying epilepsy co-morbid with psychopathology and include:

- Psychopathology co-occurs with epilepsy yet is not part of it.
- Psychopathology is co-morbid with epilepsy because they are associated through a shared underlying aetiology.
- Psychopathology and epilepsy interact through direct neural effects during interictal and ictal disturbances.
- Psychopathology in epilepsy is a secondary emotional reaction related to psychosocial problems associated with having an ongoing chronic neurological condition.

The nature of the association between the epilepsy groups and mental disorders will be investigated further in Chapter Seven.

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CHAPTER 3 METHODOLOGY

3.0 CHAPTER OVERVIEW

Section 3.1 begins with the planned study: design and task administration, inclusion/exclusion criteria for participation, and descriptions of the comparison/control groups. Participant details are tabulated including demographic details, disorder characteristics, medications, and investigative findings. Section 3.2 outlines the tests used to assess cognition, as well as internal reliability of the Emotional-Social Dysfunction Questionnaire (ESDQ) and the Everyday Functioning Questionnaire (EFQ). Sections 3.3 and 3.4 describe treatments of raw data and data-analyses respectively. Section 3.5 sets out the single-case methodology followed in this study. The chapter concludes with predictions regarding cognitive and behavioural functioning across the three epilepsy disorders (subdivided).

3.1 PLAN OF STUDY

3.1.1 DESIGN

Neuropsychological assessment of cognitive domains included pre-morbid I.Q, current estimated I.Q., intellectual abilities, attention, verbal memory, visual memory and executive functions. A neurologically healthy control group to test for individual cognitive deficits was not included, but population norms were **used to convert participants' raw data** to z-scores for comparison across tasks. With regard to the computer-based raw score analyses of single individuals' **cognitive data, the IGE participants** (n=8) acted as a control group. They were chosen because IGE is assumed

to have little (if any) impact on cognitive performance. The single individuals had NCSE, GCSE or TLE disorders.

Patients' emotional status was assessed with several measures:

- Self-ratings on 10 scales which constitute the Emotional and Social Dysfunction Questionnaire (ESDQ) (Andrewes et al., 2003);
- Self-ratings on six scales which form the Everyday Functioning Questionnaire (EFQ) (Andrewes, Hordern, & Kaye, 1998); and
- Self-ratings of 42 question-items on the Depression Anxiety Stress Scales (DASS).

Partner versions of the ESDQ and EFQ were also completed. Partners rated the patients on question-items matching those in the patient versions of the ESDQ and EFQ. Two adult control groups were included on both the ESDQ and EFQ, consisting of self-ratings by neurologically healthy participants (N=23) and their partners (N=21). Information and raw data from these control groups were provided by Associate Professor David Andrewes (The University of Melbourne). For **convenience of expression, the term "partners" was employed throughout** the study to encompass family members, partners or close friends.

With regard to normal controls for the DASS, these consisted of percentile normative data from the general Australian adult population used for the single case-control group comparisons (Crawford, Cayley, Lovibond, Wilson, & Hartley, 2011).

3.1.2 TASK ADMINISTRATION

Cognitive performance and emotional-social dysfunction were assessed by a comprehensive evaluation of each patient based on **interviews, EEG, MRI and/or CT reports, letters from the patient's**

physician, and neuropsychological test results. The intake interview and neuropsychological assessments were conducted over four sessions for each patient. Two hours were allocated for each session, depending on **the patient's convenience and degree of tiredness, or whether s/he wanted** further discussion.

For the majority of patients, tasks were administered and carried out in a set sequence. Most of the first session was devoted to an intake interview with the patient and any family member or close friend invited by the patient. The second and third sessions involved administration of the neuropsychological assessment tasks. The final session was devoted to completion of the ESDQ and EFQ (both patient and partner versions), and any outstanding cognitive tasks. An informal follow-up review of **patients' medical records and ER admission notes was conducted some 12** months after completion of the project. Appendix C contains the Intake Interview questions and also the sequence followed during task administration and time allocation. There were several exceptions to the set sequence of task administration which included patient time constraints or withdrawal from participation across the full four sessions.

3.1.3 PARTICIPANTS

Participants were 24 people with epilepsy (17 females, 7 males) with an age range of 18 - 65 years, and seven to 13 years of formal education. Exclusion criteria comprised brain injury detected on MRI or CAT scans, anoxia, drug dependence within the 24 months previous to testing, intellectual impairment or related developmental delay.

Participants were recruited from the Emergency Department and Epilepsy Clinic at the Cairns Base Hospital (CBH), Queensland by Dr. J.S. Archer, neurologist and epileptologist, running the Diagnostic Unit and Epilepsy Clinic at CBH. Some 600 medical charts of epilepsy patients **from the CBH and Dr. Archer's Epilepsy Clinic** were collected by the

researcher, chosen on the basis of this study's inclusion/exclusion criteria. From this pool, Dr. Archer selected potential participants after reviewing the medical records and taking into consideration the inclusion/exclusion criteria. The researcher then contacted those selected, about one-**third of whom volunteered to participate**. **Dr. Archer's** primary interest was SE patients who had attended CBH between 2003 and 2005, who had a history of four or less prolonged seizures of unknown aetiology. Also targeted for selection were those patients with TLE or IGE of a cryptogenic or idiopathic aetiology. Medical records of patients with symptomatic aetiologies were not reviewed for selection. Group allocation was determined by **Dr. Archer's diagnostic formulation** based on clinical history, seizure semiology, available diagnostic investigations (i.e. interictal EEG) and neuroimaging (MRI and/or CAT scan).

Participants were divided into four diagnostic groups.

1. Nonconvulsive Status Epilepticus (NCSE) = four patients: 2 with generalized absence status; 2 with complex partial status (left and right temporal lobe onset respectively).
2. Generalized Convulsive Status Epilepticus (GCSE) = 5 patients.
3. Temporal Lobe Epilepsy (TLE) = seven patients (3 right; 4 left).
4. Idiopathic generalized epilepsy (IGE) = eight patients (3 with JME; 5 with tonic-clonic seizures).

Twenty-two of the 24 epilepsy participants completed all the neuropsychological tasks, some missing data was present in two cases. With regard to measures of psychopathology (ESDQ, EFQ and DASS), two people declined to participate. The psychopathology data were based on the same 22 epilepsy participants and their partners (n=22).

Comparison/Control Groups

Cognition

The IGE group (4 females, 4 males; age range 21 to 43 years) acted as a comparison group for the individuals with NCSE, GCSE and TLE.

The IGE group's raw means and standard deviations (see Table 3.5 in this chapter) were used to calculate z-scores in statistical analyses of single cases compared to an IGE control group (see Appendix D for descriptions of Crawford's computer programs used for analyses).

ESDQ and EFQ Scales

Neurologically healthy adults (n=23) and their partners (n=21) were used as controls for the epilepsy cases and their partners in the ESDQ and EFQ response data analyses. Information and raw data from these control groups were provided by Associate Professor David Andrewes. Age of the healthy adult control group ranged from 21 to 62 years (8 males, 15 females) and years of formal education ranged from six to 15 years. The healthy control group had a high number of years schooling and tertiary completions (6-9 years n=1; 10-12 years n=7; and 13-15 years n=15).

DAS Scales

Norms taken from an Australian general adult population (N=497) were used for analyses of the epilepsy participants DASS response scores (Crawford, et al., 2011). See Appendix D for a description of the computer program MoodScore_Aus.exe used for the analyses.

Finally, demographic data and details of seizure properties for the epilepsy participants are outlined in Table 3.1, together with information pertaining to medications and investigative results. See Appendix E for extracts from the EEG recordings for some individual cases and MRI scans.

Table 3.1

Demographic details, seizure properties, medications and investigative results

Case ¹	Sex	Age	School ²	Syndrome ³	Age ⁴ Onset	Years ⁵ Burden	Status ⁶ Seizure	Seizure ⁷ Burden	Medication ⁸	EEG Result ⁹	MRI/CT Result ¹⁰
Jill	F	67	10	Absence SE	21	36	many	42	VPA LTG ETH	NAD	CT NAD
Nell	F	31	10	CP-SE	21	10	4+	78	VPA LTG	ABN – L fronto temporal	MRI ABN Left Temporal
Caro	F	36	11	CP-SE	21	15	4+	99	LTG PHT CZP	ABN – R fronto temporal	CT NAD
Tom	M	24	10	Absence SE	16	8	2	27	VPA LTG	ABN – generalized	CT NAD
Ron	M	36	10	GC-SE	33	3	3	3	CBZ	NAD	CT NAD
Mena	F	31	10	GC-SE	27	4	3	12	VPA	NAD	CT NAD
Lori	F	30	7	GC-SE	11	19	4	19	CBZ	ABN – generalized	n/a
Lana	F	47	10	GC-SE	22	25	2	37	CBZ	NAD	CT n/a
Ken	M	51	12	GC-SE	50	<1	1	1	CBZ	NAD	CT NAD
Gwen	F	34	13	IGE-JME	17	17	0	8	VPA	NAD	n/a
Sher	F	21	11	IGE-JME	18	3	0	8	VPA CBZ	ABN – generalized PPR	n/a
Mary	F	23	12	IGE-JME	13	10	0	5	nil	ABN - generalized PPR	CT NAD
Josh	M	41	10	IGE	35	6	0	4	nil	ABN - bi-occipital PPR	CT NAD
Jon	M	43	13	IGE	7	36	0	6	PHT	ABN - R occipital PPR	CT NAD
Hal	M	39	10	IGE	16	23	0	44	PHT	NAD	CT scar tissue
Mat	M	24	12	IGE	23	2	0	1	VPA	ABN – generalized	CT NAD
Bela	F	35	9	IGE	7	28	0	56	CBZ TPM	ABN – generalized	MRI NAD
Alana	F	30	12	TLE-R	13	17	0	94	CBZ	ABN – R fronto- temporal	n/a
Peg	F	65	10	TLE-R	17	48	0	288	GBP	NAD	n/a
Etta	F	38	12	TLE-R	21	17	0	48	LTG	ABN – R temporal	CT NAD
Leti	F	30	9	TLE-L	28	2	0	2	nil	NAD	MRI NAD
Josie	F	35	11	TLE-L	25	10	0	234	LTG	ABN – L anterior temporal	CT NAD
Jana	F	23	10	TLE-L	6	17	0	374	LTG	n/a	MRI lesions
Cath	F	20	12	TLE-L	7	13	0	364	nil	NAD	MRI sclerosis

Notes

To protect confidentiality, case names are pseudonyms.

Years School = number of years of formal education.

SE = status epilepticus, CP = complex partial, IGE = idiopathic generalized epilepsy, JME = juvenile myoclonic epilepsy,

TLE-R = right temporal lobe epilepsy, TLE-L = left temporal lobe epilepsy

Age at onset = age at seizure onset.

Years burden = number of years living with epilepsy.

Status seizures = number of prolonged seizures.

Seizure Burden = number of brief seizures in lifetime (approximate estimate only).

VPA = Sodium Valproate. LTG = Lamotrigine. ETH = Ethosuxamine. PHT = Phenytoin. CBZ = Carbamazepine.

GBP = Gabapentin. TPM = Topamax.

L = left R = right. NAD = no abnormality detected. ABN = abnormal activity. PPR = photoparoxysmal response.

n/a = result not available.

Jana = MRI Lesions in right temporal lobe posterior and left temporal lobe near hippocampus

Cath = MRI Left temporal lobe mesial sclerosis.

3.2 PSYCHOLOGICAL MEASURES

3.2.1 COMPONENT TASKS FOR COGNITIVE DOMAINS

The cognitive domains chosen for assessment were pre-morbid intelligence and current intellectual abilities, attention factors, executive functions, verbal memory and visual memory. At least two component tasks were used to measure each sub-domain.

Tasks were chosen for their sensitivity to even mild impairment. Preference was given to choosing those measures with parallel forms, to enable re-evaluation of the same patients should this be indicated (Goldstein, 1997; Hebben & Milberg, 2002; Seidenberg, O'Leary, Giordani, Berent, & Boll, 1981). Since four participants were indigenous, the possibility of cultural bias had to be taken into consideration when choosing the tests and interpreting data (Fletcher-Janzen, 2000; C. R. Reynolds, 2000). Helmes (2000) advice was followed with all participants: obtain as much information about the perceived problem as possible, establish good rapport during the interview, put the client at ease especially during testing, and check that the test instructions are fully understood.

Detailed information pertaining to the cognitive measures employed and the treatment of cognitive data can be found in Appendices C and D respectively.

Pre-morbid and current estimated I.Q.

Wechsler Test of Adult Reading (WTAR)

Each patient's predicted I.Q. was derived from his/her performance on the Wechsler Test of Adult Reading (WTAR) (The Psychological Corporation, 2001) together with demographic details such as age, gender, education and **occupation. The WTAR tests people's ability to read** irregular words, thus drawing on their knowledge of the word, rather than their current ability to utilize grapheme-phoneme relationships to decipher the word (Esther Strauss, Sherman, & Spreen, 2006). Significantly higher scores for pre-morbid I.Q. compared to the current estimated I.Q. are taken as evidence of possible deterioration in cognition. The WTAR was chosen for this study because it is co-normed with the WAIS-III (Wechsler, 1997a) and the WMS-III (Wechsler, 1997b).

Wechsler Adult Intelligence Scales (WAIS-III)

To minimize the assessment burden on participants, a six sub-test short form of the WAIS-III was employed to estimate current I.Q., producing a Deviation Quotient (DQ). The DQ is referred to hereafter as *estimated I.Q.*, and was based on three Verbal sub-tests (Vocabulary, Similarities, Digit Span) and three Performance sub-tests (Block Design, Matrix Reasoning, Digit-Symbol Coding).

Procedures for computation of I.Q., Verbal I.Q. and Performance I.Q., were based on the guidelines and examples provided by Sattler (2001, p. 256 Exhibit 8-4), together with calculations for reliability (.96) and validity (.85) for the particular short form used in this study. (For further details about measures of estimated I.Q., see Appendix C).

Intellectual functions

The component tasks measuring intellectual abilities included the six WAIS-III sub-tests used to estimate current I.Q. and also measures of spatial abilities (Judgement of Line Orientation), speed of processing (Map Search – 1 minute), and language (Boston Naming Test). The indices of intellectual ability and their component tasks were:

- Verbal Abilities: Vocabulary, Similarities, Boston Naming Test;
- Visual Abilities: Block Design, Matrix Reasoning, Judgment of Line Orientation;
- Working Memory: Digit Span, Spatial Span (WMS-III); and
- Speed of Processing: Map Search 1 (TEA); Digit-Symbol Coding.

Choice of the particular WAIS-III sub-tests was guided by several requirements. One aim was to select tests known to access one of the four indices of intellectual functioning: Verbal Abilities, Visual and Spatial Abilities, Working Memory and Speed of Processing. Second, contrasting measures were considered useful, for example, **Vocabulary is a “hold task”** i.e. resilient to acquired impairment. By contrast, **Digit-Symbol Coding is a “fluid task”** i.e. vulnerable during recall of novel visual stimuli (Groth-Marnat, 2003). Abstract reasoning functions as accessed by verbal or visual materials (Similarities – Matrix Reasoning) were considered a useful comparison for the TLE participants; and Digit Span and its visual analogue Spatial Span were chosen for contrasting scores on visual and auditory working memory (for a discussion contrasting Digit Span and Spatial Span, see Esther Strauss, et al., 2006, pp. 875-878).

Most of the tasks chosen have been found to be sensitive to different cerebral regions e.g. Similarities and the left temporal and frontal regions; Matrix Reasoning activates the right frontal areas, while Spatial Span

(WMS-III) performance has been associated with right temporal regions; Block Design is said to access right parietal lobe functions, as does Judgment of Line Orientation (JLO) (Groth-Marnat, 2003).

Judgment of Line Orientation (JLO)

The test measures spatial perception and orientation, correlates significantly with Block Design, and is also sensitive to right parietal dysfunction or damage (Strauss et al, 2006). Performance scores have been shown to be affected by age, gender and male sexual orientation (Rahman & Wilson, 2003); psychotic disorder (Hardoy et al., 2004); and ethnicity (T. M. C. Lee & Cheung, 2005). The JLO test manual provides point corrections for age and sex (Benton, Sivan, Hamsher, Varney, & Spreen, 1994).

Boston Naming Test (BNT)

The scores used for data-**analyses were each patient's sum total of** pictures correctly named. Sum total consisted of number of spontaneous correct responses plus the number of correct responses to a semantic cue. Recent research has shown that BNT performance is best predicted by years at school and pre-morbid verbal I.Q. (see Esther Strauss, et al., 2006).

(For further background information on **this study's** particular versions of the JLO and BNT together with the norms used for standardization of participant data, see descriptions of cognitive measures contained in Appendix C. **For epilepsy participants' (n=24) results of** normality tests and inter-correlations of the tasks constituting the various Intellectual factors, see Appendix Table 5 in Appendix D).

Attention

Test of Everyday Attention (TEA)

Development of the TEA was based on Posner and Peterson's theory (1990) which describes attention as a semi-independent controller of **action and perception governed by the brain's three supramodal attention control systems: orientation, vigilance and selection.** Thus, the TEA's attention factors are theoretically linked to these separate neuroanatomical systems (Bate, Mathias, & Crawford, 2001). The eight sub-tests of the TEA act as components of these four attention factors, three of which are of interest in this study: attention switching or flexibility; sustained attention; and visual selective attention (Bate, et al., 2001; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994, 1996).

- Visual selective attention = Map Search and Phone Search;
- Attention switching = Elevator Counting with Distraction and Elevator Counting with Reversal;
- Sustained attention = Lottery and Visual Elevator, as found in the Bate et al. (2001) study.

Sustained attention

The TEA administration manual (Robertson, et al., 1994) defines sustained attention as a vigilance system which maintains a readiness to respond in the absence of external cues. Two studies (Bate, et al., 2001; Robertson, et al., 1996) found that vigilance, measured by the Lottery sub-test, was a component of Sustained Attention. However, they differed in their findings on the second component measure of Sustained Attention. The developers of the TEA battery (Robertson, et al., 1996) identified the second component as a dual-task measure of divided attention. Bate et al. (2001), on the other hand, found that the second component involves

attention control and flexibility (as measured by the Visual Elevator sub-test). They concluded that the nature of divided attention remains debateable, that is, whether it is a component of Sustained Attention or an attention factor in its own right, and whether Sustained and Divided Attention access different neuroanatomical sites. The current study uses the Vigilance and Visual Elevator tasks to measure the Sustained Attention factor (Bate, et al., 2001).

Attention switching

This study uses the two component tasks of Elevator Counting with Distraction and Elevator Counting with Reversal to measure flexibility of attention. According to Robertson et al. (1994), the tasks require manipulation and sequencing of auditory-verbal information in working memory. In contrast, Bate et al. (2001) found that the two component tasks measuring this factor were found to align with tests of attention switching rather than those for selective attention such as SDMT-oral, Selective Attention Test and the Stroop test.

Visual selective attention

TEA component sub-tests measuring the selective attention factor are Map Search (2 minutes) and Telephone Search (time per target). Both timed tests measure the ability to select target stimuli from a complex array while not selecting competing distracters (Robertson, et al., 1994). Subsequent studies of the TEA-based attention factors agree that these two tasks are components of Visual Selective Attention (Bate, et al., 2001; Chan, 2000; Chan, Hoosain, Lee, Fan, & Fong, 2003; Robertson, et al., 1996).

The primary reason for choosing the TEA is its unique approach which allows assessment of separate attention factors. Equally important is the **nature of the tasks' stimuli materials, which reflect everyday actions and strategies**, thus enhancing ecological validity.

(See Appendix C for further discussion on ecological validity. Also, see Appendix Table 6 in Appendix D for the inter-correlations of component tasks in each attention factor for the 24 epilepsy participants).

Verbal Memory Domain

Auditory Verbal Learning Test (AVLT)

Logical Memory (WMS-III)

The verbal memory domain is comprised of two sub-domains of verbal declarative knowledge: logical or semantic memory for sequential details connected by a logical narrative text, and episodic memory for lists of unconnected words.

Episodic Memory

The Auditory Verbal Learning Test (AVLT) assesses episodic memory for word-lists. The AVLT version used here is provided by Geffen, Butterworth, and Geffen (1994b) and includes word-lists A and B, each containing 15 unrelated words. Immediate recall of List A after several trials assesses learning (sum of trials 1-5, List A). After a distractor task, participants recall List A without a prior presentation (retention trial 7, List A). After a twenty minute interval, participants delayed memory for List A (trial 8) is tested, then their recognition of words from List A (trial 9). The actual words comprising Lists A and B are listed in Strauss et al. (2006, pp. 777 - 778). The AVLT was chosen because its words are unrelated by meaning i.e. they are measuring new (episodic) lists, rather than learning and recall aided by stored concepts from semantic memory.

Semantic Memory

The three Logical Memory tasks from the Wechsler Memory Scales – 3rd edition (WMS-III) measure memory for narrative, and were chosen because they access semantic knowledge and schematic memory. The participant recalls details from two separate paragraphs which, when read aloud, follow a logically sequential narrative. Memory for each story and the sequence of details is tested, first immediately after their presentation (learning or immediate recall); second, after a 30 minute interval (delayed recall); and third, a yes/no recognition task.

(For information on the population norms used in standardization **of the participants' raw scores, see Appendix C.** See Appendix Table 8 in Appendix D for the inter-correlations of component tasks in each sub-domain of verbal memory).

Visual Memory Domain

Medical College of Georgia Complex Learning Test (MCG-CFT)

Continuous Visual Memory Test (CVMT)

The original forms of the four Medical College of Georgia Complex Figure Test (MCG-CFT) were used for this study (see Loring & Meador, 2003). The test measures intentional explicit learning and visual delayed recall. Together with the Continuous Visual Memory Test (CVMT) which measures visual recognition, the **MCG-CFT is a component of this study's** Visual Memory sub-domain.

Visual Recall

The Complex Figure Test (CFT) assesses visual spatial constructional ability and visual learning and recall. CFT versions include the Rey-Osterrieth CFT (Barr, 2003; Meyers & Meyers, 1995a), the Taylor figure (Hubley & Tombaugh, 2003), and the four Medical College of

Georgia forms (Ingram, Soukup, & Ingram, 1997; K.J. Meador et al., 1991; K.J. Meador et al., 1993). (See Knight and Kaplan (2003) for applications of a variety of complex figure tests).

The MCG version was chosen for inclusion in this study because it provides alternate forms. Also, the MCG administration gives prior warnings of up-coming memory tests (once before the Copy trial and again after the Immediate Recall trial), thus testing explicit or intentional **learning, as in this study's other memory tasks** (Ingram, et al., 1997). One known draw-back for any versions of complex figure tests is that some patients apply a word-labelling strategy for later recall of the various components in the complex figure (J. H. Kramer & Wells, 2004). In this study, upon completion of the MCG-CFT task, participants were asked if they had used labels or other verbal strategies to aid recall.

Visual Recognition

The Continuous Visual Memory Test (CVMT) assesses visual recognition of abstract figures which cannot be readily verbalized to aid recall, a primary incentive for its use in the current study (Trahan & Larrabee, 1988). For a discussion on the accuracy of assessment when using abstract versus complex figures as task materials, see Bigler (2003) on verbal labels, for example, rectangle, circle. Compare Bigler et al. (1996) and Piguet, Saling, and O'Shea (1994); for a summary, see Strauss et al. (2006). A second reason for choosing the CVMT is that it provides an alternative form for repeat testing (Trahan, Larrabee, Fritzsche, & Curtiss, 1996). It has also been reported to be an excellent measure of visual memory in some factor analytic studies (Larrabee, Trahan, & Curtiss, 1992) although this has not been a consistent finding (Larrabee & Curtiss, 1995).

Additional information about the CFT versions, together with the norms used for standardization of participants' raw scores for Visual Memory measures, can be found in Appendix C. See Appendix Table 9 in Appendix D for the inter-correlations of component tasks in abstract and **complex figures' measures of visual memory** for the 24 epilepsy participants.

Executive Functions

Delis-Kaplan Executive Dysfunction System (D-KEFS)

The Executive Functions domain was assessed with four measures selected from the Delis-Kaplan Executive Function System (D-KEFS) (i.e., Verbal Fluency, Design Fluency, Sorting, Colour-Word Interference). The fundamental elements of these measures are summarized below. (A more comprehensive discussion can be found in Strauss et al. (2006, p. 444 Table 8-21).

- *Verbal Fluency Test* = fluent verbal productivity.
- *Design Fluency Test* = fluent visual productivity.
- *Sorting Test* = problem-solving, verbal and nonverbal concept formation.
- *Colour-Word Interference* = a variant of the Stroop procedure which measures inhibition of over-learned responses and control between conflicting over-learned responses (attention).

These measures do not access all frontal lobe functions or anatomic systems, but were selected because they are sensitive to impairment in epilepsy disorders. They include lateralized functions (verbal/visual fluency; sorting into verbal/perceptual categories), and control of attention responses (colour-word interference). An equally important reason for including these particular tests was their quantitative assessment of what

are usually qualitative characteristics: flexibility of processing, distractibility (or set-loss errors), perseveration, and repetition errors. Another consideration in choosing the D-KEFS battery was its large standardization samples (N=1750) with a wide age range (8 to 89 years) and stratified data (according to gender, ethnicity, education level and geographic region).

(For more detailed descriptions of tasks, error measures, and reliability data, see Appendix C. See Appendix Table 7 for the inter-correlations of component tasks in each of the executive functions for the 24 epilepsy participants).

3.2.2 PSYCHOPATHOLOGY SCALES

The mental health of the epilepsy participants was assessed using partner and self-ratings on the Emotional-Social Questionnaire (ESDQ), Everyday Functioning Questionnaire (EFQ) and the Depression, Anxiety and Stress Scale (DASS). (See Appendix D for the SPSS scale syntax used for the ESDQ and EFQ, together with the question-items used for each ESDQ scale in the patient version).

Emotional Social Dysfunction Questionnaire (ESDQ)

The ESDQ (Andrewes, et al., 2003) consists of eight component scales developed to assess personality changes following neurosurgery including seizure surgery. The ESDQ consists of two versions: the self-rated Patient version and the Partner version. In this study, the ESDQ aims to assess the emotional and social functioning of patients with epilepsy. Its 10 scales are devised to access dysfunction aligned with particular systems in the frontal lobes (Andrewes, 2001).

Adaptation of ESDQ for this study

Two scales (*Maladaptive Behaviour* and *Lack of Insight*) were included in the Partner version in Andrewes' ESDQ, while another two scales (*Inertia* and *Euphoria*) were used only in the Patient version of his ESDQ. In this study, to facilitate comparisons between Patient and Partner ratings, all 10 scales were included in both the Patient and Partner versions.

Patient version

The question-item numbers which constituted the Partner's *Maladaptive Behaviour* and *Lack of Insight* scales were applied to the Patient rating responses. The patients were answering the same questions but with adapted wording. For example, the adapted *Lack of Insight* (Patient version) consists of five questions that are based on the equivalent items in the Partner scale.

- **Item 7: Do you find it difficult to pick up on other people's feelings?**
- Item 45: Do others sometimes say you have difficulties in some of these areas which you do not see yourself?
- Item 57: Do others sometimes say that you have difficulties in communicating with others that you do not see yourself?
- Item 58: Do others sometimes say that you have memory difficulties that you do not see yourself?
- Item 59: Do others sometimes say that you have difficulties with personal relationships that you do not see yourself?

Partner version

The question-item numbers which made-up the **Patient's** *Inertia* and *Euphoria* scales were applied to the Partner responses. Andrewes et al. (2003) note that some scales (e.g. *Maladaptive* or *Inappropriate Behaviour* and *Emotional Dyscontrol*) are measuring impaired social judgment and/or disinhibition which past research has associated with frontal lobe dysfunction. Other scales (*Lack of Insight*, *Inertia*, *Indifference*) also seem to be measuring dysexecutive behaviour associated with frontal lobe dysfunction, especially the ventromedial prefrontal region (Andrewes, et al., 2003). Past research has used the ESDQ Scales to assess personality changes in patients with lesions in the frontal lobes and other brain sites (Andrewes, et al., 2003). In contrast, the majority of participants in this study had no known lesions. The ESDQ is used to investigate possible effects associated with ongoing interictal epileptiform activity and/or personal life circumstances. (Descriptions for each of the ESDQ scales used in this study together with their reliability co-efficient can be found in Table 3.2).

Table 3.2
Descriptions and internal reliability of Emotional-social dysfunction scales

Emotional-social dysfunction scales	
Anger	(Alpha = Patient .923 and Partner .913)
Items enquire about feelings of anger, hostility and aggressive behaviour. Anger contributes to poor social and occupational adjustment.	
Helplessness	(Alpha = Patient .922 and Partner .905)
These items inquire about feelings of depression and/or anxiety, and about hope/despair for the future.	
Emotional Dyscontrol	(Alpha = Patient .924 and Partner .787)
Questions concern the patient's ability to control or express emotions appropriately, such as crying or laughing.	
Inertia	(Alpha = Patient .764 and Partner .786)
Questions concern patient's ability to initiate or complete actions and projects.	
Fatigue	(Alpha = Patient .392 and Partner .665)
Information about energy levels, such as sleeping during the day, is requested.	
Indifference	(Alpha = Patient .904 and Partner .907)
Patient is asked about changes in attitude to things which would normally elicit concern.	
Inappropriate Behaviour	(Alpha = Patient .715 and Partner .873)
Questions address whether the patient talks too openly about embarrassing topics of a sexual nature, which would be evidence of disinhibition, a frontal lobe executive dysfunction.	
Euphoria	(Alpha = Patient .655 and Partner .828)
Items include questions about the patient's concern about his/her health and well-being.	
Maladaptive Behaviour	(Alpha = Patient .868 and Partner .882)
The patient is asked for self-ratings about his/her own poor judgment in social situations. Some examples include childish behaviour, talkativeness and inappropriate comments.	
Lack of Insight	(Alpha = Patient .613 and Partner .787)
The patient is asked to judge how others might see him/her, in such areas as difficulties in personal relationships.	

Note:

Magnitude of reliability co-efficients (internal consistency) from Strauss, Sherman and Spreen, 2006, Table 8-23, page 447. Very High = .90+; High = .80 - .89; Adequate = .70 - .79; Marginal = .60 - .69; Low = <.59.

Each scale label is accompanied by alpha co-efficients produced by a reliability analysis of participants' responses (raw score scale-items). For comparison with Andrewes's reliability analyses, see Box 9.5 in Andrewes' text (2001, p.426).

Source: ESDQ scales have been adapted from Andrewes et al., 2003).

Everyday Functioning Questionnaire (EFQ)

Andrewes, Hordern, and Kaye (1998) identified a need in the area of neuropsychological rehabilitation for a broad measure of everyday cognitive and emotional dysfunctions. The questionnaire aims to quantify the *perceived gravity* of this dysfunction from the **patient's and partner's** perspective. Both the patient and his/her partner answered questions about the patient on aspects of his/her everyday psychological functioning.

The sub-scales of the EFQ measure distinct functional areas (see Table 3.3). The behaviour assessed by each subscale is associated with known lesion sites (Andrewes, et al., 1998).

Table 3.3
Descriptions and internal reliability of Everyday functioning scales

Everyday functioning scales	
<p>Concentration Question-items concern patient difficulties in concentration during everyday activities e.g. watching television; following a conversation; reading; ignoring background noise.</p>	<p>(<i>Alpha</i> = Patient .891 and Partner .904)</p>
<p>Memory Question-items ask about difficulty in everyday remembering e.g. planned and past events, names, recipes, directions, telephone numbers, to take something when leaving, where something has been put, grocery items to buy.</p>	<p>(<i>Alpha</i> = Patient .927 and Partner .873)</p>
<p>Emotions Question-items concern depression, anxiety, emotional dyscontrol, anger and irritability, inappropriate laughter, euphoria.</p>	<p>(<i>Alpha</i> = Patient .900 and Partner .783)</p>
<p>Organization Question-items concern planning or organization e.g. getting things done, not knowing when to stop, preparing shopping list, how to use phone, setting priorities for daily activities.</p>	<p>(<i>Alpha</i> = Patient .898 and Partner .747)</p>
<p>Communication Question-items ask about communication with others e.g. holding a conversation, understanding others, speech difficulties, when to take turns in speaking.</p>	<p>(<i>Alpha</i> = Patient .765 and Partner .742)</p>
<p>Lack of Insight Question-items concern difficulties in recognizing problems in communication, emotions, memory</p>	<p>(<i>Alpha</i> = Patient .720 and Partner .680)</p>

Note: Alpha co-efficients were produced by reliability analyses of raw scores for participants' responses to scale items. Magnitude of reliability co-efficients (internal consistency) was taken from Strauss, Sherman and Spreen, 2006, Table 8-23, page 447. Very high = .90+ ; High = .80 - .89; Adequate = .70 - .79; Marginal = .60 - .69; and Low = <.59.

Depression Anxiety Stress Scales (DASS)

Crawford, Cayley, Lovibond, Wilson, and Hartley's (2011) computer program MoodScore124_Aus was used to give each participant's mean Scale scores a percentile ranking based on norms taken from an Australian general adult population (N=497). Crawford et al's 2011 article on percentile norms gave results on Chronbach's alpha for sub-scales as Depression 0.95; Anxiety 0.88; Stress 0.94. Also, the program produces a general psychological distress (GPD) composite score for each individual compiled from the sum of his/her raw scores for the three scales, together with its percentile ranking. See Appendix D for a description.

3.3 DATA TREATMENTS

This section reports on transformations of raw data, treatment of outliers and missing values, with cognitive and emotional-social data being reported separately. (For further details, see Appendix D).

3.3.1 TREATMENT OF COGNITIVE PERFORMANCE DATA

Z-Score transformations

Raw data from cognitive task performance were converted to z-scores to enable comparison across different tasks. The conversion formula involved means and standard deviations drawn from normal populations, so each patient's z-scores for a task would represent deviation or distance from the normal population mean for that task. Most of the necessary information about raw score population norms could be found in test manuals or reported in research articles. For example, the raw score norms used for validating the TEA were provided courtesy of the test battery's constructors (Dr. Nimmo-Smith). With regard to the test batteries of the WAIS-III, WMS-III and the D-KEFS, the raw score means and standard deviations for these test batteries were manually calculated, using the test manuals' data tables.

Outliers and Missing Values

Outliers were identified via box-plots of **each task's z-scores**. A very few outliers were more than or equal to ± 4.00 which were replaced with a z-score of ± 3.50 . Several patients attempted but did not complete a task. In such cases, the extreme outliers were replaced with -1.64 ; the cut-off score signifying very mild impairment. Missing values were entered into SPSS as 9999.

I GE control/comparison group

The IGE control group's raw means and standard deviations (set out in Table 3.5) were used to calculate z-scores during statistical analyses of **single cases** (see Appendix D for descriptions of Crawford's computer programs used for analyses). Since several of the IGE individuals had comorbid disorders, their outlier performance scores (either too high or too low) were adjusted to preserve the homogeneity of a control group. Outlier z-scores ($z = \pm 1.64$) were replaced with raw score equivalent of $z = 0.00$.

3.3.2 TREATMENT OF ESDQ AND EFQ RATINGS DATA

SQRT transformations

Raw data from the ESDQ and EFQ ratings (self-ratings and partner ratings) showed a negative skew in most of the Scales. To gain as normal a frequency distribution as possible, raw score Scales were transformed by taking the square root before data-analyses. Where the objective was to correlate ESDQ and EFQ Scales with performance scores from cognitive tasks, the raw score Scales were not transformed but were converted to z-scores directly. The conversion formula used the Scale means and **standard deviations extracted from the normal controls' and their partners' ESDQ and EFQ Scale ratings**. Raw fluency error scores were not

transformed when used to correlate with the z-scores on ESDQ and EFQ Scales.

Outliers and Missing Values

There were no missing values in any of the Questionnaires completed by the epilepsy participants; and their outliers remained as is. The normal controls and their partners produced several isolated incidents of very high raw scores, that is, Scale means over 5.00. In such cases, the outlier Scale means were replaced with their next highest score under 5.00.

3.4 DATA-ANALYSES

3.4.1 ANALYSES OF COGNITIVE PERFORMANCE DATA

Cognitive weaknesses and strengths in people with epilepsy were assessed using SPSS Version 17 for descriptive statistics, correlations, scatter-plots and t-test analyses. Microsoft Excel was used to generate Bar Charts. Results are reported in the following sequence.

- Individual performances in cognitive domains are set out in Bar Charts and Summary Tables of individual deficits (z-scores), in each Case Study Chapter.
- Correlations between seizure-properties (e.g. number of years with epilepsy) and task performance in each epilepsy group tested for time-related effects of chronic epilepsy. Scatter-plots of strong associations are included in Case Study Chapters.
- Single case - comparison group programs were used to statistically **analyze individuals' raw performance data. Tables listing computer output for each person's results can be found in Chapters Six (Tables 6.4 and 6.5) and Seven (Table 7.2).**

- Finally, interpretation of the z-score data is based on impairment levels listed in Table 3.4.

Table 3.4
Levels of Impairment: Critical values of Z

	<u>Z value</u>	<u>Significance</u>		<u>% ile*</u>	<u>Scaled Scores**</u>
		<u>(2-tail)</u>	<u>(lower)</u>		
Borderline	-1.51	.065			
Very mild impairment	-1.645	.10	.05	5 th	5
Mild impairment	-1.960	.05	.025	2.5	4
Mild to moderate	-2.170	.03	.015	1.5	4
Moderate impairment	-2.326	.02	.010	1.0	3
Moderate to severe	-2.576	.01	.005	0.5	2
Severe impairment	-3.090	.002	.001	0.1	1
Very severe impairment	-3.290	.001	.005	0.05	< 1
Off the scale	-4.00				

Note: % ile* = Percentile Scaled Scores **M = 10; SD = 3

The critical values were compiled from Howell (2007, pp. 694-697), Coakes, Steed, and Dzidic (2006, p. 260 Table 1), Gregory (1992, p. 621), and Strauss et al. (2006, p. 5 Table 1-1).

3.4.2 ANALYSES OF ESDQ AND EFQ RATINGS

First, overall psychological abnormality in the four groups (NCSE, GCSE, IGE and TLE) was compared to that of the normal controls (n=23). Each individual's **self**-ratings on the ESDQ Scales were summed to provide a composite score representing overall abnormality of emotional-social functioning in that person. Mann-Whitney U tests were carried out on the composite scores to compare the epilepsy group (n=22) with the normal controls (n=23). The same procedure was used with the EFQ Scales to assess overall everyday dysfunction. Square-root transformations of raw data were used for the analyses.

Next, each epilepsy group (NCSE, GCSE, TLE and IGE) was compared to the normal controls group (n=23) using 95% confidence intervals, based on the means and standard deviations of the composite scores derived from the combined ESDQ Scales. The same procedure was used with the combined EFQ Scales. SQRT transformed data were used.

Group means of patient responses and patient-partner response discrepancies on each of the 10 ESDQ Scales are set out in separate charts. Bar charts have also been compiled from the eight EFQ Scales. Z-score data were used. In each epilepsy group, self-ratings on *Lack of Insight* were correlated with cognitive performance accuracy (using SQRT transformed data) and raw error scores.

3.5 CASE-BASED METHODOLOGY

Hilliard (1993) defines *case study* as involving narrative data and qualitative methods of analysis (see Jones, 1993). For others (Edwards, et al., 2004) the term *case-based research* is preferred because rigid distinctions between qualitative and quantitative data-analysis are not made, rather the two methods complement each other. This is not a

common position among psychologists who have long been biased against small number or case studies since it does not allow generalization of principles of behaviour to broader populations. For example, when small case studies have refuted a theoretical principle or model they have been dismissed as *anecdotal* (Edwards, et al., 2004).

Qualitative methods of analyses need to follow a prescribed sequence of reasoning aligned with empirical data if their conclusions can claim any validity (Yin, 2009). For example, one way to test a theory, model or assumption is to examine extreme, deviant or critical cases for consistency or falsification of the theory (Flyvbjerg, 2006). When rare cases are involved, cross-case analyses of pairs or multiple cases serves to identify essential shared characteristics in common or differentiating features (Yin, 2009). When the general nature of a disorder is already known, a comparison of illustrative cases as exceptions to the norm can yield new insights about variations in different contexts (Yin, 2009). Of course, a great deal depends on the availability and selection of cases.

3.5.1 QUANTITATIVE MEASURES OF SINGLE CASES

It has been argued that single and small number case studies have fallen short in the past because they do not provide rigorous mathematical and statistical methods as a basis for their conclusions (Andrewes, et al., 2003; Crawford, 2007). **Crawford's programs for single case versus control group data analyses** (involving comparison with a small control group) will be employed in this study to statistically test hypotheses for significant differences and deficits in individual cases; and draw inferences from the results when a Bayesian approach to data analysis is taken (Crawford, Garthwaite, & Howell, 2009).

Compared to **z-scores based on normal populations**, Crawford's tests enable a more accurate accept/reject decision to be made about the null hypothesis (Crawford, 2006). His mathematical methods (e.g. Monte

Carlo simulations, Bayesian computations) aim to reduce the high probability of Type I errors (over-estimating the abnormality of a score) and can be found in many of the papers accompanying the programs and on his web-site (Crawford, 2007). See Appendix D for a description of **some of Crawford's computer programs for single case analyses used in this study.**

Most importantly for this study's purposes, Crawford's methodology (Crawford, 2006) was specifically developed for single case studies where the control sample is small (<10, and often as little as 5 people). In this **study, the IGE control group for the epilepsy participants' cognitive** performance scores is small (n=8). Descriptive statistics used in the various computer analyses for conversion to standardized scores and generated by the IGE comparison group are set out in Table 3.5.

Table 3.5
IGE comparison group: Descriptive statistics of raw accuracy

Tasks	n	Mean	(SD)
Test of Everyday Attention			
Phone Search (Selective Attention) *	8	2.82	(0.44)
Phone Search while Counting (Divided Attention)*	8	0.93	(0.77)
Lottery (Vigilance)	8	9.12	(0.83)
Counting with Distraction (Switching Attention)	8	8.5	(1.31)
Counting with Reversal (Switching Attention)	8	5.25	(1.58)
D-KEFS battery - Colour-Word Interference			
Response Inhibition (attention control)*	8	52.00	(8.23)
Response Switching (attention flexibility)*	8	61.25	(11.89)
D-KEFS battery – Verbal & Design Fluency			
Letter Fluency (word-generation)	8	38.13	(8.32)
Category Fluency (generation of verbal categories)	8	36.88	(5.84)
Category Switching (verbal flexibility)	8	12.37	(2.72)
Filled Dots Fluency (production of dot designs)	8	9.86	(2.25)
Boston Naming Test			
Confrontation naming of object-pictures	8	14.37	(0.52)
Auditory Verbal Learning Test			
Episodic Memory – Learning (trials 1-5)	8	52.12	(5.59)
Episodic Memory - Delayed recall (trial 8)	8	12.25	(2.25)
Complex Figures Test			
Visual Memory – Learning of complex figures	8	29.75	(3.06)
Visual Memory – Delayed recall	8	29.93	(2.41)
Continuous Visual Memory Test			
Visual Memory – Learning of abstract figures	8	77.5	(2.07)
Visual Memory – Delayed recognition	8	4.5	(0.92)

Note: * Raw scores of timed tasks are in seconds (longer times = less ability).

(a) To preserve IGE homogeneity in each of above domains, outlier z-scores ($z = \text{over or under } 1.64$) were replaced with raw score equivalent of $z = 0.00$.

(b) The Pearson co-efficients required for the Dissociation analyses with the DissocsBayes_ES.exe computer programs, were as follows:

Phone Search while Counting r Lottery = -0.398

Episodic Learning (AVLT 1-5) r Visual Learning (CVMT) = $+0.006$

Delayed Recall (AVLT-8) r Delayed Recognition (CVMT) = -0.274

3.6 HYPOTHESES

3.6.1 COGNITIVE FUNCTION

- The participants with temporal lobe epilepsy will have impaired memory abilities compared to their functioning in other cognitive domains.
- The participants with idiopathic generalized epilepsy will have generalized impairment such as lowered intelligence and/or memory, rather than localized deficits.
- The participants with prolonged complex partial and convulsive status will exhibit impaired performance on tests of memory and related cognitive domains, consistent with focal damage to mesial temporal structures and diffuse cortical regions.
- The participants with absence status will display minimal cognitive impairment.
- The quality of performance in cognitive domains will be a function of epilepsy chronicity.

3.6.2 AFFECTIVE AND SOCIAL FUNCTION

- Participants with chronic epilepsy will have similar levels of psychosocial dysfunction across all epilepsy syndromes.
- Participants with even a few prolonged seizures will have psychosocial dysfunction.

3.6.3 SUMMATION

As stated in Chapter Two, the aim of the thesis is to investigate the nature of the possible cognitive, emotional and everyday psychological dysfunction associated with epilepsy.

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CHAPTER 4

CASE STUDIES IN IDIOPATHIC GENERALIZED EPILEPSY

4.0 CHAPTER OVERVIEW

Chapter Four investigates the general assumptions of IGE and its benign outcomes as described in Chapter Two (section 2.2.5). It begins with a brief description of research addressing the clinical issues in IGE to be investigated. Case reports on co-morbidity and reflexivity in the IGE participants are given. Individual performances pertaining to each cognitive sub-domain are then presented, followed by correlational analyses of chronic seizures and cognitive task performances. The general assumptions of generally benign outcomes are then evaluated in the **context of the participants' results.**

4.1 CLINICAL ISSUES

Primary epilepsy or IGE disorder is composed of a heterogeneous collection of sub-syndromes, each with its own symptomatology, characterized by seizure-type, age at onset, presence of a family history and diurnal seizure pattern (see Wolf, 2005). The various IGE syndromes are united by the pathognomonic spike-and-wave pattern observed on EEG, but show some differences in their genetic aetiology and evidence of abnormal anatomical elements (as outlined earlier in Chapter Two).

4.1.1 IGE AETIOLOGY AND COGNITION

Historically, IGE was known as *primary* epilepsy because it is often accompanied by a family history suggesting an underlying non-symptomatic genetic disorder. Consequently, IGE disorders were

considered to be benign and without associated neuropsychological compromise (but see Janz, 1997). This view remained the prevailing notion for many years since the cumulative impact of seizures may take decades to develop (see C. Dodrill, 2002) and early instruments were insensitive to subtle neuropsychological and/or structural damage (Hommet, et al., 2006).

Some early studies, however, did raise the possibility of cerebral compromise secondary to IGE seizures (Meencke, 1985; Meencke & Janz, 1984). In particular, some studies have found that while global intelligence might be expected to be within the normal range, some cognitive domains (e.g. attention) are somewhat lower than in the general population, and localized cognitive deficits are absent (Cutting, Lauchheimer, Barr, & Devinsky, 2001; Farwell, Dodrill, & Batzel, 1985; Mandelbaum & Burack, 1997). For reviews, see Mirsky, Duncan and Levav (2001), and Pavone et al. (2001).

More recent psychological and imaging studies have also served to contradict the traditional view of IGE as a benign disorder (Henric Jokeit & Schacher, 2004; Savic, et al., 1998) although these have not been consistent findings (Labate, Briellmann, Abbott, Waites, & Jackson, 2005). Evidence is accumulating that generalized epilepsies are most often associated with pathophysiology of the frontal lobes (Simister, McLean, Barker, & Duncan, 2003). The cognitive deficits found to be most often associated with IGE involve disruptions to executive control and include mild difficulties with abstract reasoning and attention dysfunction (e.g. perception, selection, maintenance or detachment from stimuli). See Hommet et al. (2006) for a review of research on executive difficulties associated with IGE.

A related clinical issue asks whether all IGE syndromes exhibit the same deficit patterns and level of impairment (Dulac, 2000). The heterogeneity of task performance across IGE sub-syndromes, their

differing course and cognitive outcomes would argue against this (Hommet, et al., 2006). For example, JME deficits of executive function have been found to be associated with cortical dysfunction of the pre-frontal cortex (particularly the anterior cingulate) and so contrast with the subcortical deficits found in some other IGE syndromes (De Toffol, Van der Linden, & Rolland, 1997; Devinsky et al., 1997; Lavandier et al., 2002).

While all IGE syndromes show spread of epileptiform activity in all areas of the thalamic-cortical loop, they might differ as to which cognitive domains are affected. Some sub-syndromes have been shown to have cognitive dysfunction in the mild to moderately severe range. For example, idiopathic epilepsy is often accompanied by attention problems, irrespective of the intellectual level of the patients (Williams, 2003) and sometimes attributed to interictal epileptiform activity (Aldenkamp, 1997; Aldenkamp & Arends, 2004). In contrast, verbal memory and language capacity are usually intact (Pavone, et al., 2001).

Poor academic attainment has been reported (Seidenberg et al., 2007; Sturniolo & Galletti, 1994), encompassing primary learning difficulties (Bulteau et al., 2000); and attentional dysfunction (Sanchez-Carpintero & Galletti, 1994). For children with epilepsy, inability to maintain attention has been found to be a better predictor of academic performance than memory or socioeconomic factors (Williams, Griebel, & Dykman, 1998; Williams, Phillips, & Griebel, 2001). In one study comparing children with IGE (and their siblings) versus children with migraine, the former group yielded reduced memory performance and psychomotor slowing, despite normal intelligence and no detectable abnormalities (Baillet & Turk, 2000).

In spite of the cumulative recent evidence, IGE is expected to have less impact on cognition than other epilepsy disorders. For example, **Dodrill's** (2002) research findings on an IGE pattern of very slow cognitive

deterioration over many years contrasts with that of GCSE, where permanent damage can be found after any isolated but prolonged attacks (Archer & Bunby, 2006). The genetic and idiopathic nature of IGE aetiology has been favourably compared with that of symptomatic TLE, known to have more deleterious effects than a non-symptomatic aetiology.

4.1.2 IGE CHRONICITY

Whether chronic brief seizure epilepsies have an impact on cognition is controversial (Meldrum, 1991; Shinnar & Hauser, 2002). Some researchers have found little, if any impairment (Vingerhoets, 2006), whilst others maintain an opposing view (see Motamedi & Meador, 2003 for a review). The literature also contains numerous animal studies assessing the impact of seizures on cognition and day-to-day functioning (for a review, see Majak & Pitkanen, 2004). Researchers have employed various measures of chronicity including total number of seizures over a lifetime, number of years living with chronic epilepsy, and the frequency, severity, or duration of seizures.

Number of lifetime seizures

Abundant evidence exists in the literature indicating that an increasing number of seizures can precipitate cognitive decline (Duncan & Thompson, 2003; Engel, 2002; G. P. Kent et al., 2006). Chronic IGE seizures have sometimes been associated with a steady decline in intelligence (Duncan, 2005b; Seidenberg, et al., 1981). Dodrill (2002) reviewed both cross-sectional and longitudinal research studies which investigated the cumulative impact of single brief seizures on cognitive functioning. His review included studies of the severity of such effects across different seizure disorders: localized versus generalized, and idiopathic versus symptomatic (Dikmen & Matthews, 1977; C. Dodrill, 1986). Most of these studies found some interaction (ranging from mild to strong) between number of lifetime seizures and cognitive decline. Five of

the eight longitudinal studies reviewed found the interaction to be confined to generalized tonic-clonic seizures; partial seizures having no significant effect. The primary drawback of the longitudinal studies related to the test-retest intervals. The longest follow-up study reviewed by Dodrill (2002) had a maximum 10 years of chronic seizures (Holmes, Dodrill, Wilkus, Ojemann, & Ojemann, 1998). Such short intervals do not allow accurate estimates of accumulated seizure-effects over a lifetime (C. Dodrill, 2002).

Age at Onset

Age at onset can be part of the syndrome's **biological** aetiology (as in idiopathic epilepsy) or an indicator of time with the disorder (as in symptomatic seizures). Age at onset of epilepsy can be deleterious for cognitive functioning, depending on

- **a person's developmental stage, as different abilities mature at different ages** (Helmstaedter, 2002); and
- type of genetic aetiology e.g. some IGE sub-syndromes have a pre-determined onset of epilepsy in childhood (Janz, 1997).

Age at onset can determine whether certain deficits appear or not. For example, an early age of onset can be an advantage for language due **to the brain's plasticity early in life which allows intra-hemispheric** reorganization of language functions such as naming ability (Stafstrom, 2002). Similarly, motor skills are not affected when age at onset is early childhood, and are more likely to be present when onset is in late childhood (Motamedi & Meador, 2003). Verbal memory functions were not affected in children with a late age of seizure onset in frontal lobe epilepsy (Upton & Thompson, 1997). Children with onset at less than 5 years have lower I.Q. regardless of the seizure-type, while those with onset after 5 years show more behavioural problems than cognitive deficits (Meador, Gilliam, Kanner, & Pellock, 2001). In IGE, some benign syndromes with

early onset (e.g. Childhood Absence Epilepsy) have minimal impact on cognition, while others like Lennox-Gastaut syndrome contain a genetic susceptibility for learning difficulties, depending on age at onset, seizure frequency and active EEG (Grosso et al., 2005).

Number of years living with epilepsy

There are few (if any) prospective studies showing deterioration of cognition in IGE (K. J. Meador, 2002). (The TLE studies relating to lifetime epilepsy burden are described in Chapter Five).

4.1.3 PREDICTIONS FOR CASES WITH IGE

This study's participants had all participated in mainstream education and were within the average range of I.Q. or above. The aim was to discover whether their cognitive profile was normal, which would be in keeping with the traditional view of IGE. Falsification of such an assumption would require the following predictions be fulfilled.

- If an IGE disorder has adverse cognitive effects (Hommet, et al., 2006), then the participants will have impaired performance on tests of attention and executive control consistent with frontal lobe dysfunction.
- If chronic IGE is associated with deteriorating cognitive functions, then the participants will show lower intelligence levels as a function of number of seizures (C. Dodrill, 2002).

4.2 CASE REPORTS: IGE

When details about each individual's particular syndrome and its signs and symptoms were examined, two areas emerged where expectations of normal neuropsychological functioning in IGE were not borne out in actual performance:

1. When an individual had epilepsy with a co-morbid disorder; or
2. **An individual's primary epilepsy disorder included** reflex seizure components additional to the generalized convulsive seizure-types.

A summary table of disorder characteristics for each patient described in the case reports can be found in Section 4.2.3.

4.2.1 CO-MORBIDITY

MAT: Autism Spectrum Disorder (ASD)

History and investigations

Mat was 24 years of age, worked as a retail assistant, with no family history of epilepsy. His mother reported onset of very brief staring spells at around 10 months to one year, with some retained awareness, and occurring several times per week. These events remained undiagnosed for 20 years. At the time of assessment, only one convulsive seizure had occurred at 23 years of age. EEG confirmed the diagnosis of IGE and neuroimaging was negative.

At school, Mat was an average student with some difficulties in subjects requiring verbal abilities. At primary school, he had been **assessed as having Asperger's Syndrome (AS)**. His mother reported a developmental delay in language acquisition but childhood speech therapy had eliminated all but the most noticeable effects: speech was slightly hesitant with little expressive cadence and some monotonous intonation. During the interview, he commented "**I cannot understand when someone is explaining when they talk too fast**". Severely impaired confrontation naming together with slowed word generation during a verbal fluency sub-test revealed a focal word retrieval deficit. Outside of these domains, other test performance scores were in the average to high average range.

Conclusions

Mat had localized verbal deficits associated with executive dysfunction during retrieval processes. With regard to the early diagnosis **of Asperger's Syndrome**, he did not show a typical profile. His social skills were normal, he maintained eye contact during a conversation, showed social reciprocity and interest in others, and had developed a number of peer relationships. No repetitive and stereotyped patterns of behaviour were observed, no obsessive hobbies and his outside interests were within normal limits. The lack of evidence indicates ASD was a misdiagnosis.

HAL: Diffuse axonal shearing (DAS)

History and investigations

Hal was 39 years of age, and worked for his father as a licensed tradesman, with no known family history of epilepsy. Post-traumatic amnesia might have accompanied two serious accidents: a bad fall from a horse at 8 years of age with loss of consciousness lasting two or more hours, and a tackle during a rugby game at 28 years with brief loss of consciousness. An EEG taken at the time of the first seizure (16 years old) documented a persistent right temporal-parietal slow-wave abnormality. Hal remembered that a CT scan taken at the same time revealed scar tissue. After the rugby injury, his G.P. reported that Hal **“felt neck crack and go numb, then neck pain, no abnormalities detected”**. He could not remember what happened for nearly a day, suggesting post-traumatic amnesia. Some 22 years after seizure onset, an EEG recorded normal brain activity.

Sequelae of concussion and coma together with diffuse axonal shearing (DAS) within the brain-stem can have long term effects on arousal and the various attention systems (Andrewes, 2001). At the intake interview, Hal was one of very few participants who did not speak at length about his illness and/or his social life. Yet lack of arousal and

disengaged interest were **not reflected in his vigilance task's high average** score. His mother **described him as "indifferent distant ... difficult to have a conversation with him"**. This could not be attributed to deficits in verbal comprehension: vocabulary definitions were high average, as were confrontation naming and abstract thinking abilities.

Conclusions

Based on diagnostic criteria for concussion (Lezak, et al., 2004, p. 170 Table 7.2) and duration of coma and post-traumatic amnesia as a basis for estimates of severity (Lezak, et al., 2004, p. 160 Table 7.1), there is a possibility that Hal suffered a mild brain injury. Nothing was detected by his G.P. after the rugby incident but that would not eliminate axonal shearing which creates microscopic white matter lesions. These are difficult to detect even by the more sensitive neuro-imaging techniques (Bigler, 2001a, 2001b; see Lezak, et al., 2004, pp. 170-171 for discussion on this issue; Ruff, Crouch, & Troster, 1994).

4.2.2 REFLEXIVITY

Idiopathic Occipital Lobe Epilepsies?

In their review, Taylor, Scheffer, and Berkovic (2003) wrote that occipital lobe epilepsies can be misdiagnosed as they often present as other seizure syndromes. The following two cases were diagnosed with idiopathic generalized epilepsy, with occipital lobe epilepsy (OLE) as a differential diagnosis. Both participants seemed to have migraine headaches, and migraines and epilepsy have been shown to have a common genetic susceptibility (Ottman & Lipton, 1996). **Jon's migraine diagnosis was changed to IGE, while Josh's migraine symptoms were accepted as such.**

JOSH:

History and investigations

Josh was 41 years old, single and employed as manager in the hospitality and tourism industry, with excellent communication skills. There was a family history of epilepsy, which is an equally valid indicator of idiopathic generalized or idiopathic occipital epilepsy. Epilepsy diagnosis was at 35 years of age and at time of assessment he had experienced four IGE seizures.

An EEG recorded at 40 years of age detected bilateral abnormalities predominant in the occipital region during intermittent photic stimulation (IPS). **Josh's** neurologist interpreted the EEG patterns as possible IGE but suggested occipital epilepsy as an alternative diagnosis. The IGE diagnosis was supported by the clinical history – sleep deprivation trigger, complete loss of consciousness while falling backward, observed retropulsion of the eyes, and tongue-biting. Further, some of the clinical signs for IOE were absent: no preceding aura or the visually colourful hallucinations characteristic of occipital epilepsy, and no side-deviation of the head or eyes. A CT scan taken at the time of assessment and after the most recent seizure was unremarkable.

Conclusions

Josh also had weekly migraines since age 25, triggered by chocolate and alcohol, associated with vomiting or nausea. He reported sensitivity to lighting which sometimes brought on a head-ache but no preceding visual aura (Yalcin, et al., 2000). The strobe lighting in his work-place had not triggered convulsive seizures to date. A localized memory impairment suggested the possibility that what had been diagnosed as head-aches might have been brief episodes of OLE remaining untreated since the age of 25. Mildly impaired retrieval from visual memory (see Table 4.2),

contrasted with a superior Verbal I.Q. (Figure 4.1) and verbal fluency dysfunction (Figure 4.4).

JON:

History and Investigations

Jon was 43 years old, married with children, and held a senior position in a machinery business. There was a family history of epilepsy. Seizure onset was at 7 years of age but originally diagnosed as migraines. Frequency declined after correct diagnosis and treatment during mid-teens and four generalized episodes occurred over the next 20 years. Also, **very brief** “turns” (10-15 seconds) occurred weekly, with sensations of spatial disorientation in usually familiar settings (e.g. “**where’s the door to my house?**”). **All Jon’s seizures have been triggered by flickering lights.**

At 33 years of age, an EEG detected slight abnormalities in the right occipital lobe. Further investigations at 44 years of age (MRI and EEG) were normal. A tentative diagnosis of possible right occipital lobe epilepsy was maintained. Results of cognitive assessment were in the average to above average range, with estimated I.Q. at the superior level. The one exception was markedly reduced scores for recognition memory for visual abstract figures (Figure 4.6) when compared to high average recognition for narrative (z-score discrepancy = 3.40).

Conclusions

Family history and the sole trigger (flickering lights) suggest a purely photosensitive base for **Jon’s seizures** (Guerrini et al., 1995; Zifkin & Inoue, 2004). In flicker-induced occipital partial seizures, the initial visual symptoms may be followed by versive movements and motor seizures (Guerrini & Genton, 2004; Yalcin, et al., 2000; Zifkin & Inoue, 2004). **Jon’s seizure onset** is accompanied by elementary visual scintillations and

head and eye deviations to the left, which are clinical signs of an occipital onset (Guerrini, et al., 1995; Zifkin & Inoue, 2004).

Minor spells of spatial disorientation suggest either of two visual-perceptual systems (Barton & Caplan, 2001; Goodale, 2000; Levine, Warach, & Farah, 1985). The temporal-occipital pathway facilitates recognition of shapes, patterns and familiar landmarks (Levine, et al., 1985; Turnbull, Carey, & McCarthy, 1997). Sensations of disorientation (e.g. “Where’s the door to my house?”) support a temporal-occipital pathway **in Jon’s case**, as does his reduced functioning in visual recognition of abstract figures (Figure 4.6). The alternative parietal-occipital pathway (Turnbull, et al., 1997) is not impaired, as evidenced by his performance on the Block Design task which accesses the right parietal lobe ($z=1.27$) and on Judgment of Line Orientation which measures spatial conceptualization of angles ($z=1.25$).

Overall, Jon’s symptoms and signs are consistent with some rare cases (see Zifkin & Kasteleijn-Noist Trenite, 2000) where EEG and clinical evidence favoured a right occipital lobe origin and involved a temporal-occipital pathway. However, his superior intellectual abilities do not accord with findings of generalized lowering in both intelligence and memory for patients with idiopathic occipital lobe epilepsy (Gulgonen, Demirbilek, Korkmaz, Dervent, & Townes, 2000).

Photosensitivity

MARY: JME with “pure” photosensitivity

Mary was 23 years old, single, with a family history of epilepsy, and working as a receptionist. Seizure onset was at 13 years of age and all seizures had been triggered while sitting in close proximity to the television. She was reluctant to commit to a medication regime as the seizures were infrequent (once every 18 months). Diagnosis was JME, with

EEG findings consistent with IGE and providing evidence of photosensitivity to flickering lights. There were no notable cognitive impairments. (An extract copy of this EEG recording can be seen in Appendix E).

SHER: JME with absences, eyelid myoclonia and photosensitivity

History and investigations

Sher was 21 years of age, single and unemployed, of indigenous extraction. Epilepsy onset was at 18 years of age when bright uninterrupted lights triggered a major myoclonic seizure. The following three years saw another seven major convulsive episodes. Sher described seizure onset as rapid eyelid fluttering and blinking before an episode which acted as a warning to lie down: **“my eyes and head start to jerk back, I lie down, the big fit comes. I’m really tired afterwards”**.

An EEG at time of assessment reported a posterior dominant rhythm of 10Hz alpha which was symmetric and responsive to eye opening. Throughout the resting record there were runs of generalised polymorphic theta and delta slowing, and moderately frequent 1-2 second bursts of generalised sharp and slow wave activity at 3-5 Hz frontocentrally. Photoc stimulation at 7 Hz was associated with a train of generalised discharges, resulting in a diagnosis of JME with photosensitivity (Demirci & Saygi, 2006). (An extract copy of this EEG recording can be seen in Appendix E).

Mild to moderately impaired functions of attention and working memory were found, executive dyscontrol of attention, and an estimated I.Q. was borderline. Mildly impaired vocabulary and naming scores most likely reflected poor school attendance due to cultural factors (see Table 4.2). Impaired control of attention responses matched the EEG report of frontocentral focus for abnormal activity.

Sher's condition reflected a homogenous set of symptoms found in people presenting with eyelid myoclonia, and consisting of eyelid fluttering, typical EEG pattern, and impaired intellectual function (Capovilla, Striano, et al., 2009).

Conclusions

Rapid blinking, eyeball and head retropulsion fit a diagnosis of eyelid myoclonia with absences (EMA): minor partial seizures followed by a convulsive seizure. Panayiotopoulos (2005a) has referred to this sequence as Jeavons Syndrome. The presence of photosensitivity and overlap with **JME increases the likelihood of Sher's seizures being EMA** (Yalcin, Forta, & Kilic, 2006). **Sher's younger sibling had several repetitive episodes of** prolonged eyelid myoclonia with absences, which might be a form of NCSE (Panayiotopoulos, 2005a). This familial occurrence reflects the expert view that EMA is genetically determined.

BELA: IGE with absences, perioral myoclonia and photosensitivity

History and investigations

Bela was a 35 year old female, married, with a family history of epilepsy. Seizure onset was at 7 years of age with brief tonic-clonic seizures sometimes triggered by strobe lights. Later seizures with loss of consciousness lasted 20 minutes, with tongue-biting and occasional incontinence, followed by lethargy and sleep for up to six hours. **Bela's** husband described her as being "**dazed and twitching** all day before an **attack**". Similar accounts are reported in the literature, of prolonged absences with perioral myoclonia which end in generalized tonic-clonic seizures (Bilgic, et al., 2001; Panayiotopoulos, 2005a).

An EEG at 35 years of age recorded facial twitching episodes associated with discharges of generalized 3 Hz spike-and-wave activity. (An extract copy of this EEG recording can be seen in Appendix E).

Neuro-imaging was normal. A diagnosis of IGE was made together with perioral myoclonia with absences (Bilgic, et al., 2001).

Cognitive assessment found moderate to severely impaired control of attention responses, a function associated with the anterior cingulate gyrus. Also found were mildly impaired tasks of visual selective attention and flexibility of attention, both functions associated with the right pre-frontal cortex (**see Table 4.2**). **Bela's attentional control deficits and impaired episodic memory** might have been due to a recent change in medication at time of assessment. Several months after she had switched to lamotrigine, during the final feed-back session she reported a much improved memory for recent events (for cognitive side-effects of AEDs, see Ortinski & Meador, 2004).

Conclusions

Unlike the EMA seizure-type, the ILAE Commission have not classified PMA as a separate entity (Berg et al., 2010). A greater awareness of the condition in the medical profession might prevent some misdiagnoses of this rare syndrome (Bilgic, et al., 2001). When she first **attended the epilepsy clinic Bela's seizure** control was poor, a situation her husband attributed to misdiagnoses by several general practitioners resulting in incorrect medication regimes (see Baykan & Noachtar, 2005 for a discussion of frequent misdiagnoses of this condition).

GWEN: JME without other seizure-types

History and investigations

Gwen was 34 years old, married with children and working in a finance company. There was a family history of epilepsy. Seizure onset was at 17 years of age, she had experienced a maximum 8 major seizures in her lifetime. Her account of events was reminiscent of myoclonic seizures which were preceded by a period of confusion followed by a loss

of consciousness, and abrupt movements of the arms and hands. The events occurred within 30-45 minutes of awakening, and were triggered by lack of sleep. Her interictal EEG disclosed intermittent spike and slow wave activity consistent with IGE, with no evidence of photosensitivity. Neuropsychological assessment revealed an estimated I.Q. at the superior level, and all cognitive domains canvassed were intact.

Conclusions

Both Gwen and Mary were diagnosed with juvenile myoclonic epilepsy, but neither conformed to the pattern of cognitive deficits reported in the more recent research literature which predicts widespread deficits in executive functions such as problem-solving, concept-formation, and automatic response inhibition. On the other hand, both Sher and Bela had multiple seizure-types with widespread attention and working **memory impairments**. **Sher's deficits might** have been associated with her **EMA condition**, while **Bela's lowered cognitive functioning was probably** due to having just changed medication regime at time of assessment. See **Table 4.2 for summary of individuals' cognitive deficits**.

4.2.3 SUMMARY OF DISORDER CHARACTERISTICS

Summary Table 4.1 details the diagnostic criteria for each **participant's epilepsy disorder, the presence of any reflexive components** in the seizure semiology, and possible co-morbidities.

Table 4.1
Disorder characteristics in eight IGE cases

Disorder characteristics of IGE participants	Mat T-C	Hal T-C	Josh T-C	Jon T-C	Gwen JME	Mary JME	Sher JME	Bela T-C
Mode of onset								
Generalized	√	√	√	√	√	√	√	√
Localization-related			√	√				
Aetiology								
Idiopathic/Genetic	√		√	√	√	√	√	√
Reflex Components								
Absences							√	√
Photosensitivity			√	√		√	√	√
Eyelid Myoclonia							√	
Perioral Myoclonia								√
Co-Morbid Disorders								
Autism	√							
Axonal Shearing (DAS)		√						
Seizure Properties								
Age at onset	23	16	35	7	17	13	18	7
No. years burden	2	23	6	36	17	10	3	28
Seizure burden	1	44	4	6	8	5	8	56
Reserve Capacity								
Years Schooling	12	10	10	13	13	12	11	9

Note: T-C= tonic-clonic seizures; JME= juvenile myoclonic seizures.

4.3 RESULTS

This section summarizes neuropsychological functioning in the eight IGE participants:

Figures 4.1 to 4.6 represent individual performance in six cognitive domains. (See Table 3.4 for qualitative descriptions and levels of cognitive impairment).

- Table 4.2 summarizes the relative severity and spread of cognitive deficits in each case.
- Table 4.3 lists comparisons of pre-morbid and current intelligence (based on WTAR-demographic scales).
- Table 4.4 is a correlation matrix of IGE chronicity and cognition.

4.3.1 COGNITIVE DOMAINS

Figure 4.1 depicts Verbal and Performance score indices, which together constitute the current estimated I.Q. There was a wide range in estimated I.Q. (i.e. low average to superior), evidence for a wide variety in levels of **individuals'** performances. Perhaps for this reason, no consistent pattern of strengths and deficits emerged.

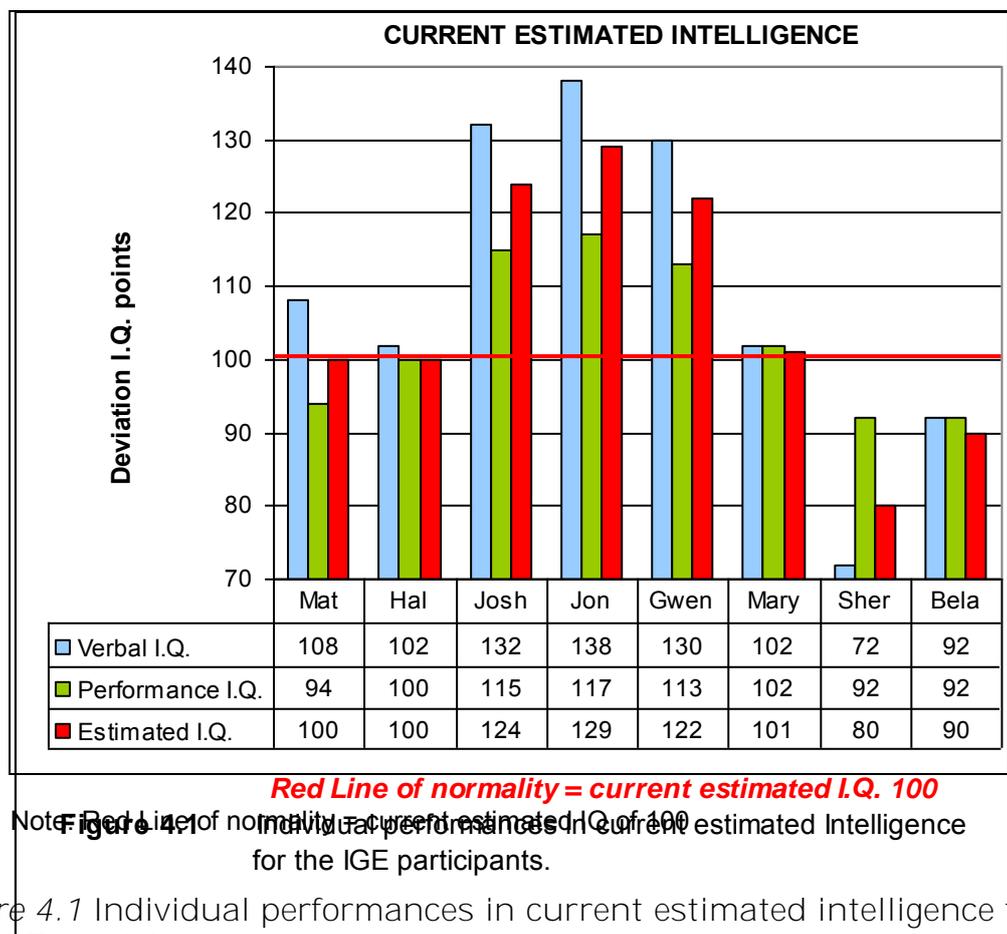


Figure 4.1 Individual performances in current estimated intelligence for the IGE participants.

Figure 4.2 shows that a consistent pattern of strengths and weaknesses was absent for cognitive tasks measuring intellectual abilities. Performances across the four aspects of intellectual functioning reflected an average level of achievement. Two cases (Josh and Jon) produced higher than average scores on Working Memory.

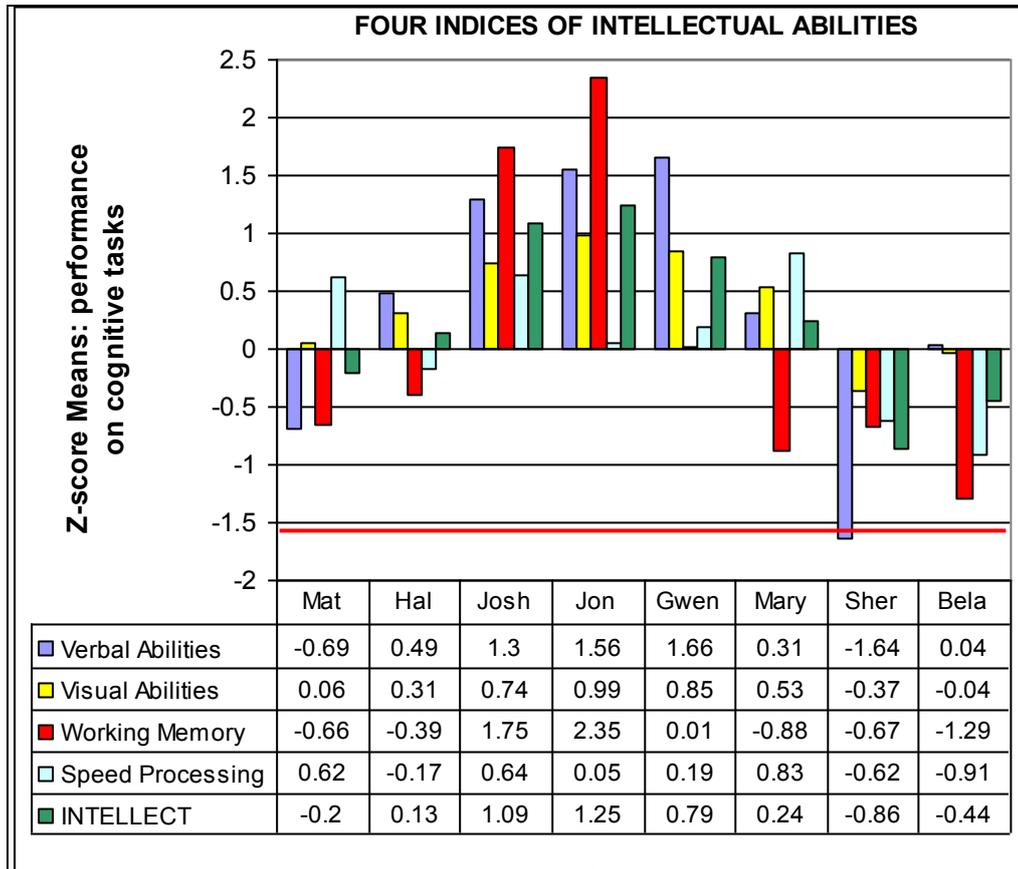
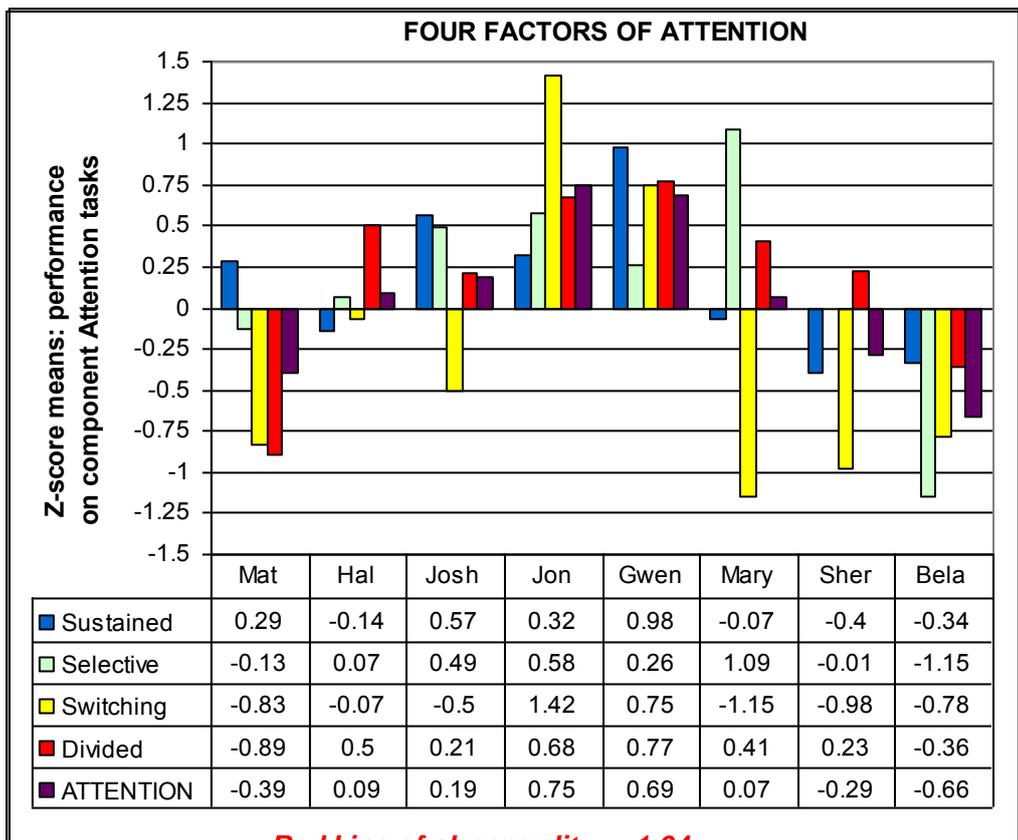


Figure 4.2 Individual performances in Intellectual Abilities for the IGE participants.
Note: Red Line of abnormality = -1.64

Figure 4.2 Individual performances in Intellectual Abilities for the IGE participants.

Figure 4.3 depicts an average level of performance in Attention factors by most individuals. Again, there is no consistent pattern of deficits. Such a lack of impairment in a cognitive domain associated with the pre-frontal cortex argues against the presence of ion channelopathies in the frontal lobes of people with JME, as reported by some researchers.



Red Line of abnormality = -1.64

Figure 4.3 Individual performances in Attention for the IGE participants.
Note: Red Line of abnormality = -1.64

Figure 4.3 Individual performances in Attention for the IGE participants.

Figure 4.4 reflects mean scores for four kinds of executive functions. As in the previous charts, the majority of IGE participants produced an average level of performance in the tested areas, although Sher had borderline I.Q. Two cases show moderate to severe deficits in control of attention responses, an executive function associated with the anterior cingulate area of the medial frontal lobes. These two cases (Sher and Bela) have produced results consistent with the research evidence implicating localized deficits in some IGE disorders.

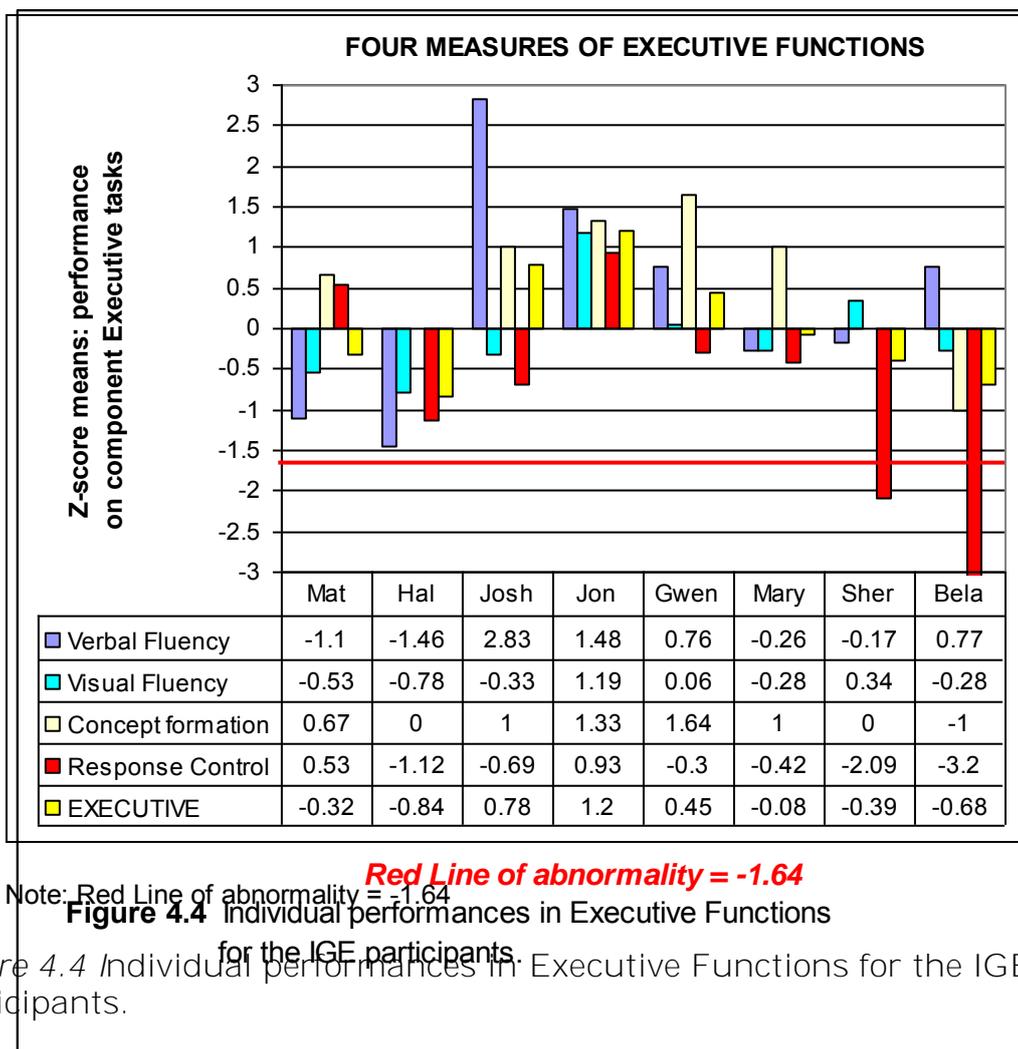
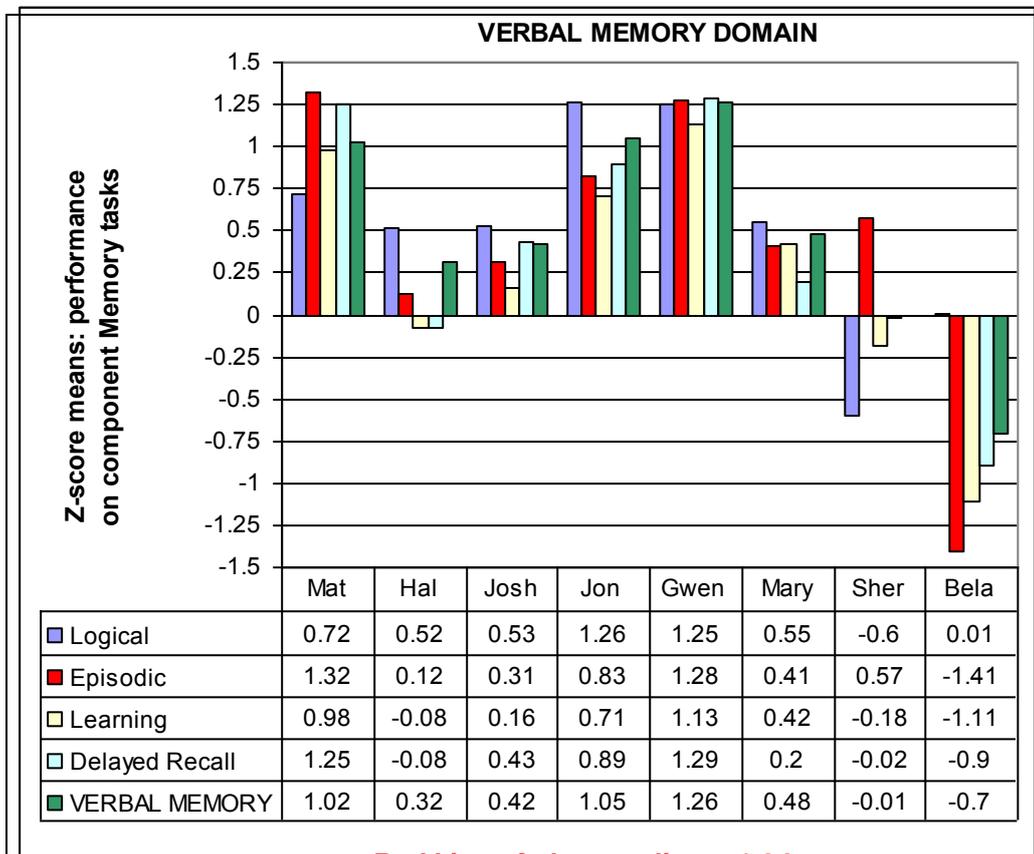


Figure 4.4 Individual performances in Executive Functions for the IGE participants.

Figure 4.5 demonstrates that the majority of IGE participants achieved an average to above average level of verbal memory performance. One participant (Bela) displayed a trend towards lower scores for Episodic Memory which hovered above mild dysfunction levels.



Red Line of abnormality = -1.64

Figure 4.5 Individual performances in Verbal Memory

Note: Red Line of abnormality = -1.64 for the IGE participants.

Figure 4.5 Individual performances in Verbal Memory for the IGE participants.

The profiles outlined in Figure 4.6 contrast sharply with those in Figure 4.5 (Verbal Memory). The IGE participants demonstrated a downward trend in Visual Memory performance. Two cases of interest (Josh, Jon) gave reduced performance scores for Visual Memory tasks when compared to their overall above average performance across other cognitive domains.

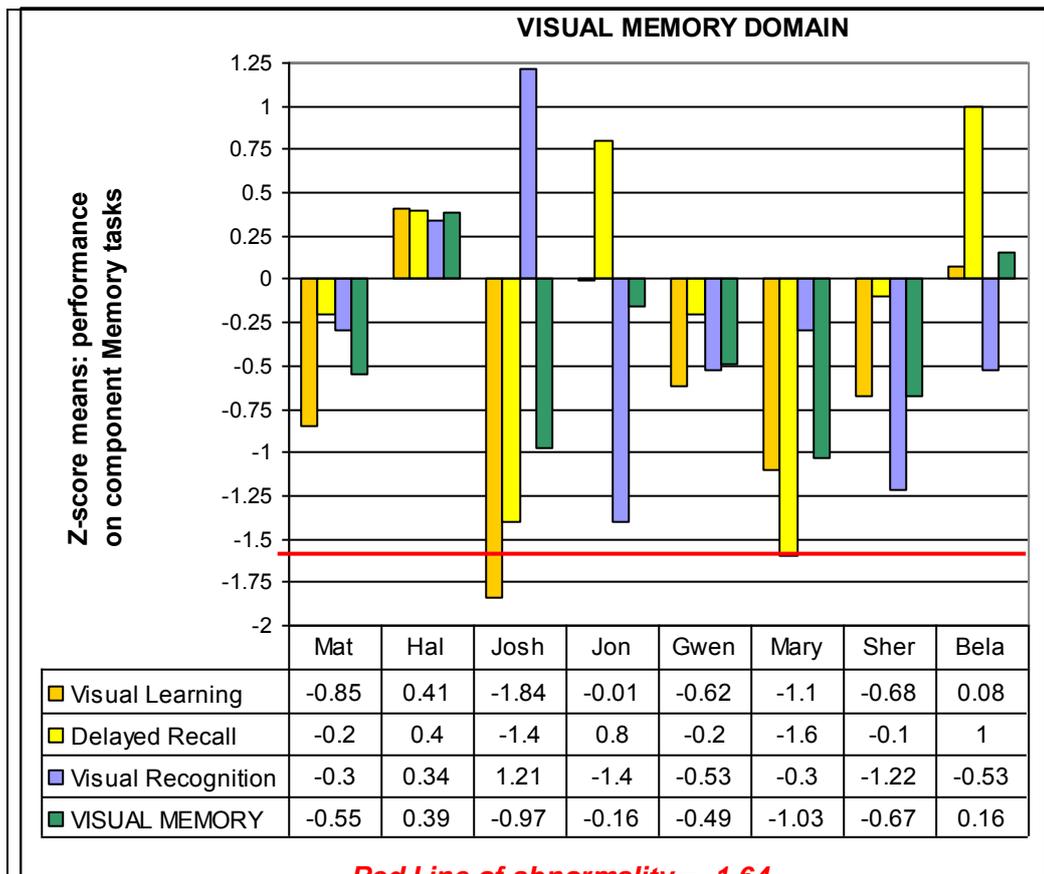


Figure 4.6 Individual performances in Visual Memory

Note: Red Line of abnormality = for the IGE participants.

Figure 4.6 Individual performances in Visual Memory for the IGE participants.

4.3.2 SUMMARY OF INDIVIDUAL DEFICITS

Table 4.2
Severity and spread of cognitive deficits for the IGE participants

Cognitive Domains	Mat	Hal	Josh*	Jon*	Gwen	Mary*	Sher* +	Bela* &	% Cases
Attention									25%
Response Inhibition							-1.96	-3.00	
Response Switch							-2.23	-2.86	
Selective Attention								-1.83	
Flexibility Attention							-1.64	-1.64	
Language									37.5%
Letter Fluency	-1.54	-1.90				-1.51			
Vocabulary							-1.92		
Naming	-3.00						-2.00		
Episodic Memory									12.5%
Learning								<i>E</i> -1.88	
Delayed Recall								-1.54	
Visual Memory									25%
Learning	-1.64			<i>R</i>					
Retrieval			-1.89	<i>R</i>		-1.60			
Working Memory									25%
Digit Span							-1.67	-1.59	
Digit-Symbol								-1.79	
¹Total spread over cognitive domains	2	1	1	0	0	0	3	3	

Note:

1 = Spread of impairment i.e. number of cognitive domains found to be impaired.

* = Photosensitivity is present.

* + Photosensitivity and eyelid myoclonia with absences.

* & = Photosensitivity and perioral myoclonia with absences.

R = Reduced, compared to own performance scores in Verbal Memory domain.

E = New medication regime commenced just before assessment. Client reported problems with memory for single events, and ability to concentrate.

Levels of impairment (z-scores in bold):

borderline -1.51; very mild impairment **-1.64**; mild impairment **-1.96**; moderate **-2.33**; severe **-3.09**.

The levels of impaired performance in some of the IGE participants are summarized.

- Language (mild dysfunction - moderately impaired).
- Visual Memory (lowered performance to mildly impaired).
- Attention control (very mild - moderately impaired).
- Working Memory (borderline - very mildly impaired).

Table 4.2 also demonstrates that the prevalence of deficits was spread reasonably equally over the four cognitive domains. No individual, however, had more than two affected cognitive domains, hardly a generalized lowering of I.Q. as predicted. Two exceptions (Bela and Sher) had a lower current I.Q. than their pre-morbid intelligence (see Table 4.3).

Table 4.3

Comparisons of pre-morbid and current intelligence for the IGE participants

Case Name	I.Q	V.I.Q.	P.I.Q
Name BELA (IGE)			
Current estimated I.Q.	90	92	92
WTAR-demographic predicted I.Q. ¹	99	98	100
Current versus predicted I.Q. discrepancy	-9	-6	-8
Significantly <i>lowered</i> intelligence (p < .05)? (10 – 24% cumulative percentage)	Yes	No	No
Name SHER (IGE)			
Current estimated I.Q.	80	72	92
WTAR-demographic predicted I.Q. ¹	84	85	86
Current versus predicted I.Q. discrepancy	-4	-13	+6
Significantly <i>lowered</i> intelligence (p < .05)? (25 – 49% cumulative percentage)	No	Yes	No

Note:

1 = Prediction interval for WTAR-demographic predicted I.Q. is 95%.

Some participants had significantly *higher* current intelligence scores than their predicted I.Q. (based on the WTAR-demographics scales) as follows:

Hal, Gwen, Josh had higher current I.Q and V.I.Q.;

Mary had higher P.I.Q.;

John had higher current estimated I.Q., V.I.Q. and P.I.Q.

Sher had higher P.I.Q.

4.3.3 CHRONIC SEIZURES

Possible relationships between seizure-properties (i.e., number of seizures in a lifetime, number of years living with epilepsy), disorder characteristics (i.e., age at seizure onset), psychosocial factors (i.e., years of formal education) and cognitive tasks were investigated (see Table 4.4). One salient finding was that Verbal Memory and concept-formation were:

- negatively associated with number of seizures over a lifetime; and
- positively associated with years of education.

Table 4.4's correlation results do not support the research literature which reports that impairments become evident only after many years of living with IGE (C. Dodrill, 2002). Table 4.4 does show, however, that performance on these same memory and concept-formation tasks improves with increasing years of education.

Table 4.4
Chronicity correlations for the IGE participants

Variables	¹ No. of Seizures	Educ. Years	Percep Sorting	Episodic Memory	Verbal Learn
Education Years ²	-.725 p= .042				
Perceptual Sorting ³	-.813 p= .014	.964 p=.000			
Episodic Memory ⁴	-.853 p=.007	.851 p=.007	.859 p= .006		
Verbal Learning ⁵	-.783 p=.022	.886 p=.003	.940 p= .001	.928 p= .001	
Verbal Recall ⁶	-.773 p= .025	.836 p=.010	.895 p= .003	.917 p= .001	.975 p= .000

In Bold =

Pearson correlation is significant at p(2-tail) < .05 and < .01.

Note:

1 = number of seizures during a lifetime

2 = number of years of completed education

3 = perceptual sorting (concept-formation task from D-KEFS)

4 = episodic memory (2 tasks learning and delayed recall from AVLT word-lists)

5 = verbal learning (2 tasks narrative and episodic learning from WMS-III & AVLT)

6 = verbal delayed recall (2 tasks narrative and episodic delayed recall from WMS-III & AVLT).

4.3.4 SUMMARY OF MAIN FINDINGS

- The widest variation in performance was seen in current estimated I.Q. and Executive Functions domains.
- Individual deficits occurred with a suspected co-morbid disorder or in those whose epilepsy had reflexive components.
- Two of the eight IGE individuals showed a lowering of intellectual functions compared to their pre-morbid intelligence.

- The number of seizures was negatively related to concept-formation (perceptual) and various memory measures. In contrast, the number of years of formal education was positively associated with the same cognitive tasks.

4.4 DISCUSSION

The clinical issue concerned the nature of deficits associated with IGE: the **disorder's idiopathic aetiology and** generalized nature of seizures means that any cognitive deficits would manifest as a general lowering of cognitive abilities, rather than localized deficits in a single domain. The findings did not fully bear out the predictions across the sample.

- The prediction of a generalized lowering of intellectual or cognitive abilities was not supported in six participants, who had average, above average or superior abilities. A significant lowering of intellectual abilities (compared to pre-morbid intelligence) was found in two participants (Bela and Sher). (See Table 4.3).
- The prediction that the IGE participants would exhibit frontal lobe dysfunction again was not supported with these participants *except* for two cases (Bela and Sher) (see Table 4.2). However, chronic seizure numbers correlated with decreasing concept-formation which is associated with regions in the pre-frontal cortex.
- The traditional view about the neuropsychology of IGE was found with only one case, and partially with three others. These all had borderline or very mildly impaired retrieval from visual memory in the context of photosensitive epilepsy.
- The remaining four cases all had localized deficits, three of whom were severely impaired. It seems likely that their deficits were not part of their IGE aetiology, but perhaps formed additional components to his/her particular syndrome. One case (Mat) had early language and communication difficulties which might have

contributed to his slowed word retrieval difficulties. Josh had very mild visual memory deficits which could not be attributed to epilepsy (four diagnosed IGE seizures). Sher and Bela had similar reflex seizure-types with photosensitivity (eyelid myoclonia and perioral myoclonia) and the same attention and working memory deficits. These combined disorders suggest the presence of sub-syndromes within the IGE disorder, as suggested by Hommet et al. (2006) and Panayiotopoulos (2005b). Equally possible explanations might involve idiosyncratic factors, lowered performance related to a particular test session, task reliability secondary to other factors.

4.4.1 CO-MORBIDITY

It is conceivable that having a co-morbid disorder will increase severity or frequency of seizures and thus adversely affect cognitive functions. The mechanisms underlying both epilepsy and co-morbid disorder are discussed below, since they seem to have also affected the nature of cognitive dysfunction in some participants.

The main point which emerged from the two cases with co-morbid communication difficulties was that their localized deficits seemed to be tied more with the nature of their co-morbid disorder than with their IGE disorder. **Mat's severely impaired confrontation naming of pictures might** be associated with delayed language acquisition as a child. Apart from **slowed generation of words**, **Hal's** cognitive assessment was normal. Both **his mother's report and observed** behaviour, however, indicated difficulties in social interaction. **The nature of Hal's** executive dysfunctions (impaired verbal retrieval, lack of spontaneous social interaction and disengagement during conversations) are known to occur in injuries of white matter tracts. These commonly involve violent abrupt head movements such as might occur in car accidents, punches or rugby tackles. They are difficult to detect with most imaging tools.

4.4.2 REFLEXIVITY

Although IGE patients are known to have diffuse cortical hyperexcitability, it may not necessarily be uniform across both hemispheres with reflex seizures (Ferlazzo, Zifkin, Andermann, & Andermann, 2005; Zifkin & Inoue, 2004). Reflex seizures tend to activate unilateral cortical systems or functional-anatomic networks (Zifkin, 2010). It would follow, then, that the isolated deficits affecting one cognitive domain (**found in the majority of this study's IGE participants**) might be the result of one or more reflex seizure-types activating unilateral cortical systems or functional networks (rather than solely attributable to their IGE disorder).

Researchers have differentiated between two types. *Purely photosensitive epilepsy* involves idiopathic generalized seizures which occur only with a flickering light source or during intermittent photic stimulation (IPS) in the laboratory. *Epilepsy with photosensitive traits* is found in patients who have both spontaneous seizures and those triggered by visual stimuli (Zifkin & Kasteleijn-Noist Trenite, 2000). Two participants (Jon and Mary) had seizure episodes only when triggered by flickering lights, such as television. This exclusive sensitivity suggests a pure or genetic photosensitivity. Their memory functions were reduced but not actually impaired. There is some research evidence that genetic photosensitivity is not associated with impaired cognition (Zifkin & Kasteleijn-Noist Trenite, 2000).

Severity of epilepsy (as defined by the number of seizure-types) has been linked to adverse neuropsychological outcome (C. Dodrill & Matthews, 1992; Seidenberg, et al., 2007). The difference in level of performance between those with purely photosensitive epilepsy and the other two cases (Sher and Bela) might be explained by the fact that the latter have various seizure-types including those triggered by sensitivity to lights. Sher was sensitive to both flickering lights and bright,

uninterrupted lights. The latter is a trigger for eyelid myoclonia and absence spells, which precede or trigger a convulsive JME seizure (Covanis, 2005). **Bela and Sher's disorders differed insofar that** Bela was in the process of changing her medication regime which might have impacted on her task performance. Both were on two types of medication and had EEG abnormalities.

A recent study (Rodin, 2009) statistically isolated some of the variables which define and contribute to severity of illness in chronic epilepsy, including among others: more than one seizure type, amount of EEG abnormalities, and psychomotor seizures. The researcher concluded that those syndromes which carry a bad prognosis have serious abnormalities on three or more variables.

Eyelid myoclonia and perioral myoclonia

The research literature on seizure-types such as perioral myoclonic and eyelid myoclonic has shown that they are genetically independent of the epilepsy syndrome with which they might be associated (Covanis, 2005; Mayer, et al., 2006; Panayiotopoulos, 2005a; I. Taylor, et al., 2003). Several types of reflex seizure triggers are restricted to a known localization such as the occipital lobe (Zifkin, 2010), and eyelid or perioral reflex myoclonia whose seizure symptoms remain restricted to localized areas of the face (Mayer, et al., 2006; Zifkin & Inoue, 2004). It is conceivable, therefore, that localized myoclonia seizures might produce mild and localized cognitive dysfunction. For example, Sher and Bela both had specific deficits of attention control and mildly impaired working memory, but no visual memory deficits. They contrasted with the visual memory deficits of the other two cases with pure photosensitivity (Jon and Mary).

The main point which emerged from the case studies in reflexivity was that cases whose epilepsy had several reflex seizure components showed a greater severity and/or spread of cognitive impairment than the other IGE participants.

4.4.3 CHRONICITY AND CAPACITY

The significant correlation results contradict the literature which says impairment becomes evident only after many years of living with IGE. A more hopeful finding is that the adverse impact associated with IGE in these participants has been counter-acted by increasing years of education. An equally valid interpretation, however, might be that participants with a greater seizure burden were those less likely to have the necessary abilities to stay on at school (see Table 4.4).

Although few severe individual deficits were actually found, investigation of seizure chronicity did detect some interesting results. In his extensive review on epilepsy and cognition, Dodrill (2004) described several studies reporting that increasing numbers of tonic-clonic seizures are connected to *general losses in “mental abilities” and more specifically,* decreasing intelligence over time. This study did not find any such association with decreasing intelligence. Also important, an increasing number of chronic IGE seizures were associated with deterioration of abilities in concept-formation, episodic memory and declarative memory processes. Concept-formation (Sorting tasks) is an executive function, **and this result accords with Hommet et al.’s** (2006) review which reported that cognitive control tasks accessing the pre-frontal cortex are those most affected in IGE disorders.

4.4.4 SUMMARY AND CONCLUSIONS

Overall, for these participants, the traditional view was upheld. The findings to arise from the series of case studies of IGE failed to concur with the view that IGE impacts on general cognitive function. Against this background, isolated deficits were found in some cases, involving attentional control and memory systems. The latter findings raise the relevance of additional seizure-types, co-morbid disorder or idiosyncratic factors.

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CHAPTER 5

CASE STUDIES IN TEMPORAL LOBE EPILEPSY

5.0 CHAPTER OVERVIEW

Chapter Five investigates clinical issues arising from the material-specificity principle in TLE which posits a modularity of mind description of cognition (Fodor, 2000, 2005; Saling, 2009). Modular models of memory functions give rise to two assumptions.

The *Localization* assumption cannot account for the wider impact on cognition of neuropathology spread and secondary generalization of seizures. The chapter organized the participants according to the severity of their condition: TLE with complex partial seizures; TLE with secondarily generalized seizures; and TLE with structural abnormalities. The variety of cognitive deficits other than memory increased with the complexity of the TLE condition.

The *Lateralization* assumption is based on the domain-specific view of memory which claims the left and right memory systems are independent and self-contained. *Lateralization* cannot account for the lateralization results (partial or none at all) in studies of TLE patients with normal neuro-imaging and/or non-surgery patients. The chapter found evidence of asymmetry of impairment e.g. use of verbal strategies to recall visual figures, and executive dysfunction of verbal abilities associated with the pre-frontal cortex in some left-TLE participants.

Findings on individual deficits for cognitive sub-domains in seven female TLE participants are reported, as are results from within-case comparisons of verbal and visual memory. Cognitive phenotypes consisting of both strengths and weaknesses are described.

5.1 CLINICAL ISSUES

The first question is whether widespread cognitive dysfunction might occur in a TLE disorder which is characterized by the spread of abnormal brain activity to extra-temporal regions and/or the spread of hippocampal pathology. The research literature has reported evidence of deficits other than memory in TLE patients including executive dysfunction, language and I.Q. impairments as well as localized memory deficits. The second question is whether verbal versus visual memory deficits lateralize as predicted by the material-specificity principle.

5.1.1 LOCALIZATION

The material-specificity principle predicts that cognitive functions other than memory should not be affected when seizure onset is localized in the temporal lobes and/or the hippocampus. If the site of pathology or lesion is well-defined and a relatively discrete task is used, then episodic memory loss is the most common cognitive dysfunction (Barr & Goldberg, 2003). As these researchers have commented, however, pathology is rarely confined within a particular location. When sclerosis (i.e. severe neuronal loss and gliosis in the hippocampal formation) spreads to other locations such as the lateral temporal regions, then some generalized cognitive impairment might be expected, suggesting damage to the hippocampus might mediate other deficits as well as memory (Bell & Davies, 1998; Giovagnoli & Avanzini, 1995).

One explanation for cognitive deficits other than memory might lie with the presence of focal epileptogenic tissue in the temporal lobes adversely affecting distant neural systems, including their cognitive functions. Hermann and Seidenberg (1995) tested contrasting hypotheses about causes of executive system dysfunction using 73 patients who underwent an anterior temporal lobectomy. One theory was that ictal and inter-ictal abnormal discharges from an epileptogenic

cortex adversely affect extra-temporal regions that mediate executive system abilities thus resulting in performance deficits. In comparison, the hippocampal theory suggests such impairments are due to the hippocampi being directly involved in mediation of some executive system functions, so impaired performance is directly attributable to hippocampal damage (Hermann & Seidenberg, 1995).

Patients were tested pre-operatively on their task performance in the Wisconsin Card-Sorting Test (WCST), and again six months post-operatively. **Improvement (or not) in patients' performance was tested** by comparing those with resection of sclerotic hippocampus versus resection in those with a non-sclerotic hippocampus. The hippocampal theory predicts that resection of a nonsclerotic hippocampus should result in significant worsening of WCST performance post-operatively. Results supported the epileptogenic cortex theory, with TLE patients who had become seizure free showing more normal WCST performance. They had had a complete resection of their epileptogenic region and had decreased propagation of abnormal epileptiform activity as a consequence (Hermann & Seidenberg, 1995).

Cognitive Phenotypes in TLE

One study demonstrated that deficits associated with TLE can range from localized memory dysfunction to widespread cognitive impairment, organizing the TLE participants into three groups according to their cognitive profiles (Hermann, Seidenberg, Lee, Chan, & Rutecki, 2007). The researchers assessed 96 epilepsy participants whose scores ranged from normal to severe generalized impairment. Cluster analysis was used to divide the participants into groups based on their overall cognitive performances across domains including intelligence, language, visual-perceptual abilities, memory (immediate and delayed), executive functions, and psychomotor speed. Three distinct clusters emerged.

- 47% were minimally impaired in language, delayed memory and executive functions;
- 24% were mildly to moderately impaired in memory, both immediate and delayed; and
- 29% had moderate to severely impaired memory, executive functions and psychomotor ability and speed.

Levels of impairment severity were found to be associated with clinical characteristics such as age at onset, duration of epilepsy disorder and number of medications. Four years later, follow-up assessments found that all three clusters showed a poorer cognitive course compared to controls, but the third cluster was significantly poorer than clusters 1 and 2 across all domains except intelligence. The researchers described these three clusters as distinct cognitive phenotypes in TLE and concluded that memory is not the only domain to be impaired (Hermann, et al., 2007).

A related study complemented Hermann et al.'s (2007) findings on cognitive phenotypes. Dabbs, Jones, Seidenberg and Hermann (2009) investigated the neuroanatomical correlates of cognitive phenotypes, using MRI of healthy controls and TLE patients (n=53). Assessment of cognitive domains included intelligence, language, perception, immediate and delayed memory, executive function, motor and psychomotor speed. Compared to healthy controls (n=53), cluster analyses identified three distinct groups i.e. cognitive phenotypes.

- Cluster 1 (47% of participants): minimally impaired language and speed ($z = 0.00$ to -1.00).
- Cluster 2 (27% of participants): immediate and delayed memory impaired ($z = -1.00$ to -2.00).
- Cluster 3 (24% of participants): Overall impairment ranged from $z = -1.75$ to -4.25 . Specific domains included I.Q., language, and

perception ($z = -1.75$ to -2.00); memory and executive functions ($z = -2.75$ to -3.25); and psychomotor speed ($z = -4.25$).

The third phenotype with the most widespread cognitive impairment also had the most neuroanatomical abnormalities in temporal and also extra-temporal structures, including the hippocampus, thalamus and basal ganglia, callosal regions and cerebellar networks. The minimally impaired phenotype had the most intact brain anatomy, followed by the memory impaired phenotype. Dabbs et al. (2009) concluded that cognitive phenotypes are associated with the presence and widespread distribution of neuroanatomic abnormalities.

To sum up the localization issue, researchers have found cognitive deficits other than episodic memory with strong evidence for frontal lobe involvement. Cognitive phenotypes studies have found executive dysfunction (decision-making, problem-solving strategies, verbal or design fluency, social cognition), and seizure chronicity has been associated with deteriorating intelligence.

5.1.2 LATERALIZATION

The clinical issue arising from the lateralization assumption is whether participants will show memory deficits lateralizing on the basis of material-specificity: verbal learning deficits associated with the language dominant hemisphere versus figural learning deficits when seizure onset is in the non-dominant hemisphere.

People with symptomatic TLE

Most of the evidence for a material-specific lateralization of memory comes from TLE patients whose seizures are symptomatic of neuronal injury, lesions or structural abnormalities. Evaluations for pre-surgery or post-surgery follow-ups have provided consistent

evidence supporting lateralization of verbal deficits associated with language dominant TLE. However, results are less conclusive when the lesion is in the non-dominant hemisphere (see Bell & Davies, 1998 for a review).

Kim, Yi, Son, and Kim (2003) cited results supporting a lateralization model of episodic memory in TLE. They include study comparisons of hemispheric differences in memory functions using the intracarotid amobarbital procedure (Glosser, Saykin, Deutsch, O'Connor, & Sperling, 1995), group studies of patients with left versus right medial TLE (Delaney, et al., 1980; Kim, et al., 2003), and functional neuroimaging of asymmetric brain activation during performance on a variety of verbal and nonverbal tasks (Golby, et al., 2001). These studies all support the presence of a double dissociation of verbal and non-verbal deficits according to left or right seizure onset in TLE.

Other studies have found a single dissociation of verbal memory deficits in left-onset TLE groups relative to right TLE groups, but no significant differences in non-verbal deficits (Giovagnoli & Avanzini, 1999; Selwa et al., 1994). In short, research evidence for visuospatial memory deficits is less solid than that for verbal deficits, but this might be reflective of the relative sensitivity of the measures being employed.

The severity level of any cognitive impairment depends on whether structural neuropathology is present or not, and to what degree. Sawrie et al. (2001) examined the lateralization utility of verbal retention (as measured by the WMS-III Logical Memory percentage retention sub-score), and found that patient with bilateral atrophy gave the worst performance, followed by those with unilateral atrophy, then the group with bilaterally normal hippocampal volumes. As severity of impairment increased, predictability of lateralization improved (Sawrie,

et al., 2001). The results from studies which involve brain-intact TLE patients are less supportive of lateralization of memory.

People with cryptogenic or idiopathic TLE

Among clinicians, *cryptogenic* is usually understood to mean of *unknown aetiology, probably symptomatic*. In this study, five of the TLE participants were lesion-negative, their TLE aetiology was cryptogenic, and probably familial in some cases. Some cryptogenic temporal lobe epilepsies have been found to have a genetic component which carries a susceptibility or tendency for developing the disorder (Vadlamudi, Scheffer, & Berkovic, 2003). There is a lack of consensus among researchers about the presence/absence of memory impairments in TLE patients with normal neuroimaging. Some studies have found a lesser degree of lateralization of dysfunction, while others have found only partial lateralization or none at all (Vadlamudi, et al., 2003).

Lesser degree of lateralization

Surgery and lesion patients might produce marked dysfunction and a clear-cut lateralization of deficits. Neurologically intact patients, however, might show the same lateralization but to a lesser degree of severity (Delaney, et al., 1980; Loring, et al., 1988; Mathern, Pretorius, & Babb, 1995; Sutula & Pitkanen, 2001). In the absence of any overt neuronal damage, Stafstrom (2002) used rats to show that subtle cognitive, motor and social dysfunctions (such as anxiety and social maladaptation) still might occur. He noted that seizure-induced mechanisms created persistent neuronal disturbances such as epileptiform brain activity and these interfered with the **rats'** normal cognitive functioning.

These findings might be relevant particularly for those five TLE participants with normal neuroimaging, if their assessments

demonstrate some subtle localized dysfunction during task performance including mild laterality effects.

Partial or no lateralization

Some studies have partially supported the material-specific distinction. For example, Wilde, Strauss, Chelune, et al. (2001) used neurologically intact TLE patients and found that *within*-subject comparisons between auditory and visual WMS-III scores were more sensitive to side of temporal dysfunction than other measures. They concluded that within-subject comparisons might be of clinical utility to the practitioner, who looks for intra-individual patterns and discrepancies on a case-by-case basis.

Various studies using lesion-free out-patients have failed to find this differential impairment altogether (Barr, et al., 1997; Naugle, et al., 1993; Naugle, Chelune, Schuster, & Luders, 1994). One explanation might be that not all tasks are sensitive to very mild or mild impairment (Loring et al., 2008). An alternative is the inadequacy of some visual tests, for example, complex figures can evoke verbal labelling strategies whilst abstract figures are less easy to verbally label. In such **situations, participants' learning strategies (and so recall task performance)** can vary (Bigler, 2003; Bigler, et al., 1996; Piguet, et al., 1994).

To sum up the lateralization issue, the literature supports findings of verbal episodic memory deficits in TLE cases with seizures confined to the dominant temporal lobe, but provides less conclusive evidence for a visual memory impairment associated with right TLE. In the context of lesion-negative TLE, the laterality of deficits might be better detected by within-subject comparisons rather than between groups (Kim, Yi, Son, & Kim, 2004; Wilde, et al., 2001).

5.1.3 TLE CHRONICITY

The number of years living with chronic epilepsy has been identified as a contributor to the development of hippocampal sclerosis and atrophy in patients with chronic partial seizures (Fuerst et al., 2001; Motamedi & Meador, 2003). Longitudinal studies (Helmstaedter, 2002; Helmstaedter, Kurthen, Lux, Reuber, & Elger, 2003) have investigated whether chronic TLE (without hippocampal sclerosis) is associated with progressive memory impairment over a number of years, and whether cognitive abilities other than memory are affected. Their conclusions are that chronic TLE is associated with a progressive impairment of memory, but does not involve other cognitive domains.

5.1.4 PREDICTIONS FOR CASES WITH TLE

Five participants in this study were lesion-free, while two had known neuropathology (hippocampal sclerosis and familial cavernous haemangioma respectively).

- If the localization assumption is supported, then any deficits should be confined to the memory domain. Alternatively, TLE profiles inconsistent with a modularity of mind theory would show other cognitive impairments as well as memory deficits.
- If TLE is associated with a lateralized memory deficit (Wilde, et al., 2001), then participants with dominant hemisphere TLE will show verbal memory deficits, whilst those with non-dominant TLE will show nonverbal memory impairments.
- Chronic TLE seizures will be associated with a progressive decline in memory function (Helmstaedter, 2002; Helmstaedter, et al., 2003).

5.2 CASE REPORTS: TLE

ALANA (RIGHT TLE)

Background information

Alana was 30 years old, married with children, and a family history of epilepsy. She was left-handed with no family history of sinistrality. Infrequent simple partial seizures began at 13 years of age and, after her first pregnancy, increased to several complex partial seizures per month. An aura of déjà vu and panic preceded the seizure which ended with a headache, and memory loss.

Review of previous investigations

At 30 years of age, the neurologist diagnosed right TLE, based on an abnormal EEG which reported runs of right frontal delta slowing, suggestive of epileptiform activity. An MRI was normal with no evidence of hippocampal sclerosis.

Neuropsychological status

Alana's I.Q. was in the superior range and cognitive domain scores ranged from high average to superior. With such high levels of functioning, weaknesses are discerned by lowered functioning rather than significant deficits. These were evident in tasks accessing right frontal regions, supporting her EEG taken at 30 years of age: visual selective attention, working memory and design fluency. In contrast, a high level of functioning was evident in a left frontal task (category switching); and also abstract thinking in both verbal (Similarities task) and visual skills (Matrix Reasoning). Her one (very mild) deficit was learning of abstract figures.

PEG (RIGHT TLE)

Background information

Peg was 65 years old, married with two grown children. Epilepsy onset was at 17 years, with complex partial seizures occurring every six to seven weeks. An aura of déjà vu was **followed by a “blank spell”** which lasted from 5-10 seconds, and recovery was slower and included shakiness and confusion. An EEG at 64 years of age found no epileptiform abnormalities. Her neurologist diagnosed right TLE.

Neuropsychological and emotional status

Peg had none of the visual memory impairment associated with right TLE, and her score for visual recognition of abstract figures was only slightly reduced. She gave strong performances in the Similarities task (verbal abstract thinking) and in Map Search (visual selective attention). She enjoyed cross-words and sudoku games, the latter requiring spatial visualization and forward planning. Peg reported moderate levels of general psychological distress (DASS), specifically self-rated anxiety (98th percentile) and depression (94th percentile).

ETTA (RIGHT TLE)

Background information

Etta was 38 years old, married with children, and no family history of epilepsy. The first seizure probably occurred in her early twenties but right TLE was not diagnosed until 18 months prior to study participation when complex partial seizures increased in frequency and generalized to convulsions.

Review of previous investigations

At 38 years of age, a sleep-deprived EEG recorded activity consistent with right TLE. (An extract copy of the EEG can be seen in

Appendix E). When reviewed some twelve months later, a CT scan (taken at 39 years) found no abnormalities in the temporal lobes or hippocampal sclerosis.

Neuropsychological and emotional status

Etta's mildly impaired visual memory was consistent with right TLE, but verbal episodic memory was also impaired, the latter perhaps indicative of generalized seizure impact. Inhibition of attention responses was moderately impaired and perhaps associated with the secondarily generalized seizures. Alternatively, her attention might have been affected by her mood state. Etta had a history of depression, recently aggravated by financial worries and work-related stress. She had no support network, no family in Australia, and was homesick for England. DASS results were moderate general psychological distress, with self-rated moderate depression and stress, and normal anxiety levels.

LETI (LEFT TLE)

Background information

Leti was 30 years old, with two children and a partner, and no family history of epilepsy. Auras commenced at age 25 and took the form of a metallic taste and a sense of déjà vu. They did not progress to seizure events until twenty months prior to her participation in the current study, during which she was aware of experiencing two complex partial episodes. Both the interictal EEG and MRI were normal. Her neurologist diagnosed left TLE.

Neuropsychological status

Leti presented as articulate and intelligent. Vigilance was reduced but not impaired. Both her episodic learning and visual learning of abstract figures were mildly impaired, while semantic memory was high average. The small number of seizures cannot explain these impaired scores. They might reflect attention difficulties which led to leaving school in Year 9. Another explanation lies with week-end alcohol binges and regular cannabis use.

JOSIE (LEFT TLE)

Background information

Josie was 35 years old and lived with her partner, and no known family history of epilepsy. Partial seizures commenced at 25 years of age, beginning with a wave of déjà vu, nausea and dread, with a cold sweat lasting about five minutes. She could talk during the partial seizure, without memory loss. The first secondarily generalized seizure with loss of consciousness had occurred at 31 years of age. At the time of study participation, their frequency was increasing, with one major seizure occurring every few months. Previous sodium valproate regime was associated with sedation and weight gain, and she was transferred to lamotrigine with fewer negative side-effects.

Review of previous investigations

Aetiology was unclear. Both MRI (taken at 31 years age) and CT scans (at 35 years) were normal. An EEG (35 years of age) **found “some bursts of generalized higher voltage slow wave discharges, but with no definite associated spikes or sharp waves.”** Early in the drowsy phase, there were slow waves over the left anterior temporal lobe. The EEG also showed bilateral generalized activity maximally frontally. After some discussion among neurologists about a late onset JME or TLE, the final consensus was left TLE with rapid generalized spread.

Neuropsychological and emotional status

Josie presented as socially relaxed with a pleasant personality. Her cognitive profile supported the final diagnosis of left TLE with secondary generalization involving the frontal lobes: mildly impaired episodic memory with moderately impaired control of attention responses as measured with the Colour-Word Interference task which is associated with the anterior cingulate in the mediofrontal regions. On the DASS, she rated her affective status as moderately anxious (87th percentile) and severely stressed (97th percentile) and general psychological distress reached the 92nd percentile.

JANA (LEFT TLE)

Background information

Jana was 23 years old and had complex partial seizures from the age of 6 years. They were infrequent in the early years but at the time of study participation, they were occurring every one to two weeks, lasting about one minute. A seizure was preceded by an aura which **“starts good” then developed** into a sense of panic and déjà vu. She could understand but not answer questions, and afterwards she was dazed for about 2 minutes. Her neurologist diagnosed left TLE.

Review of previous investigations

Jana’s epilepsy was caused by several inherited cavernous haemangiomas (Awad & Jabbour, 2006). Her father had left TLE and the same structural **abnormalities**. **At 23 years of age, Jana’s** MRI scan reported that “(a) the left hippocampus is smaller than the right, with a typical cavernous haemangioma in the left temporal lobe close to the hippocampus; and (b) the second haemangioma is on the right side lying in the posterior temporal region.” (**Jana’s MRI scan can be found** in Appendix E).

Neuropsychological and emotional status

Generally, cognition was not affected. Jana produced average memory scores on three different verbal memory tasks. There were some mild word-finding deficits associated with the left hemisphere. Visual selective attention, a function associated with the frontal lobes, was the most severe deficit. The atypical cognitive profile might be explained by **Jana's** young age of seizure onset (6 years) which might have allowed re-organization of memory functions (Seidenberg et al., 1997); but see Hermann, Seidenberg and Bell (2002) and Strauss, Loring, Chelune, Hunter, et al. (1995) for different findings on early age of seizure onset.

While participating in this study, Jana had undergone STD tests and was awaiting results. Self-rated DASS results did not reflect this, with stress at normal levels (39th percentile), as was anxiety (30th percentile) and depression (10th percentile) was below the norm.

CATH (LEFT TLE)

Background information

Cath was 20 years of age, living with her partner and six months pregnant. She had stopped medication to avoid teratogenic effects. Cath had febrile convulsions during infancy and complex partial seizures commenced in childhood at 6 or 7 years of age. Her first convulsive seizure at age 19 years was triggered by excessive alcohol intake for a few days beforehand, and the latest episode prior to study participation consisted of four seizures over six hours. Cath reported that episodes began with an aura of nausea, followed by a complex partial seizure then generalized to tonic-clonic convulsions. Her neurologist diagnosed left TLE.

Review of previous investigations

At 20 years of age, an EEG showed a generalized excess of slow activity, no epileptiform or focal abnormalities. A brain MRI **found** “long-standing left mesial temporal sclerosis”. (See Appendix E for a copy of **Cath’s** MRI scan). Some six months after this assessment was **completed**, **Cath’s medical chart** listed three more tonic-clonic seizures.

Neuropsychological and emotional status

Cath was very relaxed during the initial interview and testing sessions. Cognitive deficits were associated with left TLE functions: confrontation naming was the most severe deficit, yet vocabulary and verbal fluency skills were only mildly impaired (See Gleissner & Elger, 2001 on semantic word fluency and the hippocampus). Verbal episodic delayed recall was very severely impaired (in contrast to average semantic memory) which supports the MRI report of long-standing hippocampal sclerosis.

Her emotional status on the DASS was ambiguous insofar that she rated herself as below the norm for anxiety (11th percentile) and stress (4th percentile). Her performance during assessment of verbal episodic memory and confrontation naming was severely impaired, yet this did not seem to affect her peace of mind.

5.2.1 SUMMARY OF DISORDER CHARACTERISTICS

Table 5.1 summarizes **each participant’s** disorder characteristics. The aetiology of TLE is most often associated with a symptomatic (rather than genetic) origin. In this study, two participants were lesion positive (hippocampal sclerosis and inherited haemangioma), five people had a cryptogenic aetiology, and two participants had a known family history of epilepsy.

Table 5.1
Disorder characteristics in seven TLE cases

Disorder Characteristics of TLE participants	Alana (right)	Peg (right)	Leti (left)	Josie (left) ¹	Etta (right) ¹	Jana (left) ²	Cath (left) ^{3 1}
Mode of onset							
Localized	√	√	√	√	√	√	√
2 nd Generalization ¹				√	√		√
Aetiology							
Origins disorder ⁴	F	C	C	C	C	F	C
Structural abnormality	n/a	n/a	NAD	NAD	NAD	MRI	MRI
Abnormal activity	EEG	NAD	NAD	EEG	EEG	n/a	NAD
Seizure Properties							
Age at Onset	13	17	28	25	21	6	7
No. of Years Burden	17	48	2	10	17	17	13
Handedness	left	right	right	right	right	right	right

Note:

NAD = no abnormality detected. N/a = not available.

1 = Secondary generalization of seizures.

2 = MRI revealed two cavernous haemangioma; one near the left hippocampus and another in the posterior section of the right temporal lobe. Left hippocampus is smaller than left one.

3 = MRI revealed left hippocampal sclerosis.

4 = F = Familial; C = Unknown; S = Symptomatic.

5.3 RESULTS

This section details the neuropsychological performance by the seven TLE participants.

- **Figures 5.1 to 5.6 represent individuals' performances in six cognitive domains.** See Table 3.4 for qualitative descriptions and levels of cognitive impairment.
- Table 5.2 summarizes severity and spread of cognitive deficits in each case.
- Table 5.3 contains within-case z-score comparisons of episodic verbal memory (AVLT) versus visual memory (CVMT and MCG-CFT) in TLE individuals.
- **Table 5.4 summarizes the participants' cognitive strengths and weaknesses.**

5.3.1 COGNITIVE DOMAINS

Figure 5.1 depicts Verbal and Performance score indices, which together constitute the estimated Full-Scale I.Q. No TLE cases had below average I.Q. scores, several had high average current estimated I.Q. or above.

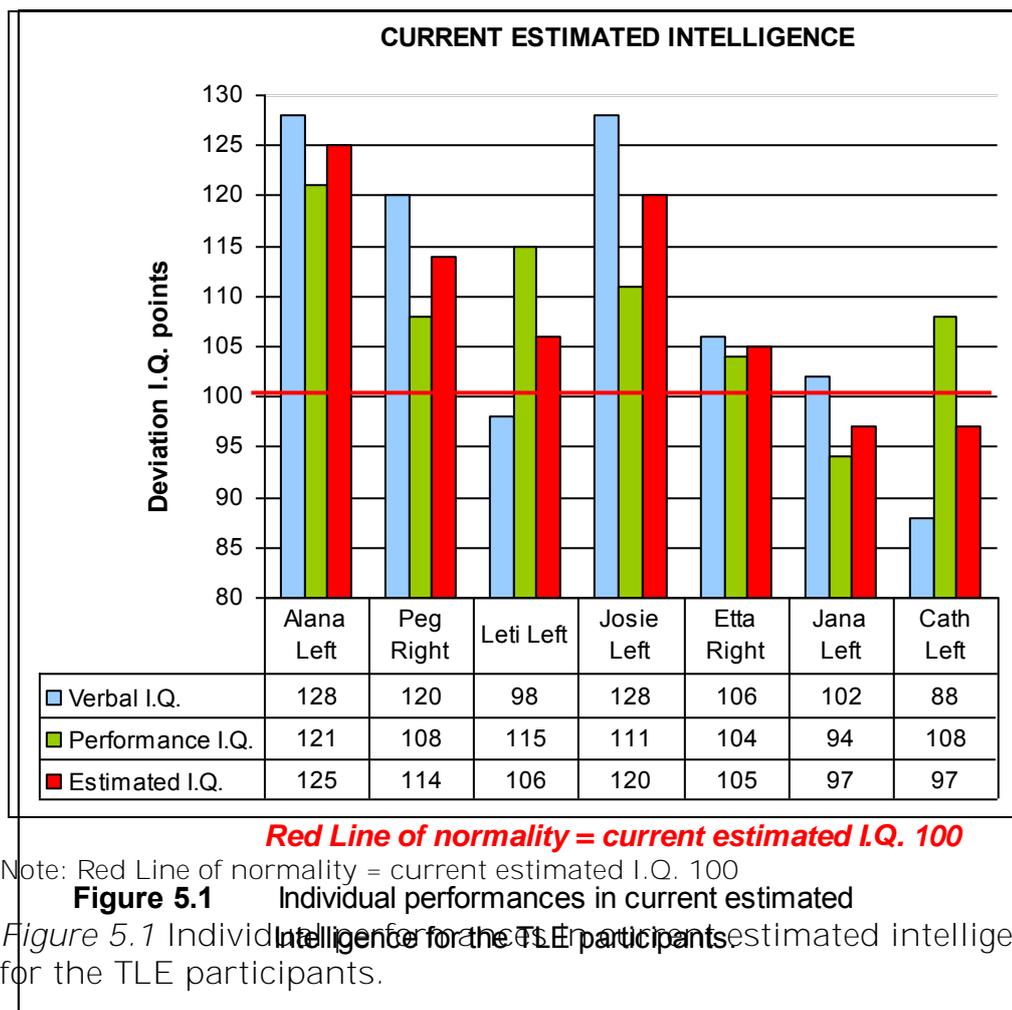


Figure 5.2 indicates that, based on the total z-score means for the Intellect domain, the TLE individuals functioned overall at an average level, including the two lesion-positive participants (Jana and Cath).

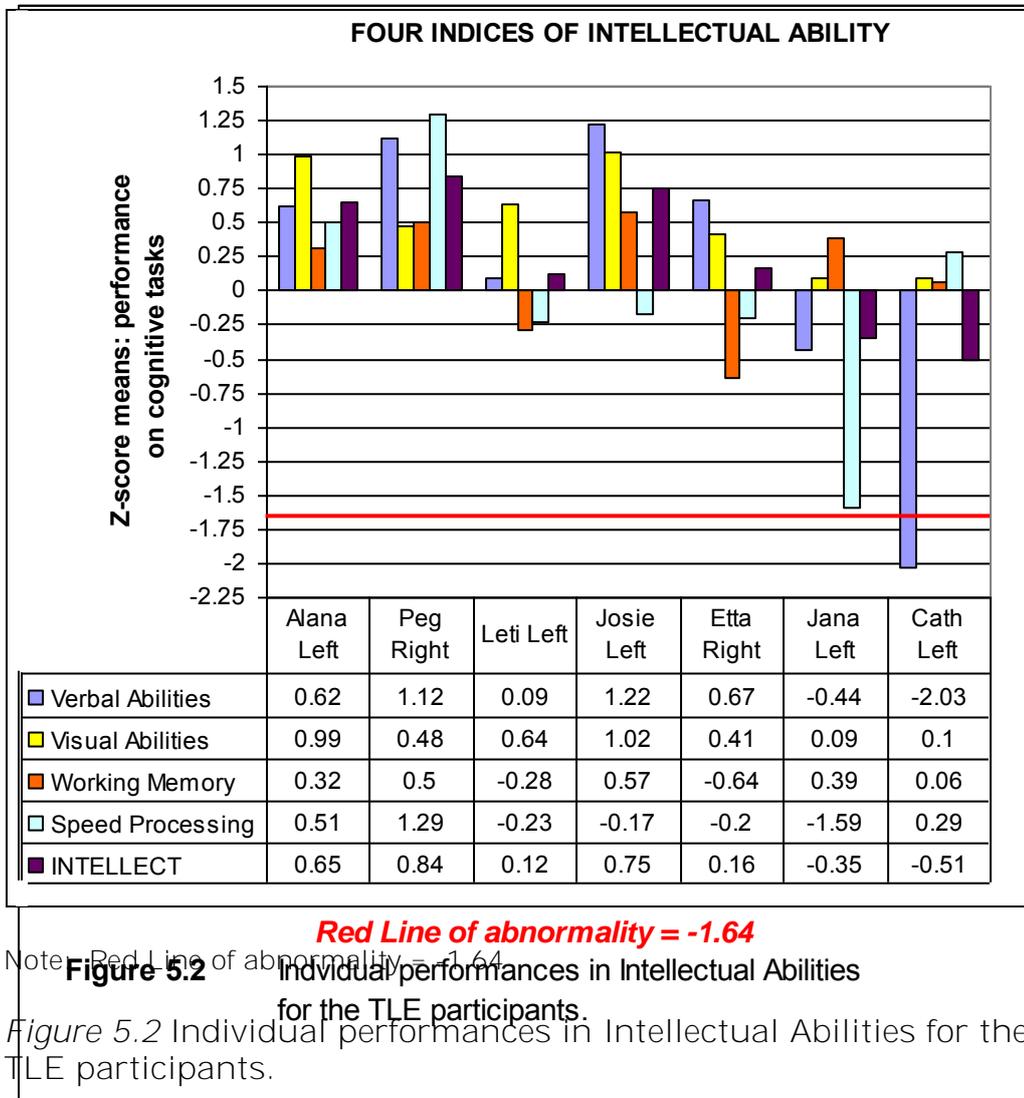


Figure 5.3 represents four factors which constitute the Attention Domain: sustained attention; visual selective attention; switching attention and divided attention. Most z-score means for the various Attention factors indicate an average level of performance. However, when broken down into their component tasks, several cases showed mild to severe impairments (see Table 5.2).

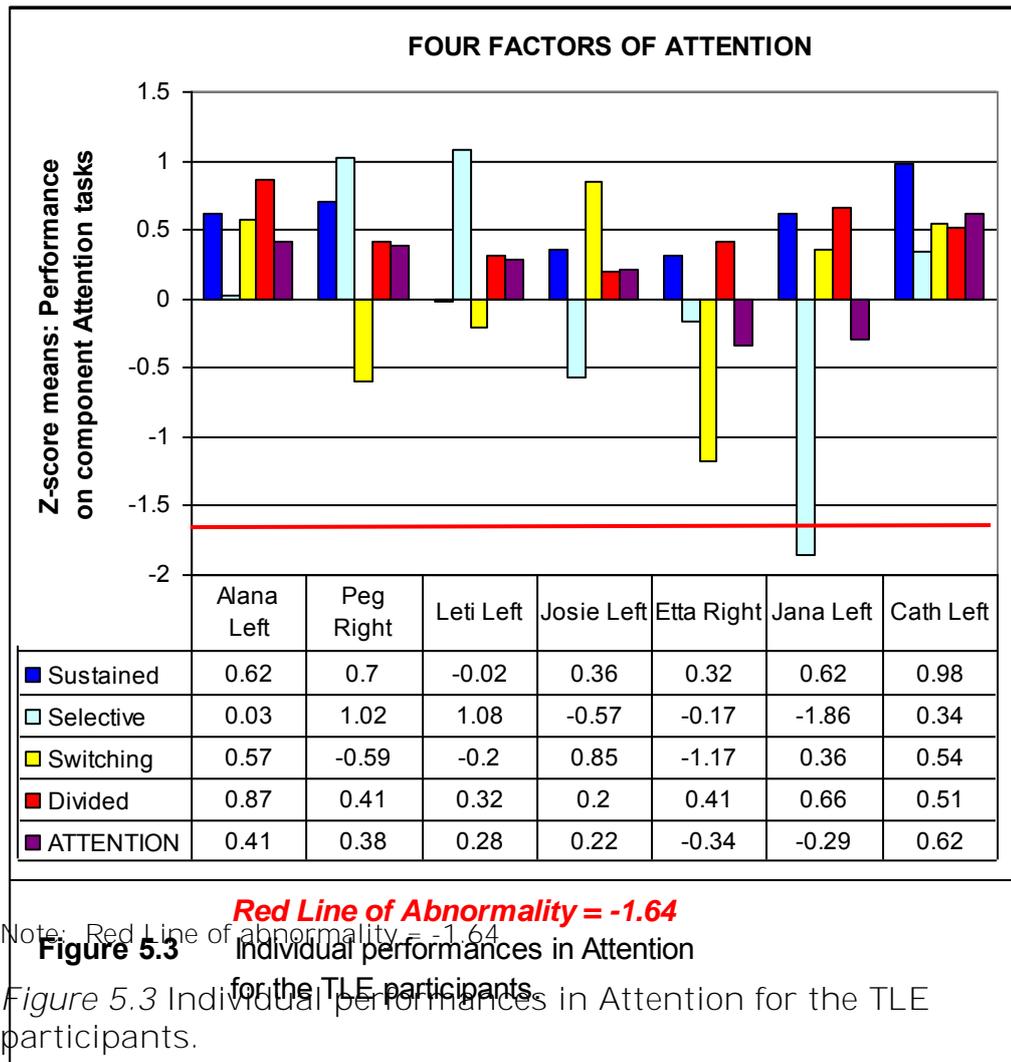
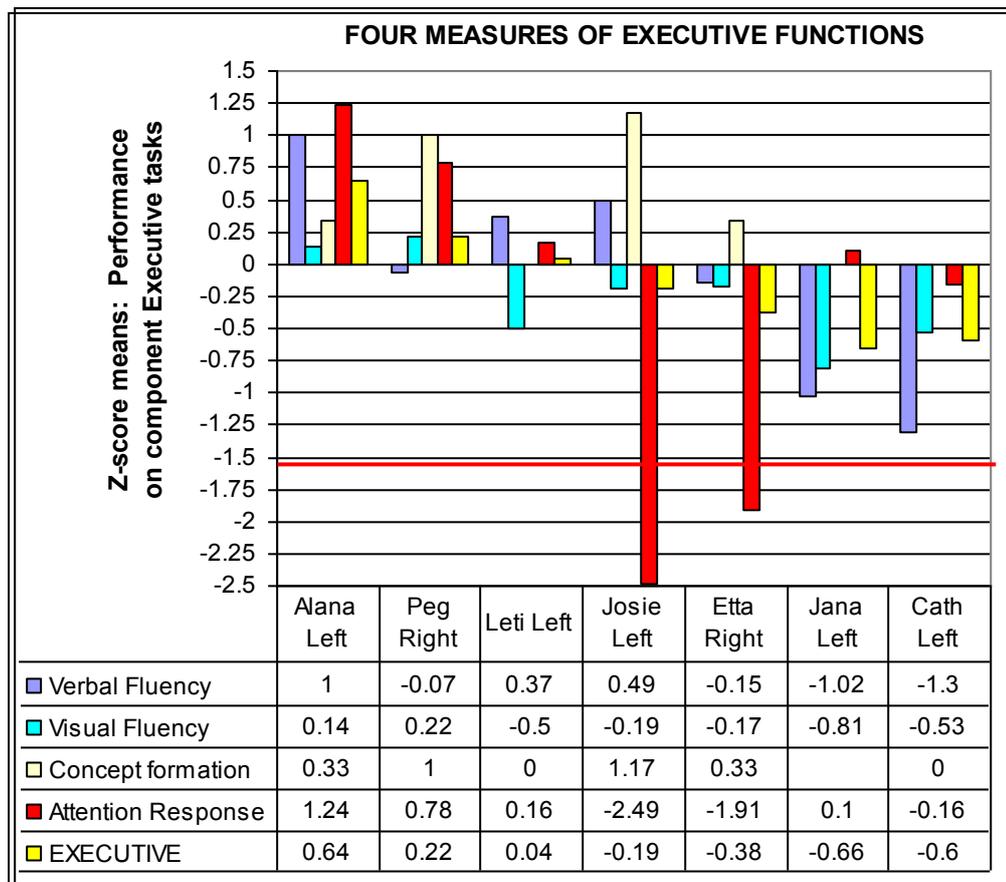


Figure 5.4 represents four executive functions: verbal fluency of FAS words and category members; visual fluency in generation of designs, concept formation from verbal or perceptual stimuli, and control of automatic attention responses. Each z-score represents the mean for two or three component tasks. The two lesion-positive cases (Jana and Cath) gave mild to severely impaired performances in the Attention Response component tasks, as did two cases with secondarily generalized seizures (Josie and Etta). See Table 5.2.



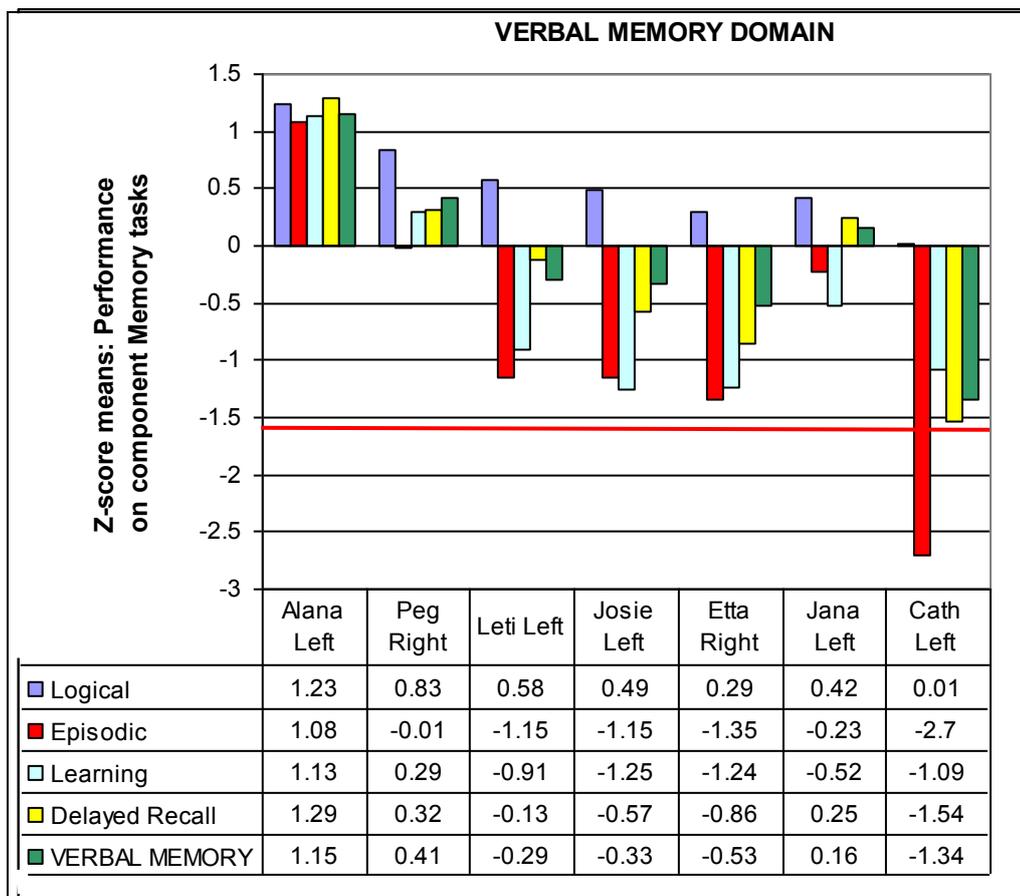
Red Line of Abnormality = -1.64

Figure 5.4 Individual performances in Executive Functions
for the TLE participants

Note: Red Line of abnormality = -1.64

Figure 5.4 Individual performances in Executive Functions for the TLE participants.

Figure 5.5 represents performance on measures of semantic memory, verbal episodic memory, verbal learning and verbal delayed recall. Overall, TLE participants showed average performance in the Verbal Memory domain, with normal semantic memory functions. In comparison, when scores for the individual component tasks for Episodic Memory were examined, a lower level of functioning was found in three cases (Josie, Etta and Cath) with secondarily generalized seizures (see Table 5.2).

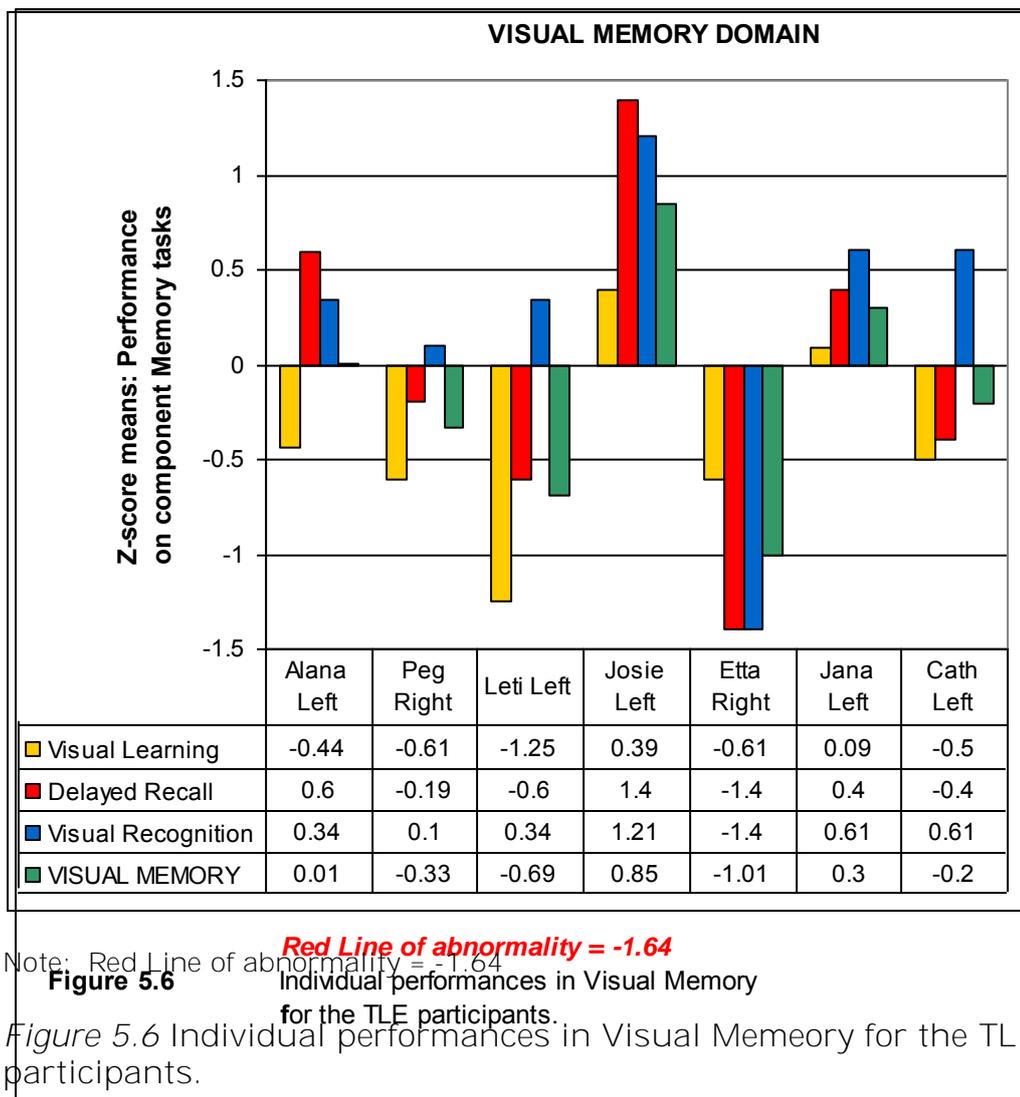


Red Line of abnormality = -1.64

Note: Figure 5.5 shows individual performances in Verbal Memory for the TLE participants.

Figure 5.5 Individual performances in Verbal Memory for the TLE participants.

Figure 5.6 reflects performances on measures of visual memory: visual learning, visual recall and visual recognition. Overall, the TLE participants achieved average z-scores for the Visual Memory domain. Finally, comparison of z-score means for the Verbal and Visual Memory indicates that most **participants'** z-scores did not lateralize according to material-specific theories of left or right TLE. Within-individual comparison of sub-test scores for visual and verbal memory might be more productive (see Table 5.3).



5.3.2 SUMMARY OF INDIVIDUAL DEFICITS

Table 5.2 shows that cognitive impairment in the TLE participants was not widespread. The domains most affected were verbal episodic memory (57% of cases) and attention (57% of cases), followed by visual memory and language.

Table 5.2
Severity and spread of cognitive deficits for the TLE participants

Cognitive Domains	Alana (right)	Peg (right)	Leti (left)	Josie (left) ⁶	Etta (right) ⁶	Jana (left)	Cath (left) ⁶	% Cases
Estimated I.Q.	125	114	106	120	105	97	97	
Attention¹								57%
Response Inhibit				-2.13	-2.46			
Response Switch				-2.86	<i>R</i>			
Select Attention				-1.55		-2.25		
Switch Attention		-1.64			-1.64			
Language								28.5%
Category Fluency ²						-1.87	-1.65	
Vocabulary ³							-1.60	
Naming ⁴						-2.00	-4.00	
Episodic Memory⁵								57%
Episodic Learning			-2.00	-1.64	-1.88		-1.91	
Delayed Recall				-1.55	-1.86		-3.37	
Visual Memory⁵								28.5%
Learning (CVMT)	-1.68		-2.10					
Retrieval (CVMT)					<i>R</i>			
⁷Total Spread over cognitive domains	1	1	2	2	2	2	2	

Note:

- 1 = Tasks measure response control (D-KEFS) and attention factors (TEA).
- 2 = Category Fluency task controls semantic recall and accesses the frontal lobes.
- 3 = Vocabulary task accesses the lateral temporal lobe.
- 4 = Confrontation Naming (BNT) accesses the anterior temporal lobe.
- 5 = Episodic Memory tasks (AVLT) access the hippocampus and medial temporal lobe. Visual Memory deficits found with CVMT, but not with the CFT.
- 6 = Secondary generalization of seizures.
- 7 = Spread of impairment i.e. number of cognitive domains found to be impaired.

R = reduced but not impaired

Levels of impairment (z-scores in **bold**)

Borderline -1.51; very mild impairment **-1.64**; mild impairment **-1.96**;
moderate **-2.33**; severe **-3.09**; very severe **-3.29**.

Cognitive phenotypes

The cognitive impairments in Table 5.2 do not reflect one cognitive profile, rather they divide into three classes or phenotypes as described in studies by Hermann et al. (2007) and Dabbs et al. (2009).

- Complex partial seizures only. 42.86% of participants (Alana, Peg, Leti) showed very mild to mild impairment of memory and working memory.
- Cryptogenic complex partial seizures with secondary generalization. 28.57% of participants (Josie and Etta) showed mild to severe deficits in memory and attention.
- Structural abnormalities. 28.57% of participants (Jana and Cath) showed mild to very severe deficits of language, memory and executive functions (verbal fluency and attention control).

Within-case lateralization of impairments

The material-specificity model predicts that lateralization in verbal or visual memory impairments is determined by the stimulus materials being learned/or recalled in memory tasks. Table 5.3 allows z-score comparisons of verbal and visual memory within each TLE participant. The cut-off z-score for notable difference was set at ± 1.64 .

With regard to the MCG-CFT measure, notable within-case differences between verbal and visual episodic memory were found for Josie and Cath, who also had lateralization of memory impairment for the CVMT measure. Alana showed impaired visual memory for abstract figures (CVMT) but not the MCG-CFT. She had used verbal labeling strategies to recall the latter, but this was not possible with the abstract figures.

Table 5.3

Lateralization: within-case comparisons of verbal episodic memory (AVLT) versus (a) visual memory for complex figures (MCG-CFT) and (b) visual memory for abstract figures (CVMT).

Names	Verbal Memory for word-lists ¹	Visual Memory complex figures ²	Difference (in z-scores)	Visual Memory abstract figures ³	Differences (in z-scores)	Strategies ⁴
Class One						
Alana (R-TLE)	1.24	0.70	0.54	-0.67	1.91 (p=.05)	Yes
Peg (R-TLE)	-0.13	-0.16	0.03	-0.49	0.36	Yes
Leti (L-TLE)	-1.57	-0.50	-1.07	-0.88	-0.69	No
Class Two						
Josie (L-TLE)	-1.57	1.20	-2.77 (p=.005)	0.50	-2.07 (p=.025)	Yes
Etta (R-TLE)	-1.87	-1.10	-0.77	-0.91	-0.96	No
Class Three						
Jana (L-TLE)	-0.23	0.50	-0.73	0.30	-0.53	No
Cath (L-TLE)	-2.64	-0.20	-2.44 (p=.010)	-0.40	-2.24 (p=.015)	No

Note:

Notable difference in z-score means was set at $z = +/- 1.64$.

1 = Verbal memory (AVLT) consists of mean z-score for episodic learning trials 1-5 and episodic delayed recall trial 8.

2 = Visual memory for complex figures (MCG-CFT) consists of mean z-score for CFT learning and delayed recall tasks.

3 = Visual memory for abstract figures (CVMT) consists of mean z-score for immediate and delayed recognition tasks.

4 = After the MCG-CFT, participants were asked if they had used word labelling strategies as an aid for recall.

Material-specificity cannot account for Josie's more severe attention deficits or Cath's additional executive dysfunction (category fluency) and language deficits (vocabulary, naming). Hermann, Seidenberg, Schoenfeld and Davies (1997) found patients with left TLE (and no other abnormalities than hippocampal sclerosis, as in Cath's case) had general cognitive impairment including intelligence, language, visuospatial dysfunction, but excluding executive functions, attention and concentration. As described in section 5.1.1 of this chapter, Hermann and Seidenberg (1995) have explained the phenomenon of widespread cognitive impairment as being due to a "nociferous cortex" rather than directly attributable to hippocampal pathology.

5.3.3 STRENGTHS AND WEAKNESSES

Table 5.4 gives a summary of notable strengths, impairments and/or fluency errors in each individual. Qualitative measures of perseveration and distractibility (repetition errors or set-loss errors respectively) were of interest as indicators of a person's potential to adapt cognitively (or not) to her epilepsy disorder.

The nature of the errors made during a memory test can be as instructive as accuracy scores. One researcher has noted that a qualitative scoring system of visual memory for complex figures would enhance the utility of this measure (Helmes, 2000). For example, the nature of the errors made during a memory task could distinguish between those participants with right TLE and those with left TLE, whilst accuracy scores did not (Loring, et al., 1988; Loring, et al., 2008). As can be seen in Table 5.4, the nature of the repetition errors during verbal fluency tasks (D-KEFS) could identify left-TLE (Cath) while set-loss errors could not identify right-TLE (Etta).

Table 5.4
Cognitive profiles of TLE participants organized into three classes

	Cognitive Deficits (in z-scores)		Inflexibility, Distractibility, Perseveration Contrast Measures and/or Error-types (standard scores)		Adaptability/Strengths (in z-scores)	
Class One						
Alana (R-TLE)	Visual Learning	-1.68			Verbal I.Q.	128
					Similarities	2.20
					Matrix Reasoning	1.95
					Category Switching	2.33
Peg (R-TLE)	Working Memory	-1.64			Verbal I.Q.	120
					Selective Attention	2.20
Leti (L-TLE)	Verbal Learning	-2.00		Verbal Set-Loss SS6		
Class Two						
Josie (L-TLE)	Response Inhibition	-2.13	Inhibition - Naming SS7		Verbal I.Q.	128
	Response Switching	-2.86	Switching - Naming SS3		Matrix Reasoning	1.75
	Verbal Learning	-1.64				
Etta (R-TLE)	Response Inhibition	-2.46	Inhibition - Naming SS2	Verbal Set-Loss SS5		
	Working Memory	-1.64	Switching - Naming SS5	Visual Set-Loss SS12		
	Verbal Learning	-1.88				
	Verbal Recall	-1.86				
Class Three						
Jana (L-TLE)	Selective Attention	-2.25				
	Category Fluency	-1.87				
	Naming	-2.00				
Cath (L-TLE)	Category Fluency	-1.65		Verbal Repetition SS6		
	Vocabulary	-1.60		Visual Repetition SS12		
	Naming	-4.00				
	Verbal Learning	-1.91				
	Verbal Recall	-3.37				

5.3.4 CHRONIC TLE SEIZURES

Correlations run between measures of chronic TLE seizure-properties and cognitive task scores failed to find any notable associations. In this TLE group, memory functions did not decline over time or with increasing numbers of seizures. This finding would be in keeping with a study (U. Kramer et al., 2006) which failed to find significant correlations between seizure-properties (age at onset, number of years with TLE, cumulative number of complex partial seizures) cognitive performance and secondarily generalized seizures. The researchers concluded that chronic seizures are not responsible for cognitive dysfunction.

5.3.5 SUMMARY OF MAIN FINDINGS

To sum up the Results section, the individual performances did not wholly bear out predictions about localization or lateralization of memory dysfunction. The most notable findings were as follows.

- Memory was impaired in most cases but participants had other cognitive deficits also, including attention and/or language.
- Profiles of impairment were asymmetric rather than lateralized i.e. other same-hemisphere verbal deficits were found in those with left TLE (e.g. category fluency, language), while some right TLE participants used verbal strategies to diminish/eliminate difficulties with visual recall.

5.4 DISCUSSION

The first assumption stated in Chapter Two was that impaired memory is the only deficit associated with a TLE disorder. As can be seen from the results in Table 5.2, memory was not the only domain affected,

which is not consistent with theories of domain-specificity for cognitive dysfunction.

The second assumption was that memory impairments would lateralize according to the verbal or visual nature of stimuli materials and dominant hemisphere, and this was tested with within-case comparisons. Table 5.3 shows that, of the seven participants, only one (Alana) was found to have lateralization of memory impairment with no detection of other cognitive deficits. Other participants (Josie and Cath) produced lowered scores for executive attention dysfunctions and/or language abilities, as well as lateralized memory impairments for both complex and abstract figures.

No individual profile was consistent with what might be expected of a clear-cut lateralization or localization of memory deficits. At best, performances only partially fulfilled the material-specificity predictions. Further, because the nature of the anomalies differed across participants, the results were not suggestive of any specific memory model.

A possible pattern, however, did emerge from the variety of affected domains. The impairments found in this study (impaired language and verbal fluency, verbal and visual memory, auditory working memory and executive dysfunction) were similar to the cognitive phenotypes described **in Hermann et al.'s study** (2007) although different tasks were used. Unlike Hermann et al. (2007), however, the three classes in the current study did not organize strictly according to levels of impairment severity, while a loose association with complexity of seizure-type and structural abnormality was also present (see Dabbs, et al., 2009 for neuroanatomical correlates of cognitive phenotypes).

5.4.1 COGNITIVE PHENOTYPES

The TLE participants' cognitive strengths were allocated to the same three classes as their impairments and processing errors (see Table 5.4). Cognitive adaptability diminished as individual syndromes became more complex, so that class three had the most affected domains (memory, language and executive dysfunction).

Class One

Participants in this class had complex partial seizures and demonstrated several cognitive strengths which allowed cognitive adaptability to possible memory problems. Levels of impairment ranged from very mild to mild dysfunction of memory and working memory.

Alana (right TLE) had a superior Verbal I.Q. and above average competence in abstract reasoning (verbal or perceptual) which had been found to access left or right areas of the pre-frontal cortex (Groth-Marnat, 2003). She also showed superior semantic flexibility (category switching was significantly higher than verbal fluency tasks). Peg (right TLE) had very mild working memory dysfunction, yet her disorder was of 48 years duration. Her Verbal I.Q. was above average and another strength was speed in the ability to identify symbols located on a map (visual selective attention as measured by the TEA sub-test, Map Search). **Leti's (left TLE)** verbal and visual memory deficits probably pre-dated her epilepsy disorder since she had had two seizures over five years. She produced an above average number of distractibility errors and reported academic learning difficulties.

Asymmetry not lateralization

Classes One and Two might be explainable by examining normal memory processes in healthy volunteers. Golby, Poldrack, Brewer,

Spencer, Desmond, Aron & Gabrieli (2001) used fMRI to compare the effects of four different stimuli (words, faces, scenes and abstract patterns) during learning and recognition tasks. Recognition memory (old/new judgments) did not differ across the four stimulus task-materials, which is to be expected with normal participants. Their main findings contain two **points relevant for this study's TLE participants.**

First, the four stimuli-types elicited different patterns of bilateral activation which lateralized across the pre-frontal cortex. Also important, mediofrontal areas were involved (the cingulum and/or anterior cingulate) during encoding (Golby, et al., 2001). Thus, activation was asymmetric in differing degrees across types of stimulus materials so that learning and recognition of task materials did not lateralize absolutely but occurred along a continuum (Golby, et al., 2001). With regard to Class Two in the current study, their profiles contradict a *process-specific* model of memory, since their learning and retrieval functions do not reflect a neat hemispheric lateralization of learning and retrieval functions. Their memory scores also contradict a *material-specific* model since the attention deficits would suggest that medio-frontal areas were activated irrespective of type of stimuli material.

Second, and more relevant for Class One, Golby et al. concluded **that learning and subsequent recognition was determined by the stimuli's degree of verbalizability.** They suggest that the greater bilateral and contralateral hemisphere activation elicited by the faces or scenes stimuli indicates individuals may have been using different strategies when learning these intermediately verbalizeable stimuli (Golby, et al., 2001). With regard to the current study, their second point implies that individual variations in cognitive strengths and weaknesses are probably **contributing to the seven participants' apparent lack of a predictable** pattern for memory task performances.

Class Two

Both participants in this class had complex partial seizures with secondary generalization. They did not have the kind of cognitive strengths which might counter-act attention deficits, and which research has associated with secondarily generalized seizures (Hermann & Seidenberg, 1995). Indeed, attention task performances reflected an inflexible quality underlying their responses (see Table 5.4).

At 35 years of age, **Josie's EEG had recorded rapid secondary** generalization bilaterally to the frontal lobes. Her strengths included above average Verbal I.Q., abstract reasoning, with no language or verbal executive dysfunction. Very mildly impaired verbal learning of word-lists was present as might be expected. Like Etta, she had a normal ability to name and read colours but significantly less skill when inhibiting or switching attention. Attention dysfunction during memory tasks would be in keeping with a non-modular model of multiple memory circuits (Wagner, et al., 1998).

Etta's right TLE disorder included secondarily generalized seizures, and was an example of atypical right TLE cognition insofar that she showed both verbal episodic memory deficits and somewhat reduced task performance on memory for visual abstract figures. She had an unusually high number of set-loss distractibility errors in both her verbal and design fluency tasks. Her deficit profile does not fit the predictions of a material-specificity model since both executive functions and memory are impaired.

The two TLE cases' impaired executive attention (switching and inhibition of responses) has been associated with the pre-frontal areas of the brain. Their attention deficits are in keeping with memory research which includes executive functions and verbal strategies in memory models involving neurologically healthy participants (Golby, et al., 2001). The greater number of components in secondarily generalized complex

partial seizures might explain the severity of executive attention deficits.

Another possibility is that Josie's stress and Etta's depression might have contributed to the severity levels.

Class Three

Both participants (Jana and Cath) had complex partial seizures which might have had their origins in structural abnormalities. Cognitive strengths were not detected during assessment. Jana and Cath could be distinguished according to severity levels of impairment, which might have been influenced by their brain plasticity during childhood development.

Jana's performance was atypical of cognition in TLE because, after many years of the disorder with an underlying neuropathology, no memory deficits were detected. She had some mild executive impairments associated with the pre-frontal cortex (category fluency, selective attention), and mild to moderate dysnomia associated with the left lateral temporal lobe. She had several cavernous haemangioma of familial origin.

In contrast, Cath (left hippocampal sclerosis) had very severe deficits in naming and delayed episodic recall of word-lists. Her performance (significant difference between verbal episodic memory and CVMT scores) only partially fulfils the predictions of a material-specificity model. She had an average verbal I.Q. and showed mild verbal dysfunction during category fluency and vocabulary tasks. Of some interest, her perseveration errors seemed to lateralize according to her left-TLE disorder. Repetition errors during the verbal fluency task indicated borderline impairment, while produced minimal repetition errors during above average performance in the visual fluency task.

Brain plasticity during childhood might be associated with the nature of the underlying neuropathology, which in these two participants involved cavernous haemangioma (Jana) and hippocampal sclerosis

(Cath). Dabbs et al. (2009) found that the most impaired cognitive phenotypes were associated with the presence and widespread distribution of neuroanatomic abnormalities. Mathern, Pretorius and Babb (1995) found that lesions (e.g. sclerosis) confined to the hippocampus might have more localized cognitive effects than other kinds (e.g. haemangioma) located in other areas of the brain. One study (Helmstaedter, Grunwald, Lehnertz, Gleissner, & Elger, 1997) compared cognitive dysfunction across groups with different histological damage (hippocampal sclerosis, mesial tumour, lateral tumour). Patients with hippocampal sclerosis scored significantly worse than those with other lesions (lateral temporal pathology) in delayed recall, while lateral versus medial tumours did not differ in effects on the specific memory tasks employed.

Finally, the seven TLE participants produced a wide range in levels of ability and impairments. In some cases, strengths in executive functions associated with the pre-frontal cortex would suggest the ability to compensate or adapt to memory problems. In other cases, the presence of moderate to severely impaired attention associated with medio-frontal areas indicated inflexibility of information processing rather than adaptability (Stuss, 2006).

5.4.2 KINDS OF ADAPTABILITY

At an individual level of cognitive functioning, intellectual reserve and brain capacity might influence degrees of adaptability. Reserve capacity has not been rigorously defined, but rather might represent a brain potential present at birth, an acquired factor such as a proliferation of synaptic connections related to long-term cognitive stimulation, or ability to use effective compensatory cognitive strategies (see Barnett, Salmond, Jones, & Sahakian, 2006; Lezak, et al., 2004 for detailed discussions; Stern, 2002).

Reserve capacity in neuropsychiatry has also been explored by Barnett, Salmond, Jones, and Sahakian (2006), who have separated current research into various reserve models. *Passive* models focus on individual differences in brain structure, and pre-morbid details such as number/density of neurons prior to pathology. *Cognitive reserve* usually refers to the condition of exclusively healthy individuals prior to pathology. *Active* models focus on individual differences in brain processes and functions, such as efficiency of neural processing (Oyegbile et al., 2004) or ability to recruit alternative brain networks to compensate for effects of pathology (Barnett, et al., 2006; Richards & Deary, 2005).

The study of brain reserve capacity first gained **neuropsychologists'** attention when dementia studies showed that brain pathology does not necessarily equate with deteriorating cognition or behaviour. Researchers attributed such findings to **"neural reserve" i.e. a genetically endowed** advantage based on increased neuronal numbers (Katzman, 1997; Katzmann, Terry, & DeTeresa, 1988). Investigations into the interaction of brain reserve capacity and dementia have been extended to epilepsy, together with the application of concepts like cognitive or intellectual reserve (Pai & Tsai, 2005; Stern, 2002), neurocomputational flexibility (Stuss, 2006), and education level (Pai & Tsai, 2005).

With regard to the cases in this study, other factors such as neuropathology, seizure chronicity, interictal epileptiform activity might be present, but the strengths and weaknesses most evident in Table 5.4 all involve frontal lobe functions to some extent. Such interactions between vulnerabilities associated with the disorder and cognitive reserve would produce highly individualized neuropsychological profiles, at least partially contributing to the presence or absence of dysfunction in individual patients.

Cognitive adaptability to task demands

Cognitive or intellectual reserve has been described as **“how well we use what has been left behind, rather than how much of it remains”** (Valenzuela, 2008, p. 297), who reviews various conceptualizations or models of brain or cognitive reserve in dementia. Epilepsy models look at long-term effects of refractory TLE on intellectual functions (Helmstaedter, et al., 2003; Hermann, et al., 2002; H. Jokeit & Ebner, 1999). Years of education can protect against decline in verbal fluency (but not attention) (Pai & Tsai, 2005) whilst education has been shown to have no effect on the impact of progressive hippocampal sclerosis (Marques et al., 2007).

Psychosocial measures of reserve strength ask how mentally active and engaged a person might be with his/her environment. Studies have included such proxy measures as level and duration of formal education (Pai & Tsai, 2005), nature and complexity of occupational history, and diversity, frequency and cognitive challenge of past and present leisure activities (Valenzuela & Sachdev, 2007).

Both Alana and Peg had higher than average verbal I.Q. scores, together with specific cognitive abilities which would have enabled competent performance of visual memory tasks notwithstanding their right-TLE. The most important finding for these two cases is that their high reserve in certain verbal abilities seems to have matched or compensated for any memory deficits usually associated with right TLE.

Alana’s scores were impaired for a visual abstract figures task (CVMT), but not a complex figures task (CFT). Her verbal flexibility and problem-solving skills could compensate for any visual memory vulnerability in those tasks where verbal strategies can aid learning of complex figures for example. Verbal labelling strategies would not work so well, however, for difficult-to-verbalize materials such as abstract figures (G. P. Lee, Loring, & Thompson, 1989). Thus, Alana did produce mildly

impaired CVMT performance. **Peg did not have Alana's variety of** strengths in measurable executive abilities, but she did have what Valenzuela (2008) calls psychosocial strengths: success in several diverse occupations in her life-time, the most recent involved running a news agency, and participation as a volunteer in several community groups.

Golby **et al's.** (2001) concept of *degrees-of-verbalizability* (inherent in task stimuli-materials) seems to provide the most likely explanation for **the two right TLE participants' cognitive adaptability to visual memory** task demands. In particular, the CFT tasks lent themselves to verbal labelling strategies, thus reducing their sensitivity to visual memory dysfunction.

Neurocomputational Flexibility

The neurocomputational theory of brain reserve is an interaction of both neuronal and cognitive reserve (for reviews, see Stern, 2002; Valenzuela, 2008). Those individuals who have developed a range of conscious and preconscious cognitive strategies for solving complex problems, such as performing well on neuropsychological tests, are more likely to remain unimpaired for longer than those who show rigidity of thinking when addressing problems (P. S. Sachdev & Valenzuela, 2009; Valenzuela & Sachdev, 2009). They also have a greater number of potential neural pathways for execution of cognitive processes. Brain plasticity seems to be an advantage, using their brain networks more efficiently because they are capable of switching to alternative networks or cognitive strategies in response to increased demand (Stefan & Pauli, 2002; Sutula, 2004).

The most important finding for two of the three cases (Josie, Etta) with secondary generalization of seizures is their inflexible switching and inhibition of attention responses, functions said to access the medial area of the pre-frontal cortex, more specifically the anterior cingulate. Golby et

al. (2001) found this area activated in normal volunteers during memory task performance

Neurodevelopmental Plasticity

Brain reserve might be one reason why individuals differ in their level of neuropsychological and behavioural dysfunction in the face of seemingly similar severity of a disease (Satz, 1993). Other contributory factors include genetic background which has been found to influence susceptibility to seizure-induced damage over time (Schauwecker, 2002; Schauwecker & Steward, 1997; Stefan & Pauli, 2002; Sutula, 2004).

The type of neuropathology and age when brain injury occurred might impact differently on cognitive functions, as in the two cases (Jana and Cath) with structural abnormalities (Mathern, et al., 1995). Both had epilepsy onset at an early age, but they differed greatly in the kind and level of cognitive impairments. In spite of several genetic haemangioma, Jana lacked memory deficits, suggesting early re-organization of language (**“good” plasticity**). **In contrast, the case with hippocampal sclerosis (Cath) showed cognitive deterioration already occurring (“bad” plasticity) in spite of her young adulthood. In his book “The Brain which changes itself”, Norman Doidge put forward the concept of “bad” plasticity which happens when the brain becomes fixed in an addictive habit or pain reaction even though the original reason for it might be long past (Doidge, 2008).**

The kind of parents might be at least as important as the type of **neuropathology or whether plasticity is “good” or “bad”**. **Jana’s father** (also with structural haemangioma) was highly educated and in a professional occupation (Stefan & Hammen, 2000). Cath had had a mother with alcohol addiction who had not stopped drinking during her pregnancy with Cath, and died young of alcohol poisoning.

5.4.3 SUMMARY AND CONCLUSIONS

At best, the predictions of an associative networks model were partially fulfilled but each person showed some anomaly in her assessment scores (if a material-specificity model is assumed). The idiosyncrasy of individual cases can greatly influence cognitive and emotional presentations. Current models should be able to explain more complicated cases, but they do not. Individual variations can over-ride the simplicity of these models used to explain cognitive functions in surgery patients. As Saling (2009) concluded in his review paper on material-specificity, the concept is inadequate on a number of levels which might equally well be said of a process-specificity model or models of multiple memory circuits.

However, an organization into three classes of deficits and strengths might be evident, based on seizure-types and the presence of structural abnormalities. Adaptability of cognitive skills to alleviate possible memory **problems seems to have been possible through an individual's reserve** strengths (Alana, Peg), not possible when attention responses and fluency errors reflected a quality of rigidity (Josie and Etta), or when generalized impairment was associated with compromised brain reserve such as hippocampal sclerosis (Cath).

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CHAPTER 6

CASE STUDIES IN STATUS EPILEPTICUS SEIZURE-TYPES

6.0 CHAPTER OVERVIEW

Chapter Six investigated the assumptions underlying SE described in Chapter Two (section 2.4.6), and tested predictions with varieties of SE-types. These included Absence Status (n=2), Complex Partial Status (n=2), and Generalized Convulsive Status (n=5). The chapter begins with research pertaining to the specific issues being investigated. Section 6.2 reports on nine cases. Section 6.3 presents performance data in relation to each cognitive domain and a table summary of individual deficits. This is followed by analyses of single cases versus the IGE comparison group, and task dissociations using the IGE people as a control group.

6.1 CLINICAL ISSUES

SE is viewed as a prolonged version of brief seizure syndromes. This assumption gives rise to clinical issues regarding cognitive outcomes. If correct, then cognition should be more severely affected by SE seizures than brief seizures; ASE, CPSE and GCSE should differ in the nature of their cognitive deficits; and cognitive impairment should worsen with increasing number of GCSE seizures.

6.1.1 PROLONGED VERSUS BRIEF SEIZURES

In the majority of cases, cognitive deficits associated with brief seizure syndromes such as IGE are mild at worst, and emerge over many years of chronic epilepsy. Such effects are listed in the DSM-IV under the category of Mild Neurocognitive Disorders (Motamedi & Meador, 2003).

However, depending on presence and degree of underlying abnormal brain activity and neuropathology, global functions such as consciousness, energy and drive can be affected, as well as specific cognitive functions such as attention, memory and language (Rausch, Le, & Langfitt, 1997).

Prolonged seizures differ from brief seizures in their course of cognitive decline or stability, chronicity effects, and in cognitive outcome (i.e. transience or chronicity of cognitive dysfunction) (Bauer et al., 2006; Fernandez-Torre, 2006). In comparison to brief seizures, prolonged episodes have been associated with a more rapid course of cognitive deterioration (Engel, Ludwig, & Fetell, 1978; Haut, Shinnar, & Moshe, 2005). Impairment has been found to be clearly more severe and widespread in some prolonged seizure-types than with brief IGE seizures or even symptomatic TLE (Fountain, 2000; Shirasaka, 2002; Shorvon & Walker, 2005).

Duration and number of GCSE seizures

Permanence and severity of impairment is much more likely when an SE episode is not treated promptly. Research studies in Chapter Two describe permanent neuronal injury found after only a few prolonged convulsive seizures which occurred when immediate medical services could not be accessed due to geographical location (Archer & Bunby, 2006; see Majak & Pitkanen, 2004 for a review of animal studies). Cognitive impairment in such untreated cases is severe, widespread and long-lasting or permanent. However, when the SE episodes are promptly terminated, the presence of cognitive deficits becomes less certain (Pellock, Marmarou, & DeLorenzo, 2004; Treiman & Walker, 2006). **Appendix E contains Dr. Archer's investigative reports on four indigenous cases whose treatment of an SE episode was delayed due to transport difficulties from remote areas of Far North Queensland.**

Much animal research has been concerned with how many status seizures are required, and how long the duration before an on-going seizure produces permanent brain damage (Mikati, et al., 2001; Pitkanen et al., 2002). Just one episode of status can damage the brain, the most vulnerable structures being the hippocampus and surrounding areas (DeGiorgio, Tomiyasu, Gott, & Treiman, 1992; Mathern, Adelson, Cahan, & Leite, 2002; Shorvon, 1994, 2002).

For humans, the same questions are ongoing: does significant cognitive decline begin from the first episode of status, or is impairment only transient with the first and/or second episode (Duncan, 2002b; Duncan & Thompson, 2003). The matter remains unresolved since most research is cross-sectional, and more longitudinal studies are needed (C. Dodrill & Wilensky, 1990). More recently, Dodrill (2002) reviewed studies on the neuropsychological effects of brief and prolonged seizures, and his **overall impression was “that losses in mental abilities are most easily** connected with generalized tonic-clonic seizures, especially when experienced in a serial fashion (status epilepticus) (C. Dodrill, 2002, p. S24).

Transient or irreversible seizure-effects

.... there is no doubt from individual cases that permanent cognitive sequelae can result from a severe episode of convulsive SE. Acute intellectual disturbances often improve over the months following SE, and the timing of testing is important. Conversely, serial imaging evidence suggests that consecutive atrophy may progress in the months after an episode of SE

(Shorvon, 2002, p. 89).

Of the many patients with CPSE seizures, few have convincingly shown *lasting* cognitive changes with most cognitive deficits resolving over weeks to months (Kaplan, 2000). Besag (2005) suggests that transience of impairment has become more likely since SE is now promptly treated in modern Western countries. This was not always the case, however, and

cognitive deficits after longer-term CPSE were often irreversible. The majority of research articles find that nonconvulsive SE (whether ASE or CPSE) is associated with transient impairment (Kaplan, 2000, 2002), while longer-lasting or even permanent impairment is more likely to be found with convulsive SE (Krumholz, 1999; Krumholz, et al., 1995; Shorvon, 2002).

6.1.2 SEIZURE-EFFECT OR NEUROCOGNITIVE MARKER?

A controversy exists about whether cognitive deficits are the product of SE seizure impact or whether they are acting as neurocognitive markers for an underlying neuropathology already present and caused the SE. Helmstaedter (2007) claims that similarity in cognitive profiles for both convulsive SE and nonconvulsive SE would indicate that brain damage and cognitive impairments *preceded* the SE condition (Hilken & de Weerd, 1995). Thus, the same cognitive deficits across the SE seizure-types would suggest they are not the consequence of SE *per se*, but rather neurocognitive markers for an underlying neuropathology.

SE-types differ in nature of deficits

The SE seizure-types have been shown to differ in their pathophysiology (Fountain & Lothman, 1995; Lothman, 1990). It is generally agreed that ASE is not associated with discernible cognitive impairment (Shorvon & Walker, 2005), while CPSE has been found to have cognitive sequelae, but their relative permanence is unclear. Transience of any cognitive dysfunctions is considered to be more likely in ASE or CPSE, while GCSE seems to have the greatest adverse impact (Shorvon & Walker, 2005). The research literature contains findings of specific deficits associated with the different SE seizure-types (Riggio, 2005; Wasterlain & Treiman, 2006).

Absence Status is most often associated with a clouding of consciousness during the ictal and postictal phases (Epstein, Diu, Abeysekera, & Chan, 2009; S. I. Lee, 1985). Several studies have also found disordered affect and emotional instability (Tatum, et al., 2001; Thomas, et al., 2006b; Thomas et al., 1999).

Complex Partial Status might result in transient cognitive deficits. While there is variability in findings, difficulties with memory predominate (Thomas, et al., 2006a). Several studies have reported difficulties with concentration (Duncan & Thompson, 2003; Thomas, et al., 1999), and behavioural disturbances including automatisms and psychotic states (Adachi, et al., 2005; Tatum, et al., 2001). In addition, CPSE with secondarily generalized convulsions is known to have a symptomatic aetiology and arguably greater impact than nonconvulsive complex partial SE seizures (Krumholz, 1999; Shinnar & Babb, 1997). For another interpretation, see Kaplan (2000) and Helmstaedter (2007).

Generalized Convulsive Status Epilepticus studies of the impact on cognitive and emotional functioning are fewer in number. One study reports that memory and personality change is common after a prolonged bout of convulsive SE (DeGiorgio, et al., 1992). Another found a very **slight adverse effect on mental abilities, but as the GCSE participants' baseline had been lower than normal controls, it was concluded that SE is more common in those who are neurologically impaired before the seizures** (C. Dodrill & Wilensky, 1990; Shinnar & Babb, 1997). Another reason for the conflicting reports about SE having greater cognitive impact than brief seizures is age-related differences in vulnerability to SE (Holmes, Khazipov, Liu, Sarkisian, & Stafstrom, 2006).

Neurocognitive markers of aetiology across SE-types

If cognitive deficits act as neurocognitive markers for underlying brain abnormalities giving rise to **seizures, then individuals' profiles of cognitive impairment** should not differ according to whether they had convulsive or nonconvulsive SE seizures. Several reviews have come to the conclusion that it is the SE aetiology itself which is responsible for rapid cognitive decline rather than duration or number of promptly treated SE episodes (Berg, 2002; Besag, 2005; Helmstaedter, 2007). See section 2.3.5 in Chapter Two for research studies testing the issue whether the epilepsy disorder itself or the underlying clinical condition is causative for the after-math (e.g. cognitive dysfunction).

See **Salmenpera, Kalvianen, Partanen, Mervaala, and Pitkanen's** (2000) report on MRI findings *after* SE. Such aetiologies include:

- A pre-existing brain injury (Majak & Pitkanen, 2004; Shinnar & Babb, 1997; Sutula & Pitkanen, 2002);
- A pre-existing symptomatic epilepsy disorder (Shorvon & Walker, 2005);
- A concurrent or co-morbid medical problem (Riggio, 2005);
- A neurodegenerative disorder (Kaplan, 2000, 2002).

In his review, Helmstaedter (2007) reported a retrospective analysis of his own patients with focal epilepsy and a history of SE (convulsive CPSE and nonconvulsive CPSE) versus those with epilepsy without episodes of SE (n=88). Cognitive profiles did not differ across seizure-types. Both convulsive SE (n=36) and nonconvulsive SE (n=30) had poorer education, lower I.Q., impaired motor functions, and reduced attentional abilities. Helmstaedter (2007) concluded this might be an indicator of retarded intellect or a less healthy brain, rather than decline or loss of partial functions resulting from prolonged seizures.

Finally, Helmstaedter (2007) provided a summary of the variables which influence cognitive functioning in SE, which include:

- type of epilepsy (symptomatic or idiopathic aetiology);
- the aetiology of the SE (acute or progressive underlying neurological condition versus slow evolution in the setting of pre-existing epilepsy);
- severity of the status episode (generalized versus focal, convulsive versus nonconvulsive);
- number and duration of prolonged seizures (prompt treatment); and
- age of the patient (i.e. very young/elderly are most vulnerable).

6.1.3 PREDICTIONS FOR CASES WITH SE

The fundamental question to be addressed is whether SE is simply a more severe version of brief seizures. The aim is to evaluate the general assumption that prolonged seizures are associated with more adverse cognitive effects than observed with brief seizures. The broad hypotheses are as follows.

- SE participants will have greater severity of cognitive impairments than people with brief seizures.
- Different cognitive domains will be adversely affected across the ASE, CPSE and GCSE seizure-types.
- Accuracy of cognitive performance will decline with increasing number of GCSE seizures.

Absence Status

- If ASE disorders are associated with *executive dysfunction* (Andermann & Robb, 1972; Guberman, et al., 1986) then participants will show deficits of planning and reasoning, poorly

sustained attention, lack of flexibility in processing information, and lack of initiative.

- If ASE disorders involve only a mild to moderate clouding of consciousness during the actual status seizure (Agathonikou, et al., 1998; Riggio, 2005), then the cognitive profile should be normal.

Complex Partial Status

- If CPSE has only transient effects on cognitive functioning (Riggio, 2005), then the CPSE participants will show focal deficits associated with the brief seizures of TLE. Deficits will include memory or language deficits consistent with laterality of seizure focus.
- If CPSE produce persistent cognitive deficits (Wasterlain & Treiman, 2006), then CPSE participants will produce a broader pattern of cognitive impairment.

Generalized Convulsive Status

- If GCSE has only a transient adverse effect on cognition (Adachi, et al., 2005; C. Dodrill & Wilensky, 1990), then cognitive performance should be normal.
- If a GCSE disorder is deleterious to cognitive function (Shorvon, 2002), then cognitive deficits will be documented across the canvassed domains.
- If an increasing number of status episodes is associated with reduced mental abilities (Shorvon, 2002), then a negative relationship with performance on cognitive measures should be present.

6.2 CASE REPORTS: STATUS EPILEPTICUS

6.2.1 ABSENCE STATUS EPILEPTICUS

Absence status (ASE) is a prolonged state of altered consciousness, associated with generalised 3Hz spike-wave EEG activity. No cases of early childhood ASE cases have been reported, and onset of ASE is usually at a time of life when brief absences are diminishing. Isolated brief absences are accompanied by momentary disruptions of cognition, while memory and speech responses are preserved during prolonged ASE (Koutroumanidis, 2005; Thomas, et al., 2006b). Most ASE research agrees that Absence Status seizure-types are not associated with impaired cognition, although several studies have found behavioural disturbance and/or mental illness (Thomas, et al., 2006b).

JILL

Background

Jill was 57 years old, married with two grown children, and a retired public servant. She was diagnosed with IGE and absences when aged 21, and at the age of 52 years, had developed absence status with some episodes being prolonged for 8 to 12 hours.

Previous Investigations

An EEG taken at 56 years of age documented an episode of non-convulsive status, while neuroimaging was normal. (An extract copy of this EEG recording can be seen in Appendix E) Following a review of her medication regime, a subsequent EEG taken at 57 years was normal.

Neuropsychological and Emotional Status

As part of this study, a neuropsychological assessment reported that cognitive functioning fell within the average to above average range. Jill represented a classic case of ASE since her cognitive abilities had not been affected. Her concentration was disrupted, but this was probably due to a long-standing affective disorder. She rated herself on the DASS as anxiety = 98th percentile, and stress = 97th percentile (General Psychological Distress = 96th percentile). She adhered to an AED regime and had no addictive behaviours. She was older than Tom, had many more ASE seizures and years of chronic epilepsy, but her overall cognitive performance was intact.

TOM

Background

Tom was 24 years old, single and with no family history of epilepsy. Episodes of juvenile myoclonic epilepsy and absence spells began at age 15 or 16 years, with frequency of some 4-5 episodes annually. At 19 years of age and against medical advice, he discontinued his AED regime for **three years and increased his alcohol intake “a lot”**. **He was also smoking cannabis “to help with epilepsy”**. **The first absence status seizure** occurred at age 23, and a second at age 24 years.

Previous Investigations

The EEG performed following the first ASE episode documented continuing abnormal activity, with a bi-frontal predominance, typical for IGE. (See Appendix E). An MRI failed to detect any structural abnormalities.

Neuropsychological and Emotional Status

On examination, overall cognitive performance fell within the average to high average range. The only finding of note was a very severe deficit on a dual-task measure of divided attention, still evident 5 months post his most recent episode of absence status. It is also of interest that this deficit was assessed several months *prior* to his first GCSE seizure, which might support the theory that cognitive deficits are neuropsychological markers for underlying neuropathology (rather than the accumulative product of absence SE seizures).

In contrast to **Jill's management of her condition**, Tom did not adapt well. He could not accept the limitations it imposed on his alcohol intake and recreational drugs, nor did he avoid sleep deprivation, a potential trigger for JME. Sporadic adherence to a medication regime did not allow neuroprotection to build up. His status condition worsened several months after participation in this study, when he suffered a prolonged seizure with convulsions. The GCSE seizure lasted approximately 45 minutes before treatment, and was associated with a persistent retrograde amnesia spanning several weeks (Gordon & Devinsky, 2001; Walker, 2007).

6.2.2 COMPLEX PARTIAL STATUS EPILEPTICUS

Complex partial status is accompanied by a disturbance of awareness - an epileptic twilight state caused by prolonged focal epileptic discharges from temporal or extratemporal regions of the brain (Treiman, 2005). The confusion and clouding of consciousness may be accompanied by automatic behaviour (Meierkord & Holtkamp, 2007). Also, CPSE has been found to affect emotional status, memory, and abstract reasoning (Kaplan, 2000, 2002). Findings of behavioural and cognitive impairment in CPSE vary widely, raising the possibility that there may be distinct

CPSE sub-types with frontal or temporal lobe onset (Thomas, et al., 2006a).

NELL

Background

Nell was 31 years old at assessment, with two young children and six weeks pregnant. She had a history of polysubstance abuse for about 8 years. At 21 years of age, she began to use street drugs (cocaine, cannabis) for about four years, then replaced these with heavy ingestion of alcohol for another four years. Complex partial seizures began at 21 years of age. She described stopping all addictive behaviours at 29 years of age when a brief TLE seizure developed into the first CPSE. These took the form of repeated brief seizures without recovery of full consciousness in-between, sometimes continuing to secondary generalization. At least four status episodes had occurred over the eighteen months preceding participation in the current study, together with weekly brief seizures.

Previous Investigations

An MRI disclosed an abnormal area in the tip of the left temporal lobe, largely in the white matter of the brain, with no hippocampal sclerosis. An ictal EEG recorded maximal involvement of the left fronto-temporal regions.

Neuropsychological and Emotional Status

Although diagnosed with left TLE, verbal functions were not found to be affected while non-verbal learning and design fluency were impaired. Her left hemisphere might have been non-dominant and responsible for visual and spatial functions. She was left-handed although it is not known if the sinistrality was familial. Episodic memory was affected to the extent that personal history details were rarely precise, and after 3 sessions, she was still confused about the way to the assessment room.

Nell rated her affect levels on the DASS as being severe to very severe (GPD = 98th percentile), yet gave no outward signs of this. Indeed she happily described plans for her up-coming marriage. She was aware of the worsening of her condition (secondary generalization of seizures) but minimized its potential consequences (such as cognitive deterioration) as shown by her self-ratings on the EFQ.

CARO

Background

Caro was 36 years old, in a de facto relationship, with two children living with their father. There was no family history of epilepsy and, like Nell, Caro was left-handed. She began to use street drugs (heroin, speed, pot, no alcohol) at 22 years of age. At the intake interview, she claimed to have **been “clean” for about** 24 months before participation in the study. She was certain that brief complex partial seizures began before her addiction, about 21 years of age. At 34 years of age, the seizures became more frequent and prolonged for hours (witnessed by hospital staff), sometimes generalizing into tonic-clonic seizures lasting up to five minutes. She was not certain, but thought more than five prolonged episodes had occurred in the past 20 months.

Previous Investigations

An MRI detected no structural abnormalities, but an EEG showed diffuse excess of slowing with right frontotemporal epileptiform discharges suggesting right TLE.

Neuropsychological Status

Cognitive evaluation some five weeks after **Caro’s last episode of SE** found impaired verbal memory, language and category fluency deficits consistent with secondary generalization of seizures which might have

been triggered by the history of drug abuse. She had not been aware how much her memory had deteriorated until asked to do the tasks, and became distressed by her inability to recall during an episodic memory task. She refused to go on to one visual memory test (the MCG-CFT) and did not return for the last session of questionnaires and DASS.

CPSE and addictive behaviours

The two cases reported in this study both had a significant history of polysubstance abuse (Medalia, Merriam, Barnett, & Upton, 1988), but **each claimed to have been “clean” for almost two years before their** participation in this study. The main point to emerge from Caro and **Nell’s** assessments was the similarity between them in spread and severity of cognitive impairment, in spite of the different elapse of time between their latest SE seizure and date when testing began (6 weeks and 3.5 months respectively). This slow recovery indicates their SE condition was already entrenched when assessment sessions began. **Each one’s TLE disorder** had deteriorated to include secondary generalization. Some twelve months after completion of assessment sessions, their medical files recorded several hospital admissions during more SE episodes.

6.2.3 GENERALIZED CONVULSIVE STATUS EPILEPTICUS

LORI

Background

Lori was 30 years old with one daughter and no family history of epilepsy. IGE seizures began at 11 years of age. Her mother reported early prolonged seizures lasting 10 to 15 minutes and post-ictal impaired consciousness lasting 20 minutes. At 27 years of age, the duration of subsequent seizures lengthened after family members returned home to find Lori alone and experiencing a seizure. There was no way of knowing the duration of this episode. At 30 years of age, she had four convulsive

seizures within 30 minutes without recovery consciousness. At the time of study participation, Lori had experienced four episodes of prolonged seizures. She began drinking alcohol socially in her late teens then began regular week-end binges in her early twenties (Gordon & Devinsky, 2001).

Follow-up investigations

During Lori's participation in the study, MRI or CT scans were not possible since she repeatedly failed to keep appointments. At 30 years of age and several months after completion of her study participation, an EEG revealed generalized abnormal activity (see Appendix E). Some twelve months subsequent to testing, her medical chart recorded hospitalizations during further SE episodes with lengthened duration.

Neuropsychological and Emotional Status

Of the five GCSE cases, Lori was the youngest adult with the youngest age at SE onset yet her cognition was the most severely impaired. Severe attention and language deficits had still not resolved when tested some 2.5 to 3 months after the latest SE episode.

During the intake interview and subsequent sessions, Lori gave an overall impression of a care-free enjoyment of life. Her mother was concerned Lori would not take her condition seriously, since she dismissed the need to cut down on alcohol intake or adhere to a medication regime. Such an attitude to her illness might be at least partly responsible for the deterioration in her condition (W.A. Hauser & Lee, 2002; Walker, 2007). Some twelve months subsequent to testing, her medical chart showed further SE episodes with lengthened duration.

RON

Background

Ron was 36 years old, a landscape gardener, married with four children. A male relative had IGE but not SE. At 33 years, the first SE occurred without warning and lasted more than an hour before treatment was possible. His ability to remember events did not return for some three weeks. After the first SE episode, Ron was seizure-free for two years and so discontinued his medication. At 35 years of age, however, a second status seizure occurred. CT and MRI investigations did not detect structural abnormalities while an inter-ictal EEG was normal.

Neuropsychological and Emotional Status

Ron's cognitive assessment (carried out 5 months after the last SE) was normal, with at least average functioning in all domains and no deficits detected. Following each SE, he experienced a period of uncharacteristic fear and anger, sometimes lasting several days. During a **holiday with his wife's parents, he had reacted violently when his father-in-law had attempted to restrain him during recovery from an SE episode.** This had caused a good deal of ill-feeling within the family. His G.P. said that Ron **"has always had a problem with accepting that he has epilepsy" but, with his wife's encouragement, he was adhering to an AED regime at time of testing.**

MENA

Background

Mena was 31 years old with five children and a family history of epilepsy. Tonic-clonic convulsions began at 27 years of age, occurring three-four times annually. At 29 years of age, she experienced the first prolonged episode, triggered by her alcohol withdrawal when she discovered she was pregnant. This consisted of repeated brief seizures

with no recovery of consciousness in-between. Following the first prolonged seizure, Mena eliminated alcohol and kept to her medication regime.

Previous investigations

At 31 years of age, an MRI was normal and two EEGs (at 28 and 31 years) both found a right frontotemporal abnormal brain activity (see Appendix E).

Neuropsychological and Emotional Status

Consistent with the EEG findings, the cognitive assessment revealed mildly impaired visual learning and visual retrieval. A severe deficit in letter fluency was present when tested ten days after the latest SE, and had faded to an average level of performance when re-tested with a parallel form some four weeks later.

When her participation in the study commenced, Mena had just been through a court hearing to recover her children. She had lost them to the Child Safety Unit after a neighbour reported Mena as an irresponsible mother who did not supervise her children during a prolonged SE seizure. In spite of these very recent experiences, she rated herself on the DASS with a general psychological distress at the 61st percentile, which is within normal limits.

KEN

Background

Ken was 50 years old, single and a retired office worker, with no family history of epilepsy. He did not have epilepsy previous to his first SE episode, which lasted about 45 minutes before treatment. Testing took place a month later. All investigations (MRI, CT, and EEG) failed to find

any abnormalities, and he was diagnosed by his neurologist as having IGE with status.

Neuropsychological and Emotional Status

Overall, Ken's cognitive profile was normal. His Verbal I.Q. was above average and his memory was unimpaired. The one exception was in the Attention domain: moderately impaired selective Attention during a time-based test, reduced vigilance, and very mildly impaired category switching. These are dysfunctions associated with the mediofrontal lobe. His DASS rating for General Psychological Distress was at the 66th percentile which is within normal limits.

LANA

Background

Lana was 47 years of age, unemployed with four adult children. In early adolescence, infrequent IGE seizures followed a car accident even though she had not sustained a head injury. At 38 years, living in a remote town, she had several hours of repeated brief convulsions before admittance to a hospital in coma. Memory returned slowly over more than a year. Seizures increased in frequency after that, but SE did not recur until nine years later. At 47 years of age, at the time of study participation, her EEG was normal.

Neuropsychological and Emotional Status

She began participation in the study some five weeks after the second SE seizure, and was diagnosed with leukaemia shortly thereafter. Cognitive evaluation found slowed speed of attention responses and reduced ability to maintain vigilance. In spite of her recent diagnosis of leukaemia, her DASS self-ratings revealed a general psychological distress at the 42nd percentile, which is within normal limits. In the six months

after testing sessions were completed, her condition deteriorated with more frequent seizures and accompanying fatigue.

Compared to the other GCSE cases, Ken and Lana had normal cognitive abilities overall, but like the other SE cases, they had attention difficulties. Indeed, attention dysfunctions (ranging from reduced scores to severe impairment) were found in eight of the nine SE cases.

GCSE – lifestyle, medication and neuroprotection

Adherence to a medication regime is especially important for people with SE seizures since the failure to terminate an SE seizure promptly is known to increase the likelihood of a chronic epilepsy disorder and/or more prolonged seizures (W.A. Hauser & Lee, 2002; Sutula & Pitkanen, 2002). Lana, Ron and Mena all had further SE episodes after discontinuing their medication, but they subsequently developed more healthy neuroprotective behaviours (Simon, Henshall, Stoehr, & Meller, 2007; Walker, 2007). During the 12 months after completion of testing, the records show no further hospital admissions for Ron and one for Mena.

6.2.4 SUMMARY OF DISORDER CHARACTERISTICS

Table 6.1 summarizes each participant's disorder characteristics, details about the occurrence of SE episodes, and course of the SE illness. Three NCSE cases (Tom, Nell and Caro) had subsequent generalization of **seizures to convulsive status. Participants' demographic details and** investigative results can be found in Table 3.1.

Table 6.1
Disorder characteristics in nine SE cases.

SE and epilepsy disorder	Jill	Tom	Nell	Caro	Ken	Lana	Ron	Mena	Lori
	IGE	JME	TLE-L	TLE-R	IGE	IGE	IGE	IGE	IGE
Features									
Age at onset	21	16	21	21	50	22	30	27	11
Years epilepsy	36	8	10	15	<1	25	3	4	19
Age onset of SE	40s	22	29	34	50	37	33	29	26
Handedness	right	right	left	left	right	right	right	right	right
Occurrence SE									
SE seizure-type	ASE	ASE	CPSE ²	CPSE ²	GCSE	GCSE	GCSE	GCSE	GCSE
Etiology ¹	cryp	cryp	cryp	cryp	cryp	cryp	cryp	cryp	cryp
Initial trigger ²		a+c	b	b		d	c	a+c	c
EEG records	NAD	ABN	ABN	ABN	NAD	NAD	NAD	NAD	ABN
Course of SE illness									
No. years with SE ³	15	2	2	2	<1	8-9	3	2	4
No. SE seizures ⁴	many	2	4+	many	1	2	3	3	4
Changes ⁵	N	Y	Y	Y	N	Y	N	N	Y
Duration of SE ⁶	1-2 days	1-2 days	3-4 hrs Repeat	3-4 hrs Repeat	40 mins	40 mins	45 mins	30-45 mins	Dnk Repeat

Note: NAD = no abnormality detected. ABN = abnormal activity.

1 = cryp = cryptogenic; idio = idiopathic; symp = symptomatic

2 = a = alcohol; b = drug addiction; c = non-compliance; d = co-morbid with medical condition.

3 = Indicates whether evolution of condition was slow or relatively rapid.

4 = Indicates frequency of SE episodes in that time period.

5 = Denotes any deterioration in seizure-type or frequency/ duration of SE.

6 = Duration was 30-60 minutes. Most participants did not know (dnk) precise duration.

6.3 RESULTS

The section details the neuropsychological performance of the SE participants.

- **Figures 6.1 to 6.6 outline the participants' performance in each cognitive domain.**
- Table 6.2 summarizes the severity and spread of cognitive deficits in each of the seven cases. These deficits were then selected for further comparisons of single cases with the IGE comparison group, **using IGE "norms" (as set out in Table 3.5, Chapter 3).**
- Table 6.3 reports results of comparison between pre-morbid intelligence (based on WTAR-demographic predictions) and current estimated I.Q., Verbal I.Q. and Performance I.Q.
- Table 6.4 sets out a correlation matrix for significant associations between cognitive tasks and number of GCSE seizures, age of epilepsy onset, and years of education.

Analysis of raw data was in two steps, using the single case methodology outlined by Crawford (Crawford & Garthwaite, 2007; Crawford, et al., 2009).

- **First, each of the SE participants' raw scores was compared to the IGE comparison group, and notably, elapsed times between previous SE episodes and date of testing.** Significant results are summarized in Table 6.5.
- Second, results from dissociations analyses for single SE cases compared to the IGE comparison group are shown in Table 6.6. Standardized scores on two TEA component tasks of the Sustained

Attention factor (Phone Search while Counting, and Lottery) are compared.

6.3.1 COGNITIVE DOMAINS

Figure 6.1 shows the current estimated I.Q. of nine SE individuals with prolonged seizure-types. Their I.Q. scores have a narrow range, suggesting homogeneity of intelligence irrespective of seizure-type. The highest current estimated I.Q. was for the two ASE participants (Jill and Tom), followed closely by two GCSE cases (Ken and Lana) with only 1 or 2 GCSE episodes. The two lowest I.Q. scores were associated with GCSE (Lori with 4 status seizures and alcohol abuse), and CPSE with secondarily generalized seizures (Nell with 4 or more status seizures and polysubstance abuse). See Table 6.3 for significant decline from pre-morbid I.Q. in four cases.

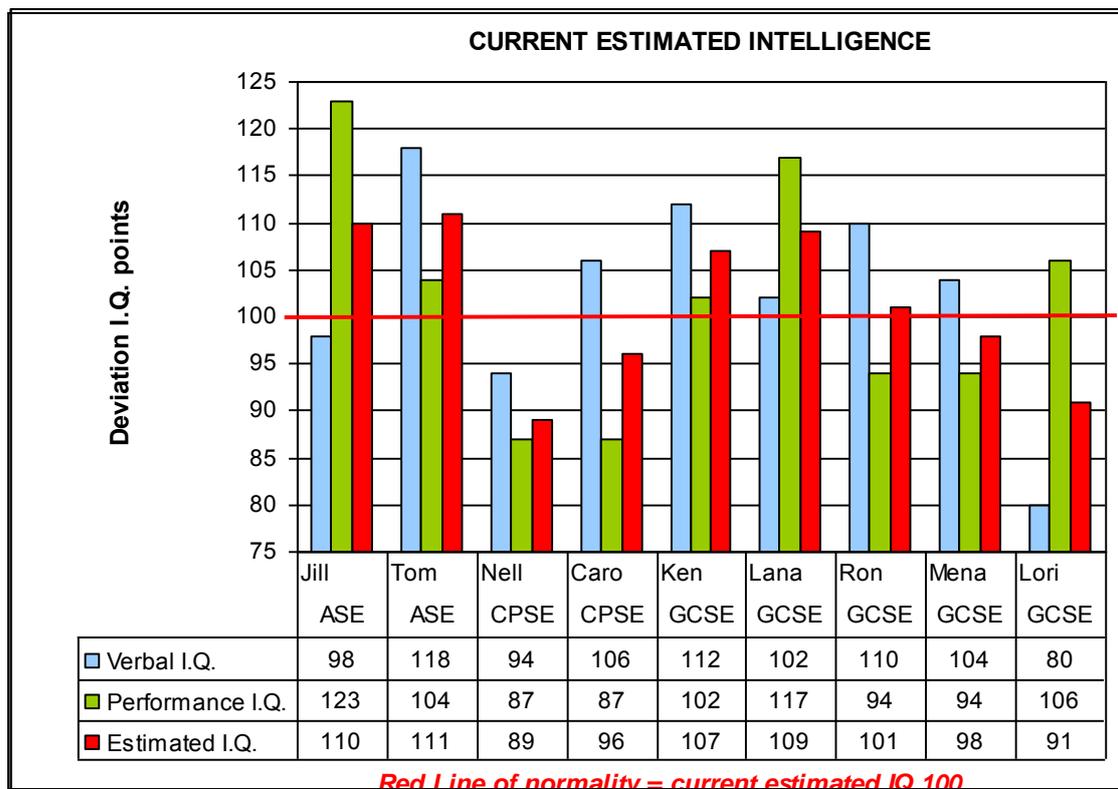


Figure 6.1 Individual performances in current estimated intelligence for the SE participants.
Note: Red Line of normality = current estimated IQ 100
Figure 6.1 Individual performances in current estimated intelligence for the SE participants.

Most of the component tasks used to measure the intellectual abilities listed in Figure 6.2 come from the WAIS-III but other tasks with strong validity are also included (BNT, JLO, Spatial Span from the WMS-III, and Map Search from the TEA). **Each participant's Intellect domain is** quantified by the z-score mean for 10 tasks. The participants cannot be claimed to differ in their intellectual abilities. A pattern consistent with that shown in Figure 6.1 was present: Jill, Tom (ASE) and Lana (GCSE) have the highest intellectual ability; while Nell, Caro (CPSE) and Lori (GCSE) have the lowest.

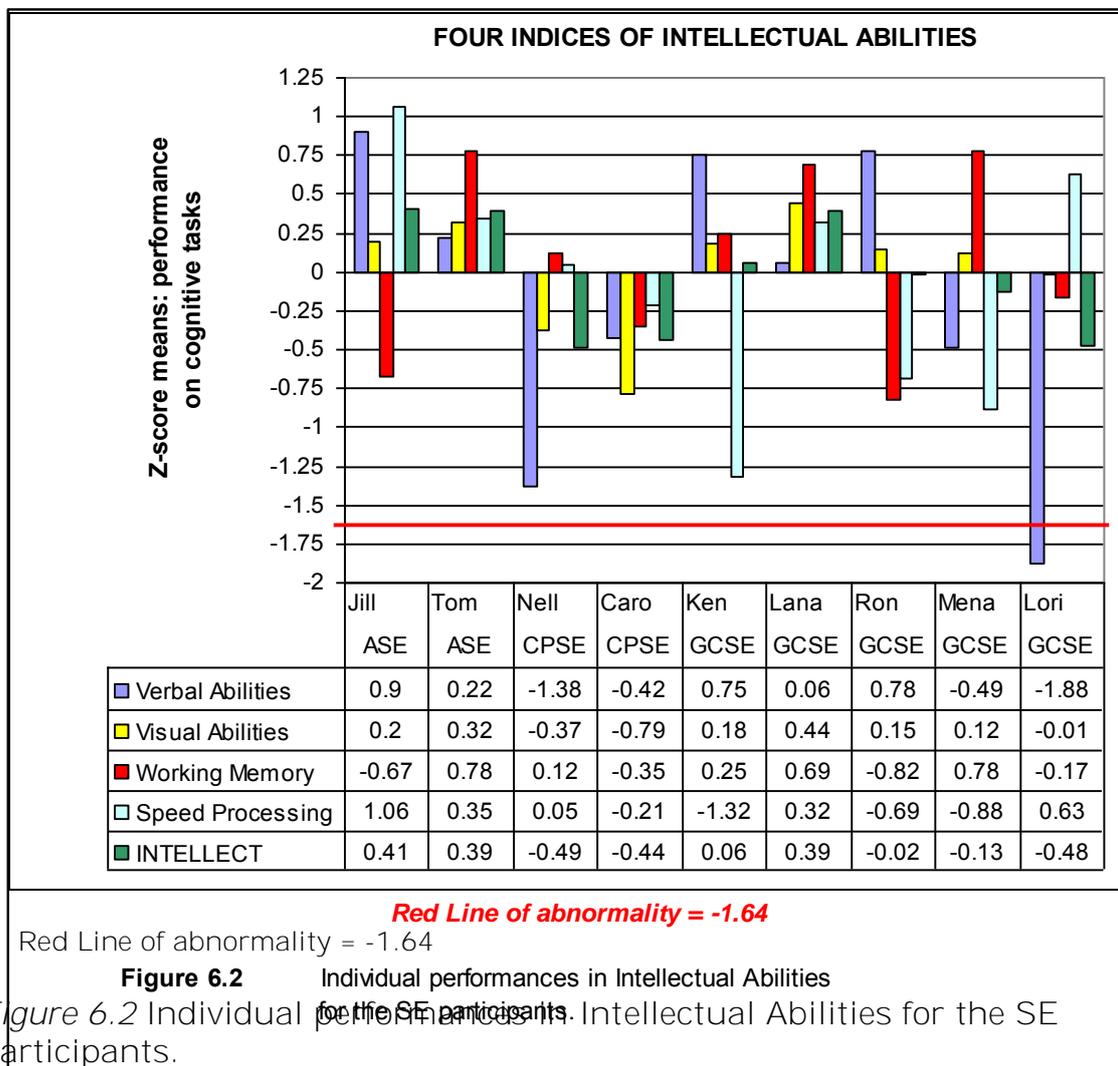
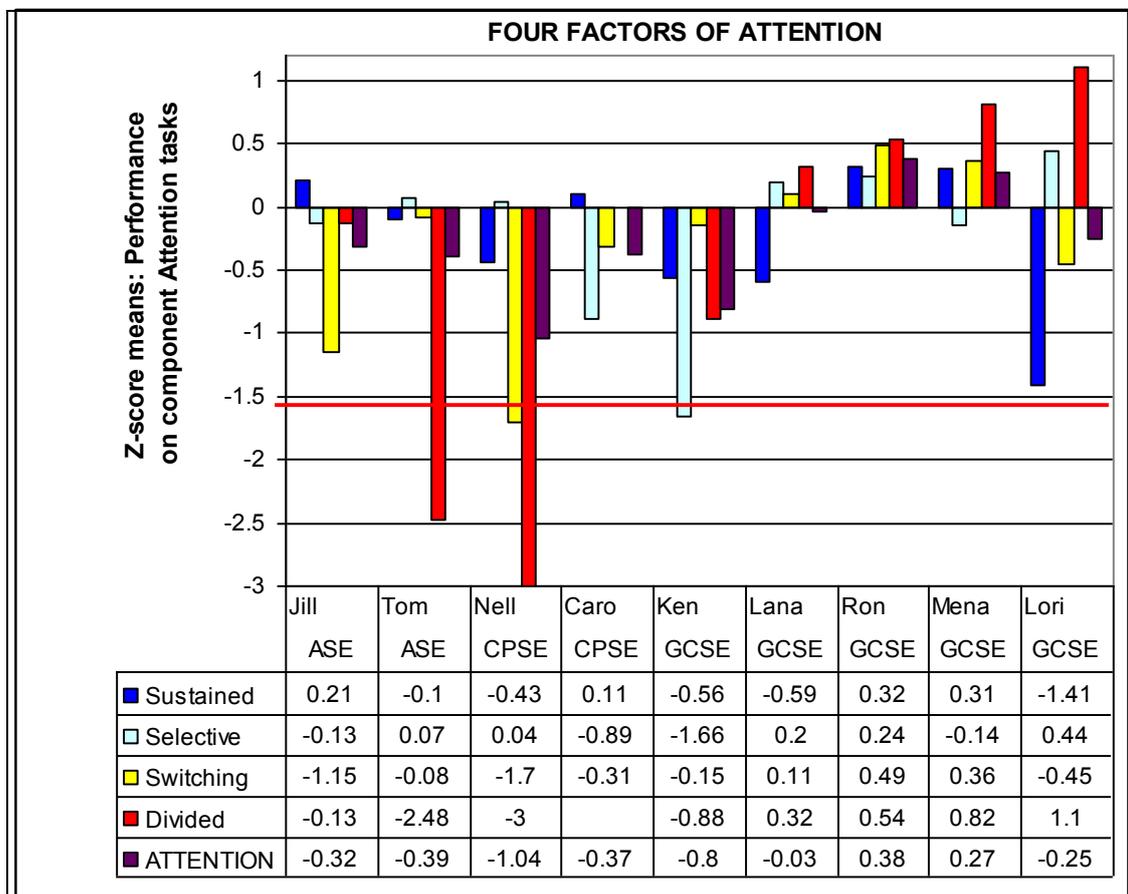


Figure 6.3 depicts **participants' performance in four factors of Attention**, with three of the factors consisting of several component tasks each (see Chapter 3, section 3.2.1). Bate, Mathias and Crawford (2001) **found that the TEA's *Phone Search while Counting* dual-task does not fit with any of the three factors, and suggested the possibility of an attention factor in its own right i.e. Divided Attention.** The task elicited poor performance in the NCSE people (Jill, Tom, Nell, Caro) but the data-table in Figure 6.3 shows that the GCSE people, showing impaired performance on the dual-task, all gave reduced or impaired scores on the *Lottery* (vigilance) task compared to their overall TEA performance.



Red Line of abnormality = -1.64

Figure 6.3 Individual performances in the Attention domain for the SE participants.

Figure 6.3 Individual performances in Attention for the SE participants.

Figure 6.4 depicts an average level of performance for executive function measures of Visual Fluency and abstract Concept Formation. In contrast, three GCSE people (Ken, Mena, Lori) had reduced means for the component tasks of the Verbal Fluency function. Tasks involving control of attention responses also elicited reduced performances. As in Figure 6.3 (attention factors), the scores for the actual component tasks might be more informative (see Table 6.2).

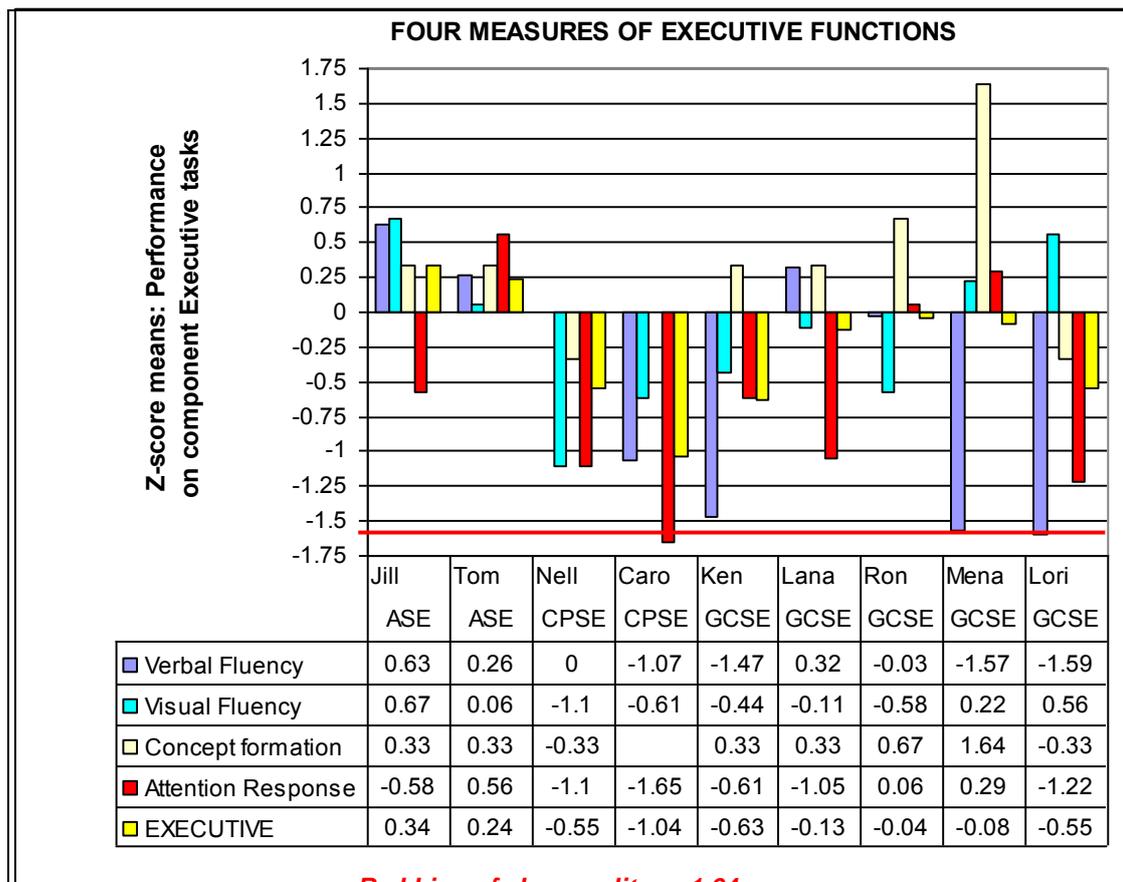


Figure 6.4 Individual performances in Executive Functions
Red Line of abnormality = -1.64 for the SE participants.

Figure 6.4 Individual performances in Executive Functions for the SE participants.

Reference to Figure 6.5 shows that, except for Caro, neither the NCSE nor the GCSE people had a dysfunctional Verbal Memory domain. In contrast, all **Caro's** verbal memory scores (except for Logical Memory) were impaired. She did not have any of the predicted visual memory deficits which might be expected with her type of TLE (right onset with secondary generalization of seizures). Her sinistrality might account for the verbal episodic memory deficits if these functions resided in her right hemisphere.

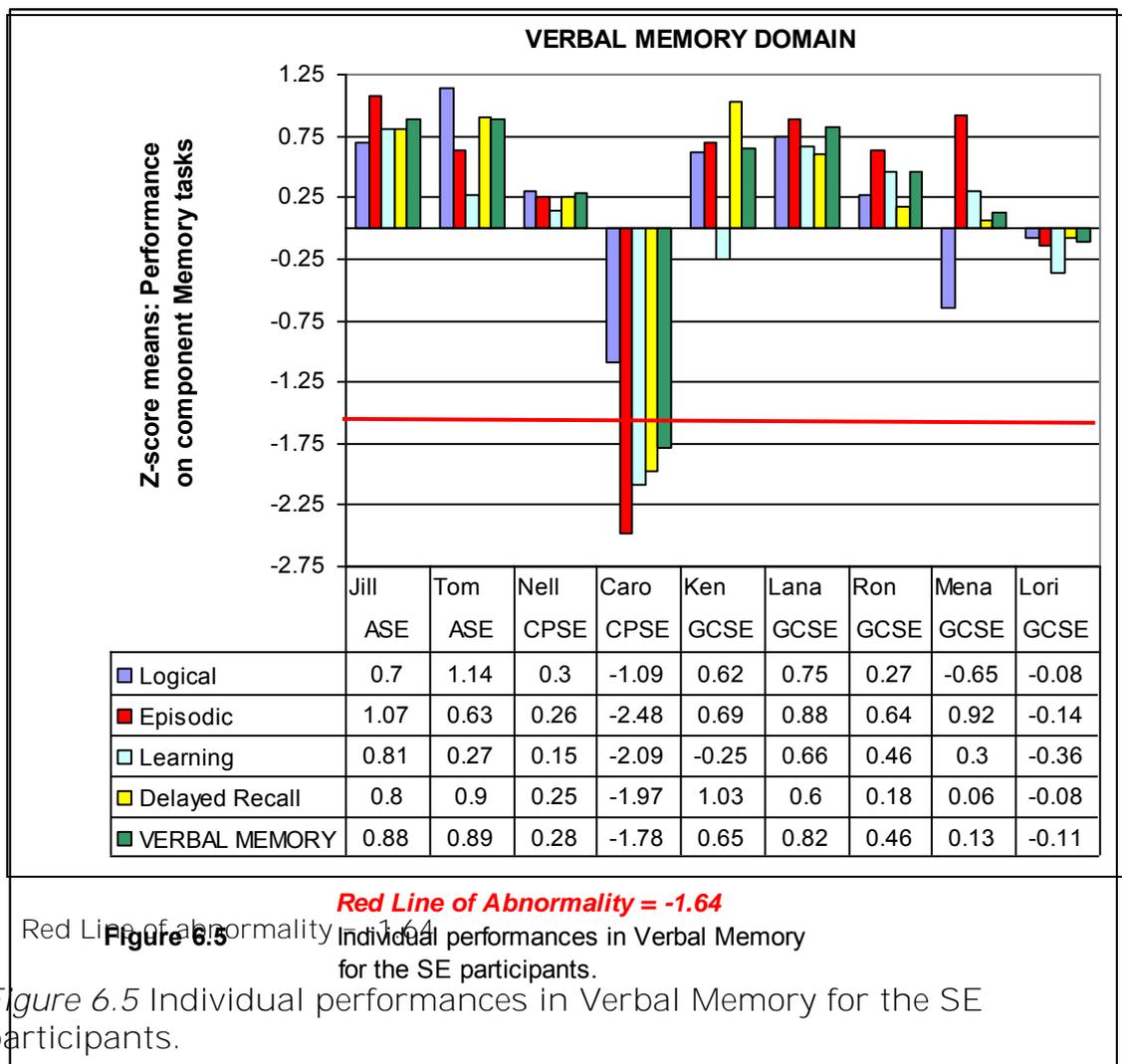
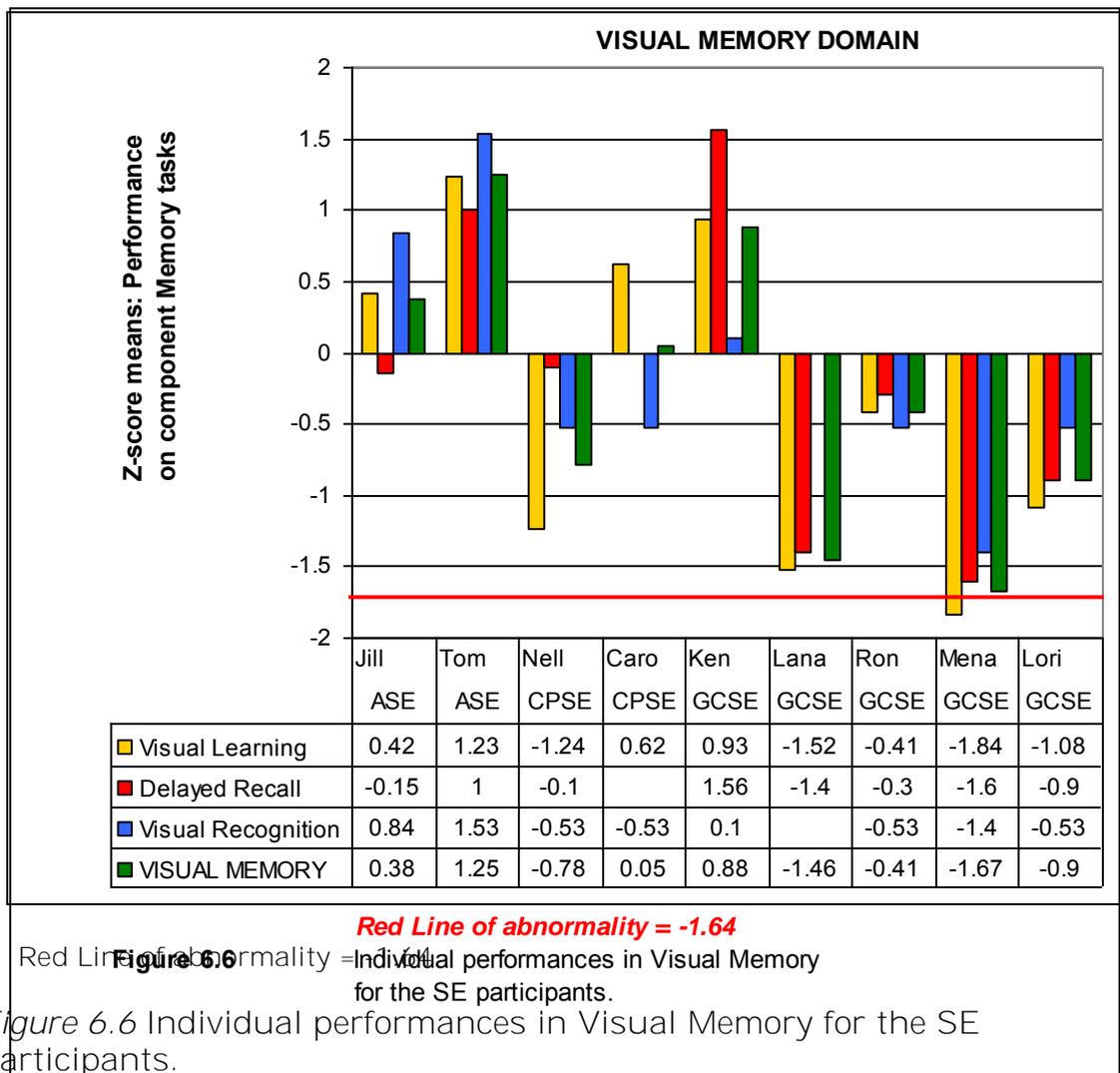


Figure 6.6 depicts the SE participants' performance in measures of the Visual Memory domain. It should be noted that Caro completed only the CVMT but not the MCG-CFT. Although the nature of Nell's TLE disorder (left onset of seizures with secondary generalization) would predict deficits of verbal memory, her found deficits involved the visual memory domain. Nell is left-handed, so possibly her left hemisphere was non-dominant i.e. visual memory functions rather than verbal functions.



6.3.2 SUMMARY OF INDIVIDUAL DEFICITS

Table 6.2 shows cognitive impairment in the SE participants. The two CPSE individuals (both with a history of polysubstance abuse) were the most affected by prolonged seizures (domains of attention, executive functions, language and memory). **Lori's (GCSE) affected domains were attention, executive functions, and language (naming) but not memory.**

In this study, cognitive performance was most probably affected by the number of SE seizures experienced by a participant, and the time elapsed between the most recent SE episode and date of testing. Since attention was the domain most often affected, the time elapsed between the last SE episode and date of testing attention tasks is included in Table 6.2. The times elapsed between the most recent SE episode and date of testing for Verbal Fluency and Memory are in Table 6.5.

Table 6.2
Severity and spread of cognitive deficits for the SE participants.

Cognitive Domains	Jill ASE	Tom ASE	Nell CPSE Left	Caro CPSE Right	Ken GC SE	Lana GC SE	Ron GC SE	Mena GC SE	Lori GC SE	% Case
Attention										77.7
Response Inhibit				-2.29					-2.29	
Response Switch						-1.94				
Selective Switching	-1.76		-1.70	-1.83	-2.36				-1.65	
Divided Attention		-2.48	-3.10	-2.93						
Vigilance					<i>R</i>	<i>R</i>		<i>R</i>	-2.67	
Executives										55.5
Letter Fluency								2.50		
Category Fluency				-1.87				-1.87	-2.53	
Category Switch					-1.97				-1.65	
Design Fluency			-1.64							
Language										33.3
Naming			-2.00	-2.00					-3.00	
Memory										33.3
Episodic Learning				-2.96						
Episodic Recall				-2.57						
Visual Learning			-1.89					-2.00		
Visual Retrieval								-1.65		
Spread over four domains	1	1	4	4	2	1	0	2	3	
Time elapsed¹	2.5 m	5 m	3.5 m	6 w	5 w	2 m	5 m	2 w	3 m	
No. SE seizures	many	2	4+	many	1	2	3	3	4	

Note:

1= Time elapsed between last SE episode and date of testing the various Attention tasks.
R = Reduced scores. Individual's performance on Lottery (vigilance) is significantly lower than his/her overall mean for 7 TEA sub-tests' scales.

Levels of impairment (z-scores in **bold**)

Borderline -1.51; very mild impairment -1.64; mild impairment -1.96;
 moderate -2.33; severe -3.09; very severe -3.29.

The primary finding to emerge from Table 6.2 was that Attention is the most affected domain associated with SE, with 77.7% of SE cases having some attentional impairment. Divided Attention (TEA dual-task *Phone Search while Counting*) and Vigilance (TEA *Lottery*) were performed at a reduced or impaired level in seven of the nine participants.

Table 6.3 sets out results from four cases (Nell, Caro, Ron, Lori) with significantly lowered current intelligence scores compared to their pre-morbid I.Q. scores (predicted scores based on WTAR-demographic norms. Three cases (Nell, Caro, Ron) maintained their Verbal I.Q. but Lori (an indigenous person) maintained her average Performance I.Q. while showing a decline in both Verbal I.Q. and current estimated I.Q. As noted in Figure 6.1, the two cases with ASE (the SE condition assumed to have the most benign impact) also had higher estimated I.Q. scores than other SE participants.

Also of interest, Ron had no specific cognitive deficits, but Table 6.3 indicates he did have a generalized lowering of intellectual functions (i.e. estimated I.Q. and Performance I.Q.) after three prolonged seizure episodes, including one episode of 45 minutes approximately, when treatment was delayed.

Table 6.3
Comparisons of pre-morbid and current intelligence for the SE participants.

Case Name	I.Q.	V.I.Q.	P.I.Q.
Name NELL (left CPSE)			
Current estimated I.Q.	89	94	87
WTAR-demographic predicted I.Q. ²	95	94	97
Current versus predicted I.Q. discrepancy	-6	0	-10
Significantly <i>lowered</i> intelligence (p < .05)?	No	No	Yes
PIQ = 10 – 24% cumulative percentage			
Name CARO (right CPSE)			
Current estimated I.Q.	96	106	87
WTAR-demographic predicted I.Q. ²	105	104	105
Current versus predicted I.Q. discrepancy	-9	+2	-18
Significantly <i>lowered</i> intelligence (p < .05)?	Yes	No	Yes
I.Q. = 10 – 24% cumulative percentage			
PIQ = 2 - 4% cumulative percentage			
Name RON (GCSE)			
Current estimated I.Q.	101	110	94
WTAR-demographic predicted I.Q. ²	108	109	105
Current versus predicted I.Q. discrepancy	-7	+1	-9
Significantly <i>lowered</i> intelligence (p < .05)?	Yes	No	Yes
I.Q. = 25 – 40% cumulative percentage			
PIQ = 10 – 24% cumulative percentage			
Name LORI (GCSE) ¹			
Current estimated I.Q.	91	80	106
WTAR-demographic predicted I.Q. ²	86	88	86
Current versus predicted I.Q. discrepancy	+5	-8	+20
Significantly <i>lowered</i> intelligence (p < .05)?	No	Yes	No
VIQ = 25 – 49% cumulative percentage			

Note:

1 = Lori's WTAR-demographic predictions were based on Afro-American norms

2 = Prediction interval for WTAR-demographic predicted I.Q. is 95%.

Some participants had significantly *higher* current intelligence scores than their predicted I.Q. (based on the WTAR-demographics scales) as follows:

Tom had higher current estimated I.Q and V.I.Q.

Jill had higher current estimated I.Q. and P.I.Q.

Lana had higher current estimated I.Q., V.I.Q. and P.I.Q.

Lori had higher P.I.Q.

6.3.3 SE CHRONICITY

A correlational analysis was undertaken between number of prolonged GCSE episodes (n=4), age at epilepsy onset, years of education, and cognitive performance. Table 6.4 sets out the results.

The number of GCSE seizures had an adverse impact on the **participants' scores for delayed verbal recall (combined semantic and episodic memory)** and were also associated with an adverse impact on the current estimated I.Q.

The age of onset of the epilepsy disorder and number of years of education were also significantly correlated with number of prolonged SE seizures. The number of SE seizures was higher when epilepsy onset was at a younger age, while they were also negatively associated with the number of years of formal education.

Table 6.4
Chronicity correlations for the GCSE participants.

Variables	No. of GCSE seizures	Age at onset	Years at school	Verbal Recall ¹	Episodic Recall ²
Age at Onset	-0.952 p=.013				
Years of Education	-0.907 p=.034	0.975 p=.005			
Verbal Recall	-0.979 p=.004	0.907 p=.033	0.821 p=.088		
Episodic Recall	-0.852 p=.066	0.964 p=.008	0.967 p=.007	0.794 p=.109	
Current I.Q.	-0.898 p=.038	0.862 p=.060	0.816 p=.092	0.856 p=.064	0.709 p=.180

Note:

Each cell contains a Pearson correlation co-efficient.
Significance level p (2-tail) < .05 (**in bold**).

1 = Verbal delayed recall (WMS-III narrative + AVLT word lists).

2 = Verbal episodic delayed recall (AVLT word-lists).

6.3.4 SINGLE SE CASES COMPARED WITH IGE GROUP

The SingleBayes_ES.exe computer program (Crawford & Garthwaite, 2002, 2007; Crawford, Garthwaite, & Porter, 2010; Crawford & Howell, 1998) compares individual task scores with those of an IGE comparison group. Table 6.5 sets out the results. These include 2-tail values for a credible difference between the SE participant and the IGE control group, together with effect size. Explanatory notes are included.

Table 6.5
Single SE cases (convulsive CPSE and GCSE) (n=7) compared to IGE group (brief convulsive) (n=8).

Sub-Domain and Case	<u>Significance Comparison</u>	<u>¹Effect Size Esimated Z-CC</u>	<u>²Abnormality Percentage</u>	<u>³Time Elapsed</u>
	t-test (df) p	Point (95% CI)	Point Estimate	mth/wk
Naming				
Nell (left-CPSE)	-4.297 (7) .003	-4.558 (-6.98 to -2.12)	0.179%	3.0 mth
Lori (GCSE)	-6.110 (7) .000	-6.481 (-9.86 to -3.10)	0.02%	2.5 mth
Design Fluency				
Nell (left-CPSE)	-2.455 (7) .043	-2.604 (-4.09 to -1.09)	2.188%	3.0 mth
Category Fluency				
Lori (GCSE)	-2.564 (7) .037	-2.719 (-4.26 to -1.15)	1.87%	2.0 mth
Letter Fluency				
Mena (GCSE)	-2.734 (7) .029	-2.900 (-4.52 to -1.25)	1.458%	10 days
Selective Attention				
Caro (right-CPSE)	-5.528 (7) .000	-5.864 (-8.93 to -2.79)	0.044%	6 wks
Ken (GCSE)	-4.564 (7) .002	-4.841 (-7.41 to -2.27)	0.130%	5 wks
Switch Attention				
Nell (left-CPSE)	-3.958 (7) .005	-4.198 (-6.45 to -1.94)	0.274%	3.5 mth
Inhibit Response				
Caro (right-CPSE)	-3.208 (7) .015	-3.402 (-5.26 to -1.52)	0.745%	3 wks
Lori (GCSE)	-3.208 (7) .015	-3.402 (-5.26 to -1.52)	0.745%	2 mth
Switch Response				
Lana (GCSE)	-2.676 (7) .032	-2.839 (-4.43 to -1.21)	1.586%	1 mth

Sub-Domain and Case	Significance Comparison	¹ Effect Size Estimated Z-CC	² Abnormality Percentage	³ Time Elapsed
	t-test (df) p	Point (95% CI)	Point Estimate	month/wk
Visual Learning				
Nell (left-CPSE)	-3.416 (7) .011	-3.623 (-5.59 to -1.64)	0.560%	3.5 mth
Mena (GCSE)	-3.004 (7) .020	-3.186 (-4.94 to -1.40)	0.99%	12 days
Visual Recall				
Mena (GCSE)	-3.493 (7) .010	-3.705 (-5.71 to -1.68)	0.504%	12 days
Episodic Learning				
Caro (right-CPSE)	-3.899 (7) .006	-4.136 (-6.35 to -1.90)	0.295%	5 wks
Episodic Recall				
Caro (right-CPSE)	-3.457 (7) .010	-3.667 (-5.66 to -1.66)	0.529%	5 wks

Note: $p < .05$ (2-tail). Raw score data.

1= Effect Size (Z-CC) of estimated standardized scores – difference between SE case and IGE comparison group (plus 95% confidence interval).

2= Abnormality Percentage = abnormality of a person's score, quantified as estimated percentage of the IGE group falling below the SE case's score.

3= Time Elapsed = time elapsed between latest SE episode and date of testing.

Deficits and elapsed time: Transience or slowed recovery

Conclusions can be drawn about cognitive functions' transience or slowed recovery from the information about estimated elapsed time (between most recent SE episode and date of testing) in Table 6.5.

Ken, Lana, **and Mena's deficits** seem to have resolved rapidly over **time. For example, Mena's letter fluency was severely impaired at 10 days** but not when re-tested after six weeks. Ron, who began testing 3.5 months after his latest SE episode, performed competently on all tasks. He did report memory difficulties for a month after the episode, and Table 6.3 shows his current I.Q. was lower than pre-morbid I.Q.

Yet Table 6.5 also shows that Lori still had widespread impairment even though she began testing two months post-seizure, so in her case passage of time was slower in aiding recovery of attention, language, memory and executive functions.

6.3.5 DISSOCIATION OF ATTENTION COMPONENTS

Both *Lottery* and *Phone Search while Counting* are component tasks of the Sustained Attention factor (Bate, et al., 2001; but see Robertson, et al., 1996). They measure different aspects of sustained attention: parallel processing of simultaneously presented auditory and visual stimuli (dual-task of Divided Attention) versus sequential processing of a string of auditory stimuli (maintained Vigilance for a specific sound) (Bate, et al., 2001). Table 6.6 sets out results for (1) a comparison of a single performance on *Lottery* and *Phone Search while Counting* tasks; (2) effect size of such discrepancy compared to IGE group; and (3) how abnormal **each SE individual's difference in tasks' performances** might be. The DissocsBayes_ES.exe computer program (Crawford, 2007; Crawford & Garthwaite, 2005, 2006a, 2006b; Crawford, et al., 2010) was used.

Table 6.6

Sustained Attention component tasks: dissociation between Lottery and Phone Search while Counting in single SE cases compared to IGE controls.

Case	Disorder	Frequentist	Effect Size ²	Abnormality ³
		<u>Comparison</u> ¹	<u>Estimated Z-DCC</u>	<u>Percentage</u>
		RSDT (df) <i>p</i>	Point (95% CI)	Point Estimate
Nell	(left-CPSE)	2.410 (7) .047	-2.694 (-4.74 to -1.04)	2.126%
Caro	(right-CPSE)	6.704 (7) .000	-7.735 (-2.00 to -3.47)	0.015%
Tom	(ASE)	2.443 (7) .044	-2.731 (-4.52 to -1.18)	1.675%
Lori	(GCSE)	3.077 (7) .018	3.450 (1.534 to 5.76)	0.688%

Note: $p < .05$ (2-tail). Raw score data.

- 1 = Revised Standardized Difference Test (RSDT) on the difference between each case's standardized scores on the two tasks.
- 2 = Effect Size = estimated standardized scores - difference between SE case and IGE comparison group (Z-DCC) (plus 95% Bayesian credible interval).
- 3 = Abnormality percentage is a Bayesian point estimate. Percentage of the IGE comparison group which exhibited a more extreme discrepancy in same direction as the SE case.

Two points of interest emerged from the findings summarized in Table 6.6.

1. Course of SE condition.

The four cases (Nell, Caro, Tom and Lori) listed in Table 6.6 all experienced a deteriorating course of illness such as secondary generalization of seizures, and/or more frequent prolonged seizures of longer duration. In addition, Tables 6.2 and 6.5 indicate enduring cognitive deficits some months after their latest SE episode. Those cases with a slower evolving condition with few changes did not show a classical dissociation between *Lottery* (vigilance) and *Phone Search while Counting* (divided attention). It is of interest for further research that impaired performance on either of these two tasks might be cognitive markers for a deteriorating SE condition.

2. Secondary convulsive SE versus generalized convulsive SE.

All three cases with SE and secondarily generalized seizures had moderate to severe deficits of divided attention. Those cases with GCSE had moderately severe deficits (Lori) or reduced scores (Ken, Lana, Mena) for vigilance. It is of interest for further research that different kinds of convulsive SE seizures might be associated with dysfunction in different factors of Sustained Attention (Bate, et al., 2001; but see Robertson, et al., 1996) although some debate exists over whether the dual-task might be a separate factor (of the Attention domain) in its own right.

6.3.6 SUMMARY OF MAIN FINDINGS

Section 6.1.3 listed specific predictions for the SE seizure-types.

- Absence Status

One case (Jill) with many years of ASE did not have notable impairments, while the second case (Tom) had moderately impaired **Divided Attention**. The latter would accord with the “**poorly sustained attention**” reported by early researchers (Andermann & Robb, 1972; Guberman, et al., 1986).

- Complex Partial Status

Both these cases were significantly impaired in language and memory as might be expected, but no clear lateralization of memory deficits was found. One CPSE case with right TLE (Caro) had severely impaired verbal episodic memory. The case with left TLE (Nell) continued to have significant memory deficits when tested 3.5 months after an SE episode. Nell and Caro also had secondarily generalized convulsions which are known to be associated with severe cognitive deficits.

- Generalized Convulsive Status

Only one case (Lori) fulfilled the prediction that GCSE is deleterious to cognitive functioning, with longer-lasting and more widespread cognitive impairment compared to the other four GCSE participants. The other four cases had transient cognitive dysfunctions.

- GCSE Chronicity and Pre-Morbid I.Q.

The prediction that the five GCSE participants would have a global reduction of memory and intellectual abilities (Shorvon, 2002) was confirmed by negative correlations found between number of prolonged GCSE episodes and Verbal Recall (combined verbal episodic and semantic recall tasks), as well as current estimated I.Q. (See Tables 6.3 and 6.4).

6.4 DISCUSSION

The fundamental question addressed in this chapter was whether SE is simply a more severe version of brief seizures. The aim was to investigate whether, for these participants, cognition would be more **adversely affected than observed with brief seizures**. The study's findings indicate that SE is more than a prolonged version of brief seizures, at least where the **participants' cognitive outcome is concerned**.

The results would indicate that, in these participants, not all SE seizure-types had an adverse effect on cognitive functioning. While convulsive SE seizures were associated with cognitive dysfunction, the impairment was transient in most people. In contrast, for those participants whose cognitive deficits were slow to resolve, there is the possibility that Divided Attention and Vigilance acted as neurocognitive markers for underlying neuropathology since they all four experienced deterioration of their SE condition. Interestingly, the nature of cognitive dysfunction did not differ widely across the SE seizure-types, the attention domain being impaired in most SE participants.

6.4.1 PROLONGED VERSUS BRIEF SEIZURES

The first prediction in section 6.1.3 was that SE participants would have greater severity of cognitive impairments than people with brief seizures. Comparison of single SE cases with the IGE comparison group (see Table 6.5) can be summarized as follows.

- There were significantly higher levels of impairment in the CPSE cases compared to the IGE comparison group across measures of attention, naming, memory and executive fluency. The CPSE individuals and TLE group did not differ on memory tasks.

- There were significantly higher levels of impairment in the GCSE individuals compared to the IGE comparison group in the spheres of attention control, executive verbal fluency, and visual memory.

Not only were cognitive deficits at a greater level of severity than those of the IGE comparison group, but they were also more widespread across cognitive domains. As summarized in Table 4.2, the majority of the IGE people (except for 2 cases with multiple seizure-types) had no impairments in attention control or sustained attention. In sharp contrast, eight of the nine SE people had impaired or reduced functioning in attention tasks. Not all, but some SE and IGE cases shared impaired verbal fluency, language and memory problems. For details of individual deficits, see Summary Tables 4.2 (IGE), 5.2 (TLE) and 6.2 (SE).

6.4.2 SE-TYPES: SIMILARITIES AND DISSOCIATIONS

The second prediction was that different cognitive domains would be adversely affected across the ASE, CPSE and GCSE seizure-types.

Similarities across SE seizure-types

As argued in Section 6.1.2, similar cognitive profiles across different seizure-types would suggest that abnormal brain activity and underlying neuropathology *preceded* the status seizures (Helmstaedter, 2007; Hilkens & de Weerd, 1995). In this study, the pattern of sub-domain impairment did not differ across the ASE, CPSE and GCSE participants. All eight participants were similar insofar as they shared impaired or reduced scores in Sustained Attention, and in other Attention factors. In addition, five of nine participants were dysfunctional or moderately impaired in verbal/design fluency.

If cognitive impairment forms part of the aetiology of status epilepticus as argued by some researchers (rather than being a consequence of prolonged seizures) then the cognitive deficits could be markers for an underlying neuropathology (Helmstaedter, 2007). In this study, available imaging scans failed to detect structural abnormalities in any of the participants. Further, only four cases (Nell, Caro, Tom and Lori) had abnormal EEG records. It could be argued that the attention deficits found **in most of this study's SE participants were markers for an underlying brain abnormality *not necessarily discernible*** through imaging investigations. The hypothetical neuropathology might have been aggravated in the four cases (Nell, Caro, Tom and Lori) by their lifestyle, history of drug/alcohol abuse, and/or non-adherence to a medication regime. As the neuropathology worsened, so did their attention deficits.

Dissociations between component tasks

The most frequently impaired domain across SE participants was that of Sustained Attention, or rather two of its known component tasks: divided attention and vigilance. When compared to the IGE comparison group, three of the NCSE participants showed impaired dual-task performance (divided attention, while one GCSE case produced vigilance scores significantly lower than those of IGE controls (see Table 6.6).

This does not mean that the NCSE and GCSE could be neatly separated on the basis of divided attention versus vigilance. Rather, the division was on the basis of those with secondarily generalized convulsive status versus those with primary generalized convulsive status (Lori). Classical dissociation between vigilance and divided attention were found in the same four cases with abnormal EEG recordings.

- Cases with secondarily generalized convulsive status (Nell, Caro and later Tom) displayed severe divided attention deficits while their vigilance task performance was average to high average.

- Lori (with repeated GCSE episodes without recovery of consciousness in-between) displayed a severe vigilance deficit, although her divided attention was average.

There was no immediately obvious explanation why these four should differ from the other five SE cases. One possible factor might be related to the higher number of seizures, although this would not account for all cases (i.e. Tom).

6.4.3 DEFICITS: TRANSCIENCE OR SLOWED RECOVERY

The third prediction listed at the beginning of Section 6.1.3 was that cognitive functioning would deteriorate with increasing numbers of GCSE seizures. A significant negative association was found with regard to verbal recall of narrative details and verbal episodic word-lists, and consistent with findings from the research literature, current estimated I.Q. was also significantly affected (see Table 6.4). Further, when all three seizure-types are considered, a higher number of SE seizures did not always associate with severe or widespread cognitive impairment (see Jill, Ron in Table 6.2).

Cognitive functioning associated with chronic epilepsy can change in at least two ways over time. One, cognitive dysfunction resolves as the SE episode becomes more distant in time; or two, recovery might take a slower course to partial or complete reversal of impairments (if at all) (Fujikawa, 2005; Licht & Fujikawa, 2002).

Shorvon (2002) and other researchers have recommended that the time elapsed since the most recent SE episode be noted for assessment purposes. Clinical history, task performance and results for five of the cases (Jill, Ken, Lana, Ron, Mena) suggested transient impairment, with three achieving a partial or complete reversal by time of testing (Jill, Lana, Ron). When originally tested some 10 days after her third SE episode

Mena's lowest performance was in verbal fluency tasks (i.e. moderately impaired), but upon informal re-testing with an alternative form some months later, she produced average scores. Ron reported a memory loss for a month after his third SE episode, but presented as normal when tested some five months later. However, he did show a lowering in general intelligence compared to estimated pre-morbid I.Q. (see Table 6.3). Overall, these five cases suggest cognitive recovery which may take days or weeks but whose course over time is essentially similar to that of brief seizures (Helmstaedter, Elger, & Lendt, 1994).

Recovery of some cognitive functioning, however, seems to have been slower in the remaining four cases. Tom remained moderately impaired in divided attention when tested some five months after his second ASE episode. When Nell was tested 3.5 months after her latest SE episode, she was at the same levels of impairment as Caro, who had been tested only 5 weeks after an episode, suggesting little (if any) reversal in **Nell's deficits**. **When tested some 2.5 months after a prolonged convulsive seizure**, Lori still had several moderate to severe impairments across three cognitive domains.

Course of SE condition

Some twelve months after their cognitive assessments had been completed, the admission notes and a follow-up revision of the relevant medical records showed that the SE condition for the same four cases (Tom, Nell, Caro, Lori) had deteriorated in several ways. Each had suffered at least one prolonged seizure within three months after completion of the **study participation**. **The duration of Lori's repetitive GCSE episodes had increased**, and Tom developed GCSE in addition to his existing ASE. Caro was hospitalized during a total of seven episodes of generalized tonic-clonic convulsions repeated every 20 minutes without recovery of consciousness in-between. An MRI scan taken some six months after Nell had completed her study participation detected

abnormal white matter in the tip of her left temporal lobe. In contrast, the SE condition for the other five participants either improved or remained the same when their records were reviewed after twelve months.

Idiopathic epilepsies are said to have a more favourable prognosis than symptomatic epilepsies (Shorvon & Walker, 2005). The initial SE disorder can be triggered by an acute event (e.g. stroke, alcohol or drug withdrawal) and such a symptomatic aetiology predicts a less favourable course (Fugikawa, 2005). The condition can evolve slowly within the course of a pre-existing epilepsy disorder, or decline faster than brief seizure syndromes (Helmstaedter, 2007). Deterioration can manifest as secondarily generalized convulsive seizures perhaps reflecting a degenerative neurological condition (Berg, 2002, 2011; Shinnar & Babb, 1997).

The participants in this study all had cryptogenic aetiologies for their epilepsy disorder, but in four cases (Tom, Nell, Caro and Lori), a possible underlying neuropathology giving rise to their SE episodes might have been aggravated by substance abuse and/or alcohol withdrawal. All four participants displayed abnormal EEG recordings. Their life-style was deleterious to their condition and included alcohol/cannabis abuse (Tom), history of polysubstance abuse (Nell and Caro) and alcoholism (Lori). Neither Tom nor Lori adhered consistently to their medication regimes, **and both Nell and Caro's regimes included several AED medications.**

6.4.4 MALADAPTIVE BEHAVIOURS AND AGE AT ONSET

The age at onset of SE is crucial, since it can affect the level of cerebral development (Shorvon, 2007). Further, adolescence and early adulthood is the time when the brain is not yet fully mature and still vulnerable to behaviours such as drug abuse, alcohol intake, and non-adherence to prescribed medication – all which diminish neuroprotection. The youth of the four cases (Tom, Nell, Caro and Lori) at epilepsy onset

suggests their executive functions (e.g. good judgment and decision-making) associated with the pre-frontal cortex might not yet have been fully developed. The lack of judgment evidenced by their life-styles and maladaptive behaviours might have reduced the natural neuroprotection of their young brains. Consequently, they were placing themselves at increased risk of longer-lasting cognitive deficits and a deteriorating SE condition.

In contrast, none of the five other cases (Jill, Mena, Ron, Ken, Lana) reported current drug intake or anything other than social drinking. They all maintained their medication regime. These results bear out the claim that a “fit and healthy brain” is less likely to fall into status (Shorvon, 2007).

6.4.5 SUMMARY AND CONCLUSIONS

Overall, the results did not show that *all* prolonged seizures are associated with long-standing cognitive deficits and a poor prognosis. Further, the GCSE participants did not demonstrate the greatest deficits. Rather, the CPSE cases with secondary generalization to convulsive status proved to be the most vulnerable, with their histories of polysubstance abuse also contributing to cognitive impairments. The study results concur with the view that SE seizures are more likely to occur in an abnormal brain (Berg, 2011; Helmstaedter, 2007).

Another potentially useful finding for further investigations was that of a classical dissociation in component tasks of Sustained Attention. Divided Attention was dissociated from Vigilance in the same four cases with abnormal EEG recordings. The cases with secondarily generalized convulsions had Divided Attention deficits, while the cases with primary generalized convulsions gave reduced or severely impaired Vigilance scores. It is concluded these attention deficits were acting as neurocognitive markers for less fit and vulnerable brains of young adults.

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CHAPTER 7

EPILEPSY CO-MORBID WITH PSYCHOPATHOLOGY

7.0 CHAPTER OVERVIEW

In this chapter, an investigation of the nature of the co-morbid relations between epilepsy and psychopathology will be outlined, based on the assumptions outlined in chapter two (section 2.5.6). A brief description of clinical issues surrounding co-morbidity will be addressed, and specific hypotheses to be tested will be detailed. The results, together with their related implications for epilepsy research, will then be discussed. Illustrative case material will be provided.

7.1 CLINICAL ISSUES

If epilepsy and psychopathology are independent and co-incidental, then the frequency of mental disorders (e.g. personality and affective disorders, behavioural disturbances) should be consistent with the incidence in the general adult population (G. P. Lee, 2004). There is evidence from prevalence studies that psychological disorders are more common in epilepsy than in the general population, even in the context of well-controlled seizures (see Jacoby, Baker, Steen, & Potts, 1996 for a review). In one prospective study of 337 children with partial epilepsy and normal intelligence, emotional and social dysfunction was present at higher rates than in the general population (Camfield, Camfield, Gordon, Smith, & Dooby, 1993).

One issue which has not yet achieved consensus is whether other chronic illnesses and epilepsy differ in severity of mental illness. One review of early studies comparing the incidence of depression in patients with epilepsy versus its incidence in other chronic illnesses revealed no

significant differences in depression between epilepsy groups and those with other chronic illness. Both groups, however, were significantly higher in depression than in normal controls (Altshuler, 1991; Wells, Golding, & Burham, 1988).

7.1.1 SHARED PATHOGENIC AETIOLOGIES

Mental disorders and epilepsy may be linked through a shared pathogenesis (e.g. abnormal brain structures, biochemical abnormalities, or pathophysiological mechanisms) (see Kanner & Balabanov, 2002 for details).

Aetiology

Epilepsy with a symptomatic aetiology (e.g. abnormal brain structure) has been associated with more severe mental disorders than an idiopathic aetiology. For example, the degree of hippocampal atrophy may play a pathogenic role, with one study reporting TLE patients with temporal sclerosis had higher depression scores than those without a symptomatic aetiology (Kanner, 2003; Quiske, Helmstaedter, & Lux, 2000). Researchers, however, have failed to establish a relationship between severity of depressive symptoms and magnitude of hippocampal atrophy (Kanner, 2003).

Epilepsy in this study's participants had an idiopathic or cryptogenic aetiology which is associated with less severe levels of mental illness. For these participants, a psychopathology which is a component of their epilepsy syndrome should not differ in *levels of severity* across the epilepsy groups. However, *the nature* of the mental illness might vary according to the type of epilepsy e.g. affective disorders are more common in TLE than in IGE syndromes.

Pathophysiological Mechanisms

It is conceivable that, in this study, the SE seizure-types will differ in both *levels of severity* and *nature* of their psychopathology. The three SE seizure-types differ in their pathophysiological processes (Chen & Wasterlain, 2006). A text by Wasterlain and Treiman (2006) has comprehensively described the ictal EEG patterns in each of the SE seizure-types, with several researchers linking psychopathology with these pathophysiological mechanisms (Thomas, et al., 2006a; Thomas, et al., 2006b; Treiman, 2006).

- Absence Status

The most consistent findings in Absence Status involve apathy and decreased spontaneity of behaviour (Guberman, et al., 1986; Thomas, et al., 2006b), and lack of initiative (Andermann & Robb, 1972). The research literature has fewer reports of psychotic or affective states, though some common symptoms (e.g. fluctuating states of arousal, blinking or confusion) have been misdiagnosed as psychiatric phenomena (Marsh & Rao, 2002).

- Complex Partial Status

Research findings on the psychopathology of CPSE have not reached a consensus. Reported evidence includes dyscontrol of emotions (Kaplan, 2002), mood disturbance (Thomas, et al., 1999), affect (depression, anxiety) and lack of self-initiated behaviours (Profitlich, et al., 2008). Researchers have described prolonged states of fear, mood changes, automatisms, or psychoses (delusions or hallucinations) that resemble an acute schizophrenic or manic episode (Marsh & Rao, 2002; Trimble, 1991).

- Generalized Convulsive Status

There is little systematic enquiry into mental illness of people with GCSE. Such research usually is part of an overall cognition and/or medical study, but personality change has been reported (DeGiorgio, et al., 1992; Hoch, Hill, & Oas, 1994).

7.1.2 COMPLICATIONS OF RECURRENT SEIZURES

The cerebral effects of repeated seizures over time may lead to functional changes in limbic and related brain structures that eventually give rise to psychopathology (G. P. Lee, 2004; Trimble, 1991). For example, part of the limbic system (e.g. amygdala) is located in the medial temporal lobe. Localization of seizure onset and lateralization might determine the *nature* of mental disorder in people with TLE (Gianotti, 1972), while increasing numbers of recurrent chronic seizures can impact on its *severity* (see Hixson & Kirsch, 2009 for a review). Although researchers tend to focus on TLE, psychiatric complications occur in all epilepsy syndromes. One study (Sengoku, Toichi, & Murai, 1997) found psychotic symptoms of people with IGE were distinct from TLE, with incessant epileptic discharges of the different cerebral regions a key factor in pathogenesis and its manifestation.

There is continuing controversy in the literature about patients with focal epilepsy being at increased risk of developing psychiatric disorders, when compared with patients to other epilepsies such as primary generalized epilepsy (Kanner & Barry, 2003). One review (Rodin, Katz, & Lennox, 1976) reported that patients with TLE are at greater risk of psychiatric disturbances (see also Gureje, 1991). Others have failed to find significant differences in severity of mental illness between different epilepsy syndromes (Manchanda, et al., 1992; Swinkels, Kuyk, De Graaf, Van Dyck, & Spinhoven, 2001).

Epilepsy and the development of psychiatric disorders was studied by Perini, Tosin, and Carraro (1996) who found TLE patients had a higher frequency of diagnosed emotional and affective disorders (80%) than patients with JME (22%) or diabetes (10%). The researchers concluded that TLE seizures lead to a high rate of mood and personality disorders and attributed this finding to limbic dysfunction rather than psychological adjustment to living with epilepsy and/or stigma (Perini, et al., 1996; Swinkels, et al., 2005). Other researchers have not found that locus of seizures can determine the nature of mental disorder (e.g. mood, personality traits) (Swinkels, et al., 2003).

The controversy about a higher frequency of affective disorders in TLE might be explained by the fact that some TLE patients have more than one seizure-type (e.g. secondarily generalized seizures). Several studies have failed to separate such cases from those with complex partial seizures only (Altshuler, 1991; Swinkels, et al., 2005). An epilepsy disorder with several seizure-type components will generally have greater impact on mental health than the number of chronic seizures (C. Dodrill, 1984; Hermann, Dikmen, & Wilensky, 1982). Most participants in the current study had syndromes with more than one seizure-type, so the number of seizure-types might contribute to the severity of their disorder.

7.1.3 LIVING WITH AN EPILEPSY CONDITION

Dodrill (2008) commented that psychopathology in epilepsy might be a secondary emotional reaction related to psychosocial problems associated with having a chronic neurological condition. Another possibility is that psychopathology is a negative side-effect of anti-epileptic drugs (Reijs, et al., 2004). The comparatively high incidence of depression in epilepsy (see Jacoby, et al., 1996 for a review) illustrates the dangers of psychiatric co-morbidity including suicidal behaviour and attempted suicide (Mendez & Doss, 1992; Mendez, Lanska, & Manon-Espaillet, 1989). Suicide rates in people with epilepsy are four times higher than

rates in the general population. More specifically, for patients with partial seizures with secondary generalization, suicide rates have been reported as high as 25 times that of the normal population (Barry et al., 2008; Fukuchi et al., 2002; Kanner, 2003). These suicide statistics are strong evidence for higher rates of mental illness in people with epilepsy (for a review, see Gilliam & Kanner, 2002). See Appendix B for studies which outline some of the psychosocial difficulties in various areas of life (e.g. culture, family, interactions with professionals, unemployment) for people with epilepsy.

7.1.4 SELF-APPRAISAL OF DISORDERS AND DEFICITS

All three measures of psychopathology (DASS, ESDQ, EFQ) used in the present study involve self-rating responses, but an inherent draw-back **of such measures is the participants' biased perceptions of their own** cognitive deficits or mental disorders. Investigators have used various strategies to control for **biased participants' responses such as comparison with formal assessment tasks or significant others' ratings**. Some researchers have questioned the objectivity of reports by significant others **about a patient's mental disorder or cognitive deficits** (Trosset & Kaszniak, 1996). However, when **patient versus significant others' reports are** compared to objective assessments, it is **the partners' reports** which are generally far more reliable (Andrewes, et al., 1998; Sunderland, Harris, & Gleave, 1984).

One problem associated with self-report measures of metamemory **involves rating scales that depend on discrepancy scores between patients' self-report and care-givers' report of cognitive functioning**. Discrepancy scores alone cannot discriminate between patient overestimations of **abilities and caregivers' underestimation** (Pannu & Kaszniak, 2005; Trosset & Kaszniak, 1996). Comparison with a normal controls group and/or comparison with objective assessments of cognitive dysfunction will clarify the situation.

A patient's estimations of abnormality or cognitive dysfunction can also be biased by other factors, and studies have concluded that the value of self-reports is as indicators of the degree of objectivity in the **participants' responses, rather than serving as ecological extensions** for objective testing (Banos et al., 2004; Carr, Gray, Baty, & Morris, 2000). Unbiased responses would require self-awareness, which has been defined as **"the capacity to perceive the *Self* in relatively objective terms while maintaining a sense of subjectivity"** (G.P. Prigatano & Schacter, 1991, p. 13). Good judgment and understanding are required for insight, but poor insight into an illness (its consequences or implications) is a common clinical phenomenon found across affective, psychotic and neurological disorders (Beitman, Nair, & Viamontes, 2005; Ghaemi, Hebben, Stoll, & Pope, 1996).

Finally, participant self-perceptions can be influenced by depressed mood and/or AED neurotoxicity, as shown in a study where these factors were significantly correlated with poorer self-reported health status (Gilliam, 2002). **In a study of 125 TLE patients' assessment of their own health status** some 12 months post-surgery, mood status was found to be **the strongest clinical predictor of patients' self-ratings** (Gilliam, Kuzniecky, & Meador, 1999).

7.1.5 HYPOTHESES FOR PSYCHOPATHOLOGY CASES

The aim was to investigate the relationship between epilepsy and psychopathology in these participants. Possibilities generated by the kinds of co-morbid relations are set out as follows.

- Psychopathology is merely concurrent with epilepsy. It neither shares the underlying cause for epilepsy, nor is the consequence of epilepsy seizures, and so is not likely to be more severe in people with epilepsy than in a normal population. If so, these epilepsy

participants' overall abnormality will not be significantly higher than that of the normal adult controls.

- Psychopathology and epilepsy are *directly linked* through a shared pathogenesis e.g. aetiology or pathophysiological mechanisms during seizures. Thus, the psychopathology is a component of the underlying epilepsy condition, and so *the nature* of the psychopathology should differ across the epilepsy groups (TLE and IGE and SE seizure-types).
- Psychopathology is *indirectly linked* to chronic epilepsy through **recurrent seizures which change the brain's neuronal functions over time**. If so, then mental disorders are a complication of the seizures and *levels of severity* of psychopathology in each epilepsy group should increase with number of seizures over time.
- Psychopathology in epilepsy is *a secondary emotional reaction* to psychosocial problems (e.g. social stigma) associated with having a chronic condition. If so, then level of difficulties as rated on the ESDQ and EFQ should increase with lifetime burden (number of years living with epilepsy).

7.2 RESULTS

The sequence of analyses presented in this section is set out below.

Group Comparisons

- Table 7.1 gives significant mean differences between four epilepsy groups and neurologically healthy controls, using confidence intervals.
- Overall abnormality in the epilepsy group (n=22) was compared with adult controls (n=23), on the ESDQ and EFQ, using Mann-Whitney U tests.

Nature and severity of dysfunction

- Figure 7.1a depicts patient responses to the ESDQ; Figure 7.1b charts patient-partner response discrepancies.
- Figure 7.2a represents patient responses to the EFQ; Figure 7.2b charts patient-partner response discrepancies.
- Table 7.2 gives performance percentiles on the Depression Anxiety Stress Scales (DASS) by epilepsy participants.

Correlates of ESDQ and EFQ Scales

- Tables 7.3 set out significant correlates (affect scales and number of SE seizures) of self-ratings on the ESDQ and EFQ scales.
- Table 7.4 sets out significant cognitive correlates for self-rated responses on *Lack of Insight* (ESDQ) for GCSE and TLE participants.
- Figures 7.3 to 7.6 depict cognitive correlates for *Lack of Insight* on the ESDQ and EFQ.

Awareness and insight

- Table 7.5 sets out intra-individual z-score comparisons between self-estimated everyday cognitive dysfunction (EFQ) and actual performance on cognitive tasks from the AVLT and TEA.

Treatment of data for analyses

Treatment of data was as described in Chapter Three.

- The overall abnormality score for each individual was a composite sum of mean self-rating responses for all 10 ESDQ Scales or for all 6 EFQ Scales. Mann-Whitney U test analyses on transformed data from the ESDQ or the EFQ compared the epilepsy group and normal adult controls on their overall abnormality.

- For cognitive task correlations with *Lack of Insight*, z-scores were used. Raw error data was used for correlations with *Lack of Insight*.
- For bar charts and scatter-plots, z-scores were used. Means and standard deviations of neurologically healthy controls (n=23) and their partners (n=21) were used for conversion of epilepsy **participants' raw data to z-scores**. Qualitative descriptions were similar to those for levels of impairment in Table 3.4.

7.2.1 EPILEPSY PATIENTS VERSUS CONTROLS

Table 7.1 sets out the descriptive statistics on the ESDQ and EFQ data for the four epilepsy groups (NCSE, GCSE, TLE and IGE) and a group of neurologically healthy controls. The epilepsy groups were compared with each other and with controls using 95% confidence intervals (CI). The CI for the TLE and controls group did not overlap, indicating their notable difference. All epilepsy group means had overlapping 95% confidence intervals.

Table 7.1
Descriptive statistics for epilepsy groups and adult controls

N	ESDQ	Mean (SD)	95% CI for mean
3	NCSE	18.45 (3.63)	9.43 – 27.47
5	GCSE	10.15 (3.63)	5.64 – 14.66
7	IGE	13.64 (5.88)	8.20 – 19.08
7	TLE	15.02 (2.82)	12.41 – 17.62
23	Controls	9.78 (4.83)	7.69 - 11.87
N	EFQ	Mean (SD)	95% CI for mean
3	NCSE	9.76 (2.06)	4.65 – 14.88
5	GCSE	6.00 (1.80)	3.76 – 8.24
7	IGE	8.60 (3.59)	5.27 – 11.92
7	TLE	8.90 (3.18)	5.96 – 11.83
23	Controls	6.48 (2.44)	5.43 – 7.53

As described in section 7.1.5, the first possibility is that the relationship underlying epilepsy and psychopathology is purely coincidental. In other words, mental disorder is neither a component of the epilepsy syndrome nor a complication of seizures. If psychopathology simply co-occurs with **epilepsy then patients' self-ratings** as a whole (n=22) should not differ significantly from those for the healthy control **group (n=23)**. **The epilepsy groups' overall abnormality was compared to the controls' self-rating responses** on the ESDQ and the EFQ using Mann-Whitney U tests.

The output indicated that the result, with correction for ties and z-score conversion, was significant for the ESDQ responses. $Z = -2.77$, asymptotic significance (2 tailed) = -0.006. Thus, the epilepsy participants were found to be significantly more dysfunctional than the controls in their ESDQ responses regarding emotional-social functioning. This result suggests that psychopathology is linked to epilepsy more significantly than it is in a normal adult population.

A Mann-Whitney U test comparing the same two groups on their EFQ responses indicated they did not differ significantly on overall dysfunction of everyday living skills (EFQ). Z-score = -1.589 (p>.05).

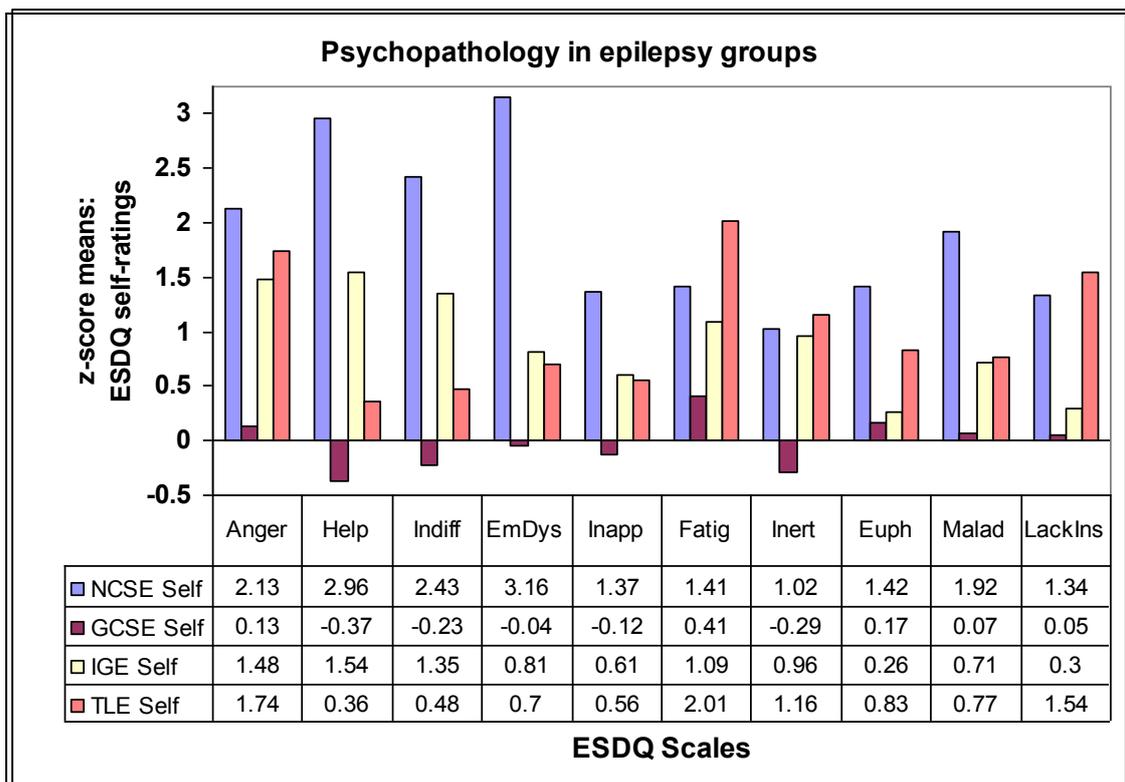
7.2.2 NATURE AND SEVERITY OF DYSFUNCTION

Personality and Behaviour Disorders (ESDQ)

Figure 7.1a allows a visual comparison of the z-score means for **each epilepsy group on the 10 ESDQ Scales**. **The four epilepsy groups' z-scores** were based on the raw means and standard deviations of the neurologically adult controls group in each ESDQ scale (n=23). The scale means for the control group are not included in Figure 7.1a.

Figure 7.1a demonstrates that self-rated problems with emotions or behavioural disturbance did not differ systematically amongst the four epilepsy groups. The notable contrast was between the comparatively high self-estimated abnormality of the three people with NCSE (*Anger, Helplessness, Indifference, Emotional Dyscontrol, and Maladaptive Behaviour*) and the self-rated normality of the GCSE group.

- NCSE (n=3) Abnormality levels ranged from 1.92 to 3.16
- GCSE (n=5) No abnormal self-ratings were found.
- IGE (n=7) No psychological dysfunction was found.
- TLE (n=7) *Anger and Fatigue.*



Note:
Abbreviations: See Table 3.2 for descriptions of ESDQ scales.
Help = Helplessness; Indiff = Indifference; EmDys = Emotional
Dyscontrol; Inapp = Inappropriate Behaviour; Fatig = Fatigue; Inert = Inertia;
Euph = Euphoria; Malad = Madadaptive Behaviour; LackIns = Lack of Insight.

Figure 7.1a Self-rated levels of emotional-social dysfunction in epilepsy groups.

Figure 7.1b represents the response discrepancies between patient and partner ratings on the ESDQ. Significance level for group differences was set at $z = \pm 1.64$. SE participant-partner discrepancies were significant when compared to those of the control-partner pairs. The NCSE group rated higher than their partners in *Anger, Emotional Dyscontrol, Helplessness, Indifference* and *Maladaptive Behaviour*. The GCSE participants rated lower than their partners on *Anger, Emotional Dyscontrol, Helplessness, Inertia, Indifference, Maladaptive Behaviour* and *Lack of Insight*. Neither the TLE nor IGE response discrepancies differed from those of the control-partner pairs.

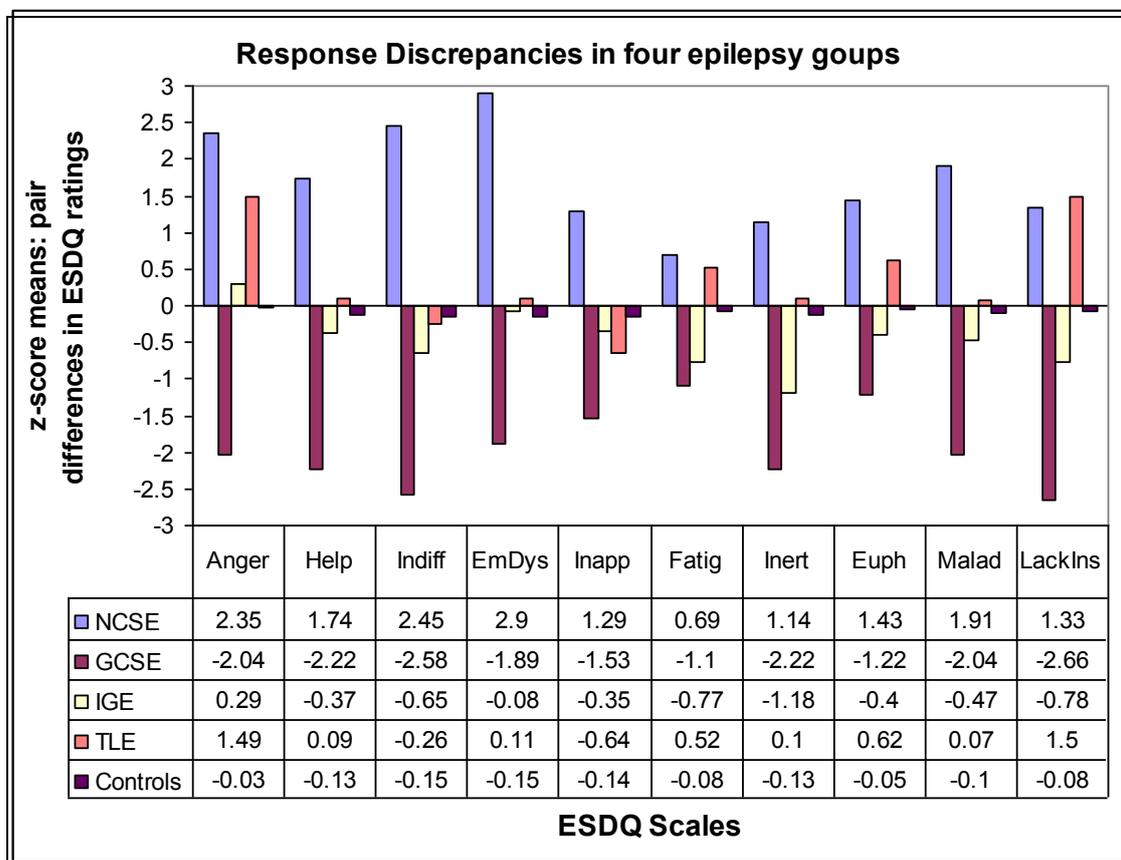
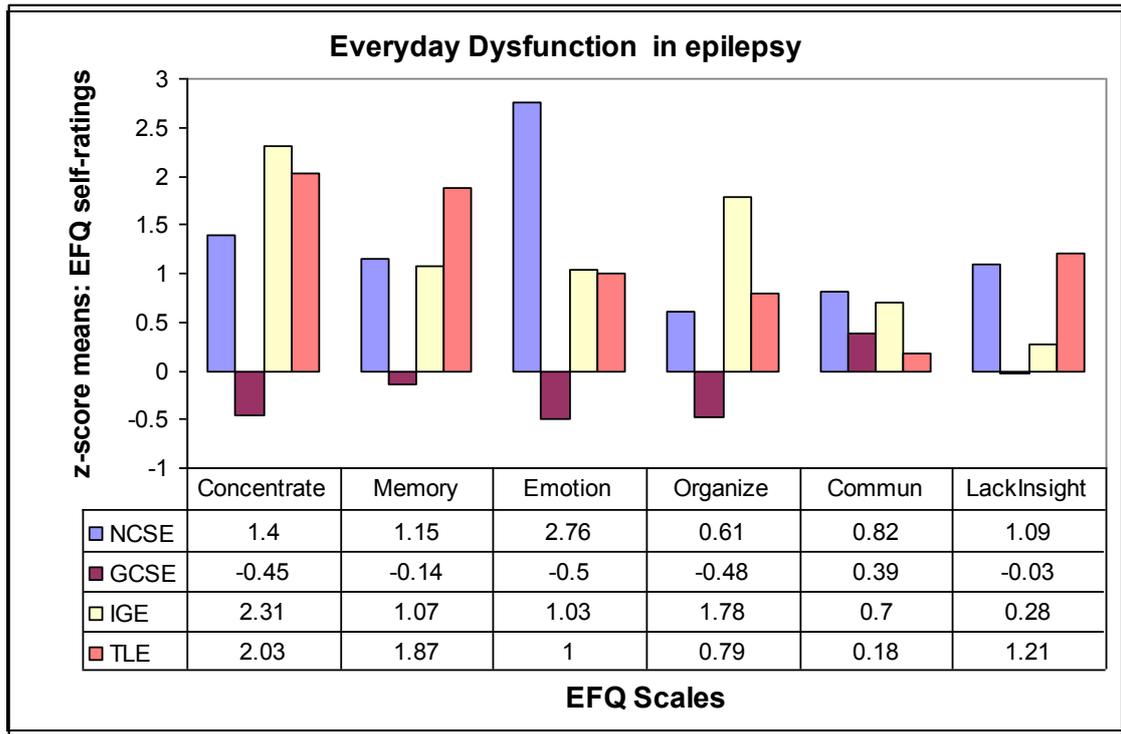


Figure 7.1b Response Discrepancies in patient-partner and control-partner pairs on the ESDQ Scales.

Everyday Living Skills and Abilities (EFQ)

Figure 7.2a allows a visual comparison of the z-score means for each epilepsy group on the 6 EFQ Scales. The four epilepsy **groups' z-**scores were based on the raw means and standard deviations of the neurologically adult controls group in each scale (n=23). The scale means for the control group are not included in Figure 7.2a.

Figure 7.2a demonstrates that the groups did not differ greatly in their difficulties with skills required for everyday functioning. Three NCSE cases felt their greatest area of impairment was *Emotions*, the IGE cases self-rated as impaired in *Concentration* and *Organization*, and the people with TLE self-rated *Concentration* and *Memory* as most dysfunctional. The GCSE group rated themselves as having fewer everyday living problems than the adult controls group.



Abbreviations: See Table 3.3 for descriptions of EFQ scales.
 Concentrate = Concentration; Memory = Everyday Memory;
 Emotion = Emotions; Organize = Organization; Commun = Communication;
 LackInsight = Lack of Insight.

Figure 7.2a Self-rated levels of everyday psychological dysfunction in epilepsy groups.

Figure 7.2b reveals that *Emotions* elicited the largest response discrepancies between NCSE patient-partner pairs. Similar to their ESDQ under-estimation of difficulties, the GCSE participants rated themselves lower than their partners (when compared to control-partner response discrepancies) on *Organization* and *Communication*. The TLE participants over-estimated their everyday dysfunction (compared to control-partner discrepancies) on *Concentration* and *Memory*, and the IGE participant-partner discrepancies were significantly higher than control pairs for *Concentration*.

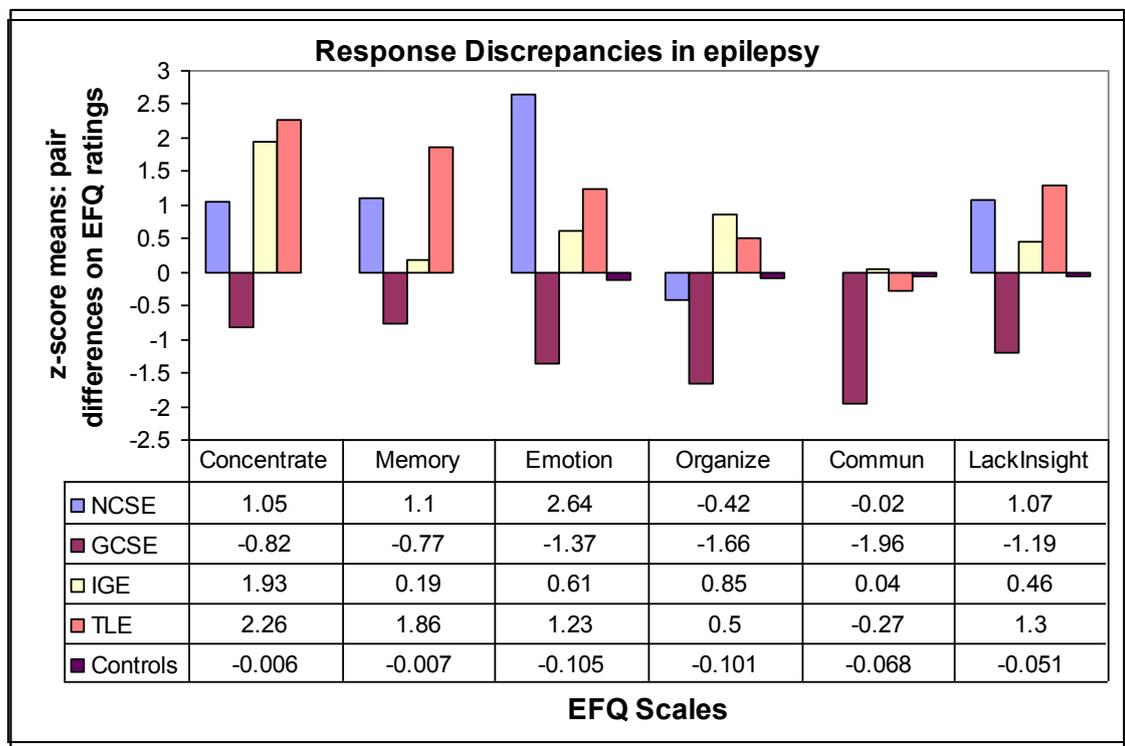


Figure 7.2b: Response Discrepancies in patient-partner and control-partner pairs on the EFQ Scales.

Levels of Depression, Anxiety, Stress (DASS)

The full-length DASS was used to **measure the patient's affective** state over the previous week, using single-case program MoodScore_Aus for data-analysis (Crawford, et al., 2011).

Table 7.2
Percentile rankings for affect in epilepsy participants (n=22).

CASE	Syndrome	Depression	Anxiety	Stress	GPD*	95% CI on PR
Jill	ASE	87	98	97	96	94 to 98
Nell	CPSE	96	97	97	98	96 to 99
Tom	ASE	62	82	55	63	53 to 72
Ron	GCSE	44	47	44	42	37 to 48
Mena	GCSE	44	82	55	61	56 to 66
Lori	GCSE	89	82	63	79	75 to 83
Lana	GCSE	44	19	50	42	37 to 48
Ken	GCSE	80	72	44	66	61 to 71
Gwen	IGE-JME	83	72	83	80	76 to 84
Mary	IGE-JME	10	11	32	21	14 to 30
Josh	IGE	95	89	59	87	83 to 93
Jon	IGE	55	47	78	68	64 to 73
Hal	IGE	55	89	59	72	67 to 76
Mat	IGE	35	52	32	38	29 to 47
Bela	IGE	99.5	100	98	99	95.5 to 99.9
Alana	TLE-right	55	47	75	66	61 to 71
Peg	TLE-right	94	98	89	94	91 to 96
Etta	TLE-right	92	77	91	89	85 to 92
Leti	TLE-left	18	63	36	37	32 to 43
Josie	TLE-left	63	87	97	92	89 to 95
Jana	TLE-left	10	30	39	28	20 to 37
Cath	TLE-left	26	11	4	8	2 to 16

Note:

* GPD = General Psychological Distress; and PR = percentile ranking on GPD.
Qualitative descriptions for percentile rankings: normal (15 - 78th); mild (78th - 87th); moderate (87th - 95th); severe (95th - 98th) and very severe (98th - 99.5th).

Table 7.2 displays the distribution of the 22 epilepsy participants across percentile ranks of general psychological distress (GPD).

- 7 participants self-rated below the 50th percentile (below average);
- 6 people had a GPD within the 50th – 77th percentile range (normal);
- 3 had GPD percentiles within the 78-87th range (mild);
- 3 were between the 88-95th percentile (moderate); and
- 3 participants had a GPD between the 95 -99th percentile (severe).

The GCSE participants DASS self-ratings were normal, which is consistent with their response pattern of under-estimation of problems on the ESDQ and EFQ

7.2.3 CORRELATES OF THE ESDQ AND EFQ SCALES

Several factors were tested for their impact on participants’ responses on the ESDQ and EFQ: chronicity over time, psychosocial context, affect states and neurocognitive factors. Seizure-related measures included number of years living with epilepsy, number of prolonged seizures (for the GCSE group only), and the age at onset of seizures. The time-related, psychosocial measures (e.g. number of years living with epilepsy, number of years at school) were not significantly associated with any of the ESDQ or EFQ responses. It is likely that the small sample sizes limited detection of small correlations.

Affect States

Table 7.3 lists significant correlates for the ESDQ and EFQ scales, with number of GCSE seizures being the only significant epilepsy-related correlate.

Table 7.3
Correlates of self-rated responses on Everyday Functioning Scales and Emotional-Social Dysfunction Scales.

	<u>Generalized Convulsive SE cases</u>		<u>Temporal Lobe Epilepsy cases</u>	
	No. of SE seizures	Depression	Depression	Anxiety Stress (DASS)
ESDQ Scales				
Inertia	r = -0.908 (p=.033)			
Fatigue		r = -0.973 (p= .005)		
Inappropriate Behaviour		r = -0.959 (p= .010)		
Maladaptive Behaviour		r = -0.887 (p= .045)		
Anger		r = -0.890 (p= .043)	Stress	r= 0.767 (p= .044)
Helplessness			Depression	r= 0.880 (p= .009)
Indifference			Depression	r= 0.883 (p= .009)
EFQ Scales				
Concentration	r = -0.998 (p= .000)		Depression	r = .808 (p= .029)
			Anxiety	r = .818 (p= .025)
Everyday Memory	r = -0.989 (p= .001)		Depression	r = .823 (p= .023)
			Anxiety	r = .949 (p= .001)
			Stress	r= .908 (p= .005)

Table 7.3 shows that *Depression* (DASS) was a strong correlate of several ESDQ Scales in both the GCSE and TLE groups and also correlated with EFQ Scales for the TLE group.

Notably, the GCSE and TLE groups can be differentiated on the negative or positive direction of their correlations. Thus, the GCSE **group's estimations of emotional**-social and everyday living problems decreased as their perceived *Depression* increased, and also number of prolonged seizures increased. This suggests that the GCSE participants' under-estimation response pattern was linked to both chronic seizures (*Inertia, Concentration, Everyday Memory*) and depressed mood.

In contrast, the TLE responses on the EFQ and ESDQ scales increased as did their self-ratings on the DASS. It is of interest that their responses were influenced solely by their affect and mood, and that neither chronic seizures nor psychosocial measures were found to be significant associates. A larger sample might have detected such relationships.

Neurocognitive Factors

Lack of Insight was not found to be significantly associated with epilepsy variables, years of education or affective status. Correlational analyses were then run between *Lack of Insight* (ESDQ) and executive functions: attention factors (TEA and D-KEFS), Verbal and Design Fluency (D-KEFS) and associated errors (repetition and set-loss), Sorting (D-KEFS) and current estimated I.Q.

ESDQ: Lack of insight in self-perceived Personality and Behaviour.

Table 7.4 indicates *Lack of Insight* was significantly correlated with attention factors, visual set-loss and visual perseveration errors. All

neurocognitive correlates in Table 7.4 and insight are said to access the areas of the frontal lobes associated with executive functions.

The GCSE participants' **under**-estimated responses on *Lack of Insight* all involved impaired attention: attention flexibility, attention inhibition and control, and sustained attention. With regard to the TLE participants, inaccuracy (repetition errors) decreased as the TLE participants' **self**-ratings on *Lack of Insight* increased. The implication is that some TLE participants were accurate when giving self-estimations **above the adult controls' norm, and above their partners' judgments.**

Table 7.4
Correlates of Lack of Insight (ESDQ) self-rated responses by the GCSE and TLE participants.

Correlate Task	<u>Generalized Convulsive SE cases</u>					<u>Temporal Lobe Epilepsy cases</u>				
	Lack of Insight ¹	Sustain Attention	Switch Attention	Interfere Attention	Set-Loss Errors	Lack of Insight	Sustain Attention	Switch Attention	Interfere Attention	Set-Loss Errors
Sustained Attention ²	.986 p= .002					.446 .316				
Switching Attention ³	.946 p=.015	.960 p= .010				.068 .885	.322 .482			
Interference Attention ⁴	.904 p=.035	.941 p=.017	.829 .083			-.271 .556	.326 .475	.065 .891		
Set-Loss Errors ⁵	-.967 p=.007	-.979 p=.004	-.981 p=.003	-.857 .063		-.569 .182	-.552 .199	-.289 .530	.017 .972	
Repetition Errors ⁶	-.668 .218	-.639 .240	-.619 .266	-.444 .453	.735 .157	-.834 p=.020	-.371 .413	-.241 602	.655 .110	.579 .173

Note:

In Bold = Pearson coefficient significance level p (2-tail) <.05 or <.01. Participant numbers GCSE = 5 and TLE = 7.

1 = self-rating on *Lack of Insight* (ESDQ).

2 = Sustained Attention (TEA) (mean of Vigilance and Visual Lift tasks). 3 = Switching Attention (TEA) (mean of 2 auditory tasks).

4 = Colour-Word Interference (D-KEFS) (mean of two Colour-Word response inhibition tasks).

5 = Distractibility Errors (D-KEFS) made during Design Fluency tasks.

6 = Perseveration Errors (D-KEFS) made during Design Fluency tasks.

Scatter-plot in Figure 7.3 shows that Vigilance was a significant correlate of *Lack of Insight* for the GCSE cases. Pearson correlation = .953 (p 2-tailed =.012). Vigilance improved as self-ratings increased.

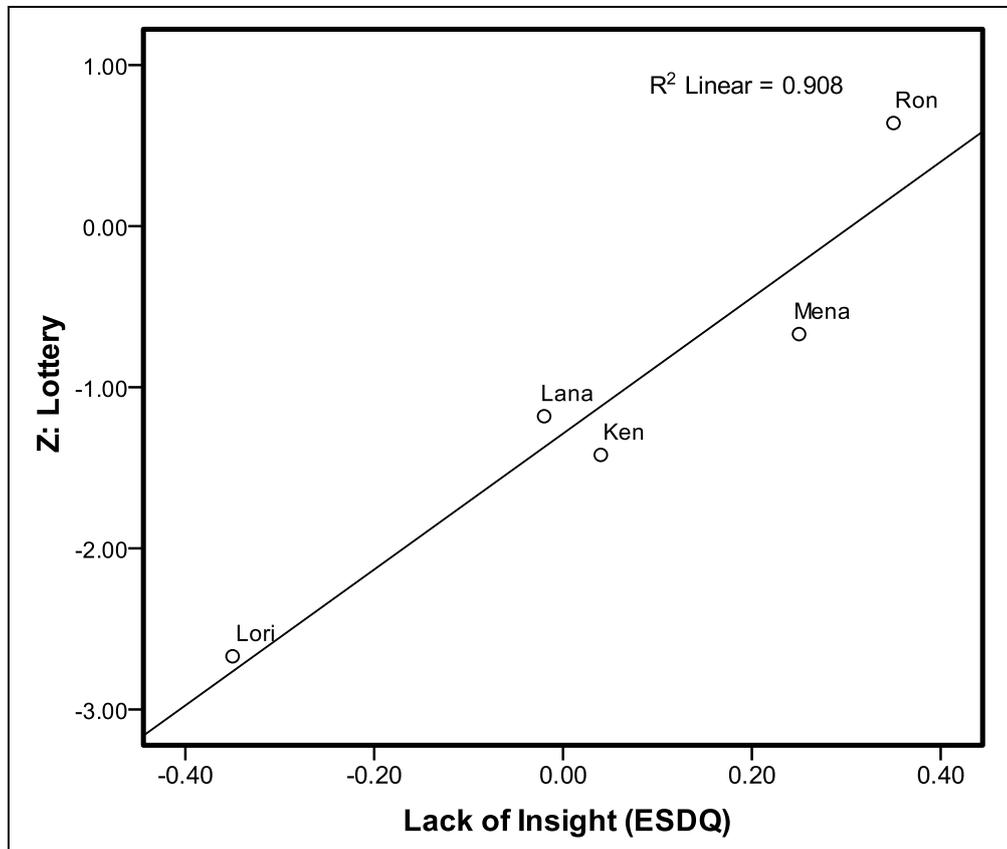


Figure 7.3 GCSE Vigilance task performance and perceived Lack of Insight (ESDQ).

Figure 7.4 depicts Distractibility (visual fluency task's set-loss errors) in the GCSE cases, indicating inaccuracy decreased as perceived *Lack of Insight* increased. Pearson = $-.967$ (p 2-tailed = $.007$). The implication is that they were mistaken when under-estimating their difficulties at lower than their partners' judgments, and adult controls'.

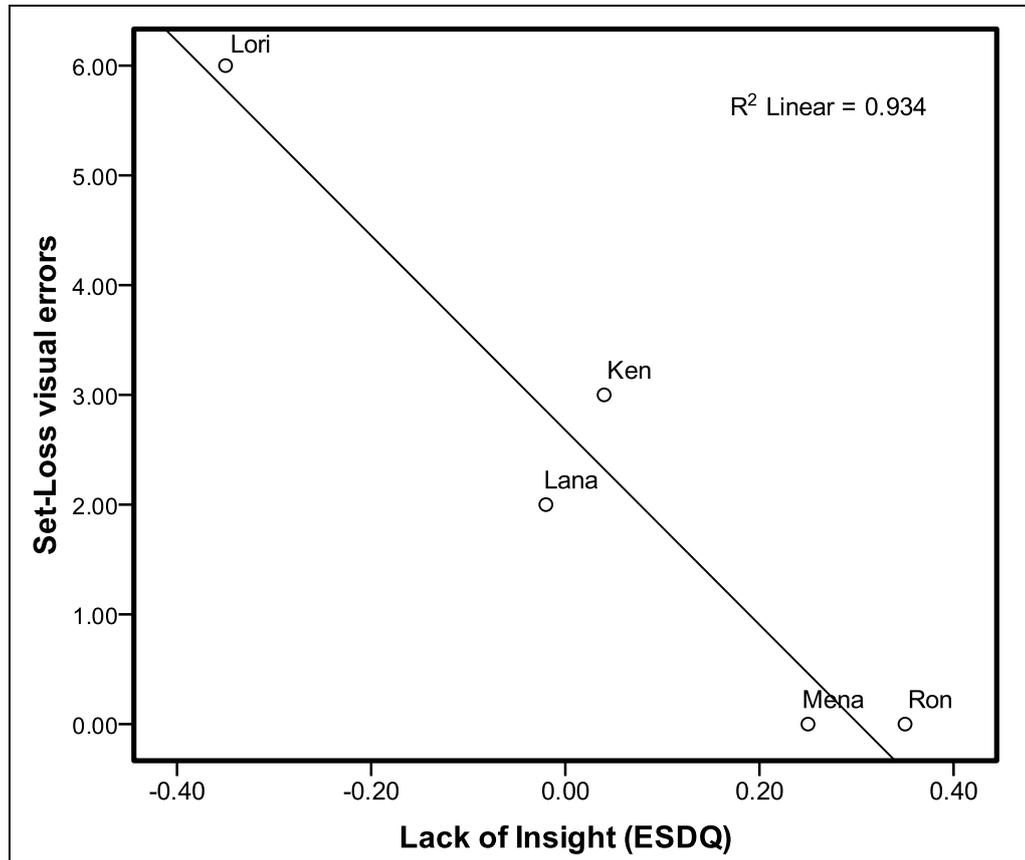


Figure 7.4 GCSE Distractibility (set-loss) errors and perceived Lack of Insight (ESDQ).

Figure 7.5 depicts a negative correlation between *Lack of Insight* (ESDQ) and **Perseveration (visual fluency task's repetition errors)** in the TLE participants, implying their higher estimations (compared to adult controls and to partners) were correct. Pearson = $-.834$ (p 2-tail = $.020$).

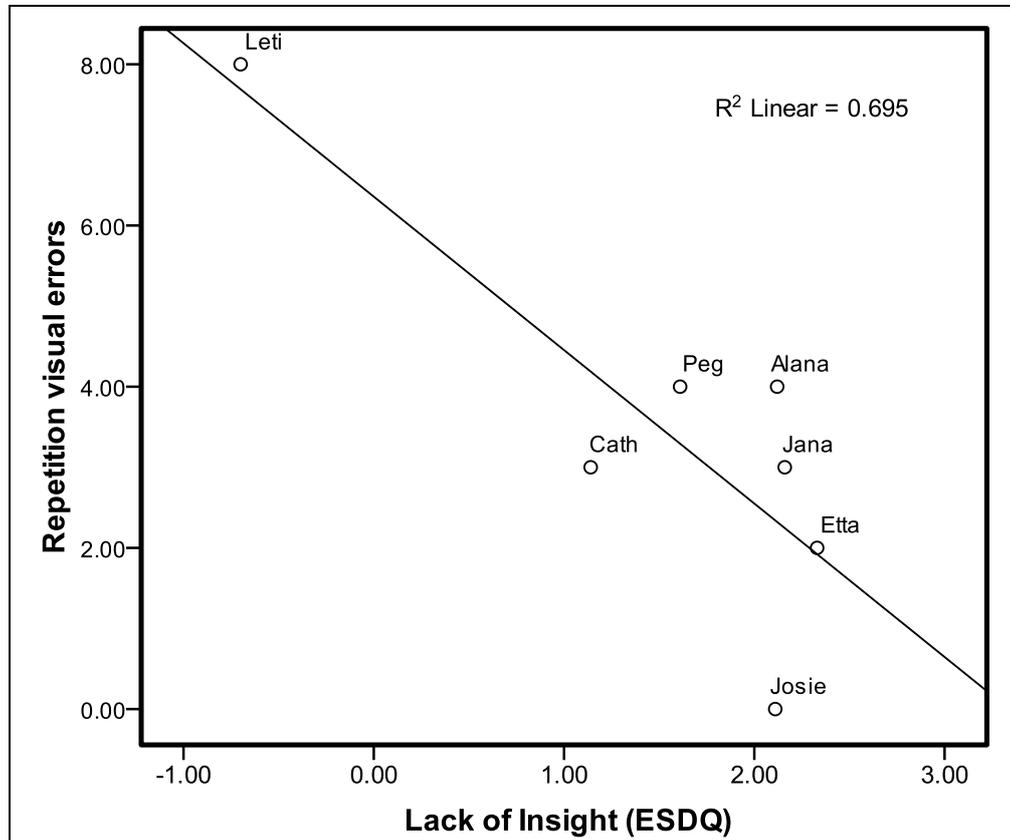


Figure 7.5 TLE: Perseveration (repetition) errors and perceived Lack of Insight (ESDQ).

EFQ: Lack of insight about coping with everyday difficulties

A correlational analysis was undertaken between *Lack of Insight* (EFQ) and various measures of attention, memory and repetition errors. For the GCSE participants, *Lack of Insight* (EFQ) did not have any significant correlates. For the TLE participants, however, flexibility of attention (as measured by the TEA Visual Elevator task) had a strong negative correlation with self-rated *Lack of Insight* (EFQ). Pearson = -0.875 (p 2-tailed = $.010$). Thus, attention flexibility decreased as the self-ratings increased. See Figure 7.6 below.

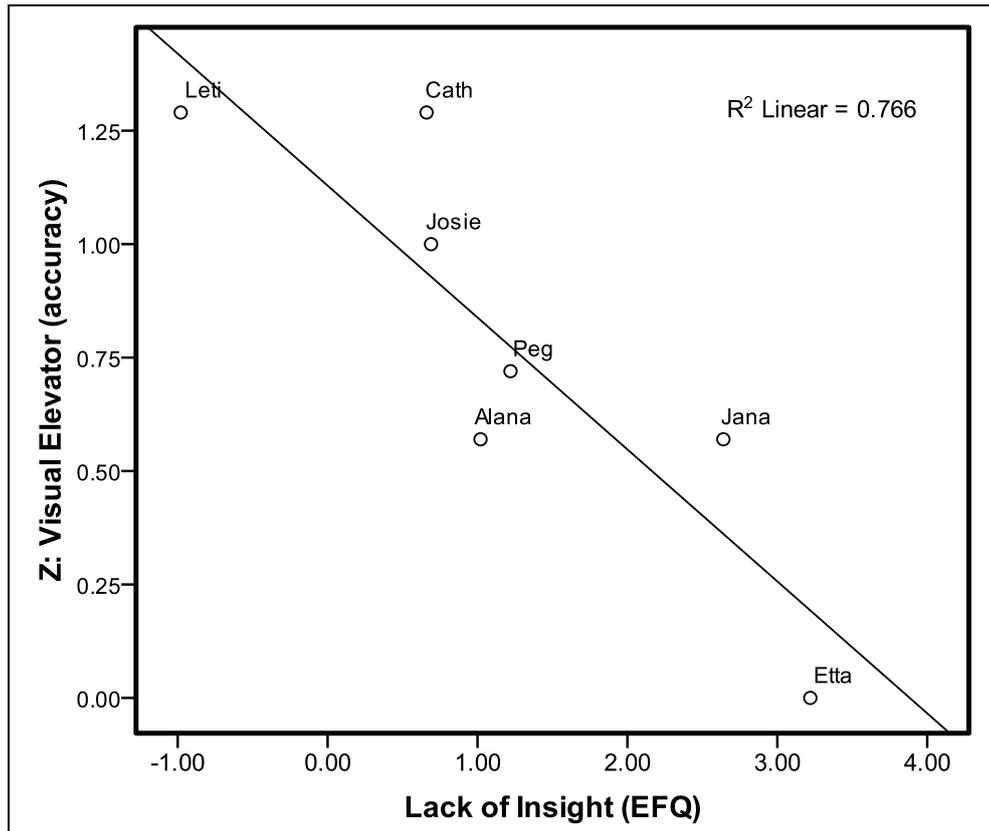


Figure 7.6 TLE: Flexibility task performance and perceived Lack of Insight (EFQ).

7.2.4 AWARENESS/INSIGHT: INTRA-INDIVIDUAL COMPARISONS

Table 7.5 compares self-perceived difficulties with cognitive functions and the person's actual task performance.

- (a) Self-rated problems with everyday memory on the EFQ versus actual performance on measures of verbal and visual episodic memory (AVLT, CVMT); and
- (b) self-rated problems with everyday concentration (EFQ) versus actual performance on measures of attention (TEA, D-KEFS).

All cognitive task performances are in z-scores. The EFQ scales show z-scores derived from **healthy controls' (n=23) means and standard deviations**. It should be noted that minus values for the EFQ responses signify a lower than normal level of everyday difficulties. In contrast, minus values for cognitive tasks signify below average abilities or impairment.

Table 7.5
Self-rated cognitive difficulties compared with formal tests of abilities (AVLT, TEA, D-KEFS).

Name & Syndrome	Event Memory			Attention Factors ¹		
	AVLT tasks <u>Episodic M</u>	EFQ ratings <u>Everyday M</u>	Descriptive <u>Qualitative</u> ²	TEA tasks <u>Attention</u>	EFQ ratings <u>Concentration</u>	Descriptive <u>Qualitative</u> ²
Jill (ASE)	no deficits	1.75	poor insight		4.04	poor insight
Bela (IGE)	-1.88	4.40	poor insight	-3.01	(inhibition) 6.99	poor insight
Etta (TLE)	-1.88	4.22	poor insight	-2.46	(inhibition) 6.99	poor insight
Josie (TLE)	-1.64	3.21	poor insight	-2.86	(switch) 3.14	good
Jana (TLE)	0.33	0.51	good	-2.25	(selective) -1.09	unaware
Cath (TLE)	-3.37	-0.84	unaware		no deficits -0.54	good
Mena (GCSE)	-2.01	-0.48	unaware		no deficits -1.28	good
Lana (GCSE)	0.56	0.36	good	-1.94	(switch) 0.09	unaware
Lori (GCSE)	-0.07	-1.22	good	-2.67	(vigilance) -1.75	unaware
Nell (CPSE)	-1.89	1.77	good	-3.23	(divided) 0.70	unaware
Tom (ASE)	0.79	-0.06	good	-2.48	(divided) -0.54	unaware
Ron (GCSE)	0.88	-0.55	good		no deficits -1.41	good
Ken (GCSE)	1.43	1.19	good	-2.36	(selective) -2.09	unaware

Note: Cut-off z-score for notable difference between formal tests and Questionnaire self-ratings = +/- 1.64.

1 = Attention Factors Select = selective attention; Switch = switching attention; Divide = divided attention (dual tasks); Vigil = vigilance i.e. sustained attention; Inhibit = attention response inhibition during word interference test.

2 = Qualitative descriptions Unaware = Self-rated as few or no problems on EFQ *Everyday Memory* and/or *Concentration* but actual cognitive performance is impaired in Episodic Memory and/or Attention.

Poor Insight = Self-rated as high level of difficulties on EFQ *Everyday Memory* and/or *Concentration* but actual cognitive performance in Episodic Memory and/or Attention tasks is average or impaired to much less degree. Good (match) = similar levels of performance on formal test and self-rated EFQ.

7.2.5 SUMMARY OF MAIN FINDINGS

First, the epilepsy group as a whole differed significantly from the neurologically healthy controls. The main finding was the contrasting response styles to both the ESDQ and EFQ question-items: GCSE cases tended to under-estimate their abnormality when compared to their **partners' ratings of them, while some TLE participants perceived their difficulties at higher levels than their partners.**

Second, the contrasting response styles were again evident in the direction of the association between affect correlates of the ESDQ and EFQ scales (Table 7.3). For the GCSE cases, self-rated difficulties in emotional-social dysfunction diminished as *Depression* and *Number SE seizures* increased. Self-ratings of everyday psychological difficulties decreased as *Number of SE seizures* increased. In contrast, the people with TLE produced positive associations between increasing ESDQ Scales and *Stress* and *Depression* (DASS), while difficulties with everyday living also increased with all DASS Scales.

Third, *Lack of Insight* scores (ESDQ and EFQ) were correlated with neurocognitive measures of executive functions, all involving attention factors or their component tasks.

- For the GCSE participants, as *Lack of Insight (ESDQ)* self-ratings decreased, so did their vigilance, attention switching, and control of attention responses. As their self-rated *Lack of Insight* increased, they were making fewer distractibility errors.
- For the TLE participants, the number of repetition errors became fewer as *Lack of Insight (ESDQ)* self-ratings increased, which suggests they were estimating abnormality in the correct direction (i.e. increasing). With regard to *Lack of Insight (EFQ)*, self-ratings increased as attention flexibility decreased.

Fourth, with regard to response patterns on the EFQ, the GCSE **participants' under-estimation** of difficulties with *Everyday Memory* and *Concentration* seem to reflect a poor metacognitive awareness of their own **attention processes**. **The TLE participants' over-estimation** of memory and concentration difficulties might be due to poor understanding of metamemory processes as expressed in disrupted judgment of personal ability to learn/recall.

7.3 DISCUSSION

The question posed in the Clinical Issues section 7.1.5 concerned the nature of the co-morbid relations underlying epilepsy and **psychopathology**. **For example, was the participants' mental illness a component** of their epilepsy condition indicated by a shared pathogenesis, or a complication developed over time and associated with seizure-type?

7.3.1 CO-MORBID RELATIONS

Chance co-occurrence

The first possible relationship outlined in section 7.1.5 was that psychopathology and epilepsy simply co-**occur**. **The study's epilepsy group** perceived themselves as having significantly higher levels of overall psychopathology than the healthy control group, indicating that for these epilepsy participants, co-morbidity with psychopathology did not occur by chance. The groups did not differ from adult controls on difficulties with everyday living skills. Further data-analyses concerned two other possibilities outlined in section 7.1.5.

Shared aetiology or seizure complications

The second possibility was that epilepsy and psychopathology share a common pathogenesis. In these participants, severity of overall

abnormality did not differ across the epilepsy groups, which would suggest that severity levels of emotional-social dysfunction were not driven by the differing epilepsy aetiologies or pathophysiological mechanisms (see section 7.1.1). However, the very small numbers in each sample means no reliable conclusions can be drawn from differences in severity amongst the epilepsy groups.

The third possibility outlined in section 7.1.5 was that psychopathology was a complication of recurrent seizures. Over time, seizures can effect adverse changes in the neural functions of the brain which in turn might result in psychopathological complications. If mental disorder was a complication of chronic seizures, then its severity should increase with number of prolonged or brief seizures over a lifetime.

With the TLE group, the number of lifetime seizures did not impact upon overall abnormality or indeed any one ESDQ or EFQ scale. Their high levels of self-rated abnormality were not associated with seizures.

Results from the GCSE group were counter-intuitive and the opposite of what might be expected considering severity of the condition as reported in the research literature. The number of prolonged seizures was negatively associated with *Inertia*, *Everyday Memory* and *Concentration* **indicating that the participants' rated difficulties on these three scales decreased** as the number of prolonged seizures increased (see Table 7.3).

It was argued in section 7.1.2 that the number of seizures might have a lesser impact on mental disorder than number of different seizure-*type* components (Altshuler, 1991; C. Dodrill, 1984, 2008; Hermann, et al., 1982; Swinkels, et al., 2005). Despite their GCSE disorder including components of brief generalized convulsive seizures and prolonged seizures, the GCSE group produced the lowest levels of self-rated difficulties, on some scales rating themselves as having fewer problems than even the neurologically healthy controls (see Figures 7.1a and 7.2a).

It is concluded that the actual severity of the epilepsy condition or any adverse impact of recurrent seizures is not reflected in the severity or extent of self-estimated difficulties.

Psychopathology as a secondary emotional reaction

No evidence was found for the fourth possibility (section 7.1.5) that psychopathology in these participants was a secondary emotional reaction to psychosocial problems (e.g. social stigma) associated with having a chronic condition. Neither of the two measures used in this study (number of years living with epilepsy, number of years in formal education) correlated significantly with the ESDQ, EFQ or DASS. However, other psychosocial measures not used in this study (e.g. number of years unemployed) might have produced evidence supporting an environmental link between epilepsy and mental disorders. See Appendix B for research literature on psychosocial factors which might contribute to psychopathology in epilepsy.

7.3.2 NATURE OF PSYCHOPATHOLOGY

Partner perceptions of abnormality

Although the epilepsy groups did not differ in severity of overall abnormality, they did differ with regard to (1) the spread of dysfunction across the separate ESDQ scales; and (2) the over- or under-estimation of their difficulties on the ESDQ, EFQ and DASS.

If most partners' responses are accepted as objective, the GCSE group had significant widespread areas of mental disorder such as emotional dysfunction, lack of psychological energy and initiative, behavioural disturbance (*Anger, Emotional Dyscontrol, Helplessness, Inertia, Indifference, Maladaptive Behaviour and Lack of Insight*). Perhaps

the GCSE participants themselves were unaware of possible problems, since they self-rated as normal on those same scales.

In contrast, the NCSE participant-partner discrepancy scores were significantly higher than those for the control-partner pairs, suggesting subjective over-estimation. It should be noted that the NCSE areas of dysfunction were similar to those as rated by the GCSE partners. Discrepancy scores from the TLE pairs did not differ significantly from the healthy control-partner pairs, indicating that (as a group) the TLE participants agreed with their partners as to their levels of emotional-social dysfunction across all ESDQ scales (see Figure 7.1b).

In short, the GCSE and NCSE participants could be differentiated with respect to the *direction* of their self-rated abnormality (over- or under-estimations). The SE participants as a whole could be differentiated from the IGE and TLE groups on the basis of *how widespread* their lack of awareness or insight might be (e.g. significant response discrepancies over seven ESDQ scales for the GCSE group versus no discrepancies for the two groups with brief seizures).

The four epilepsy groups cannot be said to differ in their spread of dysfunction in everyday living skills, since at most two EFQ scales showed above average levels of dysfunction (see Figures 7.2a and 7.2b). However, the same GCSE response pattern of under-estimation of difficulties was observed here as found with the ESDQ scales.

Self-perceived abnormality

It should be noted that while *most* partners were unbiased in their responses, some (perhaps through a sense of loyalty or over-protection) gave their significant others very low abnormality ratings indeed. Further, **the participants' responses might not be indicative of the actual** abnormality levels since some (when compared to their partners) over- or

under-estimated their abnormality. In particular, the GCSE **participants'** under-estimations for both the ESDQ and EFQ suggest that their perceptions of abnormality need to be considered.

Thus, *how* these individuals arrived at a self-estimation could be just as important as their actual scores. For this reason, factors which might influence their self-ratings on the ESDQ and EFQ measures were also investigated. They included neurocognitive and metacognitive factors and affect states.

7.3.3 ILLUSTRATIVE CASES

The nature of the psychopathology underlying the **participants'** responses was further explored by correlating scales from the two Questionnaires with affect scores from the DASS Scales (see Tables 7.2 and 7.3). For both groups, *Depression* was the main correlate in several scales from the ESDQ. (See Table 3.2 for a full description of the individual ESDQ scales).

For the GCSE participants, Table 7.3 indicates that *Depression* was negatively associated with five ESDQ scales (*Fatigue, Inertia, Inappropriate Behaviour, Maladaptive Behaviour, and Anger*). Thus, their awareness of difficulties on the five scales decreased as *Depression* increased. Taken together, the five ESDQ scales suggest problems with a lack of physical and psychological energy (*Helplessness, Inertia, Indifference*), aggressive behaviour (*Anger*) and other behavioural disturbances (*Inappropriate Behaviour, Maladaptive Behaviour*).

Also important, the **TLE group's** self-ratings on three ESDQ scales (*Anger, Helplessness and Indifference*) indicated less diffuse emotional dysfunction, and in contrast to the GCSE group, these scales were positively associated with *Depression* and *Stress*. It is not clear however, whether their difficulties did actually become worse with higher levels of

depression and/or stress, or whether their *self-perceived* difficulties were adversely influenced by higher levels of affect dysfunction.

The following are cases illustrative of some participants' response patterns in the current study. Comparisons are made between perceived cognitive abilities and actual performance on memory or attention tasks (see Table 7.5). **Each person's GPD derived from the mood/affect DASS scales is reported, and his/her overall abnormality mean based on ESDQ self-ratings is compared to that of his/her significant other.**

Over-estimation of difficulties

- Negative affect/mood and meta-cognitive dysfunction

With regard to the response patterns on the EFQ, affect and mood **had a negative impact on some participants' degree of perceived cognitive difficulties.** As can be seen in Table 7.5, three participants (Jill, Bela, Etta) showed poor insight into their meta-cognitive processes. Each participant perceived her incompetence on *Everyday Memory* and *Concentration/Attention* to be far greater than her actual performance on formal tests of episodic memory (AVLT) and attention factors (TEA).

Each participant had poor understanding of metacognitive processes involving memory and concentration, and also high levels of moderate to severe GPD (see Tables 7.2). Taken together, these two observations would suggest that negative affect impaired judgments requiring knowledge of meta-cognitive processes.

- Cognitive schemas and lack of insight

Jill and Bela illustrated the opposite of a psychological denial mechanism. They self-rated as very high on the DASS, EFQ and ESDQ, while their partners rated them with much lower levels of difficulty.

Jill (ASE) = moderate depression (87th percentile), overall abnormality ESDQ scales (2.59) compared to her partner's assessment of her (0.37).

Bela (IGE) = severe depression (99.5th percentile), discrepancy on overall ESDQ abnormality (self-perceived 4.66, partner ratings 2.26).

Both had their condition misdiagnosed in the past, resulting in adverse outcomes to medication, which probably contributed to an external locus-of-control. The impression gained at their intake interviews was of helplessness and depression, catastrophic anxiety about the future, and stress about the current week. Many years of living with an epilepsy condition (36 and 28 years respectively) would have facilitated construction of bleak world-views which were reflected in their responses, having little reference to currently more favourable life circumstances and a correct medication regime.

- Negative affect/mood and lack of insight

Etta and Nell are illustrative of the over-estimation responses (ESDQ and EFQ) influenced by negative affect levels produced by most of the TLE participants (DASS).

Etta (TLE) = moderate depression (92th percentile), overall ESDQ abnormality (self-rated 2.20 versus partner rated 0.05).

Etta had attempted suicide in the past, and she was stressed about the financial viability of their new small business. Her partner said the business was profitable and was optimistic about their future.

Nell (CPSE) = severe depression (96th percentile), overall ESDQ abnormality (self-rated 2.48 versus partner rated -0.85).

Nell gave an impression of cheerfulness, and was happy when recounting the arrangements for her up-coming wedding. The severe GPD levels on

the DASS seem to contradict this, but she had struggled as a single mother in the past.

Josie (TLE) = severe stress (97th percentile), overall ESDQ abnormality (self-rated 1.25 similar to partner rated 1.28).

Josie was an exception since her high stress levels do not seem to have influenced her self-ratings on the ESDQ. The high stress and anxiety levels on the DASS might have been due to her mother having recently been diagnosed with a terminal illness. Depression ratings on the DASS were within the normal range. Her self-perceived incapacity for everyday memory did not match her actual task performance.

Under-estimation of difficulties

In contrast to the over-estimated difficulties responses found with several TLE participants, most SE participants under-estimated their difficulties on both the EFQ and ESDQ.

- Poor awareness and meta-cognitive dysfunction

The EFQ self-ratings by the SE group of seven participants in Table 7.5 cannot be attributed solely to impaired meta-memory. Under-estimation of impairments occurred on either the *Everyday Memory* or *Concentration* scales but not on both in the same participant. Two participants (Cath and Mena) had an accurate estimate of their attention abilities, but not of their memory deficits, since they could not recognize their own dysfunction in that domain. Some people (Lana, Lori, Nell, Tom) under-estimated the attention domain but self-rated memory was accurate and matched their performance on formal tasks testing episodic memory.

Over-estimated abilities suggest poor meta-cognitive awareness of the rules governing attention processes. The fact that they all had an SE

disorder might be significant since attention deficits were associated with most of the SE participants (see Table 6.2).

- Life circumstances and poor awareness

Some participants' scores for overall ESDQ abnormality and/or their global psychological distress percentiles did not seem to equate with information gained from themselves and/or their partners. On the individual ESDQ scales some participants (Lana, Tom, Mena, Lori, Ron, Cath) did under-estimate their emotional-social dysfunction (when compared to their significant others).

Lori (GCSE) = moderate depression (89th percentile), overall ESDQ abnormality (self-rated -0.72 similar to significant other -0.55).

Lori's mother expressed deep concern about her daughter's increasing duration and frequency of prolonged seizures, as well as her maladaptive behaviours with regard to her illness (e.g. failing to maintain a medication regime, binge drinking). Lori herself did not present as depressed, and adopted a dismissive attitude when discussing possible changes to her life-style.

Lana (GCSE) = normal DASS levels, anxiety is very low (19th percentile), overall ESDQ abnormality is self-rated at 0.50.

Tom (ASE) = mild anxiety (82nd percentile), overall ESDQ abnormality self-rated at 0.68.

Mena (GCSE) = mild anxiety (82nd percentile), overall ESDQ abnormality (self-rated **0.53, less than her partner's rating 2.95**).

Cath (TLE) = below normal stress (4th percentile) and anxiety (11th percentile). Overall ESDQ abnormality self-rated at 1.00.

Five SE cases (Lori, Lana, Mena, Tom, Ron) and a TLE case with hippocampal sclerosis (Cath) seemed unaware of affective distress, giving either low normal or abnormally low scores (less than 15th percentile) on

the DASS and under-estimations of abnormality on the individual ESDQ scales. During interviews or assessment sessions, all five SE patients reported stressful life circumstances and/or maladaptive behaviours such as binge drinking and non-**compliance with medication (Lori)**. **Ron's** postictal anger had resulted in uncharacteristic physical assault, Lana had recently been diagnosed with a deteriorating medical condition, **Mena's children** had been taken into care by Child Safety during her latest SE episode, Tom was fighting an on-going court battle.

Perhaps significant, all had trouble accepting the reality of their epilepsy condition when it was originally diagnosed i.e. recognizing its consequences together with the implications for necessary changes in lifestyles. Perhaps their low DASS self-ratings and perceived normality on the ESDQ scales were a form of psychological denial, based on poor awareness arising from attention deficits.

7.3.4 PERCEIVED EMOTIONAL-SOCIAL DYSFUNCTION

Although both the TLE and GCSE groups' responses were influenced by depression, the association was in differing directions (positive versus negative correlations). For the GCSE participants, depression co-morbid with epilepsy might have impacted on their attention (vigilance, inhibition/control and distractibility) and thus lowered their awareness. In contrast, the TLE over-estimations suggest **that these people's depression probably involved catastrophic thinking** and/or learned helplessness. In short, a lack of awareness (GCSE) or poor insight (TLE) consistently biased *how* the participants perceived their psychopathology, rating themselves accordingly on the ESDQ.

Lack of Awareness: Sustained Attention/Distractibility

The GCSE participants' self-ratings on the ESDQ scales consistently underestimated their emotional-social problems (compared to their

partners' ratings of them and to normal controls') which may indicate an impaired awareness that such difficulties existed. Their perceptions of abnormality were influenced by several variables including the number of prolonged seizures (*Inertia*), depression (*Anger, Fatigue, Inappropriate* and *Maladaptive Behaviours*) and attention monitoring and control (*Lack of Insight*).

The GCSE group's *Lack of Insight* correlates were component measures of the Attention domain: vigilance and attention switching (TEA), distractibility errors (D-KEFS) (see Table 7.4). The low vigilance scores and distractibility errors both indicate impaired abilities to sustain attention. One paper reports cognitive deficits in patients with closed head injury (McAvinue, O'Keeffe, McMackin, & Robertson, 2005), who showed reduced capacity to sustain attention especially in vigilance tasks extending over long periods of time. Their patients also over-estimated their behavioural competencies, which is consistent with previous research (G.P. Prigatano, 2005). McAvinue et al. (2005) propose a lack of *global* awareness which contrasts with awareness of a local deficit at a specific time.

This study's GCSE participants, even though their MRI and CT scans failed to detect any brain abnormalities, produced similar deficits, including a tendency to under-estimate both their emotional-social dysfunction and difficulties with everyday living skills. Further, one left TLE case with hippocampal sclerosis and secondarily generalized seizures (Cath) gave lower than normal ratings on the DASS, ESDQ and EFO.

Poor Insight: Flexibility/Rigidity

Self-perceived abnormality in some TLE participants (Alana, Peg, Etta) was a mirror opposite to that of the GCSE group, rating themselves **as more abnormal than their partners' ratings**. Stress (*Anger*), and depression (*Indifference, Helplessness*) may have contributed to poor

understanding of their own emotional status. In addition, the TLE **participants'** responses on *Lack of Insight* were negatively associated with repetition errors (perseveration), suggesting that higher estimations (than those of partners or controls) were accurate and that they were aware of having emotional-social difficulties. The finding of positive associations with the DASS scales, however, suggests they had little insight as to how serious/trivial those problems might be.

An interesting finding was that the TLE participants' repetition errors (rigidity of visual fluency) were associated with *Lack of Insight* (ESDQ), while their *Lack of Insight* (EFQ) was associated with flexibility of visual attention (the opposite of rigidity) as measured by the Visual Elevator switching task from the TEA. Insight has been linked with flexibility in abstract thought in one study (Lysaker, Whitney, & Davis, 2006) where dimensions of executive function and their link to insight were investigated. Researchers administered tasks taken from the Delis-Kaplan Executive Function System to 53 participants with schizophrenia. Symptom awareness was associated with Verbal Fluency, Colour-Word, Tower, and Word Context scores. Awareness of treatment need was related to Colour-Word, Tower and Word Context tasks. Researchers concluded that insight may be related to capacities to shift attention (i.e. flexibility) between differing environmental demands (Lysaker, et al., 2006).

7.3.5 PERCEIVED COGNITIVE DYSFUNCTION

Most TLE participants (Alana, Peg, Etta, Josie) gave the same response pattern in the EFQ scales as in the ESDQ scales, rating themselves with greater than normal dysfunction in everyday life, particularly in *Concentration* and *Memory*. Participant ratings on *Concentration* and *Memory* were associated with *Depression*, *Anxiety* and *Stress*, suggesting negative affect influenced their responses.

On the EFQ scales, the GCSE participants rated themselves with fewer difficulties than their partners. This pattern was also evident in their discrepancy scores (*Emotions, Organization*), which were significantly different to those of controls-partner pairs. Results were consistent with regard to the impact of chronic GCSE on memory. As reported in chapter six, increasing numbers of prolonged GCSE seizures were associated with deteriorating verbal delayed recall (see Table 6.4). In this chapter, however, increasing numbers of prolonged seizures were associated with decreasing self-rated difficulty in *Memory* and *Concentration* (see Table 7.3). Thus, the more neurologically healthy participants (i.e. fewer prolonged seizures) tended to rate themselves as having more memory and concentration problems than those with a higher number of seizures.

Various explanations have been put forward for the discrepancy between subjective and objective memory status. Liik et al (2009) have briefly described study findings which include cognitive, psychosocial and emotional predictors of subjective reports of cognitive functioning by people with TLE. Those who believed they were more depressed also underestimated their memory abilities. Performance on formal memory tests was weakly correlated with perceived cognitive abilities, but the latter were strongly correlated with mood. Finally, neuroticism, anxiety and depression have been strong associates with subjective memory complaints in TLE patients (Liik, et al., 2009).

Meta-memory Awareness

Only moderate correlations have been found between self-reported memory complaints and results of neuropsychological memory tasks (Liik, et al., 2009). Yet meta-memory measures are essential for understanding the underlying processes involved in how people use memory in day-to-day life, such as intentional strategies to encode and retrieve information (Pannu & Kaszniak, 2005).

In the current study, different aspects of meta-memory seem to have **been affected in the TLE and GCSE participants' responses on the EFQ** scales. The latter seemed to lack knowledge of the rules of meta-memory (i.e. how memory should work) since they lacked awareness of any memory or attention dysfunction (see Table 7.5). In contrast, the TLE participants did not lack meta-memory awareness since they recognized they did have difficulties, but their application of metamemory knowledge during estimations was influenced by mood/affect.

In their review on meta-memory experiments on neurological populations, Pannu & Kaszniak (2005) conclude that depressive illness might play a role in hyperawareness. For example, some depressed people may exhibit excessive anxiety about their memory despite relatively normal memory performance, while others may underestimate their memory abilities in association with a general hopelessness in regard to self-efficacy. The reviewers did not include or consider response patterns such as that found with the GCSE participants in the current study. However, underestimation patterns, awareness and insight have been investigated in other populations with neurological disorders (Lysaker, et al., 2006; McAvinue, et al., 2005).

Finally, few studies have found epilepsy factors (e.g. seizure type, frequency, lateralization, type of epilepsy, AEDs) influencing subjective complaints about memory (Liik, et al., 2009). One study does find that TLE patients tend to overestimate their memory abilities depending on lateralization (Prevey, Delaney, Mattson, & Tice, 1991). In this current study, only one epilepsy variable (number of GCSE seizures) was found to influence self-ratings: *Inertia* (ESDQ), *Memory* (EFQ) and *Concentration* (EFQ).

7.3.6 SUMMARY AND CONCLUSIONS

Overall, this chapter's results suggest that the GCSE and TLE participants differed in the co-morbid relations underlying their psychopathology and epilepsy condition. The TLE participants' psychopathology was not a complication of chronic seizures since neither their cognition nor affective disorders were associated with number of brief seizures. Perhaps their negative affect is a product of disrupted activity in the limbic system, which has the same locus for TLE seizure onset. In contrast, the GCSE participants' lack of awareness of depression and emotional-social dysfunction was probably a component of their epilepsy condition and also a complication of prolonged seizures.

All three Questionnaires used in this study (ESDQ, EFQ and DASS) involved self-rated responses. According to their partners' reports, the GCSE participants tended to under-estimate problems, while most TLE participants were over-estimating their deficits. Thus, the most interesting finding for the psychopathology in epilepsy investigation was this contrast between a lack of understanding or insight (TLE cases) and a lack of self-awareness (GCSE cases).

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CHAPTER 8

SYNTHESIS

8.0 INTRODUCTION

The purpose of this study was to investigate the association between syndromes and/or seizure types with the cognitive and emotional-social functioning of adults with epilepsy. The situation for those people with a history of prolonged seizures was of particular interest.

The ILAE debate about classification of the epilepsies provided the theoretical context for the study. In 2010, the ILAE Commission on classification and terminology provided an update and recommendations (but see Berg, et al., 2010). The rationale for reviewing and up-dating the 1989 classification system was that it should reflect the contemporary state of knowledge within the field (Ferrie, 2010; Wolf, 2005). In the current study, the individual profiles of participants were tested against various predictions about cognitive and emotional functioning generated from the 1989 classification system and its related traditional **assumptions about the epilepsies**. **Popper's hypothetico-deductive** reasoning was then applied to test whether cognitive task performances conformed with, or contradicted, these assumptions (Berg & Blackstone, 2006; Buck, 1975).

Participants' performances also carried implications for the adequacy of the 1981 and 1989 seizures and classification systems, since their criteria were based on these assumptions (Commission on Classification and Terminology of the International League Against Epilepsy, 1981, 1989). **Crawford's computer programs for single case – control group comparisons** provided statistically-based methods so that conclusions were not based on anecdote alone.

8.1 DIAGNOSTIC RULES AND EXCEPTIONS

The 1989 organization of the classification and diagnostic system for epilepsies was based on how the epilepsy disorder was expressed (seizures are either localized or generalized); and its underlying cause (etiologies are either symptomatic/cryptogenic or idiopathic). Although widely used as guides for initial diagnostic decisions, the dichotomies were overly simplistic (Engel, 2006), and the majority of the cases in this study were (to varying degrees) exceptions to their either-or rule. The discussion that follows focuses on the exception cases with cognitive and abnormal psychology which did not conform to the predictions based on diagnostic and classification dichotomies.

8.1.1 IDIOPATHIC GENERALIZED EPILEPSY

The universal statement that *all swans are white* sums up one early assumption: IGE is a benign disorder with regards to cognition. At the beginning of this project, it was assumed that the IGE participants, at most, would have only a very mild lowering of overall intellectual abilities. Further, isolated local deficits would not be found. Indeed, for most of the IGE participants, general intellectual abilities fell within the normal range of performance, and several participants performed at a superior level.

The most interesting cases in this epilepsy group were those whose IGE disorder had a reflexivity component. Five people had photosensitive seizures, the most common form of reflex epilepsy (G. P. Lee & Clason, 2008). A distinction was found **between those people with “pure”** photosensitivity (i.e. *all* seizures were triggered by lights) who had minimal localized dysfunction versus two participants who had several kinds of reflex seizures (i.e. absences, photosensitivity, perioral myoclonia or eyelid myoclonia) as well as the typical tonic-clonic and juvenile myoclonic varieties which form part of IGE. The latter two cases exhibited severe cognitive deficits in executive control of attention and mild working

memory dysfunction. They also had significant lowering of current I.Q. compared to pre-morbid levels of intelligence. In this regard, these two **cases acted as “Popper’s *black swans*”** since they were exceptions to the early assumptions being tested. A finding of interest, whose general **application to IGE disorders with “pure” sensitivity versus reflexive seizure components** requires a larger group-based approach.

Increasing numbers of chronic IGE seizures were associated with fewer years of education, as well as diminishing abilities in perceptual concept-formation, episodic memory, verbal learning and recall. As would be expected, more years of education was positively associated with improved abilities across the same four cognitive correlates.

8.1.2 TEMPORAL LOBE EPILEPSY

The universal statement that *all finches are the same* sums up the traditional assumption that people with TLE have a recognizable profile of memory deficits. For many years, neuropsychological research (mainly with pre- or post-surgery patients) was based on a material-specificity model of TLE with cerebral lateralization and localization of memory impairments. Consequently, many studies have assumed that people with TLE generally would show the same pattern of memory deficits.

Results did not fulfill predictions of (a) TLE affects solely the memory domain; and (b) memory impairments lateralize according to the material-specificity principle. Firstly, the participants separated into three different classes or phenotypes of cognitive deficits based loosely on seizure-types and presence of structural abnormalities. Secondly, cognitive deficits were not found to be the result of material-specificity i.e. verbal impairment with the dominant hemisphere or non-verbal (visual) deficits when locus of TLE seizure was in the non-dominant hemisphere. **Like Darwin’s finches, differing deficit profiles seemed to be the result of each individual’s cognitive adaptability to her seizure-type,** presence of

structural abnormality, and clinical history. It is interesting that the number and variety of cognitive strengths (i.e. adaptability) followed the same phenotype classes as did the deficit profiles.

The interesting finding across participants was the presence of cognitive adaptability or inflexibility in their task performances. Those **“exception” cases assessed with only mild memory dysfunction (or none at all)** might have used their cognitive strengths (abstract verbal skills and/or verbal flexibility) to compensate for low cognitive impact (if any) of complex partial seizures. In contrast, two cases with secondarily generalized seizures demonstrated poor memory and moderate attention dysfunction, made distractibility and/or repetition errors, together with low scores on a cognitive flexibility measure. The finding with the third class or cognitive phenotype was somewhat different. Cath (hippocampal sclerosis) and Jana (cavernous haemangioma) had either inherited an abnormality (Jana) or developed one in early childhood (Cath). They differed on severity levels of cognitive impairments, however, which might **be attributed to the presence of “good” or “bad” plasticity during their neurodevelopmental development.** For a discussion on *the plastic paradox*, see Doidge (2008, pp. 243-244, 318).

8.1.3 STATUS EPILEPTICUS SEIZURE-TYPES

The universal statement that *all ravens are black* is an analogy for the belief that prolonged seizures are associated with adverse neurological, psychiatric and cognitive outcomes. Because GCSE seizures involve prolonged convulsions, the expectation is that they will be associated with more severe cognitive impairments than brief seizures. A similar outcome for CPSE seizures is more controversial, and ASE is generally viewed as benign with respect to any impact on cognition.

Several participants acted as Popper’s *white ravens* and did not fulfill the prediction that the SE seizure-types would be associated with

severe cognitive impairment. Two people with GCSE had mild to no deficits at all. The memory deficits found in people with brief TLE seizures were also found in the participants with prolonged CPSE seizures, but the latter also had widespread dysfunction including language, attention and executive fluency. In the past, both IGE and ASE have been assumed to be benign with regard to cognition, but one person with ASE still had moderately severe divided attention difficulties when tested some 5 months after the latest prolonged episode. In short, the presence of *white raven* exceptions contradicted predictions of long-standing adverse impact across the SE seizure-types.

Another assumption has been that impaired cognitive domains associated with the various types of SE would be the same as those associated with their brief seizure counter-parts, just more severe. That prediction was not borne out, with widespread deficits of attention being found across all three SE seizure-types. Executive dysfunctions of verbal and design fluency were found in both CPSE and some GCSE cases as were language and memory impairments.

The most interesting finding was that, for some participants, cognitive impairment was transient, resolving with the passage of time after a previous GCSE seizure. However, this seemed to apply only for those cases with neuroprotection i.e. healthy lifestyles and adherence to a medication regime. In contrast, CPSE cases with a history of addiction had widespread and severe deficits still present some 1.5 – 3.5 months after their most recent CPSE with secondarily generalized seizures. One ASE case with only two prolonged episodes but sporadic adherence to recommended medication still had a moderately severe attention deficit five months after the more recent seizure. This phenomenon of transient dysfunction versus longer-lasting deficits was found across all three SE groups.

Chronic SE seizures

Of all the epilepsy groups, GCSE seizures were associated with the most widespread impact. The highest number of prolonged episodes was four, though several episodes consisted of repeated seizures without recovery of consciousness between episodes. Increasing numbers of GCSE episodes were adversely associated with: delayed verbal recall (a composite of semantic and episodic memory scores), estimated I.Q., fewer years of education, and a younger age at onset. With regard to emotional-social dysfunction, increasing number of GCSE episodes was associated with lower self-ratings of *Inertia* and fewer problems reported on *Everyday Memory* and *Concentration*. Results suggest that lowered self-awareness **biased the participants' self-ratings** favorably.

It is possible that a lack of awareness and insight might have **contributed to some participants' poor medication compliance and lifestyle** choices. As a result, they had little neuroprotection against further seizures with a consequent worsening of their SE condition.

8.1.4 EPILEPSY CO-MORBID WITH PSYCHOPATHOLOGY

Rates of mental illness are believed to be higher in people with epilepsy than the normal population. The current study found the epilepsy participants displayed significantly higher emotional-social dysfunction than the healthy control group. The universal statement *Birds of a feather flock together* refers to shared characteristics. Possible co-morbid relations include shared pathogenic mechanisms such as biochemical abnormalities, shared neuroanatomical locations (e.g. temporal lobes), or changed neuronal functions caused by recurrent seizures.

Co-morbid relations

The results from section 7.2 of Chapter Seven suggest the GCSE and TLE participants differed in the nature of co-morbid relations linking their psychopathology and epilepsy disorder. Conceivably, some TLE **participants' exaggerated perceptions of abnormality were part of their** epilepsy condition since locus of seizure onset and affect dysfunction have a common origin in the temporal lobes and related limbic structures. The **TLE participants' psychopathology does not seem to have been a direct** complication of the seizures themselves since neither their cognition nor their psychopathology was associated with increasing seizure numbers. It is possible that inter-ictal epileptiform activity disrupted affect or mood and also influenced self-estimates of abnormality.

For the GCSE participants, their unawareness of mental illness seems to have been not only a component of their epilepsy disorder, but also a complication of prolonged seizures. First, an underlying lack of awareness seemed associated with several results (e.g. negative correlations between ESDQ self-ratings and *Depression*, participant under-estimations in patient-partner discrepancy scores). Conceivably, this quality and the reduced or impaired vigilance found with GCSE participants had a common origin in their epilepsy disorder. For example, the neurocognitive variables positively associated with under-estimated self-ratings on *Lack of Insight* (ESDQ) all involved attention (vigilance, measures of control over automatic attention responses). Attention variables themselves were not associated with increasing numbers of prolonged seizures, either negatively or positively. However, attention deficits were also present throughout the GCSE results in chapter six, and so might be best described as neurocognitive markers for the lack of awareness of mental illness associated with the GCSE condition.

Second, results suggest the lack of self-awareness was sometimes a complication of prolonged seizures. Regarding problems with *Everyday*

Memory, Concentration and Inertia, **participants' self-ratings** on these scales were found to decrease with increasing numbers of GCSE seizures. Also interesting, when it was a formal memory task providing objective assessments (not **self-rating scores**), **then participants' performance scores** (e.g. delayed verbal recall and current estimated I.Q.) deteriorated with an increasing number of GCSE seizures.

Epilepsy co-morbid with Depression

A recent consensus statement by researchers into the affective disorders in epilepsy suggests that the explanation for the high co-morbidity between depression and epilepsy lies with a shared pathogenic aetiology (Barry, et al., 2008).

It is conceivable that the GCSE participants' depression and behavioural disturbances shared the same pathophysiological imbalance associated with prolonged generalized convulsive seizure-types. The **GCSE participants' partners rated them on the ESDQ as having low** physical and psychological energy which have a global effect on brain activity and cognition (e.g. processing speed, attention). The presence of low energy and initiative is significant since they are characteristics of both depression and epilepsy, suggesting a shared pathogenic origin for their co-morbidity. It is possible the GCSE condition was co-morbid with the kind of depression similar to that specified in the DSM-IV. Since there was an element of unawareness of their mental illness, it seems likely **their depression was endogenous rather than "reactive"**.

With regard to the TLE participants, their results were consistent with research which links both affect and complex partial seizures as having a common origin in the temporal lobes. Hixson and Kirsch (2009) have described interictal disturbances when seizure foci are said to disrupt the cortical networks that carry out emotional processing by way of ongoing or intermittent abnormal epileptiform activity (Hixson & Kirsch,

2009). The interictal disturbances affect wider brain functions including mood, social relations and emotional health generally. The inter-ictal dysphoric disorder (IDD) described in the literature seems to best describe the psychopathology of the TLE participants as reflected in the ESDQ, EFQ and DASS self-rating scores.

Interictal dysphoric disorder is specific to people with epilepsy, and can be differentiated from the primary affective disorders specified in the DSM-IV on the basis of their course-of-illness (Blumer, et al., 1995; Kanner & Balabanov, 2002). Duration of IDD is in hours or at most a few days suggesting a depressive state (instead of weeks or months) but is deeper and diurnal improvement in mood has not been observed (Blumer & Altshuler, 1998). In a letter to *Epilepsy & Behavior*, Tarsitani and Bertolote (2006) noted that IDD (which has a shorter duration than major depression) may depend on specific epileptic brain-related variables e.g. direct activation of illness-induced physiological processes such as neurochemical changes in limbic structures (Tarsitani & Bertolote, 2006).

The results from the three questionnaires should be taken as a reflection of *how* the participants arrived at their self-ratings, rather than as an accurate portrayal of their emotional status.

Perceptions of abnormality

The most interesting finding in Chapter Seven was the TLE and **GCSE groups' mirror**-opposite approach to self-estimation, found consistently across several analyses. Contrasting approaches to self-rating difficulties or problems were evident on both the ESDQ and EFQ scales. Discrepancies between patient and partner ratings indicated most TLE participants tended to over-estimate their problems, while people with GCSE under-estimated them. Correlations between patient responses on the affect scales (DASS) and the ESDQ or EFQ scales were positive for the TLE cases but negative in the GCSE cases, the latter being a counter-

intuitive finding since SE is the more serious neurological condition. With regard to response patterns on the EFQ, these might be explained by a poor meta-cognitive awareness of their own attention processes in the **GCSE participants**. **The TLE participants' poor judgment of their own** everyday memory capacities may have been disrupted by meta-memory dysfunction associated with high levels of depression, anxiety and stress.

Finally, for both GCSE and TLE participants, the cognitive domains affected by their epilepsy condition were the same neurocognitive correlates (attention control and flexibility) associated with *Lack of Insight* (ESDQ and EFQ). Chapter 5 (TLE cases) reported cognition results suggesting that flexibility (or rigidity) might have facilitated (or impaired) performance of several memory tasks. Chapter 6 (SE cases) reported that the main cognitive deficits in people with GCSE, CPSE and ASE were attention factors, but also that number of GCSE seizures impacted adversely on delayed verbal memory and current I.Q. The results suggest that lack of awareness was a component of that GCSE condition, while lack of insight/judgment was associated with the TLE disorder.

8.2 BLURRED DICHOTOMIES

The ILAE Task Force's report on classification and terminology (Berg, et al., 2010) recommended that a rigid approach to classification be abandoned. The dichotomy of generalized versus focal ictogenesis has become blurred. This study followed **Popper's hypothetico**-deductive method (Berg & Blackstone, 2006; Buck, 1975) where universal statements were refuted by the presence of **"exception" cases**, thus blurring the either-or nature of dichotomous criteria. **The study's findings** from some specific exception cases are listed as follows.

- Localized visual learning or retrieval deficits were found in four IGE cases.
- Both generalized attention and memory impairments were found in two TLE cases; and generalized impairment (language, executive dysfunction and episodic memory) in another.
- Localized single deficits of attention were found in two GCSE cases; and no deficits at all were detected in another case.
- Generalized impairments of attention, language, memory and some executive processes were found in both CPSE cases.
- Localized mild attention dysfunction was found in one ASE case; and moderate to severely impaired performance in an attention task by a second ASE case.

As the above list shows, the majority of individual profiles failed to uphold predictions based on descriptive dichotomies. People with generalized brief seizures had isolated components of memory dysfunction, while single localized deficits were found in several cases with prolonged convulsive seizures. With regard to complex partial seizure-types, neatly localized and lateralized memory deficits were not found as predicted. The ILAE classification dichotomies provided an inadequate description of the individual cognitive profiles actually found.

8.2.1 CONCEPTUALIZATION: SEIZURES AND SYNDROMES

In 2008, a three-day workshop was convened by Capovilla and colleagues in Monreale (Italy), with the theme of “**Conceptual dichotomies: idiopathic versus symptomatic and partial versus generalized**” (Capovilla, Berg, et al., 2009). They recommended a re-definition of seizures to be guided by scientific evidence rather than descriptive assumptions and expert assertions. Further, new thinking on seizure pathogenesis should be used as a basis for classification (Capovilla, Berg, et al., 2009; Ferrie, 2010). The new conceptualization of generalized seizures is described by

the ILAE Commission “as originating at some point within, and rapidly engaging, bilaterally distributed networks (which can be asymmetric). Focal seizures are conceptualized “as originating within networks limited to one hemisphere” (Berg, et al., 2010, p. 658). For a discussion on these definitions, see comments by Avanzini (2010) and Wolf (2010).

Although cognitive variables do not form part of the ILAE Task Force’s considerations, the 2010 re-definition would provide a better account for the individual cognitive profiles found in the “exception cases” as it proposes a spectrum rather than a black or white dichotomy. Semiologists also favour a spectrum, describing gradations in *basic epileptogenicity* between the two extremes of generalized seizures (a high level) and localized seizures (a relatively low level) (H. Luders, Turnbull, & Kaffashi, 2009). They also argue for a mixture of genetic, triggering, and causative factors found in the aetiologies of all epilepsies as being more useful than the strictly symptomatic versus idiopathic choice. Further, they argue that seizures and aetiologies should be viewed as a continuum between the opposing extremes set by the dichotomies.

With regard to the current study, a spectrum or continuum would better account for the mixture of both generalized impairments and localized deficits of cognition found within some cases, irrespective of their seizure-type or syndrome.

In the *Epilepsia* discussion forum “Gray Matters”, Avanzini commented that the ILAE Commission had given a satisfactory report on seizure classification (Berg, et al., 2010) but had not provided a *conceptual frame-work* for an updated classification of the epilepsies (Avanzini, 2010, p. 721). Several participants in the discussion also felt that, for various reasons, a simple list or constellations of epilepsy symptoms does not provide a homogenous approach to research and clinical practice (Fisher, 2010; Guerrini, 2010; Shinnar, 2010; Shorvon, 2010).

8.3 SYSTEM EPILEPSIES

The term *system epilepsy* refers to “a chronic condition of the brain characterized by an enduring **propensity to generate epileptic seizures**” (Wolf, 2006a, p. S24). Further, this constitutional-genetic predisposition to recurrent seizures is common in both idiopathic and symptomatic epilepsies (Berg & Blackstone, 2006; Lennox, 1960; H. Luders, et al., 2009; Rodin, 2009). At the Monreale Workshop, the new term was accepted as describing epilepsies with focal seizures (depending on epileptic susceptibility of a given cerebral system), and generalized epilepsies which consist of differing sub-groups of circuits or systems (Capovilla, Berg, et al., 2009). They differ mostly due to different wiring or neurophysiological networks. Researchers have described *system epilepsies* as related variants of (functional) system disorders of the brain (Avanzini, 2010; Wolf, 2006a; Wolf, Inoue, & Zifkin, 2004).

It is possible that Wolf’s descriptions of functional-anatomic circuits might also apply to those cases in this study with cryptogenic aetiologies (Wolf, 2006a). Most TLE and GCSE cases in this study had cryptogenic etiologies, with no reported familial history and no symptomatic causes detected with neuroimaging tools. Compared to a conceptualization of epilepsies as syndromes, system epilepsies seem to better reflect the inherent **qualities of cognitive processing associated with the participants’** different seizure-types.

Automaticity or Intentional Control

For the two IGE cases with several reflexive seizure-types, their attention deficits were detected by tasks which all assessed some form of intentional control over responses. The most severely affected performances were response inhibition when faced with a choice of conflicting attention responses; and also control over switching attention between stimuli words/colours (D-KEFS Colour-Word Interference tasks).

Automaticity, or the inability to intentionally inhibit and control automatic reactions, might best describe the qualitative nature of impairments in those participants whose IGE disorders had reflexive seizure components.

Rigidity or Flexibility

For most TLE participants, visual flexibility (or lack of it) seemed to play a role in both memory task performance and self-rated lack of insight. Two cases with moderate to very severe cognitive impairments showed inflexible attention responses (Josie and Etta with secondarily generalized seizure-types) and one case with verbal perseveration or rigidity (Cath with hippocampal sclerosis). In addition, most TLE cases over-estimated their own abnormality and these perceptions correlated with accuracy of visual flexibility. In short, the quality manifested in most TLE cases was one of inflexibility and rigidity of information processing during cognition tasks and measures of emotional-social functioning.

Distractibility or Sustained Attention

Sustained attention measures assess basic states of arousal and maintenance of alertness to the outside environment. Eight of the nine SE cases showed attentional dysfunction. More importantly, seven of these cases involved deficits in components of sustained attention (divided attention or vigilance) ranging from reduced to severely impaired. Regarding psychopathology, number of GCSE seizures was strongly associated with *Inertia*, while vigilance, distractibility and other attention tasks were strong correlates of *Lack of Insight* (ESDQ). Further, all these strong associations were negative, suggesting a lack of self-awareness with regard to *perceived* abnormality. In short, a state of lowered arousal and/or diminished alertness seems to underlie the weak performances in tasks requiring sustained attention.

8.3.1 DYSFUNCTIONAL NETWORKS AND MECHANISMS

The qualities outlined above have also been associated with brain mechanisms which possibly underlie both cognitive dysfunction and mental disorder. The relevant brain structures include the medial prefrontal cortex, the posterior cingulate cortex, and the anterior cingulate cortex.

Default Mode Network (DMN) and Epilepsy

The default mode of brain activity denotes a state in which an individual is awake and alert, but not actively involved in an attention demanding or goal-directed task (i.e. a “resting state”) **brain function** (Raichle et al., 2001). Although deactivated during task performance, the default mode network is active in the resting brain with a high degree of functional connectivity between regions (see Broyd et al., 2009 for a review of DMN studies and mental disorders).

Interictal epileptic discharges have been shown to disrupt the **connectivity between brain regions during the brain’s “resting state” with** poor consequences for cognitive functioning (Archer, et al., 2003; Broyd, et al., 2009). Imaging studies with fMRI of relaxed TLE patients (Laufs et al., 2007), and patients with generalized convulsive seizures (Lui et al., 2008) have associated cognitive deficits and transient impairments with aberrant default mode brain dysfunction. Both studies implicate the posterior cingulate cortex (Laufs, et al., 2007; Lui, et al., 2008). Further, Lui et al. (2008) reports that epilepsy patients with partial versus generalized seizure-types **can be differentiated according to diverse “resting state”** patterns.

The medial prefrontal cortex is said to have a role in self-monitoring psychological states, and in interpreting the psychological states of others (i.e. theory of mind). Recent research into the medial prefrontal cortex

and social cognition has evaluated ways in which affect and mood inform different types of cognitive judgments (Ochsner & Phelps, 2007). The people with TLE were aware of having cognitive and/or emotional problems, but when their actual task performances or life circumstances are considered, their ratings on degree of abnormality were influenced by emotions and mood.

One of the posterior cingulate cortex functions is to evaluate emotionally salient environmental stimuli, including emotional processing related to episodic memory (Bush, Luu, & Posner, 2000). Studies with neurologically healthy participants have shown the posterior cingulate cortex adapts attention to external and internal environments by attenuation of activity during task-specific performance e.g. focused attention (Broyd, et al., 2009). Two IGE cases with reflexive seizures had moderate to severe deficits of attention control and selection which might **be explained if the posterior cingulate's adaptive function had been** disrupted by interictal epileptic discharges.

Finally, both the main structures with “resting state” functions are involved in introspective processes such as self-referential and emotional processing. They both mediate emotion-cognition interactions but differ in their roles (Ochsner & Phelps, 2007). The posterior cingulate cortex has an evaluative or adaptive function, while the medial prefrontal cortex plays a more executive or mediator role (Bush, et al., 2000). Activity in these two structures becomes attenuated when attention is directed toward external events including tasks (Broyd, et al., 2009).

The Task-Positive Network and Attention

The mechanisms underlying attention impairments found with the SE cases are difficult to attribute solely to interictal epileptic discharges and aberrant activity in the default-mode network. The SE deficits, particularly the GCSE cases, involved impaired components of attention

and a lack of awareness ranging from reduced and transient to severe and longer-lasting. They might be attributed to dysfunction of the anterior cingulate cortex and its underlying mechanisms which have been associated with attention deficits, at least in part (S. F. Taylor & Liberzon, 2007). Impaired attention might also affect memory functioning since animal studies have shown that the anterior cingulate cortex is involved in early stages of learning which require controlled effort and flexibility (for a review, see Bush, et al., 2000).

Bush et al. (2000) describe the anterior cingulate cortex as a component of parallel distributed attentional and emotional networks, part of a circuit which serves to regulate both processing-types (S. F. Taylor & Liberzon, 2007). The *cognitive* subdivision of the anterior cingulate is connected to the prefrontal cortex, parietal cortex and premotor areas, which are activated by cognitively demanding tasks including stimulus-response selection from competing inputs as in the Stroop tasks, divided attention tasks, verbal or motor response selection tasks, visuospatial tasks and many working memory tasks.

The *affective* subdivision is connected to the amygdala, hypothalamus, hippocampus and orbitofrontal cortex (Devinsky, Morrell, & Vogt, 1995), which are activated by affect-related tasks eliciting symptoms of various psychiatric disorders (depression, anxiety, simple phobia, obsessive-compulsive disorders) (Ochsner & Phelps, 2007; S. F. Taylor & Liberzon, 2007). One anterior cingulate cortex function is to assess salience of emotional input, and another is to regulate emotional responses (S. F. Taylor & Liberzon, 2007). **According to their partners'** ratings, the GCSE cases were only partially aware of their mood states, if at all, and they were unable to regulate emotional responses (*Anger, Emotional Dyscontrol, Maladaptive Behaviour*).

8.4 LIMITATIONS AND QUESTIONS

8.4.1 LIMITATIONS

Factors other than epilepsy-related variables

The nature of the study design (group comparisons as well as within-individuals and between them) means that the impact on cognition of variables other than epilepsy-related factors cannot be entirely ruled out.

Polypharmacy

Some individuals' medication regime consisted of several anti-epileptic drugs (polypharmacy) rather than a single AED (Jill, Nell, Caro, Sher and Bela). Nell and Caro had a history of drug abuse, but had been free of alcohol or other drugs for twelve months before testing began. Sher and Bela had never used drugs, but at time of testing, Bela had only recently changed her regime to the correct medication. Polypharmacy **does not seem to have affected Jill's cognition, since** only very mildly impaired selective attention had been detected. In contrast, Etta and Josie were on only one AED and did not abuse drugs, yet both had moderate to severe attention deficits

Non-adherence to a medication regime

Regular alcohol abuse or binge drinking, as well as non-adherence to a prescribed medication regime, meant that Lori, Tom and Cath lacked the neuroprotection enhanced by an effective medication and a drug-free life-style. Their epilepsy condition and severity levels of cognitive dysfunction were probably affected.

Elapsed Time and Longitudinal Studies

For the SE groups, the study was able to conclude which participants had more long-lasting deficits by noting time (days, weeks, months) that had elapsed since the latest prolonged seizure previous to testing. A longitudinal study design, however, would have allowed repeated testing and quantifiable change - deterioration or recovery of cognitive functions since the previous seizure.

Regular assessment of individuals was not practicable in a regional hospital where some cases were out-patients or admitted at the Emergency Department, and where prolonged seizures were not always recognized as differing from brief seizures. In short, a longitudinal study design would have had a better chance for successful completion in a capital city hospital with an established epilepsy research program.

Subjective and objective measures

A growing number of studies have found that self-ratings and/or memory complaints do not always agree with results from more objective measures such as assessment tasks or ratings by significant others (Blake, Wroe, E.K., & McCarthy, 2000; Howard et al., 2010; Liik, et al., 2009; Pannu & Kaszniak, 2005). Since self-rating responses form the basis for much research into the psychology of epilepsy (including quality-of-life, personality, emotional and affective status) factors that might bias self-ratings need to be identified and further investigated.

In a review of cognition and epilepsy, Elger, Helmstaedter, and Kurthen (2004) suggested that (a) the external or ecological validity of neuropsychological results is under-emphasized in current research; and (b) one variable receiving little attention is subjective measurement of impairment and its potential as a productive field of enquiry.

One example is a study by Fargo et al., (2004) which investigated how seizure-type affected objective versus subjective perceptions of neuropsychological dysfunction. The researchers compared accuracy of self-reported neuropsychological functioning in individuals with epilepsy seizures versus those with non-epileptic psychogenic seizures.

Ecological validity of objective measures

First, this study found that the GCSE and TLE patient's perceived skills in everyday memory and concentration did not always mirror their actual performance in parallel tasks, and the mismatch was attributed to a lack of awareness or insight. An alternative explanation would be that the actual objective tasks did not measure the same abilities as the skills used for everyday functioning (Crowe, 2005). However, objective and subjective measures did match in the IGE participants, suggesting that the objective measures of cognitive functioning had ecological validity. Thus, the mismatch found in the TLE and GCSE cases was most likely measuring *perceived* difficulties with everyday memory and concentration in these **participants' self-ratings**.

Bias-free ratings on subjective measures

Second, studies using self-report measures often compare scores to **significant others' ratings with the latter acting as a control group**. However, the discrepancy scores thus produced cannot discriminate **between patients' self-reported over-estimations of abnormality and significant others' under-estimated ratings of same** (Elger, et al., 2004; Trosset & Kaszniak, 1996).

If partners' ratings on the EFQ matched objective measures of cognitive functioning (while the participants' scores did not) that would be an indication of unbiased ratings by significant others. With regard to emotional-social functioning ratings on the ESDQ and DASS, a control

measure for bias-free self-ratings might be objective tests of psychopathology administered and interpreted by a clinical psychologist.

In this study, responses about problems on the ESDQ seemed to be consistently over-estimated by most of the TLE participants and underestimated by the GCSE cases. Since an objective measure of emotional-social dysfunction had not been included in the present study, this method could not be used to assess presence or lack of bias during **participants' self-ratings**. The alternative was to compare those participants producing larger discrepancy scores than warranted by their actual life circumstances (as recounted during their intake interviews). While such interview information might be argued to constitute **“anecdotal” evidence only, the reported facts were corroborated** by their significant others.

Indigenous language

English as a second language was not one of the exclusion criteria because many indigenous people now acquire English as a first language. Those who do have an indigenous first language rarely (if ever) need to use it as older-generation speakers pass away. Thus, using an indigenous language is unlikely to have affected these **participants' verbal abilities** to a significant extent.

Three of the four indigenous participants had naming deficits: Sher ($z = -2.00$), Cath ($z = -3.37$) and Lori ($z = -3.00$). Lana had no verbal deficits at all. It might be argued that their verbal difficulties were attributable to years of unsuccessful education rather than the impact of an epilepsy disorder. Sher had completed 11 years. Lori had grown up in a remote island in the Torres Strait and reported 7 years formal schooling but (after epilepsy onset) continued her education at home. Cath had completed 12 years of education so the severity of the naming deficits is

most likely associated with her left TLE disorder and associated hippocampal sclerosis.

Both Lori and Sher grew up in remote areas outside Cairns where indigenous language usage is more common than in city areas. They were observed in conversation with their mothers, speaking confidently in their respective indigenous languages, so it is unlikely that their impaired naming abilities (and other verbal deficits) could be attributed to either school failure or language acquisition problems. Lana and Cath were from a regional city and had never learnt their respective indigenous language.

The impact on verbal competence through acquisition of English as a second language (rather than first) has been debated for many years. Indeed, some psycholinguistic research into the simultaneous acquisition of English and another European language/s has shown that greater language proficiency, such as metalinguistic awareness of grammatical structure, is often the result (but see Roberts, Garcia, Desroches, & Hernandez, 2002). Lori and Sher reported acquiring their indigenous language and English simultaneously, using one for older-generation family members and English for same-generation siblings and cousins, later at school and any other social relations.

For indigenous people with epilepsy, it is likely their disorder might contribute to impaired verbal abilities to a greater degree than either late English acquisition or unsuccessful schooling. Usage of indigenous languages lessens with each passing generation, and (unless teachers and elders intervene) the language eventually becomes extinct.

8.4.2 QUESTIONS

The availability of only small numbers of participants meant that **this study focused on “exceptions” to traditional diagnostic criteria** such as cognitive profiles or emotional-social dysfunction (e.g. affect disorders

in the TLE group). Consequently, generalizations from the participants' performances to the larger epilepsy population cannot be made on the basis of this study's findings. Generalization of findings to principles of cognition or psychopathology was not the purpose of the study.

Components of Sustained Attention factor

The only consistent finding for the SE participants' cognition was impairment of attention. Questions remain, however, with regard to the various factors of attention associated with the SE seizure-types.

One question posed by Bate, Mathias and Crawford (2001) was raised by this study's results for SE individuals: is divided attention a component of Sustained Attention or an attention factor in its own right? Two Sustained Attention measures (*Phone Search while Counting* and *Lottery*) reflect effortful task performance (dual-task) versus a state of alertness to surrounding stimuli (vigilance) respectively. The latter perhaps reflects the "resting state" of the brain when not involved in goal-directed activity.

With regard to GCSE seizure-types, the resolution of cognitive deficits over time would be of interest to investigate, especially any interaction between longer-lasting deficits and an absence of neuroprotection (e.g. addictive life-style, non-adherence to medication regimes). Another question is whether cognitive profiles for convulsive CPSE would be more severely impaired than those of non-convulsive CPSE? The CPSE participants' cognition in this study might have been influenced by confounding variables such as a history of alcohol abuse or depression, so this question needs to be further explored in other studies. Finally, would both atypical and typical Absence Status cases have intact cognitive functioning? There was no such distinction made between Jill and Tom in this study, but their differences in cognitive profiles suggest this might prove a worthwhile investigation with other patients.

Components of meta-memory

More research is needed into the underlying variables associated with **“underawareness of memory and hyperawareness which might cause a person to report a poorer memory than they actually have”** (Pannu & Kaszniak, 2005, p. 126).

One question that should be investigated further concerns the specific components of meta-memory and how they are related to executive function processes. One way to address this issue is to include a broad range of neuropsychological tasks when assessing meta-memory in patient groups (Pannu & Kaszniak, 2005). These researchers suggest that retrieval deficits, poor attention, and other components of executive function might differentially correlate with meta-memory, thus providing indicators of the specific components necessary for accurate judgments of memory abilities. A factor analysis might identify the specific components by using frontally sensitive tests (Pannu & Kaszniak, 2005).

Perhaps the specific component processes that are involved in meta-memory could be identified by using measures such as feeling-of-knowing (fok) and feeling-of-learning (fol). The ESDQ and EFQ results distinguished between over-estimation of difficulties (lack of insight or understanding into seriousness or triviality of a problem) and under-estimation of difficulties (lack of awareness). One question of interest would be whether patient responses on a fok task equate with a lack of awareness of difficulties, and whether responses to an fol task might correlate with a lack of understanding or insight.

Cognitive phenotypes and cognitive reserve

One question concerning cognitive phenotypes in TLE asks whether their different levels of impairment and variety of cognitive deficits might

correlate with measures of cognitive reserve, such as adaptability or computational flexibility or “good” neurodevelopmental plasticity.

8.5 CONCLUSIONS

In conclusion, this study examined cognitive and emotional dysfunction in people with different types of epilepsy: idiopathic generalized epilepsy, temporal lobe epilepsy, and status epilepticus. The majority of cases failed to match the predicted profiles.

All the TLE cases in this study had a cryptogenic aetiology, and as expected, had some form of memory dysfunction. However, these **participants’ episodic memories failed to lateralize which contrasts with** many studies of TLE cases with symptomatic aetiologies. The IGE cases were used as a comparison group for single cases in the other epilepsy groups. Two cases had multiple types of reflexive seizures as components of their IGE disorder. The association of types of reflexivity (perioral and eyelid myoclonia, photosensitivity) with lowered cognitive abilities found in this study highlights the importance of further research into the nature of cognitive complaints in people with IGE.

Patients with complex partial and convulsive SE seizure-types also showed cognitive deficits. Although case ascertainment of this uncommon condition limited subject numbers and prevented definitive conclusions, overall patterns across the nine cases suggested cognitive dysfunction was distributed. Most notably, impaired attention might have been tied to other cognitive domain deficits (e.g. memory) as well as a lack of **awareness. The study’s findings align with the emerging views of the** importance of network dysfunction in the symptomatology of epilepsy.

It is concluded that the ILAE classification dichotomies of the 1981 and 1989 systems were inadequate for these participants. The nature of

its black-or-white dichotomies limited its usefulness for accurate predictions about cognition or psychopathology (Commission on Classification and Terminology of the International League Against Epilepsy, 1981, 1989).

Most importantly, these participants' epilepsies had non-symptomatic aetiologies that might partly explain task performances which did not always conform to the predicted profiles. Other **contributors to some participants' profiles include current alcohol** abuse or a history of other drug use, complex seizure-types (e.g. reflexive seizures, secondarily generalized seizures), and/or co-morbidities (e.g. mood/personality). Finally, the idiosyncrasy of individual cases greatly influenced cognitive and emotional **presentations, and the exception cases'** dysfunctions might not have been detected if the individuals had formed part of an empirical study with a large clinical sample.

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APPENDIX A: CLASSIFICATION

ILAE DIAGNOSTIC SCHEME FOR SEIZURES (1981), AND ILAE CLASSIFICATION SYSTEM FOR SYNDROMES (1989)

The 1981 diagnostic scheme for seizures below is an abbreviated extract from Table 8-23 in Smith and Wallace .

Appendix Table 1
Diagnostic Scheme for Seizures (1981)

ILAE 1981 seizure classification
<p>1. Partial Epilepsies simple partial seizures; complex partial seizures.</p>
<p>2. Primary Generalized Epilepsies typical or atypical absence seizures; tonic-clonic seizures; clonic seizures; tonic seizures; myoclonic seizures.</p>
<p>3. Status Epilepticus seizures</p> <ul style="list-style-type: none"> • <i>Generalized Status Epilepticus</i> Absence status, tonic-clonic status, clonic status, tonic status, myoclonic status, atonic and akinetic status, unclassifiable. • <i>Partial status epilepticus</i> elementary partial status; complex partial status. • <i>Unilateral status</i>
<p>4. Unclassifiable Epilepsies</p>

Seizures are classified as either partial or generalized, then divided into sub-types. Seizure onset in partial seizures begins in a focal area of the brain, during which consciousness might be impaired or altered (complex partial) or preserved (simple partial). Generalized seizures usually start in deeper central structures with a synchronous onset of electrical activity in both hemispheres, and complete loss of consciousness (Holmes, et al., 1998). As Appendix Table 2 shows, a distinction is made between brief and prolonged Status Epilepticus seizures, which include sub-types of generalized status, absence status, and complex partial status seizures.

Appendix Table 2

Classification of epilepsies and syndromes (1989)

Abbreviated extract from Lee (2004, p. 115)

Classification of epilepsies and syndromes

I. Localization-related (focal, partial) epilepsies & syndromes

- *Idiopathic (with age-related onset)*
Benign childhood epilepsy with centrotemporal spike
Childhood epilepsy with occipital paroxysms
Primary reading epilepsy
- *Symptomatic (with age-related onset)*
Chronic progressive epilepsia partialis continua of childhood
Temporal lobe epilepsies
Frontal lobe epilepsies
Parietal lobe epilepsies
Occipital lobe epilepsies

II. Generalized epilepsies and syndromes

- *Idiopathic (with age-related onset – listed in order of age)*
Benign neonatal familial convulsions
Benign neonatal convulsions
Benign myoclonic epilepsy in infancy
Childhood absence epilepsy (pyknolepsy)
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Epilepsy with grand mal (GTCS) seizures on awakening
- *Symptomatic (listed in order of age)*
West syndrome (infantile spasms)
Lennox-Gastaut syndrome
Epilepsy with myoclonic-astatic seizures

III. Epilepsies & syndromes undetermined - focal or generalized

- *With both generalized and focal features*
Neonatal seizures
Epilepsy with continuous spike-waves during slow wave sleep
Landau-Kleffner syndrome (acquired epileptic aphasia)
- *Without equivocal generalized or focal features*
Sleep generalized tonic-clonic seizures

IV. Special syndromes

- *Situation-related seizures*
Febrile convulsions
Isolated seizures or isolated status epilepticus
Seizures occurring only with an acute metabolic or toxic event (e.g. alcohol, drugs, eclampsia, hyperglycemia).
-

The 1989 ILAE system's main advantage is its problem-definition based on underlying aetiology, origin of seizures, available history and investigation of the individual patient. Also relevant is the recognition of patterns of symptoms relating to neurological and cognitive functions and probable prognosis (Smith & Wallace, 2001).

The ILAE classification system of syndromes and seizures is based primarily on two factors (G. P. Lee, 2004; Smith & Wallace, 2001): the site of seizure origin or onset; and cause of the condition.

- **Site of seizure origin.** The onset of seizures is either localized or bilateral.

Localized epilepsies tend to have recurrent partial seizures (sometimes generalizing to all areas of the brain). Partial seizures can be identified by a warning aura and/or investigative results such as an EEG or a lesion. The majority of adult-onset epilepsies are of local origin.

Generalized epilepsies manifest as a tendency to occur without warning, suggesting simultaneous involvement of both hemispheres. Generalized epilepsy is essentially based on clinical judgment, though ictal EEG patterns are bilateral during seizure onset.

- **Causes of seizures.** The underlying causes are said to be idiopathic, symptomatic or cryptogenic.

Symptomatic epilepsies. These have an obvious or known cause, such as brain tumors, trauma or developmental abnormalities.

Cryptogenic epilepsies. Since 1989, detailed neuro-imaging techniques have revealed that epilepsies which were previously labeled as cryptogenic (of unknown origin) should be reclassified as "probably symptomatic".

Idiopathic epilepsies. In 1989, this meant a primary syndrome caused by the epilepsy disorder itself, rather than secondary causes such as lesions, with a benign impact. Its features are unique to type of epilepsy *per se*, and include a suspected familiar/genetic origin, an age-specific onset, no obvious structural brain abnormalities or cognitive impairment. Also, inter-ictal EEG recordings are normal though seizure-related EEG discharges can be present. Clinical use of the term *idiopathic* continues though its meaning has changed somewhat.

TERMINOLOGY AND KEY TERMS AMENDED IN 2006

The following definitions have been selected from Engel (2006) in which he reports progress on revisions and modifications to the 1989 ILAE classification systems for epilepsy disorders and seizures.

Epileptic seizure type An ictal event believed to represent a unique pathophysiological mechanism and anatomical substrate. This is a diagnostic entity with etiological, therapeutic and prognostic implications (new concept).

Epilepsy syndrome A syndrome consists of a complex of signs and symptoms that defines a unique epilepsy condition with different aetiologies. This must involve more

than just the seizure type; thus frontal lobe seizures per se, for instance, do not constitute a syndrome (changed concept).

Epileptic encephalopathy A condition in which the epileptic processes themselves are believed to contribute to the disturbance in cerebral function (new concept).

Benign epilepsy syndrome A syndrome characterized by epileptic seizures that are easily treated, or require no treatment and remit without sequelae (clarified concept).

Reflex epilepsy syndrome All epileptic seizures are precipitated by sensory stimuli. Reflex seizures that occur in focal and generalized epilepsy syndromes that are also associated with spontaneous seizures are listed as seizure types. Isolated reflex seizures can also occur in situations that do not necessarily require a diagnosis of epilepsy. Seizures precipitated by other special circumstances, such as fever or alcohol withdrawal, are not reflex seizures (changed concept).

Focal seizures and syndromes These terms should replace *partial* seizures and *localization-related* syndromes (changed terms).

Simple and complex partial epileptic seizures These terms are no longer recommended, nor will they be replaced. Ictal impairment of consciousness will be described when appropriate for individual seizures, but will not be used to classify specific seizure types (new concept).

Idiopathic epilepsy syndromes These consist of only epilepsy and have no underlying structural brain lesion or other neurological signs and symptoms. These are presumed to be genetic and are usually age-dependent (unchanged term).

Symptomatic epilepsy syndrome A syndrome in which the epileptic seizures are the result of one or more identifiable structural lesions of the brain (unchanged term).

Probably symptomatic epilepsy syndrome Synonymous with, but preferred to, the term cryptogenic, used to define syndromes that are believed to be symptomatic, but no aetiology has been identified (new term).

PROPOSED ORGANIZATION OF THE EPILEPSIES (2010)

From 2005 to 2009, the ILAE Commission on classification and terminology reported on revised terminology and concepts for organization of seizures and epilepsies (Berg, et al., 2010).

Appendix Table 3
Revised organization of seizures by ILAE (2010)
(Berg et al., 2010, p. 678)

Classification of seizures
<p>1. Generalized Seizures</p> <ul style="list-style-type: none"> • Tonic-clonic (in any combination) • Absence <ul style="list-style-type: none"> Typical, Atypical Absence with special features: <ul style="list-style-type: none"> - Myoclonic absence - Eyelid myoclonia • Myoclonic <ul style="list-style-type: none"> Myoclonic Myoclonic atonic Myoclonic tonic • Clonic • Tonic • Atonic <p>2. Focal Seizures</p> <p>3. Unknown</p> <ul style="list-style-type: none"> • Epileptic spasms

Note: Seizures that cannot be clearly diagnosed into one of the preceding categories should be considered unclassified until further information allows their accurate diagnosis.

Berg et al. (2010) redefine generalized and focal (previously simple or complex partial) seizures as occurring in rapidly engaging bilaterally distributed networks (generalized); and within networks limited to one hemisphere and either discretely localized or more widely distributed (focal). Classification of generalized seizures has been simplified. Focal seizures should be described according to their manifestations (e.g. dyscognitive, focal motor). However, the concepts of generalized and focal do not apply to electroclinical syndromes.

Appendix Table 4

Revised organization of syndromes by ILAE (2010)
(Berg et al., 2010, p. 682)

Electroclinical syndromes and other epilepsies¹

1. Electroclinical syndromes arranged by age at onset²

- Childhood
 - Panayiotopoulos syndrome
 - Epilepsy with myoclonic atonic (astatic) seizures
 - Benign epilepsy with centrotemporal spikes (BECTS)
 - Late onset childhood occipital epilepsy (Gastaut type)
 - Epilepsy with myoclonic absences
 - Lennox-Gastaut syndrome
 - Electrical status epilepticus during slow sleep (ESES)³
 - Landau-Kleffner syndrome
 - Childhood absence epilepsy (CAE)
- Adolescence – Adult
 - Juvenile absence epilepsy (JAE)
 - Juvenile myoclonic epilepsy (JME)
 - Epilepsy with generalized tonic-clonic seizures alone
 - Progressive myoclonus epilepsies (PME)
 - Other familial temporal lobe epilepsies
- Less specific age relationship
 - Familial focal epilepsy with variable foci
 - Reflex epilepsies

2. Distinctive constellations

- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)

3. Epilepsies attributed to structural-metabolic causes**4. Epilepsies of unknown cause**

Note:

1 = For a detailed listing, see Berg et al. (2010) page 682

2 = The arrangement of electroclinical syndromes does not reflect etiology.

3 = Sometimes referred to as epileptic encephalopathy with continued spike-and-wave during sleep (CSWS).

Berg et al. (2010) report that the syndromic concepts of idiopathic, symptomatic and cryptogenic should be replaced with genetic, structural-metabolic, and unknown aetiologies. Further, organization of forms of epilepsy is first by specificity: electroclinical syndromes, nonsyndromic epilepsies with structural-metabolic causes, and epilepsies of unknown cause. Organization within these divisions can be carried out in a flexible manner depending on purpose. The Commission incorporates an early proposal to use natural classes as a basis for classification (Berg & Blackstone, 2003). They propose that natural classes (e.g. specific underlying cause, age at onset, associated seizure type), or pragmatic groupings (e.g. epileptic encephalopathies, self-limited electroclinical syndromes) may serve as the basis for organizing knowledge about recognized forms of epilepsy and facilitate identification of new forms (Berg, et al., 2010).

APPENDIX B: LIVING WITH EPILEPSY

THE CULTURAL AND PSYCHOSOCIAL CONTEXT

Cross-cultural Stereotypes

In a review of the DSM-IV and its cross-cultural applicability, Thakker and Ward (1998) reviewed research on the cross-cultural manifestation of schizophrenia and depression, found presentations varied significantly across cultures, and argued for a constructivist perspective of mental illness. They concluded that the culture-sensitive nosology of the DSM-IV is undermined by an implicit assumption of the universality of its primary syndromes. The cross-cultural literature reveals significant differences in the manifestation of these syndromes across ethnic groups, thus challenging the universalist position (Thakker, Ward, & Strongman, 1999). These investigators argue that classification of some psychopathology disorders is based on Western society's construction of reality.

The effects of culture on a society's stereotypes about people with a mental illness have been extensively researched. An anthropological analysis of family response to an ill relative with schizophrenia found their emotional expression varies across cultures (Jenkins & Karno, 1992). Perceptions of self-identity and whether the family comes from a collectivist or individualistic culture might influence their attitude to the person with psychopathology (Markus & Kitayama, 1991; Triandis, 1989). A person's expression of his/her mental distress differs across cultures, and can take a psychological form in Britain or the USA; but a somatic form in the countries of the South Mediterranean (Gaines, 1995; Liebowitz et al., 1994). Enculturation and socialization may have produced different manifestations of psychopathic personality disorder in Scotland and North America (Cooke, 1996).

Society's stereotypes about epilepsy are important because they can prevent acceptance or support of people with epilepsy, becoming obstacles to development of competent functioning. For the person with epilepsy, internalized negative stereotypes can diminish a sense of mastery and ability to cope with the limitations imposed by their condition, thus lowering levels of life satisfaction and attempts to cope actively with epilepsy. Negative stereotypes can result in lack of social support, which in turn has been associated with higher levels of patient concern with his/her epilepsy (Baker & Jacoby, 2000; Jacoby, 1994; Jacoby, Gorry, Gamble, & Baker, 2004). Finally, Western society's negative perceptions of people with a chronic condition or a mental illness (i.e. stereotypes) do not seem to be due to lack of education, since they have been found in highly educated professionals such as teachers and doctors.

The 20th century saw the acceleration of progress in Western medicine. The rest of the world, however, has not been so quick to discard its long-standing belief systems. The World Health Organization has painted a bleak picture of persisting cross-cultural beliefs which still exist today. A short list includes Cameroon, where people with epilepsy are said to be invaded by evil and the devil. In several African countries (Liberia, Swaziland, Uganda) the cause of epilepsy is still attributed to sorcery, witchcraft or evil spirits. In many countries, epilepsy is thought to be contagious, with resulting exclusion from crucial social activities e.g. the communal food-pot. Some areas of India attempt to exorcise evil

spirits from people with epilepsy by various maltreatments; while in Indonesia, epilepsy is often considered to be the fault of the sufferer. As late as 1996, religious fanatics in the Netherlands whipped and isolated a person because her seizures were thought to result from magic (World Health Organization, 2001b).

Western Stereotypes in Literature and the Media

In recent times, the research literature has included several investigations on how people with epilepsy and other epilepsy matters are depicted in the media (movies and television) and in literature. Via an internet survey of 4,605 valid responses, one study investigated the myths about epilepsy perpetuated in the media e.g. “foaming at the mouth” and frequent violence (Baxendale & O’Toole, 2007). The authors provide an interesting discussion concerning the “we see what we expect to see” phenomenon in relation to stereotypes surrounding epilepsy.

Literary accounts of epilepsy deserve our attention since they form part of the cultural history of the disease but more importantly, they often reflect current responses to it by society (Wolf, 1995). For example, physicians are presented as helpless or only marginally involved, and epilepsy is rarely viewed as a treatable disorder. In a more recent review, Wolf (2006b) has suggested that literature descriptions of clinical seizures vary according to the writer’s knowledge: some authors are factual and well-informed, but others seem fascinated with ancient beliefs relating seizures to prophecy and divinity.

In their review of why epileptiform events continue to be featured in art, film and television, Kerson and Kerson (2006) entitled their paper “Implacable Images”. They warn that, because of the increasing fictive and often incorrect images, many people who have never witnessed a seizure will think of them as accurate depictions. They came to the conclusion that visual media do not reflect contemporary scientific knowledge because it is more concerned with how an enthralling image can drive the narrative, support the genre, evoke specific emotional reactions, accentuate traits of characters with seizures, highlight qualities of other characters through their responses to same, act as catalysts for actions, and enhance the voyeuristic experience of the audience. It seems, then, that visual depictions of seizures/epilepsy are created so as to maximise entertainment value; while literary descriptions are usually based on the writer’s degree of knowledge (Wolf, 2006b).

EPILEPSY AND FAMILY

Family relations and Expressed Emotion

Epilepsy has been found to have a significant impact both for adults in terms of marriage and family life; and for children with epilepsy and their siblings (Baker & Jacoby, 2000). Adults with epilepsy are less likely to marry or have children, especially if the epilepsy is severe or is co-morbid with mental disorders or other disabilities (Jacoby, 1994). Children with epilepsy and their siblings have been shown to have difficulty in relating to one another, with healthy siblings resenting parental attention to the sick child (Jacoby, 2002). This might be why siblings of children with epilepsy appear to be at a greater risk of psychiatric dysfunction than those in a general population (Hoare & Kerley, 1991). Some families of children with epilepsy have been found to be less cohesive, have lower levels of communication and support than families of children with other chronic conditions (Austin, et al., 2007). Finally, children’s earliest experience of a seizure is often

associated with their parents' emotional reactions, and these can have long-lasting effects. For example, the child who has had poor parenting as a result of his/her epilepsy is likely to make a poor parent in turn (Betts, 1988).

- Family members and partners can be overly emotional in their reactions.

The theoretical construct of expressed emotion and its methodology provides a frame-work within which to investigate the impact of family relationships on the course and outcomes of a patient's illness. Although expressed emotion is measured in an individual, it is thought to reflect disturbances in the organization, emotional climate, and transactional patterns of the entire family system (Hooley, 2007). Expressed emotion is assessed through the Camberwell Interview, a semi-structured interview with a key family member (e.g. parent, spouse, or sibling). Data collected consist of the number of comments and statements made by the relative about the patient and his/her illness, which are judged as being one of five types. As a result, the relative is categorized as showing either high-EE (hyper-criticism, hostility or over-protectiveness and emotional over-involvement "EOI"); or low-EE (warmth, positive comments) (Wearden, Tarrier, & Barrowclough, 2000).

Measures of expressed emotion were originally developed to study the families of people with schizophrenia (Kavanagh, 1992; Leff & Vaughn, 1985; Sturgeon, Turpin, Kuipers, Berkowitz, & Leff, 1984). Living with a high-EE relative was said to operate as a physiologically arousing stressor for the patient, so that schizophrenia relapse was likely when arousal reached a certain threshold. See Wearden et al. (2000) for a history of this research area.

The EE methodology has since been extended to study a number of chronic medical conditions, including families of patients with mood or anxiety disorders; eating or substance use disorders, and personality disorders. For reviews, see Hooley (2007) and Corrigan (2000). More recently, several epilepsy studies have applied EE methodology to families of persons with epilepsy (PWE), and some areas of research are itemized below.

- Maternal expressed emotion and adjustment in children with epilepsy (Garralda, Rose, & Schwartz, 1999).
- High-EE in family members and poor control of epilepsy seizures (Jadresic, 1988).
- High-EE expressed by fathers with critical comments; while expressed by mothers as infantilisation and/or over-protection (Brown & Jadresic, 2000).
- Maternal expressed emotion and treatment compliance of children with epilepsy (Otero & Hodes, 2000).
- Association of expressed emotion and child behavioural inhibition and psychopathology (Hirschfield, Biederman, Brody, Faraone, & Rosenbaum, 1997).
- Attribution of blame for epilepsy symptoms predicts high-EE in relatives (Barrowclough & Parle, 1997; Weisman & Lopez, 1997).

The validity of the EE methodology and conceptual construct for predictions about illness course has yet to be established, any causal role for EE has yet to be demonstrated, but EE may have predictive utility for chronic epilepsy and recurrence or increased frequency of seizures (Wearden, et al., 2000). Acknowledgement must go to Dr. John O'Mahoney, Clinical Psychologist, for suggesting this area of research.

EPILEPSY AND THE PROFESSIONS

The Medical Profession and narrow experience

- General Practitioners' practice can be based on narrow experience.

In many developed countries, negative attitudes held by the lay public can also be found in health professionals and service providers, resulting both in fragmented services for epilepsy care; and a low priority for financial commitment in policy-makers (Jacoby, 2002). The majority of people with epilepsy who are seen by a medical professional are most frequently those whose epilepsy is intractable and/or are cognitively impaired and emotionally ill. This restricted experience can lead to maintenance of negative generalizations, with some general practitioners viewing patients with epilepsy as being manipulative (e.g. exaggerating seizure severity in order to gain extra drugs); or mendacious - the most common example being that all patients will lie about seizures in order to keep or gain permission for a driving license (Baker & Jacoby, 2000).

Some physicians' attitudes and beliefs are based on too little knowledge. One study compared internal medicine practitioners, general practice physicians and neurologists on their opinions regarding driving restrictions for persons with epilepsy (PWE). Non-neurologists were found to have more restrictive beliefs regarding driving and PWE and insufficient knowledge, especially about USA state-reporting laws and other aspects of epilepsy related to driving (Vogtle, Martin, Foushee, & Faught, 2007).

One unexpected drawback of the medical profession's targeting possible deficits and deterioration was that epilepsy's public image became one of great disabilities – whether intellectual, physical or psychiatric. Even among professionals, some can be found who still view epilepsy as a psychiatric disorder or an intellectual disability rather than a neurological condition (Hermann & Whitman, 1992).

This might be due to the fact that it is patients from the more severe or complicated end of the epilepsy spectrum being treated at specialized epilepsy clinics, university clinics etc. Because such patients might have a higher risk of interictal psychopathologies (Edeh, Toone, & Corney, 1990), misperceptions of the real relative risk of psychopathologies associated with even mild epilepsy might develop. Estimates of psychological and social disability associated with epilepsy have been found to be over-estimated because of reliance on special university-based clinics (Trostle, Hauser, & F.W., 1989). Studying *patients* with epilepsy does not necessarily inform us about *people* with epilepsy (Hermann & Whitman, 1992, p. 1135). Today, the majority of people with epilepsy are ordinary people living with a treatable disorder.

The Teaching Profession and Ignorance

- Teaching practice can be based on too little knowledge.

Numerous large studies of teachers' attitudes and epilepsy-related knowledge have produced some encouraging results. One study found that teachers' attitudes about epilepsy were generally positive, though there were significant deficits on the impact of epilepsy in educational settings, and appropriate management of epilepsy seizures in the class-room (Bishop & Boag, 2006; Bishop & Slevin, 2004).

Another study examined whether an epilepsy label was related to teachers' assessments of academic ability. Children with epilepsy (N=122) were divided into two groups based on teachers' awareness of the child's seizure condition (Label); and assessed with both an objective measure and a teacher questionnaire. For the Woodcock-Johnson Tests of Achievement – Revised (the objective measure), there was no effect of label on achievement. For the Child Behaviour Checklist Teacher Report Form (TRF), lower scores were observed for children who were known to have epilepsy (Labeled). Researchers concluded some teachers might under-estimate the academic abilities of children with epilepsy (Katzenstein, Fastenau, Dunn, & Austin, 2007). Such lowered expectations in a teacher, if picked up and accepted without question by the child, can lead to a self-fulfilling prophecy of academic under-achievement.

In conclusion, negative stereotypes of epilepsy held by some professionals are often implicit and might be due to an unquestioning acceptance of their society's stereotypes, not only their lack of specific knowledge of this area. Education solely about the statistics and facts of epilepsy, while helpful, does not seem to be memorable for most people. Facts presented so as to appeal to the listener on a personal, emotional level would provide a more persuasive counter against entrenched culturally-bound stereotypes.

EPILEPSY AND UNEMPLOYMENT

- Employers and employees can be rejecting or fearful of seizures in the workplace.

The employment situation for people with epilepsy has been extensively researched and reviewed (Smeets, van Lierop, Vanhoutvin, Aldenkamp, & Nijhuis, 2007). One article reviewed 34 primary research articles on the predictive factors for lack of regular employment positions for PWE. These included stigma, seizure severity, and psychosocial variables such as low self-esteem, passive coping style, and low self-efficacy (Smeets, et al., 2007).

In a survey of 262 patients from the same U.S.A. epilepsy centre, certain psychosocial factors were found to be significantly associated with employment for PWE, including higher annual family income, perceived importance of work for personal reasons and decreased fears of workplace discrimination (Bautista & Wludyka, 2007). In one British study of people with well-controlled epilepsy, 32% of patients felt their epilepsy made it more difficult for them than for others to get a job. Among this group, 39% felt this was because employers preferred not to employ people with a disability of any kind; 33% felt it was because of fear and lack of understanding; and 20% attributed their difficulties to the potential danger of seizures in the workplace. Without being asked, a number of respondents commented they had not disclosed their epilepsy for fear of discrimination (Jacoby, 1994; Jacoby, et al., 2005).

EPILEPSY AND STIGMA'S IMPACT ON MENTAL HEALTH

- People with epilepsy might accept and internalize a negative self-image.

Social interactions often involve a fear of having to cope with the seizures in public, and the fear understandably is enhanced by their unpredictability and dramatic nature (Scambler, 1989; Scambler & Hopkins, 1986). All too often, public reactions to seizures can be hostile or even accusatory, resulting in a self-perpetuating cycle common to

all stigmas (for example, race, religion, sexual orientation or physical unattractiveness) (Goffman, 1963; Ajzen & Fishbein, 1980). An uninterrupted cycle can develop into a self-fulfilling prophecy if the PWE accepts his/her society's devaluation. Public reactions can lead to negative reactions for the PWE (e.g. denial, anxiety, depression, low self-esteem) and maladaptive strategies which fail to overcome the stigma (e.g. inertia, dependency, hostility and aggression), thus confirming the stigma's validity in the eyes of the public. The stigma persists and in turn triggers repetition of the cycle (Livneh, Wilson, Duchesneau, & Antonak, 2001).

One study aimed to understand young adults' daily life by describing their experienced emotions, which have been shown to be closely related to health and well-being. The young adults experienced positive (confidence, hope and forbearance); negative (anxiety, despair, fear, resignation, indignation, insecurity and anger); and self-evaluating emotions (being valuable, being insignificant, shame, guilt and self-doubt). Two groups were identified: some members regarded themselves as "healthy", were active and flexible, focused on possibilities and planned how to handle negative emotions. Other members regarded themselves as being ill or "handicapped", were passive with negative emotions directed against self, afraid of being exposed, and focused on obstacles (Raty, Soderfeldt, & Larsson, 2007). This study failed to examine whether the negative/positive self-images were in any way related to severity of illness in actuality.

Public attitudes to epilepsy in the United Kingdom and implications for stigma were studied by interviewing a random sample of more than 1,000 members of the general public. About one-fourth of respondents knew someone with epilepsy and one half had witnessed a seizure. One-half agreed that PWE are treated differently by others – themes of exclusion, restriction and non-normality were given as reasons for this. The most discriminatory area was employment with epilepsy ranked second as a cause for concern if informants had to work with such a person. Aside from employment, most informants responded with highly favorable attitudes, but one-fifth agreed that PWE have more personality problems. Researchers added the survey revealed attitudes and knowledge gaps which had the potential for discriminatory behaviour (Jacoby, et al., 2004).

To sum up, adapting to the demands of living with a chronic illness such as epilepsy involves overcoming a variety of social, familial and psychological obstacles (Baker & Jacoby, 2000; Jacoby, 2002). Just a few examples of their impact on everyday life are listed below.

- Development of a dependent role or a view of the world as a hostile place;
- Avoidance of participation in social activities due to frequent seizures in public;
- Negative self-image and maladaptive behaviours associated with stigma; and
- Negative influence of authority figures, including teachers' lowered expectations about academic abilities; and physicians' insufficient or inaccurate knowledge.

In short, the psychosocial view assumes that neurobiological factors play a lesser role in social and emotional dysfunction in epilepsy. There is some literature looking at whether people with one epilepsy syndrome are likely to be more maladaptive than those with another syndrome, and this research uses neurobiological factors to argue its claims about specific personality characteristics associated with various specific syndromes.

There are many areas of life affected by chronic epilepsy, with adaptation to the demands of a social or familial environment being the key to competent functioning in social or emotional domains. Difficulties in psychologically adapting to these environments while living with a chronic illness can exacerbate mental illness (Hermann & Whitman, 1992); or in some cases lead to suicide (Gilliam & Kanner, 2002).

Concerning newly diagnosed patients, a longitudinal study design would establish the direction of relationships between factors, enabling the design of effective educational and management strategies for people with epilepsy (Baker & Jacoby, 2000). The process of adjustment can begin after a first seizure, which can trigger a complex adjustment process, and might require therapeutic management. A recent Australian study assessed 85 adult patients at one and three months after a first seizure, using the New-Quality of Life Questionnaire. The main psychological issue of concern for patients was losing and restoring perceived control. Two adjustment trajectories were identified: experience of a limited or pervasive loss of control. Subsequent seizure recurrence was predicted by a pervasive loss of control, anxiety and depression (Velissaris, Wilson, Saling, & Newton, 2007).

APPENDIX C: MATERIALS AND MEASURES

INTAKE INTERVIEW

Personal History

Participant I.D. _____ Syndrome Group _____ CBH Chart _____

Name: _____ Sex: F M

Address: _____ Phone: _____

Date this History taken: _____ Date Birth: _____ Age: _____

Family Doctor & Address: _____

Specialists & Addresses: _____

Place of Birth : _____ Native language _____ Handed: R L Familial?

Years of Schooling _____ Favourite Subjects _____

Current or last job _____ Previous work history _____

Marital Status : Single Married Divorced Widowed

Family relations *List all children and relatives living with the participant*

Name and age	Relation	Occupation	Health
_____	_____	_____	_____
_____	_____	_____	_____

List immediate family members not living in the home (e.g. adult son, elderly parents, etc)

Medical History

Previous hospitalizations (reason, age, length of stay) _____

Serious Illnesses _____

History of emotional disorder _____

Any current medical problems (other than epilepsy) _____

Medications (type and dose) _____

Compliant or non-compliant?

Family history of neurological disease / emotional disorder _____

Head injuries (length of l-o-c, retrograde/anterograde amnesia) _____

Other cerebral damage (CVA, hemorrhage, etc) _____

Alcohol consumption (per day or week) _____

Drug abuse _____

Food allergies and/or Drug allergies _____

List any special tests completed:

Test	Age and When	Where done	Results
Hearing/Vision			
EEG			
CT Scan			
MRI			
Psychological			

Epilepsy History

Description of first episode (where, any trigger, cause) _____

Age at onset _____ How often seizures occur _____

Status Epilepticus? (description & duration) _____

Description of seizures (any aura, warning, duration of seizure, any l-o-c, any emotions, drowsiness after episode, etc.)

Personal thoughts about seizures (e.g. changes in life or activities caused by them)

What do significant others say about seizures? _____

Additional Comments:

ORDER OF TEST ADMINISTRATION**Session One** (approximately 100')

Intake Interview (60')

DASS (to take home for completion)

MCG-CFT = copy & recall (10') followed by 20'-25' interval

WTAR = (20'-25')

CFT = delayed recall (10')

Session Two (approximately 100')

WAIS-III Digit Span (10')

WAIS-III Vocabulary (15')

WAIS-III Similarities (15')

WAIS-III Matrix Reasoning (15')

D-KEFS Letter and Semantic Fluency (15')

WAIS-III Block Design (15')

D-KEFS Card Sorting = forms verbal & perceptual categories (15')

D-KEFS Colour-Word Interference (15')

Session Three (approximately 150')

WMS-III Stories I = learning & recall (20') followed by 30' interval

WMS-III Spatial Span (15')

WAIS-III Digit-Symbol Coding (15')

WMS-III Stories II = delayed recall & recognition (10')

CVMT = learning (15') followed by 20'-25' interval

AVLT = trials 1-7 (25') followed by 30' interval

CVMT = delayed recognition (15')

D-KEFS = Design Fluency (15')

AVLT = trials 8-9 (10')

Session Four (approximately 120')

BNT = picture naming (10') followed by 10' interval

JLO = (10'-15')

BNT = delayed recall (10')

Test of Everyday Attention (45')

ESDQ for Patient and Partner (10')

EFQ for Patient and Partner (10')

Check List: After each session, add to list of "tasks completed" for participant.*Last Session:* Are all tasks completed? Consent Forms signed? History all taken?*First Session:* Intake Interview should be taken with tea/coffee to enhance informality.

MEASURES OF COGNITIVE DOMAINS

Detailed information about the measures used in this study is abbreviated below (See also Mitrushina, Boone, & D'Elia, 1999; Mitrushina, Boone, Razani, & d'Elia, 2005; Esther Strauss, et al., 2006).

COMPUTATIONS FOR ESTIMATED I.Q. SHORT-FORM

Procedures for computation of I.Q., Verbal I.Q. and Performance I.Q. followed the guidelines and examples contained in Exhibit 8-4, taken from Sattler (2001, p. 256). Guidelines included computation of Constants A and B for a six sub-test short form, together with calculations of co-efficients for reliability (.96) and validity (.85) for the particular short form used in this study.

For verification that the procedures set out in Exhibit 8-4 had been correctly carried out, comparison was made between the Deviation Quotients (DQ) estimated for various patients in this study, and the Deviation Quotients (DQ) listed in Sattler (2001) which were based on short-forms with similar component WAIS-III sub-tests. References from Sattler (2001) for the latter are as follows:

- For DQ of a six sub-test short form (C2), see Table C-25, page 835.
- For DQ of a three verbal sub-tests short form (C18), see Table C-22, p. 829.
- For DQ of a three performance sub-tests short form (C5), Table C-22, p. 829.

PRE-MORBID ESTIMATED I.Q.

The rationale underlying the WTAR is similar to that of the National Adult Reading Test (NART), but the WTAR was chosen for this study because it is co-normed with the WAIS-III (Wechsler, 1997a) and the WMS-III (Wechsler, 1997b). Australian norms are not available for the WTAR. Therefore, the American norms were used in this study rather than the alternate United Kingdom norms, since the former's standardization sample has larger numbers. In addition, the internal consistency is higher in the US population sample (ranging from .90 to .97 across various age groups). Standard errors of measurement derived from the internal consistency co-efficient are about four points. Validity is also high: the WTAR has strong correlations with other measures of reading (WRAT-R $r = .73$). Strauss et al. (2006) conclude that the combined WTAR-demographics methodology is useful in detecting impairment, and also in classifying and/or discriminating among clinical disorders.

INTELLECTUAL ABILITIES

Judgment of Line Orientation (JLO)

Lowered performance might not be indicative of actual cognitive impairment but rather reflect cultural factors such as perceived test relevance, task familiarity, motivation, level of comfort in the test situation, and educational experience (Manly, 2005; Esther Strauss, et al., 2006).

Patients with right posterior hemisphere pathology have been shown to perform worse than those with left hemisphere damage (Benton, et al., 1994). Factor analytic findings in patients with TLE (Hermann, Seidenberg, Wyler, & Haltiner, 1993) and neuropsychiatric patients (Larrabee, 2000) suggest that JLO loads with the Wechsler performance subtests and taps abilities somewhat separate from that of facial recognition.

The norms used for z-scores in this study are those set out in Table A15.7 in Mitrushina et al. (2005, p. 802). The 30-item version of the JLO used in this study was developed to assess multiple sclerosis (Rao, Leo, L., & Unverzagt, 1991). The 30-item version has an internal consistency of $r = .84$ to $.91$ (Benton, et al., 1994).

Boston Naming Test (BNT)

Data-analysis used each patient's sum total of pictures correctly named. Sum total consisted of number of spontaneously correct responses plus the number of correct responses to a semantic cue. The short form 15-item BNT used for this study is the first of the four alternate forms developed and reported in an article on shortened forms for Alzheimer's Disease (Mack, Freed, Williams, & Henderson, 1992). The norms used for z-scores in this study were taken from the 60-item version of Tombaugh and Hubley (1997), since these were based on a larger sample ($n=219$) of younger adults (59 years). The two versions have a correlation of $.98$ (P. S. Kent & Luszcz, 2002). Researchers carried out an empirical comparison of alternate forms of the BNT and results indicated that all forms possess adequate, although variable internal consistency and correlations between forms were reasonable (Frantzen, Haut, Rankin, & Keefover, 1995).

Sub-test measures of intellectual functions

Strauss, Sherman and Spreen (2006) have given reliabilities and internal consistency for the ten measures which were used in this study to assess the participants' intellectual functions.

Vocabulary and Matrix Reasoning have very high internal consistency ($.90$ to $.93$)
 Similarities and Block Design have high internal consistency ($.90$ to $.89$).
 JLO (30-item version) has a split-half reliability of $.84$ to $.91$.
 BNT (15-item version) has an adequate internal consistency.
 Digit Span has very high internal consistency of $.90$.
 Spatial Span had test-retest reliability which is adequate at $.70$ -. 79 .

ATTENTION DOMAIN

The eight sub-tests of the Test of Everyday Attention (TEA) were developed to measure four components of Attention which accounted for 62% of the variance in a factor analysis of attention sub-tests from a standardization sample ($N=154$) (Robertson, et al., 1994, 1996). These separate factors/components of attention are based on an established theory of attention (Posner & Peterson, 1990), though not all divisions have been substantiated. More recently, researchers (Bate, et al., 2001) used principal components analysis on 35 controls and severely brain injured patients to reveal a four factor attention structure similar to that found by the TEA developers (Robertson, et al., 1994), but which differed in the components for the Sustained Attention domain. Sustained Attention deficits have identified stroke patients with right-brain damage (Robertson, et al., 1996).

However, in their review of the TEA, Strauss, Sherman and Spreen (2006) note that more information is needed about the neuroanatomical correlates of some of the sub-tests.

Robertson, Ward, Ridgeway and Nimmo-Smith (1996) have provided correlations between most TEA sub-tests and other attention measures including the Stroop, WMS Digit Span backwards, Trails B and more. However, they did not include the Sustained Attention factor component tasks (Lottery, Elevator Counting) or divided attention (Telephone Search while Counting), as they did not believe that validated tests of these attentional abilities exist (Esther Strauss, et al., 2006). Bate et al. (2001) found that two TEA sub-tests (Elevator Counting, Elevator Counting with Distraction) did not correlate with any established measures of attention, although most did correlate with established attention measures. Chan (2000) found that individuals with closed head injury obtained lower scores on the TEA subtests except Elevator Counting when compared to matched controls. Another study found that fifteen patients with mild to moderate closed head injury, when compared to controls matched for age and reading ability, produced poorer scores on TEA sub-tests for selective and sustained attention (Map Search, Telephone Search, Telephone search while counting and Lottery) (Chan, et al., 2003).

One advantage of using the TEA is that single-case performance can be analysed to determine strengths and weaknesses, by using Crawford, Sommerville and Robertson's (1997) program which compares single test performance with overall performance mean for all tasks (see Strauss, Sherman & Spreen, 2006, for a review).

Finally, the tasks measure "real-life" cognitive operations rather than abstract stimuli thus enhancing ecological validity. The task stimuli materials mirror everyday actions and strategies e.g. searching a telephone book or searching a map; listening for a particular word being read out on the radio; counting the floors as a lift goes up or descends. This approach addresses a construct validity problem ubiquitous to neuropsychological testing, with one writer describing the worlds of psychological theories and everyday life as parallel universes (Crowe, 2005). Are assessment tasks directly measuring a patient's strengths and weaknesses as s/he operates in the real world, or are they assessing pure operations taking place in a psychologist's parallel world of theories about the mind (Crowe, 2005).

VERBAL MEMORY DOMAIN

For this study, the AVLT norms are both an advantage and a disadvantage. The advantage in choosing the Geffen version of the AVLT is that the researchers have collected Australian norms which are both age-related and gender-based. Thus, in this study the standardization of Episodic Memory raw scores has been based on norms contained in Tables 10-62a and 10-62b (Esther Strauss, et al., 2006, pp. 786-787). They are a composite of performance data for 16-86 year olds of average intelligence (Geffen, Moar, & O'Hanlon, 1990), together with additional data given in personal communication by G.M. Geffen to the authors in 1995 (Spreen & Strauss, 1998) and also reported in Strauss et al. (2006). It has been argued that because these norms are compiled from data generated by healthy adults, the majority of whom had above-average I.Q. and number of years schooling, they might be less appropriate when testing for potential deficits in people who might have memory impairment (Esther Strauss, et al., 2006).

VISUAL MEMORY DOMAIN

Visual Recall Medical College of Georgia – Complex Figures Test

Materials consisted of blank sheets of paper and a print of the first MCG-CFT (form A). See Table 10-34 (Esther Strauss, et al., 2006, p. 816). The test itself was administered and scored along the guidelines set out in Loring and Meador (2003). It consisted of a Copy trial of the MCG-CFT print; then 30 seconds later, an immediate recall trial was administered without the MCG-CFT print; and finally a delayed recall test after a 30 minute interval. The scoring system uses a 36-point scale, similar to the 18 unit system applied to the Rey-Osterrieth and Taylor figures (Lezak, 1995; Esther Strauss, et al., 2006).

Comparison studies have found that while the Copy trial elicits similar performance across all CFT versions, the Rey-CFT version elicits lower scores than the Taylor or MCG-CFT on the Immediate and Delayed Recall trials (K.J. Meador, et al., 1991; K.J. Meador, et al., 1993). Loring and Meador (2003) conclude that the four MCG complex figures are comparable to the Taylor figure in difficulty of learning and recall, and easier than the Rey-CFT where the scores elicited can be 3 to 6 points lower. For a comparison of norms from Rey-Taylor and the 4 alternates of the MCG-CFT, see Meador et al. (1993, p. 835 Table 1).

The primary limitation of the MCG-CFT relates to the small healthy control samples which provided normative data consisting mostly of staff and students of the Medical College with above average years of education. The majority of this study's participants range in schooling is between 10 to 12 years, while the norms used for z-score conversion were based on a sample of 21 healthy volunteers aged between 21 to 48 years (mean 34 years) and a mean education of 15 years (K.J. Meador, et al., 1991). Smaller studies have produced similar norms (see Meador, Moore, Nichols et al. (1993) and Loring and Meador (2003) and the Taylor norms are also similar.

Because CFT performance has been shown to deteriorate with increasing age (for a discussion, see Hubley & Tombaugh, 2003), it was deemed necessary to provide additional norms for the ages after the 21-48 age group. Ingram, Soukup and Ingram (1997) provided normative data based on 77 healthy older adults (ages 55-64 and 65-75) and reported in Table 11.12 of Lezak, Howieson and Loring (2004, p. 459).

Loring and Meador (2003) report on several studies of healthy volunteers which failed to find any AED and/or practice effects during MCG-CFT performance. They also report on an MCG parallel forms study with a repeated measures design which tested cognitive function in patients with poorly controlled seizures. Patients were tested twice (2 weeks apart) while on a baseline AED, then for a third time after a second AED had been added to their therapy (monotherapy and polytherapy). No practice effects were present. In contrast to the studies with healthy volunteers, however, there were similar variabilities (for Copy, Immediate Recall and Delayed Recall) across all three MCG parallel forms.

Visual Recognition – Continuous Visual Memory Test (CVMT)

Patients are presented with a series of 112 black abstract figures with seven target figure re-appearing during the task, and a limited presentation time for each item (about 2 seconds). The test includes scoring for perceptual recognition of target items during the

actual presentation; and a recognition trial after a 30 minute delay. The performance data used in this study includes immediate recognition (total accuracy) scores and delayed recognition scores. Normative data based on four age groups was used for standardization of raw scores (18-29, 30-49, 50-60, and 70+). In a review of this test, Lezak, Howieson and Loring (2004) report that the delayed recognition trial is a measure of visual memory relatively independent of visual-spatial ability (Trahan & Larrabee, 1988; Trahan, et al., 1996).

EXECUTIVE FUNCTIONS DOMAIN

Verbal Fluency Test This measures fluent productivity and flexibility in the verbal domain. The tasks require the participant to produce words that begin with a specified letter (Letter or Phonemic Fluency), produce words belonging to a named semantic category (Category or Semantic Fluency) and alternate between producing exemplars from two different semantic categories (Category Switching).

Design Fluency Test This measures fluent productivity and flexibility in the nonverbal domain. The tasks include making as many designs as possible in one minute by connecting filled dots (condition 1) then by connecting empty dots (condition 2) and by alternating connections between filled and unfilled dots (condition 3 Design Switching).

Sorting Test This measures problem-solving, verbal and nonverbal concept formation, and flexibility of conceptual thinking. The participant is presented with a set of six cards randomly arranged and is asked to sort/separate them into two groups; mix the cards up again and separate into another two groups, and to continue doing so until s/he cannot form any more categories. The cards are designed so as to elicit choice of categorization based on both verbal (animal or transportation names) or perceptual (cursive versus printed words) aspects of the cards (Free Sorting). The second task (Sort Recognition) was not carried out in this study due to time constraints.

Colour-Word Interference This test is a variant of the Stroop procedure and measures inhibition of over-learned responses and flexibility of attention. The participant is asked to name colour patches (condition 1) then read colour-names printed in black ink (condition 2), name the ink colour in which conflicting colour-names are printed (condition 3), then switch back and forth between naming the dissonant ink colours and reading the conflicting colour-names (condition 4). Scoring is in number of seconds taken to complete each task.

In addition, these particular tests were included in the study because they incorporate quantitative measures of what are often qualitative descriptions.

- Flexibility of processing is measured by switching tasks, whether the processes are conceptual, attentional or generating words/designs.
- Distractibility as measured by set-loss errors, when the participant forgets to stick to the underlying rules for the task (e.g. producing examples of fish when asked to produce only members of the Animal category).
- Perseveration as measured by repetition errors (e.g. when the participant repeats the same connections between dots which s/he has already drawn before; or repeats the same word starting with the letter “F” which s/he has already produced).

It should be noted that not all the tests have produced strong reliability coefficients (see Table 8-23 in Esther Strauss, et al., 2006, p. 447). Further, neither the D-KEFS technical or administration manuals provide any reliability data for optional measures such as Set-Loss or Repetition errors.

- Both Category Fluency and Category Switching (total switching accuracy) have only marginal (.60 to .69) internal consistency and the latter has very low (less than .59) test-retest reliability. In contrast, Letter Fluency has very high (.80 to .89) internal consistency and test-retest reliability.
- Both Design Fluency and the Sorting Tasks have low test-retest reliability, and so are not suitable for longitudinal testing. The internal consistency of Design Fluency is not mentioned in Table 8-23.
- The Sorting task has adequate (.70 to .79) internal consistency.
- Colour-Word Inhibition (condition 3) has adequate internal consistency and test-retest reliability, while its Inhibition/Switching (condition 4) has only marginal test-retest reliability.

APPENDIX D: DATA TREATMENT AND ANALYSES

HOMOGENEITY AND VARIATION IN COGNITIVE DATA

Normality tests and inter-correlational analyses were carried out on epilepsy participants (n=24) z-score data in cognitive domains of intellectual abilities, attention factors, executive functions, verbal and visual memory. Appendix Tables 5 to 9 give the results for each of these cognitive domains separately.

Each Appendix Table contains results from the following analyses:

- (a) Normality tests on homogeneity of data for a particular domain.
- (b) Inter-correlations amongst the various sub-domains which make up that domain.
- (c) Inter-correlations of the component tasks which constitute each sub-domain.
- (d) Squared Pearson correlation co-efficient (in brackets after each task) gives the percentage of the variation in the sub-domain accounted for by participants' performance in that component task.

Appendix Table 5
Intellectual Abilities: normality tests, inter-correlations of component tasks

Intelligence domain				
<ul style="list-style-type: none"> • Verbal Abilities: Vocabulary, Similarities, Boston Naming Test • Visual Abilities: Block Design, Matrix Reasoning, and Judgment of Line Orientation; • Working Memory: Digit Span, Spatial Span (WMS-III); • Speed of Processing: Map Search 1 (TEA); Digit-Symbol Coding. 				
Tests of Normality¹	Shapiro-Wilk	Skew		
Verbal Abilities	.941 n.s.	-0.625		
Visual Abilities	.965 “	-0.280		
Working Memory	.938 “	0.951		
Speed of Processing	.977 “	-0.389		
INTELLECT domain (N=24)	.969 “	0.253		
Intellect domain²	Pearson Correlation Coefficients			
<u>Intellect domain</u>	<u>Intellect</u>	Verbal	Visual	Working
Verbal Abilities	.868**			
Visual Abilities	.857**	.706**		
Working Memory	.626**	.321	.477*	
Speed of Processing	.434**	.130	.289	.099
Component tasks³	Pearson Correlation Coefficients			
<u>Verbal Abilities</u>	<u>Verbal</u>	Vocabulary	Similarities	
Vocabulary (81%)	.900**			
Similarities (62.5%)	.791**	.623**		
Boston Naming (83.5%)	.914**	.724**		.587**
<u>Visual Abilities</u>	<u>Visual</u>	Block Design	Matrix	
Block Design (61%)	.783**			
Matrix Reasoning (44%)	.663**	.254		
Judgment of Line Orientation (45%)	.673**	.384		.004
<u>Working Memory</u>	<u>Working</u>	Digit Span		
Digit Span (77%)	.880**			
Spatial Span (63%)	.793**	.407*		
<u>Speed of Processing</u>	<u>Speed</u>	Map Search		
Map Search (1min) (69%)	.829**			
Digit-Symbol Coding (57%)	.758**	.264		

Note:

n.s. = not significant. Level significance Pearson coefficient *p<.05 or **p<.01

1 = Tests compute normality of z-score means for each sub-domain.

2 = Inter-correlations amongst the four sub-domains of Intelligence.

3 = Inter-correlations amongst component tasks measuring a sub-domain.

Appendix Table 6

Attention Factors: normality tests, inter-correlations of component tasks

Attention domain			
Sustained Attention	=	Visual Elevator, Lottery.	
Selective Attention	=	Map Search (2 mins), Phone Search.	
Attention Switching	=	Elevator Counting with Distraction, Elevator Counting with Reversal.	
Tests of Normality¹			
		Shapiro-Wilk	Skew
Sustained Attention		.954 n.s.	-0.734
Selective Attention		.926 *	-0.885
Attention Switch		.977 n.s.	-0.078
ATTENTION domain (N = 24)			
Attention domain²			
<u>Attention domain</u>		Pearson Correlation Coefficients	
		<u>Attention</u>	Sustained Selective
Sustained Attention		.693**	
Selective Attention		.569**	.079
Attention Switching		.733**	.445** -0.016
Component tasks³			
Pearson Correlation Coefficients			
<u>Sustained Attention</u>		<u>Sustained</u>	Visual Elevator
Visual Elevator (accuracy) (33%)		.578**	
Lottery (69%)		.833**	.030
<u>Visual Selective Attention</u>		<u>Selective</u>	Map Search 2
Map Search (2minutes) (64%)		.799**	
Phone Search (74%)		.858**	.070
<u>Attention Switching</u>		<u>Switching</u>	Distraction
Z: Counting with Distraction (62%)		.787**	
Z: Counting with Reversal (80%)		.897**	.432*

Note:

n.s. = not significant *p < .05. **p < .01. Pearson Correlations are two-tailed.

1 = Tests compute normality of z-score means for each sub-domain.

2 = Inter-correlations amongst the four sub-domains of Intelligence.

3 = Inter-correlations amongst component tasks measuring a sub-domain.

Appendix Table 7

Executive Functions: normality tests, inter-correlations of component tasks

Executive functions domain			
<ul style="list-style-type: none"> • Verbal Fluency: FAS Letter fluency; Category Fluency; Category Switching. • Design Fluency: Empty Dots fluency; Filled Dots fluency; Design Switching. • Card-Sorting: Formation of verbal sorts; and of perceptual sorts. • Colour-Word Interference: Colour-Word Inhibition; Colour-Word Switching. 			
Tests of Normality¹	Shapiro-Wilk	Skew	
Verbal Fluency	.935 n.s.	0.595	
Design Fluency	.972 n.s.	0.637	
Sorting	.962 n.s.	-0.02	
Colour-Word Interference	.973 n.s.	-0.527	
EXECUTIVE FUNCTIONS (N=24)	.966 n.s.	0.633	
Executive Functions domain²	Pearson Correlation Co-efficients		
<u>Executive domain</u>	<u>Executive</u>	Verbal	Design Sorting
Verbal Fluency	.756**		
Design Fluency	.622**	.293	
Sorting	.609**	.197	.319
Colour-Word Interference	.558**	.030	.197 .463*
Component tasks³	Pearson Correlation Co-efficients		
<u>Verbal Fluency</u>	<u>Verbal</u>	Letter	Category
Letter Fluency (74%)	.861**		
Category Fluency (85%)	.922**	.728**	
Category Switching (69%)	.829**	.532**	.654**
<u>Visual Fluency</u>	<u>Visual</u>	Filled	Empty
Filled Dots (60%)	.776**		
Empty Dots (68%)	.828**	.489*	
Design Switching (61%)	.782**	.344	.515**
<u>Sorting Total</u>	<u>Total</u>	Verbal	
Verbal Sorts (25%)	.500*		
Perceptual Sorts (80%)	.893**	.109	
<u>Colour-Word Interference</u>	<u>Interference</u>	Inhibition	
Response Inhibition (88%)	.938**		
Response Switching (82%)	.908**	.706**	

Note:

n.s. = not significant. *p < .05 **p < .01. Pearson Correlations are two-tailed.

1 = Tests compute normality of z-score means for each sub-domain.

2 = Inter-correlations amongst the four sub-domains of Executive Functions.

3 = Inter-correlations amongst component tasks measuring a sub-domain.

Appendix Table 8

Verbal Memory: normality tests, inter-correlations of component tasks

Verbal memory domain		
<ul style="list-style-type: none"> Semantic: Stories I, Stories II, and Stories Recognition (WMS-III). Episodic: Auditory Verbal Learning Test (Trials 1-5), (Trial 8), (Trial 9). 		
Tests of Normality¹	Shapiro-Wilk	Skew
Learning (AVLT trials 1-5)	.933 n.s.	-0.52
Delayed Recall (AVLT trial 8)	.898 *	-1.06
EPISODIC MEMORY (N=24)	.873 *	-1.11
Learning (Stories I)	.986 n.s.	-0.209
Delayed Recall (Stories II)	.928 n.s.	-0.914
SEMANTIC MEMORY (N=24)	.930 n.s.	-0.824
Verbal memory domain²	Correlation Co-efficients	
<u>Verbal Memory</u>	<u>Verbal</u>	<u>Episodic</u>
Episodic	.942**	
Semantic	.769**	.510*
Component tasks³	Correlation Coefficients	
<u>Episodic Memory</u>	<u>Episodic</u>	<u>Learning</u>
Learning (87%)	.931**	
Delayed Recall (94%)	.972**	.854**
<u>Semantic Memory</u>	<u>Semantic</u>	<u>Learning</u>
Learning (74%)	.859**	
Delayed Recall (85%)	.920**	.799**

Note:

n.s. = not significant *p< .05. **p < .01. Pearson correlations are two-tailed.

1 = Tests compute normality of z-score means for each sub-domain.

2 = Inter-correlations amongst two sub-domains of Verbal Memory.

3 = Inter-correlations amongst component tasks measuring a sub-domain.

Appendix Table 9

Visual Memory: normality tests, inter-correlations of component tasks.

Visual memory domain		
<ul style="list-style-type: none"> Recall: Complex Figure Test Medical College of Georgia (CFT-MCG) Recognition: Continuous Visual Memory Test of abstract figures (CVMT) 		
Tests of Normality¹	Shapiro-Wilk	Skew
Memory Complex Figures	.972 n.s.	-0.12
Memory Abstract Figures	.927 n.s.	0.93
NON-VERBAL MEMORY domain (N=24)	.975 n.s.	0.32
Visual Memory Domain²	Correlation Coefficients	
<u>Non-verbal Memory</u>	<u>Non-verbal</u>	Complex
Complex Figures	.858**	
Abstract Figures	.912**	.552**
Component tasks³	Correlation Coefficients	
<u>Complex Figures (CFT-MCG)</u>	<u>Complex</u>	Learning
Learning Complex Figures (98%)	.988**	
Delayed Recall Complex Figures (98%)	.989**	.955**
<u>Abstract Figures (CVMT)</u>	<u>Abstract</u>	Learning
Learning Abstract Figures (69%)	.832**	
Delayed Recognition Abstract Figures (61%)	.779**	.299

Note:

n.s. = not significant. *p < .05. **p < .01. Pearson Correlations are two-tailed.

1 = Tests compute normality of z-score means for each sub-domain.

2 = Inter-correlations amongst measures of visual memory.

3 = Inter-correlations amongst component tasks in each figure-type.

SPSS SCALES SYNTAX FOR ESDQ AND EFQ**SCALE SYNTAX for ESDQ ITEMS (Patient version of ESDQ)***COMPUTE*

angslf = (seslf23 + seslf2 + seslf1 + seslf15 + seslf37 + seslf8 + seslf18)/7.
 emdyslf = (seslf52 + seslf44 + seslf35 + seslf54 + seslf56 + seslf26 + seslf12 + seslf51)/8.
 helpslf = (seslf10 + seslf17 + seslf9 + seslf4 + seslf24 + seslf16 + seslf32 + seslf42 + seslf39)/9.
 inertslf = (seslf30 + seslf22 + seslf53)/3.
 fatslf = (seslf43 + seslf5 + seslf36 + seslf50)/4.
 indifslf = (seslf29 + seslf14 + seslf34 + seslf46 + seslf49 + seslf55 + seslf47 + seslf31)/8 .
 inapslf = (seslf6 + seslf7 + seslf41 + seslf40 + seslf21 + seslf11)/6.
 euphslf = (seslf47 + seslf19 + seslf38 + seslf48 + seslf59 + seslf45)/6.
 maladslf = (seslf19 + seslf44 + seslf28 + seslf22 + seslf48 + seslf40 + seslf51 + seslf12 + seslf20)/9.
 linsighslf = (seslf57 + seslf58 + seslf59 + seslf45 + seslf7)/5.

SCALE SYNTAX for ESDQ ITEMS (Partner version of ESDQ)*COMPUTE*

angso = (seso23 + seso1 + seso2 + seso15 + seso8 + seso27 + seso18 + seso37)/8.
 emdyso = (seso42 + seso44 + seso54 + seso51 + seso35 + seso52)/6 .
 helpso = (seso10 + seso4 + seso24 + seso32 + seso17 + seso33 + seso16 + seso9)/8.
 inertso = (seso30 + seso22 + seso53)/3.
 fatso = (seso43 + seso5 + seso36 + seso50)/4.
 indifso = (seso46 + seso55 + seso31 + seso13 + seso14 + seso7 + seso29)/7.
 inapso = (seso21 + seso6 + seso41 + seso11 + seso56 + seso40)/6 .
 euphso = (seso47 + seso19 + seso38 + seso48 + seso59 + seso45)/6.
 maladso = (seso19 + seso44 + seso28 + seso22 + seso48 + seso40 + seso51 + seso12 + seso20)/9.
 linsighso = (seso57 + seso58 + seso59 + seso45 + seso7)/5.

SCALE SYNTAX for EFQ ITEMS (Patient version of EFQ)*COMPUTE*

concslf = (concen5 + concen1 + concen4 + concen3 + concen2)/5 .
 memslf = (mem12 + mem14 + mem16 + mem13 + mem10 + mem8 + mem17 + mem18 + mem6 + mem15 + mem7)/11 .
 emotslf = (emot21 + emot22 + emot20 + emot27 + emot35 + emot33 + emot25 + emot24)/8 .
 orgslf = (org43 + org40 + org42 + org41 + org39 + org38 + org44)/7.
 commslf = (comm58 + comm59 + comm54 + comm46 + comm57)/5 .
 linsighslf = (comm61 + emot37 + mem19 + emot31 + emot30)/5 .

SCALE SYNTAX for EFQ ITEMS (Partner version of EFQ)*COMPUTE*

concsso = (efso5 + efso1 + efso4 + efso3 + efso2)/5.
 memso = (efso12 + efso14 + efso16 + efso13 + efso10 + efso8 + efso17 + efso18 + efso6 + efso15 + efso7)/11.
 emotso = (efso21 + efso22 + efso20 + efso27 + efso35 + efso33 + efso25 + efso24)/8.
 orgso = (efso43 + efso40 + efso42 + efso41 + efso39 + efso38 + efso44)/7.
 commso = (efso58 + efso59 + efso54 + efso46 + efso57)/5.
 linsighso = (efso61 + efso37 + efso19 + efso31 + efso30)/5.

QUESTION-ITEMS FOR EDSQ SCALES (PATIENT VERSION)**Anger**

- Item 23: Are you short tempered (short-fused)?
 Item 2: Are you irritable?
 Item 1: Do you get angry?
 Item 15: Do you get easily annoyed or upset?
 Item 37: Do you fly off the handle for no reason?
 Item 8: Do you behave too aggressively towards the people you live with?
 Item 18: Do you get impatient for no reason at all?

Emotional Dyscontrol

- Item 52: Do you sometimes cry or laugh for no apparent reason?
 Item 44: Do you cry too easily?
 Item 35: Do you sometimes find that you show emotions that you do not seem to feel to the same extent? For example crying when your not really sad?
 Item 54: Do you cry one moment and then laugh the next?
 Item 56: Have you ever been unable to control your emotions to an extend where it has caused you distress or social embarrassment?
 Item 26: Can you be too easily moved into feeling or showing an emotion? For example, feeling emotional about something that is only slightly sad. Or laughing too much at a weak joke?
 Item 12: Do you feel unable to control your emotions?
 Item 51: Do you some- times show too much emotion?

Helplessness

- Item 10: Do you have panic attacks?
 Item 17: Do you get anxious?
 Item 9: Do you sometimes feel like just giving up?
 Item 4: Do you feel scared or worried about trying something new?
 Item 24: Do you suddenly feel depressed for no apparent reason?
 Item 16: Do you feel without hope?
 Item 32: Do you find that you feel helpless?
 Item 42: Do you feel unreasonably scared or worried about meeting new people?
 Item 39: Do you lack confidence or get nervous in areas you had previously coped?

Inertia

- Item 30: Do others sometimes remark that you never start or complete things?
 Item 22: Do other people have to prompt you to do things?
 Item 53: Do you lack any interests or hobbies?

Fatigue

- Item 43: Do you need more sleep during the day?
 Item 5: Do you feel giddy at times?
 Item 36: Have you found that you are less interested in sex?
 Item 50: Do you often feel tired and listless?

Indifference

- Item 29: Do you feel uninterested in things going on around you?
 Item 14: Do you sometimes feel that you don't care about things anymore?

- Item 34: Do you feel really high?
 Item 46: Do you sometimes feel indifferent toward things that would normally cause you concern?
 Item 49: Do you have sudden flashes of anger for no apparent reason?
 Item 55: Do you feel that you sometimes show a lack of sensitivity toward the feelings of those around you?
 Item 47: Do you feel relatively unconcerned about your well being?
 Item 31: Do you feel little interest for events concerning family or friends?

Inappropriate Behaviour

- Item 6: Do you find that you sometimes talk about sex too much?
 Item 7: Do you find it difficult to pick up on other people's feelings?
 Item 41: Do you show your sexuality in more unusual ways?
 Item 40: Does it worry you that you are sometimes too excited or "over the top"?
 Item 21: Do you sometimes find your sexual desires difficult to control?
 Item 11: Do you laugh too easily?

Euphoria

- Item 47: Do you feel relatively unconcerned about your well being?
 Item 19: Do you become over-talkative?
 Item 38: Do others think you tend to deny your illness or discomfort?
 Item 48: Do you make inappropriate comments when talking to people?
 Item 59: Do others sometimes say you have some difficulties with personal relationships that you do not see yourself?
 Item 45: Do others sometimes say you have difficulties in some of these areas which you do not see yourself?

Maladaptive Behaviour

- Item 19: Do you become over-talkative?
 Item 44: Do you cry too easily?
 Item 28: Do you behave in a way that is too silly or childish?
 Item 22: Do other people have to prompt you to do things?
 Item 48: Do you make inappropriate comments when talking to people?
 Item 40: Does it worry you that you are sometimes too excited or "over the top"?
 Item 51: Do you some- times show too much emotion?
 Item 12: Do you feel unable to control your emotions?
 Item 20: Do you find that when you start feeling an emotion you can't stop easily?

Lack of Insight

- Item 57: Do others sometimes say that you have difficulties in communicating with others that you do not see yourself?
 Item 58: Do others sometimes say that you have memory difficulties that you do not see yourself?
 Item 59: Do others sometimes say you have some difficulties with personal relationships that you do not see yourself?
 Item 45: Do others sometimes say you have difficulties in some of these areas which you do not see yourself?
 Item 7: Do you find it difficult to pick up on other people's feelings?

TREATMENT OF COGNITIVE DATA

Z-Score transformations For the WAIS-III, WMS-III and the D-KEFS, the raw score means and standard deviations were manually calculated, using the respective test manuals' data tables. Steps taken in treatment of raw data were as follows.

- Raw means and standard deviations were calculated using the raw score equivalents for the scaled scores (SS) of 7 to 13, since in the Wechsler and D-KEFS batteries, the SS mean = 10, and one standard deviation = +/- 3 scaled scores.
- To test their applicability, these calculated norms were then applied to raw scores in scaled scores other than SS7 to SS13 (e.g. scaled scores of 6 and 15). The z-score thus produced was checked against its equivalent SS in the Conversion Table 1-1 for equivalents of I.Q., Scaled Scores, Z-Scores and Percentiles (see Esther Strauss, et al., 2006, p. 5).

For example, a scaled score of 6 is known to be equivalent to a z-score of -1.34; while a scaled score of 5 = z-score of -1.64 and a scaled score of 7 = z-score of -0.99. Thus, any raw scores within the 6 scale range should produce z-scores clustered around -1.34, ranging between -1.17 to -1.49. Overall, the results showed that while the calculated raw means/standard deviations did not always produce z-score performance data which were perfectly equivalent to the data-table scales, they were close.

- SPSS syntax files programmed with the raw score means and standard deviations were run on the Wechsler and D-KEFS sub-test raw performance data of participants.
- To verify their accuracy, the resulting z-scores for each individual on a sub-test were checked against his/her scaled score gained for that test. These z-score data were used for the statistical analysis of epilepsy groups.

A speedier method - using a scaled score mean = 10, and standard deviation = 3 – would have given the same z-score for a whole range of raw scores. z-scores derived from raw score means and standard deviations might produce more significant results.

Outliers Outliers were identified via box-plots of each task's z-scores. A few outliers were more than or equal to +/- 4.00 and were replaced with a z-score of + or - 3.50. Two patients (recently changed their medication regimes) produced extreme outliers in several TEA attention tasks and attention control (Colour-Word Interference). Both were transferred to the next age group of 35-49 years for the TEA norms, which strategy produced impaired scores still within a meaningful range (not more than -4.00). This strategy was not successful for their Colour-Word Interference task scores, and any z-scores under -4.00 here were increased by an arbitrary +1.00. Further, several patients attempted a task but gave up before completion. In such cases, the extreme outliers thus produced were replaced with -1.64, this being the cut-off score signifying very mild impairment.

Missing Values Occasionally, a participant refused to attempt a task (too difficult or could not understand the instructions); or failed to attend all four sessions. These missing values were entered into SPSS as 9999.

PROGRAMS FOR SINGLE CASE - CONTROL GROUP COMPARISONS

The methods of single case – control group analyses described here were taken from the University of Aberdeen

www.abdn.ac.uk/~psy086/dept/SingleCaseMethodology.htm. (Crawford, 2007).

The actual computer programs can be accessed at

www.abdn.ac.uk/~psy086/dept/SingleCaseMethodsComputerPrograms.htm.

Crawford has given an overview of his methodology (Crawford, 2006); and also in a power-point presentation to the International Neuropsychological Society (see [INS_Boston_Workshop.ppt](#) file) available on the University of Aberdeen web-site www.abdn.ac.uk/~psy086/dept/PowerPoints/.

Over time, Crawford and his colleagues have developed and widened the scope of these programs. Initially, a frequentist or classical approach to comparisons was used in the programs (Crawford & Garthwaite, 2002; Crawford & Howell, 1998). Later, the same single-case comparisons were carried out using a Bayesian approach which takes summary statistics from a control population as inputs, allowing inferential conclusions to be drawn (Crawford & Garthwaite, 2007). Finally, Crawford and colleagues have widened the programs' scope to include an Effect Size calculation based on Bayesian methods (Crawford, et al., 2010).

- ***RSDT_ES.exe* for raw data from TLE cases.**

The computer program tests for a significant difference between a patient's scores compared to a control sample. See the accompanying papers by Crawford, Garthwaite and Porter (2010); also Crawford and Garthwaite (2005) and Garthwaite and Crawford (2004). This study used the *RSDT_ES.exe* to test for a significant difference between individual TLE patients' scores on verbal and visual memory, compared with the mean of the differences obtained in an IGE control group. The *RSDT_ES.exe* is described at the beginning of the computer program as follows.

“The program *RSDT.exe* applies the Revised Standardized Difference Test to test whether the difference between an individual's standardized scores on two tasks (X and Y) is significantly different from the differences observed in a control sample. The program also provides a point estimate of the abnormality of the individual's discrepancy i.e. it estimates the percentage of the population that would obtain a more extreme discrepancy. The *RSDT_ES* program also provides a point estimate of the effect size of the difference between case and controls with an accompanying 95% credible interval. Although the RSDT is a classical (frequentist) test, Bayesian methods are used to provide the effect size.”

The *RSDT* test controls the Type I error rate (Crawford & Garthwaite, 2005; Garthwaite & Crawford, 2004) regardless of small size of the control sample and magnitude of the correlation between tasks X and Y.

- ***SingleBayes_ES.exe* for raw data from NCSE and GCSE cases.**

The computer program tests for an individual's single deficit compared to a control sample. See the accompanying paper by Crawford, Garthwaite and Porter (2010); and also Crawford and Garthwaite (2007). This study uses *SingleBayes_ES.exe* to compare NCSE and GCSE individual's cognitive task performance scores with the mean obtained in an

IGE control group. The *SingleBayes_ES.exe* is described at the beginning of the computer program as follows.

“The program tests whether an individual’s score is significantly different from a control or normative sample. It also provides a point estimate of the Effect Size for difference between case and controls (z-cc) with an accompanying 95% credible interval. Finally, it provides a point and interval estimate of the abnormality of the case’s score i.e. it estimates the percentage of population that would obtain a lower score (together with a 95% credible interval on this percentage).”

Bayesian credible intervals and frequentist confidence intervals are equivalent, so a Bayesian interpretation can be made in either approach. *SingleBayes* has advantages over an earlier frequentist version (*SingLims*) since the Bayesian approach allows use of inferential methods and a less complicated interpretation (Crawford & Garthwaite, 2005, 2007; Crawford, et al., 2009).

- ***DissocsBayes_ES.exe* for raw data from NCSE and GCSE cases.**

This computer program tests for classical or strong dissociations between a patient’s scores on Tasks X and Y when compared to a control sample. See the accompanying papers (Crawford & Garthwaite, 2005, 2006b, 2007; Crawford, et al., 2010). This study used *DissocsBayes_ES.exe* to test for a strong or classical dissociation between NCSE and GCSE individual scores on two tasks (Phone Search while Counting and Lottery) in comparison to those obtained in the IGE control group. The *DissocsBayes_ES.exe* is described at the beginning of the computer program as follows.

“The program is used to apply Bayesian criteria for dissociations in single-case studies in which the scores of a case on two tasks are compared to those of a control sample. (The program tests for a strong dissociation or a dissociation, putatively classical).

The program first tests whether the case’s scores meet the criterion for a deficit on Tasks X and Y; the test used is Crawford and Howell’s (1998) test. Full output is provided, namely a significance test; a point estimate of effect size for differences between the case and controls with accompanying 95% confidence interval; and a point and interval estimate of the abnormality of a case’s score.

Next, the program applies the Bayesian Standardized Difference Test (BSDT) to the standardized difference between the case’s scores on Tasks X and Y. Output from this test consists of case’s scores expressed as z-scores, a significance test comparing the case’s difference to those of controls (p-value), effect size of the difference between case and controls, a point and interval estimate for abnormality of the case’s difference (percentage of control population exhibiting a larger difference).

Finally, Bayesian criteria for a dissociation are applied using results of foregoing tests. To meet criteria for a dissociation, the p-value for the BSDT must be below 0.05 (i.e. the standardized difference between the case’s scores on X and Y must be significant) and at least one of the tests for a deficit on the two tasks must also be below 0.05.

If the case’s scores *between both tasks* qualify as a deficit, then the case is classified as exhibiting a “strong dissociation”. If the score on *only one of the tasks* qualifies as a deficit, then the case is classified as exhibiting a “dissociation, putatively classical”. The above criteria are based on Bayesian inference.” (end quote).

- ***MoodScore_PRs_Aus.exe* for raw DASS data from all participants.**

This program expresses an individual's raw scores on mood scales as percentile ranks. Crawford, Cayley, Wilson, Lovibond and Hartley (2011) collected norms from the Australian general adult population. They applied these to self-report mood scales (BAI, BDI, CRSD, CES-D, DASS, DASS-21, STAI-X, STAI-Y, SRDS and SRAS) using their recently-developed computer program ***MoodScore_PRs_Aus.exe***. In this study, data from the DASS (full length) was analyzed to gain percentile ranks of the epilepsy individuals' raw scores. The point estimates of the percentile ranks are accompanied by 95% interval estimates. For the DASS, the *MoodScore_PRs_Aus.exe* program gives a General Psychological Distress (GPD) composite of the depression, anxiety and stress scale scores.

- ***TEAI.exe*** - intra-individual difference among TEA scores

Crawford, Sommerville & Robertson (1997) have developed a program to test for intra-individual deficits in the Test of Everyday Attention. The *TEAI.exe* program compares a person's performance score on one impaired TEA task to his/her overall mean for the TEA sub-tests. The overall mean for all sub-test performances must include the individual sub-test being compared in addition to all the other sub-tests. Bonferroni post-hoc tests are used (see Esther Strauss, et al., 2006 for a review of the TEA tasks).

APPENDIX E:
INVESTIGATIVE REPORTS (DR. J. S. ARCHER)
EEG RECORDINGS OF EIGHT PARTICIPANTS

(Jill, Tom, Mena, Lori, Sher, Mary, Bela, Etta)

JILL (Absence Status)

Generalized epileptiform activity in brief and longer bursts of 1-5 seconds duration, with rapid runs of polyspike and slow wave. The discharges have a generalised field with a bi-frontal predominance.

TOM (Absence Status)

An abnormal EEG with generalised epileptiform activity consistent with idiopathic generalised epilepsy. This included intermittent discharges of generalised, predominantly frontal 3 Hz spike and slow wave and polyspike and slow wave complexes.

MENA (Generalized Convulsive Status)

An abnormal EEG with intermittent runs of right fronto-temporal slowing, but no definitive epileptiform abnormalities.

LORI (Generalized Convulsive Status)

Abnormal activity consistent with IGE.

SHER (Idiopathic Generalized Epilepsy)

An abnormal EEG with generalized epileptiform discharges and photo-sensitivity, consistent with an idiopathic generalized epilepsy.

MARY (Idiopathic Generalized Epilepsy)

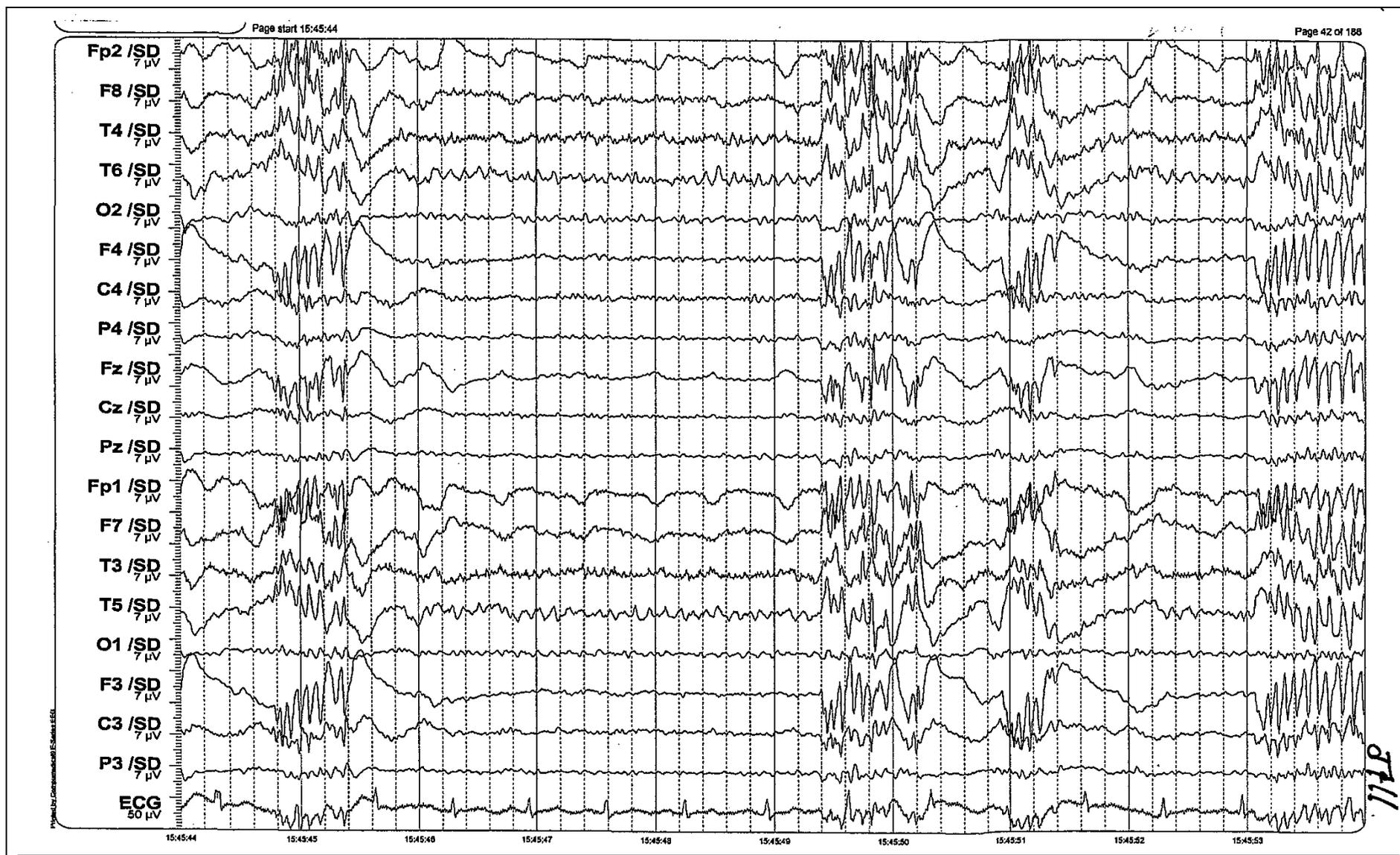
An abnormal result, with a single burst of epileptiform activity during photic stimulation consistent with idiopathic generalized epilepsy.

BELA (Idiopathic Generalized Epilepsy)

Episodes of facial twitching which are in fact minor seizures. The episodes are associated with generalized 3Hz spike-and-wave activity. Had generalized convulsion while attached to the EEG machine, and the activity recorded was consistent with IGE (diagnosis = absence epilepsy with peri-oral myoclonia).

ETTA (right onset Temporal Lobe Epilepsy)

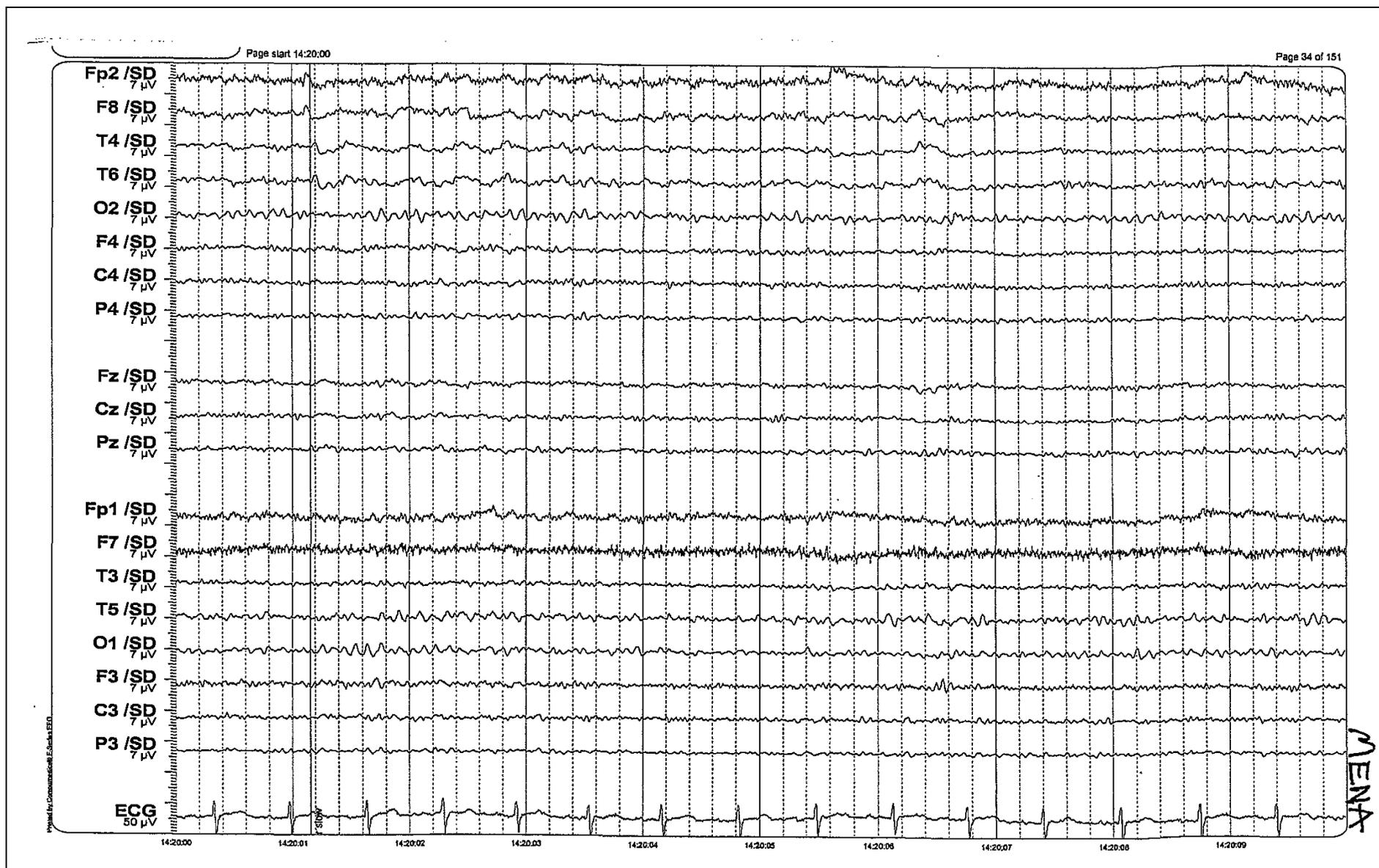
Activity consistent with right temporal lobe epilepsy.



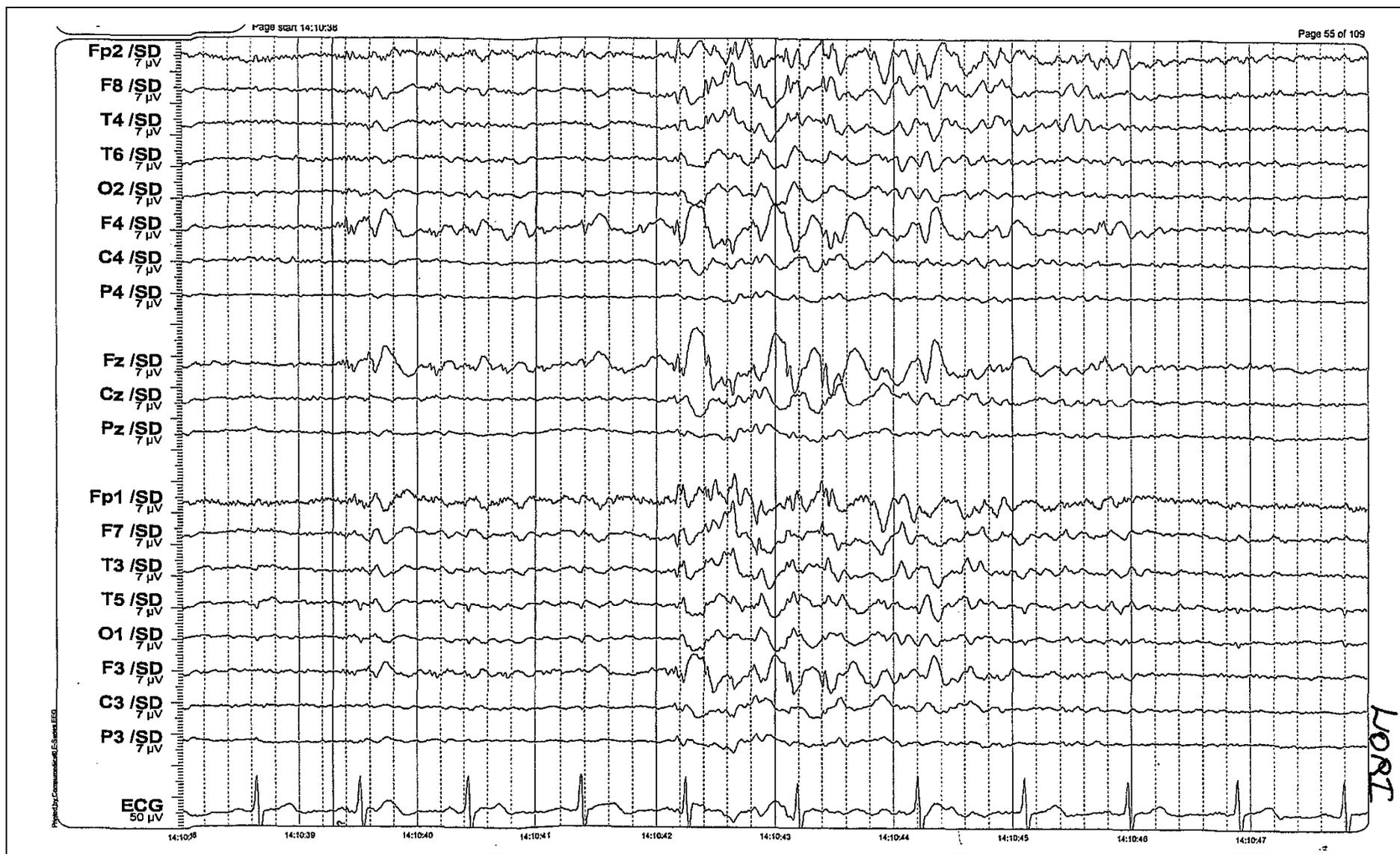
Appendix Figure 1 Jill (Absence Status)



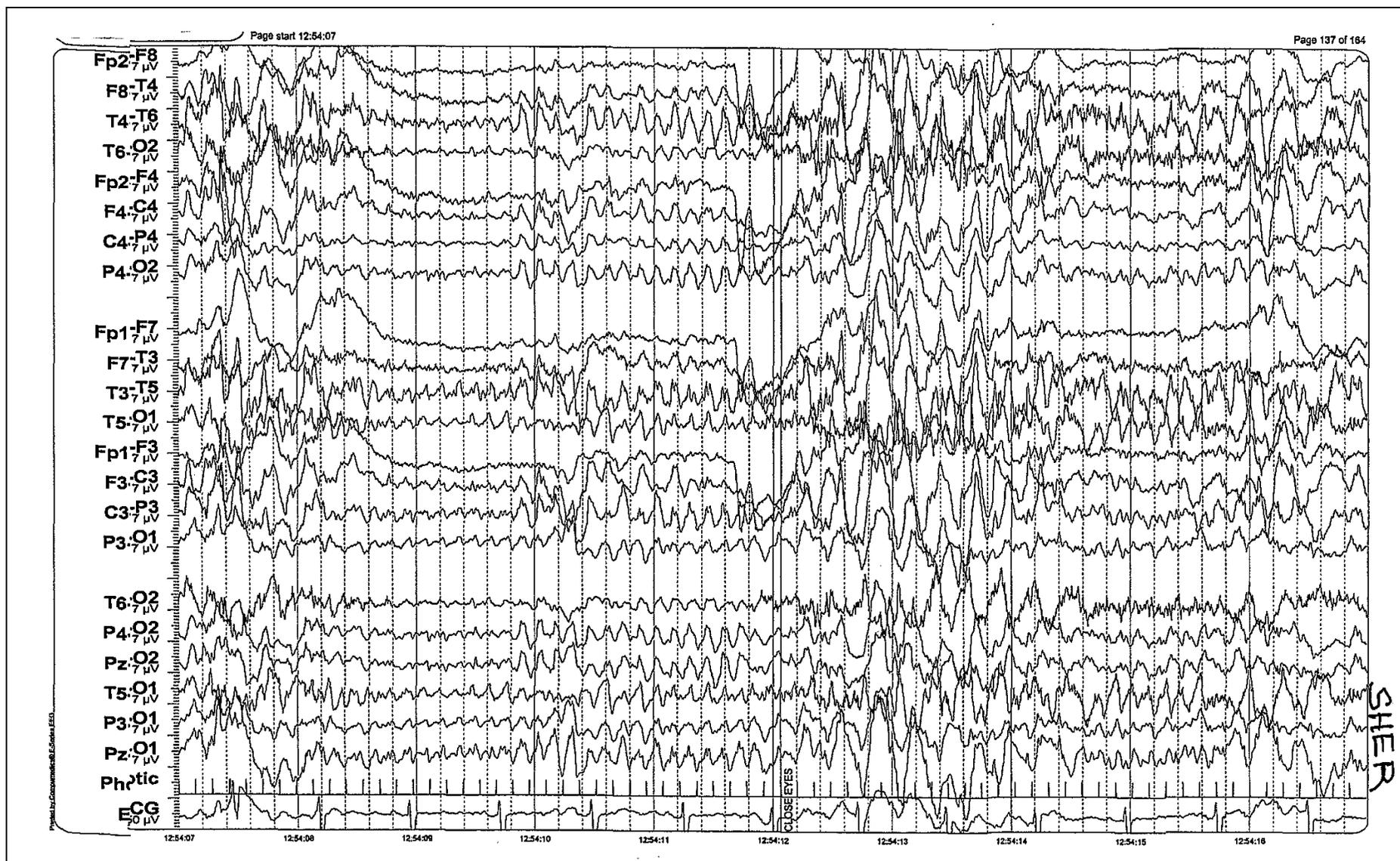
Appendix Figure 2 Tom (Absence Status)



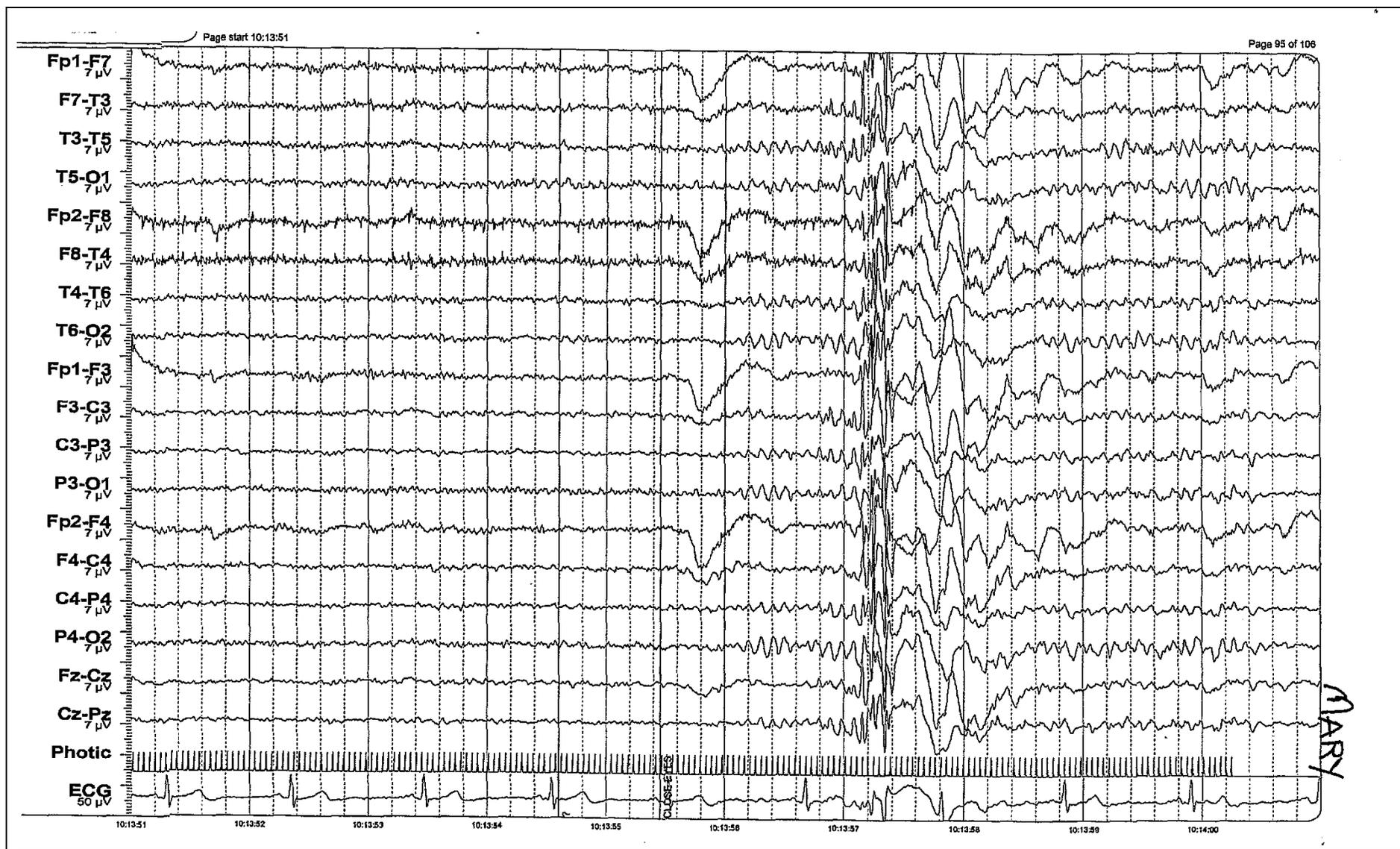
Appendix Figure 3 Mena (Generalized Convulsive Status)



Appendix Figure 4 Lori (Generalized Convulsive Status)



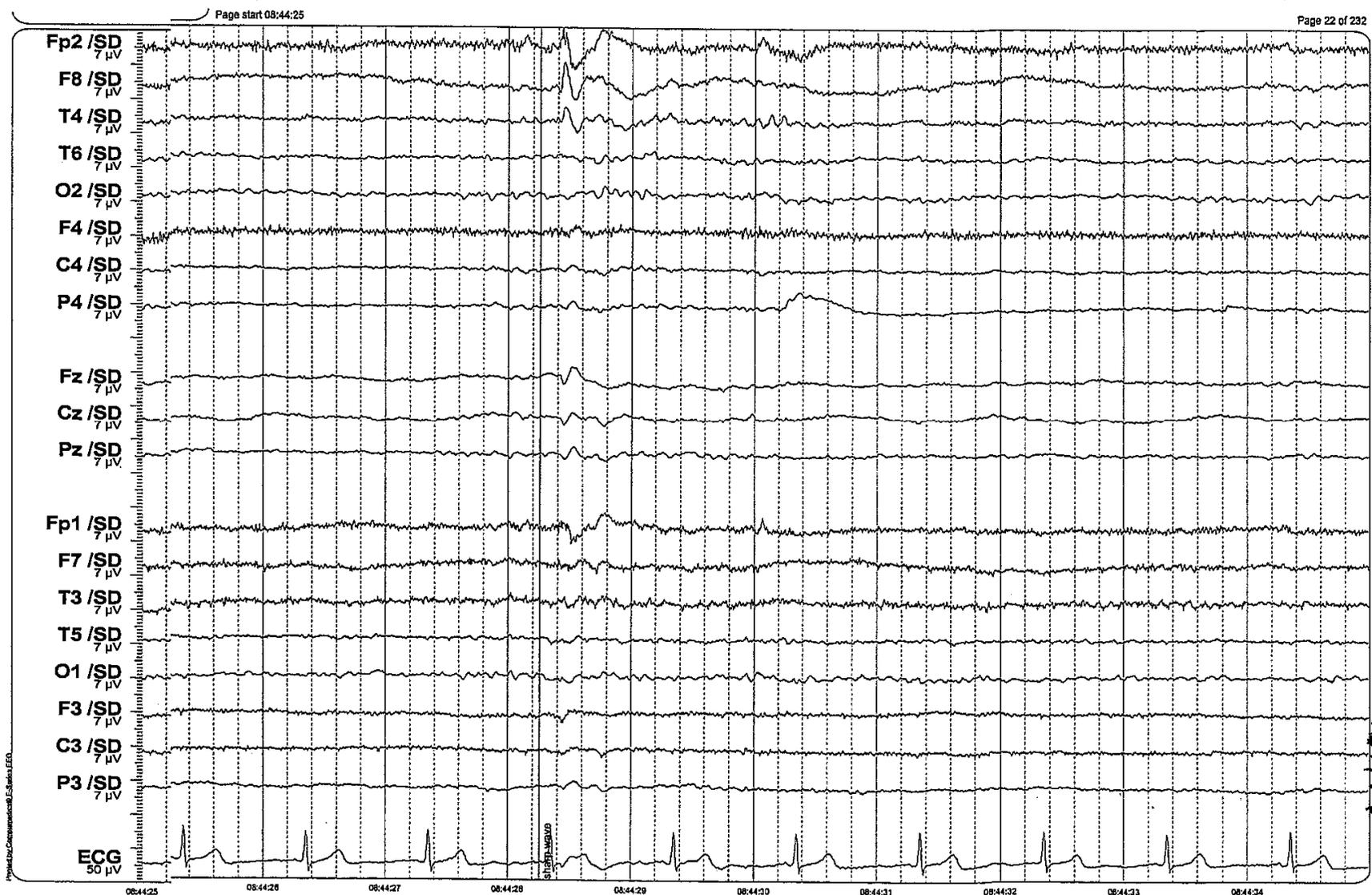
Appendix Figure 5 Sher (Idiopathic Generalized Epilepsy)



Appendix Figure 6 Mary (Idiopathic Generalized Epilepsy)



Appendix Figure 7 Bela (Idiopathic Generalized Epilepsy)



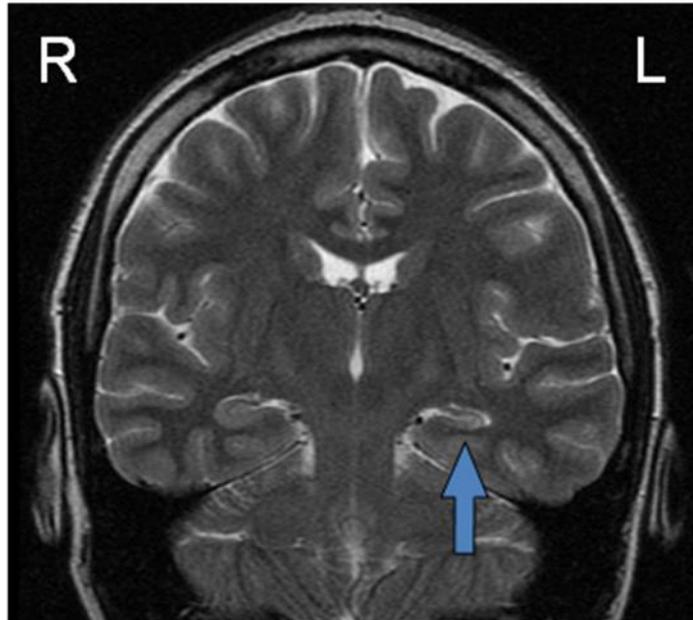
Appendix Figure 8 Etta (right onset Temporal Lobe Epilepsy)

MRI BRAIN SCANS OF TWO TLE PARTICIPANTS**(Cath and Jana)****CATH (left onset Temporal Lobe Epilepsy)**

Long-standing left mesial hippocampal sclerosis. Left hippocampus is smaller volume and has higher increased signal.

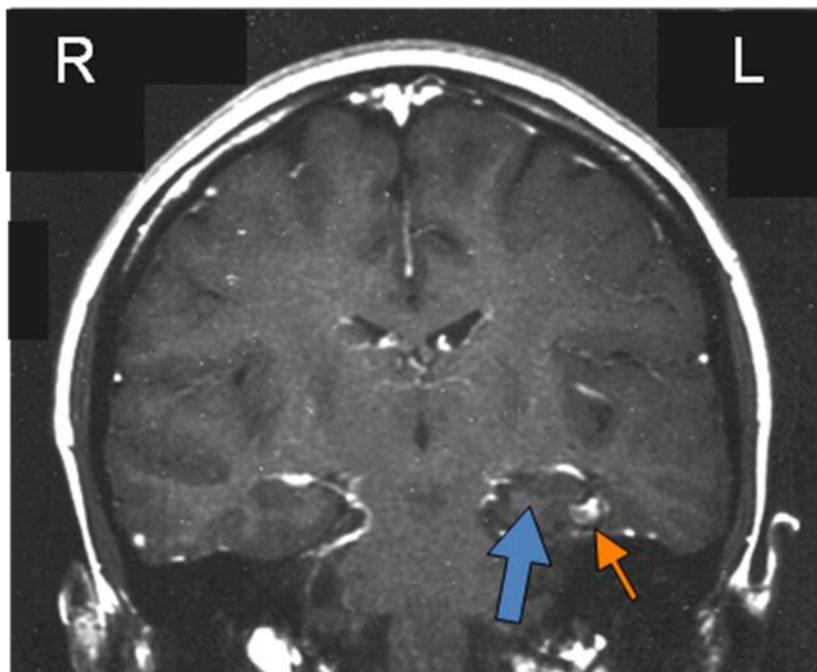
JANA (left onset Temporal Lobe Epilepsy)

Left hippocampus is smaller than the right. Found a typical cavernous haemangioma in the left temporal lobe close to the hippocampus. Another is on the right side lying in the posterior temporal region. Neither of these lesions is causing significant mass effect or other abnormality. Note: MRI of right temporal lobe cavernoma is not shown here.



Appendix Figure 9 MRI Brains: Cath (left TLE) and Jana (left TLE)

Cath, coronal T2 MRI, left hippocampal sclerosis; Left hippocampus (blue arrow) has reduced volume and increased signal.



Jana, Coronal T1, gadolinium enhanced MRI. Small arrow shows contrast in cavernous haemangioma adjacent to left hippocampus (large arrow). Left hippocampus is slightly smaller than the right.

STATUS EPILEPTICUS IN FOUR INDIGENOUS CASES FROM REMOTE FAR NORTH QUEENSLAND

In major urban centres, specialised medical care means that any status epilepticus episodes will be promptly treated, thus minimizing the seizure duration and its potential for causing brain damage. For people in rural and remote Far North Queensland, the situation is vastly different. In spite of the “flying doctor” service, patients suffering status epilepticus may be likely to have more prolonged seizure activity due to delayed treatment. For example, a patient in status epilepticus from the outer Torres Strait Islands has access to only a basic health clinic locally. Initially, s/he must be flown to Thursday Island hospital for stabilisation, before eventual transport to Cairns Base Hospital for Neurology and MRI services.

Such delays in accessing specialist medical care are not desirable but an inevitable consequence of sparse populations and distance. At times, cultural factors also may contribute to delays in seeking medical care. The implication of this situation is that the potential for gross brain damage following status is much higher in remote and rural Far North Queensland. In fact, the over-representation of indigenous people with status may be due to the brain damage associated with delayed treatment (Archer & Bunby, 2006), and which is known to facilitate further status episodes.

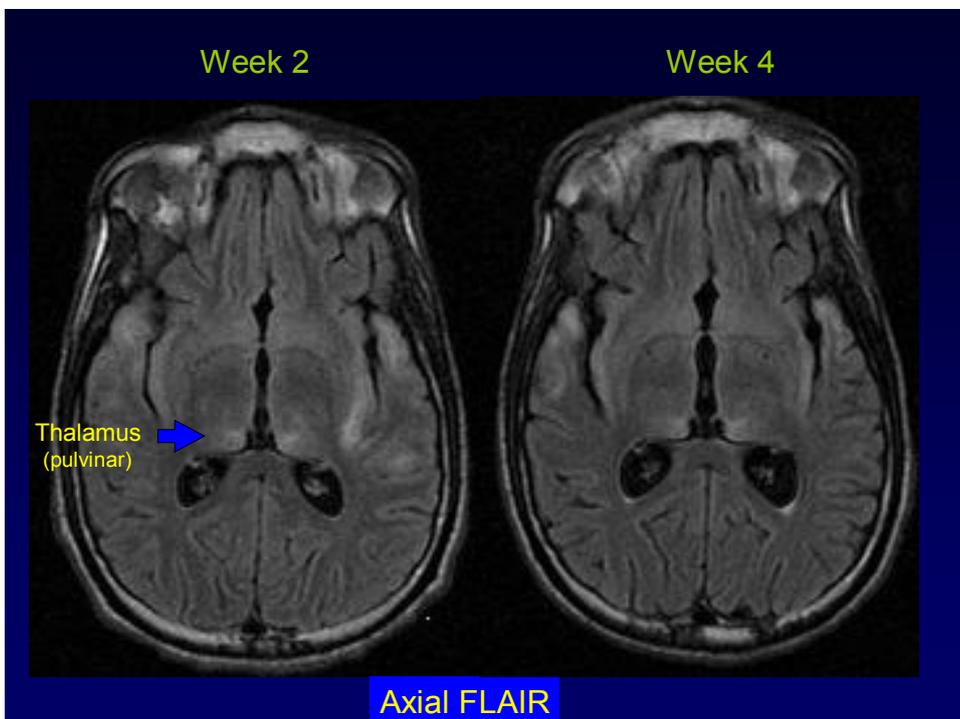
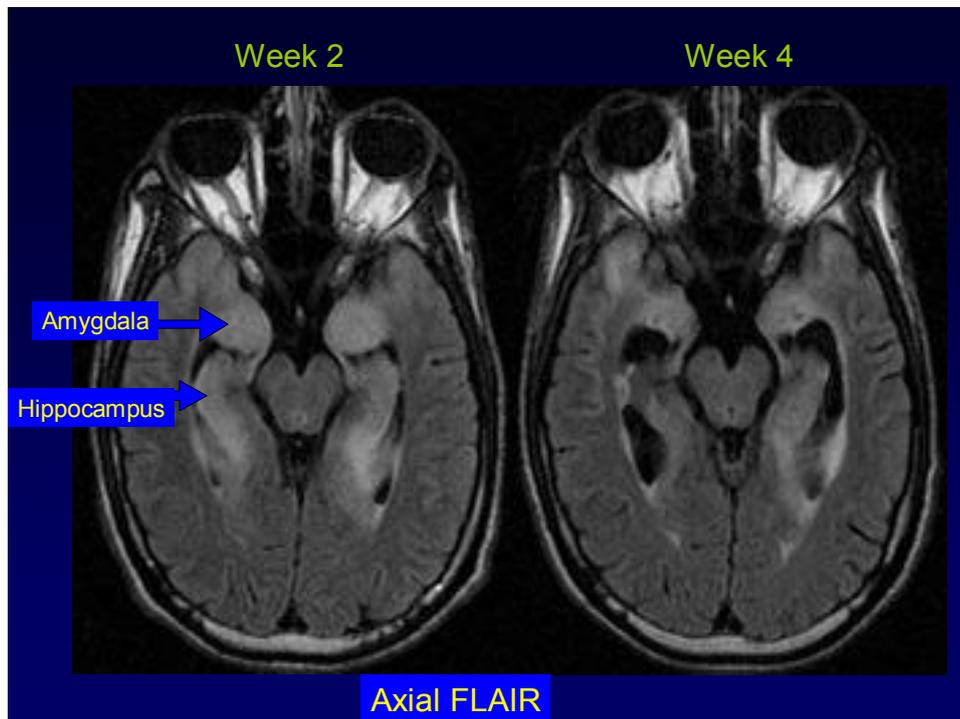
In October, 2003, Dr. John Archer and Dr. Betty Tawake provided some representative case histories of FNQ indigenous patients, which reveal the heterogenous nature of MRI changes seen in status.

CASE ONE: GENERALIZED CONVULSIVE SE

A 22 year old male was retrieved from Thursday Island, with a prolonged generalized convulsion followed by persistent oral automatisms and flickering eyelids, consistent with ongoing complex partial status. For several weeks post-status he remained profoundly agitated, confused, mute and ataxic. He eventually regained limited ability to walk and communicate. Initial CT was normal. Lumbar puncture found no evidence of encephalitis. An MRI taken two weeks post status showed increased signal in the medial temporal lobes, the thalamus and the insular cortex on FLAIR. Follow-up MRI at four weeks showed some resolution of the areas of high signal, but the clear development of generalized and especially hippocampal atrophy.

Four weeks later, it was still not possible to assess this man’s cognitive functions since his attention span and understanding of English (his second language) were both impaired to a considerable degree. However, when shown pictures from a short-form Naming Task, he could name correctly several in his own TSI language, according to his mother who was present.

CASE ONE – Generalized Convulsive SE

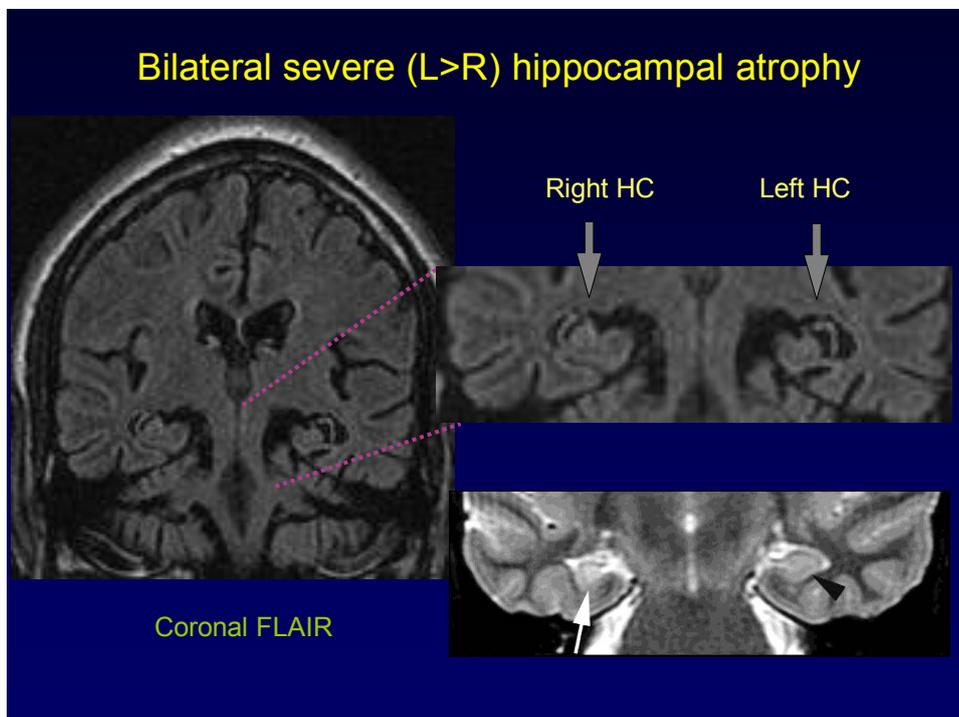
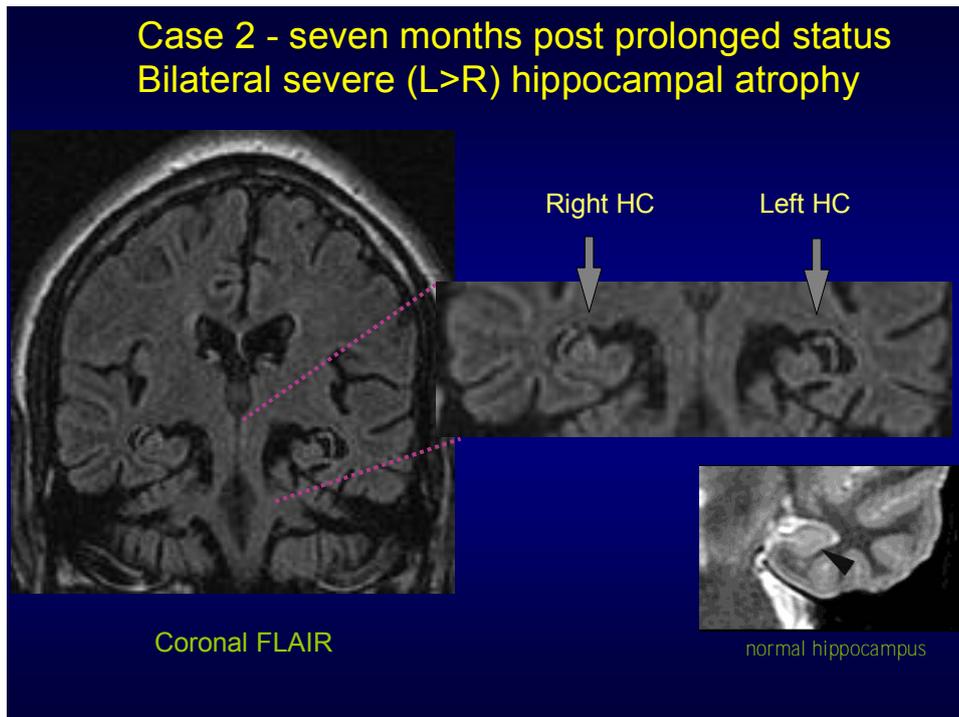


Appendix Figure 10 MRI Brains: CASE ONE – Generalized Convulsive SE

CASE TWO: GENERALIZED CONVULSIVE SE

A 35 year old male found fitting in a fishing boat was retrieved from Thursday Island following numerous generalized convulsions over approximately 24 hours. Interictally, he was aphasic with gaze deviation to the right suggesting ongoing seizure activity in the left hemisphere. There had been a single alcohol related seizure in 1999, but no pervasive alcohol abuse. For several days post-status, he was drowsy and agitated, and over several weeks regained the ability to walk and communicate. Short-term memory remained extremely poor, and he is no longer living independently. Initial CT brain was normal. MRI seven months post status revealed prominent cerebral atrophy, and gross bilateral hippocampal atrophy, more marked on the left.

CASE TWO

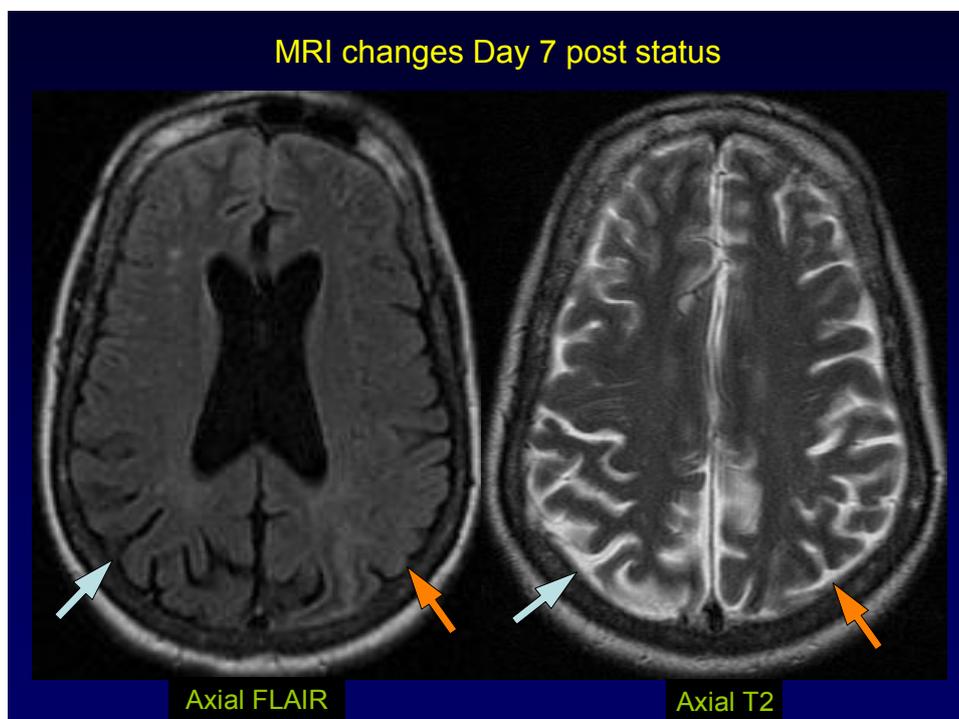


Appendix Figure 11 MRI Brains: CASE TWO – Generalized Convulsive SE

CASE THREE: COMPLEX PARTIAL SE

A 47 year old male admitted with several brief generalized convulsions. Past medical problems included chronic alcohol abuse, malnutrition, and trauma. In the ward, there was a witnessed prolonged complex partial seizure with jerking of right arm lasting greater than 30 minutes, eventually terminated with 35mg intravenous Diazepam and Phenytoin. For the next 5 days he had abnormal posturing of the right hand with gross proprioceptive failure, and mild dysphasia. Cerebral MRI showed swelling of the left fronto-parietal cortex with gyriform increased signal on FLAIR (orange arrow), with sulcal effacement compared to the normal right (blue arrow). Post-ictal EEG showed a marked excess of left hemisphere slowing.

CASE THREE - Complex Partial SE



Appendix Figure 12 MRI Brain: CASE THREE –Complex Partial SE

CASE FOUR: GENERALIZED CONVULSIVE SE

A 50 year old male from the Atherton Tableland was admitted for treatment at CBH after an SE generalized seizure lasting about an hour. A CT scan on the same day did not detect any abnormality. Patient was physically healthy. Some three weeks after the prolonged seizure he was assessed for neuropsychological status, using a battery of short-form tests (RBANS). His cognitive performance was low average for visuospatial abilities and language functions, which seem to have remained unaffected. Attention was moderately impaired. Verbal learning was severely impaired; and when re-tested after a 30 minute interval, he could not remember having taken that particular word-list test. However, while his delayed verbal recall was close to zero, he had no problems recognizing words he could not remember learning. Learning and delayed recall of both verbal and visual materials were significantly below his overall level of cognitive performance. In short, recall from episodic memory (and possibly the hippocampus) was most affected by the prolonged seizure, while verbal recognition (and possibly cortical areas) remained normal. Follow-up studies for possible transience of these cognitive effects were not possible.

OUTCOMES

All four cases were indigenous or Torres Strait Islanders. Their MRI imaging is in accord with research evidence that patients with status epilepticus are at risk of significant brain injury, especially in generalized SE where duration of the seizure can affect prognosis.

Dr. John S. Archer reports that the various MRI scans show different patterns and degrees of brain involvement in different patients. Cases 1 and 2 above suggest that generalized status can produce changes prominent in the hippocampus and thalamus; while focal status (as in Case 3 above) favours cortical areas and spares limbic structures. The author believes that, in Case 4 above, generalized status most affected cognitive functioning associated with the hippocampus, such as episodic learning and recall. The fact that the patient could recognize (but not recall) the word-lists suggests that episodic memory functions were not permanently impaired or the hippocampus damaged. This patient was closer to specialised medical treatment than the Torres Strait Islanders, but even that short delay in terminating status seems to have affected his cognitive functions. Such effects might have been only transient, but it is of interest that the area of initial vulnerability should be the hippocampus.

APPENDIX F
DOCUMENTATION

ETHICS APPROVAL NOTIFICATIONS FROM JAMES COOK
UNIVERSITY AND CAIRNS BASE HOSPITAL

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