MEMORY FUNCTIONING IN CHILDREN AND ADOLESCENTS WITH FRONTAL AND TEMPORAL LOBE EPILEPSY

Emra Lutfiye Oguzkaya

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School of Psychology and Psychiatry

Faculty of Medicine, Nursing & Health Sciences

Monash University

Clayton, VIC 3800

Australia

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ABSTRACT

Working memory (WM) refers to a temporary mental "workspace" that allows individuals to register and manipulate information to solve complex problems. The WM system acts in concert with, and has direct influence on, other memory systems, such as long-term memory (LTM), to facilitate learning and development. Many studies indicate that WM skills are vital for acquiring basic academic skills. To date, the literature investigating the memory impairments in children with focal epilepsy has been biased toward populations with temporal lobe epilepsy (TLE), with little consideration to frontal lobe epilepsy (FLE). Given theories of WM (eg Baddeley, 1974) it would be reasonable to postulate greater deficits in FLE rather than TLE as frontal systems are more pertinent to WM than other brain regions. Similarly LTM would be expected to be more vulnerable in TLE, given the role of temporal lobe structures in memory, with both deficits influencing academic achievement. This study aimed to assess the memory functioning in well-characterised samples of children with TLE and FLE, by examining not only absolute levels of impairment, though also the relationships and factors which are important to efficient memory, learning, and academic achievement, using well-validated and standardised neuropsychological measures and parent ratings. Specifically, the study sample consisted of children aged six to sixteen years with well-controlled FLE (*n*=18) and TLE (*n*=21), recruited from Royal Children's Hospital, Melbourne, Australia. Children's WM, verbal and visual LTM, and academic skills were assessed Results indicate that in many domains of memory processing children with well-controlled FLE and TLE do not differ, and seizure variables were not significantly associated with memory performance. With respect to each syndrome, children with FLE do not demonstrate wide-ranging working memory impairment, though these children demonstrated frontal lobe inefficiencies indicated by higher frequency of learning errors and impaired strategy utilisation on the CVLT-C. In contrast, children with TLE demonstrate working memory impairment, indicated by impaired performance relative to normative standards on all measures of the WMTB-C, and inconsistent strength of relationships between subcomponents of working memory. Clinical indication of a central executive deficit in this group may in actuality reflect a more primary impairment of storage capacity. Academic skills were largely at expectation relative to normative standards in both groups. The central executive remained the strongest predictor of LTM, spelling, reading, math, and sentence comprehension in both groups. Parent ratings of memory performance in children were not predicted by seizure variables or objective memory performance, highlighting the need for further work to understand the predictive factors for everyday memory.

DECLARATION

In accordance with Monash University Doctorate Regulation 17 the following Declaration is made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signed: ……………………………………………… .

Date: ....

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Sheldon Cooper PhD stated that *"one must think ahead, as the alternative would be to think backward, which is just remembering".* (Big Bang Theory: The Alien Parasite, S4; Ep10)

The finish line has been so close yet so unreachable for what seems the longest time, and it is only with the support and encouragement of a group of people from all facets of my life that the white tape could finally be broken.

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ABBREVIATIONS

AED	Anti-epileptic Drug
CVLT-C	California Verbal Learning Test – Children
CE	Central executive
DLPFC	Dorsolateral Prefrontal Cortex
fMRI	Functional Magnetic Resonance Imaging
FLE	Frontal Lobe Epilepsy
HS	Hippocampal Sclerosis
LTM	Long-term Memory
MCWM	Multi-component Working Memory Model
MRI	Magnetic Resonance Imaging
OMQ-PF	Observer Memory Questionnaire – Parent Form
PET	Positron Emission Tomography
PHL	Phonological Loop
RCFT	Rey Complex Figure Test
RCH	Royal Children‟s Hospital
SPECT	Single Photon Emission Tomography
SPSS	Statistical Package for the Social Sciences
STM	Short-term Memory
TLE	Temporal Lobe Epilepsy
WASI	Wechsler Abbreviated Scale of Intelligence
WIAT-II	Wechsler Individual Achievement Test – second edition
WM	Working Memory
WMTB-C	Working Memory Test Battery – Children
VSSP	Visuospatial Sketchpad

CHAPTER 1: THE PROBLEM AT HAND

Recent prevalence estimates place the incidence of epilepsy to be 3/1000, making it secondary to traumatic brain injury in prevalence (Eriksson & Kovikko, 1997). Epilepsy is a chronic condition of the brain that is associated with an enduring propensity to produce epileptic seizures. It is also defined according to the neurobiological, cognitive, psychological and social consequences that it produces (Avanzini, 2006), and constitutes one of the most prevalent neurological disorders of childhood (Shinnar & Pellock, 2002).

Epilepsy stands out within the literature as the single most informative neurological condition in the pursuit of understanding human cognition (Loring, 2010). Studies using epilepsy populations have informed our understanding of hemispheric specialisation, the cortical representation of sensorimotor function, and the plasticity of speech and language (Novelly, 1992; Zillmer, Spiers, & Culbertson, 2008). Most often as a consequence of undergoing surgical remediation of intractable epilepsy (Fleischman, Vaidya, Lange, & Gabrieli, 1997; McDonald, Bauer, Grande, Gilmore, & Roper, 2001), these studies collectively offer a perspective of cognition that could not be uncovered or investigated using animals.

According to Snyder (1997) epilepsy provides the most efficient “natural laboratory” (p.1) for the investigation of the neuroanatomical functionality of human memory. In particular, the syndrome of Temporal Lobe Epilepsy (TLE) has been paramount in delineating the cognitive models of memory (Kapur et al., 1997; Skotko et al., 2004), its neuroanatomical underpinnings (Zola-Morgan & Squire, 1993), and the behavioural and social consequences of pervasive amnesia (Loring, 2010; Shimamura, 1992). Specifically, it was the now infamous case of H.M that highlighted the critical functional and neuroanatomical features of the memory system. H.M underwent temporal lobe resection for amelioration of his severe temporal lobe seizures, which involved bilateral removal of the mesial temporal lobe (Scoville & Milner, 1957). What proved devastating for H.M was that a consequence of the surgery was global and persistent anterograde amnesia (Corkin, 2002; Neylan, 2000). The case of H.M provided a critical first step in understanding the mesial temporal lobes role in memory, and will be discussed further in Chapter 3.

Since this time, much of memory research has focused on the temporal cortices (Abrahams et al., 1999; Barr, 1997; Bell & Davies, 1998; Blaxton & Theodore, 1997; Gleissner et al., 2002; Gonzalez, 2005; Guimaraes et al., 2006; Hershey, Craft, Glauser, & Hale, 1998; Holdstock, Mayes, Isaac, Gong, & Roberts, 2002; Reminger et al., 2004; Squire, Stark, & Clark, 2004; Vannest, Szaflarski, Privitera, Schefft, & Holland, 2008). However, with new research comes new techniques and new theory. The current status of memory research, led by neuroimaging studies (Fletcher, Frith, & Rugg, 1997), considers not only the temporal cortices but also the neuroanatomical networks of memory (Nyberg et al., 2003; Simons & Spiers, 2003; Ungerleider, 1995; Wagner et al., 2008) At the forefront, is an emphasis on mnemonic processes mediated by the frontal lobes (Centeno, Thompson, Koepp, Helmstaedter, & Duncan, 2010; Frank, Loughry,

&

O'Reilly, 2001; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). The role of the frontal lobes in memory is distinct from temporal processes, insofar as it encompasses the strategies associated with learning and remembering information in the long-term (Centeno, et al., 2010; Fletcher & Henson, 2001). Thus, the frontal lobes are implicated in the active and working aspects of memory, namely *working memory* (WM; Muller & Knight, 2006; E. E. Smith & Jonides, 1999) which are critical to learning and remembering and will be discussed in Chapter 2.

Given the concentrated focus and significant contribution of TLE to long-term memory (LTM), a logical progression would be to investigate frontal lobe epilepsy (FLE) and working memory. It is surprising therefore that the parsimony inherent within a hypothesized TLE-LTM and FLE-WM dichotomy of dysfunction has not been investigated to the expected degree. Rather, the research investigating FLE is largely focused on executive functioning, behaviour, social, and emotional processing (Culhane-Shelburne, Chapieski, Hiscock, & Glaze, 2002; Exner et al., 2002; Helmstaedter, 2001; McDonald, Delis, Norman, Tecoma, & Iragui, 2005; Riva et al., 2005).

There are likely several reasons for this shortfall. First, it is likely that the very incentive of investigating temporal lobe function provided for by case studies such as H.M, has directed the research of these specific cognitive domains in frontal lobe function. The case of Phineas Gage, a 25-year old construction foreman who survived an injury involving the passage of a large tamping iron through his skull, can be considered a parallel historical event to that of H.M. The main outcome reported at the time of Phineas Gage‟s injury, was not the cognitive consequences, but rather the profound change in his personality (Zillmer, et al., 2008). This provided enticement to pursue this line of investigation, and contentiously had biased research of frontal lobe function at the time. The second reason is a related concept; memory impairment, in the traditional sense of an inability to recall information in the long term, is not a gross feature of frontal lobe impairment (Centeno, 2010).

Therefore the current standing of knowledge of memory impairment within either clinical syndrome could be considered as a modular and accordingly biased account in adults, and also by extension in children. The modularity of previous research is also evident when considering subjective ratings of everyday functioning. Investigations of frontal lobe epilepsy are rich with behaviour ratings assessing the presence of attention, hyperactivity, social or emotional dysfunction, as children with FLE would be considered "entitled" to such impairments (Slick, Lautzenhiser, Sherman, & Eyrl, 2006). A mirrored concept is that those with TLE would be expected to report memory deficits in their daily functioning, which is also evident within the literature (Gonzalez, Anderson, Harvey, Wood, & Mitchell, 2005). Again however, research is lacking regarding the daily impairments in children with TLE, or even the memory impairments in FLE. Thus the current standing of research, is limited not by the answers it generates, but by the failure to ask the right questions. For example, if we consider more recent research purporting the importance of the frontal lobes in working memory and by extension the importance of working memory to long-term memory consolidation (Ranganath, Johnson, & D'Esposito, 2003), then there are significant gaps within the literature on memory function as a whole. A gap that epilepsy, as a natural laboratory, can assist in addressing.

In this way the value of this thesis is two-fold. Primarily, the impetus for the current study was provided by the lack of research exploring working memory function in children with focal epilepsy. Much of what is known about memory in focal epilepsy is borne out of adult research. To apply adult models and theory to children is an oversight of the ongoing development and maturation that is quintessentially childhood, and is the forerunning explanation for incongruity between adult and child studies of epilepsy. Developmental studies of memory indicate that children are still acquiring and strengthening their memory skills, including working memory well into adolescence (Gathercole, 1998; Gathercole & Hitch, 1993; Gathercole, Pickering, Ambridge, & Wearing, 2004). Memory impairment in childhood is reported to have profound effects on later academic and social functioning (Fastenau et al., 2004; Gathercole, Lamont, & Alloway, 2006). Thus given that only a small percentage of children with complex partial seizures pursue higher education (not accounted for by low IQ alone) (O'Leary, Burns, & Borden, 2006; Shulman, 2000) it was deemed imperative that an additional goal of the current research is to explore the way poor memory disadvantages children with epilepsy, as it is unclear whether impairments in either frontal or temporal regions differentially affect the severity of academic underachievement.

Second, achieving a better understanding of memory impairments in focal epilepsies is not only beneficial in developing appropriate assessment and treatment strategies, but also in informing the neurocognitive literature on the possible effects that focal abnormalities in key memory centres may pose for the memory system as a whole, in the context of the developing brain. This is a classic approach of neuropsychological studies that utilise studies of abnormal function to infer normal function (Norman, 1968). However there are confounding variables inherent within the condition of epilepsy itself that limit its generalizability to normal function. Unlike neurological conditions such as stroke, traumatic brain injury, or brain tumours, epilepsy does not involve a transient or static event, but rather involves persistent and reoccurring seizure. The frequency, severity and duration of seizures will also vary between individuals (Desai, 2008), and need to be considered when inferring *normal* function.

The primary aim of this study therefore, is to explore and define the nature of memory impairments in children with frontal and temporal lobe epilepsy, with consideration given to all aspects of memory, from the initial registration, working memory and to the long-term recall of verbal and visual information. For this reason, this thesis has paid careful attention to the cognitive models of memory, and offers an overall framework of memory function, integrated from various research streams, including the neurocognitive and neuroimaging research paradigms. A review of the relevant literature is presented in Chapter 2 and 3. The model of memory summarised and put forth in these chapters was then used as the context to understand and interpret the previous neuropsychological studies exploring the memory impairments in children with epilepsy in Chapter 4. Finally the review of the literature concludes with an appraisal of the impact of epilepsy on academic achievement in children in Chapter 5.

CHAPTER 2: THE COGNITIVE SCIENCE OF MEMORY: THE LONG AND THE SHORT OF IT

Memory remains a complex phenomenon that is so often taken for granted in our everyday interactions. Lezak, Howieson and Loring (2004) define memory as the act of "information storage and retrieval" (p.20). Memory can also be conceptualised as a "group of mechanisms or processes by which experience shapes us, changing our brains and our behaviour" (Banich, 2004, p 324). From a cognitive perspective, memory can be described as the end-point of cognitive processing. Eliciting memory reveals the point at which the goal of attentional, executive, language, and visual processing functions are realised, integrated and displayed (Mapou & Spector, 1995). By direct implication, that statement infers that the mechanisms associated with efficient memory processing requires the integrity of many cognitive skills, neuroanatomical substrates and reciprocal connections between them.

The most profound published example of this contention is that offered by Mapou and Spector (1995). The authors offer a hierarchical framework of cognitive processing, in which learning and memory are considered *integrated skills* that require the "interaction, integration, and coordinated functioning of skills beneath it" (p.300) including modality specific (visuo-spatial and language skills), foundation (attention, executive function) skills, and global functioning (academic achievement and intelligence).

There are advantages to conceptualising memory in this way. The first is that it offers a way of understanding that impaired performance on a memory task may not represent a pure memory deficit and rather represent the consequences of impairment in a system beneath it within the hierarchy. Giving consideration to primary versus secondary memory impairments, allows for targeted treatment of memory complaints.

It is unclear however how this model generalised to children, as the framework presented is based on work with adults, where arguably each of the foundation and higher skills are fully mature and developed. In this way, memory certainly reflects the end point of cognitive processing though for the developing child where skills are still emerging (Dennis, 1989), memory also plays a role in the beginning and centre of almost all cognitive processing. For example, the model considers academic achievement to be a foundation skill on which memory efficiency will be dependent, as the grown adult arguably has established this knowledge (Mapou & Spector, 1995). During childhood however, the relationship between academic achievement and memory functioning is likely to be reversed and interdependent, whereby on-going academic achievement will rest on the child‟s memory capacity and learning efficiency, in addition to being supported by existing knowledge (Hood & Rankin, 2005). Children must continuously attempt to integrate experience and education throughout everyday living to strengthen, learn, and develop new skills. Thus in childhood, memory should be considered a foundation skill that is critical to adaptation and learning of new experiences (Banich, 2004). Unfortunately, unlike adult models of cognitive function, there exists scant literature purporting models of cognition in children or little attempt to consider the development of cognitive systems. The following chapter will initially focus on the cognitive underpinning of learning and remembering, with a focus on the mechanisms pertinent to children.

The second issue is not a limitation that is restricted to Mapou & Spector's (1995) cognitive framework, though could be considered a limitation of memory research overall. The issue is one associated with defining and operationalizing memory, and the lack of holistically considering the complexities as outlined by the cognitive literature, or the link between theory and practice application (Saling, 2009). Memory as a system represents the operations of many subsystems. It is thus more than an end-point measure of an ability to recall information presented. However, memory research using clinical samples and the conclusions therein, are largely governed by employment of one or two measures of memory and often within only one sensory modality from which generalizations about the entire system are made (Jocic-Jakubi & Jovic, 2006). There exists a general failure to consider the context of memory *processing*, as 'memory' is only a rubric for a variety of processes and must be considered as such.

It is at this junction, that the cognitive and neurosciences literature are not well married. For example, studies of memory often include measures of verbal memory, without due consideration that even different tasks of verbal memory are subsumed by different regions within the temporal cortices (Saling, 2009). The neurosciences literature which includes case studies of acquired neurological insult resulting from trauma, disease or surgery, and studies of functional imaging have served the understanding of memory and coined the term amnesia, though are all based on cases of ‟abnormal‟ memory (A Baddeley & Warrington, 1970; Bertolucci et al., 2004; Shimamura, 1992; Zola-Morgan & Squire, 1993; Zola-Morgan, Squire, & Mishkin, 1982).

Amnesia is a disorder of memory that has informed our understanding of normal memory function by way of inferring from a loss of function associated with various aetiologies how the human brain processes memory. Amnesia is associated with impaired ability to acquire new memories and thus impaired new learning (anterograde amnesia), or a loss of past memories (retrograde memory) (Zillmer, et al., 2008). It is neurological disorder that leaves other cognitive skills relatively intact (Shimamura, 1992), and although portrayed as a glamorous and mystifying condition in the popular media it is certainly rare that any similar opportunity can be observed in reality. However, our knowledge of memory processing rests almost entirely on such cases (of course without spontaneous regeneration of memory function), and none more influential than H.M (Scoville & Milner, 1957).

Cases like H.M highlight the profound clinical utility of memory research, though in order to maximise its potential, research paradigms using abnormal function to infer normality (i.e. clinical research) need to pay greater heed to the purported cognitive frameworks and models (Norman, 1968). This task is greater than can be achieved through employment of a single memory test, as a single test score cannot efficiently answer how the act and system of memory is impaired.

Thus the following chapter will also function to highlight that the act of remembering involves numerous processes and in order to draw conclusions research must operate within a clearly operationalized framework of functioning.

The following sections will review the cognitive and neurosciences literature in order to provide a systematic and integrated account of how memory is processed within a cognitive framework and then where different functions are localised within the brain. This is an important and necessary first step in discussing how memory is impaired in children with epilepsy, and a perspective that has not been given due consideration within the literature.

2.1 Memory: Process, System, or Interaction between the two.

The question of how memory functions requires a careful delineation between two distinct bodies of work, namely process-driven and systems-driven theories of memory function (Sternberg, 2009). The first is founded on the processes of encoding, storage and retrieval that are inherent in most memory systems or models. Memory as described by Tulving (2002), involves a person experiencing an event, a memory trace being formed representing the event, the procession of time, and the person retrieving that event in the present for whatever purpose it is required. This description can also be considered a summation of the process-driven theories of adult memory function.

Encoding involves registering information, and hence is considered the first stage of mnemonic processing. It may be affected by poor ability to attend to and register new information, fatigue, and also by divided attention. Once information has been encoded, it must be stored or consolidated into long-term memory (LTM), so that it may be retrieved when required. Retrieval of information may involve recognition, or recognising the encoded information from other unseen stimuli. In contrast free recall of information refers to bringing to mind information without any recognition cues (Buckner & Wheeler, 2001; Budson & Price, 2005; Gabrieli, 1998; Squire, et al., 2004). In all cases, evidence of LTM may be evident in the demonstration that information has been learnt from prior experience (Baddeley, 2002). In this way, memory processing is the stage at which our attention, speed of processing, emotions, and senses integrate to exist within a given moment. Thus according to these models, which also reflect hierarchical structures in their account of memory processing, to bring forth memory is to demonstrate the end-point of cognitive processing.

The alternative attempts to describe memory functioning have synthesised the processes inherent within them, and considered how the overall process of encoding storage and retrieval may operate as a system. According to Sherry and Schacter (1987) any theoretical account of a memory-system should characterise the type of information processed and the rules that guide the execution of that process, and are arguably more comprehensive and useful for neuropsychological research. Tulving (2002) extends this by indicating that the execution or operation of the memory system is associated with a neural network, with observable behavioural and cognitive outcomes. Each of the memory systems outlined in the following section entail encoding and retrieval processes, and in addition offer a heuristic method of exploring differences in memory functioning in different populations. For this reason, this literature review will focus on the research and current understanding of memory systems, as they will be presented in the following section.

2.1.1 Memory systems

In 1918, James (cited in Andrade, 2001) presented a dichotomous memory system comprising primary and secondary memory. Primary memory involves the experience and constant awareness of something that has just occurred, which is contrasted with secondary memory, which involves knowledge of a past occurrence. This binary memory system was supported by (Hebb, 1949) who suggested that the difference in the two systems was due to variations in permanency of neural firing and networks.

Since James‟ (cited in Andrade, 2001) early work of a dichotomous memory system, a modular and multiple component structure of memory processing has persisted. Though contrary to James, subsequent models of memory processes suggested that the immediacy of an event should not be considered the determining factor of memory system fractionation (Atkinson & Shiffrin, 1968; Waugh & Norman, 1965). Rather, the *amount* of information simultaneously presented governed whether an item would be sustained in the longer term. This helped to explain why not all things that are seen or heard are remembered. Along the lines of James‟ proposition alternative models posited that „short-term memory‟, was a limited capacity storage system that was the precursor for storage into longer-term permanent memory. Such models provided a more parsimonious account of the way in which information proceeds from a brief memory store into a more permanent store (Andrade, 2001). Arguably, the model of memory proposed by Atkinson and Shiffrin (1968) was the most accepted of these models. The model comprised a successive system of stores, based on varying capacities, and the process of remembering transient stimuli at a later time was considered a serial process, whereby information from our environment enters a brief sensory register, to a temporary short-term store, to finally become reposited in a long-term store (Figure 1). The model initially labelled each component as a store, and distinguished this from the items of information held within them as ˮmemory‟. However modern psychology research often uses the term ˮstore‟ and ˮmemory‟ interchangeably (e.g. short term store, short term memory). The model is presented in Figure 1.

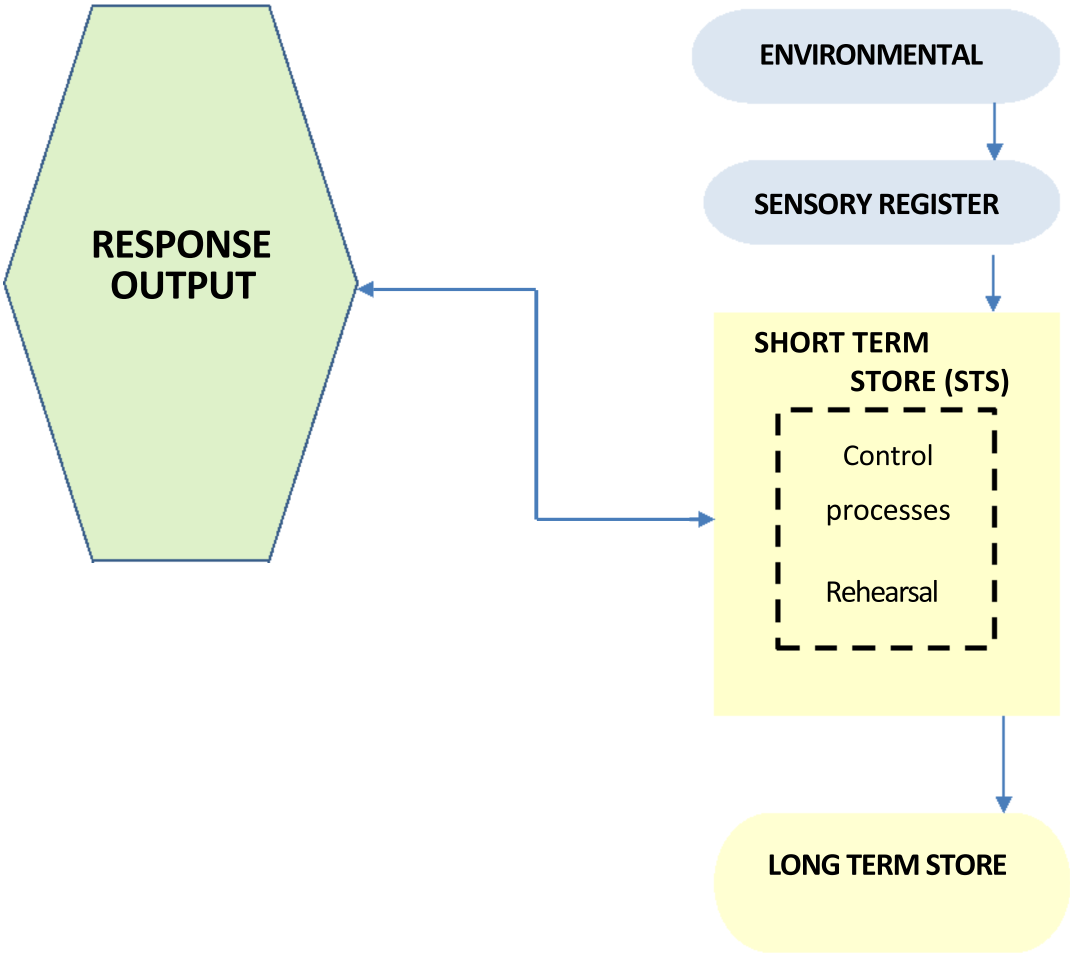

Figure 2.1. The model of memory as proposed by Atkinson and Shiffrin (1968)

The sensory register is considered a ‶temporary holding space‟, or initial processing pad for all stimuli that are registered by our senses, i.e. what is seen or heard. Information that is deemed necessary or important is then transferred to a short-term store, which is still quite limited to a period of up to 30 seconds. However, through a complex set of control processes information in the short-term store can be ‶refreshed‟ and thus maintained in the short-term store for as long as necessary, as long as the information is being consciously and continuously maintained. Thus, the short-term store functions as an interface between environmental stimuli and cognitive processing. The capacity of this immediate short-term store is generally between five and nine units (Miller, 1956) and can comprise either simple items such as a digit or more complex words. Seven, plus or minus two, appears to be a limited capacity given the complexity of information that human beings process at any given time. However, through the process of ‟chunking‟ a greater amount of information may be held in the short-term store (Rankin & Hood, 2005). The concept of capacity and the mechanisms associated with its extension have been used extensively to test memory systems and processes, and provide the foundation for many measures of memory and learning (Just & Carpenter, 1992; LaPointe & Engle, 1990; Turner & Engle, 1989; Waters & Caplan, 1996).

Finally the model posits that through processes of rehearsal, information may be transferred into a longer-term store that is limitless and arguably permanent. The authors indicate that transference of information is not meant to denote a deletion of the information within the short-term store but rather a *copying* of information to a more permanent store (Atkinson & Shiffrin, 1968).

Although this model of memory was congruent with the research of the time, it failed to adequately explain the intermediate step between the *process* and *system* through which memories are transposed into longer-term storage. The model proposed that simply holding information in short-term store for longer periods would increase the likelihood of conversion into the long-term store. Evidence for this was provided by models of ‟incidental learning‟ whereby individuals are able to learn and recall something seen or heard at a later time, without exerting effort to do so in the first instance (Atkinson & Shiffrin, 1968). However, such theoretical arguments of a downward cascade mechanism of information processing could not accommodate the case-findings that individuals with STM difficulties still possessed intact LTM (Shallice & Warrington, 1970), or patients with intact STM demonstrated poor LTM (Milner, Squire, & Kandel, 1998). These latter findings suggested a view that STM and LTM were not-interdependent but rather dissociable systems, with likely different neuroanatomical underpinnings (Gabrieli, 1998; Squire, Knowlton, & Musen, 1993; Squire, et al., 2004).

The controversy generated by these studies was better explained by subsequent studies that explored the nature of the material to be processed. For example, over several studies, Baddeley and associates (A. Baddeley, Papagno, & Vallar, 1988; Gathercole & Baddeley, 1990) have demonstrated that it is unlikely that these memory systems act in parallel, but rather consist of serial storage capacities that act in concert when processing new or consolidated memories, which further progressed the Atkinson and Shiffrin (1968) model to more of a theory of memory. Their conclusions were based on studies that explored more specifically the nature of the transfer of information. Inefficient STM processing within a particular modality (e.g. auditory-verbal information) will lead to a corresponding deficit in LTM to the extent that long-term learning is dependent on the initial processing of that specific information. That said, poor STM processing of phonological material is unlikely to impact the long-term learning of visuo-spatial material (A. Baddeley, et al., 1988; Squire, et al., 1993), and vice versa. Thus they concluded that the serial organization of STM and LTM is domain specific.

In summary, early memory research provided a framework to conceptualise the way memory is likely to be stored, which in turn provided a useful heuristic for subsequent research. Even though the validity of the specifics of this framework have been subjected to question, fundamentally the demarcation of Sensory, Short and Long Term stores holds value and remains the nomenclature of choice within the field of memory (Squire, et al., 1993).

Importantly this memory systems body of work highlights that although the storage of information involves short to long-term transference, this is not the only means of transfer, and the two systems may work independently, albeit with reduced efficiency (Jonides et al., 2008). The second important conclusion is that the systems are likely to be domain specific and also may operate on different development timetables. This poses important implications for research with children, as methods of teaching, targeting learning interventions, and assessing memory and learning difficulties must consider domain specificity (Rankin & Hood, 2005). The next phase of memory research was led by an emphasis on the processes subsumed by memory systems, and is guided mainly by these two principles: information transfer and domain specificity.

2.1.2 A system that works: working memory

If memory is the culmination of cognitive processing, then *working memory* could be considered the post-office. Working memory as a theoretical construct has been used in the literature for many years; however the operationalization of the term has differed depending on the experimental paradigm in which it tested. For example, animal studies, in which a rat has to work its way through a maze and its working memory is defined as how efficiently it can search for food (Mizumori, Channon, Rosensweig, & Bennett, 1987; Shah & Miyake, 1999). Within the cognitive sciences, working memory has been used synonymously with short-term memory, or more specifically the control processes that act upon it in the transfer of information between memory stores. Shah and Miyake (1999) also highlight the many different metaphors used to denote working memory, such as the “blackboard”, “workspace”, “juggling”, “box” or “mental energy” analogies (p. 2). Whatever the precise definition, the commonality of the term without controversy is used to describe “a limited capacity system allowing the temporary storage and manipulation of information” (A. Baddeley, 2000a, p. 418) necessary for the completion of more complex tasks. In doing so this system constitutes a platform for further cognitive processing, and functions as an interface between perception, LTM, and outcome (A. Baddeley, 2003; Miyake & Shah, 1999). At a definitional level, WM is implicated in the execution of complex tasks. However what is meant by complex? Again, the answer to this is confounded by differing opinions on the definition, as the definition is a product of the experimental paradigm (i.e. completion of algebraic terms, word span, sentence comprehension tasks). Nonetheless, it can be argued that any task requiring the individual to hold and manipulate information would fit within and constitute WM regardless of the specificities of “complex”.

In their book, “Models of Working Memory: Mechanisms of Maintenance and Executive Control” Miyake and Shah (1999) provide a systematic comparison

of existing models and theories of working memory. Their method was to approach tenants of various WM models and have them address a series of eight different theoretical questions, in order to provide a forum for comparison. Contributors to the volume included Baddeley's Multi-Component Model, Cowan's Embedded-Processes Model, and Engle, Kane and Tuholski's Controlled Attention Framework to name a few. In total, ten different theorists contributed, and the outcome, to the editor's own admission, was surprisingly uniform with few exceptions.

Regardless of the model of WM that is subscribed to, the commonalities among the different theories were that working memory is ultimately associated with the control and regulation of incoming information, and that this is achieved through an overarching mechanism. The limitation of many theories is that such an overarching controller results in a poorly defined homonculus. All theories contend with the notion that working memory is a system, and not a unitary concept. However there is a lack of consensus with respect to the number of modality specific sub-processing units that comprise the overall system. The way in which incoming information is processed differs among the models therefore, and also has bearing on the proposed reason for the limitations of the overall system. For example, Baddeley and Logie (1999b) attribute overall decay of information whereas Cowan (1999), Keiras, Meyer, Mueller and Seymour (1999), and Barnard (1999) attribute it to an inefficiency of attentional allocation, speed of processing and executive processes.

The overall structure of working memory highlights that it is not an entity, much like its counterpart LTM. It is a system, a collection of processes and sub-processes that activate according to the demands of the task at hand. For this reason, teasing out the consequences of a specific impairment in WM is much more difficult, and furthermore relating this back to the functional implications of "cognition at wild" is even more difficult. That said we know that WM is consistently implicated in long-term learning, reading, arithmetic, and reasoning skills (Gathercole & Alloway, 2004; Gathercole, Pickering, Knight, & Stegmann, 2004; Gathercole, Tiffany, Briscoe, Thorn, & team, 2004). Therefore the best, if not only approach to assess this construct is to use a battery of tests that have been known to test the conceptual system of WM empirically, and then relate this back to how LTM may be implicated.

Of all the above mentioned theories of WM to date, the most comprehensive theoretical account of a WM system is that originally proposed by Baddeley and Hitch (1974), and later modified by Baddeley (1986, 2000a, 2006). Of all the prominent WM models, the multi-component working memory model (MCWM) has received the most theoretical and experimental consideration and support, across a wide range of populations, including children, adults, and neuropsychological patient groups (Miyake & Shah, 1999). The present study adopts this influential model as the framework for discussing working memory operations, and will be investigated further in the following sections.

2.1.3. The multi-component working memory model

Baddeley (2003) views working memory as a multicomponential construct of cognition encompassing both storage and processing capacities. The most recent revision of the model (Baddeley, 2000) utilizes a quadripartite structure to convey separate yet interrelated components of memory processing, as illustrated in Figure 4.

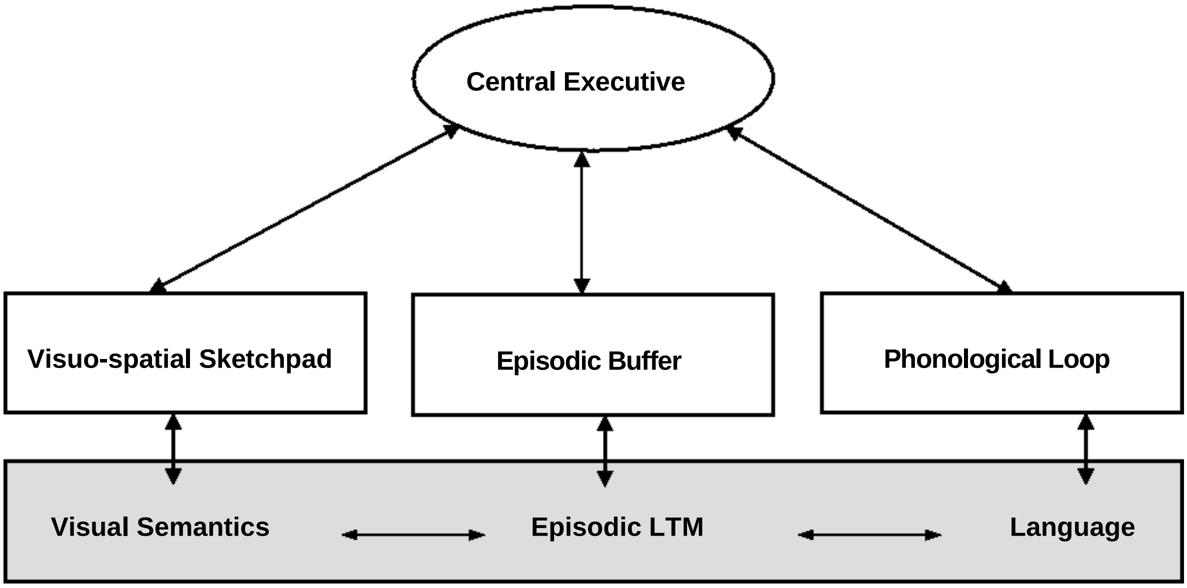

Figure 2.2. The Multi-component Working Memory Model (adapted from Baddeley, 2000).

In outline, the central executive is regarded as the overarching controller of the entire working memory system. It is the component responsible for all aspects related to the short-term processing of information. Its responsibilities may include planning, selecting and inhibiting different strategies of memory processing, interacting with LTM stores, or mediating the flow of information through the two slave-systems: the phonological loop and visuo-spatial sketchpad. The phonological loop is responsible for the storage and rehearsal of verbal information. In contrast the visuo-spatial sketchpad is responsible for the storage, generation and manipulation of mental images or visuo-spatial information

(Andrade, 2001; Baddeley, 2000, Baddeley & Hitch, 1974; Gathercole, 1994). Each of the working memory components discussed can be localized to different regions within the cortex, further supporting the notion that they are dissociable skills. These slave systems in essence refer to the verbal and non-verbal short term stores referred to previously. Consistent with theories of lateralization of memory function and domain specificity, verbal material processed by the phonological loop is subserved within the left hemisphere, whereas non-verbal material processed by the visuo-spatial sketchpad is associated with right hemisphere function (Henson, 2001).

More recently a fourth component, the episodic buffer was added to the existing model, to account for the lack of specificity assigned to the central executive (A. Baddeley, 2000a). The episodic buffer is considered to be the temporary storage centre that is capable of binding information from the two slave-systems, and from LTM. Before the inclusion of the buffer, the central executive was responsible for any function not associated with the slave systems. This resulted in a poorly defined homunculus, which was too flexible and all-encompassing to be tested empirically. The inclusion of the episodic buffer, thus meant a better account of how information is integrated between the two slave systems, and how information may be retrieved through conscious awareness. This model emphasizes processing and storage in combination and in doing so is able to consistently demonstrate the functional significance of WM for a wider range of cognitive functions. (Baddeley, 2000).

2.1.3.1 The phonological loop

The phonological loop is capable of maintaining information of either auditory or non-auditory (such as printed words or visually presented nameable objects) verbal information for a couple of seconds, which may be extended through rehearsal processes. Vocal rehearsal is not a critical aspect of effective rehearsal; rather verbalizations are maintained at a higher-order level via sub-vocal rehearsal processes (Gathercole, 1994b). However as depicted in Figure 5, the processing and maintenance of auditory and non-auditory information operates through two different pathways, the phonological store and an articulatory rehearsal process.

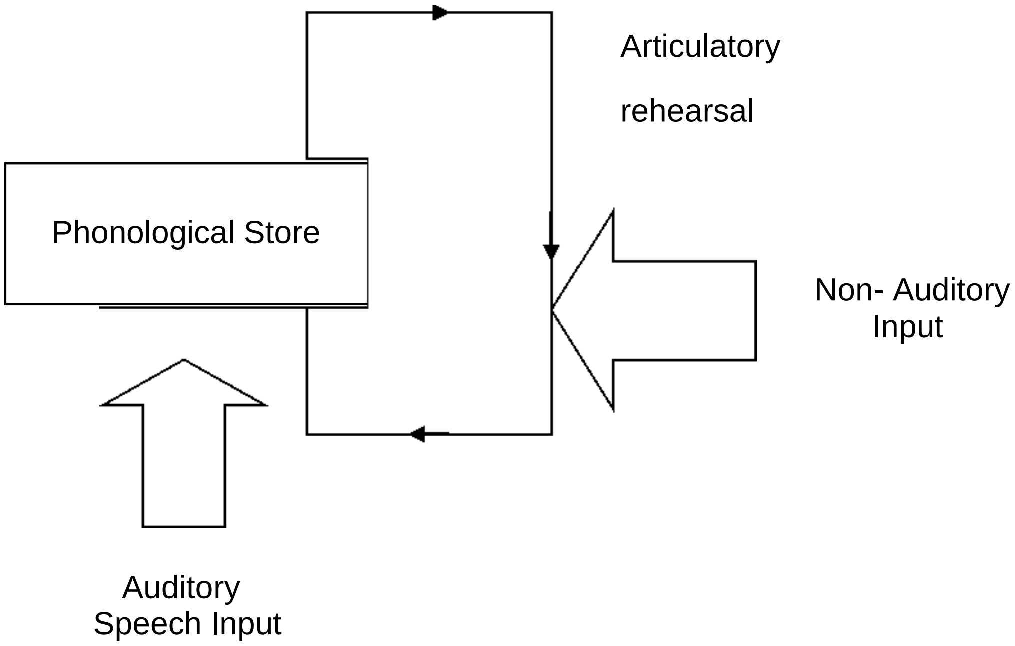

Figure 2.3. Schematic representation of phonological loop function (adapted from Gathercole, 1994).

Auditory verbal information may be stored immediately and automatically in the phonological store, whereas non-auditory input must first be rehearsed and recoded into a phonological form via sub-vocal processes (Baddeley, 1986; Gathercole, 1994). Articulatory rehearsal occurs in real time, and therefore the capacity of the system is limited by how much information may be articulated in real time. Once entered into the phonological store all information, whether auditory or non-auditory are manipulated and held in the same manner. Generally the capacity of the phonological store for simple serial recall of items is between five and eight items, though will vary significantly according to different conditions (Gathercole, 1994).

Several distinct research paradigms account for capacity variance under different conditions, and also support this framework of phonological loop function. For example it has been reported that multi-syllable words, or words high in articular duration, take longer to rehearse and therefore reduce the capacity of words that may enter the phonological store and be recalled (the word length effect) (A. Baddeley, Grant, Wight, & Thomson, 1975). Also when rehearsal is prevented by simultaneously speaking irrelevant sounds (or words) aloud, phonological loop function declines significantly, termed the articulatory suppression effect. Finally, when items to be remembered sound similar, they become increasingly more difficult to recall (A. Baddeley, 1966, 2000b; Conrad & Hull, 1964). Semantic similarity does not produce comparable effects, and therefore support the notion of an acoustic coding and storage system in phonological short-term processing (A. Baddeley, 1966). These effects have important implications for the developing child, and will be discussed further in Chapter 5.

2.1.3.2. The visuo-spatial sketchpad

The external environment is filled with images varying by shape, size colour and form. Human beings rely heavily on visual processing to interact with their surroundings, and must be able to accommodate to the constant yet changing visual stimuli of the external environment. The visuo-spatial short-term memory system is therefore responsible for processing the most salient features of the continuing memory record the visual world presents, in order to respond to and facilitate action.

Contrary to the phonological loop, the visuo-spatial sketchpad developed out of a common sense conclusion that necessitated its existence (based on the construct of the phonological loop) rather than due to vast empirical evidential demands. More recent evidence argues for the analogous symmetries of these slave-systems. Thus the visuo-spatial sketchpad is associated with establishing and manipulating visuo-spatial images (what and where) and is limited in its capacity holding between three and four objects (Baddeley, 2003).

Consistent with its name, the visuo-spatial sketchpad processes information regarding the location (spatial) and appearance (visual) of stimuli. The fractionation of visuo-spatial processing into visual (object) and spatial (location) memory components is supported by neuroanatomical findings (Henson, 2001). Accordingly Baddeley and Logie (1999a) have fractionated the sketchpad further, and current conceptualisations are depicted in Figure 4.

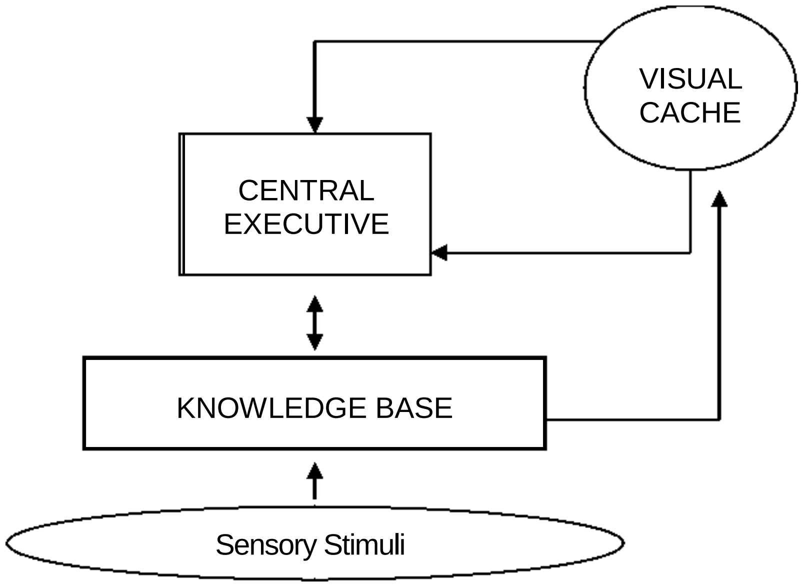

Figure 2.4. Schematic representation of the visuo-spatial sketchpad (adapted from Baddeley & Logie, 1999).

The visual cache processes information in a visual form, concentrating on form, colour and size. It is closely associated with systems involved in perception, and is mediated by both top-down cognitive processes and bottom-up perceptual experience (A. Baddeley, 2003; Repovs & Baddeley, 2006). The inner scribe is responsible for processing movement sequences or the location of objects, and updating information held within the visual cache. In this way, the inner scribe is associated with attention and action (A Baddeley & Logie, 1999a).

Interacting with the environment involves processing not only one‟s own movements and location, but also spatial changes within the environment. Therefore the inner scribe is vulnerable to interference, and is significantly impaired by poor attention. For this reason this system is vulnerable to the effects of complexity, similarity and both passive and active interference that are akin to

the word-length effect, suppression and similarity evident in phonological loop processing (Gathercole, 1998).

2.1.3.3 Central executive and episodic buffer

The central executive is described as the "most complex and powerful component of the working memory model" (Gathercole, 1994a, p. 69). Initially the central executive was seen as a "ragbag" (A. Baddeley, 1986; Alan Baddeley, 1996). It existed as nothing more than a labelled component to which all the functions of strategy selection, planning and retrieval checking were subsumed. Even more broadly, any process investigated that existed outside the processes of the two slave systems, and yet still conceptualised as a working memory process, was attributed to the responsibilities of the central executive.

More recent research argues that the main responsibility of the executive is prioritising between relevant and irrelevant stimuli in order to attend to the demands of the immediate environment. The central executive therefore is a goal-directed active mechanism that maintains the salient visual and verbal information "on-line". This active maintenance is only required, when a conflict-resolution between extraneous distracters and pertinent information exists (Repovs & Baddeley, 2006).

The mechanisms of conflict-resolution and focusing attention on pertinent stimuli was offered by the model of the Supervisory Attentional System (SAS) developed by Norman and Shallice (2000). Many activities involve the employment of schemata. Schemata are best considered automatic behavioural response sequences that are learnt and employed to perform a variety of tasks. For example brushing one‟s teeth, or driving a car, are automatic sequences of behaviour that are not consciously undertaken by the participant. However, certain tasks may require the employment of several schemata simultaneously, which may act in conflict, which requires a higher level of processing to execute. According to Norman and Shallice (2000) the SAS acts in addition to automatic conflict resolution processes that are responsible for selecting and prioritising specific schemata in consideration of various environmental cues or task demands. The SAS biases the activation of more appropriate behavioural sequences, resolving the conflict, and hence efficiently performing the task at hand. Thus, adopting the SAS enforced and provided a framework for the role of the central executive as an attentional processor, specifically involved in focusing and switching attention (A. Baddeley, 2006).

Secondary to conflict-resolution and maintenance, the central executive is also responsible for delegating resources required for manipulation of stored material within the slave-systems or the episodic buffer. Thus the executive is supported by the other components, and is responsible for selecting and implementing strategies that aid long-term memory processing (Alan Baddeley, 1996; A. Baddeley, 2000a, 2000b, 2006; A Baddeley & Logie, 1999a).

The episodic buffer was offered as the mechanism through which this strategy utilization is achieved. This system is episodic in that it provides the storage component of information manipulated and integrated from the slave-systems and from existing memory traces in long-term memory. However it is a buffer in that it is a workspace in which the information may be manipulated and integrated from different modalities (A. Baddeley, 2006). The proposed mechanism of the episodic buffer accounts for the way working memory is a conscious process that is heavily associated with long-term memory functioning. Responding to task demands requires the combination of manipulating existing schema, and novel task stimuli. Through conscious awareness the episodic buffer acts as an interface between short and long term memory processing. This interface is considered to be a modelling space for the planning of future action, and is the storage component of the central executive (A. Baddeley, 2000a) though there is relatively less research exploring this construct.

2.1.4 Long term memory (LTM)

Similar to advances in STM research, the study of LTM has also benefited from further fractionation into separate components. Squire (1992, cited in A. Baddeley, 2002) presents the following model of fractionation of long-term memory.

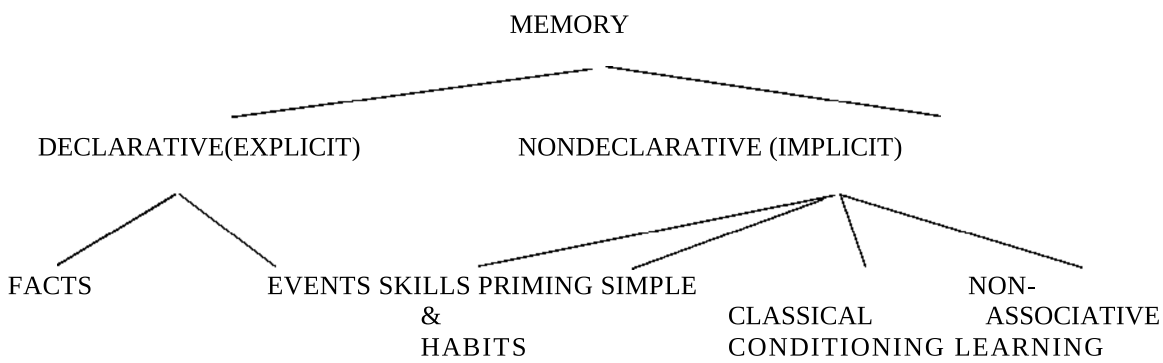

Figure 2.5. The fractionation of long-term memory (A Baddeley, 2001)

Declarative memory is associated with the capacity to remember facts or events, and non-declarative memory supports the capacity to express through performance, the acquisition of various abilities including skills and habits, priming etc (Squire, et al., 2004). Theoretically, the declarative and non-declarative categories of LTM, are best thought of as “knowing what” versus “knowing how” respectively. They do not necessarily refer to specific memory stores, but rather denote the different types of long-term memory that are processed. By nature, although implicit and explicit memory may occur together, any biases elicited by previous exposure (revealed by implicit measures) is not dependent upon explicitly remembering or declaring the previous exposure. This forms the basis for many tasks assessing skill learning or “knowing how” to do something (Banich, 2004). In contrast, explicit or direct measures of memory, call on an individual to explicitly recall what they have remembered (“knowing what”), and are tested with explicit measures (Gabrieli, 1998).

Many basic classroom skills are assessed through explicit measures of memory, as these skills rely heavily on the child's ability to recall and express the contents of the curriculum (Hood & Rankin, 2005). Hood and Rankin (2005) highlight that the dissociation of explicit and implicit memory is evident when considering the transition from beginner to proficient reader. When initially learning to read, the child is exposed to symbols and taught the grapheme-phoneme relationships that are associated with that letter-symbol. Therefore declarative memory provides a platform in which the elements of reading and language may be flexibly integrated. Over sufficient attempts and trials the child's ability to read is likely to become less effortful and more habitual, progressing into an acquired non-declarative or implicit skill. It is only when confronted with new or unfamiliar words that the child may need to revert to more effortful processing of stimuli. Therefore explicit memory functioning may be more easily measured and/or modified by intervention, as the processes or outcomes of declarative memory utilization are readily observable and flexible.

2.1.4.1 Declarative Memory – "What" do we know?

Declarative memory involves the acquisition, retention and retrieval of knowledge that is recollected through conscious awareness, and with intent. Tulving (2002) has proposed that this "knowing what" aspect of memory can be further divided into episodic memory, and semantic memory. Episodic memory is not a particular memory task or test, but rather refers to a hypothetical memory system. It encompasses those conscious memories of events, and facts that are personally experienced. As such episodic memories have a component of "what" "where" and "when" something is remembered or experienced, and thus have a "time-tag". Episodic memory is distinct from semantic memory in that the latter refers to factual knowledge, or knowledge of concepts. Both of these aspects of memory are critical for the formation of new knowledge (Banich, 2004; Scoville & Milner, 1957), and are dependent on the integrity of various brain structures within and related to the medial temporal lobe (MTL, Figure 3) as discussed in the following sections.

Adult studies indicate that although the acquisition of semantic knowledge may be achieved, poor episodic memory still significantly hampers the efficiency of learning (Skotko, et al., 2004). This highlights the critical interconnectivity between different memory processes, as it is likely that episodic memory assists semantic learning by enabling a contextual and temporal cue for the information to be learned. This is particularly important for children, where there may be significant and cumulative implications for disruption of the memory system.

CHAPTER 3: THE NEUROANATOMY OF MEMORY FUNCTION

The preceding chapter illustrated a rich and diverse literature charged with many models, flow-charts and other heuristics that have been used to depict the flow of information transfer through a memory system according to various rules of operation. The foundation of this research is based on an array of classic cognitive paradigms that are empirically robust and amenable to repetition. However, the intricacies of rule governance within each of these systems are not often easily replicable when transposing the hypothesised function to a neural substrate of human behaviour and brain function.

Traditionally our knowledge of how memory functions was borne out of case study research involving lesions or damage to various cortical regions, and the direction of the neuroscience literature have largely been governed by how a loss of function can inform normal function (Bertolucci, et al., 2004; Neylan, 2000; Scoville & Milner, 1957; Shimamura, 1992; Vanasse, Beland, Jambaque, Lavoie, & Lassonde, 2003). As discussed in earlier sections of this review, this biased investigations of how systems may operate throughout a network. This is notwithstanding the significant contribution that such studies made to our understanding, and in turn understanding them serves as a building block to understanding the system as a whole. As will be evident in the following chapter, it is with the advent of neuroimaging that the gap between the cognitive and neurosciences literature is bridged. This chapter will first review our understanding of key memory centres in the brain, before considering how the two may be interconnected.

3.1 The Role of the Frontal Lobes in Memory

The frontal lobes comprise one-third of the cerebral hemispheres and are the last to develop and reach full maturity relative to the temporal, parietal and occipital cortices (Darby & Walsh, 2004). The frontal lobes are considered to encompass four separate functional divisions including the, motor area which lies anterior to the central sulcus, the premotor area that lies anterior to the motor area, the prefrontal area and the basomedial region which together comprise the prefrontal portion of the frontal lobes. These regions are outlined in Figure 3.1

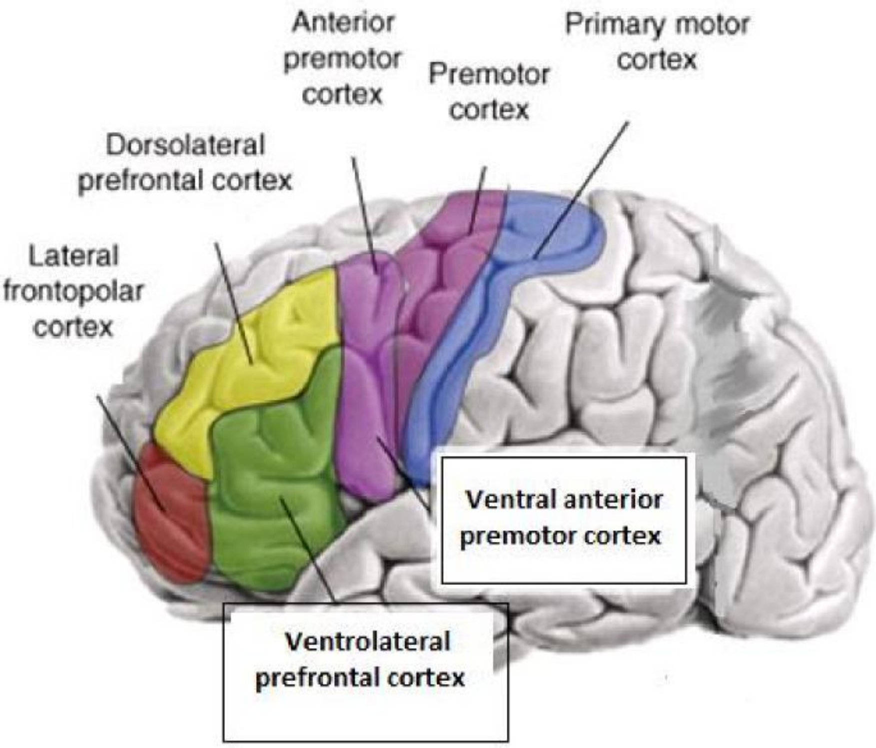

Fig 3.1 Frontal lobe divisions in the human brain (adapted from, Badre, 2008)

The frontal lobes are densely connected with other brain regions through several sub-cortical neural pathways. The vast literature investigating frontal lobe function can be summarised unequivocally to encompass executive functioning, and aspects of personality and behaviour (Zillmer, et al., 2008). In addition to these known effects however is a strong argument that focal insults to the frontal lobe may result in additional symptoms that may mimic the stereotypic impairment seen in other brain regions, such as memory impairments that have been typically reserved for characterisation of temporal lobe impairment, due to the rich connections between the frontal lobes and other brain regions (Simons & Spiers, 2003; Stuss & Levine, 2002).

That said frontal lobe damage is not a cause of amnesia per se (Gershberg & Shimamura, 1995). The nature of the impairment that frontal lobe lesions exert on the system of memory have been purported by Stuss and Levine (2002) to constitute a breakdown of strategic processes as opposed to the associative processes subsumed by the temporal cortices. Coupling the cognitive and neurological literature therefore, it is evident that the nature of the strategic processes presented by Stuss and Levine coincide with the responsibilities of the central executive. Failure of the central executive is evident in person‟s who present with rigid thought processes, and who lack the ability to plan and implement necessary strategies to respond appropriately to novel situations. Because of the close theoretical associations between executive functioning and the responsibilities of the central executive, deficits in this system mimic those seen in patients with frontal lobe pathology, within the specific construct of memory. In this way the construct of working memory is partly subsumed as an executive function skill, and therefore patients with deficient working memory may also experience wider executive function deficits due to the shared neuroanatomical localisation of these skills (Lehto, 1996; Miyake, Friedman, Rettinger, Shah, & Hegarty, 2001; Pennington, Benetto, McAleer, & Roberts, 1998).

Planning, monitoring, semantic clustering, and utilizing feedback are many skills that are affected by damage to the frontal lobes (J. H. Kramer et al., 2005). However when the frontal regions localized to the central executive are specifically affected, the result may be a more diffuse effect on memory processes that are associated with regions outside of the frontal lobe system, including the medial temporal lobes.

The entire prefrontal area is critical to many mnemonic processes and is further demarcated into the ventrolateral (VLPFC), anterior (APFC) and dorsolateral prefrontal cortex (DLPFC) (Simons & Spiers, 2003). Specifically with respect to working memory, the central executive is purported as localized to bilateral dorsolateral prefrontal cortex regions (Fletcher & Henson, 2001; Henson, 2001; Muller & Knight, 2006). These skills are not the only function of that region. In addition, Henson (2001) highlights that completing working memory tasks, even within only a verbal domain for example, is likely to show activation in numerous regions due to the interconnectivity between different functional regions and thus there is unlikely to be a very specific locality of working memory within the frontal lobes.

Haxby, Petit, Ungerleider, and Courtney (2000) investigated the neural basis for working memory, and indicated that the separation of functional regions should be based on a continuum of participation rather than a discrete modulation of functions. They found that numerous regions might be associated with multiple functions, such as the processing of visual or spatial material, but will vary in their degree of activation based on the demands of the task at hand. In addition their research highlighted six different prefrontal regions associated with working memory, indicating poor specificity of localized functions. Thus, because of the numerous prefrontal regions associated with working memory even diffuse damage within this region, as opposed to a focal lesion is likely to have a profound impact.

Consistent with the work of Haxby and colleagues (2000), D‟Esposito, and colleagues (1999) conducted a meta-analysis on the literature investigating working memory processes in patients with DLPFC lesions. Their review indicated that when the manipulation demands of the task were low, as in forward verbal or visual span tasks, patients with frontal cortex lesions were not impaired. However, when the demands of the task increased to include a delayed response trial, the results strongly indicated that the DLPFC is important in rehearsal processes, and in the discrimination and decision-making processes necessary for efficient long-term memory encoding and recall. These findings support the demarcation of slave systems versus a more complex central executive processor, and highlight that within the construct of working memory, this distinction is imperative.

Impairments in immediate auditory attention span, temporal sequencing, and organizational aspect of memory that impair the efficiency of encoding and retrieval have also been consistently reported in cases of frontal lobe pathology (Milner, Petrides, & Smith, 1985; Stuss & Levine, 2002). In addition, the inability to recall the temporal context of information learned is termed source amnesia, and is considered to be a unique frontal lobe memory function. The nature of the source memory deficit is episodic, in that there is an apparent disconnection between the autobiographical context a fact is learned. Thus the individual with frontal lesions is unable to recall when something was learned, though forcedchoice recall tests indicate retention of the information (Squire, et al., 1993). Knowing the contextual elements associated with the first presentation of a stimulus greatly aids the ability to recall that stimulus at a later time, particularly when the environmental conditions are again present when recall is necessary (Gershberg & Shimamura, 1995).

Finally, prospective memory refers to the ability to bind together necessary actions or goals with the appropriate time in which to carry out the task (Burgess, Quayle, & Firth, 2001). This skill is considered to be subsumed by the frontal lobes (Burgess et al., 2001), and is critical for the execution of everyday living tasks. Prospective memory will not be explored further in this research, as the focus of this study is to explore the interface between frontal and temporal lobe memory functioning within the limits of WM and LTM respectively. However consideration to the effects of prospective memory impairments in these groups requires further investigation.

In summary, the consequential amnestic impairments of frontal lobe pathology can be characterised as difficulties in establishing a stable mind set for recall, impairment in the mental effort required to recall past trace events and an inability to switch from one group of stimuli to another. These fundamental processes are linked with attention, initiation and long-term memory retrieval that are associated with frontal lobe functioning, and produce the net effect of poor complex memory processing as a whole, rather than primary memory impairment per se (Fernandez & Tendolkar, 2001; Stuss & Levine, 2002).

Finally, with respect to hemispheric laterality of function, there is mounting evidence directed by neuro-imaging studies in adults to indicate a lateralization of function based on the stage of task. Specifically, effective encoding of episodic memory tasks is associated with left prefrontal cortex activity, in contrast to right prefrontal cortex activation in retrieval processes (Fletcher, et al., 1997). This growing body of literature highlights the critical role of the frontal lobes, which are evident in isolation and in addition to the role of the more traditional view of temporal lobe governance of memory processing; further highlighting the memory circuit.

3.2 The Role of the Temporal Lobes in Memory

Structures within the MTL constitute systemic networks that remain anatomically distinct, yet highly integrated. Within this cortical processing system, the hippocampus (including the CA fields, the dentate gyrus, and subicular complex) constitutes the end-stage of the hierarchy. The major output from the hippocampus is the entorhinal cortex, which together with the parahippocampal and perirhinal cortices comprises the parahippocampal region (Gabrieli, 1998). These two latter cortices share connective associations with each other, in addition to comprising the major input/output pathways to the entorhinal cortex. The perirhinal and parahippocampal cortices share projections from neocortical association areas (temporal, frontal, and parietal lobes) (Simons & Spiers, 2003; Squire, et al., 1993; Squire, et al., 2004; Zola-Morgan & Squire, 1993). Key regions of the temporal lobe are highlighted in Figure 3.2.

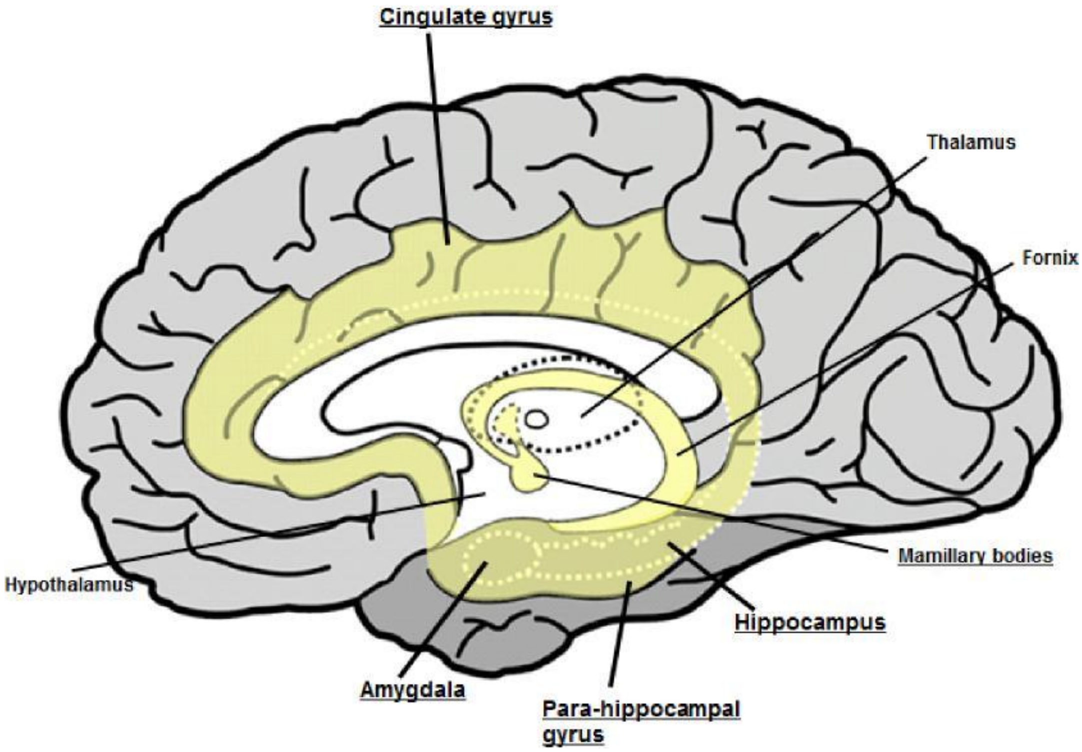

Figure 3.2 Structures of the Medial Temporal Lobe (image downloaded and adapted from www.BrainConnection.com).

Despite the common features of MTL damage there exists a debatable level of evidence to indicate that different structures within this system differentially contribute to declarative memory. Specifically, damage to the hippocampus consistently results in a failure to form episodic memories, whilst preserving the ability to acquire semantic knowledge (A. Baddeley, Vargha-Khadem, & Mishkin, 2001; Squire, et al., 1993). This finding has been illustrated in children and in adults. This dissociation of function indicates that episodic and semantic memories are associated with distinct neuroanatomical loci.

Neuro-imaging studies have implicated the middle and inferior temporal lobes for semantic memory (Squire, et al., 2004) and the hippocampus for episodic memory (Eichenbaum, 2004; Shimamura, 1992). Specifically, the hippocampus has been linked with associative representation (linking environmental cues according to time, place and person), sequential organization according to temporal sequence and relational networking or grouping of stimuli according to shared features (Eichenbaum, 2004). The hippocampus is not considered to be the final repository for all long-term memories, as damage to this structure does not result in a loss of all past memories (Squire, et al., 1993; Squire, et al., 2004; Zola-Morgan & Squire, 1993; Zola-Morgan, et al., 1982).

Lesions or damage to the MTL structures produces memory impairments that are characterised by intact immediate memory, and uncompromised perceptual and cognitive domains (including IQ) (A Baddeley & Warrington, 1970; Scoville & Milner, 1957; Squire, et al., 2004; Zola-Morgan, et al., 1982). Given that patients with damage to MTL structures mostly present with preserved STM, the vast literature exploring the role of the temporal lobes in memory have largely been directed to long-term episodic memory. However, an emerging literature also points to its involvement in STM processing, given its role in the immediate processing of information to be learned. For example, Jonides et al (2008) highlight that the unique aspect of episodic memory is the "time tag" that is critical when learning novel associations. Tasks such as binding a target list of words to the environmental circumstances in which it was learned is a task subsumed by the temporal cortices. Thus in summary, the temporal cortices and in particular the medial temporal portions play a role in both STM and LTM processing (Jonides, et al, 2008).

3.2.1 Material specificity

At its most elementary, the material specificity hypothesis of long-term memory function holds that verbal information is processed and held within the left hemisphere, and the right hemisphere processes visual information. This model, which was based on the work with patients with temporal lobe lesions or surgical resections, holds that the temporal lobes are the principle-processing unit of verbal and non-verbal information. Based largely on the work of Milner (Milner, 1970), the material specificity model can be summarised and is based on two key assumptions (Saling, 2009). First, the nature of verbal and non-verbal memory is considered to be “unitary and internally homogeneous constructs” (Saling, 2009 p.571). Second, the temporal lobes are material specific modulators of information. Specifically, the verbal memory system of the left temporal lobe does not mediate any aspects of visual memory, being responsible only for verbal information. The converse is also purported, where the right temporal visual-memory system does not partake in any aspect of verbal memory processing (Saling, 2009).

Although the appropriateness and validity of the material specificity model has recently come under scrutiny (Saling, 2009), to date its influence has resulted in a bias in clinical and research practice of over-emphasizing laterality of function. For example, many tertiary epilepsy treatment centres use the principle to guide indications for surgery. From a research perspective it has resulted in a shift of focus whereby hypotheses and test selection are largely guided by the location of clinical pathology. However, differences are apparent between adults and children in the degree of support for material specificity. In adults, the laterality of temporal lobe function has been consistently demonstrated and replicated in studies of verbal memory, though not in visual memory domains to the same degree (Saling, 2009;). Furthermore, such findings in children are equivocal, with some authors supporting it (Riva et al., 2002) and others failing to support it (Engle & Smith, 2010). The discrepancy in findings between the adult and paediatric literature will be discussed in greater detail in Chapter 4.

3.3 Interconnectivity of Function

This review has thus far highlighted that the mechanisms associated with initially registering environmental cues, to then recalling the details of what has been seen are reliant on numerous brain structures not isolated to either the temporal or frontal lobes but rather the interplay of the two.

A common trend in lesion studies is to investigate discrete and specialized constructs based on their known localization (Muller & Knight, 2006). For example, we investigate verbal memory if a patient presents with a left temporal lesion, whereas we may focus on executive functioning if a patient presents with a frontal lobe lesion. The purpose of many lesion studies therefore, is to establish a pattern or profile of impairment that is associated with dysfunction within a particular isolated region.

Within the memory domain, this review has highlighted the consequences of damage to isolated regions and presented the patterns of memory impairment expected given isolated deficits in specific neuroanatomical regions. For example, linking facts with temporal cues, or knowing when and where something has been learned is associated with frontal lobe involvement (Janowsky, Shimamura, Kritchevsky, & Squire, 1989; Janowsky, Shimamura, & Squire, 1989). The medial temporal lobe structures highlighted in Figure 3 are densely interconnected with parts of the frontal lobe, which assist in the recollection of learned information. When frontal lobe integrity is compromised the nature of the memory impairment is significantly altered (Janowsky, Shimamura, Kritchevsky, et al., 1989). This review has also highlighted how such studies have contributed to our existing knowledge base, and in conjunction with neuroimaging studies have strengthened our understanding of the localization of different functions.

However, by direct implication this approach has slightly biased our view on cognitive functioning to one of a modular account. More recent investigations broaden the scope to consider how different cognitive domains or modules may interact with one another. From a neuroanatomical perspective Simons and Spiers (2003) present the following model to illustrate how frontal and temporal lobe structures are interconnected.

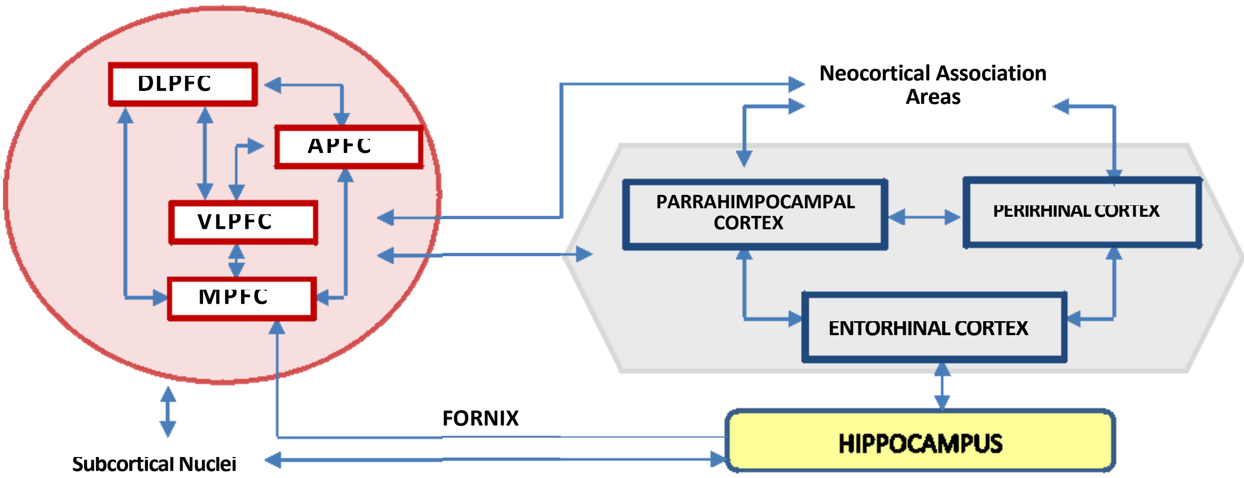

Figure 3.3. Schematic diagram of the interconnectivity between frontal and temporal cortices (adapted from Simons & Spiers, 2003).

This model emphasises that memory processing is dependent on a functional network of regions, that extends across the frontal and temporal cortices, therefore departing from traditional conceptualisations of distinct functional regions. Understanding the functional contribution of each lobe however does serve the purpose in promoting our understanding of how these regions work together.

Interactive processes may be conceptualised by a variety of means. They may be evident as a simultaneous engagement of multiple brain regions that share either unidirectional or reciprocal modes of transmission during execution of one specific task. Similarly depending on the origin of the influencing stimulus, the interaction may be a top-down cognitive process, or a bottom-up perceptual response. This type of interaction commonly involves a primary brain region influencing the action and outcome of a second region"s processing of information (Simons & Spiers, 2003). According to Simons and Spiers (2003), the contribution of each region is modulated by factors including what type of process is required (long or short term processing), the type of information to be remembered (verbal/non-verbal) and the accessibility of the long-term store of information.

Specifically as depicted in Figure 3.3, external cues from the environment are encoded and processed in the higher-level cortical areas and integrated and associated into a bound representation in LTM storage in the medial temporal lobes. Material is then manipulated and organized by the dorsolateral prefrontal cortex, in order to ensure the efficiency of the encoded material. When information needs to be retrieved from long-term stores, the dorsolateral prefrontal cortex initiates various retrieval checking strategies such as monitoring or verification to ensure the accuracy of retrieval for completion of the task at hand. This latter process is critical for functioning, as it dictates the availability of the information sought for further processing or action.

Budson and Price (2005), offer a useful simple analogy to depict this interconnectivity. They consider the frontal lobe as corresponding to a file clerk, someone responsible for filing and organizing all of the incoming information in a meaningful way. The medial temporal lobes in contrast act as a storage system, or filing cabinet for more recently filed information, and other association areas are associated with longer-term storage of remote information. Considered this way, the chain of events that may lead to poor memory processing is clearer. If information is not filed efficiently according to source, time and context due to an inefficient file clerk, then although the information may is stored within the filing cabinet, retrieving it becomes very difficult. In contrast if the file clerk is efficient, however the filing cabinet is rendered dysfunctional, then storing that information is likely to be near impossible.

To return to the earlier example therefore, given the known interconnectivity between frontal and temporal lobe structures, how do lesions in the frontal lobe affect our capacity to establish long-term learning and memory? To put another way, what does the long-term memory profile look like, if we also implicate poor frontal lobe functioning, in the context? Although the adult literature is making significant gains toward addressing such questions, the paediatric research is still in early infancy.

3.4 Development of Memory

Consideration must be given to the developmental stage during which the frontal or temporal lobe functioning is compromised. Hershey, Craft, Glauser, and Hale (1998) propose that the medial temporal-prefrontal connections change over development, which results in subsequent reorganization of the responsibilities of each. Because of the later development of the prefrontal cortex relative to the medial temporal lobe structures, these authors hypothesize that early in development, the medial temporal lobes are more likely to take on a short-term memory-processing role. However, despite the lag in development the frontal lobes are not considered functionally silent. From birth and up to two years of age the frontal lobes undergo rapid development, before the growth rate slows down between the ages of four and seven years of age. The frontal cortices, and in particular the prefrontal cortex continues to develop neural connections with more posterior cortical and subcortical regions, and is paralleled with increased efficiency of more complex executive and cognitive processing, particularly between the ages of eight and 12 years (Hernandez et al., 2002; Passler, Isaac, & Hynd, 1985).

Developmental memory studies indicate that children's ability to freely recall past events or experiences increases with age (Cycowicz, 2000). This type of efficient memory is reported to mature during adolescence. However, typically school-aged children demonstrate efficient episodic memory processing, as they are able to recall, order and sequence past events and coherently communicate them (Gathercole, 1998). This improvement of long-term memory is not solely accounted for by storage capacity, but is partly accounted for by more efficient use of mnemonic strategies that aid and strengthen long-term memory. However, even in subjects with working memory deficits, there is evidence that increasing age is associated with increased activation in medial temporal lobe structures (Adler, Holland, Enseleit, & Strakowski, 2001).

As the frontal cortices mature, the prefrontal cortex assumes this responsibility and allows the processing of more complex long-term memory traces to be controlled by the medial temporal lobes. Using structural NMI, Sowell and colleagues (2001) found that age related changes in mnemonic processing are associated with anatomical specificity of the frontal and temporal cortices, thus providing support for Hershey and colleagues' (1998) proposal.

Consistent with the interconnectivity hypothesis the specificity of functional gains made within the frontal and temporal lobes have a direct impact on the efficiency of global memory processing. For example, in general children's ability to recall a series of digits, increases in capacity from 2-3 items at four years of age, to approximately 6 items at 12 years of age (Gathercole, 1998). This change in capacity is a reflection of the increasing maturity of the articulatory rehearsal process, rather than an increase in storage ability per se. Specifically, prior to 7 years of age articulatory rehearsal strategies are not available to children to enhance retention of information, but rather beyond the age of 7 they acquire adult like skills in rehearsal (Gathercole). The increasing availability of rehearsal processes is likely to be mediated by the increasingly proficient long-term memory system. As the child's vocabulary increases and their knowledge of expected letter-sound relationships strengthens, less resources are required to process simple phonotactic structures, and the child can more effectively process new verbal information (Gathercole, 1998).

Similarly, younger children are more dependent on their visuo-spatial sketchpad when processing non-verbal material than adults (Hitch, Halliday, Schaafstal, & Schraagen, 1988). This may be directly associated with their poorly developed phonological loop, forcing them to rely on visual characteristics of newly learned information. Visual memory span, analogous to verbal memory span, steadily increases between 5 and 11 years, where adult levels are attained (Gathercole, 1998). This increase is due to two factors: the first involves a larger capacity for retention, and the second is associated with better phonological processing reducing the demands on the sketchpad (Gathercole, 1998). Thus there appears to be a reverse compensation for memory processing during development, whereby initially children rely on visual processing due to poor verbal memory processing, which then results in a shift to dependence on language-mediated processing once these skills are acquired. In turn because the phonological system is supplemented by long-term memory advancement, the entire system is interdependent for efficiency. These findings may account for the failure to consistently demonstrate lateralization of function in mnemonic processing in children, which is much more consistently reported in adult studies (Laurent & Arzimanoglu, 2006).

In general, childrens' performances on measures that tap the WM components of Baddeley's (1986) model increase linearly from the age of 4 years, and peaks in adolescence (Gathercole, Pickering, Ambridge, et al., 2004). Specifically however, Swanson (1999) investigated working memory performance across the lifespan, and indicated that skill advancement in working memory processing was not associated with development of each of Baddeley's (1986) verbal and nonverbal slave system domains, but rather reflected a general WM capacity development. Therefore maturation of the frontal cortices that mediate central executive and episodic buffer function more critically account for the variance in adult's and children's memory functioning rather than other brain regions associated with domain-specific processing.

Thus it is likely that neurological illness or injury during childhood affecting the frontal or temporal cortices, will affect this differentiation of mnemonic processing differently than that seen in adults due to the variance in cortical development, particularly of the frontal lobes. Models of memory function, from the cognitive literature to the neurosciences provide a means to assess the impact of damage to isolated areas, though it remains to be seen how well this is replicated within the clinical literature, and by extension to paediatric populations. As mentioned earlier, epilepsy is a natural laboratory that is able to assist us in answering these questions.

CHAPTER 4: EPILEPSY: 'THE NATURAL LABORATORY'

Whilst cognitive neuroscience has propelled considerable advancement of memory function over recent decades, in order to be considered a viable model or theory of function, there must be convergent evidence from clinical populations. In the field of memory, much of this convergent evidence is drawn from the epilepsy literature, specifically the focal or systematic partial epilepsies (SPE). This sub-group of epilepsies is particularly informative for memory research as these are focal disorders where seizures selectively arise from the frontal, temporal, parietal and occipital lobes respectively. The resultant clinical disorders of frontal lobe epilepsy (FLE) and temporal lobe epilepsy (TLE) are particularly informative for memory research as the function of these structures is often compromised in between seizures and are heavily implicated in memory theory.

In order to interpret this rich literature, it is useful to appreciate the clinical semiology of these disorders. According to Kramer and colleagues (1997) both disorders are characterised by partial, as opposed to generalised, seizures, reflecting that the seizure begins in a focal brain region. These seizures may be simple partial, reflecting that consciousness is preserved, or complex partial, where alertness is impaired. Although these seizures begin in a focal region they may progress into secondary generalised events, involving the whole brain. The specific manifestation of temporal and frontal seizures can be quite varied, and are dependent on the anatomic localization and aetiology of the underlying epileptogenic region (U. Kramer, Riviello, Carmanti, et al., 1997; Lawson et al., 2002). Both TLE and FLE are also largely considered disorders of childhood, with onset commonly, but not necessarily, occurring early in life (Seidenberg & Berent, 1992), therefore both afford a unique opportunity to study memory impairment in a developmental context.

4.1 Temporal Lobe Epilepsy

Temporal lobe epilepsy is the most common of the SPEs. Seizures often are quite innocuous at a behavioural level, but have been shown to be quite refractory to medication and have a potentially disastrous impact on everyday function. The temporal lobe, like the frontal lobe, is not a homogeneous structure, and two sub-types of TLE are now well described reflecting involvement of mesial (hippocampus/amygdale) and lateral structures. This distinction is particularly informative for memory research (ILAE, 1989).

The aetiological agents of TLE are likely to be diverse, and include hippocampal sclerosis, cortical dysplasia, and low grade tumours (Franzon & Guerreiro, 2006). Lawson and colleagues (2002) investigated the clinical, EEG and MRI characteristics of mesial temporal lobe epilepsy in a prospective study of children undergoing investigation for management of their epilepsy syndromes. Their findings revealed that 94% of participants with MTLE demonstrated a lesion on MRI, and 75% of these cases were identified as hippocampal sclerosis (HS). The occurrence of HS in MTLE is a consistent finding (Harvey, Grattan-

Smith, Desmond, Chow, & Berkovic, 1995; Janszky, Janszky, & Ebner, 2004; Kalvianen et al., 1998), and is identified as one of the main aetiological agents of the syndrome.

The pathological relationship between seizures and hippocampal sclerosis remains controversial. Kalviainen and colleagues (1998) investigated whether recurrent seizures were causative, or whether hippocampal damage predates diagnosis of TLE with the overall aim of clarifying whether the severity of damage is associated with seizure frequency. Their findings reflected a 16% reduction in hippocampal volume in patients with refractory MTLE on the side of the seizure onset. They did not identify any changes in hippocampal volume in new onset or in chronic well-controlled cases, however, overall, patients with a higher seizure frequency displayed more severe hippocampal reduction, suggesting seizures themselves are deleterious to hippocampal volume.

The clinical significance of HS is rooted in the importance of the cognitive function it and the surrounding parahippocampal region sub serves (Darby & Walsh, 2004). As discussed in Chapter 3, this region is associated with specific types of memory processing, most notably in initial registration of information and the subsequent registration of that memory in other areas of the brain (Eichenbaum, 2000, 2004). Thus, impaired hippocampal function is known to affect memory and new learning and therefore seizures within the temporal lobe have particular functional implications for the developing child (Squire, et al., 2004).

Harvey and colleagues (1997) undertook a longitudinal community-based prospective study of children with new-onset TLE over a four-year period. The sample of children was divided into three subgroups based on their aetiology, giving rise to a “developmental TLE”, “TLE with HS/significant antecedents”, and a “cryptogenic TLE” group. The age of onset of seizures within the *TLE with HS* group involved a bi-modal distribution with peaks in infancy and mid-late childhood. Extending the age range of their sample, Janszky and colleagues (2004) report a likely trimodal distribution of age of seizure onset, with a third peak in mid-late twenties. The authors (1997) hypothesized that those children with developmental TLE or TLE associated with HS were more likely to have a negative outcome, than those children with a cryptogenic basis for their seizures.

4.2 Frontal Lobe Epilepsy

Frontal lobe epilepsy is the second most prevalent of the localization related epilepsies. In general frontal seizures are more physically dramatic than temporal seizures, reflecting involvement or proximity of the motor cortex. No distinct subtypes have been defined by the ILAE (1989), although there is clear variability in the manifestations of seizures depending on the aspect of the frontal lobe involved, which includes the supplementary motor cortex, cingulate, anterior frontopolar region, orbitofrontal, dorsolateral, opercula and motor cortex (Commision on Classification and Terminology of the International League Against Epilepsy, 1989). The underlying aetiological agents of FLE are diverse, and can include cortical dysplasia, cortical tubers, porencephaly, tumours, or

Dysembryoplastic Neopethelial Tumours (DNET) among several (Aso, Watanabe, Negoro, & Nakashima, 1997).

The particular semiology of frontal lobe seizures is dependent on the anatomical onset of the seizure. In general, seizures of frontal lobe origin are briefer and more frequent (Sinclair, Wheatley, & Snyder, 2004), and are more likely to occur in clusters compared with seizures of temporal lobe origin (Fogarasi, Janszky, Faveret, Pieper, & Tuxhorn, 2001). With respect to seizure frequency Fogarasi and colleagues report that children with FLE were experiencing up to 40 seizures a day. A specific feature of FLE is the occurrence of nocturnal seizures. Fogarasi and colleagues investigated the seizure semiology of preschool children with FLE and found that 36% of their sample experienced seizures at night, and 47% of them experienced them during sleep. Children with FLE tend to demonstrate an earlier age of seizure onset (Lawson, et al., 2002) relative to children with TLE. Thus given the diversity of cognitive and behavioural functioning assigned to the frontal lobes, the clinical manifestations and implications of seizures are more heterogeneous than those observed in TLE (Riggio & Harner, 1995).

Similarly, due to the rapid spread of the seizures across multiple cortical regions, several different frontal areas may be implicated within an individual making it difficult to discern the consequence of their seizures (U. Kramer, Riviello, Carmant, et al., 1997). In a more recently published article, Patrikelis, Angelakis, and Gatzonis (2009) present the division of prefrontal, premotor, and precentral cortex as a basis for distinguishing the FLEs. It is important to note that temperofrontal or frontotemporal seizures are difficult to distinguish from focal frontal lobe seizures based on clinical manifestations alone. For example, both FLE and TLE syndromes can involve staring, blinking, head deviation, fear and autonomic manifestations (U. Kramer, Riviello, Carmanti, et al., 1997; Salanova et al., 1995). The clinical distinction between these clinical syndromes is confounded by the interconnectivity of neural pathways and the likely spread of seizures from frontal to temporal regions or vice versa (U. Kramer, Riviello, Carmanti, et al., 1997).

Consideration that an epileptogenic region, albeit focal, unilateral and enduring can influence other brain regions is not new, and provides opportunity to explore the interconnectivity of function. “Nociferous cortex” was first penned by Penfield and Jasper (1954) and refers to the epileptogenic and dysfunctional cerebral tissue that not only impairs the normal function of that region, though also impairs the function of other brain regions (Devinsky, 2005). Although beyond the scope of this review, the notion that a focal lesion can exert influence on other distant cerebral sites was illustrated through observation of surgical case studies. Modern neuropsychology research has implicitly tested this notion by considering how other cognitive functions, which by all intents and purposes should not be impaired if one holds true to a modular account of cerebral localisation of function, are impacted by seizure activity in other areas. The consummate example of this is the awareness that temporal lobe epilepsy may produce impairments characteristic of deficits in other brain regions such as the frontal lobes (Brown, 2006). Therefore, the argument holds that studying seizure disorders localised to the frontal and temporal lobes of the human brain which are integral in memory processing will assist our understanding of their function.

4.3 Memory Impairment in Epilepsy

With respect to memory function, the convergence of clinical and cognitive science has resulted in a robust literature, with clear and replicable conclusions based almost entirely on populations with TLE. So much so, that entire surgical programmes for epilepsy treatment adhere strictly to models of memory localisation and lateralisation in their planning (Loring et al., 2008; Saling, 2009).

The material-specificity model has been discussed previously and rests almost entirely on cases of TLE. It involves a material specific-deficit in declarative memory, or new learning that is dependent on the hemisphere that is compromised (Milner, 1970). Specifically, verbal memory is impaired in adults with left TLE (Bell, Seidenberg, Hermann, & Douville, 2003). This effect is so robust in adult research that Breier and colleagues (1996) have demonstrated that memory measures are able to predict group membership of TLE based on performance. Less consistently, right TLE is associated with impairment in consolidation and retrieval of the visual and spatial features of the environment (Blaxton & Theodore, 1997).

The impact of TLE on cognition however, as highlighted by Hermann et al (2009), extends beyond temporal lobe pathology and exerts influence on other brain regions including the basal ganglia (Geary, Hermann, & Seidenberg, 2009), thalamus (Seidenberg et al., 2008), amygdala (Tebartz Van Elst, Baeumer, Lemieux et al, 2002), and frontal lobe (Bonhila et al., 2007). Thus there is an emerging literature that the temporal lobes are not the only important structure for memory function, and that the temporal lobes are not the only region of impairment in TLE, collectively reflecting nociferous cortex at work. It is thus surprising that in this context, relatively little literature has examined other cognitive function or broader aspects of memory in TLE.

In contrast with the rich literature examining LTM and TLE, memory impairments in FLE patients are comparatively less investigated (Meitzler et al., 1996), somewhat surprisingly given that the frontal lobe is implicated in normal memory function. Individuals with frontal lobe pathology often present with a clear executive dysfunction syndrome pattern of impaired planning, inhibition and even personality changes (Darby & Walsh, 2004). However patients with a seizure focus within the frontal lobes may often present with no remarkable neuropsychological profile (Risse, 2006). When specific deficits are evident, they often comprise a high degree of variability that may or may not include memory dysfunction, which is likely associated with the heterogeneity of functions subsumed by the frontal cortices.

The absence of consistent evidence for a memory deficit in FLE should not be considered an indication that memory is not impaired in FLE. Previous chapters have argued for a reasonable expectation that dysfunctional frontal cortices will exert an influence on memory, especially insofar as working memory is likely to be effected. Unfortunately, studies with FLE rarely investigate memory function holistically, i.e. by including numerous measures of working memory, verbal and non-verbal long-term memory.

The impact of FLE on memory may be deduced post-hoc by investigating studies comparing FLE and TLE on memory function. This is described as post-

hoc, as the intent of many such studies is geared toward conceptualising the memory impairment of TLE, and therefore test selection is biased toward those sensitive to impairment in TLE. An additional consequence of this is that TLE is also compared to *extra-temporal* samples of epilepsy, namely those where seizures are not localised to the temporal lobe, therefore no fractionation of FLE is made from other seizure types. Specifically, the majority of research has focused on declarative memory impairments in adults with TLE. The converse is also applicable when reviewing comparative studies of FLE and TLE where the focus is based on executive functioning performance.

Such comparative studies generally demonstrate a dissociation of function. For example, Frisk and Milner (1990) investigated the performance of left TLE patients on tasks of sentence comprehension, story recall, and rapid-automatic naming two weeks after undergoing left temporal lobectomy. Their results indicated that left TLE patients were impaired on story recall, with intact working memory and rapid naming. In contrast subsequent experiments with a group of FLE patients indicated a double dissociation of function, whereby frontal lobectomy patients were significantly impaired on working memory and rapid naming tasks, with intact story recall.

Helmstaedter and colleagues (1996) then performed a cluster analysis to subgroup patients according to patterns of impairment, and revealed that (consistent with expected localized deficits in the frontal lobe) FLE patients were more characteristically impaired on measures on motor-coordination and inhibition, whereas TLE patients demonstrated poorer performance on measures of speed and attention.

Interestingly individual analysis of the participant‟s performance indicated high levels of variability within the sample. Nine of the twenty-three FLE participants demonstrated a profile of impairment more consistent with the TLE patient group. In addition three of the thirty-eight TLE patients demonstrated impairment indicative of FLE patients. These findings could not be explained by EEG characteristics or the specificity of lesion sites. Subjects were matched according to age, IQ, gender and age of onset, however differed significantly in their seizure severity (indicated by seizure frequency) (Helmstaedter, et al., 1996). These findings are not only support for models of interconnectivity, though given the impairment in secondary regions not associated with seizure activity, may also be indicative of nociferous cortex at work.

Exner (2002) also compared the neuropsychological profiles of patients with either FLE or TLE, and supported the findings of Helmstaedter and colleagues (1996). They included a detailed test battery of memory functioning for working memory, and verbal and non-verbal long-term memory, and perhaps offer the most representative pattern of memory profile impairments evident in these populations.

As would be expected their findings indicated that TLE patients performed significantly worse than controls and FLE patients on measures of verbal and non-verbal declarative memory, and FLE patients performed significantly worse on measures of working memory relative to both TLE and control groups. However, consistent with theories of interconnectivity, both FLE and TLE groups demonstrated impairment in working memory and long-term memory relative to control groups. The important conclusion is that the contribution of either the medial temporal lobes on working memory, or the frontal lobes on long-term memory consolidation is evident in adults with focal epilepsy.

In sum, adults with TLE demonstrate memory impairment that most often follows a pattern of material specific impairment relative to the hemisphere that is compromised. Although the pattern of memory impairment in adults with FLE is less clear, there is substantial evidence for impairment in aspects of memory that requires additional and complex processing. Extending the research to include impairments in executive functioning highlights that overall, adults with focal epilepsy of frontal and temporal origin display a double dissociation of function. The evidence for this dissociation is consistent with purported models of cognition, and therefore the current standing of research reflects a parsimonious account of cerebral function.

It is a significant shortcoming however that the convergence of the cognitive and clinical studies remains largely biased toward consideration of modular cognitive impairments, as there exists a definite impetus for further research exploring the interplay. It should no longer be considered satisfactory to infer working memory impairments where there lies a sufficient opportunity to directly examine these effects. The impetus is demonstrated by findings that FLE patients often perform normally on memory tasks that require only minimal strategic demands, such as recognition tasks, though when learned information requires manipulation, transformation or evaluation then a greater load is placed on the frontal cortices, and performance becomes impaired in this group (Drane et al., 2006; Hwang & Golby, 2006). Working memory tasks often involve retrieval of information from long-term memory, if that system is redundant due to the effect of TLE, then these patients are likely to demonstrate poor working memory on select tasks secondarily to a primary deficit in declarative memory.

4.4 Memory Impairment in Paediatric Epilepsy

The paediatric epilepsy literature has not commanded the same degree of attention and exploration as that of the adult literature. A cursory search through PubMed highlights that the number of recognition hits under the search term "adult and ((temporal lobe epilepsy) OR (frontal lobe epilepsy)) and (memory)" produce a net result of 1159 compatible publications. In contrast the same search terms, with "adult" supplemented with "child" yield only 196 fitting entries. For this reason, the known adult memory profile of epilepsy has largely guided the hypotheses regarding how the immature brain responds to focal seizures, and resulted in an oversight of the possible effects and mechanisms of epilepsy in children. Perhaps this is largely due to an implicit assumption that these processes occur in parallel in children as well as adults. However comparative studies of adults and children with epilepsy indicate that these processes function disparately across these populations, largely accounted for by developmental differences in brain maturation, different effects of seizure status and onset (Holmes, 1991).

Increasingly evident is that the actual neuropathological basis of epilepsy is different in adults and children (Lee et al., 2010). For example, studies report that children presented with less frequent auras, and more frequent motor manifestations relative to the common adult TLE profile (Bocti et al., 2003;

Sinclair, Wheatley, & Snyder, 2004). These findings highlight that not only are there between group differences in TLE seizure semiology, but also within the rubric of TLE across the lifespan. Similarly, adult models of impairment in FLE are limited in their applicability to children given the developmental trajectory of the frontal lobes and the functions subsumed by the frontal cortices appearing later in development (Risse, 2006). Thus the patterns of impairment are bound to be more heterogeneous than the patterns that can be elucidated in adults, where these functions have reached maturity.

Many paediatric studies in epilepsy fail to adequately demarcate the various epilepsy syndromes. In many cases "children with epilepsy" are cited as the research sample, which may include children with CPS, generalized seizures, absence seizures, and simple partial seizures within the one category (Everts et al., 2010; O'Leary, et al., 2006). Important conclusions have been drawn regarding paediatric epilepsy as a group, such as no significant gender differences in delayed verbal or visual recall (M. L. Smith, Elliot, & Naguiat, 2009); inconsistent impact of laterality (Jocic-Jakubi & Jovic, 2006); the influence of structural abnormality (Spooner, Berkovic, Mitchell, Wrennall, & Harvey, 2006); and influence of refractory seizures before (M. L. Smith, Elliot, & Lach, 2002) and after surgery (M. L. Smith, Elliot, & Lach, 2006b). Even though these conclusions provide value to our understanding of important factors in epilepsy, grouping patients based on an overarching category does not respect the underlying differences in neural pathology and influence of each syndrome. Furthermore, given the highlighted value that investigation of focal epilepsy syndromes can provide to our understanding of the function of specific brain regions, such research practice should be avoided if gains are to be made in understanding the impact of focal epilepsies. Thus, the merit of utilising focal epilepsy disorders in adulthood to inform clinical practice or cognitive science in children remains in its own infancy.

4.4.1 Complex partial seizures and cognitive impairment

Studies of children with focal epilepsies have demonstrated variable support for memory impairment in this group, and provide a necessary first step of evaluating the impact of epilepsy on cognition. For example, Schoenfeld and colleagues (1999) report that those children with focal seizures displayed deficits across motor control, mental efficiency, language, verbal and non-verbal memory, and academic achievement relative to control participants. This generalized pattern of impairment was upheld even whilst statistically controlling for the possible influence of IQ.

Engle and Smith (2010) also used "focal seizures" as inclusion criteria, and explored the relationship between attention and memory functioning in children. Their sample consisted of 65 children and adolescents ranging from 5 to 18 years with medically intractable focal seizure disorders of frontal, temporal, parietal, occipital and multilobar onset. Their main focus was to investigate whether attention was associated with memory performance, or whether laterality effects were evident and more strongly associated with memory performance. Engle and Smith report that laterality of seizure focus was not significantly associated with verbal or visual memory performance, thus failing to support adult models of material-specificity. This result was upheld when analyses included the entire group, or within only those with TLE. However, their results revealed a complex relationship with attention and laterality of seizure focus. Specifically, attention was significantly correlated with visual delayed memory in those with left hemisphere seizure onset, and with verbal delayed memory in those with right hemisphere seizure onset.

The results of this study combined with others, suggest that whilst evidence of material specificity in children is still equivocal (Camfield et al., 1984; Guimaraes, et al., 2006), attention plays an additional role in global memory performance. Other authors have reported deficits in sustained attention in children with focal seizure disorders (Sanchez-Carpintero & Neville, 2003) and thus the value of Engle and Smith‟s (2010) investigation lies in its consideration of the interplay between different cognitive factors on memory functioning in the context of seizure variables. This study is limited however in its sample composition which restricted analysis of comparison of focal epilepsy groups, therefore limiting conclusions regarding structure-function relationships.

Everts and colleagues (2010) assessed the correlation between language lateralisation and verbal memory performance in children with focal epilepsy of either frontal or temporal lobe origin combined. Their findings indicated that performance on neuropsychological tests were within the average range, though performance on verbal memory was below average relative to published normative expectation. This study provided new insight into how verbal memory performance may be used as an indicator of language lateralization in surgical settings. However the method of combining FLE and TLE groups for comparison to normative data confounds, and limits our understanding of the contribution of each syndrome and the possible phenotypic differences between them. This is a limitation of most studies adopting epilepsy cases of mixed aetiology and seizure localisation, as it is difficult to ascertain whether the diffuse impairment evident is a consequence of group aggregates of children with various seizure aetiology, or a genuine effect of "nociferous cortex' at play. Thus each study's generalizability to specific patient groups is limited by inclusion of any child with a focal seizure.

4.4.2 Studies of frontal and temporal lobe epilepsy

Rzezak, and colleagues (2005) reported that children with TLE present with frontal lobe dysfunction in the area of verbal fluency, inhibitory control and concept formation and for sustained attention to auditory and visual stimuli. Their sample composition allowed for analysis of the differential effects of mesial compared with neocortical temporal lobe seizure onset, and interestingly the latter group performed significantly worse on working memory tasks.

Chaix and colleagues (2006) employed the digit span subtest of the WISC-III as an indication of working memory and reported that children with TLE exhibited deficits in working memory even after controlling for several seizure variables, which has been attributed to disruption of the temperofrontal circuit (Laurent & Arzimanoglu, 2006). This study did not include FLE as a research group however, and the possible associations between working memory or memory span and long-term memory were not explored.

Riva, Saletti, Nichelli, and Bulgheroni (2002) demonstrated that children with left onset FLE performed worse than those with right onset FLE on the free recall measure of the California Verbal Learning Test- Children"s Version (CVLT-C). However in a follow-up study assessing lateralization of impairment as a function of side of seizure onset, these authors reported that laterality effects were not evident in children with FLE (Riva, et al., 2005). The authors note that failure to demonstrate laterality effects is likely due to the rapid propagation of epileptic seizures to the contralateral frontal lobe facilitated by the numerous frontal lobe connections.

Chieffo and colleagues (2011) investigated the surgical outcome of children with FLE and TLE and report that pre-surgically children with FLE displayed greater executive difficulties and less memory impairment compared with children with TLE who showed the reverse pattern. Interestingly, neither group demonstrated impairment in working memory, although this is more likely attributed to a lack of sensitivity of the digit span subtest score in measuring true working memory.

Culhane-Shelburne, Chapieski, Hiscock and Glaze (2002) investigated the neuropsychological performance of children with FLE (*n*= 12) and TLE (*n*=15) on measures of attention, memory, and executive functioning. Children were aged between 8 to 18 years of age, and all but four of the cases displayed unilateral epileptogenic foci. Although differences did not reach statistical significance on measures of memory, children with FLE displayed higher levels of impulsivity on the TOVA relative to children with TLE; however TLE children demonstrated greater inattention than those with FLE. Similarly children with TLE in this study performed below the level of the FLE children across all measures of verbal memory. Specifically, performance on a task of narrative recall in which children had to recite and then later recall a brief story following a delay yielded the greatest difference between the groups. In addition to this, performance on the delayed recall trial of the CVLT- indicated that children with TLE were not able to recall the same amount of words as children with FLE.

It is interesting to note however that performance on these measures of verbal memory performance was within normal limits for both groups. This pattern of performance was also reflected on non-verbal memory measures, however there were no significant differences between groups. Finally, consistent with the authors‟ expectation, children with TLE outperformed children with FLE on measures of executive functioning. Thus the findings reported by Culhane-Shelburne et al (2002) support the findings of adult studies that children with TLE perform more poorly on memory tests and FLE children perform more poorly on tests of executive function. This study did not however investigate working memory.

Nolan and colleagues (2004) investigated the memory profiles of different epilepsy syndromes and were the first to investigate memory profiles specifically, and collected the largest sample of FLE and TLE children to date (*n*= 25 and 32 respectively). Their results indicated that children with TLE performed worse than FLE children on several long-term memory tasks, including verbal learning and retention, and number of ideas generated from a story. Consistent with the adult literature, FLE children performed worse than the normative sample, though better than patients with TLE. Again however, working memory was not investigated.

A separate study investigated attention, memory, including working memory, in children with FLE, TLE and also children with generalized absence epilepsy (Hernandez et al., 2003). Importantly, their findings indicate that all three epilepsy groups demonstrated significant impairment relative to control groups and normative samples in measures of attention and memory. In order to assess working memory these authors adopted the Freedom from Distraction (FD) index from the WISC-III, in addition to the Continuous Performance Test (auditory working memory), which are arguably not particularly sensitive or consistent with the nature of working memory purported in the cognitive literature. Children across all epilepsy groups did not differ significantly in their performance on the FD index, though demonstrated various levels of impairment in the CPT task, which is considered by the authors to be a more difficult working memory condition. Specifically, children with FLE demonstrated the most impaired performance relative to the other syndrome groups.

Although these findings would indicate that children with FLE have significantly impaired working memory, these tasks rely heavily on attentional processes (Spreen & Strauss, 1998). Attention indeed mediates working memory performance; however attempting to differentiate whether poor performance is due to poor attention, or due to a genuine inability to maintain information in mind, and manipulate it according to task demands is relatively difficult. In addition the nature of working memory assessed by these tasks is not consistent with the theoretical conceptualisation of the multicomponential model of working memory discussed previously (A. Baddeley, 2000a; A. Baddeley & Hitch, 1974) and reflects the crude nature of measures.

In terms of performance on long-term verbal learning and memory, children with FLE did not differ in the amount of words learned or retained on the CVLT-C. Rather FLE children demonstrated more repetitions and more impulsive errors than either the TLE or GA groups. In addition, these children were prone to the negative effects of retroactive interference, and poor attention over the duration of the task was indicated by a decline in words recalled during the final list. Although all groups performed significantly below average on this task, TLE and GA groups demonstrated an increase in the number of items recalled on this last trial.

Unexpectedly no significant differences were reported among the three groups regarding the use of semantic clustering on the CVLT-C. The use of semantic clustering aids and strengthens encoding processes, and is often deficient in children with frontal lobe epilepsy (refs). Considered together with findings that FLE patients did demonstrate poor performance on the FD and CPT, would lend itself more appropriately to the conclusion that the FLE children in this sample did not possess poor executive working memory skills, but rather had deficits in their attentional capacity. The conclusion that children with FLE display greater impairments in attention relative to their TLE counterparts is strengthening (Auclair, Jambaque, Dulac, LaBerge, & Seiroff, 2005).

The conclusions from paediatric studies therefore lend variable support to the notion of a double dissociation of executive/working memory and LTM functioning in children with FLE and TLE. This is consistent with adult studies of cognitive functioning in epilepsy, though questions regarding holistic memory function cannot be deduced from these consistencies for the same limitations discussed in the previous section. Collectively, these published studies reflect that answering questions about memory functioning lack several considerations. First, none of the published studies consider memory within a conceptual cognitive framework, and therefore answering questions pertaining to mechanisms of memory is not yet achievable. Second, those including an extended or wide ranging protocol of measures, namely those that include a measure of working memory, do not consider the subcomponents of memory processing such as span or mnemonic strategy utilisation. This is important to consider as studies with normally developing children highlight that the end-point performance on a long-term memory measure is reliant on specific sub-skills such as working memory. We still lack a comprehensive study that attempts to consider a cognitive framework within a clinical sample, and therefore answering questions about memory impairment in epilepsy requires piecing together parts of a puzzle from a variety of different sources, as no paediatric studies have explored memory functioning holistically using working memory in addition to long-term memory test batteries. There is strong argument for such an approach from a cognitive science framework, and thus it remains to be seen how such a framework is replicated and impacted in childhood epilepsy.

4.5 The Influence of Seizure Variables on Cognition

The practice of adopting focal epilepsy populations to study cognition is thus valuable, and lies in our ability to infer how abnormal function within a circumscribed region can inform normal cognitive function. As discussed in Chapter 1, a caveat to the inference drawn however is that various factors are associated with the epilepsy itself and are often not delineated well in the literature (McNelis, Johnson, Huberty, & Austin, 2005; Schouten, Oostrom, Pestman, Peters, & Jennekens-Shinkel, 2002; Williams et al., 2001). A variety of psychosocial, medication and seizure-related variables are often associated with the severity of the epilepsy in addition to the pervasiveness of their effects on cognitive functioning, however it is difficult to disentangle the primary versus secondary effects of these variables as they are largely enmeshed within the disorder (Desai, 2008). Specifically, many studies report that these same variables are associated with memory impairments (Nolan, et al., 2004) and the frequency or severity of learning difficulties (Beghi, Cornaggia, Frigeni, & Beghi, 2006). Thus the main point is that given the interrelatedness of many of these seizure variables, and the inherent differences within different epilepsy syndromes, age of onset, duration, seizure frequency and medication use should be statistically controlled for in subsequent research. The following sections briefly explore some of the complexities associated with operationalizing key seizure variables, and a summary of the key points are discussed below.

4.5.1 Age of seizure onset

Age of onset is a significant factor that differentiates the way children and adults respond to epilepsy in terms of cognitive outcome (Akshoomoff, Feroleto, Doyle, & Stiles, 2002), functional changes resulting from treatment or surgery (Gleissner, Sassen, Schramm, Elger, & Helmstaedter, 2005), or impact on future learning and behavioural problems (Holmes, 1991). It is difficult to disentangle the primary impact of age of seizure onset (ASO) as it represents not only the point of disruption of cerebral development though also, when examined in either well controlled, refractory or surgical cases, is enmeshed with the effects of seizure duration, frequency, medication use, aetiology, and years of education.

With respect to adult studies, a large-scale investigation of TLE conducted by Strauss, et al (1995) indicated that age of onset of seizures has a positive linear relationship with IQ, whereby earlier age of seizure onset is associated with lower overall IQ. Age of onset was the single strongest predictor of both IQ and General Memory in their sample of 1,141 adults with refractory epilepsy of temporal lobe origin. Although included within the overall sample, the authors did not provide a detailed summary of the constituents of the "extratemporal" group however, which limits the inferences that can be made. In a sample of adults with TLE, Hermann et al (2002) reported that those participants with onset of TLE in childhood performed significantly worse on all cognitive domains (including IQ, memory and executive functions) relative to controls and late-onset participants. The pattern and influence of age of seizure onset in children with TLE is consistent with that reported in adult studies (Jocic-Jakubi & Jovic, 2006; Mabbott & Smith, 2003), whereby earlier age of onset has a greater negative impact on cognition (Schoenfeld, et al., 1999).

However, in two separate studies investigating the impact of seizure variables in adults with FLE, Upton and Thompson (1997a, 1997b), report no general systematic effect of age of seizure onset or seizure duration, but rather report that seizure duration may come into play only during execution on specific tasks, such as motor performance tasks.

In children with FLE however, the impact of age of onset is more consistently reported (Hoie, Myletun, Waaler, Skeidsvoll, & Sommerfelt, 2006; Holmes, 1991), suggesting that epileptic activity within the frontal cortices has a more diffuse effect on frontal tasks when age of onset is earlier (Riva, et al., 2002). Luton, Burns, and DeFillips (2010) report that children with FLE with seizure onset prior to 7 years displayed a greater number executive difficulties than those with onset after the age of 7.

4.5.2 Seizure duration and frequency

Findings from clinical research studies show variable effects of “duration of epilepsy” or “seizure frequency” (Dodrill & Matthews, 1992; Strauss, et al., 1995) on cognition. In a study exploring the influence of seizure-variables on memory impairment in adults with TLE Hendriks et al (2004) report that seizure frequency was the only factor that impaired performance on the Attention and Concentration index of the Wechsler Memory Scale – Revised. These authors report that “years of seizures” also influenced performance on memory tasks, though this was mediated by education level. Overall however, the impact of seizure frequency and seizure duration were not as profound when other variables were considered, and thus the authors argue that these variables are better considered to characterise the severity of epilepsy, rather than a single contributing factor per se.

The contribution of these factors in children has not been consistently investigated. Nolan and colleagues (2004) report that duration of epilepsy was significantly correlated with age of onset and therefore was not included as a predictor of cognitive performance. In a separate study Nolan et al (2004) report that duration of active epilepsy was significantly associated with memory performance in both visual and verbal domains in children with TLE, FLE and Generalised Epilepsy.

Smith, Elliot and Lach (2002) report that seizure frequency had an impact on IQ, Reading Comprehension and Arithmetic performance, where specifically IQ was higher for those children reported to have clusters of seizures rather than daily or weekly seizures. Nolan et al (2004) indicate that the occurrence of daily seizures in children with various epilepsy syndromes (including TLE, FLE, generalized and partial epilepsies) had a negative impact on IQ. Overall these seizure variables plus age of onset and number of medications collectively accounted for 26% of the variance in full-scale IQ, suggesting a strong relationship between seizures and cognitive variables. Riva, Saletti and colleagues (2002) reported that the frequency of seizures was associated with inattention and disinhibition, although the authors did not examine memory function. However in a follow-up study conducted in 2005, the authors did not find that seizure frequency influenced executive functioning. Other authors have also failed to support a relationship between seizure frequency and cognition (McDonald, et al., 2005). Collectively these studies highlight the lack of uniformity in how frequency is reported.

These factors are likely to be confounded due to the variable nature of the epilepsy within and between syndromes. Often operationalized as time from diagnosis to assessment, duration of disorder does not account for the nature or pattern of seizure activity. Harvey and colleagues (1997) illustrated in their prospective community based study of children with TLE, that the severity of seizures, associated complications, and behavioural manifestations is varied relative to surgical studies. Thus no studies explore the impact of duration of epilepsy of seizure frequency in children with well-controlled compared with treatment resistant epilepsy, and therefore interpretations as to the precise effect they exert should be made with caution.

It is important to note that our current knowledge of epilepsy has been well informed by studies employing populations with refractory epilepsy or surgical candidates. One of the issues with this is the inherent bias in our collective knowledge, and therefore controlling for the frequency of seizures and duration of epilepsy in cases of well controlled epilepsy is an important endeavour.

Second, frontal lobe seizures tend to occur in clusters with greater periods of seizure freedom between clusters than the patterns observed in TLE (Riggio et al 1995). Seizures that occur in clusters are lower in duration (relative to those that occur weekly or daily) though are occurring within a shorter time span (Lawson, et al., 2002). Therefore the frequency of seizures, when used as an average over a

short time span (i.e. within the last 90 days) is unlikely to represent a true account of the effect of seizure frequency. The impact of these variables is also confounded by methodological differences in classification which thus renders interpretation of findings difficult.

4.5.3 Medication

Bourgeois et al (1983), indicate that the best predictors of intellectual decline are both age of onset and number of medications. The relationship between medication use and cognitive decline is a contentious issue (Chaix, et al., 2006; O'Leary, et al., 2006). Given that no causal or directional relationship can be hypothesized, based on the likelihood that children with a higher seizure frequency, severity, and earlier age of onset, are likely to be receiving a higher dose, or longer course of treatment with multiple anti-epileptic medications. Awareness that anti-epileptic medications may produce a negative effect on functioning, has led to vast research (Bootsma et al., 2006) that has significantly guided clinical practice, though the precise pattern of influence remains to be elucidated (Hernandez, et al., 2003).

Medication regimes often necessitate employment of only one (monotherapy) or two antiepileptic drugs (AED), with more than two (polytherapy) being rare. Monotherapy decreases the chance of adverse or drug interaction effects. Antiepileptic drugs function to either control the initiation of the seizure, the maintenance of the electrical discharge or the possible spread to other cortical or contralateral regions (Rogawski & Porter, 1990). A review of the

AED literature is beyond the scope of this review, however of particular relevance from these studies is the recommendation that use of medication (including type, dose and number) is important in the investigation of epilepsy (Dodrill & Matthews, 1992; Hoie et al.2006).

In summary, the significant limitation of the collective of published studies is that variations in a) operationalization of seizure variables b) delineation of epilepsy syndromes, and c) statistical analysis of contribution of seizure factors makes interpretation and generalizability of findings difficult. To date research has mainly focused on refractory or surgical cases of epilepsy. The limitations of this are that children with well-controlled epilepsy comprise a large portion of the overall population of children with epilepsy. Thus it remains to be seen how well-controlled epilepsy impacts memory in the developing brain, and how this further impacts daily functioning? The scant literature that has explored well-controlled, non-surgical cases reflects a less severe profile of difficulties (Williams, et al., 2001), relative to refractory or surgical series (Fish, Smith, Quesney, Andermann, & Rasmussen, 1993; M. L. Smith, et al., 2002), that may or may not include children with demonstrable lesions. Non-surgical cases perhaps afford a purer look at brain-behaviour relationships without the secondary effects of refractory seizures. Therefore an obvious question is how does epilepsy impact a child"s cognitive and functional development if, as inherent by "well-controlled", seizures are not as high in frequency, or responsive to medication?

CHAPTER 5: IMPLICATIONS OF IMPAIRED MEMORY IN EPILEPSY

These are important questions that need addressing given that parents and children with epilepsy face the burden of understanding the possible limitations the disease may impose for educational, vocational, or social functioning. One of the foundations of the Scientist-Practitioner model of practice is to assess and implement clinical practice strategies based on empirical evidence. Although simplistic, currently the clinician's armamentarium lacks significant evidence to answer these questions beyond generic considerations of a child's entitlement to memory or executive functioning deficits based on diagnosis of TLE or FLE respectively.

For the clinician assessing a child, working memory is a critical skill for the developing child and should encompass the cornerstone of neuropsychological assessment, given the purported significance of working memory in the attainment of academic skills, and this constituting one of the main goals of childhood (Gathercole & Alloway, 2004; Gathercole, Lamont, & Alloway, 2006). WM deficits can occur even in the context of average intellectual functioning (Hood & Rankin, 2005). Therefore the child with working memory impairments may go unnoticed relative to those that express more generalized cognitive difficulties. This is important given that impaired intellectual functioning is not a hallmark feature of the symptomatic epilepsies, and this patient population still expresses academic difficulties relative to their same-age peers (Aldenkamp, Overweg-Plandsoen, & Diepman, 1999).

This review has also highlighted that WM is most likely a multi-component system that encompasses both storage and rehearsal or manipulation processes. For this reason the single-score assessment used by some studies (Chaix, et al., 2006; Chieffo, et al., 2011; Hernandez, et al., 2003) to denote WM are unlikely to truly capture its systemic nature. The need to employ a variety of measures is indicated by the research collective that reflect the differentiation of the various processes neuroanatomically, and from a cognitive perspective. The multi-component working memory model of Baddeley (1986) is one of the few models of working memory function that provides means to investigate the specific nature of WM impairments, and whether they are associated with a storage deficit or more complex manipulation component. The literature examining the association between specific working memory model sub-processes and academic skill attainment is extensive in typically developing children (see Hood & Rankin, 2005, for review).

For example verbal learning, reading, speaking and listening skills have been implicated in phonological loop functioning (Alloway et al., 2005; A Baddeley, Gathercole, & Papagno, 1998; Gathercole, Tiffany, et al., 2004; Hood & Rankin, 2005; Service & Turpeinen, 2001). A. Baddeley et al., (1998) suggest that the primary role of the phonological loop is learning different grapheme-phoneme relationships of new words. Although the storage and rehearsal of familiar words is also a function of the loop, these authors argue that this function is secondary to the crucial role the loop plays in verbal learning. This argument is supported by Ellis and Sinclair (1996). These authors argue that the acquisition of new language requires learning sequences of words, and maintaining and consolidating those sequences in LTM, (which working memory facilitates). As the child attempts to make sense of the new "word' they rely more heavily on their working memory system to negotiate its pronunciation. In addition because of its foreign properties, rehearsal requires more effort and therefore capacities for storage may also be reduced (Alloway & Gathercole, 2005; Pickering, 2006).

Using a task that requires children to recite a narrative of a story read to them, Adams and Gathercole (1996) also demonstrated that speaking skills were significantly associated with children's ability to repeat non-words. Children with better non-word repetition performance, could reproduce more detailed aspects of the story, and expressed longer utterances than children with poor non-word repetition skills. Importantly, non-word repetition performance was more significantly associated with expressive language skills than either digit or word recall tests.

Learning to spell words places heavy demands on working memory, as the child needs to retrieve an orthographic representation of a word from long-term memory in their working memory store long enough to achieve accurate spelling (Service & Turpeinen, 2001). Working memory tasks in which the central executive may be taxed include increasing the sequence length of to be remembered items (Barnard, Scott, & May, 2001). As words increase in length, demands on working memory increase, and also involves the visuo-spatial sketchpad as it is brought on board to assist conversion of the mental image of a word into an orthographic output (Service & Turpeinen, 2001).

Investigations of functional impairments associated with poor visuo-spatial short-term memory functioning is significantly lacking (Gathercole & Alloway, 2006). Furthermore the ecological validity of studies investigating visuo-spatial short-term memory impairments are reduced, as many studies investigate only the ability of patients to remember the spatial location of grids or other meaningless non-verbal stimuli, that cannot be readily translated into real-world situations (Gathercole, 1998). Gathercole (1998) purports that one purpose of the sketchpad is the maintenance of mental imagery including the appearance and location of novel stimuli. Hood and Rankin (2005) hypothesize that children with impairments in this area may present with difficulty in learning and reproducing numbers, letters and shapes. They may also demonstrate a higher frequency of inversions or omissions when learning to read and write. Another significant difficulty, may involve poor ability to copy text from a blackboard, due to the dependence on switching visual gaze from one point to another. This may also manifest as frequently losing their place within the text when reading. Alloway, Gathercole, Adams and Willis (2005), suggest that the reason for these specific impairments may be due to poor associations between the sketchpad and central executive.

Other academic skills require integration of all sub-processes, which is especially the case with mental arithmetic, given that arithmetic is unlikely to be solely mediated by visuo-spatial memory. Arithmetic requires multiple memory systems to engage simultaneously on the task, including the central executive, phonological loop and retrieval of information from long-term memory (McLean & Hitch, 1999).

Despite the evidence linking each slave system with particular academic skills, the hierarchical structure of the multi-component model implicitly presents the argument, that if a sub-component or specific process that is assigned to the general rubric of WM fails, then the failure in some way must be attributed to the central executive or connections with the central executive, or slave systems (A. Baddeley, 2003). Therefore a comprehensive assessment of working memory, with consideration given to possible slave system impairment, will provide the most informative and valuable means of translating test performance to functional class behaviour.

5.1 The Impact of Epilepsy on Academic Achievement

The combination of epilepsy and academic underachievement is common. Almost a quarter of patients with epilepsy are reported to have learning difficulties, and whilst not epilepsy per se, almost half of children with learning difficulties are reported to have a history of seizures (Lhatoo & Sander, 2001). Children with epilepsy are more frequently impaired in their cognitive functioning, compared with the general population (Bailet & Turk, 2000; Cornaggia, Beghi, Provenzi, & Beghi, 2006; Shinnar & Pellock, 2002). This stands, even though it is generally the consensus that significant impairments in IQ are not a hallmark feature of the focal epilepsies (O'Leary, et al., 2006; Riva, et al., 2002; Shulman, 2000). The impact of focal epilepsies on academic achievement therefore is more likely to be associated with specific cognitive impairment, and not a consequence of general intellectual impairment (Chaix, et al., 2006).

Unfortunately, although teacher‟s attitudes toward epilepsy are mostly positive, their general level of knowledge regarding its possible academic impact, necessary management or appropriate intervention are less well understood (Bishop & Boag, 2006), which researchers can also assist in elucidating these relationships. By direct implication, the possibility that a particular epilepsy syndrome may differentially affect specific areas of learning would be relatively new. Therefore enhancing our understanding of the relationship between academic achievement and epilepsy syndromes, may assist the clinician in educating teachers about the particular needs of children with epilepsy.

Although over half the children diagnosed with epilepsy will experience school-associated difficulties (Beghi, et al., 2006), children with SPE generally have more specific difficulties and learning problems than children with idiopathic epilepsy (Beghi, et al., 2006; Stella & Maciel, 2004). These difficulties range on a continuum of severity, from only slight-underachievement to severe problems that may require educational aide. As indicated previously, the range of difficulties may span across many basic skills including, arithmetic, spelling, reading, writing, and comprehension.

Fastenau and colleagues (2004) investigated predictors of academic achievement in children with various epileptic syndromes (15% of their sample constituted children with SPE). Their results indicated that poor academic skills (reading, writing and arithmetic) were significantly associated with poor performance on several combined factors including verbal memory/executive, working memory and rapid naming, and psychomotor performance. Additionally, their results indicate that family structure and cohesion play a significant moderating role in the eventual academic skill attainment in children with epilepsy. In sum these results highlight that poor academic achievement in epilepsy constitutes a multi-aetiological process, including altered cognition, attention, memory and seizure related variables.

Global IQ is often implicated as a strong predictor of academic achievement, and the impact of epilepsy may be evident even in cases with recent seizure-onset (M. L. Smith, et al., 2002). Often the case in recent onset epilepsy is that the frequency of seizures is high, though not sufficiently controlled. In these cases, if the situation persists, the chronicity of frequent uncontrolled seizures will lead to lower scores on academic achievement tests (Aldenkamp, et al., 1999), arguing for a direct effect of seizures on academic function. McNelis and colleagues (2005) propose that the influence of seizure frequency on academic achievement is not likely to manifest within the first year of diagnosis, and therefore a period greater than this is required when investigating academic achievement in epilepsy. This is supported by numerous studies indicating that the difference in performance in healthy children and children with epilepsy is increasingly narrow, when seizures are controlled, and severity is low (Austin, Huberty, Huster, & Dunn, 1999; Williams, et al., 2001).

Smith, Elliot and Lach (2002) report a high degree of variability in the range of IQ scores in their paediatric sample of children with epilepsy, with 14 to 70% of children demonstrating a level of impairment greater than mild. Despite these children all attending regular school the majority received further support and assistance by means of course revision, an aide, or attendance at special classes.

Williams et al (2001) indicate that when IQ is controlled for, attention is more significantly associated with academic achievement than self-esteem, socio-economic status, seizure variables or memory. Given previous discussions, and the saliency of attentional resources in Baddeley's (1986) WM model, these findings are not surprising (M. L. Smith, Elliot, & Lach, 2006a). Any generalized pattern of inattention is likely to impair the child's ability to respond to familiar or unfamiliar environmental stimuli, maintaining focus whilst completing a task, and responding appropriately.

Hoie and colleagues (2006) investigated executive function, seizure-related factors and academic functioning in children with epilepsy of various aetiologies, and indicated that some of the variance in academic achievement evident in their study may be attributed to poor frontal lobe functioning. Furthermore, because of the nature of the impairments evident in patients with frontal lesions, this group is considered to possess a higher risk of academic failure and unemployment (Prevost, Lortie, Nguyen, Lassonde, & Carmant, 2006). This is due to the nature of their difficulties encompassing many aspects of daily living that include maintaining appointments, planning and organizational skills. In addition, given the strong argument that such frontal impairments may account for secondarily poor specific memory function, the possible influences of specific frontal and temporal lobe epilepsy syndromes requires further clarification.

Certainly temporal lobe functioning and associated memory performance have been implicated in studies of academic achievement. Helmstaedter (2001) presents data that indicates an equivalent, if not greater propensity for patients with TLE to have poor education and employment prospects, although other studies have failed to find such an association (Camfield, et al., 1984; Schoenfeld, et al., 1999). Chaix and colleagues (2006) found that reading difficulties including reading speed and comprehension were more predominantly impaired in their TLE group than either idiopathic generalized or benign childhood epilepsy groups. Independent of seizure duration, and therefore not only an effect of seizures, the onset of TLE during critical developmental periods significantly impacts clinical outcome (Glosser, Cole, French, Saykin, & Sperling, 1997).

The relationship between epilepsy in the frontal and temporal lobes is consistent with the category of learning dysfunction outlined by Aldenkamp and colleagues (1990). The "memory-deficit" type of learning dysfunction is associated with specific impairment of short-term memory and memory span, which has been previously mentioned to be implicated in frontal and temporal lobe epilepsy. The way in which seizures affect new learning may comprise many processes associated with transient, distal, or permanent effects (Binnie, Channon, & Marston, 1990). Seizures may alter attentional, processing, storage or retrieval processes as a direct result of disruption due to epileptiform activity within critical neuroanatomical regions. Alternatively consolidation may be hindered by distal discharges from regions responsible for initial encoding. Finally seizures may cause permanent neurological damage to regions critical for memory processing, such as sclerotic plaques within the hippocampus (Binnie, et al., 1990; Leonard & George, 1999). The current standing of literature is eager for a more comprehensive account of the nature and cause of academic difficulties in this population; only after achieving this can attempts at prognosis and intervention be better achieved.

5.2 Objective Ratings and the Entitlement of Complaints

Despite evidence that children with epilepsy display memory impairment, little is known as to how this transfers to everyday living skills (Kadis, Stollstorff, Elliot, Lach, & Smith, 2004). Standardized and objective memory measures provide useful indices as to the child"s learning and recall capacity relative to equivalent normally developing peers; however the variability of environmental context cannot be captured by the one-to-one controlled testing situation. An emerging focus of the paediatric literature is how objective memory impairments translate to subjective memory complaints in children. Traditionally, the research investigating the everyday implications of epilepsy has suffered from the same biases discussed with respect to the objective assessment of function. Namely, memory impairments are investigated in TLE and executive deficits are investigated in FLE. Operationally, these domains have been assessed through utility of memory questionnaires and the Behaviour Rating Inventory of Executive Function (BRIEF) respectively (Gonzalez, et al., 2005; Slick, et al., 2006).

Research with adults largely fails to demonstrate a failure of subjective ratings of memory impairment to be associated with objective performance on memory measures indicating the complexity of subjective memory complaints. Although research with adult populations exist (Corcoran & Thompson, 1993; Elixhauser, Leidy, Meador, Means, & Willian, 1999; Helmstaedter & Elger, 2000), the concept in childhood is still developing. An inherent difficulty of assessing subjective complaints in childhood is that ratings of everyday difficulties are reliant on parent or teacher reports of the child's performance. Kadis and colleagues (2004) investigated the predictors of everyday memory functioning in children with epilepsy of mixed aetiology and locality, and included indices of mood state in addition to neuropsychological tests of functioning. Their results revealed that only the parent rating of attention from the Child Behaviour Checklist (CBCL) significantly predicted both the child's own ratings of memory and the parent ratings of their child's memory. Interestingly, the objective measures of attention and working memory did not significantly predict everyday memory ratings. It is accepted that objective and subjective measures of memory share a weak to moderate relationship – this weak relationship remains whether the studies are based exclusively on children (Gonzalez et al 2008) or exclusively on adults (Helmstaedter & Elger, 2000; McGlone & Wands, 1991).

The development of everyday rating scales that are capable of assessing the myriad of sub-skills that collectively account for a cognitive system is arduous. The measure of everyday memory adopted in the study by Kadis and colleagues (2004) was adapted from the Memory Observation

Questionnaire

(MOQ), for which psychometric data are not published, rendering generalisation of their findings difficult.

Gonzalez et al (2008) offer an alternative paediatric scale of everyday memory impairment, the Observer Memory Questionnaire-Parent Form (OMQ-PF) which is completed by parents. This scale is an adaptation of the Observer Memory Questionnaire which was developed by O‟Shea (1996) in an attempt to gain validation of memory functioning from a significant other of an individual with subjective memory complaint. The OMQ-PF is reported to have sound psychometric properties, with no age or gender effects indicated. Although this scale is in its infancy, the authors propose that this scale is likely to tap new learning ability, rather than capacity to recall information. This scale therefore poses significant advantages for the assessment of memory in children, as new learning is critical for the developing child. In a sample of children with TLE, the OMQ-PF revealed significantly poorer memory in children with TLE, and was significantly associated with objective associative verbal learning and visual memory tasks. Interestingly this scale was not significantly associated with crude indices of attention or working memory in the children with TLE (Gonzalez, 2008).

Consistent with the findings reported by Gonzalez et al (2008), Smith and Vriezen (1997) revealed that children with epilepsy were rated as having significantly poorer everyday memory by their caregivers. However in the latter study objective performance on memory measures was not associated with ratings of impairment. Inconsistencies across studies can be attributed to differences in rating scales, composition of epilepsy sample, and differences in attitude by the parents.

The lack of consistent statistical evidence is not indicative of a lack of relationship between clinical and subjective scales. Rather, memory is a systemic construct that neuropsychological tests function to assess compartmentally. Rating scales in contrast, are likely to capture the application of that system as it functions as a whole, and therefore the association between a specific sub-system of the overarching theoretical construct and the application of the entire system is necessarily weaker. The question remains therefore as to whether a demonstrable association between subjective and objective ratings is critical to understanding the experience of epilepsy. Pursuing this line of reasoning will hinder our understanding of the phenomenological experience of this disorder, as failing to demonstrate an association between subjective and objective ratings does not nullify the patient"s subjective complaint. Therefore a related endeavour that may prove more fruitful for understanding the impact of epilepsy should be to additionally consider what seizure factors predict subjective ratings of impairment. In adults, subjective memory ratings are more strongly related to seizure variables and mood than objective memory performance (Elixhauser, et al., 1999; Giovagnoli, Mascheroni, & Avanzini, 1997), though it remains to be seen if these same factors are at play in children. Furthermore, Slick and colleagues (2006) also make reference to the need to investigate subjective executive performance in the domain of frontal versus temporal lobe epilepsy (p.187). Thus, heeding the recommendations of Slick et al, one of the aims of this research is to explore the everyday impairments in memory in these research populations by using subjective parent ratings.

CHAPTER 6: THE PRESENT STUDY

Epilepsy is not only one of the most prevalent neurological conditions of childhood; it stands out as being particularly informative for the pursuit of understanding brain function. Epilepsy encompasses numerous syndromes that share the feature of recurrent seizures, though varying in their symptom expression, underlying aetiologies and ultimately the region and extent of brain impairment (Commision on Classification and Terminology of the ILAE, 1981; ILAE, 1989). In particular the value of focal epilepsy to cognition is rooted in the pathophysiological mechanisms that allow for investigation of how an isolated dysfunctional region impairs the function of that area, when other brain regions were thought to be largely less affected. These mechanisms have therefore enticed researchers to explore brain-behaviour relationships, and mounting evidence identified and provided support for the utility of employing epilepsy as a "natural laboratory" (Snyder, 1997, p. 1) to explore cognition.

Forerunning evidence for the utility of epilepsy is arguably the relatively consistent finding of a double dissociation of executive function and memory function in adults with FLE and TLE (Exner, 2002). Such findings meant that if localised impairment can be demonstrated in the area of pathology then the temptation and incentive is to explore the specificities of localised dysfunction using numerous testing paradigms and also other neurological populations to replicate and further characterise the function of that region.

However, as discussed in this review, the questions that epilepsy has been able to answer regarding brain-behaviour relationships have resulted in a narrow focus biased by localisation of function. A parallel scope of investigation should also involve addressing how dysfunction in one area of the brain influences the function of other regions; a mechanism of nociferous cortex that is neither novel nor unwarranted (Penfield & Jasper, 1954). As reviewed, although both avenues of research, namely lobar-specific or extralobar effects of epilepsy are explored in adult populations, there remain significant gaps within the paediatric literature.

Our understanding of brain-behaviour relationships in children, and even more specifically memory functioning is relatively limited. Models of cognition in children are almost non-existent and are dependent on generalisations made from adult models, such as Mapou and Spector‟s (1995) cognitive framework, even though it is "clear that brain behaviour relationships in adults are not analogous to those observed in children" (Peter Anderson, Anderson, & Garth, 2001, p. 82).

Thus, despite the significant gains and contributions that the study of epilepsy has provided to cognitive science, this review has highlighted that key questions remain unanswered. Most of these questions lie at the interface between the cognitive and neuroanatomical literatures of childhood, in which theories of development, cognition and localisation of function are not yet well married. Therefore without a coherent framework in which to test hypotheses, childhood-epilepsy research remains largely unfocused.

One of the most significant shortcomings within the paediatric literature is scant consideration of the systemic nature of memory processing. Restrictions to statistical analysis imposed by small sample sizes have meant an over-reliance on end point scores to characterise memory impairment profiles in epilepsy. Even though an inevitable shortcoming in clinical research is small sample size, the failure of those paediatric studies exploring memory function to adopt more than long-term memory function measures hinders the ability to understand memory system functioning.

Specifically, the research collective to date significantly lacks consideration of working memory deficits in this population, even though epilepsy has formed the cornerstone of information for more long-term memory functioning (Saling, 2009). The failure to explore working memory in an epilepsy context, and particularly in children, is surprising. Theories of academic development and skill acquisition place working memory on a pedestal of importance, with spelling, reading, and math all demonstrated to be associated with working memory function (Gathercole, et al., 2006).

In particular, the investigation of working memory in neurotypically developing children is robust using the Baddeley Working Memory model (1986) and accordingly consequences of impairment in either short term storage or complex memory span processing are established (Hood & Rankin, 2005). However, the distinction between the subcomponents of working memory as a whole is largely ignored in clinical populations. In order to address the shortfalls in the literature studies need to begin to explore and consider the difference between storage capacity and complex processing of the information held in storage, as this review has highlighted that capacity limitations can hinder the ability of further complex memory processing. This opportunity is offered only through utility and reliance on models of working memory that can account for the nature of processing. If this notion is extended and consideration given to the functional neuroanatomical correlates associated with working memory sub-components then steps toward understanding memory systems beyond boxes and flow charts, can finally be achieved.

However, such an approach has been less consistently investigated in atypically developing children, and therefore understanding the influence of cerebral dysfunction to these models of academic development is lacking. Specifically, if one takes the argument that working memory is localised to the frontal lobes, and dysfunction within the frontal lobes causes working memory impairment, then the extending argument that frontal lobe impairment would result in academic skill impairment may hold. Certainly this question is enough to initiate several research papers however the pursuit of such line of reasoning does not often consider the systemic nature of memory. An alternate consideration should wholly address whether academic achievement is more impaired following impairment to working memory or long term memory?

The interface of all these variables and constructs are displayed pictorially in the figure below. It is the aim of this study to address not only each of the constructs independently in each of the epilepsy groups of FLE and TLE, but then to examine how working memory and long-term memory are associated in each of the groups.

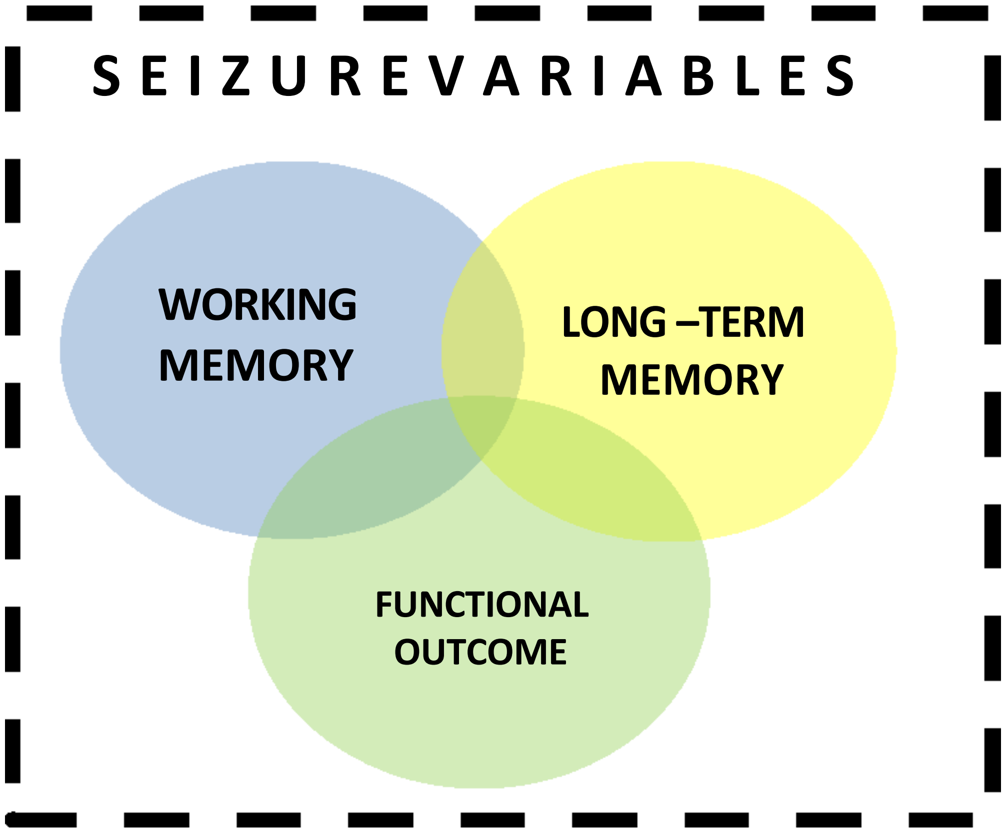

Figure 6.1. Pictorial representation of cognitive memory constructs

Initially epilepsy impairment will be analysed and discussed, which will follow with a consideration of the consistency between purported models of memory functioning and actual relationships between memory processes. Taken from a hierarchical model of information flow, the first stage of mnemonic processing is short-term storage. The multiple component model (Baddeley, 1986) arguably provides the most comprehensive account of the initial stages of working memory, or short term storage, with special attention given to verbal and visual immediate processing. These are critical skills, as at the most elementary level our capacity to retain a given amount of information is inextricably linked to how much information can be processed at a given time (A. Baddeley, 2006). Thus it is important to investigate the capacity of information processing in order clarify whether any working memory impairments were associated with a reduced capacity or a genuine inability to manipulate and hold the information in mind. The evidence of efficient working memory is expected to be reflected in efficient long-term memory by means of error-free learning, and age-appropriate use of semantic clustering.

Given the purported importance of working memory to various school-based skills, the final stage of memory processing is deemed to be reflected in level of academic proficiency relative to age expectation. The following sections will discuss these expected patterns of impairment in children with FLE and TLE separately, before considering the predictive strength of working memory and its role in subsequent memory and cognitive processing.

Thus, a focus of this study is to inform cognitive function models, as such models are well described within the adult literature (Mapou & Spector, 1995), however with few exceptions (Dennis, 1989), models of cognition in children are lacking. Inferring a deficit or impairment in a child's cognitive skills by using an adult model of expected function is erroneous in that it does not pay reverence to the fact that the child's brain is undergoing development. Thus, what would be considered impairment in adulthood may reflect a delay of development in childhood Cohen (1992).

However, due to limited previous literature exploring working memory in paediatric populations with epilepsy, guidance as to appropriate test employment is restricted. Studies with working memory indices rely heavily on digit span tasks, though this review has highlighted that digit span (as a composite), or digit span backward alone is unlikely to capture the complexities within working memory, and across modalities. This is certainly true if Baddeley's (1986) working memory model is adopted as an explanatory heuristic.

Fortunately, Pickering and Gathercole (2001) have developed a test battery of working memory specifically for children, using many of the basic paradigms that were used to construct the initial three-component model proposed by Baddeley (1986). To the author's knowledge this study is the first to attempt an investigation of working memory, using a battery of tests purported to assess all facets of working memory in children with epilepsy. In addition the utility of these tests which were developed in synergy with the cognitive model of working memory provides a valuable heuristic to explore the sequence of mnemonic processing. Given that current models of memory functioning are largely based on the adult literature (Squire, et al., 1993), and comprehensive studies of working memory in children are restricted to normally developing populations (de Jong & de Jong, 1996; Gathercole & Baddeley, 1990; Gathercole & Pickering, 2000; Schouten, et al., 2002; Swanson, 1996), it remains to be seen whether similar patterns of processing are evident in neurologically dysfunctional children. Thus the impetus for test selection was to allow better characterisation of the nature of memory difficulties in children with epilepsy from a system perspective, so as to ultimately inform cognitive models in children and clinical practice.

This study is also unique in its selection of children from early primary to secondary school. This wide age-range may promote understanding of the critical periods of development of memory functioning and how they translate into functional deficits. In addition the tests employed in the current protocol are used widely in clinical practice in Australia, and have substantial and well-validated normative data to achieve accurate comparison of functioning. Importantly the tests utilised, in particular those assessing working memory, were developed for use with children, which increases their clinical utility and the inferences that may be drawn from performance.

The selection of children with well-controlled epilepsy has also garnered limited attention from the literature, even though this population are continuously referred for review and management of any cognitive difficulties that may arise. Review neuropsychological assessments are a critical component of a child"s management of their epilepsy, as prognosticating future difficulties during early childhood when seizures most often arise is difficult due to on-going brain maturation.

Finally, the current research design departs from other research schemes in that it aims to not only investigate the nature of impairment but also the relationships between memory variables. This is considered a critical and valuable approach that offers a theoretical context in which to discuss memory impairments. For example, as highlighted by Gathercole (1998) and Gathercole and colleagues (2004), the interdependence of sub-components of the working memory model vary throughout development, where an initial stronger relationship between slave systems is evident that then weakens as the overall system matures and dependence on the central executive becomes strengthened. Such investigations, which are limited and based largely on correlational analyses, have not yet been considered in a clinical population which offers the opportunity to investigate maturity of the system when regions associated with that system are compromised.

Thus, several assumptions are fundamental to this study. First, there is a distinction between span/storage and central executive, that collectively and not in isolation encompasses working memory. Because of the methodological inconsistencies in considering span synonymous with working memory, the point is made that this study describes span as distinct from working memory, which is considered to encompass both span and complex processing of span, the latter being central executive type skills. Second, that the neuroanatomical correlates of span versus central executive skills are distinct, and the latter being associated with frontal lobe functioning (Henson, 2001).

To address these theoretical issues this study will remain rigid in its separation of FLE and TLE groups. Some studies "lump" together epilepsy groups based on whether seizures are focal or generalised (Hoie et al. 2006). However doing so belies the opportunity to extend schematics of boxes and flow charts to a more neurologically integrated model of function. Support for this approach is evident within the literature discussing the best way to utilise epilepsy in research, which has generated the terms "lumpers" versus "splitters"(Berkovic, Reutens, Andermann, & Andermann, 1994, p. 25). Lumpers emphasise that epilepsy patients do not necessarily fit into well demarcated categories and that an attempt to do so is inappropriate and does not contribute to addressing the overarching research questions. Splitters in contrast argue that distinguishing groups based on syndromes allows for more targeted research, and provides prognosticating value for the clinician (Berkovic, et al., 1994). Extending this, splitting the groups is a necessary means to expand cognitive modelling which for children remain largely in boxes.

6.1. Aims

The overall aim of this is to attempt a first step of characterising memory functioning in epilepsy from a system perspective, in school-aged children with FLE and TLE. Broadly, this was to be achieved by investigating not only the group deviations on end-point measures, but also to examine the relationships between cognitive memory constructs.

Specifically, several research questions were considered:

1. Are there measurable differences in WM and LTM that differentiate children with FLE and TLE syndromes and normally developing children?
2. What is the degree of relationship, and thus influence of each of the memory variables, and does this differ between the groups?
3. How are observed deficits in WM and LTM associated with academic achievement in children with FLE and TLE?
4. How do seizure variables influence memory systems?
5. What are the reliable predictors of parent ratings of everyday memory functioning?

6.2. Hypotheses

Part I: Profiles of Memory Impairment in Epilepsy

Based on the literature reviewed it is the expectation that:

- Children with epilepsy will demonstrate significantly negative deviations in *all* objective measures and indices of memory functioning, including working memory, LTM, semantic clustering and error performance.

However, in light of the purported models of functional localisation and interconnectivity of the cerebral hemispheres, several other key hypotheses are proposed.

A. It is expected that children with epilepsy will demonstrate reduced short term storage capacities, relative to normative standards. These impairments will be evident across both verbal and non-verbal span measures.

B. Children with FLE will demonstrate greater impairments in tasks that measure purported central executive skills relative to children with TLE.

C. In contrast, children with TLE will demonstrate greater impairments on long-term delayed verbal and non-verbal memory measures relative to children with FLE.

D. It is hypothesised that children with FLE will demonstrate more significant impairments in their ability to use strategies to enhance their learning than children with TLE.

E. It is also expected that children with FLE will demonstrate more significant errors in their verbal learning, as indicated by the number of intrusions, repetitions and false-positive errors relative to children with TLE

Part II: Investigating the Memory System in Epilepsy: Associations Between Memory Subcomponents

Expectations regarding the directions of impairment and relationships were guided largely by the established models of memory functioning in normal children, and where appropriate by those epilepsy studies that specifically addressed memory functioning in these populations. Thus, several outcomes were expected

A. Significant correlations between the central executive and each of the slave systems will be evident; though no significant correlations between the slave systems will be displayed in children with epilepsy.
B. That central executive performance will be the strongest predictor of long-term verbal and visual recall, with seizure variables and storage capacities contributing less predictive validity.

Part III: The Implications of Memory Impairment on Related Functions in Epilepsy

6.1.3.1 Academic Functioning

A. It is hypothesised that children with TLE and FLE will demonstrate impairments in their academic skills relative to normative standards.
B. It is also hypothesised that working memory performance will be the most significant predictor of academic performance in key skill areas (such as spelling, reading, and math) over and above short-term storage/span, other memory, or seizure variables in both children with FLE and TLE.

6.1.3.2 Parent Reports of Memory and Everyday Functional Skills

A. It is hypothesised that children with epilepsy will demonstrate significantly negative ratings of memory functioning relative to normative standards.

The impact of seizures on children's daily functioning is likely to be associated with parents' and caregivers' perception of severity of their child's epilepsy, and their perspective is likely to differ from that offered by conclusions drawn from performance on objective measures of memory tasks, and thus it is hypothesised that:

B. Parent ratings of memory functioning will be significantly predicted by number of medications, frequency of seizures and age of seizure onset, and not objective performance on memory measures

CHAPTER 7: METHOD

7.1 Participants

Participants comprised 39 children and adolescents aged between 6.5 and 16.8 years with an established diagnosis of FLE (*n*=18) and TLE (*n*=21). Children were recruited from the Royal Children's Hospital, Melbourne (RCH), Australia, and in all cases the child's treating neurologist confirmed the diagnosis of Symptomatic Partial Epilepsy (SPE), based on clinical evidence of unilateral focal seizure onset within either the frontal or temporal lobes. As part of their care/treatment at RCH, all children underwent diagnostic evaluation that included electroencephalogram (EEG) monitoring and Magnetic Resonance Imaging (MRI), which additionally functioned to confirm their diagnosis and seizure origin. Some, though not all children, additionally underwent Video-EEG, functional MRI, or Single Photon Emission Computed Tomography (SPECT) to assist in the classification of their seizure disorder and/or treatment plan. The presence of an epileptogenic lesion on MRI was not considered essential to address the research questions, and therefore children with non-lesional frontal (*I*=7) or temporal lobe epilepsy (*I*=12) were also included. The severity of the seizure disorder was not a marker for exclusion except where the child was incapable of participating in the cognitive assessment, such as in the case of post-ictal confusion. Similarly, no restrictions with respect to seizure frequency, or age of onset were applied, though will be controlled for in statistical analyses where significant differences between groups are evident. This resulted in a cohort of well-controlled and non-surgical sample of children.

7.1.1 Exclusion criteria

Given the underlying premise of this study was to explore the impact of different focal seizure onset regions on memory functioning, children with seizures originating from within the frontal-temporal inter-lobar junction were excluded. Exclusion of children with idiopathic focal seizures was upheld due to the likelihood that those with idiopathic seizures would introduce further confounding effects associated with aetiology and varying underlying neuropathology. Children with a history of non-epilepsy related neurological syndromes or injuries (e.g traumatic brain injury or cerebral palsy) were also excluded, as were children with significant behavioural disturbances and pervasive developmental disorders. In addition, children with a moderate intellectual disability (IQ<70) were deemed unsuitable, as an IQ score within this range has been suggested to confound results due to the more likely expression of generalized deficits across a range of cognitive domains rather than a specific memory problem per se. All participants and at least one of the primary-caregivers were proficient in English due to the demands of the child rating scales employed.

7.1.2 Demographic and seizure characteristics of the sample

Demographic and seizure variables were recorded for all participants in order to assess the relationship to cognitive function, or to account and control for possible group differences on the said variables in subsequent analyses of memory function. Specifically, demographic variables of interest were age, gender SES, and IQ, and means for each epilepsy group are presented in i(Psychological Corporation, 1999)n Table 7.1.

Table 7.1

Demographic Characteristics of the sample

	Epilepsy Group	
	FLE	**TLE**
	n = 18	n = 21
Age at assessment (years)	12.21 (2.78)	11.55 (3.33)
SES†	51.94 (24.06)	58.76 (24.37)
Males	11	9
IQ*	102.92 (13.32)	97.1414.53)

† As measured by the Australian Socioeconomic Status Index (Commonwealth of Australia, 2009)
* As measured by WASI (Psychological Corporation, 1999)

Children with FLE and TLE were matched on all of the demographic variables investigated. Specifically, as indicated in Table 7.1, children did not differ according to age, t (37) = 0.66, *p* = .51; SES, *t* (37) = -0.88, *p* = .39; IQ, *t* (33) = 1.19, *p* = .24; or gender, □^{2}= .1.30 (1, *I*=39). Clinical epilepsy variables

are displayed in Table 7.2, and full clinical details for each participant are provided in Appendix 1.

Table 7.2

Clinical epilepsy variables

	Epilepsy Group	
	FLE n = 18	**TLE** n = 21
Laterality (R:L)	10:8	10:11
Lesion (Y:N)	11:7	9:12
Age of seizure onset (years)	6.55 (3.29)	7.49 (3.82)

Children in the groups were also matched on seizure variables, and did not statistically differ in the number of right hemisphere cases □^{2}=.24 (1, *I*=39), or the presence of a lesion □^{2}=1.29 (1, *I*=39). As displayed in Table 7.2, children with TLE and FLE did not differ in age of seizure onset, t (34) = -1.25, p = .22. Three measures of seizure frequency were employed to capture this complex variable, peak and current seizure frequency, and period since last seizure. Both peak seizure frequency and current seizure frequency were determined via parent interview and review of the participant's medical file. Peak and current seizure frequency was categorised on an inverse ordinal scale where: 1 = daily; 2 = weekly; 3 = monthly; and 4 = less than one a month. Finally, the child's most recent seizure(s) were recorded (in months), in order to capture a more sensitive measure of their current seizure activity. On average children with FLE had not reported having a seizure for approximately 8 months, compared with approximately 4 months for children with TLE. Table 7.3 presents the seizure frequency characteristics of the study sample.

Table 7.3

Seizure characteristics of the sample

	Peak Seizure Frequency		Current Seizure Frequency	
	FLE n=18	TLE n=21	FLE n=18	TLE n=21
1. daily	13	8	4	2
2. weekly	3	3	0	5
3. monthly	1	4	1	1
4. greater than monthly	1	6	13	13

As indicated in Table 7.3 the frequency of seizures from the initial peak incidence to that experienced at the time of the assessment was considerably less. Specifically, 31.6% of children with TLE were experiencing daily seizures at their peak compared with 9.5% at the time of the assessment. The majority of children with TLE in the current sample were experiencing seizures less than one a month (61.9%). Similarly at its peak frequency 85.7% children with FLE reported experiencing daily seizures compared with 22.2% at the time of the assessment. Reductions in seizure frequency may be attributed to effective treatment with antiepileptic drugs (AEDs), and medication use and the frequency of polytherapy is presented in Table 7.4

Table 7.4

Number of anticonvulsant medications used at time of assessment

	FLE *n*=18			TLE *n*=21		
No. of anticonvulsants	1	2	3	1	2	3
n =	6	8	4	14	7	0

At the time of the assessment, 14 children with TLE were on a monotherapy anticonvulsant, 7 children were on two anticonvulsants and none of the children were on more than two anticonvulsants. In contrast, 3 of the children with FLE were on ore 3 anticonvulsants, 8 were prescribed two, and 6 were on monotherapy. The most commonly prescribed AEDs were carbamazepine (22.4%), oxcarbazepine (22.34%) and sodium valproate (17.2%). Other medications included Lamotrigine (12.0%), Levetiracetam (10.3%), Clobazam (6.8%), Topiramate (3.4%), Sulthiame (3.4%) and phenytoin (1.7%). All seizure characteristics of the individual participants are presented in the Appendix 1.

7.2 Measures

Given the study aims were to assess the impact of focal seizures on working memory, LTM and subsequently academic achievement, measurement of these domains formed the protocol framework of the neuropsychological tasks employed. All tests were standardised clinical measures developed for use with children aged six to16. The exception to this was the working memory tests which provided normative data for children up to the age of 15:9 months. Personal correspondence with one of principle test developers Gathercole (June, 2009), indicated that due to the peak in working memory development between the age of 14-15 years, the test would be suitable for children aged 16 years, using normative ranges for 15 year olds. These normative ranges were therefore applied to three cases that were above 15:9 months, Table 7.5 provides a summary of the tests, and variables selected to measure the specific aspect of memory. The framework was supplemented by a clinical interview that was necessary to gain information regarding seizure frequency (Refer to Appendix 1), in addition to parent memory ratings of their child‟s everyday memory.

7.2.1 Socioeconomic status (SES)

Socio-economic status (SES) was classified using the Australian and New Zealand Standard Classification of Occupations (ANZSCO) – First edition, (revision 1) (Commonwealth of Australia, 2009). This reference document is an official occupation-classification system based on data from the most recent Australian Bureau of Statistics census 2006 data. The classification system takes into account the range of complexity of skills necessary for various occupations (education, formal training etc) and is applicable to part-time, full-time, men, women, employees and the self-employed. For the purpose of obtaining a status score the ANZSCO codes are used in conjunction with the classification-to-score conversion system outlined within the Australian Socioeconomic Index 2006 (AUSEI06). The AUSEI06 is a continuous measure ranging from 0 (to denote low status) to 100 (highest ranked status). This measure was derived from parent occupations, and when both parent's occupational ranking were available, the higher ranking was used as the indicator of SES.

7.2.2. Wechsler Abbreviated Scale of Intelligence (WASI) (Psychological Corporation, 1999)

IQ was screened in the current study only to illustrate that the epilepsy groups displayed age appropriate general abilities, as more detailed intellectual assessment was beyond the scope of this research. The WASI, 2-test form was used to gain a brief screen of children's intellectual functioning, which includes the Vocabulary and Matrix Reasoning subtests, from which the Full Scale IQ:2 test (FSIQ-2) standard score was utilised. The two subtests were administered according to standardised instructions, and are reported to have sound psychometric properties, with reliability coefficients ranging from .86 to .96 in the children's sample (reference the manual). Thirteen children had undergone neuropsychological assessment which included an IQ assessment within the past 12 months as part of their management and treatment, and in these instances consent was received to access assessment results. In all of these clinical cases the Wechsler Intelligence Scale for Children- 4^{th} edition (WISC-4) was employed, and from this, the reported FSIQ standard scores were used. WISC-4 FSIQ score correlations with the WASI FSIQ-2 scores reveal excellent convergent validity (r=0.83).

7.2.3. Working Memory Test Battery-Children (WMTB-C) (Pickering & Gathercole, 2001).

This more recently developed measure of working memory is based on the theoretical conceptualisation of the multicomponential working memory model (A. Baddeley, 1986; A. Baddeley & Hitch, 1974; Gathercole & Pickering, 2000) outlined in Chapter 2. To the authors knowledge this test has not been investigated in paediatric populations with epilepsy, or other clinical samples, and rather has been used extensively with normally developing healthy children (Gathercole, Pickering, Ambridge, et al., 2004; O'Connor, Spencer, & Patton, 2003). This battery includes many of the basic paradigms that were used to construct the initial model, and is designed to reflect the three-component structure of Baddeley"s (1986) Working Memory Model, excluding the episodic buffer which is a newly developed construct. Specifically the nine subtests correspond to each of the theoretical components of the model. Listening Recall, Counting Recall, and Backwards Digit Recall provide a measure of the Central Executive. Digit Recall, Word List Matching, Word List Recall, and Non-Word List Recall indicate Phonological Loop function. Finally the Block Recall and Mazes Memory subtests are used as a measure of the Visuo-Spatial Sketchpad (please refer to Appendix 2 for full description of subtests). All tasks were administered in accordance with the standard instructions provided within the manual.

Psychometric properties of this scale reflect sound reliability and validity, and are outlined within the administration manual. Specifically, test-retest reliability coefficients for each of the subtests range from .45 to .82. Factor analysis applied to different age bands of the normative sample indicated support for a three factor model consistent with the Phonological Loop, Visuo-Spatial Sketchpad and Central Executive, thus reflecting very high internal validity of the overall battery. Analyses also demonstrated that with increasing age, variations in the relationships between each factor differed. Specifically, the association between the Phonologcal Loop and Visuo-Spatial Sketchpad declined in the older age groups, and the Central Executive became more highly associated the Phonological Loop functions. External validity was established by investigating the association between the WMTB-C subtests and various standardised measures of attainment, and reflected sound external validity.

As the current research objectives relate to the three components of the multi-component working memory model, only the composite scores for both slave-system indexes will be reported. However, given the paramount importance of the Central Executive, individual subtest performance in addition to the overall Central Executive standardised score will be reported. This was done to acknowledge that whilst composite scores provide an overall representation of a skill-set, meaningful information may be lost.

7.2.4. California Verbal Learning Test – Child Version (Delis, Kramer, Kaplan, & Ober, 1994).

The CVLT-C measures verbal learning and memory using a multiple trial list-learning paradigm within the context of an everyday memory task, a shopping list. A significant advantage of using this test is that it provides both a measure of memory ability and also indicates whether the children adopted a strategy to remember the items. In this way its utility in examining the purported frontal lobe functioning contributes to the organization of memory, and how this interacts with retrieval processes from long-term memory (Stuss & Levine, 2002). As highlighted by Stuss and Levine (2002), the CVLT-C is a measure designed more specifically at tapping into the organizational aspects of memory. This test provides an indication of general verbal learning, learning efficiency, interference or perseverative errors, and strategy utilization. Strategies may involve subjective organization (reporting same words together over multiple trials) or relaying semantically similar words together over successive trials (Gershberg & Shimamura, 1995). Thus where the CVLT test departs from other well-established tests of list learning is its ability to tap whether the participant is utilizing semantic clustering, or organization skills to aid memory processing. Therefore this index of semantic clustering provides a useful means of assessing the interface between frontal and temporal lobe functioning. In addition the development of a children"s version of this test, which is normed for use with children from six to 16 years of age increases the utility of this test in a variety of populations (Griffiths et al., 2006).

The test overall demonstrates a strong degree of internal consistency with an average alpha reliability coefficient of .85. Test-retest reliability coefficients were within expected levels, ranging from .59 to .90 for the entire sample on the Long Delay Free Recall score. Using factor analysis, the test developers also assessed the construct validity of the overall task, and indicated a similar factor structure to the adult version of the CVLT-C, with each cluster representing the experimental construct they were designed to measure.

The CVLT-C involves five learning trials, where the child is presented a list of 15 items to remember, each belonging to one of three categories: *things to wear*, *things to play with*, and *fruits* which are collectively termed the hypothetical “Monday” shopping list (List A). An interference list of 15 words is then presented to the child immediately following presentation of the fifth target list trial, which is described as the “Tuesday” shopping list (List B), which also has semantic categories. This Tuesday list is then followed by a short-delay free recall trial and a cued-recall trial, where the child is prompted with the category and is required to recall all items within that category (i.e. things to wear?). The CVLTC utilizes a 20minute delay before the long-delay free and cued-recall tasks, and recognition of Monday list items are administered.

All raw scores will be inputted into the CVLT-C computer scoring software, which generates 27 key variables reported as z-scores, which give a detailed summary of the child‟s strengths and weakness in verbal learning and memory. Only those pertinent to the research questions will be adopted in the current study, and are outlined at the end of this section.

7.2.5. Rey Complex Figure Test (Rey, 1941, 1964).

A widely used cognitive task with a visual memory component is the Rey Complex Figure Test (RCFT). This test has demonstrated differences in different epilepsy syndromes, and given that accurate performance is heavily dependent on frontal lobe functioning, children with FLE often perform more poorly than children with TLE (Hernandez, et al., 2003).

Various administration procedures are available for this task (Baron, 2004), though the method adopted in the present study provides the opportunity to examine the organizational approach to the task, in addition to overall accuracy. Specifically, in the present study the children were required to copy the RCFT geometric design (copy trial), and then to recall it after a 30-minute interval (delayed recall trial). During the copy trial the child was presented with a piece of A4 paper in the vertical plane, with a computer drawn Rey Figure occupying approximately one-third of the paper in black ink. The child was instructed to copy the design in the space underneath to the best of their ability. To facilitate scoring of the organization of the drawing the examiner changed the colour of the pen the child used during the copy trial. The child was told that this was for the benefit of the examiner, as not an indication of erroneous performance on their behalf. Upon completion, the design was removed from the child's sight, and a delay of 30 minutes initiated. The child was then instructed to recall the design (without the initial stimulus) from memory, and the accuracy of the drawing was scored according to Taylor's (1959) criteria, and yields a maximum score of 36.

Finally, the organization of the drawing was assessed using the system developed by Anderson et al (2001). Essentially, this system offers a methodical way of scoring the child's approach to copying the design by allocating points to the order in which the child draws the 18 elements of the design. This scoring system allows grading according to seven levels of organization from 1 (no organization) to 7 (excellent).

Utilising this grading system, presents a unique opportunity to assess how incidental learning matures during childhood, and how poor initial construction of the design is associated with inefficient recall after a delay. Thus in addition to an accuracy of recall score (after a delay), a score for the child"s initial ability to organize the drawing when copying is obtained. All figures were scored by the examiner to ensure coding consistency, and normative data were adopted Meyer and Meyer (1996) from which all scores were converted to z-scores.

7.2.6. Wide Range Achievement Test, 4th Edition (WRAT-4) (Wilkinson & Robertson, 2006)

Within clinical and research settings the Wide Range Achievement Test, and its various revisions have provided a valuable measure of academic achievement in key scholastic domains, in a timely and well-validated format. In addition to the Word Reading, Spelling and Math subtests, the latest revision, the WRAT-4 also includes Sentence Comprehension, which offers the examiner a means of assessing comprehension of ideas. All four subtests were administered and standardised scores generated. All subtests were administered in consecutive order, and all participants were supervised for the math computation subtest.

Reliability coefficients for the four subtests ranged from .89 to .93, with an excellent reliability of the Reading Composite of .95, which overall reflect more than adequate internal consistency. Inter-correlations between each of the subtests also demonstrate adequate divergent validity indicating that each subtest measures a unique academic skill. Furthermore, correlations of each of the subtests with other similar measures of academic skill, including for example the Spelling task from the Wechsler Individual Achievement Test-Second Edition with the WRAT4 spelling task, were all moderate to high supporting the external validity of the overall test. 67

7.2.7. Observer Memory Questionnaire - Parent Form (Gonzalez, 2008).

Investigating how the child experiences specific consequences of epilepsy, such as memory impairments, can significantly aid the way interventions may be targeted. Specifically, working memory constrains a wide range of everyday cognitive activities (Gathercole, 1999), and therefore it would not be unreasonable that these effects would be observable by the child themselves, teachers and their parents. Often children's performance on neuropsychological tests of memory, do not adequately capture the child's own subjective experiences of living with a “bad memory”. Therefore inclusion of an everyday memory rating scale is a useful adjunct to a neuropsychological test protocol.

The OMQ-PF is an adaptation of the Objective Memory Questionnaire developed by O'Shea (1996). It is a 27-item questionnaire used to assess parent's perceptions of their child's everyday memory functioning. Each item is rated on a 5-point Likert scale (1=never or strongly agree, and 5=always or strongly disagree) and a sum total generated. Normative data are available for children 5 - 16 years 11 months (Gonzalez et al., 2008). The original normative sample ranging from 5-16 years (*n* = 320) did not show any developmental trends on this measure as parents are asked to endorse items only if the child's difficulties exceed those expected for their chronological age. *Z*- scores will be generated for all participants on the basis of these data.

Although this scale is in a fairly early phase of development, it has demonstrated to correlate with objective memory task performance in previous studies, suggesting sensitivity to memory impairment, and good reliability (Chronbach‟s alpha (27-items=.87). A copy of this measure is provided in Appendix 3.

7.3 Summary of Variables Used in the Analyses

Utilisation of the measures outlined above yielded a comprehensive assessment battery. Given the potential number of variables, only those that were deemed to be most pertinent to the research questions were analysed. In addition to OMQ-PF total score the variables used in the present study are outlined in Table 7.5

Table 7.5

Summary of Variables used in analysis

Domain	Variable	Description of Variable
Working memory	Phonological Loop[a]	Verbal memory span.
	List A, Trial 1[b]	Immediate auditory attention
	Visuo-Spatial Sketchpad[a]	Visual memory span.
	Central Executive[a]	Indicative of capacity to hold and manipulate information
Verbal LTM	Total Words[b]	Number of words recalled over 5 trials.
	List A, LDF[b]	Implicit verbal long-term recall.
	Learning Slope[b]	Average number of new words learned across each subsequent trial of the CVLT-C List A word list.
Verbal Learning efficiency	Semantic Clustering[b]	Indicative of strategy utilisation. Involves the number of items stated consecutively from one semantic category (i.e. fruits, clothing, toys)
	Perseverations[b]	Indicative of monitoring. The number of times a child repeats a word freely within one trial
	Intrusions[b]	Indicative of ability to distinguish target items from distractors. Obtained by a frequency of non-target items stated across both free and cued recall trials
	False positives[b]	Recognition skill. Reflects the items incorrectly stated as belonging to the target list.
Visual LTM	Copy score[c]	Indicative of child's visuo-spatial copying skills
	Organization score[c]	Perceptual organization skills
	Delayed recall[c]	Implicit long-term visual memory skill
Academic Skills	Word Reading[d]	Letter and word decoding, and reflects letter identification and word recognition
	Sentence Comprehension[d]	Ability to gain meaning from sentences and to comprehend ideas through the use of "fill-in the blank" method
	Spelling[d]	Ability to decode spoken words into written format
	Math Computation[d]	Counting, solving mathematical problems of increasing difficulty

[a] As measured by the WMTB-C, [b] As measured by the CVLT-C, [c] As measured by the RCFT, [d] As measured by the WRAT-4

7.4 Procedures

Ethics approval was granted from the Human Research Ethics Committee of Monash University, and the ethics committee of the Royal Children's Hospital. Participants were recruited over a 3-year period from 2007-2009, and a parent or guardian provided written consent for their child to participate. In addition, children aged over 12 years also provided written consent for their participation. For children younger than this a general discussion outlining the nature of the assessment was carried out, and all children verbally consented to participate.

Recruitment comprised both prospective and retrospective recruitment. Through the prospective avenue of the study, potential participants were primarily identified by their child's treating neurologist. Retrospective recruitment encompassed a review of an existing hospital database that documented all children seen within the Neurology department from 2005 to 2008 for treatment of focal epilepsy.

Whether identified prospectively or retrospectively, the treating neurologist presented the possibility of participating in a research study with the child's family, and if they were agreeable a referral card was sent to the Psychology Department, RCH indicating that parents wished to have more information and had agreed to be contacted about the study. This approach resulted in a wider range of possible participants referred to the study, though only those who fulfilled the research criteria were contacted. The Student Investigator then discussed the study with a parent or guardian via telephone, and then plain language statements and consent forms were mailed to the family.

Parents/Guardians were then required to "opt in' to participate by returning the consent forms via mail. Arrangements were then made to conduct the assessment.

Each participant was assessed individually with the standard protocol of measures, outlined previously within the measures section. Assessments were primarily conducted at the RCH, though in some cases assessment was conducted in the child's home. All assessments were conducted between 9am and 2pm, and no participants were assessed after school hours to reduce the impact of fatigue on their performance. The protocol took approximately three hours to complete, and all children were provided with a rest break for 15-30 minutes. All assessments were administered in the same order: Vocabulary subtest (WASI); WMTB-C; RCFT: CVLT-C; Matrix Reasoning (WASI); Mathematical Computation; CVLTC recall; RCFT recall; and WRAT-4 (remaining subtests). Parents also completed the OMQ-PF independently whilst the child was being assessed. One child with FLE was unable to complete the Sentence Comprehension subtest of the WRAT-4 due to time constraints, and therefore n=17 for this subtest. Similarly, OMQ-PF ratings for one participant with FLE are unavailable as the questionnaire was not completed and provided by the parent.

At the completion of the assessment, parents were provided with a research neuropsychological report outlining their child's cognitive strengths and weakness, and where applicable were also provided with a list of strategies to accommodate their needs as highlighted by their performance at assessment.

7.5 Statistical Analysis

Statistical analysis was conducted with the Statistics Package for the Social Sciences (SPSS) version 17.0 for Windows. All test scores were converted to z-scores to facilitate cross-test comparison. Power Analysis reflected that with the reported sample size of each group, the resulting power is 0.7881 (critical $t(37)=1.69$) to detect a large effect size according to the classification outlined by Cohen (1992).

It is acknowledged that in order to address the hypotheses, multiple group comparisons will be made, although sample size limits the ability to control for the increased risk of Type 1 errors via Bonferroni corrections. This is a common limitation of clinical studies, and thus results should be interpreted with caution. To overcome the limitations borne by small sample size, effect sizes will be considered in addition to *t*-values and associated significance.

7.5.1 Establishment of normality

While being relatively large by clinical standards, $I=39$ is modest in statistical terms. Thus, the data obtained in the present study is constrained by limitations to those inherent in a vast majority of clinical research studies, principally being small sample size. Due to the difficulties and controversies associated with statistical test-selection for groups of small numbers, particular attention was paid to the issue of normal distribution.

The Shapiro-Wilks test of normality is reported to have very high power, however it is for this reason that it may indicate that the assumption of normality has been violated, i.e. that the sample distribution differs significantly from normal, even though this deviation is not large enough to impact the test statistic utility that depends on the assumption of normality. Parametric tests by and large are robust to violations of normal theory, as long as these violations are not extreme (Zimmerman, 1998), and most critically that the assumption of equality of variance has not been additionally violated. Zimmerman (1998) reports that nonparametric equivalents of the t and F test do not necessarily offer a fail-safe mechanism for the violation of the assumption of normality, especially when equality of variance is in question. Rather, he reports that the effectiveness of using a non-parametric equivalent to a parametric test should be based on the level of skewness or kurtosis of the individual variable. However, Joanes and Gill (1998) indicate that statistical measures of skewness and kurtosis in samples with small sample sizes can be biased and unlikely to be truly representative of the population distribution the sample was taken from.

Given these considerations, which are commonplace in clinical research with small samples, each variable was assessed for all of these factors before using the appropriate statistic. First, the Shapiro-Wilks Test was used as the alternative to the Kolmogorov-Smirnov test of normality due to the small sample size of the present study. Where violations of normality were indicated by p value less than .05, skewness and kurtosis statistics were investigated. Normal distributions are implied when the value of skewness is close to zero, with values greater than zero indicating a positive skew, and a negative skew where values are less than zero. Kurtosis refers to the shape of the distribution, with the appropriate peak being associated with the statistic reaching a value of three. SPSS automatically subtracts three from the statistic, and thus the value reported in the output is closer to zero (Tabachnick & Fidell, 2007). Thus, as a second qualifier these values were investigated for violations outside the acceptable parameters. Finally, histogram and Q-Q plot analysis of the distribution were analysed visually, and where in particular the obtained values did not deviate significantly from the expected value as indicated by the Q-Q plots, then the violation of normality was not held up and the parametric test was utilised.

This procedure revealed that initially nine variables deviated significantly from "normal' as indicated by Shapiro Wilks statistics. However, further analyses reflected that this violation was not likely to be large enough to impact the parametric test statistic on any of the variables. Where the violation of equality of variance was also evident, according to Levene's test, then the non-equality of variance statistic was reported.

7.5.2 Part I: Profiles of memory impairment in epilepsy

The primary research question of this study was whether there were measurable differences in WM and LTM that differentiate children with FLE and TLE syndromes, and normally developing children. The groups' equivalence on seizure and demographic factors was advantageous from a statistical perspective, as it allowed for group comparisons to be conducted without the necessary confounding effect of unmatched seizure and demographics influence. Thus in order to characterise the profiles of memory impairment between and within each group independent and single sample t-tests were used respectively. Epilepsy group (FLE or TLE) constituted the Independent Variable (IV) for all independent samples t-tests, and the dependent variable (DV) was the particular memory variable under investigation. The assumption of equality of variance was ensured through investigation of Levene"s test of equality of variance for each of the analyses.

7.5.3 Part II: Investigating the memory system in epilepsy: associations between memory subcomponents

The second aim of this study was to investigate memory function models in children with epilepsy. Attempts were therefore made to identify key components of the overall system that includes span, Central Executive and longterm memory. In order to present the pattern of associations and important features of the memory system, regression analyses were conducted to identify the predictive factors for verbal and visual LTM primarily, with correlational analyses conducted to supplement understanding of the relationships between memory and learning variables within the overall system. Ideally, path analysis would be a more appropriate statistical tool to address these research questions, however the restricted sample size prohibited its use.

Specifically, to test the hypothesis that significant correlations between the Central Executive and each of the slave systems would be evident; with no significant correlations between the slave systems indicated in either group, Pearson"s product moment correlations were conducted, between each of the slave-system composites and the Central Executive composite.

Second, to test the hypothesis regarding the predictive strength of working memory and seizure variables to long-term verbal and visual recall, consideration of the regression technique to employ was weighted by the overall aim of the study being to elucidate the *most* important or significant contributor to long-term learning.

Standard regression procedures will produce the highest explained variance given a set of predictors. However, the possible inclusion of predictors in the overall model even if they fail significance tests meant that the aim of the analyses was confounded. Similarly, the backward procedure will result in the highest explained variance however the possible cost of this, is the exclusion of the single greatest contributor of variance (Hair, Tatham & Black, 1998). Stepwise regression procedures are a valuable tool given the presence of several key variables of interest in normal memory functioning; however the theory is not prescriptive as to which of the independent variables will be more significant in the context of an epilepsy population. Stepwise affords the ability to assess all the combinations of the independent variables to best explain the dependent variable of interest (Argyrous, 2005). Thus given the aims of the study, stepwise regression procedures were utilised, which provide an additional advantage of eliminating the dangers of singularity and multicollinearity (Argyrous, 2005; Hair Jr, Anderson, Tatham, & Black, 1998; Tabachnick & Fidell, 2007).

All assumptions underpinning multiple regression were analysed. Analysis of residual scatter plots revealed a) normal distribution of residuals, b) a linear relationship with the dependent variable, and c) equal variances of the predicted scores. Intercorrelations between all variables selected to enter the regression, and the predicted factor were also analysed to ensure multicollinearity or singularity effects. With respect to ratio of cases to IV criteria for regression, it is acknowledged that the small sample size of each group will limit the responsible employment of more than three to four predictor variables for each analysis, given the samples of *n*=18, and *n*=21 in children with FLE and TLE respectively. Research indicates that a minimum ratio of 5:1 cases to IVs is required for multiple regression analyses (Coakes & Steed, 2001). Thus, it was considered that the inclusion of three variables would maintain statistical sensitivity whilst still accommodating the theoretical variables of interest. From a theoretical standpoint, prediction of LTM would need to consider Central Executive, a measure of span, and a seizure variable at the very least. Thus, the categories of relevant variables were selected on theoretical grounds, and Pearson‟s correlations will be conducted to elucidate the most suitable variable on statistical grounds.

The inclusion IQ and demographic variables such as SES, were not used as predictors or covariates in subsequent analyses for several reasons. First, the level of IQ across children with FLE and TLE did not differ between groups, and given regression analysis was limited in the number of predictors that could responsibly be included, inclusion of IQ as a predictor in was not deemed advantageous over other variables. Tabachnik and Fidell (2007) state that high correlations between variables should be avoided due to issues of multicollinearity, and an inability to explain the unique variance accounted for by a specific variable. Therefore given the expected strong correlation of IQ with memory variables, it will not be included.

Second, from a theoretical viewpoint, given the aim of the research was to investigate the nature of memory functioning, within its own system, and IQ is considered to be a general measure of ability already established to influence memory function it was not considered to assist in addressing the research questions above or beyond specific memory variables highlighted as important within the literature.

7.5.4 Part III: The implications of memory impairment on related functions in epilepsy

The final analyses aimed to explore the functional implications of memory impairments, which comprised academic functioning and parent ratings of everyday memory performance. First, single sample and independent samples t-tests were employed to test the hypothesis children with TLE and FLE will demonstrate impairments in their academic skills relative to normative standards or relative to each other respectively. Second, the most important predictor(s) of specific academic skills was assessed by adopting stepwise regression. Four academic skills were identified as the DVs in each analysis, and in each case Central Executive, a measure of span, a measure of LTM, and a seizure variable would be used as predictor variables. Again, as highlighted by previous researchers, although IQ may be important in acquiring academic knowledge insofar as it is strongly linked with memory and working memory, it is not likely to influence the scores on tests of academic skill, and will not be included in predictive analyses of academic functioning.

With respect to everyday memory ratings, between and within group deviations were reported, before considering the seizure factors underpinning these ratings. Thus, the overall OMQ-PF score was used as the criterion variable, and given the hypothesised influence of seizure variables on these ratings, age of seizure onset, current frequency of seizures and number of medications were used as predictor variables.

CHAPTER 8: RESULTS

8.1 Profiles of Memory Impairment in Epilepsy

The first phase of data analysis investigated deviations and impairment in both groups. Analysis comprised single sample *t*-tests to identify deviations of each sample relative to normative standards, and independent sample *t*-tests to explore between group differences in children with FLE and TLE, across all memory and learning variables. Data are presented in the sequence considered to represent the flow of information through the memory system, from initial storage, to more complex processing, long-term recall, and the patterns associated with learning.

8.1.1 Working Memory

8.1.1.1 Verbal and non-verbal short term capacities

Single sample *t*-tests did not reveal a significant difference in performance on the Phonological Loop composite score for children with FLE $t(17) = -0.15$, $p = .88$, $d = .03$, though did in TLE $t(20) = -2.01$, $p = .05$, $d = .44$, relative to the published normative sample. Independent sample *t*-tests between the FLE and TLE groups did not reveal significant differences on these composite measures, as indicated in Table 8.01

Table 8.01

Mean z-score performance for measures of short term storage

	FLE n=18		TLE n=21		t(37)	p	d
	M	SD	M	SD			
PhL	-0.04	1.21	-0.46	1.05	1.15	.26	.37
VSSP	-0.93	1.22	-1.45	0.98	1.48	.15	.47
CVLT-T1	-0.39	0.78	0.19	0.91	-2.11	.04	.68

PhL = Phonological Loop, VSSP = Visuo-Spatial Sketchpad, CVLT-T1= CVLTC Trial 1.

As displayed in Table 8.01, groups did not differ in performance on the Visuo-Spatial Sketchpad, however both children with TLE $t(20) = 6.77$, $p < .001$, $d = 1.48$, and FLE $t(17)=-3.23$, $p<.001$, $d = .76$, demonstrated significant impairment on the global Visuo-Spatial Sketchpad index score relative to normative standards.

The CVLT-C Trial 1 score provides a measure of how many units of verbal information the child is capable of recalling after a single presentation. As hypothesised the results indicated that children with FLE displayed significantly reduced immediate auditory attention span relative to the age-expected normative standards $t(17) = -2.12$, $p = .04$, $d = .05$ and children with TLE $t(37) = -2.11$, $p =$

0.04, d = .27. Children with TLE did not deviate significantly from normative standards $t(20) = 0.95$, $p = .35$, d =.03.

Given the findings of a distinction in verbal and non-verbal skill performance, laterality effects were explored. Results did not reveal a significant difference in performance on the Visuo-Spatial Sketchpad in children with left (M= -1.45, SD = 1.29, n = 8) and right (M= -.51, SD = 1.04, n = 10) FLE $t(16)$ = -1.70, p = 0.1, d =.80 . Similarly, children with left (M= -.02, SD = 1.27) and right (M= -.06, SD = 1.22) FLE did not display significant differences on the Phonological Loop composite score $t(16)$ = 0.06, p = 0.95, d = .03.

Effects of laterality were also not revealed for children with left (M= -.57, SD = 1.01, n = 11) or right TLE (M= -.33, SD = 1.13, n = 10) on the Phonological Loop, $t(19)$= -0.51, p = .62, d = .23 , or left, (M= -1.35, SD = 1.14) and right TLE (M= -1.56, SD = .82) on the Visuo-Spatial Sketchpad, $t(19)$= -0.47, p = .64, d = .21.

8.1.1.2 Central executive

The three measures that comprise the Central Executive composite score represent the more classical "working memory" tasks that require more complex manipulation of information held "on-line". Contrary to expectation, children with FLE did not deviate significantly from the normative sample on the overall composite score, $t(17)$ = -0.90, p = .38, d =0.21. In contrast and although not within the range of "impairment" children with TLE demonstrated significant deviations relative to the normative sample $t(20)$ = -2.77, p = .03, d = 0.60. Individual sub-test analysis failed to reveal any significant differences between the groups on the individual subtests or global composite score of the Central Executive, as indicated in Table 8.02.

Table 8.02

Mean and standard deviations of children with epilepsy on measures of working memory

	FLE *n* = 18		TLE *n*=21		*t*(37)	*p*	*d*
	M	*SD*	*M*	*SD*			
LR	0.35	1.43	0.07	1.06	0.71	.49	.22
BwdDR	-0.15	1.35	-0.50	1.06	0.91	.37	.29
CR	-0.99	1.05	-1.21	0.98	0.68	.50	.22
CE	-0.27	1.29	–0.72	1.19	1.13	.27	.36

LR= Listening Recall; BwdDR = Backward Digit Recall; CR=Counting Recall; CE=Central Executive Composite Score

With respect to deviations from normative standards on the individual subtests, as implied by the mean *z*-scores in Table 8.02, children with FLE $t(17) = -3.99$, $p < .001$, $d = 0.94$ and TLE $t(20) = -5.64$, $p < .001$, $d = 1.23$ performed significantly poorer on the counting recall task relative to normative standards. Children with TLE also demonstrated decrements in backward digit recall $t(20) = -2.14$, $p = .04$, $d = 0.47$ relative to age expectation. Neither group demonstrated significant impairment on the listening recall task relative to age expectation.

8.1.2 Long-term learning and recall

8.1.2.1 Verbal learning and memory

List learning tasks provide a valuable means of assessing the rate of learning and retention. Figure 8.1 presents the learning curve for children with FLE and TLE, from trials 1 to 5, followed by the distractor list B, and short delay free recall trial.

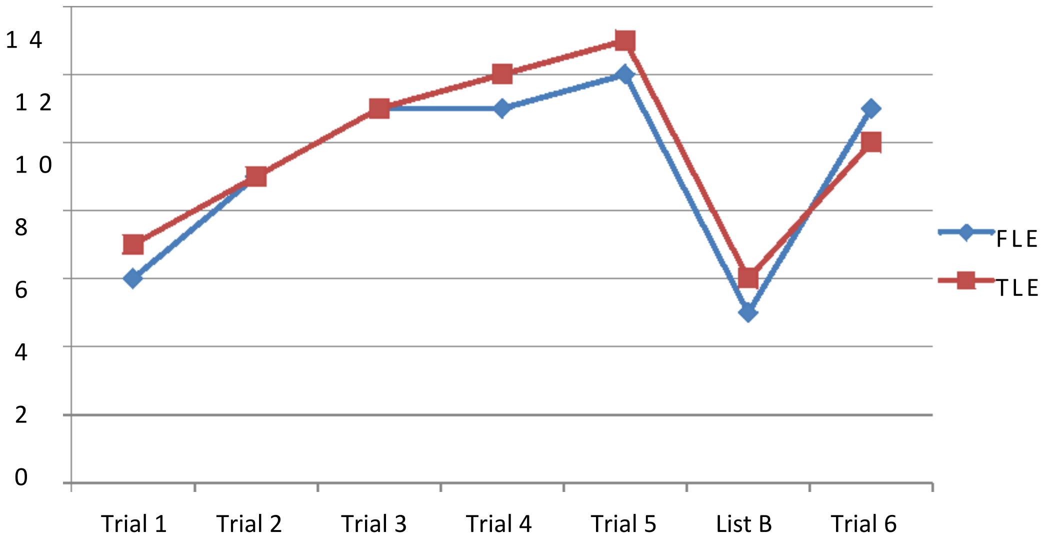

Figure 8.1. Learning curve of children with epilepsy on the CVLT-C

Figure 8.1 demonstrates a relatively equivalent rate of learning between the groups, and the groups did not differ in the Total Number of Words learned over the five trials (refer to table 8.03). Performance across the various learning trials was investigated for between group differences, and as deviations from normative standards. No significant between group differences were evident across any of the measures of learning and memory and are presented in Table 8.03.

Table 8.03

Difference in Performance on measures of Learning and Memory

	FLE		TLE				
	n = 18		*n*=21				
CVLT-C	*M*	*SD*	*M*	*SD*	*t*(37)	*p*	*d*
TW	-.27	.97	.20	.97	1.50	.14	.06
Trial5	.06	1.07	.12	.99	-.19	.85	
LDF	-.19	1.00	.17	1.08	.17	.88	

TW = Total Words Recalled (Trials 1:5); SDF = Short Delay Free Recall; LDF= Long Delay Free Recall. Degrees of freedom for each t-test are shown in parentheses

Examination of the standard deviations of the performance means for both groups indicates high variance. Relative to normative standards, the overall pattern of findings reflects long-term learning and memory within normal limits for both groups, and there were no significant differences relative to the normative mean on any of these measures in either children with FLE or TLE.

8.1.2.2 Strategy use and errors

As predicted children with FLE displayed significantly poorer use of semantic clustering strategies relative to age-expectation *t* (17) = -2.012, *p* = .03, *d*

= .48, one-tailed. Children with TLE did not demonstrate impairment relative to the normative sample $t(20)=.37$, p = .71, d =.09. As indicated in Table 8.04, there was no significant difference between the groups in the use of semantic clustering.

It was hypothesised that children with FLE would demonstrate more significant errors in their verbal learning, as indicated by the number of intrusions, repetitions and false-positive errors. Mean performance of both groups as measured by a deviation from normative standards (z-scores) are displayed in Table 8.04, with differences between the groups provided.

Table 8.04

Z-score performance on errors and strategy

	FLE *n*=18		TLE *n*=21				
	M	*SD*	*M*	*SD*	*t*(37)	*p*	*d*
Semantic Clustering	-.42	.88	.10	1.17	1.53	.14	.50
Perseverations	-.39	.56	-.70	.37	2.02	.05	.66
Intrusions	-.53	.44	-.12	.63	-2.31	.03	.75
False Positives	-.32	.56	-.31	.66	.046	.96	.015

Children with FLE made significantly greater intrusion errors, $t(17) = -5.13$, $p < 0.001$, d = .53 , perseverations, $t(17) = -2.96$, p = .01, d = .69, and false positives, $t(17)=-2.39$, p = .03, d = .57, relative to the normative sample. Children with TLE in contrast did not demonstrate impairment in the number of intrusions, though they demonstrated impairment in the number of perseverations, $t(20) = -8.55$, $p < .001$, $d = .70$, and false positives, $t(20) = -2.19$, $p = .02$, one tailed $d = .47$, relative to the normative sample.

As indicated in Table 8.04, children with FLE displayed a significantly higher frequency of intrusions relative to children with TLE, as indicated by reduced *z*-scores. However children with TLE displayed a higher frequency of perseverations relative to children with FLE. There was no significant difference in the frequency of false positive errors.

8.1.2.3 Visual memory

With respect to non-verbal memory, mean performance on the RCFT following 30-minute delay was significantly below age-expected levels for children with FLE $t\ (16) = -3.78$, $p <.01$, $d =.91$ with a mean difference of 1.12 standard deviations (SD=1.22) from the expected mean. Children with TLE also demonstrated impairment on this task $t(20) = -4.53$, $p < .001$, $d = 1.01$ with a mean difference of -1.09 standard deviations (SD=1.08). Children with FLE and TLE did not differ in their recall of the RCFT $t(35) = -0.07$, $p = .95$, $d = 1.92$.

8.2 Investigating the System: Associations Between Memory Subcomponents

The relationship between memory components were analysed separately for TLE and FLE groups as a) this method was more strongly aligned with the study aims and b) this approach allowed for investigation of differences in the structure/nature of memory function in these groups, which would be lost if the groups were to be combined.

8.2.1 Working memory

The second step in understanding memory functioning in children with epilepsy was an analysis of the associations between working memory subcomponents. Therefore the relationships between Phonological Loop function, Visuo-Spatial Sketchpad and the Central Executive were examined for each population using Pearson‟s bivariate correlations. The results are presented in Figure 8.2.

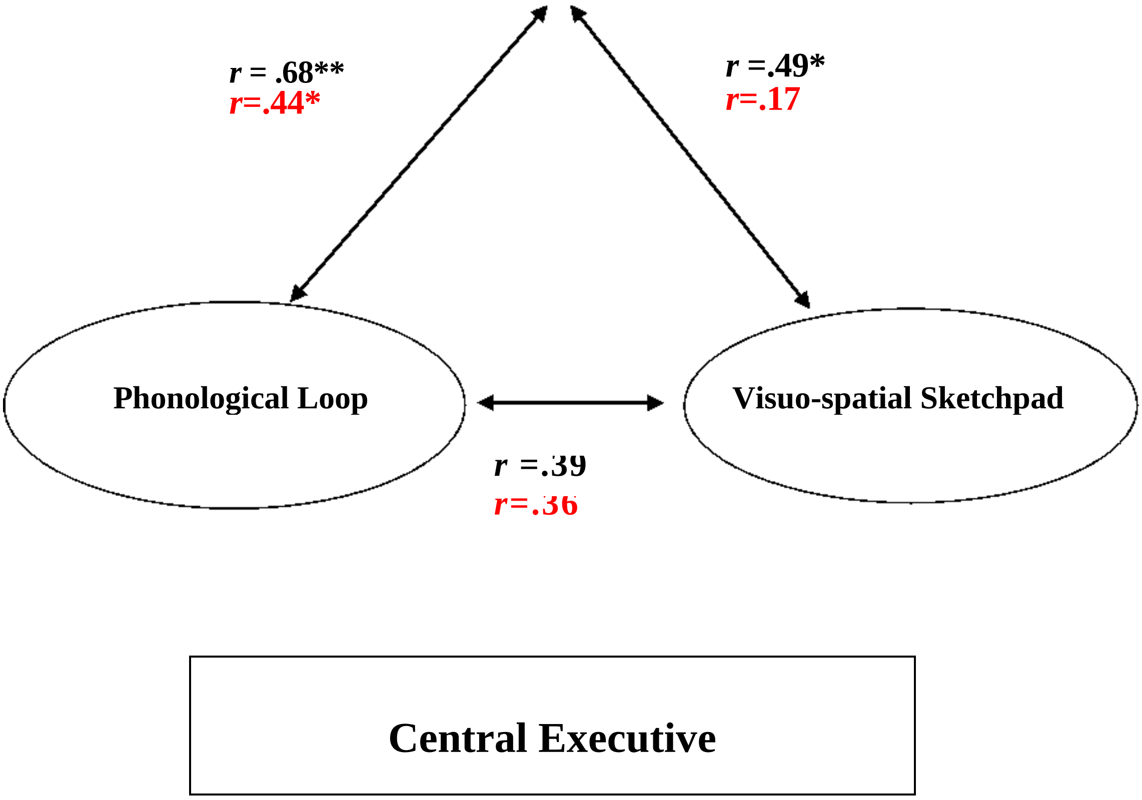

Figure 8.2 Intercorrelations between sub-components of the WM model in children with FLE and TLE.

Coefficients printed in red represent the TLE population, and black represents the FLE population. Significant correlations are indicated by asterisks, where ** $p < 0.01$, * $p < 0.05$.

As demonstrated in Figure 8.2, the pattern of inter-correlations differed according to epilepsy group. In children with FLE, stronger correlations were evident between each of the slave-systems and the Central Executive, whilst children with TLE only demonstrated a comparatively weaker relationship between the Phonological Loop and the Central Executive.

8.2.2 Verbal and visual long term memory function

8.2.2.1 Selection of variables of interest

The second stage of model building, explored the significant predictors of verbal memory. As discussed, only a limited combination of possible predictors were able to be selected given the statistical restriction imposed by small sample size. Thus, only those variables with the greatest theoretical relevance were selected to represent a) span or storage capacity, b) Central Executive and c) seizure severity in the stepwise regression analysis. Span and Central Executive performance were represented by the Phonological Loop and Central Executive composite scores respectively. Analysis of the inter-correlations between IQ and memory measures indicates the correlations between IQ and memory measures were high across all measures (refer to Appendix 6 and 7), justifying its exclusion as a predictor in analysis due to the increased potential for multicollinearity.
Theoretically, of all of the seizure variables, current seizure frequency and number of medications provide the greatest indication of seizure severity. Pearson‟s bivariate correlations were therefore run to analyse the relationship between these variables and long-term verbal memory in order to ascertain the variable with the highest correlation with verbal LTM and the lowest correlation with the other dependent variables. It was important to maintain symmetry in the analyses between FLE and TLE groups, in order to compare the findings. Therefore an additional factor that influenced selection of the appropriate variable was the strength of association in both groups. The correlations between these variables and the other variables of interest are outlined in Table 8.05.

Table 8.05

Correlation coefficients between seizure variables and predictor variables

	Current seizure Frequency		Number of medications	
	FLE	TLE	FLE	TLE
	n=18	*n*=21	*n*=18	*n*=21
PhLoop	.40	.14	-.30	.43
CE	.41	.06	-.45	.24
Verbal LTM	**.60**	-.03	-.26	.32

Correlation coefficients printed in bold were significant at .05 alpha level

As indicated in Table 8.05, current seizure frequency was significantly associated with verbal LTM in children with FLE though not TLE. The strength of correlation between number of medications and each of the other variables included in the analysis was more consistent across both groups and therefore this variable was selected to enter the model building analyses.

8.2.2.2 Stepwise regression analysis of verbal long term memory

An examination of the variables entered, based on an entry of .05 alpha level and an exit of .10 to remove, revealed that the independent variable with the highest zero-order correlation with long-delay free recall performance in children with FLE was the Central Executive performance score. Neither Number of Medications nor Phonological Loop were entered into the regression equation due to a failure to significantly increase the variance accounted for by the Central Executive since their strength of prediction exceeded the .05 cut-off level (.87, and .16 respectively). Thus, The Central Executive score accounted for 38% (adjusted R^2) of the variance in CVLT-C long-delay free recall, $F(1,16)=11.54$, $p < .001$.

The same predictor variables were entered into a stepwise regression procedure to examine the greatest predictor in children with TLE. Similarly the Central Executive performance variable was the single significant predictor, accounting for 20% (adjusted R^2) of the variance (adjusted) in CVLT-C long delay free recall performance, $F(1,19)=6.08$, $p = .02$. With the inclusion of the Central Executive variable, neither number of medications or Phonological Loop possessed enough predictive strength to be included, with significance of .31 and .64 respectively.

Table 8.06

Predictors of Verbal Long-Term Memory

Group	Included Predictor	*B*	*SE B*	*B*	Excluded Predictor	*t*	*p*
FLE	CE	.41	.12	.65		3.39	.001
					PhL	.63	.54
					No. of Meds	-.17	.86
TLE	CE	.56	.23	.49		2.47	.02
					PhL	.48	.64
					No. of Meds	1.04	.31

FLE= Frontal lobe epilepsy, TLE= Temporal lobe epilepsy, CE= Central Executive, PhL=Phonological Loop, No. of Meds= Number of Medications.

8.2.2.3 The relationship between working memory and efficient learning

Given the demonstration that working memory is influential for long-term retention of verbal information, it was expected that performance on the Central Executive would be associated with the frequency of intrusions and repetition errors. However neither group displayed significant correlations between these errors and performance on the Central Executive or Phonological Loop. In addition, it was anticipated that due to the purported frontal lobe localisation of strategy utilisation, semantic clustering would be significantly correlated with Central Executive performance, which was not demonstrated in either population (refer to Appendix 6 and 7).

8.2.2.4 Stepwise regression analysis of visual long term memory function

Prediction of visual memory was achieved using a symmetrical analysis to that conducted to predict verbal memory, with the substitution of Visuo-spatial Sketchpad for Phonological Loop. Stepwise regression analysis was used to evaluate the most significant predictor of long-term recall of the RCFT design. Using the Central Executive, Visuo-spatial Sketchpad, and Number of Medications as predictor variables, analysis revealed a varying pattern in children with FLE and TLE.

Specifically, analysis of children with FLE indicated that the independent variable with the highest zero-order correlation with RCFT recall was again the Central Executive, which significantly accounted for 51% (adjusted R^2) of the variance $F(1,16) = 18.93$, $p = .001$. However in this instance, the Visuospatial Sketchpad performance contributed an additional 11% (adjusted R^2) of variance, after having taken into account the Central Executive already in the equation. Together these variables accounted for a total of 62% (adjusted R^2) of the variance and yielded a significant predictive model of RCFT recall $F(2,15) = 14.56$, $p = .001$. This model and associated coefficients are presented in Table 8.07

The Central Executive was the most significant predictor of RCFT recall in children with TLE accounting for 25% (adjusted R^2) of the variance, $F\ (1,19) = 7.72$, $p =.01$. However, neither the Visuo-spatial Sketchpad nor Number of

Medications contributed enough predictive strength to warrant inclusion, and the coefficients associated with these variables are outlined in Table 8.07.

Table 8.07

Predictors of Visual Long-Term Memory

Group	Included Predictor	*B*	*SE B*	*Β*	Excluded Predictor	*t*	*p*
FLE	CE	.64	.16	.70		3.94	.001
	VSSP	-2.66	1.17	-.39		-2.28	.04
					No. of Meds	-1.09	.29
TLE	CE	3.93	1.41	.54		2.78	.01
					VSSP	.23	.82
					No. of Meds	.74	.47

FLE= Frontal lobe epilepsy, TLE= Temporal lobe epilepsy, CE= Central Executive, VSSP=Visuo-spatial Sketchpad, No. of Meds= Number of Medications.

As indicated in the table above, Number of Medications was not identified as a significant predictor of long-term visual memory, and neither was the Visuo-spatial Sketchpad in children with TLE.

8.3 The Implications of Memory Impairment on Related Functions

The end-stage of the efficiency of mnemonic processing over time can be observed by investigation of the functional skills acquired over childhood. The final stage of analyses explored the academic achievement and parent ratings of everyday memory in these groups.

Independent samples t-tests indicated no significant differences in any of the academic skills between children with TLE and FLE. Results of single sample *t*-tests are provided below, before the regression analyses are presented for each group.

8.3.1 Academic skills

The mean performance of children with FLE on key measures of academic skill are presented in Table 8.08

Table 8.08

Mean academic performance and deviation from the normative expectation in children with FLE

Variable	*n* =	*M* (*SD*)	Mean *z*-score	*t*	*p*	*d*
WRAT-4						
Word Reading	18	99.50 (17.51)	-0.03	-.12	.91	.02
Spelling	18	104.28 (22.78)	0.28	.80	.43	.20
Sentence Comprehension	17	97.35 (10.90)	-0.18	-1.00	.33	.24
Math	18	94.11 (17.84)	-0.39	-1.40	.18	.33

As can be inferred from the mean standardised performance scores in table 8.08, children with FLE display academic skills consistently within the average range, and thus contrary to prediction, do not deviate significantly below the normative means across reading, spelling and arithmetic skills.

The academic skills of children with TLE yielded a similar pattern of results to that of children with FLE. The mean performance and deviation from the normative mean across subtests of the WRAT-4 subtests are displayed in Table 8.09

Table 8.09

Mean academic performance and deviation from the normative expectation in children with TLE

Variable	*n*	*M* (*SD*)	Mean z-score	*t*	*p*	*d*
WRAT-4						
Word Reading	21	98.67 (17.48)	-0.09	-.35	0.73	.07
Spelling	21	98.29 (17.04)	-0.12	-.46	0.65	.10
Sentence Comprehension	21	95.90 (15.82)	-0.27	-1.20	0.25	.25
Math	21	91.81 (13.12)	-0.55	-2.91	0.01*	.62

* $p < 0.05$

Examination of the mean difference scores reveals that performance across reading, spelling, and comprehension tests are all within age-appropriate limits and do not deviate significantly from the mean. The exception to this was a significant decrement in math skill in children with TLE, $t(20) =$, p=.01, d= .62.

8.3.2 Predicting academic skills

8.3.2.1 Selecting variables for prediction of academic skills

Several stepwise regression analyses were run to elucidate the most significant predictor of various academic skills as a function of epilepsy group. Similar to previous analyses, the selection of predictor variables was constrained by sample size, and accordingly only Central Executive (working memory), CVLT-C LDF (long-term recall), CVLT-C Trial 1 Free recall (immediate auditory attention span) and Number of Medications were selected. These variables were selected as representative of each of the phases of cognition and factors purported to impact academic skills. CVLT-C Trial 1 was selected to represent immediate auditory attention span instead of the Phonological Loop, as the former task yielded a lower correlation with the other DVs included in the regression analysis relative to the Phonological Loop, which strengthened the argument for its inclusion.

This measure also taps into the type of attentional demands necessary in the classroom context in that it is a measure of span that is likely to be beyond the individual‟s capacity. Finally, the correlations between IQ and academic skills were high across all measures, ranging from .55 to .75 for both groups, and coupled with reasons outlined previously, its exclusion as a predictor in analysis of academic achievement is justified.

8.3.2.2 Math

An examination of the variables entered based on an entry of .05 alpha level and an exit of .10 to remove, the independent variable with the highest zero-order correlation with math in children with FLE was the Central Executive performance score, accounting for 63% (adjusted R^2) of the variance $F(1,16)=30.02$, $p < .001$. However in children with TLE, no significant predictors were entered into the model building equation. The standardized coefficients and *t*-values for each predictor are outlined in Table 8.10

8.3.2.3 Sentence comprehension

The independent variable with the highest zero-order correlation with sentence comprehension in children with FLE was again the Central Executive performance score, accounting for 50% (adjusted R^2) of the variance $F(1,16)=17.40$, $p = .01$. WMTB-C Central Executive was also the only significant predictor in children with TLE $F(1,19)=9.92$, $p = .01$, with 31% (adjusted R^2) variance accounted for by the Central Executive .

8.3.2.4 Word reading

An examination of the variables entered based on an entry of .05 alpha level and an exit of .10 to remove, the independent variable with the highest zero-order correlation with word reading in children with FLE was the Central Executive performance score, accounting for 46% (adjusted R^2) of the variance $F(1,16)=15.48$, $p < .001$. The same pattern of results was displayed in children with TLE, $F(1,19)=21.36$, $p < .001$, with 50% (adjusted R^2) variance in word reading accounted for by the Central Executive.

8.3.2.5 Spelling

Analysis of children with FLE indicated that the independent variable with the highest zero-order correlation with Spelling was again the Central Executive, which significantly accounted for 65% (adjusted R^2) of the variance in Spelling $F(1,16) = 32.87$, $p < .001$. However in this instance, CVLT-C List A Long Delay Free Recall score also produced a significant increment to R^2, after having taken into account the Central Executive already in the equation and together accounted for 72% (adjusted R^2) yielding a significant predictive model of Spelling $F(2,15) = 22.70$, $p < .001$. An investigation of the coefficients outlined in Table 8.10 further clarifies this solution. In children with TLE only the Central Executive accounted for 29% (adjusted R^2) variance in Spelling, $F(1,19)=8.97$, $p = .01$ and no other additional predictors contributed significant predictive strength to warrant inclusion. The results for these analyse are presented fully in Table 8.10.

Table 8.10

Predictors of Academic Achievement

Criterion	Group	Included Predictor	*B*	*SE B*	*Β*	Excluded Predictor	*t*	*p*
Math	FLE	CE	.75	.14	.81		5.48	<.001
						CVLT-C LDF	-.01	.99
						CVLT-T1	-1.40	.18
						No. of Meds	1.75	.10
	TLE	No Significant Predictors to enter the model						
Sentence Comprehension	FLE	CE	.40	.10	.73		4.17	<.001
						CVLT-C LDF	-.44	.67
						CVLT-T1	1.21	.25
						No. of Meds	-.96	.35
	TLE	CE	.52	.16	.59		3.15	<.01
						CVLT-C LDF	1.34	.20
						CVLT- T1	0.91	.38
						No. of Meds	.77	.45

FLE= Frontal lobe epilepsy, TLE= Temporal lobe epilepsy, CE= Central Executive, CVLT-C LDF = CVLT-C Long Delay Free Recall, CVLT-T1= CVLT-C Trial 1, No. of Meds= Number of Medications.

Table 8.10 Continued.

Predictors of Academic Achievement

Criterion	Group	Included Predictor	*B*	*SE B*	*B*	Excluded Predictor	*t*	*p*
Word Reading	FLE	CE	.64	.16	.70		3.94	<.001
						CVLT-C LDF	1.17	.26
						CVLT-C List A trial 1	1.40	.18
						No. of Meds	-.52	.61
	TLE	CE	.71	.15	.73		4.62	<.001
						CVLT-C LDF	1.05	.31
						CVLT-C List A trial 1	1.01	.33
						No. of Meds	-.99	.33
Spelling	FLE	CE	.69	.20	.58		3.44	<.01
		CVLT-C LDF	.69	.32	.37		2.19	.05
						List A	.63	.54
						No. of Meds	-.17	.87
	TLE	CE	.54	.18	.57		3.00	<.01
						CVLT-C LDF	.049	.96
						CVLT-C List A trial 1	-.21	.83
						No. of Meds	-.46	.65

FLE= Frontal lobe epilepsy, TLE= Temporal lobe epilepsy, CE= Central Executive, CVLT-C LDF = CVLT-C Long Delay Free Recall, CVLT-T1= CVLT-C Trial 1, No. of Meds= Number of Medications.

8.3.3 Everyday memory

Ratings on the OMQ-PF indicated that children with FLE display significantly more frequent and consistent pattern of impairments associated with everyday memory functioning $t(16) = -4.90$, $p < 0.001$, $d = 1.2$, with a mean difference of 1.56 standard deviations below the mean ($SD = 1.32$). Similarly, consistent with expectation, parent ratings on the observer memory questionnaire indicated that children with TLE display significantly more frequent and consistent pattern of behaviours associated with everyday memory functioning $t(20) = -4.18$, $p < 0.001$, $d = .92$, with a mean difference of 1.29 standard deviations below the mean ($SD = 1.42$). There was no significant difference between parent ratings of children with FLE compared with parent ratings of children with TLE on the OMQ-PF $t(36)= -.06$, $p = .56$, $d= 0.19$.

8.3.4 Predicting ratings of everyday memory

With respect to the predictive validity of seizure variables to parent ratings of everyday memory function neither current seizure frequency, number of medications or months since last seizure demonstrated sufficient predictive validity for inclusion into the stepwise regression equation in children with FLE or TLE when variables were entered based on an entry of .05 alpha level and an exit of .10 to remove.

Additional stepwise regression analyses were run to identify whether Central Executive, Phonological Loop or CVLT-C LDF recall performance was significantly correlated with OMQ-PF ratings. Analyses failed to identify any significant variables in either population, with sufficient predictive strength using the same entry and removal parameters of .05 and .10 respectively.

8.4 Overall Models of Memory Functioning in FLE and TLE Groups

The final stage of analysis was to integrate previous analyses with additional relationships explored through correlation, in an attempt to model the strength of relationships between memory components. Pearson‟s correlations were run between each of the key memory variables. The following diagrams are a pictorial representation of the relationships between each of the memory variables for both children with FLE and TLE. Solid lines depict significant correlations between variables, and as can be seen the pattern of significant correlations differ slightly across the groups. A common trend in both groups was the significant correlations between the Central Executive and a majority of other variables included in the analysis. Academic skills were associated with both Central Executive and variably verbal long-term memory.

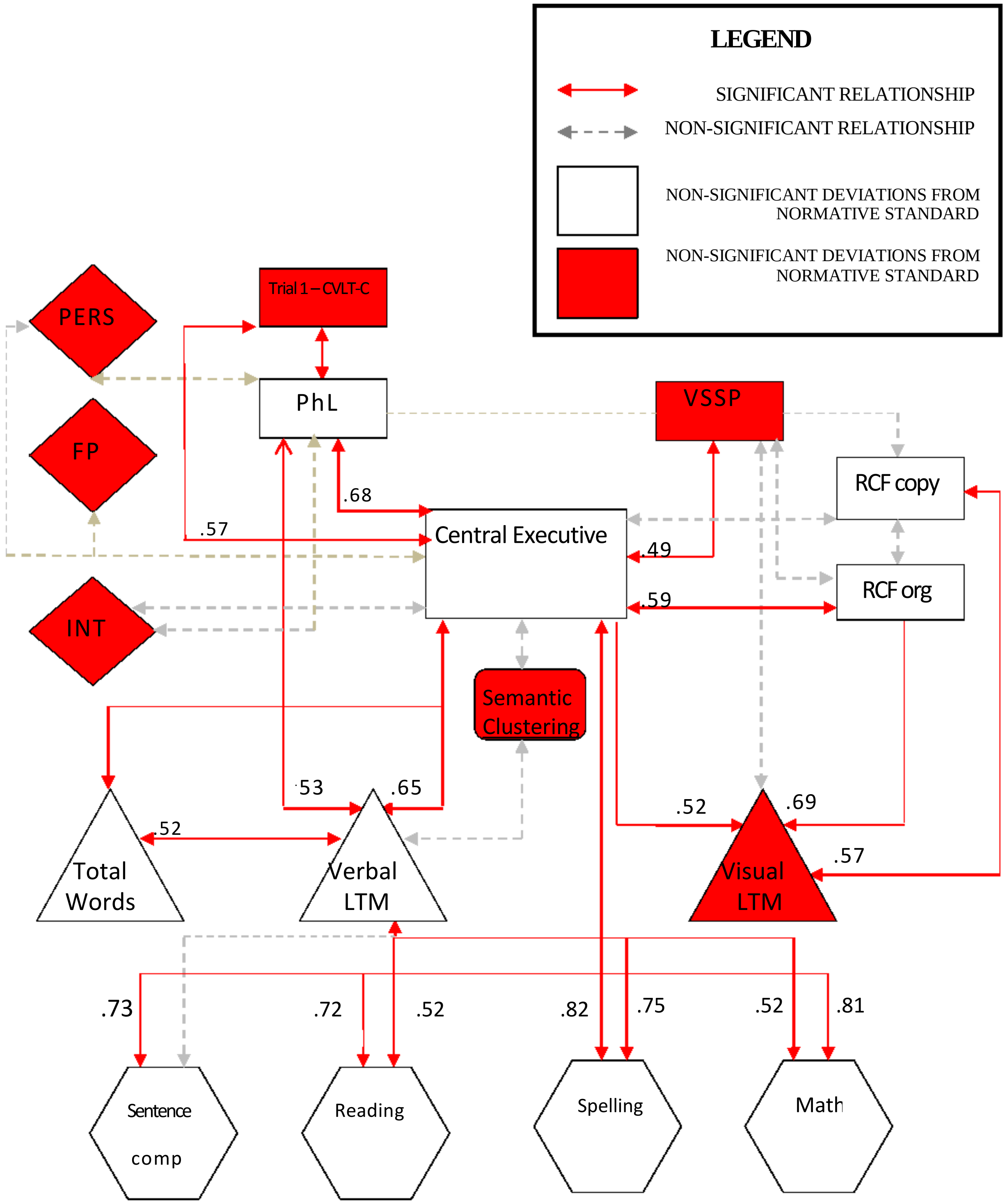

Figure 8.3. Relationships and Impairments in Frontal Lobe Epilepsy.

Coloured solid lines depict significant relationships, and dashed lines represent no significant relationships. Coloured boxes reflect those variables that were impaired relative to normative standards.

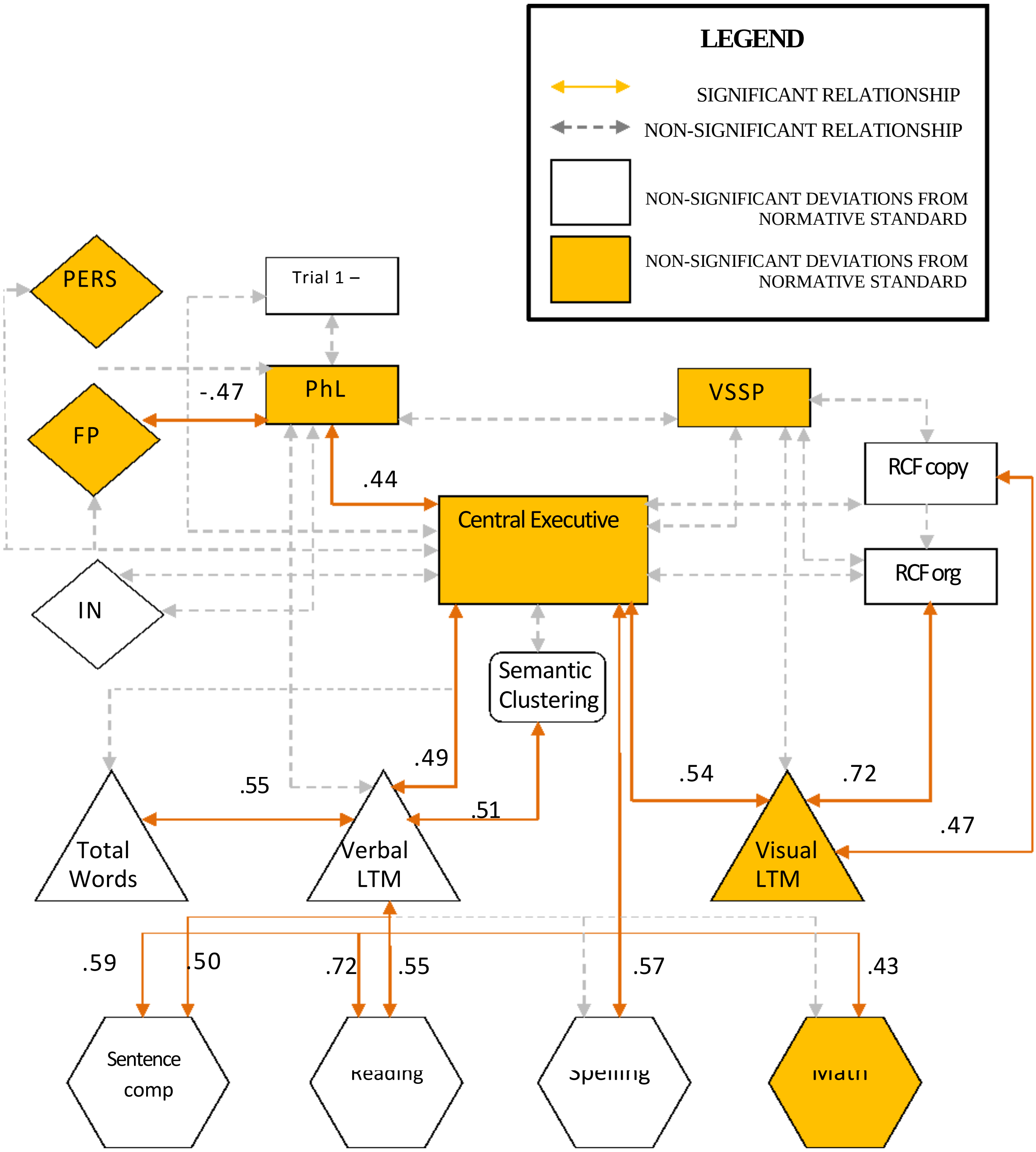

Figure 8.4 Relationships and Impairments in Temporal Lobe Epilepsy.

Coloured solid lines depict significant relationships, and dashed lines represent no significant relationships. Coloured boxes reflect those variables that were impaired relative to normative standards.

CHAPTER 9: DISCUSSION

9.1 Summary of Findings

This study explored memory function in children and adolescents with temporal and frontal lobe epilepsy, with a view to understanding the characteristics of memory dysfunction in these disorders. The value of this thesis therefore, was the comparison of these two clinical syndromes that involve disruption of the neural substrates critical to different memory processes, whilst using cognitive models to guide test selection, analysis, and interpretation. Hierarchical models provided a parsimonious account of the way in which information proceeds from a brief memory store into a more permanent store (Andrade, 2001), and facilitated a useful heuristic for this research.

Specifically, with consideration of cognitive models of memory functioning, this study aimed to a) distinguish the presence of impairment relative to normative standards in children with FLE and TLE, b) clarify whether focality differentially impacted memory sub-processes as expected given the purported localisation of memory function, and c) explore the memory processes critical for academic skill development.

Overall children in the present study were matched with respect to key seizure variables. There were no significant differences in laterality, the presence of a lesion, or age of seizure onset, and the majority of both groups were experiencing less than one seizure a month. Despite being managed at a tertiary treatment centre, none of the children were being considered for surgery, and were also considered by their treating neurologist to be well-controlled epilepsy cases. Thus, this sample of children should not be considered severe or refractory to treatment, and therefore the study findings are unique in the context of literature utilising more severe or mixed-epilepsy cases, and the well-matched nature of the sample affords a rare opportunity to examine differences in cognition relatively independently of the influence of seizure variables.

Although contrary to prediction, children with epilepsy did not significantly deviate from normative standards across most measures, the overall pattern of performance indicated that there was a trend toward significance of focal epilepsy having a detrimental effect on memory functioning as indicated by small to medium effect sizes. Specifically, with respect to short term storage of verbal information, children with FLE did not significantly deviate from normative standards, though children with TLE did. Both groups demonstrated significant impairment relative to age-expectation on visuo-spatial short term storage. These deviations were shown to have implications for working memory, of which children with TLE demonstrated impairment relative to normative standards on the global index and children with FLE did not. Furthermore, in partial support of the hypotheses, neither group deviated from normative standards on indices of long-term recall of verbal information, though long-term visual recall of a complex figure was impaired in both groups.

Although global measures of working memory were not impaired in FLE, the sample did reflect impairment on measures of semantic clustering and long-term learning errors which are indicative of frontal lobe inefficiency. In contrast, children with TLE demonstrated age-expected semantic clustering, and their pattern of learning is suggestive of inefficiencies likely associated with a reduced verbal span, rather than a working memory problem per se.

The overall pattern of between group differences when considered at the superficial level of end-point scores largely reflects a commensurate level of functioning between groups, such that children with FLE and TLE do not greatly differ in their memory functioning as indicated by the degree of difference in performance on key memory variables. These results were unexpected given models of memory functioning that would suggest a differential impact based on site of seizure onset. However an analysis of the strength of relationships between memory variables in the two study groups is suggestive of differences in the efficiency or nature of memory processing, which would not have been evident if end-point scores were solely relied on to draw conclusions as to memory functioning in these groups. A lack of significant correlation between sub-components of the working memory model in children with TLE was deemed to reflect an inefficiency of WM in these children, which was not evident in children with FLE.

Notwithstanding difficulties in the nature of working memory impairment for FLE and TLE, the central executive remained the strongest predictor of LTM, spelling, reading, math, and sentence comprehension in both groups, which was consistent with expectations.

Seizure variables were not consistently associated with objective measures of memory function in either group and contrary to expectation these variables were not significantly associated with parent ratings of memory performance, which were rated as impaired by parents and caregivers in both groups. The basis of this impairment relative to normative standards remains poorly understood for these groups.

Ultimately the results highlight the importance of working memory to long term memory and academic skill development. Importantly the results provide evidence for the phenomenological differences between well-controlled epilepsy cases and more refractory or surgical cases reported in the literature, and the need to carefully consider the sequence of memory processing and go beyond end-point scores to fully understand the difficulties experienced by these children.

9.2 Memory Functioning in FLE

Seizure variables were not significantly associated with key memory variables in children with FLE, which affords a unique opportunity to investigate memory functioning, and each of the hypotheses can be considered without a significant influence of seizure factors on performance. Based on cognitive theory for typically developing children, it was hypothesised that significant correlations between the central executive and each of the slave systems would be evident; though no significant correlations between the slave systems would be displayed in children with epilepsy. This contention was supported in children with FLE. According to Gathercole, Pickering, Ambridge and Wearing (2004) working memory and its sub-processes increase in efficiency from preschool up until adolescence, where a peak in performance is observed. The mean age of children with FLE in the current study was 12 years, and around this phase of development it is purported that the VSSP and the PhL are independent of one another.

Consistent with this, no significant associations were demonstrated in children with FLE between these indices. Children with FLE also demonstrated the expected pattern of association between slave-systems and the central executive, as according to Gathercole et al (2004) as the frontal cortices mature the relationship between the central executive and phonological loop should strengthen.

Contrary to expectation, the phonological loop was intact for children with FLE whereas the VSSP was impaired relative to normative standards. Within the FLE group, the division of children with left and right hemisphere seizures were relatively equal and laterality effects were not expected, thus the apparent poorer performance on visual storage tasks is difficult to explain from a neuroanatomical perspective. Analysis of laterality effects in children with FLE did not reveal a significant left-right difference in performance on these tasks, and therefore an alternative explanation may be associated with the nature of the interaction between the VSSP and the central executive.

Although contrary to prediction, children with FLE did not demonstrate significant reduction in central executive performance relative to normative standards, analysis of their central executive sub-test performance is suggestive of an underlying visuospatial processing difficulty. For example, children with FLE in the current study demonstrated age-appropriate performance on two of the three sub-tests, including the listening recall and backward digit recall tasks. However, they demonstrated impairment on the counting recall task which is a unique working memory task in that it is also the only central executive task that requires visuo-spatial input at the process level (Gathercole, 1998). Children with FLE demonstrated impaired visuo-spatial capacity, and therefore the impaired performance on counting recall task alone may be a reflection of the significant impairment in visuo-spatial short term storage impeding visuospatial working memory.

This finding possibly points to the need for a more detailed understanding of visuo-spatial working memory in children with epilepsy, which was previously an unrecognised area of difficulty. This area of particular weakness would have been overlooked had verbal measures, such as digit span, alone been used to assess working memory, as is the approach adopted by others (Lendt et al., 2002). There is also a parallel need to better understand this skill in normal children and other clinical groups, as at present, this is a very poorly understood and difficult to operationalize construct.

The need to recognise domain specificity in working memory was also apparent in the association between working memory performance and visual memory, consistent with the downward cascade of memory processing. Children with FLE in the current study demonstrated impaired VSSP and visual long-term memory on the RCFT task. Nolan and colleagues (2004) also reported significant deviations in performance on this task in children with FLE relative to the normative mean on measures of visual memory. Nolan and colleagues did not investigate visuo-spatial capacity and therefore the present study presents a valuable consideration of the role of VSSP in long-term visual recall, although causality still needs to be established.

In the present study, predictors of visual memory performance included the central executive, VSSP, and number of medications. The hypothesis that visual long-term recall would be predicted by central executive performance in children with epilepsy was partially supported in FLE, insofar as both central executive and visuo-spatial sketchpad performance predicted long-term visual recall. Unfortunately a limitation of the current study is that the nature of moderating relationships between the variables could not be explored statistically due to small sample size. For example, the triangular relationship between VSSP, central executive performance and visual LTM may in actuality reflect that central executive skill moderates the impact of reduced VSSP capacity on visual LTM. Certainly this would hold true from a theoretical account of working memory function in which limitations in capacity may be overcome by the central executive‟s additional flexibility and resources for complex processing (A. Baddeley, 2003, 2006). Furthermore, accurate execution of the RCFT is dependent on numerous skills including executive functioning, visuo-motor, visuo-constructional, and visual memory skills (Peter Anderson, et al., 2001), and therefore greater theoretical support would argue for the critical role of central executive over span in the execution of this task.

The issue of moderation was not highlighted within the processing of verbal information, as children with FLE did not demonstrate impairment in phonological loop or verbally mediated central executive tasks or long-term verbal memory recall. Specifically, the rate of learning in children with FLE was age-appropriate over five trials, with the exception of initial rate of registration which was below normative standards as indicated by Trial 1 of the CVLT-C. The finding of intact LTM is consistent with some but not all studies in FLE, reflecting ongoing debate as to whether long-term impairments are a feature of

FLE in childhood (Hernandez, et al., 2003; Nolan, et al., 2004; Riva, et al., 2005; Riva, et al., 2002). At the level of prediction, the central executive was indicated to be the sole predictor of verbal memory performance among those variables included in the regression equation. Both the phonological loop and central executive composite scores in addition to the number of medications were included as predictors of verbal long-term memory. However given the association between the phonological loop and the central executive, it is noteworthy that phonological loop performance did not reach a level of significance in predicting long-term verbal free recall as was evident with visuospatial processing.

The capacity of a given individual"s phonological loop will necessarily restrain or enhance the amount of information that is capable of being processed by the central executive (A. Baddeley, 2003, 2006). The contributing role of the phonological loop was not evident in children with FLE, and maybe owing to the strength of strong correlations between the central executive and phonological loop, which served to restrict the degree of unique variance explained by inclusion of the phonological loop in long-term verbal free recall prediction. An alternative explanation is that the nature of the verbal long-term task was not as sensitive to phonological loop impairment, given that successive list learning trials in effect serve to enhance rehearsal by repeated exposure. Thus, it is a shortfall of the current study that the verbal memory measure used was not supplemented by a measure of story recall to clarify whether the current contentions are displayed.

Use of the CVLT-C in epilepsy is, however, valuable due to its structure and ability to investigate the interface between temporal and frontal lobe functioning, as it allows for exploration of the influence of strategy use on learning and memory. Adult patients with frontal lobe lesions are reported to display impaired recall on unrelated lists, though when provided with suggestions to improve their strategy for recall, their performance improved (Gershberg & Shimamura, 1995). Thus, it was the contention of this study that even though significant deficits may not be apparent in children with FLE in their long term retention of verbal information, the semantic clustering index was expected to be sensitive to frontal lobe dysfunction. This variable reflects an individual"s ability to recognise the inherent categorical structure of the words to be recalled and employ the strategy of clustering semantically associated words together in order to aid recall (Gershberg & Shimamura). This was deemed to be a critical frontal lobe function that would tap into working memory ability. Although this variable was not significantly associated with working memory performance, consistent with expectation, children with FLE displayed significant deviations from normative expectation. Children with FLE in the studies conducted by Riva et al (2005) did not demonstrate any significant deviation in strategy use relative to the normative mean. Children in the mentioned study also comprised, unilateral, well-controlled cases of FLE, with an age of onset of 6 years similar to the present study. Thus, this discrepancy is an inconsistent effect, and provides strong argument for the need for future studies to explore list-learning in frontal lobe epilepsy.

An alternative means of detecting the interface between frontal lobe functioning and learning and memory is the frequency of errors across trials. The occurrence of errors such as repetitions or intrusions can be indicative of a reduced capacity to monitor the words already stated during free recall, or a source memory issue respectively. As predicted, children with FLE in the present study displayed significantly greater intrusion, repetitions and false-positive errors than age expectation, suggesting impaired frontal lobe function.

Conceptually, repetitions may reflect inefficient working memory insofar as the child is unable to efficiently monitor the words already stated. Intrusions in contrast may also reflect impaired frontal lobe function insofar as an ability to recall the temporal context of information presented is a unique frontal lobe function (Gershberg & Shimamura, 1995). In addition, the frontal lobes are critical to retrieval of learned information, as they are principally responsible for monitoring the detection of errors. Support for this is provided by Centeno and colleagues (2010) states that frontal lobe patients typically demonstrate an increase in false recognition on memory tasks.

In sum, it was anticipated that children with FLE would demonstrate impairment across all memory measures, however the most prominent impairment would be in working memory given the rich neuroanatomical literature localising the functions of storage and manipulation to the frontal cortex. Results were more complex than this prediction, but findings have progressed understanding of the nature of memory dysfunction in FLE and identified the following prominent features:

- Age consistent interrelationships between subcomponents of the working memory model.

- Central executive was significantly associated with performance on all key memory variables, in addition to being a significant predictor of LTM.
- Impaired visuo-spatial capacity, working memory impairment on a visually mediated task, and impaired visual long-term memory.
- No difference in performance based on laterality of seizure onset.
- Intact verbal capacity, working and long-term verbal memory.
- Inefficient learning indicated by reduced semantic clustering, and higher intrusions, repetitions and false positive errors.

Collectively, these results are suggestive of frontal lobe inefficiency in children with FLE, in that even though resources to accommodate more simple verbal span tasks appear intact, the effects of such inefficiency impair the accuracy of performance on more complex tasks requiring additional processing. Furthermore, this demonstration that working memory task impairment coincides with the modality and extent of storage capacity is consistent with purported models of memory function, and also suggests a serial cascading effect of reduced capacity, whereby verbal storage affects verbal tasks, and visuo-spatial capacity influences visually mediated tasks (Gabrieli, 1998; Squire, et al., 1993; Squire, et al., 2004). The predictive validity of this contention is in its infancy; though at the level of group differences, results enforce that working memory should be explored at the process level which has been largely neglected to date.

9.3 Memory Profile of TLE

Children with TLE also did not demonstrate significant relationships between seizure and memory variables, and therefore performance on memory variables can be considered largely independently of the impact of seizures affecting performance. The hypothesis that the central executive would be significantly correlated with each of the slave systems was partially supported in children with TLE, as there was a moderate relationship between the central executive and the phonological loop, but no significant relationship between the central executive and visuospatial sketchpad. As predicted no significant association was demonstrated between the slave systems in this clinical group.

The mean age of children with TLE was also approximately 12 years, and therefore cognitive theory for typically developing children would predict that both slave systems are dependent on central executive skill demonstrated via strong to medium correlations (Gathercole, 1998). In the absence of this, interpreting the significance of impairments in any component of the overall working memory system must consider the likelihood that this system is not functioning in the expected way, and therefore impairments are more likely to be associated with a working memory systemic breakdown rather than an isolated skill deficiency.

For example, children with TLE in the present study were significantly impaired on all measures of the WMTB-C. These findings unequivocally demonstrate that children with TLE experience deficits in working memory function, a finding which has not been widely appreciated previously (Auclair, et al., 2005; Hernandez, et al., 2003). Specifically, their performance on the phonological loop was almost half a standard deviation below the mean, which although is not at a range of clinical impairment, reflects a significant deviation from normative standards. In addition they demonstrated a degree of VSSP impairment of almost 1.5 standard deviations from the normative standard. And finally, as would be expected, and consistent with expectation given the significant reduction in verbal and non-verbal attention capacity, children with TLE also displayed significant impairment on the central executive composite score. Sub-test analysis indicated that the greatest decrement in central executive performance was on the counting recall task, followed by the backward digit recall task. Interestingly, the more profound impairment on the counting recall task, relative to the other more verbally mediated central executive tasks, is also consistent with the more profound impairment in VSSP capacity.

Collectively these deficits make it difficult to conclude that children with TLE have a primary impairment in central executive function, as the deficit in performance may be better explained by a reduced capacity, and again: an inefficiency in the entire system, not solely associated with an impaired central executive despite its appointment of *overarching controller* (A. Baddeley, 2003). That is, impaired central executive skill cannot be considered a primary impairment in the presence of reduced capacity. The suggestion therefore is that it is not an inability to hold and manipulate information that produces the reduced central executive scores, as this skill may or may not be intact, though if the amount of information that can be held is reduced then this will manifest as a working memory impairment.

Unfortunately due to methodological inconsistencies, previous literature provides little explanatory value to clarify this suggestion, largely due to the consistent approach of combining span and complex central executive-type tasks under one banner of "working memory". For example, Chaix et al (2006) reported that children with TLE demonstrate impairment in working memory, as represented by the digit span task. These authors did not separate the components of digit span forward and backward, and therefore limit the ability to interpret whether poor performance on digit span relative to other epilepsy groups is a consequence of span versus more complex central executive processing. Their inclusion of phonological and visual span tasks indicated that children with TLE were more impaired relative to idiopathic generalised epilepsy and idiopathic epilepsy with rolandic spikes on both these tasks, though their failure to include a purer measure of working memory (i.e one tapping into only the central executive) reduces opportunity to understand the influence of span performance.

It was expected that in the event of storage or working memory impairment, long-term memory would be impaired. Although central executive performance was demonstrated to be associated with visual and verbal long-term free recall, the patterns of impairments were not as predicted. In the TLE group, performance on the RCFT visual long-term recall was predicted solely by central executive performance, and the VSSP or number of medications did not provide sufficient predictive strength to warrant inclusion in the overall model. Initial organizational accuracy of the RCFT was highly correlated with the degree of recall of the figure (though not included in the predictive analyses), highlighting that higher order executive skills are important for accurate performance at recall.

This group was over one standard deviation below the normative expectation on long-term free recall of the RCFT. This is consistent with findings reported by Nolan and colleagues (2004) in which recall was almost 1.5 standard deviations below normative expectation. Thus one interpretation of these data may be that children with TLE appeared to demonstrate ”domain specific‟ impairment corresponding with reduced visuospatial span, central executive and long-term visual memory. Although this suggestion must be interpreted cautiously given ongoing debate as to the utility of the concept of material specificity (Saling, 2009).

With respect to verbal memory however, the findings did not provide support for a verbal memory deviation from normative standards in children with TLE. As discussed previously, this may be associated with the nature of the long-term verbal memory task employed. List learning tasks afford the child repeated attempts to consolidate and learn the information, and thus by design offer an opportunity to overcome reduced span by repeated exposure (Baron, 2004). Support for this is offered by previous literature in which variable results are evident dependent on the verbal memory measure employed. For example, Jocic-Jakubi and Jovic (2006) reported that children with TLE performed poorer than healthy controls on the long-term recall component of the Verbal Selective Reminding Test, which is purported to tap verbal learning capacity, consolidation, and retrieval from LTM. Also contrary to the current findings, Culhane-Shelburne et al (2002) reported that children with TLE demonstrated lower mean performance on all verbal memory measures than the comparison FLE group. Statistical significance was marginal and in favour of children with FLE performing better, with univariate analysis indicating this to be particularly the case with measures of story recall, which Cohen (1992) indicates to be a particularly sensitive temporal lobe memory measure.

Using the CVLT-C however, Hernandez and colleagues (2003) indicated that children with TLE performed worse than healthy controls. Differences in sample characteristics may have contributed to the inconsistent effect. Age of seizure onset in the children with TLE in the Hernandez et al., study were approximately 9 years of age, compared with children with the age of onset of children with TLE in the present study who were approximately 7 years of age. Similarly, children in the current study comprised only unilateral cases, compared with the 50% of cases in the Hernandez et al., study that were bilateral.

The conclusion from these studies therefore, may be that demonstrating group differences in verbal memory function in these two populations will be dependent on the nature of verbal learning task employed. Furthermore, it is likely that the use of this task hindered the ability to observe the true impact of impaired central executive function in this population. The impetus for use of a working memory model was that conclusions may be offered with respect to the stage at which memory processing "breaks down", which could not be easily ascertained by using this task.

By investigating error-performance this study revealed that children with TLE demonstrated significantly greater repetition and false-positive errors than the normative standards, which may reflect the true influence of overall working memory inefficiency on verbal learning. Children with TLE did not demonstrate intrusive errors beyond normative standards, and their use of strategies was age-appropriate. An error-free performance would rely on efficiently learning the target words, monitoring those recited to avoid repetition, and distinguishing target words from distractor words. Theoretically, impaired phonological loop function would restrain the amount of words that may be held on line, and may account for repetitive errors. If verbal span is reduced then the ability to monitor what has already been stated is likely to become more difficult (Delis, et al., 1994).

In sum, it was hypothesised that children with TLE would demonstrate impairments on all measures of memory function, though the most prominent feature would be associated with long-term memory. This was not supported, with the key areas of impairment identified by this study including:

- Inconsistent relationship between indices of working memory, including a lack of significant relationship between the visuospatial sketchpad and central executive.
- Impaired working memory, indicated by impaired phonological loop, visuospatial sketchpad, and central executive functioning.
- Impaired visual long term memory
- Age appropriate verbal memory
- Higher rate of false positive and repetition errors
- Age appropriate strategy use, and frequency of intrusive errors

The pattern of performance in children with TLE in many respects opposed the expected profile. For example, whilst it was anticipated that these children would demonstrate deviations relative to the normative standards across the short term storage tasks, the marked reduction in their working memory with apparent stable long-term memory functioning was not predicted. Children with TLE demonstrated impairments in verbal and visual short term storage, working memory and long-term visual memory with intact verbal delayed memory. The pattern of results however is likely to reflect a primary storage impairment that produces a cascade of impairment in other memory skills. The use of the CVLT-C allowed for exploration of the interface between frontal and temporal lobe memory processing by means of semantic clustering and error performance, though given the nature of repeated exposure was likely to have hindered the ability to appreciate the true nature of verbal long-term memory in this population. Unimpaired use of semantic clustering and intrusions is suggestive of unimpaired frontal lobe function, where repetitions are again reflective of the impact of reduced verbal span. These concepts will be explored further in the following section.

9.4 FLE and TLE: Functional Differences

Given the study aims and the rich cognitive and neuroscience theory this study was based on, group separation was maintained in order to consider both between and within group differences in children with FLE and TLE. This approach suggested subtle differences in the nature of impairment relative to normative standards. Furthermore, there were important differences in the relationships between memory components that would have been lost had the groups been combined.

The most profound and unexpected finding of the current study is that not only do children with TLE demonstrate impairment in overall working memory relative to normative standards, this impairment is greater than that observed in children with FLE. Further support for the contention that children with TLE display greater working memory difficulties than children with FLE, was that not only were TLE children impaired on slave-system functioning, the patterns of significant associations between these factors differed from the expected profile. Therefore the efficiency of working memory is distinguishable between the groups at a process level.

Specifically, the pattern of intercorrelations between the phonological loop, central executive and visuo-spatial sketchpad and central executive were stronger in children with FLE than that observed in TLE. These results are contrary to the purported direction of relationship, in that the absence and weakness of significant correlations between these factors in TLE is possibly indicative of an overall inefficient working memory system (Gathercole, 1998).

These results are in contrast to those presented by Lendt (2002), where children with FLE performed worse than those with TLE on a composite measure of short-term storage and working memory. Working memory is rarely included as a variable in studies of paediatric epilepsy and memory function and therefore explaining such inconsistencies is difficult but results point to the need to consider immediate, working and long-term memory in these populations. Within the adult literature the consideration of functional localisation of memory consistently refers to the notion that whilst temporal lobes are linked with the association of newly learned information, the frontal lobes are responsible for the allocation, coordination and processing of information resources necessary for that storage to take place efficiently (Centeno, et al., 2010). These skills fundamentally encompass working memory.

However, considering the patterns of performance difference between the two groups raises an important question as to the functioning and subsequent impact of working memory function. Theorists have argued that impairment in overall working memory involving complex span tasks can be attributed in most part to an inefficient central executive (A. Baddeley, 2000a, 2000b, 2006; Repovs & Baddeley, 2006). This is due to the modelling of the system which places the executive at the top of a hierarchical system in which the central executive processes, controls and regulates the influx of information, combining it with previously learned information to achieve the task at hand.

However this study suggests, albeit with the caveat of statistical limitation, that the influence of storage capacity limitations in children is not necessarily overcome by the powerful "overarching controller" that is the central executive. Intuitively this contention is valid. If the central executive is responsible for manipulating and coordinating information in storage, then certainly its effectiveness will be constrained by the amount of information that can be held in the first instance.

Considering this contention together with theories of cerebral and cognitive development raises the possibility that children with TLE are vulnerable to an immature working memory system, due to the earlier maturation of the temporal lobes relative to the frontal lobes (Darby & Walsh, 2004). The frontal lobes are the last of the cerebral hemispheres to reach maturation, which arguably lends itself to greater plasticity and reorganization of function following insult (Peter Anderson, 2003; B Kolb, 1999; Bryan Kolb & Whishaw, 1998). It may be that for these reasons, indications of central executive impairment are not evident at the age that the children with FLE in this study were assessed, and in comparison slave system functioning is evident earlier in development (Gathercole, 1998) and therefore these impairments are in effect for the TLE children in this study (Cycowicz, 2000; Epstein, 1986; Squire, et al., 1993; Swanson, 1999).

In children with FLE, visuospatial capacity impairment coincided with visuo-spatial working memory, and long-term memory impairment. In children with TLE the same pattern was upheld, where in addition verbal capacity reduction coincided with verbally mediated central executive impairment. Correlation however does not imply causation, and therefore more sophisticated and robust statistical techniques are required to address this issue. This study has provided preliminary data, and in its attempt to model memory function has depicted the central executive in an inverse position to that consistently published, where slave-systems are placed above the central executive to denote the likely downward cascade of processing. In this way, such a model is akin to that originally proposed by Atkinson and Shiffrin (Atkinson & Shiffrin, 1968)where information processing was seen as sequential from simple and transient to complex and enduring, which is also consistent with skill development where slave systems develop and mature first, before integration and development of the central executive.

Even though this question regarding the degree of contribution of span to central executive and subsequent processing cannot be wholly addressed, the second principle finding is that regardless of the site of seizure onset, the central executive is integral to memory functioning and accordingly the current model presented places it within the centre of all memory processing and related processes. This was indicated by the consistent finding that the central executive was predictive of long-term visual and verbal memory in both groups. In addition, the central executive was significantly associated with almost all memory variables, and storage capacity in both groups, the exception being non-significant association with the VSSP in children with TLE.

In the current study, children with FLE and TLE did not differ in their recall of a complex visual diagram but results indicated that predictors of performance differed between the groups. Specifically, VSSP additionally predicted RCFT performance in FLE, though not in children with TLE. The lack of clear group differences on a range of non-verbal memory tasks, including the RCFT, is consistent with other studies (Culhane-Shelburne et al., 2002, Nolan et al., 2004). These null findings, however, occur in the context of ongoing debate around the construct of non-verbal memory. In the absence of a gold standard or reliable measure/s of this aspect of memory, it is difficult to explore predictors of function. Though the results of the current study suggest that the impact of VSSP on non-verbal memory requires further consideration.

The demands of the RCFT should also be considered in interpreting the current results. Accurate execution of the RCFT task is reliant on intact attention, executive functioning, and numerous visual processing sub-domains such as visuomotor, perceptual, and visuospatial skills (Baron, 2004). Cohen indicates that because of the numerous cognitive domains this task demands, interpretation of the reason for impaired performance is hindered. Given the limited number of predictor variables used in the regression analysis, which did not include additional visual processing, attention or EF measures, the current results are not presented to indicate that WM is the only predictor of RCFT performance. Rather, the results further highlight that among the different factors included the pattern of prediction differs according to focality.

Recall that children with FLE displayed a moderate relationship between VSSP and central executive skill, where in contrast children with TLE did not display significant correlations between these variables. These results may reflect the stronger interplay between the VSSP and central executive in children with FLE bearing influence on the recall of the RCFT. Conversely, in children with TLE where no significant relationship between these factors was evident, possibly highlights the stronger reliance on central executive performance in this group. These results require further exploration utilising more rigorous statistical techniques, though raise awareness as to possible differences in the underlying processing of visual memory in children with focal epilepsies. The inconsistencies within the literature may also be better explained if the additional cognitive constructs purported to be important to RCFT recall outlined by Baron (2004) are included in the research protocol of future studies or a more diverse range of visuo-spatial memory tasks are employed.

As referred to previously, the failure of this study to demonstrate impairment in verbal memory in either population is likely to be associated with the nature of the task employed. Whilst statistical limitation enforces consideration that the lack of impairment may simply reflect that children with TLE and FLE are not impaired, the pattern of error performance in both groups is suggestive of inefficient learning at the very least. Thus, in as much as the presence of impairment or difficulty is descriptive of memory functioning, subtle or selective impairment is also fruitful in characterising memory functioning in these groups, and provides valuable clues for further exploration

To illustrate, children with TLE did not display intrusive errors or below age expectation use of strategies to aid their verbal learning, though displayed a higher frequency of repetitions and false positive errors. Children with FLE in contrast were impaired on all of these variables. If the cognitive mechanisms responsible for error-free performance are considered in conjunction with the associated neuroanatomical substrates subsuming them, then this comparative profile of error performance is suggestive of a different underlying cause for impairment. Thus an interesting quandary is presented.

The cognitive mechanisms underlying error-performance are not entirely capacity driven, as performance or efficiency of learning across trials is dependent on more complex processing than reciting a list of words alone (Gershberg & Shimamura, 1995). This is also evident in the finding that the central executive accounted for the greatest variance in long-term recall, above phonological loop in both groups. The neuroanatomical substrate of more complex processing is the frontal lobe (Centeno, et al., 2010). Whilst the concept of `entitlement' would warrant the claim that children with FLE display `frontal type' impairments in verbal learning, the finding that children with TLE also demonstrate errors in performance in addition to central executive impairment challenges this issue of `entitlement'.

The issue of possible `nociferous' cortex that involves disruption to an alternate brain region than that where seizure onset occurs (Penfield & Jasper, 1954) may be used as an explanation for TLE children displaying a `frontal' dysfunction in working memory. The finding that children with FLE did not display any significant working memory or LTM impairment, which would fit with a nociferous mechanism, may be attributed to the lag in development of the frontal lobes, in which the manifestation of such difficulties may become apparent as cerebral development reaches maturity.

Given that the average age of children with FLE in the current study coincides with a period of rapid frontal lobe development associated with a strengthening of working memory skills, the true impact of seizures within the frontal lobes cannot be wholly deduced. Jacobs, Harvey and Anderson (2007) indicate that children with insult to the frontal cortices between the ages of 7 and 9 years of age allows for better outcome, compared with those with frontal insult earlier in development. This was reportedly due to the rapid development of the prefrontal cortex during this phase. Importantly, the authors note that even though mean deviations from normative standards in children with focal insults beyond 7 years were not significant, a general pattern of inefficiency was observed suggesting that mild impairments in frontal lobe skills may occur at any phase of development. Thus, higher rates of errors, and poorer use of semantic clustering, provide subtle indications of frontal lobe inefficiency in the current sample of FLE.

The concept of nociferous cortex is grounded in neurological science, however if cognitive models of memory are imposed on this neurological construct, then what may be indicated is that nociferous cortex reflects the breakdown of a complicated system associated with numerous brain regions and not an actual substrate dysfunction of the second non-epileptic region. If this is the case, then the impairment in central executive skills in children with TLE may not be indicating frontal lobe impairment, but rather demonstrating the consequences of reduced span on efficiency of learning. In support of this, children with TLE did not display reduced strategy use, or higher intrusive errors, which are both strongly indicative of frontal lobe functioning, thus providing less weight to the argument that their impairment in central executive skills is due to frontal lobe impairment. In addition, children with FLE displayed reduced strategy use, and a greater number of errors than normative expectation, indicating that even in the absence of central executive impairment; such frontally driven skills are impaired and impact the efficiency of their learning. Thus overall, both groups of children demonstrate subtle impairments in aspect of LTM, when the long-term recall is within the same sensory modality, though children with FLE demonstrate additional frontal lobe skill impairments.

Notwithstanding the exploratory nature of this study, the most significant conclusion from the analysis of group deviation relative to normative standards in either population is that global composite scores of working memory or LTM will not adequately explain the underlying difficulties a child with epilepsy may experience, and as a consequence the functional implications of a "memory" deficit may go unnoticed or inappropriately targeted in treatment. Therefore composite end-point scores should be adopted with caution, with the recommendation being to primarily explore sub-test performance and consider the pattern of errors. A second and related implication of this study is that inconsistencies in the classification and consensus of what constitutes "working memory" will perpetuate our inability to truly characterise and model memory functioning in children with epilepsy.

The pattern of correlations between working memory sub-components and other memory variables reflects a moderate to strong degree of interrelationship, supporting the systemic nature of memory processing and was expected, given the importance of central executive functioning to new learning and with regard to its role in retrieval from LTM in its processing (A. Baddeley, 2003). However, inconsistent with adult models, a double dissociation of WM and LTM function was not displayed thus arguing against a modular impairment paradigm. Children with FLE were not more impaired on measures of working memory than those with TLE, and children with TLE did not display greater LTM memory impairments relative to children with FLE.

With respect to the similarity of adult models of memory function with children, several processes inherent in adult models appear to be active in children with epilepsy. Specifically, two key principles of memory in adult memory models namely transference and domain specificity were apparent in the present study. Certainly the current finding that information presented and activated in short-term is transferred to long-term memory, and in addition the nature of impairments in short term storage coincide with impairment in long-term impairments which provides supporting evidence for the primary importance of efficient short-term storage to long-term learning (Atkinson & Shiffrin, 1968; Gabrieli, 1998). Second, the demonstration that reduced storage capacity in children with epilepsy coincides with inefficiencies in compatible working memory tasks, and efficient learning or remembering supports the notion of the serial nature of memory processing. Inefficient short-term storage within a particular modality appears to extend to impaired learning in corresponding LTM (Squire, Knowlten, & Musen, 1993; Baddeley, Papagno & Vallar, 1988). Thus, it is a suggestion of this study that demarcating working memory tasks based on visual versus verbal domains is warranted.

These principles are at play in both epilepsy groups, though the additional influence of neuroanatomical dysfunction demonstrated by varying patterns of memory impairment reflects the convergence of cognitive modelling and neuroscience. Although necessarily speculative, the present findings have demonstrated that considering entitlement of impairment based solely on neuroanatomic dysfunction would prejudice the conclusions drawn and hamper any efforts of remediation. For example, if the conclusion that children with well-controlled epilepsy in the present study did not demonstrate verbal memory impairment, and children with FLE did not display frontal lobe inefficiency were put forth as the principle findings based on a) entitlement of deficit, and b) end-point score performance, then the valuable clues offered by additional analysis of process variables (such as errors) or correlations between variables is lost. If the functioning of the underlying *system* is not appreciated, then the functional outcome of the patterns of impairment will also be poorly understood.

9.5 The Implications of Memory Impairment on Related Functions

The importance of understanding memory in children with epilepsy goes beyond clarifying brain-behaviour relationships or depicting line drawings of cognitive system functioning, and rests entirely on ensuring that the quality of life or difficulties experienced by these children are appropriately targeted in treatment (Rankin & Hood, 2005; Seidenberg & Berent, 1992). The second aim of this study therefore, was to investigate the functional implications of memory system functioning on academic skills and everyday memory in these groups in order to appreciate whether specific patterns of impairment manifest differently in everyday life.

9.5.1 Academic skills

Contrary to expectation, the general pattern of performance in either group was age-appropriate academic functioning. Mathematics was the weakest skill in both groups, although the mean still fell within the average range. Numerical operations require accurate visuo-spatial representations of the equations, in addition to retrieval from LTM and numeric capacity retention. Given that math skill is reliant on visuo-spatial processing may explain that this was the weakest of all academic skills in children with FLE and TLE (McLean & Hitch, 1999).

At the outset of this study, it was deemed that the central executive would be critical to academic achievement, in key skill areas (such as spelling, reading, and math) over and above short term stores, other memory, demographic, or seizure variables in both groups. This hypothesis was largely supported, and the pattern of association between central executive performance and academic skills in the current study is consistent with previous studies of normally developing children (Gathercole & Pickering, 2000; Gathercole, Pickering, Knight, et al., 2004; Gathercole, Tiffany, et al., 2004) and clinical samples (Fastenau, et al., 2004).

Specifically, findings revealed that Word Reading, Spelling and Math were all uniquely predicted by central executive function alone in children with FLE. In children with TLE however, central executive again predicted all but Math skill, which was not significantly predicted by any of the variables included within the analysis. Finally, spelling proficiency was predicted additionally by long-term free recall in children with FLE.

Overall therefore, this study provides unequivocal support for the role of central executive in academic achievement, and serves to highlight that models of cognitive function in children are not in accordance with the hierarchical patterns of skills purported in adult models such as Mapou and Spector‟s (1995) cognitive framework. Recall from chapter 2 that in adults, cognition is modelled so that academic achievement is a foundation skill on which memory efficiency will be dependent, as the grown adult arguably has established this knowledge. This study has demonstrated that during childhood, the relationship between academic achievement and working memory functioning is likely to be reversed and interdependent, whereby on-going academic achievement will rest on the child"s memory capacity and learning efficiency, in addition to being supported by existing knowledge. In this way, working memory should be considered the foundation skill.

Whilst this is not a controversial proposal, given the findings presented thus far regarding the proposed importance of span to central executive performance, the issue of what should be deemed a primary impairment is called into question. The findings presented thus far propose that the configuration of the working memory model may be better represented with the slave systems above the central executive, to illustrate their importance to its functioning. Thus the cause of impairment in academic skills may have been equally differentiated according to the nature of specific working memory impairment, i.e that span may have been a greater or at least equal predictor of academic skill relative to the central executive.

Span tasks have been previously associated with academic achievement in mixed epilepsy samples (Schouten et al, 2002). Williams et al (2001) employed SES, verbal IQ, memory (including the CVLT-C total recall score) and other epilepsy variables as predictors of academic achievement, and reported that after IQ, attention was the most significant predictive variable of academic achievement scores. Attention is closely related to capacity, suggesting these skills have an important influence on academic function. However, this study did not demonstrate that capacity restriction was more influential to academic achievement than central executive performance, even though suggestions as to capacity's primary importance to central executive were proposed by the patterns of associations and impairments in these children.

There are likely several reasons for the inability to demonstrate the predictive strength of capacity to specific academic skills in the current study. The most obvious is that the statistical prowess was limited to inclusion of few predictor variables, and given the moderate relationships between the predictor variables, then unique variance may have been lost within the small numbers included in the analyses. Second, the measures of academic achievement employed assesses established knowledge, which is the product of repeated learning of the same skills, and in this way the transient impact of capacity restriction may not be elicited by the task.

Classrooms are often busy and loud, and when verbal span or capacity is reduced then the ability to comprehend spoken instruction would be negatively impacted (Hood & Rankin, 2005). However, the academic tasks employed in the current study were administered in a quiet one-to-one setting that didn't assess acquisition of academic skills as much as an already established skill-set in an environment that did not place significant demands on rapid comprehension.

Fastenau and colleagues (2004) also highlighted the importance of demographic and seizure variables on academic skills, the most significant being an organized and supportive home environment. The present study did not include measures of family functioning, and the measure of SES was also not included in any of the model-building analyses. This was necessary to overcome statistical limitations borne about by the small sample size, as the primary research question was concerned the specific memory factors and seizure factors that influence academic outcome, given that the role of SES and family functioning was relatively well established within the literature (Williams, 2003; Fastenau et al., 2004). In sum, although this study lacks the statistical rigor to conclusively address these issues, results suggest that working memory is a critical skill in children with epilepsy with significant academic implications.

9.5.2 Everyday memory

Thus far the results have indicated that children with epilepsy in both groups demonstrated largely commensurate objective performance on measures of memory functioning. Consistent with previous studies children with both TLE and FLE were rated as significantly impaired in their everyday memory skills by their primary caregiver. Skills were rated as almost one and a half standard deviations below the published normative mean (Gonzalez, 2008) for both groups, with no significant between groups differences in ratings. Thus these impairments were amongst the largest identified by this study.

Although it was predicted that parent ratings of everyday memory would be associated with severity of seizure disorder more so than objective test performance, this hypothesis was not supported. Performance on the OMQ-PF was not related to age at seizure onset, number of medications or frequency of last seizure. Nor was any relationship identified between cognitive measures and parent ratings of everyday memory in either population. This latter finding of a null relationship between objective and everyday memory measures is consistent with adult literature in TLE examining this issue (Giovagnoli, et al., 1997;

Helmstaedter & Elger, 2000). However, in these samples mood and seizure variables are often predictive, indicating that everyday memory is not simply proportional to objective impairment but perhaps reflects perceived burden of the illness (Corcoran & Thompson, 1993; Elixhauser, et al., 1999). In the current study the failure to find any relationship between seizure variables and everyday memory may perhaps be due to a lack of variance in these measures within this well-controlled sample. Alternatively, given the sample of well-controlled cases in the present study, the burden of ongoing seizures may not significant enough to influence everyday memory. A parallel issue is that seizure severity rating scale may have lacked sensitivity at the lower end. A more appropriate scale would have had a lower floor and included greater than quarterly and yearly intervals.

Much remains to be explored and understood about the nature of everyday memory impairment in children with epilepsy and the associated predictors. Although the OMQ-PF has been applied to a paediatric sample of TLE, the specific association between seizure variables and the OMQ-PF were not reported in the original article (Gonzalez, 2008), and therefore replication of these findings is recommended for future studies.

9.6 Limitations and Recommendations

This study was unique in its selection criteria that focused on children with symptomatic partial epilepsy of frontal and temporal lobe origin only. This was done in an attempt to capitalize on the opportunity to assess the influence of focal dysfunction in key areas associated with mnemonic functioning and was the most fruitful approach to study the research aims. However, there are a number of limitations that constrain the conclusions that can be drawn from this study.

Although focality of seizures was a specific criterion meant to restrict the confounding factors introduced by generalised seizures, the employment of a "natural laboratory" (Snyder, 1997, p. 1) is not without confounds. Children in the present study did not differ on seizure frequency, age of onset, or number of medications, however given that seizure variables are likely to be enmeshed, comparing syndromes based on these measures may not truly capture the underlying neuropathological differences between the groups.

First, children with FLE are more likely to express seizures in clusters, relative to their TLE counterparts. In this way, if a child with FLE is described as having seizures weekly, which constitute one day of multiple seizures, then is this child really comparable to a child with TLE with a solitary weekly seizure? The answer is most likely an affirmative `no'. As mentioned previously, the present study would have also benefitted from employing a more sensitive scale for seizure frequency that included fewer than quarterly or yearly seizures.

Second, as stated by Dennis and colleagues (2009) neurodevelopmental disorders differ from acquired disorders in childhood or adulthood in that a period of `normal' development is not evident. Therefore, the relationship between age of seizure onset and cognitive outcome is likely to be less accurate and post-date the actual age of onset of cerebral dysfunction. It was for this reason that children with a longer-standing history of well-controlled seizures were selected, rather than more recent diagnoses, as these established cases allow for greater consideration of developmental processes.

Even though groups were matched on seizure variables, within group variance was high, as indicated by substantial standard deviations on performance variables, and therefore average scores are unlikely to capture the participants with greater impairments. Thus, the greatest limitation in the present study was sample size, which restricted the depth of analysis undertaken and the ability to explore high within group variance.

Ideally, the questions and issues raised would be better addressed through more sophisticated regression analyses or statistical path analysis, however in the current study analysis was limited to the more preliminary techniques of t-tests, simple regressions and correlations. For example, the influence of sub-factors such as gender, age, polytherapy, lesions, or laterality within each group could not be achieved thoroughly, as further dividing each group would not have yielded sufficient numbers necessary for responsible statistical analysis.

Arguably, the limitations of sample size may have been overcome by combining the groups to yield larger numbers. Although statistically this provides more robust analysis, important questions would have remained unanswered if lumping groups together continues to be the protocol for future research (Everts, Harvey, Lillywhite, Wrennall, Abbott et a, 2010; O"Leary, Burns, & Borden, 2006). This point is further underscored given that adherence to group separation proved fruitful in uncovering some important differences between the FLE and TLE groups.

One of the advantages of investigating mnemonic function in FLE and TLE was that these syndromes stand out within the literature as the centres critical for memory processing (Budson & Price, 2005; Fletcher & Henson, 2001;

Gabrieli, 1998; Squire, et al., 2004; Zola-Morgan & Squire, 1993). However, memory functioning arguably relies on whole cerebral function, especially when considering localisation of WM slave systems lay additionally within the parietal and occipital lobes (Henson, 2001). Including cases with parietal (PLE) and occipital lobe epilepsy (OLE) would have increased understanding of how insult in any location impacts functioning. However this could not be achieved due to a lack of time and resources.

Another trade-off that limited the analysis was that between the duration of the assessment protocol and the number of measures that could be included. Assessing children, particularly those of the younger age range requires a more limited protocol as their ability to sustain their attention and motivation for extended periods is more limited than older children (Baron, 2004). It was for this reason that an extensive standardised battery of attention was not included. This would have benefited the analysis and interpretation of memory functioning, as attention is critical to efficient encoding (Lyon & Krasnegor, 1996; Norman, 1968). This study attempted to overcome this issue by including the full Working Memory Test Battery which incorporates measures of span, indicative of attention. Future studies should incorporate measures of sustained attention, and shifting attention to supplement the analysis.

In addition, more measures of long-term memory including story recall or associative learning would also have been useful and added to the conclusions made in this study, particularly in light of concerns that the nature of the CVLT-C may have mitigated working memory difficulties. The assessment of visuo-spatial memory was also limited in the present study, though this is not uncommon within the paediatric literature on epilepsy. This is a limitation caused by an inherent lack of well-validated and theoretically driven measures of visuo-spatial memory. Conclusions regarding domain specificity were based on children's performance on the RCFT, however as highlighted in previous sections, this task is not a pure measure of visual memory. This is also the case for measures of visuo-spatial working memory and span tasks, and it is for this reason that the role of the visuo-spatial sketchpad in academic skills is not as clear or well documented as that of the phonological loop (Hood & Rankin, 2005; Rankin & Hood, 2005). This line of research demands further attention, as this study has served to highlight that within a paediatric context, perhaps the demarcation of verbal and visual central executive processing is additionally warranted.

9.7 Implications

If we consider that the fundamental job or outcome of childhood is to learn, then it is imperative to understand the nature of memory limitations imposed by FLE and TLE as they are directly associated with the learning centres of the brain. To the author's knowledge this is the first attempt to utilise the well-established working memory model in children with epilepsy. In doing so, this study has generated important, albeit preliminary, steps toward understanding the nature and implications of memory in children with FLE and TLE and advancing relevant theory. It has also demonstrated that it should no longer be good enough to solely consider end-point scores in these populations, and research must consider process variables in an attempt to understand the workings of the memory system.

However within the paediatric epilepsy research collective there are significant challenges for researchers going forward. First, viable models of cognitive functioning in children are lacking. This study has made preliminary gains in this endeavour and put forth an explanatory model of memory. Even still, this model must be considered a subcomponent of a larger system that includes all other cognitive skills which were not investigated. To date, a comprehensive paediatric model of cognition is not in popular use. The ability to develop such a model in children is restricted by the need to consider to developmental factors, as a model of cognition that explains the cognitive function of a 13 year old, is necessarily different to the modelling of important skills that are critical to that of a 7 year old. Dennis‟ (1989) useful heuristic of emerging, developing and established skills partially addresses this issue, though more complex modelling of the interplay between factors is still required.

Second, the efforts to model cognition will rest on the validity of tests accurately measuring what they are purporting to measure. Only as recent as 2004, did Baron publish a compendium of normative data for neuropsychological tests for children. This highlights that formalised neuropsychological testing practice in children is not as established as testing with adult samples.

Furthermore, with the advent of neuroimaging which has allowed convergence of test performance and brain function to be tested, a shift in conceptualising specific constructs is currently at play. Within the adult memory literature Saling (2009) highlights that verbal memory encompasses a range of skills that are not given justice by being lumped within a rubric of verbal memory. This study has also highlighted that verbal list learning tasks are likely to be different from story recall tasks, even though both are verbal memory measures. Therefore a finer level of research is necessary to first and clearly specify not only the cognitive construct under investigation but to validate that what is being measured is in fact representative of that construct. It is then that we can accurately develop comprehensive models of cognition in children, which can then be used to address memory profiles in clinical samples such as focal epilepsy.

Finally, the gold standard of clinical neuropsychological assessment is proper consideration of ”convergence profile analysis‟ (Baron, p.viii). This standard makes it imperative that the clinician consider all possible cognitive skills and excludes those that are unimpaired. From this the resultant deficit can be properly identified as either primary or secondary to other factors. It is only after such consideration can treatment of any impairment be appropriately targeted and treated, which is ultimately the goal of understanding cognition in clinical samples. Thus the theoretical implications of this study demand careful consideration on behalf of the treating clinician as to the precise nature and intention of defining performance as ”memory impairment‟.

9.8 Conclusion

Overall this study aimed to assess the memory functioning in children with FLE and TLE, by examining not only absolute levels of impairment, though also the relationships and factors which are important to efficient memory, learning, and academic achievement. Key conclusions drawn from this study were that:

1. In many domains of memory processing children with well-controlled FLE and TLE do not differ, and seizure variables were not significantly associated with memory performance.
2. Children with FLE do not demonstrate wide-ranging working memory impairment, and display age-appropriate relationships between slave and central executive systems. However, these children demonstrate frontal lobe inefficiencies indicated by higher frequency of errors and impaired strategy utilisation.
3. Children with TLE demonstrate working memory impairment, indicated by impaired performance relative to normative standards on all measures of the WMTB-C, and inconsistent strength of relationships between subcomponents of working memory. Clinical indication of a central executive deficit in this group may in actuality reflect a more primary impairment of storage capacity.
4. Memory processing in children with well-controlled focal epilepsy appears to follow the pattern of domain-specific information processing that is evident in adults.

5. Academic skills are largely at expectation relative to normative standards in both groups.
6. Central executive processes are a critical foundation skill implicated in long-term learning, and academic skill attainment. The importance of central executive in this way was not differentiated according to TLE or FLE group membership
7. Parent ratings of memory performance in children are not predicted by seizure variables or objective memory performance, and further work is needed to understand the predictive factors for everyday memory.

This study is unique in that it adopted a theoretically-driven approach to exploring a broad range of mnemonic processes. These issues were explored in well-characterised and relatively large (by clinical standards) samples of children with TLE and FLE. The findings make a unique contribution to the literature and offer an unbiased account of the nature of impairment in this group of children. Such studies are critical for the advancement of clinical practice efficiency and also to strengthen our knowledge regarding cognition in children, which is significantly lacking, relative to the rich adult literature. Further work is, however, necessary to bridge the gap between cognitive models, neuroscience and clinical practice. This is particularly the case for paediatric FLE where memory is largely forgotten.

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Appendix 1. Background Information and Clinical Interview

BACKGROUND INFORMATION INTERVIEW

ID NUMBER: ______________________________ UR: ____________

D.O.B.: AGE: ____________

DATE: GRADE: ____________

OCCUPATION:

MOTHER'S: _______________________ FATHER'S ____________________

____

SEIZURE STATUS:

FIRST SEIZURE: ____

AGE AT DIAGNOSIS: _______________________________________

LAST SEIZURE: ____

SEIZURE FREQUENCY: ______________________________________

ADDITIONAL SEIZURE INFORMATION: _________________________________

____

OTHER MEDICAL PROBLEMS (LOC, Head injury)

____

____

MEDICATIONS: ____

____

MEMORY FUNCTIONING

AT SCHOOL: ____

____

____

____

____

AT HOME: ____

____

____

____

____

BEHAVIOURAL ASPECTS

ANY AREAS OF CONCERN: ____________________________________

BEHAVIOUR PROBLEMS HOME Y/N: ____________________________

____

____

BEHAVIOUR PROBLEMS SCHOOL Y/N: __________________________

____

____

DIFFICULTIES RELATING TO SIBLINGS Y/N: ____________________

____

____

____

____

DIFFICULTIES RELATING TO PEERS Y/N: ______________________________

ACADEMIC ACHIEVEMENT

Kindergarten? ❑ Yes ❑ No Age, ___________

Age commenced Primary School: ____________

Current Academic Performance ❑ Good ❑ Average

❑ Poor

Strengths/Weaknesses

REPEATED YEARS AT SCHOOL? ❑ Yes ❑ No Year: _____________________

Remedial Class/Aide/Tutoring: ❑ Yes ❑ No Hrs/week

APPENDIX 2. WMTB-C SUBTESTS

Order	Subtest	Description of task
1	Digit Recall	Digits spoken aloud at the rate of one per second, and child required to recite digits in correct sequence
2	Word List Matching	Sequence of words spoken twice and child is required to indicate whether second sequence was different to first.
3	Word List Recall	One-syllable words spoken aloud, and child is required to recite words in correct sequence.
4	Block Recall	Sequences of blocks are tapped at the rate of one per second, and child is required to tap the sequence in the correct order.
5	Nonword List Recall	Sequences of one-syllable nonsense words are spoken at the rate of one per second. Child is required to recite the nonsense words in the correct sequence
6	Listening Recall	Short sentences are read aloud, and child is required to indicate if the sentence is true or false, and then to recall the final word spoken in the sentence.
7	Counting Recall	Child is presented with an array of dots to count per page. At the completion of the set, the child is required to recall the tally of the dots counted per page in the set.
8	Mazes Memory	Following presentation of the "correct path" through a maze of increasing length, the child is required to replicate the path
9	Backward Digit Recall	Sequence of digits are spoken aloud at the rate of one per second, and the child is required to recite the digits in the reverse order.

These descriptions are taken from the Working Memory Test Battery for Children (WMTB-C) manual (Pickering & Gathercole, 2001, p 34)

APPENDIX 3. OBSERVER MEMORY QUESTIONNAIRE - PARENT FORM (OMQ-PF)

This questionnaire is designed as a measure of how your child remembers day-to-day information. We are trying to identify problems, *beyond what is normal for your child's age group,* therefore, it may be useful to keep in mind the abilities of other children of the same age.

CHILD'S NAME:______________________ **TODAY'S DATE:** ________

DATE OF BIRTH: ____________________ **AGE:**___________________

COMPLETED BY (RELATIONSHIP TO CHILD): _________________________

1.	Does your child frequently lose important information (eg. notes to and from school)?	1. never 2. rarely 3. sometimes 4. often 5. always

2.	Does your child become anxious when he/she forgets things that other people appear to remember easily?	1. never 2. rarely 3. sometimes 4. often 5. always
3.	Does your child recall details of previous conversations?	1. never 2. rarely 3. sometimes 4. often 5. always
4.	Do you have to provide reminders for him/her?	1. never 2. rarely 3. sometimes 4. often 5. always
5.	When your child is speaking, does he/she lose track of what they are trying to say?	1. never 2. rarely 3. sometimes 4. often 5. always

6.	Does your child forget where he/she has put things in the house?	1. never 2. rarely 3. sometimes 4. often 5. always
7.	Compared with other children of the same age, his/her memory ability is poor.	1. agree strongly 2. agree 3. undecided 4. disagree 5. disagree strongly
8.	Is he/she reliable at giving messages (eg. telephone messages) to others?	1. never 2. rarely 3. sometimes 4. often 5. always
9..	Does your child repeat him/herself unintentionally in conversation (e.g. asking the same question)?	1. never 2. rarely 3. sometimes 4. often

		5. always
10.	If your child did not place things in the same location he/she would have difficulty finding them again (eg. school bag).	1. agree strongly 2. agree 3. undecided 4. disagree 5. disagree strongly
11.	Do others (including teachers) comment that your child appears to have a poor memory?	1. never 2. rarely 3. sometimes 4. often 5. always
12.	Your child‟s memory has progressed at the same rate as his/her peers.	1. agree strongly 2. agree 3. undecided 4. disagree 5. disagree strongly
13.	Does your child have to write themselves reminder notes if they are to remember to do things (eg. take a	1. never 2. rarely

	book to school)?	3. sometimes 4. often 5. always

14.	Of all your child‟s abilities memory is his/her weakest skill	1. agree strongly 2. agree 3. undecided 4. disagree 5. disagree strongly
15.	Does your child set off to do something then forget what it is he/she wanted to do (eg, going into another room to fetch something, then wondering what it was)?	1. never 2. rarely 3. sometimes 4. often 5. always
16.	Your child has a limited concentration span.	1. agree strongly 2. agree 3. undecided 4. disagree 5. disagree strongly

17.	Does your child get flustered when someone gives him/her a list of things to do (eg, errands to perform)?	1. never 2. rarely 3. sometimes 4. often 5. always
18.	He/she has a poor memory.	1. agree strongly 2. agree 3. undecided 4. disagree 5. disagree strongly
19.	He/she forgets details of significant family events, such as birthdays and Christmas.	1. agree strongly 2. agree 3. undecided 4. disagree 5. disagree strongly
20.	He/she brings the correct books home for homework tasks.	1. agree strongly 2. agree 3. undecided 4. disagree 5. disagree strongly

21.	If your child does not do things as soon as he/she thinks of them he/she will forget them altogether.	1. agree strongly 2. agree 3. undecided 4. disagree 5. disagree strongly
22.	Does he/she learn new things quickly and easily (eg. rules of a game)?	1. never 2. rarely 3. sometimes 4. often 5. always
23.	Does your child complain that his/her memory is poor?	1. never 2. rarely 3. sometimes 4. often 5. always
24.	Does your child require information to be repeated several times before they grasp what they are being asked to do?	1. never 2. rarely 3. sometimes 4. often

		5. always
25	Does forgetting interfere with his/her day-to-day activities?	1. never 2. rarely 3. sometimes 4. often 5. always
26.	Your child‟s memory is limiting his/her achievements at school.	1. agree strongly 2. agree 3. undecided 4. disagree 5. disagree strongly
27.	Your child is easily disrupted by changes to his/her routine.	1. agree strongly 2. agree 3. undecided 4. disagree 5. disagree strongly

Do you have any additional concerns/comments about your child"s memory?

THANK-YOU FOR YOUR CO-OPERATION

APPENDIX 4. SEIZURE CHARACTERISTICS OF THE FLE SAMPLE

ID	Age	Gender	Side	Presence of Lesion	Age at CPS onset	Peak seizure frequency	Period since last seizure	Current Seizure Frequency	AED's
1	180	Female	Left	Yes	144	Daily	4	Greater than monthly	CBZ
8	129	Male	Right	No	72	Daily	0	Daily	VPA SUL
12	119	Male	Right	No	60	Weekly	1	Greater than monthly	CBZ TPM
13	148	Male	Left	Yes	96	Daily	0	Daily	LTG CLB
14	119	Female	Left	No	36	Weekly	1	Greater than monthly	VPA LEV LTG
15	166	Male	Right	Yes	96	Weekly	3	Greater than monthly	VPA LTG
16	173	Male	Right	Yes	60	Daily	9	Greater than monthly	OXC PHT
19	96	Male	Left	Yes	72	Daily	24	Greater than monthly	VPA
22	78	Female	Left	No	18	Daily	0	Daily	VPA LTG SUL

AED= anti-epileptic drug; CBZ = carbamazepine; cps = complex partial seizures; CLB = clobazam; CZP = clonazepan; GBP = gabapentine; GTCS = generalised tonic clonic seizure; ICU = intensive care unit; LEV= levetiracetam, LTG = lamotrogine; OXC = oxcarbazepine; PFC = prolonged febrile convulsion; PHT = phenytoin; SUL= Sulthiame, TPM = topiramate; VGB = vigabatrin; VPA = sodium valproate

Appendix 4 continued…

ID	Age	Gender	Side	Presence of Lesion	Age at CPS onset	Peak seizure frequency	Period since last seizure	Current Seizure Frequency	AED's
23	155	Female	Right	Yes	84	Daily	3	Greater than monthly	OXC
26	167	Female	Right	No	72	Daily	8	Greater than monthly	VPA LEV
29	199	Male	Right	Yes	168	Greater than monthly	23	Greater than monthly	CBZ
30	147	Male	Right	Yes	60	Daily	12	Greater than monthly	OXC TPM
31	107	Female	Right	No	89	Monthly	5	Greater than monthly	CBZ
34	136	Male	Left	Yes	24	Daily	0	Daily	OXC CLB
35	185	Male	Left	Yes	132	Daily	0	Greater than monthly	CBZ VPA LTG
36	178	Male	Right	No	84	Daily	2	Greater than monthly	
39	156	Female	Left	Yes	48	Daily	12	Monthly	CBZ

AED= anti-epileptic drug; CBZ = carbamazepine; cps = complex partial seizures; CLB = clobazam; CZP = clonazepan; GBP = gabapentine; GTCS = generalised tonic clonic seizure; ICU = intensive care unit; LEV= levetiracetam, LTG = lamotrogine; OXC = oxcarbazepine; PFC = prolonged febrile convulsion; PHT = phenytoin; SUL= Sulthiame, TPM = topiramate; VGB = vigabatrin; VPA = sodium valproate

APPENDIX 5. SEIZURE CHARACTERISTICS OF THE TLE SAMPLE

ID	Age	Gender	Side	Presence of lesion	Age at CPS onset	Peak seizure frequency	Period since last seizure	Current Seizure Frequency	AED's
2	140	Female	Left	No	108	Greater than monthly	13	Greater than monthly	CBZ
3	86	Female	Left	No	13	Greater than monthly	1	Greater than monthly	OXC
4	130	Male	Right	No	35	Weekly	0	Weekly	OXC
5	120	Male	Right	No	100	Monthly	1	Greater than monthly	CBZ
6	191	Female	Left	Yes	168	Greater than monthly	3	Greater than monthly	VPA LEV
7	134	Male	Left	No	127	Weekly	0	Weekly	OXC
9	165	Male	Left	No	154	Daily	0	Daily	LEV
10	202	Male	Right	No	168	Monthly	4	Greater than monthly	OXC
11	180	Female	Left	Yes	132	Daily	1	Greater than monthly	OXC LTG
17	121	Female	Left	Yes	108	Daily	4	Greater than monthly	CBZ OXC
18	159	Male	Right	Yes	132	Daily	27	Daily	CBZ

AED= anti-epileptic drug; CBZ = carbamazepine; CLB = clobazam; CZP = clonazepan; GBP = gabapentine; GTCS = generalised tonic clonic seizure; ICU = intensive care unit; LTG = lamotrogine; OXC = oxcarbazepine; PFC = prolonged febrile convulsion; PHT = phenytoin; TPM = topiramate; VGB = vigabatrin; VPA = sodium valproate

Appendix 5 Continued…

ID	Age	Gender	Side	Presence of lesion	Age at CPS onset	Peak seizure frequency	Period since last seizure	Current Seizure Frequency	AED's
20	171	Male	Right	Yes	150	Daily	17	Greater than monthly	OXC VPA
21	117	Female	Right	No	72	Weekly	0	Weekly	LEV LTG
24	191	Male	Left	Yes	24	Greater than monthly	1	Greater than monthly	CBZ
25	104	Female	Right	Yes	74	Greater than monthly	12	Greater than monthly	CBZ
27	95	Female	Right	Yes	72	Daily	0	Weekly	CBZ LEV
28	78	Female	Left	Yes	52	Daily	2	Greater than monthly	CBZ
32	93	Female	Right	No	60	Daily	2	Greater than monthly	VPA
33	84	Female	Left	No	72	Greater than monthly	1	Greater than monthly	CBZ
37	171	Male	Left	No	108	Monthly	0	Monthly	OXC
38	181	Female	Right	No	84	Monthly	1	weekly	OXC LTG

AED= anti-epileptic drug; CBZ = carbamazepine; CLB = clobazam; CZP = clonazepan; GBP = gabapentine; GTCS = generalised tonic clonic seizure; ICU = intensive care unit; LTG = lamotrogine; OXC = oxcarbazepine; PFC = prolonged febrile convulsion; PHT = phenytoin; TPM = topiramate; VGB = vigabatrin; VPA = sodium valproate

APPENDIX 6. THE RELATIONSHIPS BETWEEN MEMORY MEASURES IN FLE

	FLE	IQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	IQ	1	**.813****	.327	**.748****	**.459**	**.555***	**.497***	.283	.192	.209	-.298	**.534***	**.508***	**.625****	**.563***	**.667****	**.497***
1	**PhLp**		1	.385	**.680****	.426	**.543***	**.530***	.242	.279	-.051	-.288	**.516***	**.693****	**.778****	**.624****	**.556***	**.695****
2	**VSSP**			1	**.488***	.208	.099	.210	.275	-.102	.048	**-.476**	.061	.300	.245	.362	.335	.286
3	**CE**				1	**.636****	**.573***	**.647****	.172	-.061	-.066	-.268	**.523***	**.701****	**.733****	**.820****	**.808****	**.720****
4	**Total Words**					1	**.879****	**.515***	.121	.406	-.227	**-.486***	.389	**.683****	**.656****	**.695****	.408	**.626****
5	**List A Trial 1**						1	**.601****	.201	**.547***	-.250	-.346	**.488***	**.601****	**.613****	**.617****	.298	**.546***
6	**List A LDF**							1	.342	.191	-.257	.179	-.052	**.611****	.410	**.745****	**.521***	**.522***
7	**Semantic Cluster**								1	.220	.313	-.108	-.096	.001	.001	.042	.315	-.008
8	**Pers**									1	.074	.063	.065	.290	.246	.248	.013	.220
9	**Intrusions**										1	-.085	-.146	-.221	-.245	-.138	.136	-.265
10	**False Pos**											1	-.408	-.316	-.307	-.202	.012	-.218
11	**RCF- Recall**												1	.362	**.685****	.260	.292	.485
12	**Word reading**													1	**.850****	**.887****	**.610****	**.969****
13	**Sentence Comp**														1	**.724****	**.674****	**.929****
14	**Spelling**															1	**.689****	**.855****
15	**Math Comp**																1	**.691****

APPENDIX 7. THE RELATIONSHIP BETWEEN MEMORY MEASURES IN TLE

	TLE	IQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	IQ	1	.678**	.151	**.551****	.440*	.120	.229	.089	.033	-.380	-.428	.314	**.651****	**.717****	**.650****	**.561****	**.753****
1	**PhLp**		1	.357	**.440***	.333	-.053	.305	.061	.181	-.238	**-.471***	**.695****	.313	**.557****	.240	.339	**.479***
2	**VSSP**			1	.172	.379	.333	.143	.309	-.215	.138	.092	.325	.177	.049	-.118	.556**	.120
3	**CE**				1	.382	.080	**.492***	.266	.144	-.051	-.112	.419	**.727****	**.586****	**.566****	.425	**.723****
4	**Total Words**					1	**.625****	**.546***	.417	-.028	-.139	**-.447***	.424	.414	**.459***	.258	.118	**.481***
5	**List A Trial 1**						1	-.013	.193	-.368	-.219	.059	.152	.217	.216	.004	-.033	.235
6	**List A LDF**							1	**.508***	.083	.195	-.406	.415	**.502***	**.501***	.287	.096	**.552****
7	**Semantic Cluster**								1	-.187	.338	.028	.242	**.513***	.370	.210	.237	**.481***
8	**Pers**									1	.327	-.001	.108	-.122	.085	-.050	-.014	-.017
9	**Intrusions**										1	.393	-.051	-.002	-.263	-.225	.096	-.145
10	**False Pos**											1	**-.543***	-.055	-.319	-.139	.089	-.209
11	**RCF- Recall**												1	.305	.344	-.041	-.020	.368
12	**Word reading**													1	**.657****	**.790****	**.452***	**.917****
13	**Sentence Comp**														1	**.556****	.339	**.902****
14	**Spelling**															1	**.437***	**.750****
15	**Math Comp**																1	**.430**

THESIS ADDENDUM

I. GENERAL COMMENTS

1. With regard to the Rey Complex Figure Test Copy and Organization scores, these variables were included as an exploratory analysis, and therefore only included within the models depicted in Figure 8.3 and 8.4. Both of these scores were correlated with long delay free recall of the RCF, though not with non-verbal span (Visuospatial Sketchpad) in either population, and therefore it was considered to shift the focus of the research into executive functioning rather than memory and therefore more thorough investigation using these variables was not pursued.

2. The RCFT, although used widely as a measure of visual memory in both clinical and research settings, is undoubtedly an impure measure of visual memory insofar as it has an inherent executive functioning component. For this reason, the RCF long delay free recall score was also not used as a predictor of any of the academic skill performance variables, which are largely verbally based. We were aware of the limitations associated with the RCFT as a memory measure during the planning phase of our study and indeed considered alternatives. As you are aware, there is no gold standard to assess visual memory and we were at a loss to find a task that was superior to the RCFT. The Nine Box Maze Test – Child Version (Pentland et al., 2002) was developed by the primary supervisor of this project and was considered as an alternative measure of visuo-spatial memory. However, the construct validity of this task is not fully understood, particularly in terms of the weight of working memory versus long term memory demands. Whilst it would have been extremely interesting to include this task, it may have been difficult to determine if findings were due to differences specific to the clinical populations or task effects. Further, the task is quite long and limits needed to be placed on the protocol, which was already in the order of 3 hours. Thus after much thought, we elected to persist with the RCFT, primarily because it's widely utilized and data can be interpreted in terms of its known limitations.

3. Multiple correlations depicted in Figure 8.3 and 8.4 were not corrected for statistically, as this would have almost eliminated any ability to detect significant associations. This is recognized as a significant limitation, and therefore this model was offered as a very preliminary and exploratory investigation of the possible relationships between memory and learning factors that may serve as a starting point for future research. Statistical modeling/path analysis would be the optimal approach though could not be undertaken due to restrictions of sample size.

4. Given the primary aims were to characterize the nature of impairment and investigate possible influences for such impairments, more thorough investigation of the developmental trajectories in learning and memory were not conducted initially. However, adding age as an independent predictor would have added to our understanding of developmental influences on working memory. As per your suggestion, age was entered into a Stepwise Regression analysis with Central Executive as the dependent variable, and both span tasks (Phonological Loop and Visuospatial Sketchpad) included with Age as predictor variables. The results have been included and strengthen the interpretations and conclusions of this study. Specifically, given that Age was not found to be a significant predictor of WM in children with FLE may be reflective of conclusions that WM as a system is more mature within this group. In contrast, the additional influence and predictive value of Age in children with TLE strengthens the conclusion that children with TLE appear to demonstrate a more immature working memory system overall.

5. Page 172 “age consistent interrelationships between subcomponents of the working memory model” refers to the pattern of correlations observed between subtasks of the WMTB-C. Children with frontal and temporal lobe epilepsy demonstrated non-significant relationships between the verbal and non-verbal span tasks, though demonstrated significant associations with the central executive. According to Gathercole (1998) this is a typical pattern of performance for children at 12 years of age, which coincides with the mean age of both the FLE and TLE children in the current study.

II ADDENDUM

p.40, last sentence, Add:

Finally, prospective memory refers to the ability to bind together necessary actions or goals with the appropriate time in which to carry out the task (Burgess, Quayle, & Firth, 2001). This skill is considered to be subsumed by the frontal lobes (Burgess et al., 2001), and is critical for the execution of everyday living tasks. Prospective memory will not be explored further in this research, as the focus of this study is to explore the interface between frontal and temporal lobe memory functioning within the limits of WM and LTM respectively. However consideration to the effects of prospective memory impairments in these groups requires further investigation.

p.66, at the end of the first paragraph (beginning on p.65) Add:

Futhermore, neuroimaging studies have indicated that symptomatic partial epilepsies do not by definition exclude extralobar pathology. Widjaja, Mahmoodabadi, Snead III, Almehdar, and Smith (2011) were able to demonstrate that cortical changes and thinning occur in temporal lobe regions in children with intractable FLE. Similarly, Kaaden, et al., (2011) reported that early onset TLE negatively impacted neurodevelopment, though excess grey matter was not restricted to the temporal cortices and was found mainly in frontal regions.

p.73 para 3, replace first sentence with:

There is mounting evidence to support the impact of epilepsy on memory functioning in children. Neuroanatomical studies indicate that not only is FLE in children associated with widespread cortical thinning (Widjaja, 2001), but also that TLE impacts development of gray matter within the frontal lobes. These conclusions coupled with those from pediatric studies lend variable support to the notion of a double dissociation of executive/working memory and LTM functioning in children with FLE and TLE.

p.113, Table 7.3, p.137, Table 8.01 and p.139 Table 8.02 Add:

FLE= Frontal lobe epilepsy; TLE = Temporal lobe epilepsy

p.140 Figure 8.1:

Y- axis to denote raw scores on CVLT-C, X-axis to denote trial condition of CVLT-C; CVLT-C = California Verbal Learning Test-Children

p.143 para 2, add new paragraph:

There were no significant differences between children with left (M=-.6 , SD=1.38) and right (M =.35, SD =1.18) temporal lobe epilepsy on performance on the CVLT-C Long Delay Free Recall $t(19)=-1.75$, p =.09. There were also no significant differences between left (M=-1.33, SD=1.04) and right (M=-.80, SD=1.12) TLE on the RCF long delay free recall trial $t(18)=-1.08$, p = .29.

Similarly, there were no significant differences between children with left (M=-.5, SD=1.0) and right (M=.20, SD=.48) frontal lobe epilepsy on performance on the CVLT-C Long Delay Free Recall $t(16)=-1.96$, p =.07. Children with left (M=-.85, SD=.80) and right (M=-1.35, SD=1.51) FLE also did not display any significant differences on the RCF long delay free recall trial $t(15)=.83$, p = .42.

p.147 para 1, add new paragraph:

Analysis of children with FLE indicated that the independent variable with the highest zero-order correlation with Central Executive performance was the Phonological Loop score, which significantly accounted for 43% (adjusted R^2) of the variance in Central Executive performance $F(1,16) = 13.80$, $p < .05$. Neither Age ($t(16)=1.45$, $p=.17$) nor Visuospatial Sketchpad ($t(16)=1.38$, $p=.19$) performance added sufficient predictive strength to warrant inclusion.

Stepwise regression analysis in children with TLE indicated that Phonological Loop displayed the highest zero-order correlation with Central Executive performance and significantly accounted for 15% (adjusted R^2) of the variance in Central Executive performance ($F(1,19)=4.55$, $p=.05$). However in this instance, Age also produced a significant increment to R^2, after having taken into account the Phonological Loop predictor already in the equation. Together these variables accounted for 32% (adjusted R^2) of the variance in Central Executive performance ($F(2,18)=5.59$, $p=.01$). Visouspatial Sketchpad was not a significant predictor of Central Executive performance ($t(19)=.51$, $p=.62$).

p.159 para 1, line 4,second sentence should read:

Similarly, consistent with expectation, parent ratings on the observer memory questionnaire indicated that children with TLE also display significantly more frequent and consistent pattern of everyday memory functioning impairments.

p. 161 and 162; Figure 8.3 and 8.4 respectively: Add underneath the Figure Title:

PERS = perseverations; FP=false positives; INT=intrusions; CVLT-C= California Verbal Learning Test-Children's version; PhL= phonological loop; VSSP= Visuospatial Sketchpad; RCF=Rey Complex Figure; LTM=Long term memory; Comp=comprehension

III. TYPOGRAPHICAL ERRATA

p. 24 para 1, sentence 3: "Figure 2.3" for "Figure 5"

p.24 Figure 2.3: "Articulatory Rehearsal" for "Articulatory rehearsal"

p. 26 para 3, last sentence: "Figure 2.4" for "Figure 4"

p.36, Figure 3.1: "Lateral frontal lobe divisions in the human brain" for "Frontal lobe divisions in the human brain"

p.39 para 2 sentence 3: "with" for "between"

p.73 para 3 first sentence: "impairments" for "functioning"

p.76 para 1 first sentence: remove "is a significant factor that"

p.79 para 1 first sentence: "Identifying the impact of the abovementioned factors is" for "These factors are"

p.81 para 1 first sentence: add "for childhood epilepsy populations as a whole" at the end.

P.99 para 1line 4: add “primarily” between “working memory” and “is”

p.100 para 1 first sentence: end sentence following discussed with “.” for “,”

p 101. Line 3: “were” for “are”

p.111 para 1 last sentence: remove “(Psychological Corporation, 1999)”

p. 110 para 1, line 10: “mild” for “moderate”

p.161 Figure 8.3, and p.162 Figure 8.4; Legend, Line 6: “Significant deviations…” for “Non-significant deviations…”

p.141 para 1: remove first sentence

p.125 Table 7.5: remove Copy Score and Organization Score from Table 7.5

IIII ADDITIONAL REFERENCES

Burgess, P.W., Quayle, A., & Frith, C.D (2011). Brain regions involved in prospective memory as determined by positron emission tomography. *Neuropsychologia, 39* p. 545-555

Widjaja, E., Mahmoodabadi, S.Z., Snead II, O.C., Almehdar, A., & Smith, M.L (2011). Widespread cortical thinning in children with frontal lobe epilepsy. *Epilepsia, 52*(9) p. 1685-1691

Kaaden, S., Quesada, C.M., Urbach, H., Koenig, R., Weber, B., Schramm, J., Rudinger, G., & Helmstaedter, C. (2011). Neurodevelopmental disruption in early-onset temporal lobe epilepsy: Evidence from a voxel based morphometry study. *Epilepsy and Behavior, 20* p.694-699