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Long-Term Memory in Children with Epilepsy

Michael Benjamin Gascoigne

A thesis submitted in fulfilment of the requirements for the degree of Doctor of
Clinical Psychology/Doctor of Philosophy

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LIST OF ABBREVIATIONS

ADHD: Attention Deficit Hyperactivity Disorder
AH: Abnormal Hippocampus
AI: Autobiographical Interview
ANCOVA: Analysis of Covariance
ANOVA: Analysis of Variance
AED: Anti-epileptic drug
ALF: Accelerated Long-Term Forgetting
CAI: Children’s Autobiographical Interview
CCT: Classic Consolidation Theory
CHW: The Children’s Hospital at Westmead
CMS: Children’s Memory Scale
CVLT-C: California Verbal Learning Test - Children’s Version
DA: Developmental Amnesia
EEG: Electroencephalogram
EMQ: Everyday Memory Questionnaire
FSIQ: Full-Scale Intelligence Quotient
GASE: Global Assessment of Severity of Epilepsy
HC: Healthy Control
IGE: Idiopathic Generalised Epilepsy
IQR: Interquartile Range
LD: Learning Difficulty
MRI: Magnetic Resonance Imaging
MTT: Multiple Trace Theory
MTL: Mesial Temporal Lobe
NH: Normal Hippocampus

SES: Socioeconomic status

TEA: Transient Epileptic Amnesia

TLE: Temporal Lobe Epilepsy

WASI: Wechsler Abbreviated Scale of Intelligence

WISC-IV: Wechsler Intelligence Scale for Children Fourth Edition

WMTB-C: Working Memory Battery for Children

WRAML2: Wide Range Assessment of Memory and Learning: Second Edition
CERTIFICATION BY CANDIDATE

The work contained in this thesis has not been submitted for a higher degree to any other university or institution. All of the work was carried out during my PhD candidature at the University of Sydney under the supervision of Dr Suncica (Sunny) Lah. The studies reported in this thesis were conducted at the Children’s Hospital at Westmead, Sydney, Australia, and The Hospital for Sick Children, Toronto, Canada. All data in these studies was acquired through direct client contact. Treating neurologists and a neuropsychologist assisted with patient recruitment and the preparation of these manuscripts; they appear as co-authors in the manuscripts contained within this thesis.

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ABSTRACT

Memory difficulties represent a common clinical complaint in patients with epilepsy, yet these complaints are often unrelated to learning and recall of this newly learned information after short (20-30 min) delays employed on standardised memory tests. It has been proposed that reported memory difficulties may refer to (i) a faster rate of forgetting of newly-learned materials over long delays relative to standard, short delays (accelerated long-term forgetting; ALF) or (ii) impaired recall of information from the past: autobiographical memory that contains episodic (re-experiencing of personal events) and semantic (factual information) components. To date, studies of ALF and autobiographical memory have largely focussed on adults, with relatively little attention given to children with neurological disorders. This represents a notable gap, as the underlying substrates of neurological problems can differ between the mature and developing brain. These two memory deficits have also been largely studied in patients with temporal lobe epilepsy (TLE) and often attributed to disruption of the mesial temporal lobe function or the presence of hippocampal lesions. As long-term memory formation is thought to demand an interaction between medial temporal and neocortical networks, it is possible that memory consolidation could be disrupted by seizures themselves. Thus, long-term memory deficits could feasibly be found in epilepsy patients who have no detectable cortical pathology, such as those with idiopathic generalized epilepsy (IGE). This thesis includes studies which assess ALF and autobiographical memory in children with TLE and in those with IGE. A general introduction to memory deficits in patients with epilepsy is presented in Chapter 1, while Chapter 2 examines literature related to the phenomenon of ALF and memory consolidation theory. In Chapter 3, the existence of
ALF is assessed in 23 children with TLE and 58 healthy control participants of comparable age, sex, and parental socioeconomic status. All participants completed a battery of neuropsychological tests, which included a measure of verbal learning and recall after short (30-min) and long (7-day) delays. Compared to the control group, the TLE group recalled significantly fewer words at the 7-day delay compared with the 30-min delay. Age was also negatively correlated with the recall of words after short- and long-term delays within the TLE group, where older age was associated with worse memory. Using a similar methodology, Chapter 4 examines ALF in 20 children with IGE and 41 similarly-matched controls. Children with IGE recalled significantly fewer words after a 7-day, but not 30-min delay relative to the control participants. Moreover, greater epilepsy severity was associated with poorer 7-day verbal recognition.

Chapter 5 introduces the concept of autobiographical memory deficits and the theories that attempt to account for them, namely Classic Consolidation Theory and Multiple Trace Theory. In Chapter 6, the Children’s Autobiographical Interview was used to assess autobiographical memory performance in 21 children with TLE and 24 healthy controls. Children with TLE were found to recall fewer episodic details than controls (but only when no retrieval prompts were provided), while no between-group difference was found for the recall of semantic autobiographical details. Unlike controls, the number of episodic details recalled did not increase significantly with age among patients with TLE and was also found to be unrelated to a range of epilepsy factors, including epilepsy severity, side of seizure focus or the presence of structural hippocampal abnormalities. In Chapter 7, an identical methodology is used to assess autobiographical memory deficits in 18 children with IGE and 42 controls.
Children with IGE recalled significantly fewer episodic details than controls, irrespective of whether retrieval support was provided. Earlier age of seizure onset and higher proportion of life spent with epilepsy were both associated with the recall of fewer episodic details.

In summary, first, findings of our studies revealed deficits in long-term memory in children with TLE, but also in children with IGE. The detection of memory deficits in children with IGE suggests that long-term memory consolidation may not only be disrupted by temporal lobe pathology or seizure focus, but also by generalised seizures, which could contribute to ALF and deficits in autobiographical recall. Second, our findings suggest that long-term memory deficits may gradually emerge in children with TLE, where older children are more likely to present with deficits in recalling past events and newly-learned information.
CHAPTER 1: General Introduction
Core Epilepsy Background Information

Epilepsy is a relatively common brain disorder, which often has onset during childhood. Epilepsy is characterized by predominantly unpredictable and recurrent interruption to normal brain function through epileptic seizures (Fisher et al., 2005). Epilepsy is not a singular disease, but encompasses a variety of disorders that emanate from dysfunction within the brain, which may be due to different causes. In Australia, the estimated prevalence of epilepsy is 4-8 per 1000 children aged 0-14 (AIHW, 2005).

Seizures, manifestations of epilepsy, are transient events that usually occur when there is a sudden disruption in the electrical activity of the brain. They may be accompanied by altered consciousness and/or other behavioural manifestations. Most seizures have little long-lasting consequences, however, recurrent seizures can result in a number of health consequences, including cognitive deficits, brain damage, physical injury to both the patient and others (Ficker et al., 1998). Status epilepticus, a potentially life-threatening condition characterised by continuous seizures, can lead to sustained loss of consciousness and respiratory distress.

A widely-accepted classification system of epilepsies and seizures is important for both research and clinical practice with epilepsy patients. Commonly used classification schemes were those published by the International League Against Epilepsy (ILAE) during the 1980s, for both seizures (Commission on Classification and Terminology of the International League Against Epilepsy, 1981) and epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). This classification system separated epilepsies with generalized
seizures (generalized epilepsy) from those with partial or focal seizures (localization-related, partial or focal epilepsies) (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) and also categorised epilepsy syndromes as symptomatic (where seizures are the result of one or more identifiable structural lesions), idiopathic (a syndrome with no accompanying structural lesions or other neurological signs; presumably a genetic cause) or cryptogenic (syndromes that are believed to be symptomatic, but no aetiology can be identified) (Engel, 2006).

However, as this classification system predated modern neuroimaging, genomic technologies and concepts in molecular biology, the classification for seizures and epilepsy was again recently updated by the ILAE (Berg et al., 2010). In this new classification system tracing the causal factor of epilepsies plays a major role (van Campen, Jansen, Brouwer, Nicolai, & Braun, 2013). One of the main changes brought about by this recent revision of the classification system was the re-categorisation of epilepsies by aetiology. Epilepsies were therefore no longer classified as “symptomatic”, “idiopathic” or “cryptogenic”, but were instead categorised into genetic, structural-metabolic and unknown causes. Given that the new classification system was published after commencement of the present project and has still not been regularly implemented in clinical practice, this thesis adopts terminology from the earlier classification system.

Idiopathic Generalised Epilepsy (IGE) is the most common form of the disorder in children and adults, representing about 60% of cases worldwide (World Health Organisation, 2012). Patients with IGE present with primary generalised seizures (Mattson, 2003) which originate within networks distributed across both hemispheres.
On electroencephalogram (EEG) measures, these discharges are generalized, bilateral, synchronous and symmetrical (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). IGE does not have an obvious cause (although a genetic predisposition may exist) and is characterised by a macroscopically normal brain, as per structural MRI/CT brain scans. Children with IGE typically present with average intelligence and have normal clinical neurological examination. IGE is also considered to be a relatively benign form of childhood epilepsy, as seizures are usually easy to control with medication and many children “grow out” of this form of epilepsy. Nevertheless, children with IGE have a substantially increased risk of cognitive, academic and behavioural difficulties (Bailet & Turk, 2000; Echenne, Cheminal, Roubertie, & Rivier, 2001). Given that there is no evidence of focal structural or functional brain abnormalities either on brain scans or on EEG, IGE populations can therefore be employed to examine the impact of seizure activity itself on various cognitive functions, including memory.

Temporal Lobe Epilepsy (TLE), a form of focal epilepsy, often has an identifiable cause, such as a tumour, congenital abnormality, head trauma, brain damage from birth (such as from a lack of oxygen) or an infection, such as encephalitis. TLE is characterized by complex partial seizures, which start focally within the brain and affect either one lobe or an entire hemisphere (Berg et al., 2010). Complex partial seizures may also spread to the rest of brain, known as secondary generalized seizures.
The classification of epilepsy syndromes in the papers presented in the current thesis was conducted in accordance with ILAE guidelines by treating neurologists in specialized epilepsy programs within children’s hospitals.

**Brief History of Memory Research in Patients with Epilepsy**

The number of studies examining memory in patients with epilepsy increased markedly following the publication of the case study of H.M., a 29 year-old patient with a long history of major and minor intractable seizures, who developed amnesia following a bilateral hippocampal excision (Scoville & Milner, 1957). Following the operation, H.M. could not recognise the staff, navigate through the building or recall day-to-day events of his recent life in hospital. He was also unable to recall some personally-experienced events, such as the death of a favourite uncle three years previously. This experimental and radical procedure (albeit justified by the severity of the patient’s seizures) nevertheless highlighted the importance of the hippocampal region for normal memory function.

Since the publication of this case study, memory research in patients with epilepsy has largely involved adults with TLE. While bilateral temporal lobectomy has been long abandoned, unilateral temporal lobectomy has remained a treatment of choice for patients with intractable epilepsy. In 1968, Milner’s observations of memory outcomes in patients who underwent unilateral TLE gave rise to the theory of Material Specificity (Milner, 1970). She noticed that patients presented with a specific memory deficit that was related to the side of surgical treatment, often with unilateral temporal lobe epilepsy.
These deficits are understood to be limited to a particular type of stimulus material, though not necessarily a particular sensory mode (Milner, 1968). For instance, damage to the left, language-dominant, hippocampus has been associated with difficulties in learning and short-term recall of verbal materials such as words and prose passages, either before or after mesial temporal lobe excision (Davies, Bell, Bush, & Wyler, 1998; Hermann, Seidenberg, Schoenfeld, & Davies, 1997; Rausch et al., 2003; Tanriverdi & Olivier, 2007). Similarly, but somewhat less consistently, damage to the right, language non-dominant hippocampus, has been linked with difficulties in the learning and retention of nonverbal materials, such as faces (Barr, 1997), and other visuospatial information (Bengner et al., 2006; Gleißner, Helmstaedter, & Elger, 1998; Glosser, Cole, Khatri, DellaPietra, & Kaplan, 2002; Nunn, Polkey, & Morris, 1998; Smith & Milner, 1989).

Several other epilepsy-related variables have also been shown to increase a risk of impaired learning and recall of information after short delays: (i) mesial (rather than lateral) site of lesion within the temporal lobe (Burgerman, Sperling, French, Saykin, & O'Connor, 1995; Gonzalez, Anderson, Wood, Mitchell, & Harvey, 2007; Helmstaedter, Grunwald, Lehnertz, Gleißner, & Elger, 1997), (ii) a greater number of anti-epileptic drugs (Alessio et al., 2004), (iii) earlier age of seizure onset (Kaaden & Helmstaedter, 2009) and (iv) higher proportion of life spent with epilepsy (Jokeit & Ebner, 1999; Jokeit & Ebner, 2002).

Recently, a focus of memory research in patients with epilepsy has shifted from learning and recall of information after short delays to the formation of long-term memory and recall of information from the past. Barr, Goldberg, Wasserstein and
Novelly (1990) conducted the first group study that examined this aspect of memory in patients with TLE. Deficits were found in memory for famous faces and events, and in recall of autobiographical information. Studies that followed confirmed that patients with unilateral TLE have significant deficits in recall of autobiographical memories (Herfurth, Kasper, Schwarz, Stefan, & Pauli, 2010; St-Laurent, Moscovitch, Levine, & McAndrews, 2009) and factual information from the past, such as public events (Haag et al., 2010; Lah, Grayson, Lee, & Miller, 2004) or famous faces (Voltzenlogel et al., 2006). Finally, studies into long-term memory formation that examine the recall of newly-learned information after long delays have also taken hold in the adult literature. Several studies of adults with TLE have observed a faster rate of forgetting of newly-learned information over long delays (i.e. days or weeks) relative to shorter delays (i.e. 30-mins), for both verbal (Blake, Wroe, Breen, & McCarthy, 2000; Martin et al., 1991) and visual information (Muhlert et al., 2011).

Memory Research in Children with Epilepsy

In children with TLE, a number of studies have found evidence of deficits in the learning and recall of both verbal and nonverbal information after short delays employed by standardised tests (Cohen, 1992; Rzezak, Guimarães, Fuentes, Guerreiro, & Valente, 2011; Rzezak, Guimarães, Fuentes, Guerreiro, & Valente, 2012; Schoenfeld et al., 1999). Moreover, these memory deficits appear to be particularly severe in children with TLE, when compared to children with different seizure types and epilepsy syndromes. For instance, compared to children with IGE, those with TLE have been shown to have greater deficits in short-term verbal and nonverbal recall (Jambaqué, Dellatolas, Dulac, Ponsot, & Signoret, 1993). A later
study also found that children with TLE had the worst memory function on all verbal and most visual standardised tests of memory, compared to children with several other types of epilepsy, including IGE (Nolan et al., 2004).

In children with TLE, the pattern of memory impairments appears to differ to the pattern found in adults. For example, verbal memory deficits that are often found in adults with left-TLE, were found to be unrelated to the side of seizure focus in children with TLE (Gonzalez et al., 2007; Lendt, Helmstaedter, & Elger, 1999; Mabbott & Smith, 2003). Similarly, deficits in memory for visual information, which tend to be associated (albeit inconsistently) with a right-hemisphere seizure focus in adults, are often found to be unrelated to the side of seizure focus in children with epilepsy, with the possible exception of facial recognition (Beardsworth & Zaidel, 1994; Chiaravalloti, Tulsky, & Glosser, 2004; Gonzalez et al., 2007; Mabbott & Smith, 2003).

Some evidence also suggests that these memory deficits in patients with TLE gradually emerge between childhood and adolescence. For example, a large-scale cross-sectional study of patients with TLE found that deficits in the short-term recall of verbal information were not evident in children, but were only apparent in older members of the cohort, suggesting that memory deficits may emerge during young adulthood or adolescence (Helmstaedter & Elger, 2009). In a subsequent longitudinal study, Gonzalez et al. (2007) found no evidence of verbal memory deficits in a group of children with TLE, but later found evidence of these deficits when the group were reassessed during their teenage years (Gonzalez, Mahdavi, Anderson, & Harvey, 2012).
Although learning and recall of information after short delays has been examined in children with epilepsy, long-term memory abilities nevertheless remain under-researched in this population. One study, however, has examined recall of newly-learned information in children with epilepsy beyond a standard 30-minute delay (Davidson, Dorris, O'Regan, & Zuberi, 2007), while virtually none have examined autobiographical memory in this population.

The lack of research into long-term memory deficits within a paediatric epilepsy population also represents a notable gap that needs to be addressed for several reasons. Firstly, there remains a possibility that deficits in autobiographical memory or accelerated forgetting may partly contribute to memory complaints in children with epilepsy. These memory deficits may not be adequately addressed by standardised memory assessments which typically only test recall after a maximum delay of 30 minutes, which could potentially mean that long-term memory deficits remain undetected. A failure to detect a long-term memory deficit could adversely impact the child’s self-esteem, especially if the memory deficit is contributing to a cognitive, behavioural or academic difficulty (Bailet & Turk, 2000; Jackson et al., 2013) or will limit their independence and productivity during adulthood (Butler & Zeman, 2008).

Secondly, when assessing potential long-term memory deficits in children with epilepsy, paediatric neuropsychologists should be able to rely on research conducted specifically with paediatric epilepsy populations, rather than adults, as the underlying substrates of neurological problems appear to differ between these populations (Smith, 2010). Furthermore, the emergence of epilepsy will have different effects on adult and child populations: in the former group, epilepsy could lead to the loss of an
established cognitive function, whereas it is more likely to interfere with the development of one in children.

**Aims of this Thesis**

This thesis aims to examine two interrelated forms of explicit memory impairment, accelerated long-term forgetting and autobiographical memory impairment, in children with epilepsy. The existence of both of these memory deficits will be explored in separate samples of children, diagnosed with either TLE or IGE, and compared to a sample of healthy control children. Exploring these memory deficits in different sub-types of epilepsy will help determine whether these memory abilities are adversely affected by primary generalised seizures and in what way temporal lobe abnormalities may affect memory, over and above seizures themselves. Chapter 2 reviews the literature related to ALF and memory consolidation theory, while Chapters 3 & 4 examine the existence of ALF in children with TLE and IGE, respectively. Evidence from adult studies and theories related to autobiographical memory deficits is reviewed in Chapter 5, while autobiographical memory deficits are examined in children with TLE and IGE in chapters 6 and 7, respectively.

**References**


Glosser, G., Cole, L., Khatri, U., DellaPietra, L., & Kaplan, E. (2002). Assessing nonverbal memory with the Biber Figure Learning Test—Extended in temporal lobe epilepsy patients. *Archives of Clinical Neuropsychology, 17*(1), 25-35. doi: http://dx.doi.org/10.1016/S0887-6177(00)00093-7


CHAPTER 2: Accelerated Long-Term Forgetting in Children with Epilepsy
Long-term memory formation is thought to require consolidation, which refers to the stabilization of a memory trace after the initial acquisition of information and is divided into two specific processes: i) synaptic-level consolidation, which refers to the rapid cascade of changes within local neurons hours after learning (Dudai, 2004) and ii) systems-level consolidation, a comparatively slower process involving interaction between different neural systems, resulting in the reorganization of memories into different parts of the brain that support memory storage (Squire, 1986; Squire & Alvarez, 1995). The latter process is the focus of this chapter.

Contemporary theories of systems-level memory consolidation have been informed by experimental observations dating back to the late 19th and early 20th centuries. For instance, the idea of memory reorganization was originally suggested by Ribot, after he observed that physical damage to the brain was more likely to result in temporally graded amnesia, manifested by deficits in the recall of recent, rather than remote events (Ribot, 1882). This pattern of amnesia is known today as Ribot’s law and implies that memories need time to be fully consolidated.

Experiments conducted by Muller and Pilzecker (1900) provided further empirical support for the idea of consolidation, after they observed that the learning of new information could disrupt the memory of previously-learned information if insufficient time had passed to allow the original information to be consolidated. This suggested that new memories are vulnerable to disruption and that learning does not necessarily result in an instantaneous formation of a permanent memory, but rather takes time to become fixed. Once experienced, a memory can be processed and
stabilized from a vulnerable to secure state in permanent long-term memory stores (Lechner, Squire, & Byrne, 1999).

Traditional models conceived memory as a single entity with consolidation taking place over one stage of processing. For instance, according to Hebb’s dual-trace hypothesis (Hebb, 1949), reverberatory neural activity formed a short-term memory trace and the repetition of this activity could bring about cellular changes which lead to synaptic connections, which were thought to form the basis of long-term memory (Seung, 2000). The formation of long-term memories was also assumed to take place rapidly, with some believing that memories could be fully consolidated into long-term memory stores after one hour (Kapur et al., 1997).

Instead of conceptualizing memory as a single entity or unitary phenomenon, McGaugh (1966) proposed that different systems may be responsible for initial learning, short-term memory and long-term recall. This idea was partly based on evidence from studies which suggested there was a distinction between short-term and long-term memory, such as the case of patient HM, who exhibited temporally-limited amnesia for past events and an inability to learn and recall new information following bilateral medial temporal lobe excision (Scoville & Milner, 1957) or patients with closed head injuries who exhibited temporally-graded memory loss for past events that could last for months (Russell & Nathan, 1946). These studies suggested that memory was not a unitary phenomenon, but rather a fractionated system with distinct components responsible for forming long-term memories (Squire & Zola-Morgan, 1991).
Distinct brain regions were also identified to participate in the system-level consolidation process. For instance, a model devised by Marr (1971) identified the hippocampus as a short-term memory storage site, holding information from the day’s events before transferring this information to the neocortex where it is reorganized (largely taking place during sleep). Components of this model, particularly the time-limited role of the hippocampus in the storage and retrieval of memory, form the basis of memory consolidation models that are used today.

In 1984, Squire, Cohen and Nadel proposed a two-stage model of memory consolidation, termed the standard consolidation model (or Classic Consolidation Theory, henceforth referred to as CCT), which suggested that multiple processing stages were involved in memory consolidation. According to this model, any perceptual, cognitive or motor information registered during wakeful experience is initially encoded in several cortical regions, including the neocortex and hippocampus. The hippocampus then rapidly forms an association between various elements of events and experiences to form a coherent memory trace, allowing for explicit retrieval of the contents of the experience (Eichenbaum, 2004; McClelland, McNaughton, & O'Reilly, 1995).

Due to the fast changing synapses within the hippocampus, a memory trace can only be stored in this region temporarily. In order for memories to be permanently stored, the hippocampus relinquishes its storage role before gradually transferring information to neocortical regions, which contain comparatively slower-changing connections that are capable of longer-term storage.
This gradual transfer of memory to the neocortex involves a prolonged, longer-term interaction between the hippocampus and extratemporal circuits, achieved through the reactivation of hippocampal-cortico networks by either recalling or rehearsing the material or via offline processing (i.e. the processing of memories out of conscious awareness, such as during sleep) (Squire & Alvarez, 1995). The reactivation of these networks strengthens existing cortico-cortical connections and also establishes new ones within neocortical areas, which eventually allows memories to become independent of the hippocampus and integrated with pre-existing memories based in the neocortex (McClelland et al., 1995). Systems-level consolidation, which according to Squire, Cohen and Nadel (1984) may take weeks, months or even years, is complete when information is completely independent of the hippocampus and permanently stored in extrahippocampal circuits (Alvarez & Squire, 1994). By this stage, memories have been transformed from a temporary to a more permanent state, where they are less vulnerable to disruption.

From the perspective of CCT, the storage of long-term memory could feasibly be compromised by disruption to the consolidation process, or by damage to neocortical storage sites or the hippocampus itself. Because of the latter reason, it is perhaps not surprising that many studies of long-term memory formation have focussed on patients with TLE.

Some studies of patients with TLE have found that, compared to healthy controls, they exhibit an unusually rapid rate of forgetting over long delays, such as days or weeks (Blake, Wroe, Breen, & McCarthy, 2000; Jansari, Davis, McGibbon, Firminger, & Kapur, 2010; Kapur et al., 1997; Mameniskiene, Jatuzis, Kaubrys, &
This phenomenon has been referred to as “accelerated long-term forgetting” (henceforth referred to as ALF) or long-term amnesia (LTA; Kapur et al., 1997; Mayes et al., 2003). Originally noticed in a series of case studies, ALF was initially found in patients with encephalitis (O’Connor, Sieggreen, Ahern, Schomer, & Mesulam, 1997), head injury (Kapur et al., 1996), or for unknown reasons (Kapur et al., 1997). Notably, however, all of these patients also suffered from epilepsy.

A number of explanations have been put forward for ALF. As CCT proposes that sleep plays a role in memory consolidation (Squire & Alvarez, 1995) and epilepsy itself has been associated with sleep disturbances (De Weerd et al., 2004; Lopez-Gomariz, Hoyo-Rodrigo, & Rodriguez-Nieto, 2004), a possible association between ALF and abnormal sleep patterns has been previously raised (e.g. Muhlert et al., 2011). No study to date, however, has specifically examined the relationship between ALF and sleep variables. Consistent with CCT and the role of the hippocampus in encoding new memories, ALF has been found in patients with TLE and attributed to the presence of hippocampal pathology or temporal lobe seizure focus (Blake et al., 2000; Jansari et al., 2010; Kapur et al., 1997; Mameniskiene et al., 2006; Martin et al., 2005; Muhlert et al., 2011; O’Connor et al., 1997; Wilkinson et al., 2012). ALF has also been documented in patients with transient epileptic amnesia (TEA) (Butler et al., 2009; Manes, Graham, Zeman, de Luján Calcagno, & Hodges, 2005; Muhlert, Milton, Butler, Kapur, & Zeman, 2010), a form of epilepsy related to TLE, characterized by recurrent brief episodes of memory loss and difficulties with autobiographical memory.
Numerous questions about the nature of ALF remain, such as the role of the hippocampus in this memory deficit. ALF has been documented in adults with TLE, even when samples included only a small proportion of patients with demonstrable hippocampal lesions (Blake et al., 2000; Mameniskiene et al., 2006; Manes, Graham, Zeman, de Lujan Calcagno, & Hodges, 2005). Moreover, in the study by Mameniskiene et al. (2006), ALF for both visual and verbal material was exhibited over a four-week delay, even when patients with identifiable hippocampal lesions were removed from the sample. Although hippocampal lesions have resulted in short-term recall deficits for visual (Bengner et al., 2006) and verbal material (Wilkinson et al., 2012), only small and nonsignificant correlations have been found between hippocampal volume and the recall of verbal materials and abstract designs following delays of six weeks (Wilkinson et al., 2012). Although Narayanan et al. (2012) found ALF for both verbal and nonverbal material in adult patients with TLE with hippocampal abnormalities, but not in those without hippocampal abnormalities, this finding was contradicted by small and insignificant correlations between ALF and hippocampal volume. Muhlert et al. (2011) found that adult TLE patients with mesial temporal sclerosis were more likely to have impaired three-week recall for both verbal (4 out of 7 patients) and visual material (7 out of 7 patients), compared to those without mesial temporal sclerosis, (1 out of 7 patients; only on the visual task). However, the small dataset made it impossible to conduct any formal statistical analyses and draw any definitive conclusions about the impact of hippocampal lesions on ALF. Finally, in patients with TEA, hippocampal atrophy was found to be associated with retention following a 30-min, but not three-week delay (Butler et al., 2009).
It is also unclear whether material-specific memory impairments are found in relation to ALF. For instance, Blake et al. (2000) reported significantly worse eight-week verbal recall in patients with left-TLE compared to those with right-TLE and control participants. However, another study found that patients with left-TLE recalled significantly fewer story details compared to both patients with right-TLE and control participants at a one-hour, but not six-week delay (Wilkinson et al., 2012). To date, research on ALF has largely focussed on adult patients with either TLE or temporal lobe dysfunction. However, no study has explored the presence of ALF in children with TLE.

The potential contribution of seizure activity to ALF has also received some attention. Mayes (2003) suggested that seizure activity may partly explain ALF in patients for a number of reasons, such as by interfering with the function of the medial temporal lobe, directly degrading neocortical storage sites (thus preventing consolidation), or by disrupting the interaction between the hippocampus and neocortex, which is vital for the transfer of information during the memory consolidation process. Because of this latter possibility, ALF could also feasibly be found in patients with extra-temporal or generalized epilepsy. Detecting ALF within these patients would be of theoretical significance, as it would indicate that initial learning of material may be intact but (consistent with CCT) the slower consolidation process into long-term memory stores may be compromised.

The idea that the seizure activity itself could disrupt the consolidation process seems plausible, given findings from studies of patients undergoing electroconvulsive
therapy (ECT). For instance, in one study, patients failed to exhibit any significant memory deficits when recalling newly-learned information at separate delays of ten minutes and two hours following exposure to ECT, but nevertheless exhibited significantly poorer recall performance following a delay of 32 hours (Squire, 1981). Results such as this suggest that memories may be vulnerable to disruption while they are in a consolidation phase (Squire, Cohen, & Nadel, 1984). A recent study that monitored epilepsy patients over five days with constant ambulatory EEG showed that subclinical seizure activity was correlated with ALF, thereby providing direct support for the notion that interictal discharges can disrupt memory consolidation (Fitzgerald, Thayer, Mohamed, & Miller, 2013).

However, the association between seizure activity and ALF remains unclear, as studies of adult TLE or TEA patients have provided equivocal results. For instance, seizure activity during long-term retention periods has been associated with ALF and attributed to greater seizure severity (Mameniskiene et al., 2006) or frequency (Wilkinson et al., 2012). In contrast, other studies have found similar levels of ALF between patients who experienced seizures and those who were seizure-free during the retention interval (Bergin, Thompson, Fish, & Shorvon, 1995; Blake et al., 2000). Moreover, ALF has also been demonstrated in patients who were seizure-free during testing and for several months before the assessment (Butler et al., 2007; Muhlert et al., 2010).

As patients with IGE do not present with any obvious cortical pathology or malformations, they are ideal candidates for research aimed at investigating the effects of seizures alone on memory function. To date, however, only two studies
have explored the presence of ALF in patients with IGE. Utilising a sample of adults with IGE, Muhlert et al. (2011) observed that these patients did not differ from healthy controls in the 3-week recall of either verbal or visual information. In the other study, Davidson et al. (2007) examined ALF in children with IGE, requiring them to learn two short stories to a criterion (90% accuracy) before asking them to recall and recognise the story details after a 30-min and 7-day delay. Although no between-group difference was found in story recall or recognition after a 30-min delay, children with IGE nevertheless recalled significantly less story details than their healthy control peers after a 7-day delay. It was also found that children with IGE required significantly more learning trials to reach the story memory learning criterion, and the between-group difference in 7-day recall was eliminated when learning efficiency was controlled for. The authors concluded that difficulties in recall of information after a long delay were secondary to inefficient learning. Muhlert et al. (2011) also attributed the absence of ALF in their sample of adult IGE patients to the fact that learning efficiency was matched between the patient and control groups.

However, some methodological shortcomings within the study by Davidson et al. (2007) may have contributed to the between-group disparity in learning efficiency and the failure to detect long-term memory deficits. For instance, the use of short stories meant that participants were required to learn complex verbal materials that are thought to be heavily dependent on other cognitive skills, especially language skills (Hermann, Seidenberg, Haltiner, & Wyler, 1992; Saling, 2009) and semantic memory (Smith & Lah, 2011). Moreover, participants were not given the opportunity to completely learn this material (as the learning criterion was set at 90%). Finally, the recognition condition of the stories subtest used in this study (from the Children's
Memory Scale; Cohen, 1997) has a low sensitivity, which could have contributed to the lack of a significant finding.

Tasks that require associative learning and verbal list-learning are thought to be a more pure measure of memory formation. In our studies, we utilised materials from the California Verbal Learning Test for Children (CVLT-C, Delis, Kramer, Kaplan, & Ober, 2000), which is based on a list-learning paradigm. Moreover, children were required to learn the list completely, reaching 100% accuracy on two consecutive learning trials [it is acknowledged, however, that reaching 100% accuracy can nevertheless still result in recall deficits following a short delay (McGibbon & Jansari, 2013)]. The recognition condition of this test was also developed using signal detection theory (SDT) and found to have adequate sensitivity. The fact that this test is based on SDT makes it particularly advantageous for the assessment of long-term verbal recognition, as it can distinguish between “false-alarm” errors and “true hits”.

Parents of children with IGE have reported that memory problems were frequent and often caused problems in day to day activities (Dickson et al., 2006). Exploring the presence of ALF in children with epilepsy is therefore especially important, as the presence of this memory deficit could partly explain these subjective memory complaints. The fact that patient memory complaints are not reflected in neuropsychological test scores may also suggest that standardised tests include overly short delays. Therefore, exploring ALF in children is important for clinical reasons but may also provide further insight into the role of the hippocampus.
In the next two studies we aim to examine ALF in children who have epilepsy arising from the temporal lobes (Chapter 3), children with IGE (Chapter 4) and in healthy control children. This will allow us to determine whether and in what way temporal lobe pathology disrupts memory consolidation over and above seizures themselves.

References


CHAPTER 3: Accelerated Long-Term Forgetting in Children with Temporal Lobe Epilepsy

Unpublished paper
Abstract

Adults with temporal lobe epilepsy (TLE) have been found to have accelerated long-term forgetting, but this phenomenon has not yet been investigated in children. Although deficits in short-term recall have been shown to slowly emerge from childhood to adolescence in children with TLE, it is unknown whether such a trend will also be found in long-term memory. This study examined the presence of accelerated long-term forgetting in children with TLE and how it relates to chronological age. Twenty-three children with TLE and 58 healthy controls of similar age, sex distribution and socioeconomic status completed a battery of neuropsychological tests, including tests requiring the learning of words and design locations to a criterion, both of which assessed recall after short (30-min) and long (7-day) delays. Compared to the control group, the TLE group recalled significantly fewer words at the 7-day delay compared with the 30-min delay and also exhibited worse 30-min recall performance on a standardized test of story recall. Although seven children (30.4%) with TLE had experienced temporal lobe resection, accelerated forgetting nevertheless remained when these children were removed from the TLE sample. No between-group differences were found with respect to the design location task. Age negatively correlated with the recall of words after short- and long-term delays within the TLE group, where older age was associated with worse memory. This association was not present in the control group. To our knowledge, this is the first study to show evidence of accelerated long-term forgetting in children with TLE. Additionally, these results suggest that the developmental trajectory of long-term memory in children with TLE is similar to that of short-term memory: deficits gradually emerge, therefore older children are more likely to present with long-term memory deficits.
**Introduction**

Previous studies of adults with temporal lobe epilepsy (TLE) have found evidence of anterograde memory deficits, as shown by poor learning and/or recall of materials after short (20- to 30-min) delays (i.e. Scoville and Milner, 1957; Hermann et al., 1987; Frisk and Milner, 1990; Jones-Gotman et al., 1997; Helmstaedter et al., 1998; Bell et al., 2005; Bell, 2006). Furthermore, the memory deficits seem to be material-specific (Milner, 1968), related to the side of epilepsy focus. While dominant (typically left hemisphere) TLE has been associated with impaired verbal memory (Sass et al., 1995; Helmstaedter et al., 1997; Hermann et al., 1997; Helmstaedter and Elger, 1998), non-dominant TLE has been linked (albeit less consistently) with impaired visual memory (Helmstaedter et al., 1991; Breier et al., 1996; Barr, 1997; Baxendale et al., 1998; Smith et al., 2011). In addition to the side, the site of epilepsy focus within the temporal lobe was found to be critical for memory. Smaller hippocampal volume was found to correlate with poorer learning and recall of both verbal (Sass et al., 1994; Wilkinson et al., 2012) and visual information (Baxendale et al., 1998) after short (up to 30 minutes) delays.

Long-term memory formation, however, is not completed after short delays. Instead, Classic Consolidation Theory has proposed that long-term memory formation requires further consolidation, which may take days or months to complete (Squire et al., 1984). Moreover, consolidation requires interaction between the hippocampus, which is critical for the initial memory formation, and distributed neocortical storage sites (Squire and Alvarez, 1995; Mayes et al., 2003). On completion of consolidation, memories are independent of the hippocampus and stored in the neocortex. It has been proposed that damage to any of the components of the consolidation network as
well as disruption of the interactions between the medial temporal lobe and temporal neocortex, may compromise consolidation (Mayes et al., 2003). Consistent with Classic Consolidation Theory, is a recently described phenomenon of accelerated long-term forgetting (ALF): a faster rate of forgetting over long delays (i.e. days or weeks) relative to shorter delays. ALF has been found in several studies that involved adults with TLE (Martin et al., 1991; Blake et al., 2000; Muhlert et al., 2011), with some exceptions (Giovagnoli et al., 1995; Bell et al., 2005; Bell, 2006). In adults with TLE, a relationship between this long-term memory deficit and seizure frequency has been found (Mameniskiene et al., 2006). However, some seizure-free patients have also exhibited ALF (e.g. Narayanan et al., 2012) and the only study that employed ambulatory EEG monitoring to investigate the relations between epileptic discharges and ALF, found that subclinical epileptiform discharges (rather than yearly seizure frequency) contributed to ALF (Fitzgerald, Thayer, Mohamed, & Miller, 2013). Nevertheless, material-specific memory impairments have not been consistently found on long delays. For instance, in one study patients with left-TLE recalled significantly fewer story details compared to both patients with right-TLE and control participants at a one-hour, but not at six-week delay (Wilkinson et al., 2012). In contrast, in another study (Blake et al., 2000), recall of stories at long delay (8 weeks) was significantly worse in patients with left-TLE relative to patients with right-TLE and control participants. Anti-epileptic medication has also been shown to have a negligible effect on ALF (Jansari et al., 2010).

Studies that examined the role of hippocampal pathology in ALF have provided equivocal results. Recently, Wilkinson and colleagues (2012) found that neither structural hippocampal abnormality nor hippocampal volume was related to either
ALF or recall of information after a long (six-week) delay. Similarly, in a study that tested recall of verbal and visual information following a four-week delay, ALF was evident for both types of materials in patients with TLE, even when those with an identifiable hippocampal lesion were removed from the sample (Mameniskiene et al. (2006). In contrast, Muhlert et al. (2011) reported that a larger number of patients with mesial temporal sclerosis exhibited impaired three-week recall for both stories (4 out of 7 patients) and visual scenes (7 out of 7 patients) than those without mesial temporal sclerosis (1 out of 7 patients; visual task only). However, formal statistical analyses could not be performed on this small dataset. Lastly, Narayanan et al. (2012) reported conflicting findings, as ALF was related to compromised hippocampal integrity in one instance, but not in another. TLE patients with hippocampal abnormalities exhibited ALF, but TLE patients who were free of hippocampal abnormalities did not. On the contrary, the correlations between hippocampal volume and ALF were all small and insignificant.

Thus far there has been little work on long-term memory formation in children with epilepsy. This situation represents a major gap, as long-term memory is critical for developmental and academic progression. Importantly, findings of adult epilepsy studies are not directly applicable to children, as the impact of seizures and underlying substrates on cognitive function has been shown to differ between the mature and developing brain (Smith, 2010). Specifically, first, while material specific memory deficits are often found in adults with TLE, findings are inconsistent in children. Several studies have found that verbal memory deficits were comparable in children with left- and right-TLE (Lendt et al., 1999; Mabbott and Smith, 2003; Nolan et al., 2004). Furthermore, material-specific memory deficits were more likely to be
found for visual (especially face recognition tasks), rather than verbal material (Mabbott and Smith, 2003; Gonzalez et al., 2007). Second, recent studies revealed that memory deficits become more noticeable as children with TLE grow older. For instance, in a longitudinal study, verbal memory deficits became apparent during adolescence or young adulthood in a sample of patients with left TLE (Gonzalez et al., 2012) who were free of such impairments in childhood (Gonzalez et al., 2007). Similarly, in a large cross-sectional study involving 1000 healthy control subjects (aged 6-80) and 1157 patients with TLE (aged 6-68 years) Helmstaedter and Elger (2009) found that deficits in recall of verbal information following short delays were not evident in children, but became apparent (relative to healthy controls) during teenage years/young adulthood. Moreover, differences in verbal memory between left and right TLE patients also emerged at this age, with the former group exhibiting poorer performance. It is unknown, however, whether long-term memory deficits also increase in a similar fashion over the course of development. Third, while the impact of site of epilepsy focus within the temporal lobe has been shown to be important for the pattern of memory impairment in adults with TLE, in children with TLE the findings are equivocal. One study found that children with lateral temporal lobe lesions displayed intact visual memory and associative learning, relative to normative standards, whereas children with mesial lesions were impaired (Gonzalez et al., 2007). In contrast, another study found that verbal and visual memory performance was not significantly different between children with mesial TLE and those with seizure foci in other areas of the temporal lobe (Nolan et al., 2004).

Although studies that have found ALF in adults have almost exclusively involved patients with TLE, no study to date has examined ALF in children with TLE. There
has been a small amount of research on children with idiopathic generalised epilepsy (IGE). In that work, ALF has been attributed to the poor initial learning of material (Davidson et al., 2007), or to seizure activity disrupting the consolidation process, which is critical for long-term memory formation (Gascoigne et al., 2012).

In the current study we aimed to examine long-term memory formation in children with TLE, and explore how it relates to deficits in initial learning, epilepsy variables (side and site of epilepsy focus/lesion) and chronological age. Performance of children with TLE was compared with healthy controls on two measures of long-term memory formation: one verbal and one visual.

Based on the reviewed literature we hypothesized that, compared to healthy controls, children with TLE would show deficits in long-term memory formation, but that deficits would not be material specific. Moreover, we predicted that for children with TLE, older age would be associated with greater long-term memory difficulties. Finally, we expected children with an abnormal hippocampus (resulting either from pathology or surgical resection) to have more severe long-term memory impairments than those with an intact hippocampus.

**Method**

**Subjects**

Twenty-three children with TLE (21 with unilateral foci, two with undetermined laterality) and 58 healthy children (the control group) participated. Inclusion criteria were: aged six to 16 years, fluent in English, and Full Scale Intelligence Quotient (FSIQ) ≥ 80. Exclusion criteria were the presence of: (i) a major sensory deficit; (ii)
another neurological disorder, or (iii) significant neurodevelopmental disorder (e.g. autism, but not learning disability or ADHD). Temporal lobe resection had been performed on seven TLE participants. One TLE participant was left-handed and one had a diagnosed learning disability.

All TLE participants were recruited through specialized epilepsy services at the Hospital for Sick Children, Toronto, Canada; McMaster Children’s Hospital, Hamilton, Canada or The Children’s Hospital at Westmead (CHW), Sydney, Australia. Potential participants were identified by review of patient files. Electroencephalography (EEG) records, medical history, and imaging data (where available) were reviewed by the treating paediatric neurologists, who determined that potential participants met the International League Against Epilepsy criteria for TLE (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Thirty-one TLE participants were approached; 25 (81%) consented. Two TLE participants were excluded: one obtained an FSIQ score < 80 and the other refused to co-operate with the examiner.

Sixty healthy participants (free of a history of epilepsy) were recruited for the control group via word-of-mouth recruitment (snowball recruitment), through the peer networks of both TLE and other healthy participants in Canada and Australia. Two control participants were excluded as they refused to complete the long-term recall tasks.

Materials

Neuropsychological Measures
(i) *Intelligence.* Participants were administered the two-subtest version (Vocabulary and Matrices) of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). The FSIQ was derived ($M = 100, SD = 15$).

(ii) *Standard Memory Tests.* Two measures of short-term memory and learning were included: the Story Memory subtest from the Wide Range Assessment of Memory and Learning: Second Edition (WRAML2; Sheslow and Adams, 2003) and the Dot Location subtest from the Children’s Memory Scale (CMS; Cohen, 1997). Age scaled scores have $M = 10, SD = 3$. A 7-day memory trial is not part of these standardised tests.

(iii) *Experimental Measure of Verbal Memory (Word Recall).* Participants were administered word lists derived from the California Verbal Learning Test - Children's Version (CVLT-C; Delis et al., 1994). Children < 9 and ≥ 9 years of age were administered a 9-word and 12-word list, respectively. Firstly, this 9- or 12-word list (list A) was read aloud until the participant either recalled the entire list of words (in any order) on two consecutive trials or reached a maximum of 12 learning trials. Secondly, an additional 9- or 12-word list (list B, the “interference list”) was read and recalled once. Thirdly, a recall of list A was requested following two short delays of two minutes (after recall of list B) and 30 minutes, and one long delay (seven days), without forewarning (i.e. no participant was notified in any way in advance of the 7-day delay trial). The testing of long delay recall was conducted over the telephone. The following scores were used in the current study: (a) learning efficiency: number of learning trials and (b) recall: a percentage of words recalled (max 100%) relative to the last learning trial.
Experimental Measure of Visual Memory (Design Location): This task was modelled on a spatial memory task developed by Hepworth & Smith (2002). Stimuli included abstract designs that were contained within a 6 x 4 grid and presented on a computer screen. Participants were asked to remember the designs and their respective locations. After presentation of each array of designs, the screen showed an empty grid, next to which were the designs, and participants were asked to drag-and-drop the designs to their correct locations. Following each trial, visual feedback was given for five seconds: correctly placed stimuli were highlighted in green with a checkmark, while incorrectly placed stimuli were highlighted in red with an X (see Figure 1).

This computerised task consisted of practice, learning and two test phases (administered after 30-min and 7-day delays). In each phase participants were presented with the identical 6 x 4 grid. During the practice phase the grid contained three abstract designs and was exposed for ten seconds. If the participant made a design location error during this phase the presentation was repeated (allowing up to a maximum of five attempts). During the learning phase participants were again presented with the grid which now contained ten new abstract designs (i.e. not identical to the practice phase designs), presented for 15 seconds. This phase continued until participants either reached the learning criterion (placing all stimuli correctly on two consecutive trials) or 12 trials had been reached. During the recall test phases (following a 30-min and 7-day delay) participants were presented with an empty grid and were again asked to place stimuli in the correct locations. However, no on-screen feedback was given during either of the
recall test phases. For the 7-day delay test, participants were contacted by phone and asked to complete the task online after accessing it via a link emailed to their parent/guardian. The following scores were used: (a) the number of learning trials (learning efficiency) and (b) the proportion of stimuli correctly placed (max 100%) relative to the last learning trial (recall).

Figure 1: Example of the presentation of stimuli during the learning phase of the Design Location task and the on-screen feedback for that trial.
Epilepsy Severity

Treating neurologists rated epilepsy severity on the Global Assessment of Severity of Epilepsy (GASE) scale (Speechley et al., 2008). This single-item, seven-point rating scale assesses overall epilepsy severity and takes into consideration the frequency and intensity of seizures, injuries during seizures, severity of post-ictal period, number and side-effects of antiepileptic drugs and the interference of epilepsy or drugs with daily activities. Severity ratings ranged from 1 (Not at all severe) to 7 (Extremely severe).

Procedure

The study was approved by the ethics committees of all participating institutions. Only children who agreed to participate and whose parents gave informed consent were included in the study. Children were tested individually over one 90-minute session and contacted by telephone seven days later. Tests were administered in the same order to all participants. Information relating to developmental history, socioeconomic status (SES; i.e. parental years of education) and relevant epilepsy variables (i.e. medication taken at the time of assessment) was collected during structured parent interviews. Information about the child’s epilepsy was verified by treating paediatric neurologists and review of the medical records. Neurologists were blind to children’s scores on neuropsychological tests when completing the GASE scale.

Statistical analysis

All statistical analyses were performed using SPSS statistical software, with a standard alpha of 0.05, unless stated otherwise. Data were screened using
Kolmogorov-Smirnov tests to check suitability of variables for parametric analyses. Independent t-tests (or Mann-Whitney U tests) and chi-square ($\chi^2$, with Bonferroni corrections) tests were used to examine between group differences on continuous and categorical background variables, respectively. Fisher’s exact test was used when chi-square assumptions were not met.

Analysis of covariance (ANCOVA) was employed to compare the TLE and control groups on standardised tests of short-term memory. Repeated measures ANCOVA (Group x Delay), followed by Sidak post-hoc tests, investigated main effects of group, delay and interaction on the Word Recall and Design Location tasks (although analyses for the latter task did not include covariates). All covariates were centered before performing the repeated measures ANCOVA. When data normality assumptions were not met, Kruskal-Wallis tests with Mann-Whitney U post-hoc tests (and a Bonferroni adjusted alpha of 0.008) were employed.

Pearson’s (or Spearman’s) correlations were used to assess the relationship between age and scores obtained on the Word Recall and Design Location tasks. Finally, seven exploratory simultaneous regression analyses were also undertaken for the Word Recall and Design Location tasks. Only those variables that were found to result in significant between group differences/interactions or correlated significantly with the outcomes were included in the simultaneous regression analyses.

In order to determine clinical significance of our findings, i.e. whether ALF is present in children whose scores on standardised tests of verbal memory were not impaired, patterns of performance on two memory tests were examined in each individual child.
Performance of each child on the Word Recall task and WRAML2: Story Memory (delayed recall) was classified as impaired if their score was less than 1.96 z-scores below the control mean, as previously used in an adult study by Muhlert et al., 2011. Moreover, chi-square analysis was used to determine whether there is a between-group difference in the number of children who showed impairments on these experimental and standardized tests.

**Results**

Clinical characteristics for the TLE group are presented in Table 1. TLE participants had been diagnosed with epilepsy at a mean age of 6.4 (SD = 3.8) years and had experienced epilepsy for an average of 6.1 (SD = 4.0) years. Twenty-one children with TLE were taking anti-epileptic drugs (AED): 14 on mono- and seven on poly-therapy. Six separate drugs were taken, with Carbamazepine (n = 8) and Levetiracetam (n = 8) being the most frequently used. The mean seizure severity rating (M = 2.6, SD = 1.2) on the GASE scale corresponded to a rating between “A little severe” and “Somewhat severe”. Demographic and additional clinical characteristics are presented in Table 2.

The TLE and control groups did not differ in age, years of parental education or sex distribution. While the mean FSIQ for the TLE group was within the average range, it was significantly lower than that of the control group.
<table>
<thead>
<tr>
<th>Participant</th>
<th>Laterality</th>
<th>Surgery</th>
<th>HC status</th>
<th>MRI</th>
<th>Epilepsy Severity</th>
<th>EEG</th>
<th>Seizure types experienced</th>
<th>AEDs</th>
<th>Age Diagnosed (years)</th>
<th>Duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left</td>
<td>Non-surgical</td>
<td>Normal</td>
<td>Normal</td>
<td>Moderately severe</td>
<td>Left</td>
<td>CPS</td>
<td>LAC</td>
<td>5.0</td>
<td>9.0</td>
</tr>
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<td>2</td>
<td>Left</td>
<td>Non-surgical</td>
<td>Normal</td>
<td>Asymmetry with a slightly dilated left temporal horn compared to the right</td>
<td>Somewhat severe</td>
<td>Left</td>
<td>CPS</td>
<td>CRB, LEV</td>
<td>1.0</td>
<td>12.0</td>
</tr>
<tr>
<td>3</td>
<td>Left</td>
<td>Non-surgical</td>
<td>Normal</td>
<td>Normal</td>
<td>A little severe</td>
<td>Left</td>
<td>CPS</td>
<td>OXC</td>
<td>8.6</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>Left</td>
<td>Non-surgical</td>
<td>Normal</td>
<td>Normal</td>
<td>Somewhat severe</td>
<td>Left</td>
<td>CPS</td>
<td>SVP</td>
<td>5.7</td>
<td>2.4</td>
</tr>
<tr>
<td>5</td>
<td>Left</td>
<td>Non-surgical</td>
<td>Abnormal</td>
<td>Abnormal signal in left mesial temporal lobe and left HC</td>
<td>Moderately severe</td>
<td>Left</td>
<td>CPS</td>
<td>CRB, LEV, SVP</td>
<td>13.6</td>
<td>2.7</td>
</tr>
<tr>
<td>6</td>
<td>Left</td>
<td>Non-surgical</td>
<td>Abnormal</td>
<td>MRI showing increased volume of the temporal horn of the left lateral ventricle with decreased size of the left hippocampus</td>
<td>A little severe</td>
<td>Normal</td>
<td>CPS</td>
<td>LMT, OXC</td>
<td>4.0</td>
<td>5.8</td>
</tr>
<tr>
<td>7</td>
<td>Left</td>
<td>Non-surgical</td>
<td>Abnormal</td>
<td>Small well-defined lesion is seen in the left medial temporal lobe supero-medial to the left temporal horn measuring about 10.5mm in maximum anterior posterior, 9mm in transverse and 7.5mm in craniocaudal dimensions.</td>
<td>Not at all severe</td>
<td>Normal</td>
<td>CPS, GTCS</td>
<td>LEV</td>
<td>2.0</td>
<td>12.6</td>
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<tr>
<td>8</td>
<td>Left</td>
<td>Time 1: temporal lobe - amygdala and hippocampus preserved. Time 2: temporal lobe, including amygdala and hippocampus</td>
<td>Abnormal</td>
<td>Left miocortical dysgenesis. Heterotopic neurons and patchy gliosis</td>
<td>Moderately severe</td>
<td>Left</td>
<td>CPS</td>
<td>CRB, LMT</td>
<td>2.5</td>
<td>6.74</td>
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<tr>
<td>9</td>
<td>Left</td>
<td>Left anterior lateral temporal lobectomy - hippocampus spared.</td>
<td>Normal</td>
<td>Left Ganglioglioma</td>
<td>A little severe</td>
<td>Left</td>
<td>CPS</td>
<td>None</td>
<td>2.5</td>
<td>12.33</td>
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<tr>
<td>10</td>
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<td>Temporal lobe, including amygdala and hippocampus</td>
<td>Abnormal</td>
<td>Left Gliosis - cortical and hippocampal</td>
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<td>Left</td>
<td>CPS</td>
<td>OXC, LEV</td>
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<td>11</td>
<td>Left</td>
<td>Temporal lobe, including amygdala and hippocampus</td>
<td>Abnormal</td>
<td>Left MTS</td>
<td>Somewhat severe</td>
<td>Normal</td>
<td>CPS</td>
<td>CRB, LEV</td>
<td>5.0</td>
<td>10.7</td>
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<td></td>
<td>Side</td>
<td>Surgical/Non-surgical</td>
<td>Abnormal/Normal</td>
<td>Diagnosis</td>
<td>Severity</td>
<td>Side</td>
<td>AEDs</td>
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<tr>
<td>12</td>
<td>Left</td>
<td>Non-surgical</td>
<td>Abnormal</td>
<td>Lateral neocortex: subpialgliosis, Inferior temporal lobe: subpialgliosis, Hippocampus: Mesial temporal gliosis</td>
<td>A little severe</td>
<td>Left</td>
<td>CPS, LEV, SVP</td>
<td>3.5</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Left</td>
<td>Non-surgical</td>
<td>Normal</td>
<td>Malformation of cortical development, bilateral periventricular nodular heterotopia and left temporal polymicrogyria.</td>
<td>Somewhat severe</td>
<td>Left</td>
<td>GTCS, CRB</td>
<td>12.5</td>
<td>3.8</td>
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<tr>
<td>14</td>
<td>Left</td>
<td>Non-surgical</td>
<td>Abnormal</td>
<td>Mild T2 hyper intensity of the left hippocampal body</td>
<td>A little severe</td>
<td>Left</td>
<td>CPS, OXC</td>
<td>5.4</td>
<td>8.6</td>
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<tr>
<td>15</td>
<td>Left</td>
<td>Non-surgical</td>
<td>Abnormal</td>
<td>Dysplasia in left temporal lobe</td>
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<td>Left</td>
<td>CPS, None</td>
<td>2.5</td>
<td>9.6</td>
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<td>16</td>
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<td>Normal</td>
<td>Neuronal tumour (non-progressive) (right side)</td>
<td>A little severe</td>
<td>Right</td>
<td>SPS, GTCS, LEV</td>
<td>7.1</td>
<td>6.3</td>
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<td>17</td>
<td>Right</td>
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<td>Normal</td>
<td>Abnormal signal in right hippocampal head and amygdala; interdigitations in hippocampal head are attenuated as is gray-white contrast layering</td>
<td>Moderately severe</td>
<td>Right</td>
<td>CPS, CRB</td>
<td>6.8</td>
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<td>18</td>
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<td>Abnormal</td>
<td>Right MTS</td>
<td>Moderately severe</td>
<td>Right</td>
<td>CPS, SVP</td>
<td>4.0</td>
<td>7.6</td>
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<td>19</td>
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<td>Normal</td>
<td>Abnormal signal in right hippocampal head and amygdala; interdigitations in hippocampal head are attenuated as is gray-white contrast layering</td>
<td>Somewhat severe</td>
<td>Right</td>
<td>CPS, CRB</td>
<td>8.8</td>
<td>2.1</td>
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<td>20</td>
<td>Right</td>
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<td>Abnormal</td>
<td>Right angiocentric glioma</td>
<td>Not at all severe</td>
<td>Right</td>
<td>CPS, GTCS, LEV</td>
<td>9.0</td>
<td>7.1</td>
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<td>21</td>
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<td>Abnormal</td>
<td>Right angiocentric glioma</td>
<td>Not at all severe</td>
<td>Right</td>
<td>CPS, CRB</td>
<td>4.2</td>
<td>5.2</td>
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<td>22</td>
<td>Undetermined</td>
<td>Non-surgical</td>
<td>Normal</td>
<td>Abnormal signal in right hippocampal head and amygdala; interdigitations in hippocampal head are attenuated as is gray-white contrast layering</td>
<td>Moderately severe</td>
<td>-</td>
<td>CPS, GCTS, SVP</td>
<td>11.0</td>
<td>0.5</td>
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<tr>
<td>23</td>
<td>Undetermined</td>
<td>Non-surgical</td>
<td>Normal</td>
<td>Abnormal signal in right hippocampal head and amygdala; interdigitations in hippocampal head are attenuated as is gray-white contrast layering</td>
<td>Not at all severe</td>
<td>Normal</td>
<td>CPS, OXC</td>
<td>10.5</td>
<td>0.5</td>
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</table>

AEDs, Anti Epileptic Drugs; SPS, Simple Partial Seizures; CPS, Complex Partial Seizures; GTCS, Generalised Tonic-Clonic Seizures; CRB, Carbamazepine; LAC, Lacosamide; LEV, Levetiracetam; LMT, Lamotrigine; MTS, Mesial Temporal Sclerosis; OXC, Oxcarbazepine; SVP, Sodium Valproate
Table 2: Background and Clinical Data by Group and TLE subgroup

<table>
<thead>
<tr>
<th></th>
<th>TLE (n = 23)</th>
<th>Control (n = 58)</th>
<th>Left TLE (n = 15)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Right TLE (n = 6)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Test</th>
<th>p</th>
<th>Normal HC (n = 11)</th>
<th>Abnormal HC (n = 12)</th>
<th>Test</th>
<th>p</th>
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<tr>
<td><strong>Age</strong></td>
<td>12.5 (2.8)</td>
<td>11.4 (2.8)</td>
<td>14.0 (5.9)</td>
<td>11.3 (5.2)</td>
<td>χ²</td>
<td>3.6</td>
<td>0.17</td>
<td>11.0 (4.8)</td>
<td>13.4 (4.6)</td>
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<tr>
<td><strong>Sex (F/M)</strong></td>
<td>13/10</td>
<td>31/27</td>
<td>9/6</td>
<td>4/2</td>
<td>χ²</td>
<td>0.1</td>
<td>0.80</td>
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<tr>
<td><strong>SES (Years)</strong></td>
<td>14.3 (1.7)</td>
<td>14.9 (2.5)</td>
<td>14.3 (3.0)</td>
<td>14.0 (1.3)</td>
<td>χ²</td>
<td>1.4</td>
<td>0.50</td>
<td>14.0 (2.0)</td>
<td>14.3 (3.0)</td>
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<tr>
<td><strong>FSIQ</strong></td>
<td>96.4 (12.2)**</td>
<td>112.3 (11.9)</td>
<td>96.0 (17.0)**</td>
<td>99.0 (27.3)</td>
<td>χ²</td>
<td>21.9</td>
<td>&lt;0.001</td>
<td>96.0 (14.0)**</td>
<td>95.0 (26.8)**</td>
<td>&lt;0.001</td>
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<tr>
<td>Number of AEDs</td>
<td>1.3 (0.7)</td>
<td>-</td>
<td>1.0 (1.0)</td>
<td>1.0 (0.0)</td>
<td>U</td>
<td>30.0</td>
<td>0.27</td>
<td>1.0 (1.0)</td>
<td>1.5 (1.0)</td>
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</tr>
<tr>
<td>Age diagnosed (Years)</td>
<td>6.4 (3.8)</td>
<td>-</td>
<td>5.0 (6.1)</td>
<td>7.0 (4.7)</td>
<td>U</td>
<td>30.5</td>
<td>0.27</td>
<td>7.1 (5.5)</td>
<td>4.1 (5.4)</td>
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<tr>
<td>Epilepsy life duration (%)</td>
<td>47% (29%)</td>
<td>-</td>
<td>64% (56%)</td>
<td>46% (42%)</td>
<td>U</td>
<td>26.0</td>
<td>0.15</td>
<td>23% (56%)</td>
<td>64% (26%)</td>
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<tr>
<td>Comorbid LD (Yes/No)</td>
<td>1/22</td>
<td>-</td>
<td>1/14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0/6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>χ²</td>
<td>0.4</td>
<td>0.52</td>
<td>1/11</td>
<td>0/10</td>
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</tr>
<tr>
<td>Surgery (Yes/No)</td>
<td>7/16</td>
<td>-</td>
<td>6/9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1/5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>χ²</td>
<td>1.1</td>
<td>0.31</td>
<td>1/10</td>
<td>6/6</td>
<td>0.29</td>
</tr>
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<tr>
<td>Epilepsy severity rating</td>
<td>2.6 (1.2)</td>
<td>-</td>
<td>2.0 (1.0)</td>
<td>3.5 (3.0)</td>
<td>U</td>
<td>36.5</td>
<td>0.52</td>
<td>3.0 (2.0)</td>
<td>2.0 (3.0)</td>
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</tr>
<tr>
<td>Seizure focus (Left/Right)</td>
<td>15/6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>15/0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0/6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td></td>
<td>6/3</td>
<td>9/3</td>
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<td></td>
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</tr>
<tr>
<td>HC (Abnormal/Normal)</td>
<td>12/11</td>
<td>-</td>
<td>9/6</td>
<td>3/3</td>
<td>χ²</td>
<td>0.5</td>
<td>0.48</td>
<td>0/11</td>
<td>12/0</td>
<td>-</td>
</tr>
</tbody>
</table>

*Adjusted Mean with Standard Error in parentheses; <sup>b</sup>Laterality undetermined for two TLE participants. AED: Anti-epileptic drug; FSIQ: Full Scale Intelligence Quotient; HC: Hippocampus; LD: Learning Disability; SES: Socioeconomic status; TLE: Temporal Lobe Epilepsy.
Analysis 1: Patients versus Controls

Scores obtained on standardized and experimental memory tests are summarised in Table 3. After controlling for FSIQ, no significant differences were found between the TLE and control groups on tests of immediate and short-term visual memory (CMS: Dot Location). However, on the tests of immediate and delayed verbal memory (WRAML2: Story Memory) the TLE group scored significantly lower than controls. Within the TLE group, delayed recall on WRAML2: Story Memory was found to correlate with 2-min Word Recall ($r = 0.4$, $p = 0.05$) while FSIQ correlated with seven-day Word Recall ($r = 0.5$, $p = 0.03$). Because we were interested in recall of information after long delays, FSIQ was included as a covariate in the subsequent ANCOVAs.
<table>
<thead>
<tr>
<th>Table 3: Memory Data by Group and TLE subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TLE</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>(n = 23)</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>CMS Dot Location</td>
</tr>
<tr>
<td>Immediate Recall</td>
</tr>
<tr>
<td>30-min Recall</td>
</tr>
<tr>
<td>WRAML2 Story Memory</td>
</tr>
<tr>
<td>Immediate Recall</td>
</tr>
<tr>
<td>30-min Recall</td>
</tr>
<tr>
<td>Word Recall Task</td>
</tr>
<tr>
<td>2-min Recall</td>
</tr>
<tr>
<td>30-min Recall</td>
</tr>
<tr>
<td>7-day Recall</td>
</tr>
<tr>
<td>Design Location Task</td>
</tr>
<tr>
<td>30-min Recall</td>
</tr>
<tr>
<td>7-day Recall</td>
</tr>
</tbody>
</table>

*aAdjusted Mean with Standard Error in parentheses; bLaterality undetermined for two TLE participants. CMS: Children’s Memory Scale; HC: Hippocampus; TLE: Temporal Lobe Epilepsy; WRAML2: Wide Range Assessment of Memory and Learning, Second Edition. *p < 0.05, ***p < 0.001*
Figure 2 shows scores obtained on the Word Recall task. A two-way repeated measures ANCOVA found a significant interaction between Group and Delay ($F(2, 150) = 4.2$, $p = 0.02$). While the between-group differences in the proportion of words recalled following either the 2-min or 30-min delays were not significant, the TLE group recalled significantly fewer words relative to controls at seven days. In addition, a significant main effect of Delay ($F(2, 150) = 92.8$, $p < 0.001$) and Group ($F(1, 75) = 7.3$, $p = 0.008$) was also found. Post-hoc tests indicated that the number of words recalled at the 7-day delay was significantly fewer compared to both the 2-min ($p < 0.001$) and 30-min delays ($p < 0.001$), but no difference was found between the 2-min and 30-min delays ($p = 0.89$). Across all delays, TLE participants recalled a mean of 9.6% (SE = 3.2%) fewer words than control participants ($p = 0.008$).

**Figure 2: Recall scores obtained on the Word Recall task by the TLE and control groups.**

Recall scores obtained on the Design Location task are presented in Figure 3. A two-way repeated measures ANOVA found a main effect of Delay ($F(1, 47) = 169.9$, $p < 0.001$), but no main effect of Group ($F(1, 47) = 1.7$, $p = 0.20$) and no interaction ($F(1, 47) = 0.4$, $p = 0.55$). Participants across both groups recalled significantly fewer
correct design locations following the 7-day delay, relative to the 30-min delay ($p < 0.001$).

**Figure 3: Recall of information on the Design Location task by TLE and control groups.**

Correlations between age and performance on the Word Recall task are depicted in Figures 4 a) to c). Within the TLE group, age was negatively correlated with word recall at the 2-min, 30-min and 7-day delays. After adjusting for the proportion of life spent with epilepsy, all correlations remained significant [2-min ($r = -0.5$, $p = 0.02$), 30-min ($r = -0.7$; $p = 0.02$) and 7-day recall ($r = -0.6$, $p = 0.002$)]. Within the control group, no correlations were found between age and word recall after any delay. On the Design Location task, age did not correlate with design location recall within the TLE group at either the 30-min ($r = -0.3$, $p = 0.28$) or 7-day delay ($r = -0.2$, $p = 0.38$). No significant correlations were found between age and recall for the control group.
Figure 4: Correlation between participant age with recall following immediate (2-min) (A), short-term (30-min) (B) and long-term (7-day) delays (C) on the Word Recall task.
GASE scores did not significantly correlate with 2-min ($r_s = 0.2; p = 0.5$), 30-min ($r_s = -0.03; p = 0.9$) or 7-day word recall ($r_s = -0.01; p = 0.95$), nor with 30-min ($r_s = -0.1; p = 0.66$) or 7-day design location recall ($r_s = -0.2; p = 0.32$).

**Is ALF related to incomplete learning?**

On the Word Recall task, significantly more TLE participants ($n = 7, 30.4\%$, Fisher’s exact test, $p < 0.001$) failed to reach the learning criterion compared with the control group ($n = 1, 1.7\%$). All TLE participants who failed to meet this criterion had an abnormal hippocampus; six had a left- and one had a right-hemisphere seizure focus. When only children who reached the learning criterion were examined, an ANCOVA showed that the TLE and control groups did not differ in the number of learning trials taken [TLE: $M = 6.8, SD = 2.4$; control: $M = 5.9, SD = 2.1$; $F(1, 74) = 0.5, p = 0.82$].

In order to determine whether ALF found in the initial analysis was due to incomplete learning, only participants who had met the learning criterion on the Word Recall task were included in the subsequent ANCOVA (with FSIQ as a covariate). A significant Group x Delay interaction ($F(2, 132) = 4.4, p = 0.015$) was found. No significant between-group difference was evident in the proportion of words recalled at either the 2-min ($F(1, 69) = 1.2, p = 0.29$) or 30-min delay ($F(1, 69) = 0.1, p = 0.91$); however the TLE group recalled significantly fewer words relative to controls at the 7-day delay ($F(1, 66) = 4.4, p = 0.02$). Additionally, a main effect of Delay ($F(2, 134) = 81.2, p < 0.001$) and Group ($F(1, 67) = 5.1, p = 0.027$) was obtained. No difference in the proportion of words recalled was found between the 2-min and 30-min delays ($p = 0.98$), however, significantly fewer words were recalled at the 7-day delay, relative to both 30-min ($p < 0.001$) and 2-min delays ($p < 0.001$). Across all delays, the TLE
group recalled a mean of 7.7% (SE = 3.4%) fewer words than the control group ($p = 0.027$).

On the Design Location task significantly more TLE participants ($n = 4, 17.4\%$, Fisher's exact test, $p = 0.001$) failed to reach the learning criterion, compared to the control group ($n = 0$). All children who failed to reach criterion had an abnormal hippocampus and a left-hemisphere seizure focus. Nevertheless, the TLE ($M = 7.5$, $SD = 2.3$) and control ($M = 6.9$, $SD = 2.6$) groups did not differ significantly in the number of learning trials when only those who learned to criterion were considered ($t(44) = 0.7, p = 0.46$). When only children who reached the Design Location learning criterion were included in an ANOVA, no interaction effect ($F(1, 44) = 0.004, p = 0.95$) or main effect of Group ($F(1, 44) = 0.04, p = 0.85$) was found. However, a main effect of Delay was obtained ($F(1, 44) = 173.2, p < 0.001$), where participants across both groups recalled significantly fewer correct design locations at the 7-day delay, relative to the 30-min delay ($p < 0.001$).

**Individual Analysis**

To establish whether children who were found to display ALF on the experimental task also had impaired performance on a standardized task of verbal memory, scores on these two tasks were examined for each and every participant. A significantly higher proportion of patents with TLE (26.1\%, $n = 6/23$) exhibited impaired 7-day recall (less than 1.96 z-scores relative to the mean of controls) compared to the control participants (5.5\%, $n = 3/53$; $\chi^2 = 6.8, p = 0.009$). Of these nine participants across both groups, none displayed impaired delayed recall performance on the
standardized test of verbal memory, WRAML2: Story Memory (i.e. a scaled score of 4 or less; 1.96 standard deviations below the mean score of 10).

Is ALF related to temporal lobe resection?

Surgery had been performed on seven children with TLE. In order to determine whether ALF was related to surgery, an ANCOVA (using FSIQ as a covariate) was conducted on only those TLE participants who had not undergone any neurosurgical procedure and who had met the learning criterion (n= 12). A significant Group x Delay interaction \( F(2, 126) = 3.6, p = 0.03 \) was found. The TLE group recalled significantly less words than the control group following the 7-day delay \( F(1, 63) = 8.1, p = 0.01 \), but not at either the 30-min \( F(1, 66) = 2.2, p = 0.14 \) or 2-min delay \( F(1, 66) = 1.4, p = 0.25 \). Main effects of Delay \( F(2, 126) = 61.8, p < 0.001 \) and Group \( F(1, 63) = 6.1, p = 0.02 \) were found. No difference in the proportion of words recalled was found between the 2-min and 30-min delays \( p = 0.84 \), however, significantly fewer words were recalled at the 7-day delay, relative to both 30-min \( p < 0.001 \) and 2-min delays \( p < 0.001 \). Across all delays, the TLE group recalled an average of 9.2\% \( (SE = 3.7\% \) fewer words than the control group \( p = 0.016 \).

When these participants were included in an ANOVA related to performance on the Design Location task, no interaction effect \( F(1, 37) = 0.48, p = 0.49 \) or main effect of Group was observed \( F(1, 37) = 0.15, p = 0.70 \). A main effect of Delay was found \( F(1, 37) = 109.8, p < 0.001 \), as participants across both groups recalled fewer correct design locations from the 30-min to 7-day delay \( p < 0.001 \).
Analysis 2: Relationship between side of seizure focus and long-term memory formation.

In the following analysis, TLE patients with either a left-hemisphere \((n = 15)\) or right-hemisphere \((n = 6)\) seizure focus were compared to control patients (note that it was not possible to determine the laterality of seizure focus in two patients with TLE). The two patient subgroups did not differ on any epilepsy-related variables (see Table 2 for details).

Kruskal-Wallis tests found significant between-group differences in FSIQ, but not in any demographic variables. Subsequent pairwise comparisons revealed that the left-TLE (but not right-TLE) group had significantly lower FSIQ \((z = -4.9, p < 0.001)\) scores than the control group. On standardized tests of short-term recall, significant between-group differences were evident on CMS: Dot Location (delayed recall) and WRAML2: Story Memory (both immediate and delayed recall). Pairwise comparisons showed that relative to the control group, but not the right-TLE group, the left-TLE group had significantly lower scores on immediate \((z = -5.1, p < 0.001)\) and delayed recall \((z = -5.1, p < 0.001)\) on WRAML2: Story Memory and delayed recall \((z = -2.5, p < 0.001)\) on CMS: Dot Location.

When scores were examined on the Word Recall task, significant between-group differences were evident in recall at the 2-min and 7-day delays, with a marginally non-significant difference found at the 30-min delay. Pairwise comparisons revealed that, compared to the control group, the left-TLE group had worse recall of words at the 2-min \((z = -2.5, p = 0.01)\) and 7-day delays \((z = -2.7, p = 0.021)\). The right-TLE group did not differ significantly from either the left TLE or the control groups on
word recall. With respect to the Design Location task, no between-group difference was found in the proportion of design locations recalled at either the 30-min or 7-day delays.

Analysis 3: Long-term retention in patients with a normal or abnormal hippocampus

The final analysis compared TLE participants whose hippocampus was either normal (NH, \(n = 11\)) or abnormal (AH, \(n = 12\)) with control participants. Background and epilepsy variables of the two groups were compared using Kruskal-Wallis tests (see Table 2). A significant between-group difference was evident in FSIQ, but not in any demographic variables. Compared to the control group, FSIQ was significantly lower in both the NH (\(z = -3.6, p < 0.001\)) and AH groups (\(z = -3.3, p = 0.001\)), although mean FSIQ did not differ between the NH and AH groups. On epilepsy variables, the groups did not differ, except for treatment variables; significantly more participants in AH group had undergone surgery or were receiving polytherapy than those in the NH group.

When scores obtained on standardized memory tests were compared, significant between-group differences were evident for delayed recall on CMS: Dot Location; the AH group (but not NH group) obtaining significantly lower scores for delayed recall (\(z = -2.5, p = 0.012\)) relative to the control group. In addition, the groups also differed in immediate and delayed recall on the WRAML2: Story Memory subtest. Compared to the control group, both patient groups recalled significantly fewer details on immediate and delayed recall (NH: \(z = -3.3, p = 0.001\) and \(z = -3.4, p = 0.004\), respectively; AH: \(z = -4.2, p < 0.001\) and \(z = -3.9, p < 0.001\), respectively). The AH group also exhibited significantly lower immediate (\(z = -2.6, p = 0.01\) and delayed
recall \( (z = -2.4, p = 0.02) \) on the WRAML2: Story Memory subtest than the NH group.

On the Word Recall task, a between-group difference was found in the proportion of words forgotten at the 7-day delay, but neither at the 2-min or 30-min delays. Pairwise comparisons showed that, compared to the control group, only the AH group had significantly poorer recall at the 7-day delay \( (z = -2.7, p = 0.023) \), with no difference observed between the AH and NH groups \( (z = -0.8, p = 0.45) \). No difference in word recall at any delay was found between those on monotherapy and polytherapy \( [2\text{-min} \ (z = -1.2, p = 0.21), \ 30\text{-min} \ (z = -0.2, p = 0.84), \ 7\text{-days} \ (z = -1.1, p = 0.28)] \), or between those who had and had not undergone surgery \( [2\text{-min} \ (z = -0.9, p = 0.36), \ 30\text{-min} \ (z = -0.04, p = 0.97), \ 7\text{-days} \ (z = -0.3, p = 0.76)] \).

A between-group difference was found in the performance on the Design Location task at the 30-min, but not 7-day delay. Pairwise comparisons showed that the AH group had significantly poorer recall of design locations following the 30-min delay, compared to both the control \( (z = -2.6, p = 0.025) \) and NH groups \( (z = -2.5, p = 0.034) \).

Analysis 4: Regression Analyses

Regression exploratory analyses were performed in the TLE group for recall at each delay, for both the Word Recall and Design Location tasks (see Table 4). For the Word Recall task, the variables age, side of seizure focus and hippocampal integrity were not significant at predicting recall at the 2-min or 30-min delays, but significantly predicted 7-day recall \( (p = 0.04) \), explaining 53\% of the variance. Age
alone was a significant predictor of recall at the 7-day delay \( (p = 0.01) \); older age was associated with worse recall. Laterality, hippocampal damage and WRAML2: Story Memory (both immediate and delayed recall) did not make significant, independent contributions when included in the model alongside age. For the Design Location task, none of the variables (age, side of seizure focus or hippocampal integrity) were significant predictors for performance in recall, either at the 30-min or 7-day delay.
Table 4: Simultaneous multivariate regression analyses of age and clinical variables in predicting experimental memory task performance

<table>
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<tr>
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<td></td>
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<td>0.03</td>
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<tr>
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<td>-0.21</td>
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*p < 0.05
Discussion

In this (to our knowledge) first study of long-term memory formation in children with TLE, we found evidence of ALF for verbal, but not visual material. Moreover, ALF was not related to epilepsy variables, such as the side of seizure focus, an abnormal hippocampus, epilepsy severity or temporal lobe resection. Interestingly, significant negative correlations between age and recall of verbal information were found in the TLE, but not the control group. That is, deficits in recall of verbal information after long, but also short, delays became apparent as children with TLE aged: they appeared to grow into their memory deficits.

Children with TLE in the present study were found to perform more poorly on a standardised memory test that required recall of short stories immediately after initial hearing and after a 30-min delay. Nevertheless, scores obtained on this standardised task did not correlate significantly or predict the recall of words after a long delay. On the experimental task that demanded recall of verbal information at short and long delays, the group by delay interaction was significant. The between group difference was significant only at long, but not short delays. Furthermore, this between-group interaction remained significant even when those who had not reached the learning criterion and who had undergone temporal lobe resection were excluded from the analyses. Together, these findings indicate that ALF is present in some children with TLE in the context of specific experimental learning conditions, which cannot be explained by poor initial learning efficiency or surgical history. Moreover, performance on standardized memory tests is not predictive of ALF, although a standardized verbal memory test did reveal memory impairment after a 30-min delay. Finally, an additional analysis of individual participants indicated that a significantly
higher proportion of patients with TLE displayed impaired 7-day recall, compared to control participants, none of whom displayed impaired short-term verbal recall on a standardised tests, which suggests that standardised memory tests do not adequately measure ALF.

Of particular interest are the developmental trajectories of verbal memory abilities in children with TLE. Previously, a large-scale cross-sectional study found that recall of verbal information after short (30-min) delays progressively worsened in children with TLE, resulting in an increasing gap between children with TLE and healthy control peers which reached peaks during adolescence/early adulthood (Helmstaedter and Elger, 2009). A similar trend was observed in the current study; a significant negative correlation was found between recall of verbal information after a short delay and age in the TLE group. Nevertheless, our study extends the findings of Helmstaedter and Elger (2009) to long-term memory. The proportion of verbal information recalled at 7-days, relative to the last learning trial, declined with age within our TLE sample, but not within the control group. Moreover, recall performance differed between the two groups among older, but not younger, participants. This pattern suggests that children with TLE grew into their memory deficits. It is possible that such a phenomenon could be secondary to the cumulative adverse effect of seizures on hippocampal maturation (Mitchell et al., 2003; Sutula et al., 2003). Contrary to such an explanation, however, after accounting for life spent with epilepsy, the relationship between age and verbal recall at short and long delays remained significant in the patient group. Such findings suggest that seizures and verbal memory deficits may represent behavioral manifestations of the same underlying temporal lobe pathology, which may be predominantly long-standing rather than progressive in nature. Nevertheless, as verbal
memory is relatively late to mature (Gathercole, 1998), mild deficits in verbal memory may not be detectable at a young age, but become more apparent at a later age.

When examining the impact of side of seizure focus on verbal memory, we found that only patients with left-TLE performed below the control participants on several standardised memory tasks. These patients also recalled significantly fewer words on short and long delays on the experimental task. Patients with TLE recalled significantly fewer story details on standardised tests relative to control participants regardless of the presence or absence of hippocampal abnormalities. However, on the experimental task, only patients with a hippocampal abnormality recalled significantly fewer words at long, but not short delays and also exhibited poorer long-term verbal recall performance. We found that neither the side of seizure focus nor hippocampal damage were significant predictors of patients’ verbal recall at any delays of the experimental verbal memory task. Only age was a significant predictor of word recall at a long delay: older age predicted worse recall. Although ALF has been previously associated with seizure severity (Mameniskiene et al., 2006), seizure frequency (Wilkinson et al., 2012) and even subclinical discharges in adults (Fitzgerald et al., 2013), there was no association between ALF and epilepsy severity in the current study. Future studies could include a more direct measure of seizures, in order to assess their impact on ALF in children. Although the GASE scale used in the current study takes into account the frequency and intensity of seizures, it also considers a variety of other epilepsy-related variables, such as seizure-related injuries and number of prescribed anti-epileptic drugs, making it impossible to assess the impact of individual epilepsy-related factors on long-term memory.
In contrast to ALF for verbal material, we found no evidence of ALF for visual material. This difference may be partly due to the potential of inadequate sensitivity of the test specifically developed to measure visual long-term memory formation. We found no differences between the TLE and control groups in recall of visual information at short or long delays. Nevertheless, when patients were sub-divided according to hippocampal integrity status, those with hippocampal abnormality had significantly poorer recall of item locations on the (i) short (but not long) delay of the experimental task relative to those without hippocampal abnormalities and to control children and (ii) short delay of the standardized visual memory task. Also, children with a left (rather than right) hemisphere seizure focus performed poorer on the short delay of the standardised, but not experimental, visual memory test compared to controls. The presence of a short-term visual recall deficit in left-TLE patients was unexpected, given that some previous studies have found visual recall deficits to be confined to children with a right-sided temporal lobe seizure focus (e.g. Mabbott and Smith, 2003; Nolan et al., 2004; Gonzalez et al., 2007). However, the presence of deficits in our left-TLE patients may be partly explained by a comparatively high proportion of children with an abnormal hippocampus in this group. In addition, hippocampal abnormality was predictive of recall of design locations on the visual experimental task on short delay only. The side of seizure focus and age were not significant predictors of performance on this task after any delays. It should also be noted that it is not unusual for adult left-TLE patients to demonstrate visual memory deficits (e.g. Glosser et al., 2002; Smith et al., 2011).

Several limitations of the present study should be acknowledged. First, while regression analyses suggested that the side of seizure focus and presence of hippocampal structural abnormality were not predictive of recall of information after
long delays, this non-significant finding should be taken with caution. Our regression analyses were exploratory and limited by our sample size. Nevertheless, it is important to note that such findings are consistent with several adult studies which provided evidence of ALF in patients with TLE, but found that (i) the side of seizure focus was not related to material specific memory deficits at long delays (Martin et al., 1991; Wilkinson et al., 2012) and (ii) recall of information after long delays was not correlated with hippocampal volumes (Narayanan et al., 2012) or the presence of structural lesions (Mameniskiene et al., 2006; Wilkinson et al., 2012). As this is the first study to examine long-term memory formation in children with TLE, it would be important to conduct large scale studies which use volumetric and/or functional imaging data techniques to validate our findings. Second, it was not possible to monitor seizure activity during the retention period in the current study. This lack of information on seizures during this interval is important, as ALF has been associated with the frequency of epileptic seizures (Wilkinson et al., 2012) and with subclinical discharges in a study that used EEG telemetry (Fitzgerald et al., 2013). Therefore seizure activities should be monitored in future studies. Third, while we found consistent evidence of an association between older age and worse recall of verbal information after short and long delays in the TLE group, our study was cross-sectional, rather than longitudinal, and thus only offers indirect evidence about trajectories of verbal memory development in children with TLE.

Although not without some methodological limitations, our study identified a notable memory deficit in children with TLE and therefore has several significant clinical implications. Importantly, the results of this study suggest that long-term memory deficits in children with TLE may not be adequately addressed by standardised memory tests. Not only can these tests fail to detect a memory deficit, they may even
classify the child’s memory performance as falling within the average range, thereby misleading parents and clinicians, as well as possibly resulting in additional anxiety and lowered self-esteem in children with TLE. Our data also extend previous findings on the development of memory deficits in children with TLE, suggesting that memory performance may progressively worsen from childhood to adolescence, relative to their healthy control peers. Therefore, the monitoring of memory performance in patients with TLE may be especially important between childhood and teenage years.

Acknowledgements

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CHAPTER 4: Accelerated Long-Term Forgetting in Children with Idiopathic Generalized Epilepsy

This paper was accepted for publication in *Epilepsia*.

Reference:
Summary

Purpose: The rapid forgetting of information over long (but not short) delays (accelerated long-term forgetting, [ALF]) has been associated with Temporal Lobe Epilepsy but not Idiopathic Generalised Epilepsy (IGE). Long-term memory formation (consolidation) is thought to demand an interaction between medial temporal and neocortical networks, which could be disrupted by epilepsy/seizures themselves. The present study investigates whether ALF is (i) present in children with IGE and (ii) relates to epilepsy severity. Methods: Sixty-one children [20 IGE and 41 healthy controls (HC)] of comparable age, sex and parental socioeconomic status completed neuropsychological tests, including a measure of verbal learning and recall after, short (30-minute) and long (seven-day) delays, and recognition. Epilepsy severity was rated by treating neurologists. Key Findings: A two-way repeated measures ANCOVA found a significant Group x Delay interaction; the children with IGE recalled (and recognized) significantly fewer words after a long, but not short (2- and 30-minutes) delay relative to the HC children. Moreover, greater epilepsy severity was associated with poorer recognition. Significance: This study demonstrates, to our knowledge for the first time, that children with IGE present with ALF, which is related to epilepsy severity. These findings support the notion that epilepsy/seizures themselves may disrupt long term memory consolidation, which interferes with day-to-day functioning of children with IGE.
Introduction

Memory difficulties represent the most common clinical complaints in patients with epilepsy (Corcoran & Thompson, 1992; Vermeulen et al., 1993; Blake et al., 2000). Yet both adult (Elixhauser et al., 1999; Piazzini et al., 2001) and child (Kadis et al., 2004) studies suggest that these memory complaints (i) are often unrelated to scores obtained on standardised memory tests, and (ii) are not confined to patients with Temporal Lobe Epilepsy (TLE). This paradoxical lack of correspondence between memory complaints and neuropsychological test scores may (in part) be due to overly-short delays used on the tests. Interestingly, some patients with TLE have difficulties recalling information after long delays despite intact recall on short delays used on neuropsychological tests: they exhibit accelerated long-term forgetting (ALF) which has been attributed to hippocampal pathology/seizure focus (Martin et al., 1991; Kapur et al., 1997; O'Connor et al., 1997; Blake et al., 2000; Mameniskiene et al., 2006; Jansari et al., 2010; Muhlert et al., 2011; Wilkinson et al., 2012). However, the role of the hippocampus in ALF is not proven as (i) several studies that involved patients with TLE failed to find evidence of ALF (Giovagnoli et al., 1995; Bell et al., 2005; Bell, 2006; Howard et al., 2010) and (ii) in patients with transient epileptic amnesia (TEA) hippocampal atrophy did not correlate with ALF (Butler et al., 2009).

It has been proposed that long-term memory formation requires a consolidation process that may take hours, days or months to complete (Squire et al., 1984), and demands an interaction between the hippocampus and neocortex (Squire & Alvarez, 1995; Mayes et al., 2003). Thus, not only hippocampal pathology, but also disruption (such as from seizure activity) of the transfer of information between the hippocampus and neocortex during the memory consolidation could cause ALF
(Mayes et al., 2003). Therefore, ALF could be found in patients with generalised seizures who have no detectable cortical pathology: Idiopathic Generalized Epilepsy (IGE; Davidson et al., 2007).

To date, two studies have examined ALF in IGE populations: one involved adults (Muhlert et al., 2011) and another children (Davidson et al., 2007). The former found no evidence of memory deficits on short (30-minute) and long delays (three weeks) in patients with IGE. Findings of adult studies, however, should not be automatically generalised to children, as children’s cognitive skills and functional brain organisation are still developing. Indeed, in children with IGE, Davidson and colleagues (2007) found evidence of ALF, but attributed this finding to poor initial learning efficiency. While seizures were proposed to play a critical role in long-term consolidation, 24% of Davidson and colleagues’ sample had been seizure free for two years and the adult study did not state whether seizure-free participants were included. Inclusion of seizure-free participants could have reduced the likelihood of finding ALF in these studies. Nevertheless, adult TLE studies have yielded inconsistent findings on the role of seizures in ALF: two studies found significant associations between seizures and rate of forgetting over long delays (Mameniskiene et al., 2006; Wilkinson et al., 2012), and one study did not (Blake et al., 2000). It is possible that instead of a single factor, a combination of epilepsy related factors play a significant role in ALF, which could account for inconsistent findings. For example, greater seizure severity (Mameniskiene et al., 2006), longer duration of epilepsy disorder (Blum, 2001; Nolan et al., 2004; Wang et al., 2011) and the use of poly-pharmacy (Alessio et al., 2004) were all found to be associated with poor learning and recall after short delays. Thus,
a measure that considers overall epilepsy severity, rather than epilepsy factors separately, could be related to the rate of long-term forgetting.

This study aimed to examine long-term verbal memory formation in children with IGE and determine whether it relates to epilepsy severity and day-to-day memory difficulties. To overcome the shortcomings of previous studies we included only children who had experienced at least one overt seizure in the last two years and examined the relationship between epilepsy and long-term memory formation using a validated epilepsy severity scale. We hypothesized that (i) children with IGE will have poorer recall and recognition of verbal information after long, but not short delays and (ii) poorer long-term memory will be associated with more severe epilepsy and everyday memory complaints.

Methods

Sample
Twenty children diagnosed with IGE and 41 healthy control (HC, free of epilepsy history) participants: aged 6-16 years, fluent in English, with Full Scale Intelligence Quotient (FSIQ) >79, free of pre-existing diagnoses of major: sensory, neurodevelopmental [but not Attention Deficit Hyperactivity Disorder (ADHD) or learning difficulties] and other neurological disorders. Children with IGE were recruited through the Neurology Department, The Children’s Hospital at Westmead (CHW). Medical history, electroencephalography and imaging data were reviewed by treating neurologists against the International League Against Epilepsy criteria for IGE (Commission on Classification and Terminology of the International League
Against Epilepsy, 1989). Only children who had experienced at least one seizure in the two-year period prior to the assessment and whose clinical MRI scans (when available, n=14) were free of structural abnormalities were considered for the study; 27 of 31 (87%) consented. Seven were excluded because subsequent findings disqualified IGE diagnosis (n=6) or long-term verbal memory materials were noted and rehearsed, invalidating the test (n=1). Control participants were recruited via word-of-mouth (snowball recruitment), through the peer networks of both IGE and other control participants.

Materials

Socioeconomic status (SES): Daniel’s Scale of Occupational Prestige (Daniel, 1983) rates parental occupation on a 7-point scale, with higher scores reflecting lower SES. Mean parental occupation scores were used, except for single parent families.

Neuropsychological Measures

Clinical Neuropsychological Instruments: are summarised in Table 1.
<table>
<thead>
<tr>
<th>Domain</th>
<th>Test: Subtest</th>
<th>Score Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intelligence</td>
<td>WASI: Vocabulary</td>
<td>Full Scale Intelligence Quotient (FSIQ)</td>
</tr>
<tr>
<td></td>
<td>and Matrices</td>
<td>M = 100, SD = 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everyday Memory</td>
<td>EMQ</td>
<td>Raw score</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 to 112</td>
</tr>
<tr>
<td>Working Memory</td>
<td>WISC-IV: Digits Span</td>
<td>Age scaled scores</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M = 10, SD = 3</td>
</tr>
<tr>
<td></td>
<td>WMTB–C: Block Recall</td>
<td>Age scaled scores</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M = 10, SD = 3</td>
</tr>
<tr>
<td>Short-term Memory</td>
<td>WRAML2: Story</td>
<td>Age scaled scores</td>
</tr>
<tr>
<td></td>
<td>Memory</td>
<td>M = 10, SD = 3</td>
</tr>
<tr>
<td></td>
<td>CMS: Dot Location</td>
<td>Age scaled scores</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M = 10, SD = 3</td>
</tr>
</tbody>
</table>


*Experimental Verbal Memory Measure:* Word lists were derived from the California Verbal Learning Test – Children’s Version (CVLT-C, Delis et al. 1994), which has been shown to have acceptable reliability [coefficient alpha ranging from .72 to .85 (Delis et al., 1994)] and construct validity (Griffiths et al., 2006) in children with epilepsy. A 9- and 12-word list were devised for children <9 and ≥9 years of age,
respectively. Firstly, this list (A) was read until all words were recalled on two
consecutive trials or 12 learning trials (2 IGE participants) were completed. Secondly,
list B (interference) was read and recalled once. Thirdly, a recall of list A was
requested following two short (2- and 30-minute) and one long (one week) delay,
without forewarning. Fourthly, on completion of the long delay recall, a recognition
list was presented. Long delay recall and recognition were conducted via telephone.
The following scores were used: (a) number of learning trials (learning efficiency), (b)
percentage of words recalled (max 100%) relative to last learning trial (recall) and (c)
d prime (d', recognition), which takes into account the proportion of correctly and

Epilepsy Variables
Epilepsy severity: The Global Assessment of Severity of Epilepsy (GASE, Speechley
et al., 2008) rates overall epilepsy severity on a scale from 1 (Not at all severe) to 7
(Extremely severe). It considers the frequency and intensity of seizures, injuries
during seizures, severity of post-ictal period, number and side-effects of antiepileptic
drugs and interference of epilepsy or drugs with daily activities. This scale has good
construct validity as well as high inter-rater (weighted kappa = .85) and test-retest
(weighted kappa = .90) reliability.

Procedure
The study was approved by the CHW and University of Sydney Ethics Research
Committees. Parents gave informed consent and children were tested individually
over one 90-minute session and contacted seven days later via phone. Memory
questionnaires were completed by parents. Developmental history, SES and
information about relevant epilepsy variables were gathered via parental interview.
Information about epilepsy was verified by treating paediatric neurologists and review of medical records. Neurologists, who were blinded to children’s scores on neuropsychological measures, completed the GASE scale.

**Statistical analysis**

All tests were two-tailed, with $\alpha < .05$. Groups were compared using (i) independent t-tests and chi-square tests on background variables and (ii) analysis of covariance (ANCOVA, with centered FSIQ as a covariate) on other measures. Spearman’s rho ($r_s$) was used to assess strengths of correlations between epilepsy severity and everyday memory with long-term and short-term memory measures.

Scores obtained on the experimental measure of verbal memory were analysed using a two-way [Group x Delay] repeated measures ANCOVA, followed by Sidak post-hoc tests. A priori hypotheses concerning ALF were assessed with the following planned contrasts; the 30-minute and 7-day, and the 2-minute and 30-minute delays.

**Results**

IGE participants were diagnosed at a mean age of 6.09 (SD=3.25) years and had experienced epilepsy for an average of 4.54 (SD=2.18) years (Supporting Table 1). All IGE children were taking AEDs: 18 monotherapy and 2 polytherapy. The mean epilepsy severity score (M=2.17, SD=1.69) corresponded to a rating between “A little severe” and “Somewhat severe”. The IGE and control groups did not differ in age, SES, sex distribution and frequency of ADHD or learning difficulties diagnosis (see Table 2). Mean FSIQ of the IGE group was significantly lower than that of the control group.
<table>
<thead>
<tr>
<th></th>
<th>IGE ($n = 20$)</th>
<th>Control ($n = 41$)</th>
<th>Test of Significance</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>10.76 (2.47)</td>
<td>11.23 (2.63)</td>
<td>$t_{(59)} = -0.68$</td>
<td>0.50</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>10/10</td>
<td>21/20</td>
<td>$\chi^2 = 0.01$</td>
<td>0.93</td>
</tr>
<tr>
<td>SES</td>
<td>4.08 (1.31)</td>
<td>3.70 (1.08)</td>
<td>$t_{(59)} = 1.13$</td>
<td>0.27</td>
</tr>
<tr>
<td>FSIQ</td>
<td>102.00 (10.60)</td>
<td>111.32 (11.22)</td>
<td>$t_{(59)} = -3.10$</td>
<td>0.003</td>
</tr>
<tr>
<td>Comorbid ADHD/LD</td>
<td>1/0</td>
<td>0/0</td>
<td>$\chi^2 = 2.1$</td>
<td>0.15</td>
</tr>
</tbody>
</table>

IGE: Idiopathic Generalised Epilepsy; SES: Socioeconomic status; FSIQ: Full-Scale Intelligence Quotient; ADHD: Attention Deficit Hyperactivity Disorder; LD: Learning difficulty

On the EMQ ANCOVA revealed significantly lower parental ratings in the IGE compared to the control group (Table 3). No significant differences were found between the groups on tests of working or visual memory. However, on the verbal memory test (WRAML2: Story Memory) the IGE children recalled a significantly smaller number of details immediately after the presentation and on 30-minute delay relative to the control group.
Table 3: Scores Obtained on Clinical Neuropsychological Instruments

<table>
<thead>
<tr>
<th></th>
<th>IGE ($n = 20$)</th>
<th>Control ($n = 41$)</th>
<th>Test of Significance</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted Mean (SD)</td>
<td>Adjusted Means (SE)</td>
<td>Unadjusted Means (SD)</td>
<td>Adjusted Means (SE)</td>
</tr>
<tr>
<td>EMQ$^a$</td>
<td>72.84 (12.31)</td>
<td>73.35 (3.16)</td>
<td>87.29 (13.21)</td>
<td>87.06 (2.09)</td>
</tr>
<tr>
<td>WMTB-C Block Recall</td>
<td>93.95 (15.18)</td>
<td>97.05 (4.64)</td>
<td>93.63 (22.32)</td>
<td>92.12 (3.16)</td>
</tr>
<tr>
<td>WISC-IV Digit Span</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digits Forward</td>
<td>8.85 (2.52)</td>
<td>9.33 (0.59)</td>
<td>10.95 (2.66)</td>
<td>10.72 (0.40)</td>
</tr>
<tr>
<td>Digits Backward</td>
<td>8.70 (2.31)</td>
<td>9.01 (0.64)</td>
<td>9.95 (2.92)</td>
<td>9.80 (0.44)</td>
</tr>
<tr>
<td>WRAML-2 Story Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>9.85 (2.89)</td>
<td>10.34 (0.51)</td>
<td>12.10 (1.97)</td>
<td>11.86 (0.35)</td>
</tr>
<tr>
<td>Delayed Recall (30 mins)</td>
<td>9.30 (2.94)</td>
<td>9.75 (0.52)</td>
<td>11.83 (1.95)</td>
<td>11.61 (0.35)</td>
</tr>
<tr>
<td>CMS Dot Locations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>9.85 (3.41)</td>
<td>10.33 (0.75)</td>
<td>10.17 (3.20)</td>
<td>9.94 (0.51)</td>
</tr>
<tr>
<td>Delayed Recall (30 mins)</td>
<td>10.70 (3.18)</td>
<td>10.98 (0.71)</td>
<td>10.46 (2.93)</td>
<td>10.33 (0.48)</td>
</tr>
</tbody>
</table>

Experimental Measure of Verbal Memory

ANCOVA yielded no significant difference between the IGE ($M = 6.57, SD = 2.59$) and control ($M = 5.85, SD = 2.15$) groups in the number of trials needed to reach the learning criterion ($F(1, 60) = 0.39, p = 0.54$).

Recall and recognition data are presented in Figures 1 a) and b) respectively. A two-way repeated measures ANCOVA found a significant interaction between Group and Delay ($F(2, 116) = 8.39, p < 0.01$). Planned contrasts revealed that, compared to the control group, the IGE group recalled significantly fewer words from 30 minutes to 7 days ($F(1, 58) = 9.89, p = 0.003$), but not from 2 to 30 minutes ($F(1, 58) = 0.74, p = 0.39$). Additionally, a main effect of Delay ($F(2, 116) = 81.08, p < 0.001$), but not Group ($F(1, 58) = 1.36, p = 0.25$) was evident. No significant difference in recall was found between the 2- and 30-minute delays. However participants recalled fewer words from the 30-minute to 7-day delay ($p < 0.001$). Finally, the ANCOVA indicated that IGE participants had significantly poorer verbal recognition ($d'$) compared to control participants ($F(1, 60) = 17.82, p < 0.001$).
Figure 1: Mean (standard error bars) recall (a) and recognition (b) scores obtained by the IGE and control groups on the experimental measure of verbal memory covaried for FSIQ.

A

B

*** p < 0.001, ** p < 0.01
Is ALF related to incomplete learning and poor verbal memory (Story Memory)?

To address this question, a repeated measure ANCOVA that only included participants who learned all words (IGE, n = 18; HC, n = 41) was re-run, with Story Memory (immediate and delayed) and FSIQ as covariates. This ANCOVA again yielded a significant interaction between Group and Delay ($F(2, 108) = 7.96, p = 0.001$) and a significant main effect of Delay ($F(2, 108) = 74.84, p < 0.001$), but not Group ($F(1, 54) = 2.60, p = 0.11$). Planned contrasts showed that the IGE group recalled significantly fewer words from 30-minute to 7-day ($F(1, 54) = 10.81, p = 0.002$), but not from 2- to 30-minute ($F(1, 54) = 0.21, p = 0.65$) delays relative to the control group. Across groups, no differences were found between the number of words recalled on 2-minute and 30-minute delays; however, less information was recalled from the 30-minute to 7-day delay ($p < 0.001$). Finally, IGE participants had significantly worse recognition ($d'$) compared to control participants ($F(1, 56) = 23.13, p < 0.001$).

**Relations between experimental memory measure, epilepsy severity and everyday memory**

A significant negative correlation was found between epilepsy severity ratings on the GASE scale and long-term verbal recognition accuracy ($d'$: $r_s = -0.49, p < 0.05$); greater epilepsy severity was associated with worse long-term verbal recognition. However, epilepsy severity did not correlate with recall of information at any delay (2-min: $r_s = -0.10$; 30-min: $r_s = -0.18$; 7-days: $r_s = -0.21$; all $ps > 0.05$).

Significant correlations were found between the EMQ scores and i) recall of words on 7-day ($r_s = 0.33, p < 0.05$), but not 2- ($r_s = 0.02$) and 30-minute ($r_s = 0.09$; all $ps >$
delays and ii) 7-day recognition accuracy ($d': r_s = 0.44, p < 0.001$); better everyday memory was associated with higher recall and better recognition accuracy.

**Discussion**

This study found evidence of ALF in children with IGE. Moreover, children with more severe epilepsy had poorer long-term recognition of newly-learned verbal materials. Memory problems displayed in day-to-day life were greater in IGE than control children and were significantly associated with poorer recall and recognition after long, but not short, delays.

We found that children with IGE had difficulties with recall of information after long, but not short delays, which is typical of ALF. In our study (unlike in Davidson at al., 2007) ALF was not explained by reduced learning efficiency as (i) there was no between-group difference in the number of learning trials, (ii) exclusion of participants who did not learn materials to criterion did not eliminate ALF, and (iii) on the long delay the IGE participants had deficits not only in recall, but also in recognition of previously learned words. Taken together, our findings suggest that IGE participants have impaired long-term retention and impoverished long-term memory stores.

Importantly, all IGE children in our study were still being treated for epilepsy and had experienced at least one overt seizure in the last two years, whereas 24% of children in the Davidson et al. study (2007) were in remission. Furthermore, we found that greater epilepsy severity was associated with worse long-term recognition. Thus, the between study difference in epilepsy status may, in part, explain why the ALF was
found only in our study. Nevertheless, whether seizures themselves (or a combination of epilepsy factors) compromised long-term memory formation is difficult to ascertain, as in our study seizure activity was not monitored during the retention period, and several studies of TLE patient (except Jokeit et al., 2001 and Mameniskiene et al., 2006) found comparable forgetting rates during retention periods, regardless of seizure activity (Bergin et al., 1995; Blake et al., 2000; Muhlert et al., 2011). In patients with IGE, ALF may also be secondary to the reduced capacity of neocortical storage sites (critical for long-term memory) due to diffuse neocortical abnormalities beyond the resolution of structural brain scans (Woermann et al., 1998). Additionally, AEDs could have contributed to ALF, although most patients were on monotherapy, which is less deleterious to cognitive functions than polytherapy (Jokeit et al., 2005).

In our study, parental ratings of children’s everyday memory were related to long-term (but not short-term) recall and recognition. This is consistent with previous adult studies that involved patients with a left-hemisphere epilepsy focus (Blake et al., 2000) and patients with TEA (Butler et al., 2009). These findings are not surprising, as in everyday life, information frequently needs to be retained and recalled after long periods of time (i.e. days or months, rather than minutes). This pattern also testifies to the ecological validity of paradigms that require recall of information after long delays, and suggests that parental memory questionnaires may be used to screen for ALF.

Notably, prevalence of ADHD in our IGE sample was lower than in previous studies that involved children with epilepsy (Hermann et al., 2007; Dunn et al., 2003; Dunn
This was possibly due to a reliance on pre-existing diagnoses, rather than formal diagnostic assessments being conducted, which represents a limitation of our study. At present, however, there is no evidence that ADHD increases a risk of ALF.

In conclusion, this study provided evidence of ALF in patients with epilepsy who do not have a temporal lobe seizure focus/pathology; in children with IGE. Our findings are consistent with the consolidation theory, and suggest that factors other than a temporal lobe seizure site, such as epilepsy severity, may play significant roles in consolidation of memories into long-term stores. Clinically, it is important to note that (i) parental reports of everyday memory difficulties are related to long-term (but not short-term) memory recall, and (ii) scores obtained on standardised memory tests that require recall of information after short delays do not account for deficits in long-term memory formation. Specifically, children with more severe epilepsy whose parents report higher levels of memory difficulties in day-to-day life are at risk of ALF, which can remain undetected on standardised testing. Given that standardised instruments do not capture this phenomenon, the development of appropriate clinical assessment tools is essential to improve diagnosis and develop treatments.
Acknowledgements

The authors thank the children and parents for their participation, Dr. Margaret Charles for her data analysis assistance, and acknowledge a University of Sydney scholarship awarded to Mr. Michael Gascoigne.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References


CHAPTER 5: Autobiographical Memory in Children with Epilepsy
A memory system unique to humans, autobiographical memory, consists of both episodic and semantic memory components (Tulving, 2002). Episodic memory involves the ability to recall an event that is specific to a time and place (such as a recent family event), which may include an array of sensory, emotional, cognitive and perceptual details. Moreover, episodic memory is characterized by re-experiencing an event, where the individual mentally travels back in time. This state of mind is referred to as “autonoetic consciousness” (Tulving, 2002). In contrast, semantic memory involves the ability to recall factual autobiographical information or other components of self-knowledge that are not specific to a time or place, such as one’s age or gender.

Autobiographical memory is a relatively new area of neuropsychology research, with many studies focusing on the role of the hippocampus in the formation and retrieval of personally-experienced past events (e.g. Addis, Moscovitch, & Mc Andrews, 2007; Noulhiane et al., 2007; St-Laurent, Moscovitch, Levine, & Mc Andrews, 2009; Viskontas, Mc Andrews, & Moscovitch, 2000a). Initially, it was thought that the hippocampus did not play a significant role in the recall of autobiographical memories. For instance, early studies with patient H.M. suggested that his bilateral hippocampal excision did not result in temporally extensive retrograde memory deficits, as his memory deficit appeared to be limited to recent events (Scoville & Milner, 1957). Even some recent case studies suggest that this mesial temporal lobe (MTL) structure is unrelated to the recall of distant memories. For instance, complete bilateral damage to the hippocampus and adjacent MTL areas has been shown to result in an inability to acquire new spatial knowledge (Reed & Squire, 1998), without affecting the ability to recall remote autobiographical event or spatial layout details,
compared to healthy controls (Teng & Squire, 1999). This suggests that the hippocampus may not be necessary for the retrieval of either episodic event or spatial details from long-term memory stores.

The results of the above studies are therefore consistent with Classic Consolidation Theory (CCT; Squire, Cohen, & Nadel, 1984). According to CCT, the retrieval of remote memories greatly depends on neocortical regions, thought to be responsible for the long-term storage of memories, rather than the hippocampus, which only stores memories temporarily. This theory predicts that hippocampal damage should result in a temporally-graded remote memory impairment, where deficits are more likely to occur for recent, rather than remote memories. Furthermore, CCT does not draw a distinction between episodic and semantic details, as it assumes that hippocampal damage will result in a temporally-graded deficit for all memories. As consolidated information is understood to reside within extrahippocampal circuits, CCT predicts that the retrieval of remote autobiographical memories will not be accompanied by any activity in the hippocampus.

Inconsistent with CCT, however, are studies that have nevertheless revealed an association between hippocampal damage and temporally-extensive retrograde memory deficits. For instance, in a much more recent study with H.M., episodic memory deficits were evident for memories from before his surgery. He failed to recall events specific to time and place from those that took place during his childhood and early adulthood (Steinvorth, Levine, & Corkin, 2005). Other studies have also found that patients with MTL lesions exhibit amnesia for events that took place over a period of several decades and thus should have already been
consolidated. For instance, adults with unilateral MTL lesions have exhibited episodic memory deficits for events that occurred throughout their entire lifespan, including early childhood experiences (Lah, Lee, Grayson, & Miller, 2008; St-Laurent, Moscovitch, Levine, & McAndrews, 2009; Viskontas et al., 2000a; Viskontas, McAndrews, & Moscovitch, 2002; Voltzenlogel et al., 2006). Also inconsistent with CTT is the fact that several of these studies demonstrated an episodic, but not semantic memory deficit, suggesting that these memory types may undergo different consolidation processes.

Several other shortcomings of CCT have been noted, including a lack of detail about the length of the consolidation period (Nadel, Winocur, Ryan, & Moscovitch, 2007). According to CCT, the consolidation period of explicit memories in humans ranges from 3 months to 10 years (McClelland, McNaughton, & O'Reilly, 1995). Therefore, memories that were formed more than 10 years ago should be preserved in patients with hippocampal lesions. However, studies of patients with extensive mesial temporal lobe (MTL) lesions have given equivocal results (see Lah & Miller, 2008 for a review). For instance, although some patients with bilateral hippocampal lesions were found to present with temporally-graded episodic deficits for personally-experienced events (Eslinger, 1998; Hepner, Mohamed, Fulham, & Miller, 2007; Mattioli et al., 1996; Rempel-Clower, Zola, Squire, & Amaral, 1996), other patients displayed deficits in episodic recall for all events that have occurred across an entire lifespan (Calabrese et al., 1996; Damasio, Eslinger, Damasio, Van Hoesen, & Cornell, 1985; Hirano & Noguchi, 1998; Kapur et al., 1996; Kartsounis, Rudge, & Stevens, 1995).
Partly due to the inadequacy of CCT to account for some of these findings, Nadel and Moscovitch (1997) developed the alternative theory: Multiple Trace Theory (henceforth referred to as MTT). This theory distinguishes between episodic and semantic memories, where the former are dependent on the hippocampus indefinitely. Whereas CCT assumes that memory reactivation generally results in the reorganization of memories within cortical areas, MTT claims that the rehearsal of episodic memories leads to the creation of additional hippocampal traces. According to MTT, the hippocampus is essential for the formation of long-term declarative memory and remains necessary for recalling the temporal and spatial context of past events indefinitely (Nadel & Moscovitch, 1997). However, MTT states that the hippocampus is not essential for the recall of any autobiographical details that are free of a temporal or spatial context, that is, semantic memory. Consistent with MTT, difficulties in the recall of past episodic details, but not semantic, details have been observed in adults with unilateral hippocampal lesions, and attributed to temporal lobe damage or dysfunction (Addis et al., 2007; Barr, Goldberg, Wasserstein, & Novelty, 1990; Lah, Lee, Grayson, & Miller, 2006; St-Laurent et al., 2009; Viskontas, McAndrews, & Moscovitch, 2000b; Voltzenlogel et al., 2006). Although MTT does not clearly state its position on semantic memory, it does not explicitly reject the possibility that semantic memory can be impaired when episodic is preserved.

As the hippocampus is understood to play a central role in the retrieval of long-term episodic memories, MTT predicts that damage to this structure will lead to episodic, but not semantic, deficits in autobiographical recall, which will be commensurate with the extent of the hippocampal lesion (Nadel & Moscovitch, 1997). Incomplete hippocampal lesions, however, may result in a temporal gradient that does not affect
the recall of remote memories, however, complete lesions will result in the loss of all memories across the lifespan. Temporally-extensive (ungraded) amnesia for episodic details from past events has been demonstrated in patients with complete bilateral lesions (Bayley, Gold, Hopkins, & Squire, 2005; Haslam, Cook, & Coltheart, 2001; Rosenbaum et al., 2005; Steinworth et al., 2005; Van der Linden et al., 2001) and similar results have also been observed in animal studies (e.g. Kim & Fanselow, 1992). However, the findings are equivocal, as incomplete hippocampal lesions have resulted in temporally-extensive memory loss (Cipolotti et al., 2001; Grewal, 2003). Moreover, remote memory retrieval ability has been spared even in patients with bilateral lesions (Bayley, Hopkins, & Squire, 2003).

MTT has also gained support from neuroimaging studies, conducted with both TLE and healthy control samples. For instance, hippocampal activity has been detected in healthy individuals engaging in a variety of autobiographical memory tasks, such as freely recalling a personally-experienced event (Maguire, 2001; Maguire, Frackowiak, & Frith, 1997; Maguire, Vargha-Khadem, & Mishkin, 2001; Rekkas & Constable, 2005) or retrieving a personally-experienced event in response to an arbitrary word cue (Conway et al., 1999; Ryan et al., 2001). Although the hippocampus has been shown to be more active in the retrieval of recent, rather than remote memories (Söderlund, Moscovitch, Kumar, Mandic, & Levine, 2012), it remains a crucial structure for the re-experiencing of any episodic autobiographical memories, with the CA1 neurons within the hippocampus playing a critical role (Bartsch, Döhring, Rohr, Jansen, & Deuschl, 2011). Improvements in autobiographical recall performance have also been associated with increased blood flow within MTL structures in healthy middle-aged adults, including the hippocampus.
(Piolino et al., 2008), while hippocampal volume has also been positively correlated with the recall of both recent and remote autobiographical memories in patients who have undergone temporal lobe resection (Noulhiane et al., 2007).

Neuroimaging evidence suggests that the ability to remember events from one’s own past, however, may also be supported by a network that extends beyond the hippocampal formation (Buckner & Carroll, 2007; Svoboda, McKinnon, & Levine, 2006). For instance, the recollection of positive or happy memories (compared to negative or sad ones) in healthy participants has been associated with activity in the medial orbitofrontal/subgenual cingulate (Markowitsch, Vandekerckhove, Lanfermann, & Russ, 2003) and the orbitofrontal cortex (Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003). Recalling recent (compared to remote memories) has also been associated with bilateral activation in the retrosplenial cortex (Piefke et al., 2003).

Given that neuroimaging studies implicate an extended network of structures being engaged in the recall of past personal events, it is possible that the function of the extended network responsible for the storage and maintenance of autobiographical memories could be disrupted by generalised seizures in patients who do not present with any obvious cortical pathology; that is, in patients with IGE.

The development of both aspects of autobiographical memory has also received attention. Semantic memory develops early in life, as young children acquire vast amounts of information with respect to language and other skills, in the absence of autonoetic consciousness, or a sense of self in subjective time (Tulving, 2002).
Episodic memory, on the other hand, has been shown to develop later than semantic memory and is generally not present prior to the age of four (Perner & Ruffman, 1995; Wheeler, Stuss, & Tulving, 1997). Evidence also suggests that episodic memory continues to develop throughout childhood and adolescence (Billingsley, Smith, & McAndrews, 2002), with a more gradual trajectory. For instance, Piolino et al. (2007) assessed the ability to recall personal events (e.g. school or family events) and personal information (e.g. names of acquaintances) from three different life periods in healthy children aged between 7 and 13, finding that chronological age only correlated significantly with the ability to recall personal events. A similar improvement in the recall of episodic details with age was also observed by Willoughby et al. (2012) in a group of 182 healthy participants aged between 8 to 16, using a child-adapted version of an autobiographical interview originally designed for adult participants (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). However, this study along with another (Picard, Cousin, Guillery-Girard, Eustache, & Piolino, 2012) also found comparatively smaller improvements in semantic memory, suggesting that semantic memory may develop earlier and perhaps provide a basis for the later development of episodic memory.

Children who experience early bilateral hippocampal damage have also been shown to have deficits in the recall of episodic details, despite having relatively preserved semantic recall (Cooper, Vargha-Khadem, Gadian, & Maguire, 2011; Vargha-Khadem et al., 1997; Vargha-Khadem et al., 2003), a condition referred to as “developmental amnesia”. The memory impairment in these patients is typified by impaired learning of new information and impaired recall of this information after short delays (Vargha-Khadem et al., 1997) in addition to poor everyday memory
(Gadian et al., 2000; Vargha-Khadem et al., 2003), but relatively preserved semantic knowledge (Gardiner et al., 2006). During early adulthood, these patients have been shown to recall fewer episodic, but not semantic details, compared to healthy controls on autobiographical memory tasks (Kwan et al., 2010; Rosenbaum et al., 2011). Moreover, in children with developmental amnesia, smaller hippocampal volume (both right and left) has also been associated with poorer episodic recall (Cooper et al., 2011).

To date, only one study has directly examined autobiographical memory in paediatric epilepsy (Cronel-Ohayon et al., 2006). This single case study included a boy who was initially seen for a neuropsychological assessment at 9 years of age (some 1.5 years after the onset of TLE). His mother expressed concerns about his ability to recall personal events, but the child’s ability to recall newly-learned information after a one-hour delay was nevertheless within the age appropriate range. On the other hand, he recalled fewer autobiographical events than his twin brother on an autobiographical memory questionnaire. He underwent temporal lobectomy at ten years of age and a follow-up (at 18 years of age) showed the same pattern of results. In addition, his retention of information over a long period (1 week) was measured and found to be reduced. The authors suggested that his autobiographical memory deficits may be secondary to ALF, rather than the presence of temporal lobe pathology. This raises a possibility that deficits in the recall of past experiences could potentially be found in patients who do not present with hippocampal lesions, such as patients with IGE.

Remote memory deficits have been identified as the primary complaint of some adult epilepsy patients (Gallassi, 2006; Gallassi, Morreale, Di Sarro, & Lugaresi, 1992).
Establishing the existence of this autobiographical memory deficit within a paediatric population is important for several reasons. Firstly, deficits in recalling personal events from the past could affect the construction of an individual’s personal identity, as a patient’s current view of themselves can be influenced by what they remember about themselves from the past (Wilson & Ross, 2003). Secondly, it has been suggested that the development of autobiographical memory corresponds with everyday memory, possibly because these abilities are dependent on the maturation of similar brain regions (Willoughby et al., 2012). Therefore, deficits in autobiographical memory may also have a detrimental effect on everyday memory performance and, in a similar manner to ALF, partly contribute to the discrepancy between subjective memory complaints and objective memory performance. The early identification and assessment of these deficits is obviously important for clinical reasons, as developing an understanding of the specific nature and development of these deficits will allow them to be addressed with targeted interventions.

The following studies aim to examine autobiographical memory in children with TLE and in children with IGE. This set of studies may help to clarify how autobiographical recall is related to the hippocampus and to a more widely distributed core brain system.
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CHAPTER 6: Autobiographical Memory in Children with Temporal Lobe Epilepsy

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Reference:
Abstract

Autobiographical memory involves the recall of personal facts (semantic memory) and re-experiencing of specific personal events (episodic memory). Although impairments in autobiographical memory have been found in adults with unilateral temporal lobe epilepsy (TLE) and attributed to compromised hippocampal integrity, it is not yet known whether this occurs in children with TLE. In the current study, 21 children with TLE and 24 healthy controls of comparable age, sex and socio-economic status were administered the Children’s Autobiographical Interview. Compared to controls, children with TLE recalled fewer episodic details, but only when no retrieval prompts were provided. There was no difference between the groups for semantic autobiographic details. Interestingly, the number of episodic details recalled increased significantly from 6 to 16 years of age in healthy control children, but not in children with TLE. Exploratory analyses revealed that, within the group of children with TLE, epilepsy factors, including presence or absence of structural hippocampal abnormalities, did not relate to the richness of episodic recall. Our results provide the first evidence of autobiographical episodic memory deficits in children with TLE.

Keywords/Mesh terms: Episodic Memory, Long-Term Memory, Hippocampus, Seizures, Remote Memory, Memory Disorder
Introduction

Temporal lobe epilepsy (TLE) often has onset in childhood and persists into adulthood. Interestingly, distinct neurological and neuropsychological features of this type of epilepsy are not apparent in infants and preschool children, but gradually emerge, as the brain matures and a range of physiological and behavioral manifestations develop. For example, in adults with TLE, memory deficits (learning and/or retention of information over 20-30 minute delays) are often found to be material-specific. Impaired memory for verbal materials is evident in patients with a left temporal lobe seizure focus (Hermann et al., 1987; Frisk & Milner, 1990; Seidenberg et al., 1996; Jones-Gotman et al., 1997; Bell et al., 2005). Impaired memory for visual materials tends to be found (albeit less consistently) in patients with a right hemisphere seizure focus (Jones-Gotman, 1986; Smith & Milner, 1989; Jones-Gotman et al., 1997; Pillon et al., 1999; Chiaravalloti et al., 2004; Bell et al., 2005). Memory deficits are also evident in children with TLE, but the findings relating to material-specificity tend to differ from the findings in the adult literature. In children, verbal memory deficits are often found to be unrelated to laterality of seizure focus (Lendt et al., 2002; Mabbott & Smith, 2003; Gonzalez et al., 2007; but see: Cohen, 1992; Gleissner et al., 2002), whereas visual memory deficits have been found in children with right hemisphere seizure focus in some (i.e. Nolan et al., 2004; Beardsworth & Zaidel, 1994), but not in other studies (e.g. Gonzalez et al., 2007). Interestingly, a recent longitudinal study revealed a change in the pattern of memory deficits from childhood to adolescence/young adulthood (Gonzalez et al., 2012). Initially, verbal memory deficits in children were unrelated to the laterality of seizure focus, but lateralized verbal memory deficits were evident at follow-up, during adolescence or young adulthood. Similarly, in a large cross-sectional study examining
verbal memory across a wide age-span (6-68 years) impact of laterality was not evident in children, but was apparent in adolescence/early adulthood (Helmstaedter & Elger, 2009). Inspection of verbal memory scores across childhood and adolescence/early adulthood was indicative of a developmental hindrance (rather than cognitive decline) in patients with epilepsy relative to healthy participants. This hindrance resulted in a gap that widened from childhood to adolescence/early adulthood. Interestingly, the emergence of lateralized verbal memory deficits coincides with the endpoint of functional cerebral plasticity and increased hippocampal activation as children move into adolescence (Ghetti et al., 2010).

Importantly, for our study, the hippocampus is also proposed to be critical for recollection of past autobiographical memories irrespective of their distance from the present (Nadel & Moscovitch, 1997). Moreover, adults with unilateral TLE have been found to experience difficulties in autobiographical recall (Addis et al., 2007; Viskontas et al., 2000). It is not known, however, whether children with TLE experience similar difficulties.

Autobiographical memory is a complex, uniquely human memory system that contains semantic and episodic components. While the semantic component involves recall of factual autobiographical information, the episodic component relates to the ability to recollect personally experienced events of a known temporality that are rich in contextual details (Tulving, 2002). Moreover, recalled episodes (but not semantic details) are often emotionally salient (Piefke et al., 2003), vivid and associated with the sense of re-experiencing (Hassabis & Maguire, 2007). These two components of autobiographical memory were proposed to be supported by different neural networks (but see Squire et al., 1984) and to have different developmental trajectories. While the semantic memories can be supported by neocortical structures, the retrieval and
re-experiencing of autobiographical episodes require hippocampal involvement. With respect to developmental trajectories, marked improvements have been documented in the recall of episodic details from childhood to adolescence in the general population (Picard et al., 2009; Picard et al., 2012; Piolino et al., 2007; Willoughby et al., 2012), while increases in the recall of semantic details over the same developmental period have either been small (Willoughby et al., 2012) or insignificant (Piolino et al., 2007).

Given the role of the hippocampus in autobiographical memory, studies of TLE patients are particularly relevant, as seizures often [but not always (Cascino, 1992)] emanate from the hippocampus within this patient group (Spencer et al., 1987; Spencer et al., 1990). Several recent studies of adults with TLE [but not all, Upton et al. (1992)], have found evidence of impaired autobiographical memory, but the patterns of impairments differed. Impairments have been found in the recall of (i) semantic, but not episodic, memories (Barr et al., 1990; Lah et al., 2004); (ii) episodic (Noulhiane et al., 2007; O’Connor et al., 1999; Voltzenlogel et al., 2007), but not semantic memories (Addis et al., 2007; St-Laurent et al., 2009; Viskontas et al., 2000; Voltzenlogel et al., 2006), and (iii) both episodic and semantic memories (Herfurth et al., 2010; Lah et al., 2006). Although it is possible that these inconsistencies are partly due to variations in methods, test protocols, or sample characteristics, they may also be due to between-study differences in hippocampal status, as functional neuroimaging studies have found that the activity of the residual hippocampal tissue was significantly reduced in an autobiographical memory task relative to a control task in pre-surgical patients (Addis et al., 2007). Furthermore, it has been found that the volumes of residual mesial temporal structures were correlated with episodic
autobiographical memory scores (Noulhiane et al., 2007). Finally, regional cerebral blood flow in the medial temporal lobe, including the hippocampus, has also been associated with the recall of episodic events from all stages of life (Piolino et al. 2008), providing further support for the notion that the hippocampus is necessary for re-experiencing episodic memories, irrespective of their age (Steinvorth et al. 2005).

In addition to hippocampal integrity, other clinical variables (i.e., laterality of seizure focus and epilepsy treatment) have also impacted autobiographical memory recall in adults with TLE, although findings have been inconsistent. Deficits in episodic recall were found to be more severe in patients with a seizure focus in the left (Barr et al., 1990; Leeman et al., 2009; Voltzenlogel et al., 2006) or in the right (Lah et al., 2006) temporal lobe. Moreover, in patients who underwent temporal lobectomy, the absence of seizures and being off anti-epileptic drugs was associated with better semantic recall (Lah et al., 2004). In pre-surgical patients with TLE, those on polytherapy have exhibited poorer episodic recall than those on monotherapy (Lah et al. 2006). Finally, as the hippocampus is purported to be critical for both new learning and recall of past personally experienced episodes, it was expected that the correlations between scores obtained on these two types of memory tests will be high. Instead, significant correlations have been found between new learning and semantic autobiographical details (Lah et al., 2006), but not between new learning and recall of personally experienced episodes (Herfurth et al., 2010; Lah et al., 2004; Lah et al., 2006). Finally, seizures themselves may interfere with consolidation (in adults: Blake et al., 2000; Mameniskiene et al., 2006; Muhlert et al., 2011; in children: Gascoigne et al., 2012), which in turn could compromise autobiographical memory.
To our knowledge, no study has systematically examined autobiographical memory in children with TLE, although Smith, Elliot and Lach (2006) noted that children with epilepsy (among whom were a large proportion with TLE) reported difficulties recalling events from their lives. This lack of research represents a notable gap, as these children are likely to be at risk of autobiographical memory impairments, which is of clinical significance. In addition, studies involving children with TLE may offer further insight into the role of the hippocampus in autobiographical memory. Of relevance are studies involving patients with developmental amnesia (DA) arising from early bilateral hippocampal damage (e.g. from perinatal hypoxia or ischemia). The memory impairment in these patients is characterized by severely impaired new learning and recall of this newly-learned information after short delays (Vargha-Khadem et al., 1997) and poor everyday memory (Gadian et al., 2000; Vargha-Khadem et al., 2003), but relatively preserved semantic knowledge (Gardiner et al., 2006). As young adults, these patients tended to recall significantly fewer episodic details, but not semantic details relative to healthy controls on autobiographical memory tasks (Kwan et al., 2010; Rosenbaum et al., 2011). Moreover, in a recent study that examined 24-hour recall of staged events typically encountered during a neuropsychological assessment, Cooper et al. (2011) found that, relative to controls, school-aged children with DA exhibited poorer recall of spatiotemporal and episodic information (while being able to recall the gist of the event). Additionally, within the DA group, smaller hippocampal volume (both right and left) was associated with poorer episodic recall (Cooper et al., 2011).

This study aimed to examine autobiographical memory in children with TLE. We hypothesized that, in a test of autobiographical recall, children with TLE would recall
fewer episodic details relative to their healthy control peers. Further exploratory analyses were conducted to investigate potential relationships between performance on the autobiographical memory task, tests of new learning and short-term memory, chronological age and relevant epilepsy variables (presence of hippocampal abnormality, laterality of seizure focus, surgical treatment, mono vs. poly-therapy, epilepsy severity, age at diagnosis and proportion of life with epilepsy).

Method

Participants

Twenty-four healthy children (the control group) and 21 children with TLE were recruited for the present study. Inclusion criteria were: aged 6 to 16 years at the time of assessment and fluency in English. Exclusion criteria were: (i) Full Scale Intelligence Quotient (FSIQ) < 80; (ii) presence of a major sensory deficit; (iii) significant neurodevelopmental disorder (e.g. autism, but not learning disability or ADHD), or (iv) the presence of another neurological disorder.

TLE participants were recruited from specialist epilepsy programs within three children’s hospitals: The Children’s Hospital at Westmead (Sydney, Australia) and The Hospital for Sick Children (Toronto, Canada) and McMaster Children’s Hospital (Hamilton, Canada). The study was approved by ethics committees of participating hospitals and The University of Sydney. Potential participants with TLE (pre-surgical, post-surgical and non-surgical) were identified by review of patient files. Electroencephalography (EEG) records, medical history, and imaging data (where available) were reviewed by the treating pediatric neurologists, and only children who met the International League Against Epilepsy criteria for TLE (Commission on
Classification and Terminology of the International League Against Epilepsy, 1989) were invited to participate. Clinical data for all TLE participants are summarized in Supporting Table 1.

Of the 21 children with TLE, 13 had seizures emanating from the left temporal lobe (including six postoperative patients), six from the right temporal lobe (including one postoperative patient) while the laterality of seizure focus could not be satisfactorily determined in two participants. A total of six participants who had not undergone surgery had MRI evidence of a hippocampal abnormality, involving either hippocampal sclerosis ($n = 2$), tumour ($n = 1$), dysplasia ($n = 2$) or gliosis ($n = 1$). Of the seven postoperative TLE patients, six had undergone a resection that involved the hippocampus, as a result of mesial temporal gliosis ($n = 3$), sclerosis ($n = 1$), microcortical dysgenesis ($n = 1$) or dysplasia ($n = 1$). One patient with TLE underwent a left anterior lateral temporal lobectomy (due to ganglioglioma), which spared the hippocampus. One participant was left-handed. Complex partial seizures were the most common seizure type. Seventeen participants experienced only one seizure type, while four experienced a combination of seizure types. Two participants were not taking any anti-epileptic drugs (AEDs). Twelve were on monotherapy and seven on polytherapy. Six different AEDs were represented within the TLE patient group. One TLE participant was reported to have a diagnosed learning disability, however no control participant was diagnosed with a comorbid developmental disorder.

Control participants were recruited via word-of-mouth through the peer networks of both TLE and control participants (snowball recruitment). Only children who met
inclusion/exclusion criteria, and were free of a history of epilepsy, as per intake interviews with the parents/guardians, were invited to be control participants.

Measures
Socioeconomic status (SES) was measured by average years of parent/guardian education. Intelligence (FSIQ; $M = 100$, $SD = 15$) was assessed with the two-subtest version (Vocabulary and Matrices) of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler 1999). New learning and short-term memory were evaluated with the Dot Location subtest from the Children’s Memory Scale (CMS; Cohen 1997) and the Story Memory subtest from the Wide Range Assessment of Memory and Learning: Second Edition (WRAML2; Sheslow & Adams 2003). Age scaled scores were used ($M = 10$, $SD = 3$).

Epilepsy Severity
Treating pediatric neurologists completed the Global Assessment of Severity of Epilepsy (Speechley et al., 2008), an instrument which has high test–retest (weighted $j = 0.90$) and inter-rater reliability (weighted $j = 0.85$), in addition to good construct validity. When giving a severity rating, neurologists considered the frequency and intensity of seizures, severity of postictal period, injuries during seizures, number and side effects of antiepileptic drugs, and interference of epilepsy or drugs with daily activities. Epilepsy severity was rated from 1 (Not at all severe) to 7 (Extremely severe).
Children’s Autobiographical Interview

The Children’s Autobiographical Interview (CAI; Willoughby et al., 2012) is an adapted version of the Autobiographical Interview (AI; Levine et al., 2002), which was originally developed for adults. Children were asked to recall two separate events (specific to a time and place) which they were personally involved in from any period during their lives, except for the preceding month. To aid the selection of appropriate memories, all children were provided with a list containing examples of 18 different life events (such as a birthday party or school excursion), but reminded that they were free to recall any event, irrespective of the suggestions contained in the list.

The CAI involved administration of three conditions: Free Recall, General Probe and Specific Probe. In the Free Recall condition, which was administered first, participants were given up to five minutes to recall as much information as possible about a specific event without any interruptions or prompting from the interviewer. In the General Probe condition, administered immediately after the Free Recall of an event, participants were either i) given a general prompt to recall any additional details or ii) asked to choose and clarify the event if multiple or non-specific events had been recounted during Free Recall. The Specific Probe condition was the final stage of the CAI, administered only once the Free Recall and General Probe conditions had been completed for both events, in order to prevent any contamination of the Free Recall of the second event. During the Specific Probe, children were asked a set of standardized questions relating to types of details (Event, Time, Place, Perceptual, and Emotion/Thought) that were not recalled in the previous two conditions.
The recall of both memories was recorded and transcribed (see example in Figure 1). Each memory was scored according to the AI scoring manual (Levine et al., 2002). Two main types of details were identified within each memory: i) episodic details, that pertain directly to the main episode and are placed in a particular spatio-temporal context, suggestive of the re-experiencing of the main event and ii) semantic details, representing general autobiographical information that is not integral to the main event. The average score of the two recalled memories was obtained separately for episodic and semantic details for each of the three conditions: i) Free Recall, ii) General Probe (Free Recall + General Probe) and iii) Specific Probe (Free Recall + General Probe + Specific Probe). See Figure 1 for a scored example of a transcribed memory.
Figure 1: Scored shortened example of a transcribed memory from the Children’s Autobiographical Interview

<table>
<thead>
<tr>
<th>Time</th>
<th>Time</th>
<th>External Event</th>
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</table>


“*Well, it was actually a Wednesday and it was just after school. I had found a dog breeder’s website and we decided to buy a pet. We drove there and at the farm we chose two dogs. I didn’t want to take the dogs home then but the farmer sort of forced us. We paid $70 for both of them, They were black and still quite small. We put them in the car and I remember both of them became quite stressed.*”

**General Probe**

**Q.** Is there anything else you remember about that?

“*Not really, no.*”

**Specific Probe**

**Q.** Do you know what year you got your pet dogs?

“*Five years ago, It was in February I think.*”

**Q.** Do you know what date?

“*In the last week of February, I think.*”

Each transcribed memory was initially scored by one experimenter (MG) who had previously completed training by scoring a practice set of memories provided with the AI scoring manual (Levine et al., 2002), achieving correlations ranging from 0.89 to 0.99 with the practice set. Another trained staff member independently scored ten randomly selected memories. Intra-class inter-rater correlations for the composite scores obtained on the CAI were (i) Free Recall: 0.77 and 0.71 for episodic and
semantic details, respectively (ii) General Probe: 0.82 and 0.88 for episodic and semantic details, respectively, and (iii) Specific Probe: 0.98 and 0.75 for episodic and semantic details, respectively.

Procedure
Parents gave informed consent and children gave informed assent for participation in the study. Medical records were reviewed to obtain relevant medical information, which was verified by treating paediatric neurologists. Parents of control and TLE participants were interviewed regarding their child’s developmental and medical history, relevant epilepsy and SES variables, and completed questionnaires about their child. All children underwent a 90-minute assessment, conducted by a psychologist, which included a battery of intelligence and memory tests, administered in a set order. The CAI, administered at the end, took approximately 25 minutes to complete. One interviewer (MG) conducted 33 (73%) of the interviews, while the remaining 12 (27%) were conducted by another psychologist (MLS) and other trained support staff. Treating neurologists assessed epilepsy severity in the children with TLE.

Statistical Analysis
Preliminary analyses investigated all variables for outliers (i.e. 3 SD > M) and normality of distributions using the Shapiro-Wilk test. Two control participants were identified as outliers on the General Probe stage of the CAI and had their answers adjusted to the next most extreme value (Tabachnick & Fidell, 1996). For variables that were normally distributed, between-group differences were examined using independent t-tests. Where normality assumptions were not met Mann-Whitney U tests were employed to examine between-group differences, and Spearman’s rho ($r_s$)
was used for correlational analyses. With a sample size of 21 TLE patients, only correlations above \( r = 0.52 \) would be detected as statistically significant (Machin et al., 1997).

Chi-square tests were conducted for categorical variables, such as sex, surgical history, presence of hippocampal abnormality and comorbid disorders. Effect sizes (Cohen’s \( d \)) were calculated for all stages of the CAI and post-hoc power calculations carried out for the General and Specific Probe stages of the CAI. As our data were not normally distributed, effect sizes (\( r \)) were calculated and converted to Cohen’s \( d \) as described in Fritz et al. (2012).

**Results**

**Background demographic, cognitive and clinical variables**

The left- and right-TLE groups did not differ on any demographic variables, including: age, sex distribution or SES (see Table 1). Similarly, scores obtained by left- and right-TLE groups on Story Memory (WRAML2) and Dot Location (CMS) were comparable. Furthermore, the left- and right-TLE groups did not differ on clinical variables, including age of epilepsy diagnosis, proportion of life spent with epilepsy, mean number of prescribed AEDs, surgical history, epilepsy severity rating, presence of hippocampal abnormality or presence of a comorbid neurodevelopmental disorder.

As the left- and right-TLE groups were comparable on all background variables, and in order to increase statistical power, the two TLE groups, and two TLE participants in whom the laterality of seizure focus could not be satisfactorily determined, were
merged into a single patient group and compared to the control group in subsequent analyses. No differences were found between the TLE and control groups for age, sex or SES. However, the TLE group had significantly lower FSIQ than the control group. Moreover, the TLE group obtained significantly lower scores than the control group on immediate and delayed recall on Story Memory (WRAML2), but not on Dot Location (CMS; see Table 1)
### Table 1: Demographic, Cognitive and Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>Left TLE (n = 13)</th>
<th>Right TLE (n = 6)</th>
<th>Test of Significance</th>
<th>p</th>
<th>TLE (n = 21)</th>
<th>Control (n = 24)</th>
<th>Test of Significance</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>12.97 (5.57)</td>
<td>11.26 (5.21)</td>
<td>U = 28</td>
<td>0.37</td>
<td>12.29 (2.78)</td>
<td>12.16 (2.80)</td>
<td>t(43) = 0.16</td>
<td>0.88</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>7/6</td>
<td>4/2</td>
<td></td>
<td></td>
<td>11/10</td>
<td>14/10</td>
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<tr>
<td>SES (years)</td>
<td>13.50 (15.50)</td>
<td>14.00 (4.88)</td>
<td>U = 37</td>
<td>0.90</td>
<td>10.95 (6.45)</td>
<td>10.11 (7.14)</td>
<td>t(43) = 0.41</td>
<td>0.68</td>
</tr>
<tr>
<td>FSIQ</td>
<td>94.00 (16.50)</td>
<td>99.00 (27.25)</td>
<td>U = 22.5</td>
<td>0.15</td>
<td>95.81 (12.09)</td>
<td>106.46 (10.05)</td>
<td>t(43) = -3.23</td>
<td>0.002</td>
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<tr>
<td>WRAML2 Story Memory</td>
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<tr>
<td>Immediate Recall</td>
<td>7.00 (2.50)</td>
<td>9.50 (4.75)</td>
<td>U = 22</td>
<td>0.15</td>
<td>8.76 (2.51)</td>
<td>11.92 (2.15)</td>
<td>t(43) = -4.55</td>
<td>&lt; 0.001</td>
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<tr>
<td>Delayed Recall (30 mins)</td>
<td>7.00 (3.00)</td>
<td>9.50 (4.00)</td>
<td>U = 19</td>
<td>0.09</td>
<td>8.52 (2.44)</td>
<td>11.67 (2.16)</td>
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<td>&lt; 0.001</td>
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<tr>
<td>CMS Dot Locations</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>9.00 (6.00)</td>
<td>9.50 (7.75)</td>
<td>U = 38</td>
<td>0.97</td>
<td>9.48 (3.41)</td>
<td>10.21 (3.49)</td>
<td>t(43) = -0.71</td>
<td>0.48</td>
</tr>
<tr>
<td>Delayed Recall (30 mins)</td>
<td>7.00 (5.00)</td>
<td>9.50 (6.00)</td>
<td>U = 27</td>
<td>0.32</td>
<td>9.05 (2.97)</td>
<td>10.33 (3.32)</td>
<td>t(43) = -1.36</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean number of AEDs</td>
<td>2.00 (1.00)</td>
<td>1.00 (0.00)</td>
<td>U = 24</td>
<td>0.21</td>
<td>1.19 (0.75)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age diagnosed (years)</td>
<td>4.00 (4.69)</td>
<td>6.99 (4.70)</td>
<td>U = 22.5</td>
<td>0.15</td>
<td>6.21 (3.70)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Proportion of life with epilepsy</td>
<td>68.21% (55.00%)</td>
<td>45.73% (42.00%)</td>
<td>U = 20</td>
<td>0.11</td>
<td>47.88% (29.71%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid LD (Yes/No)</td>
<td>1/12</td>
<td>0/6</td>
<td></td>
<td></td>
<td>1/18</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Surgery (Yes/No)</td>
<td>6/7</td>
<td>1/5</td>
<td></td>
<td></td>
<td>7/12</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Epilepsy severity rating</td>
<td>2.00 (2.00)</td>
<td>3.50 (3.00)</td>
<td>U = 32</td>
<td>0.58</td>
<td>2.57 (1.25)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hippocampal abnormality (Yes/No)</td>
<td>9/4</td>
<td>3/3</td>
<td></td>
<td></td>
<td>12/7</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

AED: Anti-epileptic drug; CMS: Children’s Memory Scale; FSIQ: Full Scale Intelligence Quotient; IQR: Inter-Quartile Range; LD: Learning Disability; SES: Socio economic status; TLE: Temporal Lobe Epilepsy; WRAML2: Wide Range Assessment of Memory and Learning, Second Edition
Although the FSIQ of the TLE group was significantly below that of the control group, FSIQ was unrelated to the recall of autobiographical memory details within the TLE group during either the Free Recall (Episodic: $r_s = 0.28, p = 0.22$; Semantic: $r_s = -0.07, p = 0.76$), General Probe (Episodic: $r_s = 0.31, p = 0.17$; Semantic: $r_s = -0.10, p = 0.68$) or Specific Probe (Episodic: $r_s = 0.27, p = 0.23$; Semantic: $r_s = -0.38, p = 0.87$) conditions. Additionally, Dennis et al. (2009) pointed out that when a clinical group is significantly different from the control group on a variable that is integral to the condition, it is not necessary to control for this variable. Low FSIQ had previously been found to be an integral part of TLE (Hermann et al. 1997); FSIQ < 85 was found in approximately 30% of TLE patients (Helmstaedter & Kockelmann 2006). Moreover, in our study, the between-group difference in FSIQ could not be attributed to differences in the demographic variables, such as SES, as our groups were well matched on these variables. For these reasons, FSIQ was not used as a covariate in the subsequent analyses.

**Children’s Autobiographical Interview (CAI)**

Total episodic and semantic scores obtained by two groups on the CAI across the three recall conditions are presented in Figure 2. Mann-Whitney U tests revealed that the TLE group recalled significantly fewer episodic details (median = 16; interquartile range (IQR) = 11.00) than the control group (median = 21.8; IQR = 20.88) in the Free Recall condition ($p = 0.02, d = 0.67$). However, no between-group differences in the recall of episodic details were found during either the General Probe ($p = 0.07, d = 0.61$) or Specific Probe conditions ($p = 0.46, d = 0.47$). Furthermore, no between-group differences were found for the recall of semantic details during the Free Recall
(p = 0.62, d = 0.03), General Probe (p = 0.44, d = 0.09) or Specific Probe stages (p = 0.43, d = 0.07).

Post-hoc calculations indicated that to detect a significant statistically difference between the TLE and Control groups at the General and Specific probe stages of the CAI, with power of 0.80 and α at 0.05, a total of 36 TLE participants and 59 TLE participants, respectively, would be required.

**Figure 2: Children’s Autobiographical Interview: Number of Episodic and Semantic Details by Group and Recall Condition.**

*p < 0.05; TLE: Temporal Lobe Epilepsy. Boxes represent the Inter-Quartile Range, which contains data between the 25th and 75th percentiles. The median is represented by a horizontal line within each box. Whiskers represent minimum and maximum values.
Similarly, no differences between the TLE and control groups were found in the proportion of episodic details, relative to semantic details, recalled during either the Free Recall (median = 81.3%, IQR = 27.0% vs. median = 88.0%, IQR = 14.0%, respectively; \( p = 0.13 \)), General Probe (median = 82.1%, IQR = 27.0% vs. median = 87.5%, IQR = 15.0%, respectively; \( p = 0.10 \)) or Specific Probe (median = 85.5%, IQR = 11.0% vs. median = 90.6%, IQR = 10.0%, respectively; \( p = 0.32 \)) conditions.

Due to the absence of between-group differences in the recall of semantic details in all conditions, and episodic details in the General and Specific Probe conditions, and to minimise the number of comparisons, we only undertook further analyses for episodic scores obtained in the Free Recall condition. Given the small sample sizes in these analyses, they should be considered as exploratory.

**Exploratory Analyses**

**Relations with chronological age**

Relations between chronological age and recall of episodic details were separately examined in the TLE and control groups (see Figure 3). A significant correlation was found in the control group \( (r_s = 0.45, p < 0.05) \); that is, older children recalled more episodic details. There was no significant correlation for the TLE group \( (r_s = 0.34, p = 0.11) \).
Figure 3: Children’s Autobiographical Interview: Free Recall Condition. Number of Episodic Details Recall by Age and Group

- **TLE**
- **Control**

Number of Episodic Details vs. Age

- $r_s = 0.45$
- $r_s = 0.34$
Relations with tests of new learning and short-term memory

Within the TLE group, relations were examined between the Free Recall of episodic details and scores on standardized tests that required new learning and short-term memory on which significant between-group differences were found. Correlations with Story Memory (WRAML2): immediate \( (r_s = 0.08, p = 0.72) \) and delayed \( (r_s = 0.15, p = 0.50) \) recall, and Dot Location (CMS): immediate recall \( (r_s = 0.08, p = 0.72) \) were small and non-significant.

Relations between epilepsy-related factors and CAI

Hippocampal abnormality

To explore the potential relationship between hippocampal integrity and the recall of episodic details in the Free Recall condition of the CAI, TLE patients with an intact hippocampus \( (n = 9; \text{median} = 16; \text{IQR} = 7.50) \) were compared with those whose hippocampus was abnormal \( (n = 12, \text{median} = 15.5; \text{IQR} = 19.63) \). A Mann-Whitney U test showed that the two groups did not differ significantly in the number of episodic details recalled \( (p = 0.97, d = 0.23) \).

Other epilepsy variables

Mann-Whitney U tests revealed no significant differences between right-TLE \( (n = 6, \text{median} = 24; \text{IQR} = 22) \) and left-TLE children \( (n = 13, \text{median} = 13.5; \text{IQR} = 9.25, p = 0.11, d = 0.97) \) in the Free Recall of recall of episodic details. Inspection of boxplots and scores for individual participants in Figure 2 suggests that laterality played little role in recall of autobiographical memory. Moreover, correlations between episodic recall and age at diagnosis \( (r_s = 0.20, p = 0.39) \), proportion of life with epilepsy \( (r_s = -\)
0.07, \( p = 0.39 \) and epilepsy severity ratings (\( r_s = 0.03, p = 0.90 \)) were small and not significant.

**Epilepsy treatment**

Children who underwent surgical treatment (\( n = 7, \text{median} = 17.5; \text{IQR} = 11.5 \)) did not differ significantly (\( p = 0.91, d = 0.09 \)) from children who did not undergo surgery (\( n = 14, \text{median} = 16; \text{IQR} = 13.38 \)) in the number of episodic details recalled. Finally, no significant difference (\( p = 0.15, d = 0.33 \)) was found between children who were on monotherapy (\( n = 12, \text{median} = 16; \text{IQR} = 15.38 \)) compared to those on polytherapy (\( n = 7, \text{median} = 17.5; \text{IQR} = 13 \)).

**Discussion**

In this, to our knowledge, first study of autobiographical memory in children with TLE, significant deficits were evident in the free recall of episodic (but not semantic) autobiographical details. Exploratory analysis suggested that hippocampal abnormalities may not appear to be associated with worse recall of episodic details in the TLE group. Moreover, epilepsy variables (seizure laterality, duration and severity of epilepsy disorder), treatment variables (surgery, drug polytherapy) and scores on standardized memory tests were not associated with episodic recall. The richness of episodic recall did not improve with age in children with TLE, unlike the healthy control group.

Interestingly, the between-group difference in recall of autobiographical events was not present when children were prompted. This raises a possibility that, within the TLE group, impairments in episodic recall were largely due to retrieval difficulties,
rather than memory storage. Moreover, episodic recall was not associated with standardized memory test scores, even though it has been proposed that episodic recall and recall of newly-learned material are both related to hippocampal integrity. While puzzling, this is consistent with other adult studies that have not reported a significant association between autobiographical recall and standardized memory test scores (Herfurth et al., 2010; Lah et al., 2004; Lah et al., 2006). Moreover, and again contrary to our expectations, no between-group difference in episodic recall was found when children with a hippocampal abnormality were compared with children without a hippocampal abnormality. Together, our findings raise a possibility that other cognitive deficits, such as executive dysfunction, contribute to impaired episodic recall in patients with TLE and/or that contralateral or surrounding ipsilateral brain regions support the functions of the abnormal hippocampus in children with unilateral TLE.

Other epilepsy variables, such as epilepsy severity ratings, lifetime duration of active epilepsy and age at diagnosis were also unrelated to episodic recall in children with TLE. It is possible that these factors may have a cumulative, but gradual impact on formation and retrieval of autobiographical memories. Thus the effect of these factors may not become apparent until adulthood.

The relationship between chronological age and number of episodic details recalled was somewhat different in children with TLE and control children. Like previous developmental studies (Picard et al., 2009; Picard et al., 2012; Piolino et al., 2007; Willoughby et al., 2012), we found that, within the control group, the richness of episodic recall appeared to increase in older children. While in children with TLE the
same trend was observed, the strength of the association between the richness of episodic recall and age was slightly weaker, and did not reach statistical significance. This correlation, however, was medium in size ($r = 0.34$), which suggests that the relation between chronological age and richness of episodic recall needs to be explored in larger samples of children with TLE. Although based on a small number of participants and related to recall of memories from the past, however, our findings are consistent with a large cross-sectional study that compared learning and word recall between patients with chronic TLE (n=1156, aged 6 to 68) with control subjects (n=1000, aged 6 to 80) (Helmstaedter & Elger, 2009). Patients made much smaller gains in recall of newly-learned material during childhood and adolescence in particular, as learning peaked at an earlier age in patients (16-17 years) compared to controls (23-24 years). In addition, lack of significant developmental gains in memory for arbitrarily related word pairs from childhood to adolescence was also evident in another longitudinal study (Gonzalez et al., 2012). Together, these findings suggest that children with TLE “grow into their deficits”. This suggestion raises a possibility that in our study, the lack of between-group differences in episodic recall, despite after retrieval support, was due to participants being rather young. This conclusion, however, seems at odds with findings of studies involving patients with DA, where memory deficits were evident in childhood rather than appearing in teenage years (Vargha-Khadem et al., 1997; Vargha-Khadem et al., 2003). Nevertheless, while patients with DA had severe episodic memory deficits arising from bilateral hippocampal pathology, children in our study had mild episodic memory deficits arising from unilateral temporal lobe abnormalities/seizure foci. These milder episodic deficits may not be evident early but are likely to come to light gradually,
over the course of episodic memory development, which unlike semantic memory, continues to develop into adolescence.

Our study has several limitations. First, the heterogeneity of the TLE sample is acknowledged. A more homogenous sample of TLE participants would have been preferable, as those in the current study varied with respect to surgical history, laterality of seizure focus and presence of hippocampal lesions. Second, the analyses of the relationship between hippocampal integrity and episodic recall relied on visual inspection by experienced neuroradiologists of clinically obtained MRI rather than quantified structural or functional neuroimaging data, which would provide more precise information about this relationship. It is also possible that the comparatively lower episodic recall scores within the TLE group could be due to subtle hippocampal structural or functional abnormalities that could not be detected by visual inspection of the clinical scans. Third, our clinical sample was too small to undertake statistical analyses (such as regression) that would allow us to concurrently examine contribution of different variables on episodic memory. Fourth, it is acknowledged that our findings are based on cross-sectional data, which address the relationship between age and memory development only indirectly. Accordingly, longitudinal studies are needed to yield more precise data about episodic memory development, and factors that may interfere with its development in children with TLE. Fifth, it is unclear whether difficulties in episodic recall were secondary to poor executive or reduced naming skills, which were not measured in our study, but were previously found to contribute to recall of event details in typically developing children (e.g. Piolino et al., 2008). Sixth, while the CAI protocol does not require memories to be dated this information would be useful to further examine the relationship between
seizure onset and episodic recall. Seventh, it is acknowledged that some of our null findings should be treated with caution, as the modest sample size limited statistical power to detecting large effect sizes. Replication of our findings in a large sample is warranted. Eighth, our patients were recruited from specialized, tertiary health care facilities, which limits generalizability of our findings. Nevertheless, it is important to note that in patients with TLE seizures are more likely to be difficult to control with medication than in patients with other types of epilepsy. Hence patients with TLE are often referred to specialised tertiary epilepsy facilities. Thus participants of our study may not be dissimilar to other children with TLE. Ninth, future studies could examine the impact of other potentially important epilepsy-related factors such as seizure frequency, which has been associated with a decline in hippocampal volume (Fuerst et al., 2003) and could thereby lead to deficits in the recall of autobiographical events (Addis et al., 2007; Noulhiane et al., 2007). Finally, it is acknowledged that the autobiographical memory assessments used in this study may not have had adequate sensitivity to detect between-group differences among younger participants.

Although with limitations, our study has provided novel findings that are theoretically intriguing and clinically relevant. Theoretically, our findings raise a possibility that the nature of autobiographical memory deficits changes in children with unilateral TLE with age, in a similar fashion to changes in memory for new verbal materials previously demonstrated in this patient population (Gonzalez et al., 2012; Helmstaedter & Elger, 2009). Our findings raise a possibility that the contralateral hippocampus or temporal structures that surround the abnormal hippocampus, support autobiographical memory in children, but not in adolescents with unilateral TLE. This issue warrants further examination, ideally using functional neuroimaging. The
findings of our study are also of clinical significance. They suggest that older children/adolescents with TLE are at risk of episodic autobiographical memory deficits, which has not been recognized until now. This risk is important, as autobiographical memory has been found to play a significant role in everyday life and adaptive functioning. For example, in adults with TLE poor recall of past autobiographical event details was associated with reduced social problem solving (Sheldon et al., 2011). Thus early diagnosis and intervention that enhances retrieval of memories is likely to be important for children with TLE.

References


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Disclosure

None of the authors has any conflict of interest to disclose
CHAPTER 7: Autobiographical Memory in Children with Idiopathic Generalised Epilepsy

Unpublished paper
Abstract

Autobiographical memory involves the recall of both personal facts (semantic memory) and the re-experiencing of past personal events (episodic memory). The recall of autobiographical episodic details has been associated with a specific network which involves prefrontal and medial temporal lobe regions, in addition to posterior regions. Seizure activity has been previously shown to disrupt the consolidation of newly-learned information into long-term memory, however it is not yet known whether primary generalized seizures could affect the network associated with the recall of autobiographical details. In this study, 18 children with IGE and 42 healthy controls of comparable age, sex and socio-economic status were administered the Children’s Autobiographical Interview. Compared to controls, children with IGE recalled fewer episodic details, even when retrieval prompts were provided. In contrast, no between-group difference was found for the recall of semantic autobiographic details. Within the IGE group, age of onset and proportion of life spent with epilepsy were both related to the free recall of episodic details: earlier age of onset and longer proportion of life spent with epilepsy were associated with poorer recall of episodic details. In addition to providing the first evidence of autobiographical episodic memory deficits in children with IGE, these findings also suggest that early age of seizure onset may adversely affect the development of autobiographical memory.

Keywords/Mesh terms: Episodic Memory, Long-Term Memory, Seizures, Remote Memory, Memory Disorder
Introduction

Autobiographical memory consists of a collection of personally-experienced events from throughout our lifetime which can contribute to the formation of our own personal identity (Addis & Tippett, 2004; Wilson & Ross, 2003). Recalling these events involves mental “time travel” and re-experiencing unique constellations of specific emotional, perceptual, cognitive and temporal details: episodic memory (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002; Tulving, 2002). Episodic memories are event-specific and thus only encountered once. These memories of past events are often embedded within a context of personal factual information (Levine, 2004): semantic memory. Semantic memories are typically acquired through repeated exposures (e.g. own name or address) and do not involve re-experiencing.

Traditional developmental literature has demonstrated that semantic and episodic memory have different developmental trajectories (Tulving, 1985, 2002). While semantic memory has been found to develop rapidly during infancy and preschool years (Piaget, 1954; Quinn & Eimas, 1997), episodic memory has been found to emerge after early childhood and to continue developing during adolescence (de Haan, Mishkin, Baldeweg, & Vargha-Khadem, 2006; Wheeler, Stuss, & Tulving, 1997). Studies that examined developmental gains in episodic and semantic components of autobiographical memories have shown a significant increase in the amount of episodic details recalled (Picard, Reffuveille, Eustache, & Piolino, 2009; Piolino et al., 2007; Willoughby, Desrocher, Levine, & Rovet, 2012), but comparatively smaller (Picard et al., 2009; Willoughby et al., 2012) or no increase (Piolino et al., 2007) in the amount of semantic details recalled over the course of development.
The major neuropsychological theories of autobiographical memory have focused on the role of the hippocampus. Multiple Trace Theory (MTT) proposes that the hippocampus is involved in the recall and recollection of personally experienced events indefinitely (Nadel & Moscovitch, 1997). Thus, damage to the hippocampus is expected to result in temporally extensive deficits, involving remote as well as recent personally experienced events. Within the framework of Classic Consolidation Theory (CCT), the hippocampus has a temporally limited role in memory formation in general. Information is initially stored in the hippocampus and gradually transferred into the neocortex via a process of consolidation (Squire & Alvarez, 1995). Therefore, hippocampal damage is expected to result in a “temporal gradient”, characterized by the impaired recall of recent, but not distant, autobiographical episodes.

Given that the theoretical debate has focused on the role of hippocampus in episodic memory, it is not surprising that studies examining recall of autobiographical memories in patients with epilepsy have been focused on patients with temporal lobe epilepsy (TLE). Several adult (Addis, Moscovitch, & McAndrews, 2007; St-Laurent, Moscovitch, Levine, & McAndrews, 2009; Viskontas, McAndrews, & Moscovitch, 2000; Voltzenlogel et al., 2006) and one child study (Gascoigne et al., 2013) have found deficits in recall of episodic, but not semantic details of personally experienced episodes in patients with TLE. Nevertheless, in adults with TLE, two studies have found the opposite pattern of impairments: impaired semantic, but not episodic components of autobiographical memories (Barr, Goldberg, Wasserstein, & Novelly, 1990; Lah, Grayson, Lee, & Miller, 2004), and two have found impairments in both
components of autobiographical memories (Herfurth, Kasper, Schwarz, Stefan, & Pauli, 2010; Lah, Lee, Grayson, & Miller, 2006).

These two types of memory (episodic and semantic) are supported by distinct, yet overlapping brain networks. The recall of episodic details has been associated with activity in the medial temporal lobe, in addition to the parahippocampal gyrus and retrosplenial cortex (Addis & Schacter, 2008; Hassabis, Kumaran, & Maguire, 2007). The recollection of semantic details is thought to depend on anterior medial regions (Visser, Embleton, Jefferies, Parker, & Lambon Ralph, 2010), the left inferior temporal gyrus and bilateral temporal poles (Irish, Addis, Hodges, & Piguet, 2012).

As the widespread networks of brain structures have been implicated in recall of autobiographical memories, it is possible that these networks could be disrupted by seizure activity, which, according to Mayes et al. (2003), may block maintenance or disrupt already-established (but insufficiently rehearsed) memories. If this is the case, patients with generalised seizures may be at risk of autobiographical memory deficits. Moreover, given that episodic (but not semantic) memories are unique and, once compromised, cannot be completely re-established, they may be more affected than semantic memories by generalized seizures.

The possibility that generalised seizures could compromise autobiographical memories has not received much attention. In one study, however, Lah et al. (2006) compared patients with temporal lobe epilepsy (TLE) who experienced generalised seizures (in combination with complex partial seizures) with controls and patients who experienced complex partial seizures only (Lah et al., 2006). Compared to
control participants, both TLE patient groups recalled significantly fewer autobiographical episodes and semantic information, although the two patient groups did not differ significantly from each other. In this study, however, the temporal lobe seizure focus/abnormality alone could have compromised the recall of autobiographical memories, as temporal lobe pathology has been previously found to disrupt the recollection of episodic and semantic autobiographical details even in patients who do not have a history of seizures, such as those with Alzheimer’s Disease (Dorrego et al., 1999; Greene & Hodges, 1996; Irish et al., 2011; Irish, Piguet, Hodges, & Hornberger, 2013; Sexton et al., 2010) or Semantic Dementia (Graham & Hodges, 1997; Irish et al., 2012; Matuszewski et al., 2009; Snowden, Griffiths, & Neary, 1996).

In order to investigate the disruptive potential of generalised seizures alone on autobiographical memory, a study would need to involve patients who experience generalised seizures exclusively and have no identifiable temporal lobe abnormalities, such as patients with idiopathic generalised epilepsy (IGE). This form of epilepsy is a common type of epilepsy in childhood, representing approximately 20% of all epilepsies found in children (Jallon & Latour, 2005). Accordingly, the current study aimed to assess autobiographical memory performance in children with IGE.

This study also considered other epilepsy-related factors which have been previously found to adversely impact memory. For example, epilepsy treatment has been found to play a significant role in adults with TLE; patients on antiepileptic drug polytherapy have recalled significantly fewer autobiographical events relative to patients on monotherapy (Lah et al., 2006). Nevertheless, a recent study found no
relationship between polytherapy and recall of autobiographical events in children with TLE (Gascoigne et al., 2013). Moreover, factors such as severity (Helmstaedter, 2002) and longer duration of epilepsy disorder were previously found to have impact on learning and recall of information in adults (Mameniskiene, Jatuzis, Kaubrys, & Budrys, 2006) and children (Nolan et al., 2004) with epilepsy, but were not found to relate to autobiographical memory in children or adults with epilepsy (Lah et al., 2004). Evidence also suggests that children with TLE may grow into their memory deficits. For example, a longitudinal study of patients with left TLE found that verbal memory deficits eventually became apparent during teenage years or young adulthood (Gonzalez, Mahdavi, Anderson, & Harvey, 2012) when no such deficits were obvious during childhood (Gonzalez, Anderson, Wood, Mitchell, & Harvey, 2007). A large cross-sectional study involving 1000 healthy control subjects (aged 6-80) and 1157 patients with TLE (aged 6-68 years) also found that deficits in recall of verbal information after short delays were not evident in children, but became noticeable (relative to healthy controls) during adolescence or young adulthood (Helmstaedter & Elger, 2009).

In addition to epilepsy-related factors, it has been suggested that autobiographical memory deficits in patients with epilepsy may also be secondary to other underlying cognitive deficits, such as impaired recall of newly-learned materials after short delays that is evident on standardised memory tests (Lah et al., 2004; Lah et al., 2006). In fact, deficits in the recall of newly-learned information have been associated with autobiographical memory impairments in non-epilepsy patients (Mayes, Daum, Markowisch, & Sauter, 1997; Schmidtke & Vollmer, 1997; Shimamura & Squire, 1986). Interestingly, among patients with TLE, although deficits in episodic aspects of
autobiographical memory and in recall of newly-learned materials after short delays have been found in adults (Herfurth et al., 2010; Lah et al., 2004; Lah et al., 2006) and children (Gascoigne et al., 2013) no correlations have been found between these two memory types. Compared to healthy controls, children with IGE have exhibited significantly worse performance on standardised memory tests (Gascoigne et al., 2012), but whether these deficits contribute to deficits in autobiographical recall is unknown.

The current study investigated recall of memories in children with IGE. It was hypothesized that children with IGE would exhibit worse episodic recall than their healthy control peers on a test of autobiographical recall. Exploratory analyses were also conducted to assess the impact of other relevant epilepsy variables (such as mono vs. poly-therapy, epilepsy severity, age at diagnosis and proportion of life with epilepsy) as well as potential associations between performance on the autobiographical memory task, tests of new learning and short-term memory and chronological age.

Method

Participants

A total of 18 children with IGE and 42 control children were recruited for the present study. All participants were fluent in English and aged between 6 and 16 years at the time of assessment. Participants were excluded for the following reasons: (i) Full Scale Intelligence Quotient (FSIQ) < 80; (ii) presence of a major sensory deficit; (iii) significant neurodevelopmental disorder (e.g. autism, but not learning disability or ADHD), or (iv) another neurological disorder.
All IGE participants were recruited from The Children’s Hospital at Westmead (CHW), after the ethics committees of both CHW and The University of Sydney approved the study. Paediatric neurologists reviewed electroencephalography (EEG) records, medical history, and clinical imaging data in order to identify participants who met the International League Against Epilepsy criteria for IGE (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Control participants were free of a history of epilepsy and recruited through the peer networks of the IGE patients and other control participants (snowball recruitment).

Clinical data for the 18 IGE participants are summarized in Table 1. The average age of diagnosis was 6.2 years of age (SD = 3.3) and mean epilepsy severity rating was 2.2 (SD = 1.8), equivalent to a rating between “A little severe” and “Somewhat severe”. One IGE participant had been previously diagnosed with Attention Deficit Hyperactivity Disorder. All participants were taking anti-epileptic drugs (AEDs) at the time of assessment, sixteen were on monotherapy and two on polytherapy. Eight different AEDs were represented within the IGE sample, with sodium valproate the most commonly prescribed drug \((n = 8)\). Of the 18 children with IGE, nine met criteria for the Childhood Absence Epilepsy syndrome, three with Febrile Seizure +, two with Epilepsy with Myoclonic Absences, one with Juvenile Absence Epilepsy and another with Epilepsy with Generalized Tonic-Clonic seizures alone. Two patients could not be classified into an IGE syndrome.
<table>
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<th>Participant</th>
<th>Syndrome</th>
<th>Comorbid disorder</th>
<th>Seizure Frequency</th>
<th>EEG</th>
<th>Seizure types</th>
<th>AEDs</th>
<th>Epilepsy Severity</th>
<th>Age Diagnosed</th>
<th>Duration (years)</th>
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<tr>
<td>1</td>
<td>Childhood Absence Epilepsy</td>
<td>ADHD</td>
<td>Daily</td>
<td>Spike and Wave</td>
<td>Absence</td>
<td>ETH</td>
<td>Very severe</td>
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<td>3.7</td>
</tr>
<tr>
<td>2</td>
<td>Childhood Absence Epilepsy</td>
<td>None</td>
<td>Daily</td>
<td>Spike and Wave</td>
<td>Absence</td>
<td>SVP</td>
<td>Quite severe</td>
<td>3.6</td>
<td>5.3</td>
</tr>
<tr>
<td>3</td>
<td>Childhood Absence Epilepsy</td>
<td>None</td>
<td>Annually</td>
<td>Normal</td>
<td>Absence</td>
<td>LMT</td>
<td>A little severe</td>
<td>6.3</td>
<td>5.8</td>
</tr>
<tr>
<td>4</td>
<td>Childhood Absence Epilepsy</td>
<td>None</td>
<td>Daily</td>
<td>Spike and Wave</td>
<td>Absence</td>
<td>LMT</td>
<td>Moderately severe</td>
<td>4.0</td>
<td>3.4</td>
</tr>
<tr>
<td>5</td>
<td>Childhood Absence Epilepsy</td>
<td>None</td>
<td>Daily</td>
<td>Spike and Wave</td>
<td>Absence, GTCS</td>
<td>PHY</td>
<td>Not at all severe</td>
<td>6.5</td>
<td>5.9</td>
</tr>
<tr>
<td>6</td>
<td>Childhood Absence Epilepsy</td>
<td>None</td>
<td>Daily</td>
<td>Spike and Wave</td>
<td>Absence, GTCS</td>
<td>CLB</td>
<td>Not at all severe</td>
<td>9.8</td>
<td>6.8</td>
</tr>
<tr>
<td>7</td>
<td>Childhood Absence Epilepsy</td>
<td>None</td>
<td>Biannually</td>
<td>Spike and Wave</td>
<td>Absence, GTCS</td>
<td>CLB</td>
<td>Not at all severe</td>
<td>8.4</td>
<td>1.6</td>
</tr>
<tr>
<td>8</td>
<td>Childhood Absence Epilepsy</td>
<td>None</td>
<td>Daily</td>
<td>Spike and Wave</td>
<td>Absence</td>
<td>ACE, LEV</td>
<td>Quite severe</td>
<td>8.0</td>
<td>1.3</td>
</tr>
<tr>
<td>9</td>
<td>Childhood Absence Epilepsy</td>
<td>None</td>
<td>Annually</td>
<td>Spike and Wave</td>
<td>Absence, GTCS</td>
<td>SVP</td>
<td>A little severe</td>
<td>12.6</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>Febrile seizures +</td>
<td>None</td>
<td>Biannually</td>
<td>Normal</td>
<td>Absence, GTCS</td>
<td>SVP</td>
<td>Not at all severe</td>
<td>2.4</td>
<td>7.0</td>
</tr>
<tr>
<td>11</td>
<td>Febrile seizures +</td>
<td>None</td>
<td>Biannually</td>
<td>Spike and Wave</td>
<td>Absence, GTCS</td>
<td>SVP</td>
<td>A little severe</td>
<td>2.5</td>
<td>6.3</td>
</tr>
<tr>
<td>12</td>
<td>Febrile seizures +</td>
<td>None</td>
<td>Biannually</td>
<td>Spike and Wave</td>
<td>GTCS</td>
<td>SVP</td>
<td>Not at all severe</td>
<td>4.0</td>
<td>4.4</td>
</tr>
<tr>
<td>13</td>
<td>Epilepsy with Myoclonic Absences</td>
<td>None</td>
<td>Biannually</td>
<td>Spike and Wave</td>
<td>Absence, GTCS</td>
<td>SVP</td>
<td>Not at all severe</td>
<td>2.4</td>
<td>8.6</td>
</tr>
<tr>
<td>14</td>
<td>Epilepsy with Myoclonic Absences</td>
<td>None</td>
<td>Biannually</td>
<td>Spike and Wave</td>
<td>Absence, GTCS</td>
<td>LEV</td>
<td>Moderately severe</td>
<td>2.9</td>
<td>5.9</td>
</tr>
<tr>
<td>15</td>
<td>Juvenile Absence Epilepsy</td>
<td>None</td>
<td>Biannually</td>
<td>Spike and Wave</td>
<td>Absence</td>
<td>LEV</td>
<td>Not at all severe</td>
<td>7.3</td>
<td>4.4</td>
</tr>
<tr>
<td>16</td>
<td>Epilepsy with Generalized Tonic-Clonic Seizures alone</td>
<td>None</td>
<td>Quarterly</td>
<td>Normal</td>
<td>GTCS</td>
<td>CRB</td>
<td>A little severe</td>
<td>12.2</td>
<td>2.2</td>
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<tr>
<td>17</td>
<td>Unclassified</td>
<td>None</td>
<td>Annually</td>
<td>Multifocal spike and wave</td>
<td>Absence</td>
<td>SVP</td>
<td>A little severe</td>
<td>8.0</td>
<td>5.0</td>
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<tr>
<td>18</td>
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<td>None</td>
<td>Biannually</td>
<td>Normal</td>
<td>Absence</td>
<td>LEV, SVP</td>
<td>Not at all severe</td>
<td>7.5</td>
<td>7.2</td>
</tr>
</tbody>
</table>

ADHD, Attention Deficit Hyperactivity Disorder; AEDs, Anti Epileptic Drugs; GTCS, Generalised Tonic-Clonic Seizures; ACE, Acetazolamide; CLB, Clobazam; CRB, Carbamazepine; ETH, Ethosuximide; LEV, Levetiracetam; LMT, Lamotrigine; PHY, Phenytoin; SVP, Sodium Valproate; PPR, Photoparoxysm
Measures

The clinical neuropsychological instruments used in this study are summarised in Table 2 while the Children’s Autobiographical Interview (CAI) is described below. Average years of parent/guardian education was used as a measure of socioeconomic status (SES).

The Global Assessment of Severity of Epilepsy (GASE; Speechley et al., 2008) scale was used by treating paediatric neurologists to assess the severity of epilepsy in IGE participants. Epilepsy severity ratings [ranging from 1 (Not at all severe) to 7 (Extremely severe)] were based on the frequency and intensity of seizures, injuries during seizures, number and side effects of antiepileptic drugs, severity of postictal period, and interference of epilepsy or drugs with daily activities. This instrument has been shown to have good construct validity in addition to high inter-rater (weighted $j = 0.85$) and test–retest reliability (weighted $j = 0.90$).
<table>
<thead>
<tr>
<th>Domain</th>
<th>Test: Subtest</th>
<th>Score Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intelligence</td>
<td>WASI: Vocabulary &amp; Matrices</td>
<td>Full Scale Intelligence Quotient (FSIQ)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M = 100, SD = 15</td>
</tr>
<tr>
<td>Short-Term Recall</td>
<td>WRAML2: Story Memory</td>
<td>Age Scaled Scores</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M = 10, SD = 3</td>
</tr>
<tr>
<td></td>
<td>CMS: Dot Location</td>
<td>Age Scaled Scores</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M = 10, SD = 3</td>
</tr>
</tbody>
</table>


**Children’s Autobiographical Interview**

Autobiographical recall was assessed with the Children’s Autobiographical Interview (CAI; Willoughby et al., 2012, manual acquired through personal communication), a child-adapted version of the Autobiographical Interview (Levine et al, 2002). Originally developed for adults, the AI requires participants to recall and elaborate on personally experienced events, specific to a time and place, from five separate periods of their lives. In contrast, the CAI requires children to recall two separate events, experienced at any point in their relatively short lives (except from the month prior to assessment). All participants administered the CAI were also provided with a sample list of life events, in order to help generate the recall of appropriate events, although participants were free to recall any event, irrespective of the suggestions contained in the list.
Each memory was recalled over three separate stages of the CAI: i) Free Recall, ii) General Probe and iii) Specific Probe. The initial stage, Free Recall, required participants to recall as much information as possible about an event (up to five minutes in duration) without any interruptions from the interviewer. During the General Probe stage, participants were prompted to recall any additional details. In the event of a vague or non-specific memory being recalled, participants were asked to clarify the event. Finally, during the Specific Probe condition, participants were asked a standard series of questions about the event, pertaining to time, location, sensory/perceptual and emotional/cognitive details. In order to prevent any contamination, the Specific Probe stage was only administered once the Free Recall and General Probe stages had been administered for both events.

On completion of all stages of the CAI, participants were asked to rate each memory, using a scale of 1 to 7, on each of the following domains: Visual Intensity, Emotional Change, Current Importance, Past Importance, Confidence and Strength. Visual scales, which included pictures depicting possible response options, were provided to participants, in order to aid their understanding of the rating task.

The entire CAI was recorded and transcribed before each memory was scored according to the guidelines contained within the AI scoring manual (AI; Levine et al., 2002). Details within each memory were classified as either i) episodic (pertaining directly to the main episode and placed in a particular spatio-temporal context, suggestive of the re-experiencing of the main event) or ii) semantic (representing general autobiographical information that is not integral to the main event). Composite scores \([(memory 1 + memory 2)/2]\) were obtained for both episodic and
semantic details for each stage of the CAI interview: i) Free Recall, ii) General Probe (Free Recall + General Probe) and iii) Specific Probe (Free Recall + General Probe + Specific Probe). Finally, examiners also assigned a composite rating (ranging from 0 to 18) to each memory, in order to reflect the overall richness of the episodic details within each memory (see Levine et al., 2002 for a description of these ratings).

This composite score is based on ratings of between 0-3 of the overall richness of the internal place, perceptual, time and emotion/thought details contained in the interview. A rating between 0-6 is also assigned to the overall richness with which the episode is described. This final rating is a measure of the extent to which the recollection represents a true re-experiencing of a specific moment in time and place in which the participant is able to re-create the perceptual, emotional and cognitive contextual detail of an event in the past.

The transcription of each memory was initially scored by one experimenter (MG) before another staff member scored ten randomly selected memories. Both scorers had been previously trained, having completed the practice set of memories provided with the AI scoring manual (Levine et al., 2002) and achieved intra-class inter-rater correlations ranging from 0.89 to 0.99. The intra-class inter-rater correlations for the composite scores obtained on the CAI were (i) Free Recall: 0.96 and 0.80 for episodic and semantic details, respectively (ii) General Probe: 0.96 and 0.80 for internal and external details, respectively, and (iii) Specific Probe: 0.91 and 0.76 for internal and external details, respectively.
Procedure

Only participants who themselves agreed to take part and whose parents gave informed written consent participated in the study. The medical records of participants with IGE were reviewed to obtain information of relevance for the study, which was later verified by treating paediatric neurologists. Prior to the assessment, parents were interviewed about their child’s medical and developmental history, relevant epilepsy and SES variables, and asked to complete a set of questionnaires. All children were seen for an assessment on their own. The assessment took approximately 90 minutes to complete and included a battery of tests administered in a set order. The CAI took an average of 25 minutes to administer. One researcher (MG) administered all of the assessments.

Statistical Analysis

Preliminary analyses assessed the normality of distributions using the Shapiro-Wilk test and investigated all variables for outliers (i.e., 3 SD > M). For variables that were normally distributed, between group differences were examined using independent t-tests and one-way Analyses of Variance (ANOVA) with Sidak post-hoc tests. Where normality assumptions were not met, Mann-Whitney U tests were employed to examine between group differences. Pearson’s correlation coefficient and Spearman’s rho (\( r_s \)) were used for correlational analyses. Chi-square tested between groups on categorical variables, such as sex distribution and comorbid disorders.
Results

Background demographic, cognitive and clinical variables

The IGE and control groups did not differ significantly in age, sex distribution or SES (see Table 3). However, compared to the control group, the IGE group was found to have lower FSIQ scores. No between-group differences were found on the CMS Dot Location subtest, however the IGE group obtained significantly lower scores in immediate and delayed recall on the WRAML2 Story Memory subtest.
<table>
<thead>
<tr>
<th></th>
<th>IGE</th>
<th>Control</th>
<th>Test of Significance</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>10.7 (2.5)</td>
<td>11.7 (2.8)</td>
<td>$t_{(57)} = -1.3$</td>
<td>0.21</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>8/10</td>
<td>21/21</td>
<td>$\chi^2 = 0.16$</td>
<td>0.69</td>
</tr>
<tr>
<td>SES</td>
<td>12.4 (5.1)</td>
<td>10.1 (7.4)</td>
<td>$t_{(57)} = 1.2$</td>
<td>0.24</td>
</tr>
<tr>
<td>FSIQ</td>
<td>101.8 (8.7)</td>
<td>112.4 (10.3)</td>
<td>$t_{(57)} = -3.8$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WRAML2 Story Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>9.7 (2.9)</td>
<td>12.2 (1.9)</td>
<td>$t_{(57)} = -4.0$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delayed Recall (30-mins)</td>
<td>9.0 (2.9)</td>
<td>11.9 (2.0)</td>
<td>$t_{(57)} = -4.3$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CMS Dot Locations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>9.6 (3.6)</td>
<td>10.2 (3.1)</td>
<td>$t_{(57)} = -0.7$</td>
<td>0.49</td>
</tr>
<tr>
<td>Delayed Recall (30-mins)</td>
<td>10.2 (3.2)</td>
<td>10.4 (3.0)</td>
<td>$t_{(57)} = -0.2$</td>
<td>0.83</td>
</tr>
<tr>
<td>Mean number of AEDs</td>
<td>1.2 (0.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>6.2 (3.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Proportion of life with epilepsy</td>
<td>46.7% (22.6%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Comorbid LD (Yes/No)</td>
<td>1/17</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ADHD (Yes/No)</td>
<td>1/17</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Epilepsy severity rating (GASE)</td>
<td>2.2 (1.8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

AED: Anti-Epileptic Drug; CMS: Children’s Memory Scale (Cohen, 1997); FSIQ: Full Scale Intelligence Quotient; GASE: Global Assessment of Severity of Epilepsy (Speechley et al., 2008), IGE: Idiopathic Generalised Epilepsy; LD: Learning Disability; SES: Socioeconomic status; WRAML2: Wide Range Assessment of Memory and Learning, Second Edition (Sheslow & Adams, 2003).
Although the FSIQ of the IGE group was significantly below that of the control group, FSIQ was not included as a covariate in the subsequent analyses for two main reasons: First, among the IGE participants, FSIQ was well within the average range and was not related to the recall of autobiographical memory details in the CAI, either during the Free Recall (Episodic: $r_s = 0.12, p = 0.63$; Semantic: $r_s = 0.01, p = 0.96$), General Probe (Episodic: $r_s = 0.09, p = 0.72$; Semantic: $r_s = 0.02, p = 0.93$) or Specific Probe stages (Episodic: $r_s = 0.22, p = 0.38$; Semantic: $r_s = 0.13, p = 0.62$). Second, lower FSIQ in the IGE group is an expected, integral part of this neurological condition in children (Nolan et al., 2004; Singhi, Bansal, Singhi, & Pershad, 1992), in which case it was not necessary to include it as a covariate (Dennis et al., 2009).

**Children’s Autobiographical Interview (CAI)**

Scores obtained across the three stages of the CAI are presented in Figure 1. Mann-Whitney U tests showed that the IGE group recalled significantly fewer episodic details than the control group in the Free Recall [median = 14.5, interquartile range (IQR) = 13.0 vs median = 21.8, IQR = 20.9; $p = 0.03$], General Probe (median = 16.0, IQR = 15.1 vs. median = 22.0, IQR = 22.8; $p = 0.02$) and Specific Probe (median = 24.3, IQR = 21.1 vs. median = 38.0, IQR = 25.1; $p = 0.001$) stages of the interview. In contrast, no differences were found between the IGE and control groups in the recall of semantic details at either the Free Recall (median = 2.0, IQR = 5.0 vs. median = 3.5, IQR = 4.5; $p = 0.15$), General Probe (median = 2.0, IQR = 5.0 vs. median = 3.5, IQR = 4.5; $p = 0.17$) or Specific Probe stages (median = 4.3, IQR = 6.3 vs. median = 6.3, IQR = 9.3; $p = 0.22$).
Figure 1: Children’s Autobiographical Interview: Mean Number of Episodic and Semantic Details by Group and Recall Condition.

* $p < 0.05$; ** $p < 0.01$; IGE: Idiopathic Generalized Epilepsy
As no between-group differences were found for the recall of semantic details during any stage of recall, and to reduce the number of unnecessary comparisons, we only undertook further analyses on the recall of episodic details.

**Relations with chronological age**

Correlational analyses examining the association between age and recall of episodic details, were performed separately for the IGE and control groups. A significant correlation was found between age and the Free Recall of episodic details within the control ($r_s = 0.50, p = 0.001$), but not IGE group ($r_s = 0.41, p = 0.09$). However, significant correlations between age and episodic recall were found for both the control and IGE groups during the General Probe ($r_s = 0.51, p = 0.001; r_s = 0.49, p = 0.04$, respectively) and Specific Probe stages ($r_s = 0.54, p < 0.001; r_s = 0.56, p = 0.02$, respectively).

**Relations with learning of new material and short-term recall**

Within the IGE group, correlational analyses were undertaken to examine relations between the recall of episodic details and scores obtained on standardized memory tests that required recall of newly learned materials immediately after exposure and following a short (30-min) delay. Correlations approaching significance were found between the recall of episodic details at all stages of the CAI and scores obtained on the immediate ($r_s = 0.45$ to $0.48, p = 0.051$ to $0.07$) and delayed WRAML2 Story Memory recall ($r_s = 0.42$ to $0.48, p = 0.051$ to $0.09$).
Relations between epilepsy-related factors and CAI

After controlling for chronological age, a significant correlation was found between the recall of episodic details during the Free Recall stage and age at IGE diagnosis \((r = 0.54, p = 0.024)\), where children diagnosed later recalled more episodic details. The proportion of life spent with IGE also correlated with the recall of episodic details during the Free Recall stage \((r = -0.52, p = 0.034)\) with a larger proportion of life spent with epilepsy being associated with the recall of fewer episodic details. However, no correlations were found between age at diagnosis/proportion of life with epilepsy and recall of episodic details in the General Probe \((r = 0.48, p = 0.053 / r = -0.46, p = 0.062)\) or Specific Probe stages \((r = 0.41, p = 0.10 / r = -0.40, p = 0.12)\).

Finally, no correlations were found between the recall of episodic details at any stage of the CAI and epilepsy severity ratings on the GASE scale \((ps > 0.81)\) or the number of anti-epileptic drugs taken \((ps > 0.52)\).

Memory ratings

Examiner ratings of the overall richness of autobiographical recall were found to be significantly lower for the IGE group compared to the control group in the Free Recall \((M = 5.7, SD = 2.3 vs M = 8.4, SD = 3.4, respectively; t = -3.30, p = 0.002)\) and Specific Probe stages \((M = 8.9, SD = 3.1 vs M = 12.9, SD = 2.8, respectively; t = -4.46, p < 0.001)\).

Analysis of participants’ ratings of the phenomenological qualities of recalled events showed that on the memory strength domain, IGE participants’ ratings were significantly lower compared to the controls. However, no between group difference
was found on the remaining domains: visual intensity, emotional change, current
importance, past importance and confidence.

Table 4: Children’s Autobiographical Interview: Participants’ Ratings of
Phenomenological Qualities, by Group

<table>
<thead>
<tr>
<th></th>
<th>IGE</th>
<th>Control</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 18)</td>
<td>(n = 42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How clearly can you visualize this event?</td>
<td>4.93 (1.34)</td>
<td>4.94 (1.13)</td>
<td>-0.24</td>
<td>0.98</td>
</tr>
<tr>
<td>How much did your emotional state change after it happened?</td>
<td>4.29 (1.22)</td>
<td>4.01 (1.51)</td>
<td>0.61</td>
<td>0.54</td>
</tr>
<tr>
<td>How personally important is this event to you now?</td>
<td>3.75 (1.60)</td>
<td>4.33 (1.41)</td>
<td>-1.27</td>
<td>0.21</td>
</tr>
<tr>
<td>How personally important was this event to you then?</td>
<td>4.75 (1.60)</td>
<td>5.16 (1.29)</td>
<td>-0.97</td>
<td>0.34</td>
</tr>
<tr>
<td>On average, how often do you think or talk about this event?</td>
<td>3.21 (1.74)</td>
<td>3.85 (1.68)</td>
<td>-1.21</td>
<td>0.23</td>
</tr>
<tr>
<td>How sure are you of what you just remembered?</td>
<td>5.04 (1.65)</td>
<td>5.60 (0.98)</td>
<td>-1.21</td>
<td>0.24</td>
</tr>
<tr>
<td>How strong is the memory of the event?</td>
<td>4.27 (1.65)</td>
<td>5.38 (1.03)</td>
<td>-2.87</td>
<td>0.01</td>
</tr>
</tbody>
</table>

IGE: Idiopathic Generalized Epilepsy

Regression Analyses

Exploratory regression analyses were performed in the IGE group for episodic recall
performance at each stage of the CAI (see Table 5). The variables age of epilepsy
diagnosis, proportion of life spent with epilepsy and WRAML2: Story Memory (both
immediate and delayed recall) were significant in predicting episodic recall
performance during the Free Recall stage (explaining 55% of the variance), but not at
the General or Specific Probe stages. However, no variable made a significant,
independent contribution in predicting Free Recall performance.
Table 5: Simultaneous multivariate regression analyses of epilepsy and cognitive variables in predicting episodic autobiographical recall performance

<table>
<thead>
<tr>
<th>Multivariate Analysis</th>
<th>B</th>
<th>SE</th>
<th>β</th>
<th>p</th>
<th>R²</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Free Recall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of epilepsy diagnosis</td>
<td>0.23</td>
<td>1.54</td>
<td>0.10</td>
<td>0.88</td>
<td>0.74</td>
<td>3.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Proportion of life spent with epilepsy</td>
<td>-20.86</td>
<td>19.00</td>
<td>-0.59</td>
<td>0.29</td>
<td></td>
<td></td>
<td></td>
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**Discussion**

To our knowledge, this is the first study to examine recall of autobiographical memories in patients with epilepsy who are free of structural brain abnormalities; children with IGE. While these results are of theoretical relevance, they also carry significant clinical implications. First, the most striking finding of our study is of deficits in the recall of episodic, but not semantic, autobiographical details in children with IGE. This deficit was evident, irrespective of whether children with IGE recalled
episodic details spontaneously or if they received general or directed retrieval support. In addition, children with IGE rated their memories for personally experienced events as being weaker than controls. Second, amongst epilepsy factors, the age of seizure onset and proportion of life spent with epilepsy both appeared to be associated with recall of episodic details, where an earlier onset and longer duration were associated with poorer recall, but only when no prompts were given. Third, correlations between recall of episodic details and anterograde verbal memory were moderate in size and marginally significant.

Previous adult studies have attributed deficits in recall of autobiographical episodes to the presence of temporal lobe pathology (Addis et al., 2007; Irish et al., 2011; Lah et al., 2006; Matuszewski et al., 2009). Findings of our study indicate that temporal lobe pathology is not the only instance when recall of episodic details may be disrupted in patients with epilepsy. Instead, generalised seizure activity itself may affect either the storage or retrieval of episodic memory details, even in the absence of temporal lobe pathology. It is possible that this seizure activity disrupted (i) the consolidation of information, which according to the classic consolidation theory takes a long time to complete and/or (ii) the function of select cortical areas within the distributed network that have been associated with the recall of autobiographical memories, such as the prefrontal cortex (Conway et al., 1999; Maguire, 2001; Svoboda, McKinnon, & Levine, 2006) or lateral and medial parietal cortices (Hassabis et al., 2007; Wagner, Shannon, Kahn, & Buckner, 2005) and/or (iii) the integration of information from various brain regions that may be required to form a gestalt of an episode.
The fact that the provision of retrieval support did not remove deficits in the recall of personally-experienced events suggests that children with IGE may have difficulties with both the storage and retrieval of information. This result is consistent with other studies that have failed to find any beneficial effect of retrieval support on episodic recall, either in adult patients with hippocampal damage (Rosenbaum et al., 2011; St-Laurent et al., 2009; Steinworth, Levine, & Corkin, 2005) or transient epileptic amnesia (Milton et al., 2010), or in children with hippocampal dysfunction due to thyroid hormone deficiency (Willoughby, McAndrews, & Rovet, 2013).

Like many (but not all) previous studies conducted with patients with (albeit temporal lobe) epilepsy (e.g. Addis et al., 2007; St-Laurent et al., 2009; Viskontas et al., 2000; Voltzenlogel et al., 2006), we found that children with IGE had deficits in the recall of episodic, but not semantic details of personally experienced episodes. This finding may be due to the fact that the measure used in the current study, the CAI, was originally developed to capture details that are internal to a specific episode, episodic details. The CAI also provides a score for recalled details that were not internal to the specific event, semantic details. Nevertheless, this score is based on not only facts, but also other extraneous data, such as repetitions and editorialising statements, which suggest that a more precise measure of semantic details may be warranted. However, our findings could also be explained by the greater vulnerability of episodic memory to disruption. That is, episodic memories are experienced only once, meaning that the record of the memory is unique and cannot be re-established. In addition, the ability to recall episodic details may also not have reached full maturity in some participants. Consistent with previous developmental studies (Picard et al., 2009; Piolino et al., 2007; Willoughby et al., 2012), significant correlations were found between recall of
episodic details and chronological age in both groups, except in the spontaneous recall condition within the IGE group. Nevertheless, this correlation was of moderate size and the lack of statistical significance was likely to have been due to the limited power of the sample.

With respect to epilepsy variables, recall of fewer autobiographical episodic details was associated with early age of seizure onset and lifetime duration of epilepsy, but not with the overall rating of epilepsy severity or polytherapy, suggesting that seizures may have a cumulative adverse impact on the ability to freely recall details of personally-experienced events. In our study, these deficits may be secondary to the effects of seizures on the distributed network of structures which play a role in the storage and retrieval of autobiographical episodic details. Consistent with this possibility is the observation of Kaaden and Helmstaedter (2009) who pointed out that in patients with TLE early age of onset did not appear to affect abilities typically associated with temporomesial structures (such as short-term recall), but instead seemed to interrupt distant cortical networks, thereby affecting tasks which rely to a degree on extramesial or “whole-brain” functioning.

Deficits on standardized tests of memory were found in our patients with IGE, however, in a similar fashion to TLE studies with both adults (Lah et al., 2006) and children (Gascoigne et al., 2013), these deficits were not found to correlate with episodic aspects of autobiographical recall. In studies using non-epilepsy patients, both Shimamura & Squire (1986) and Mayes et al. (1997) found that the strength of the association between recall for newly-learned information and autobiographical details was dependent on the time period assessed; the correlation was stronger for
more recent autobiographical memories, suggesting that remote autobiographical recall may be distinct from and unrelated to new learning ability. As only recent autobiographical memories were assessed in the current study, the marginally non-significant correlation suggests that shared brain mechanisms may have been involved in the recall of these recent memories and for newly-learned information on standardized tests.

It is important to note that our study is not without limitations. First, it is acknowledged that seizure activity may not be solely responsible for the memory deficit found in this study. It is also possible that diffuse neocortical abnormalities that have been documented in patients with IGE and are beyond the resolution of current structural brain scans (Woermann, Sisodiya, Free, & Duncan, 1998) may have also compromised the capacity of neocortical storage sites which are critical for the retention of autobiographical memories. Second, we did not measure seizures directly, instead relying on an epilepsy severity scale which considered a variety of variables, including seizure severity. Third, our study was based on a small sample of epilepsy patients.

Despite these limitations, our novel findings are of clinical relevance and challenge the notion that the episodic autobiographical recall is largely determined by hippocampal integrity. These findings raise a possibility that generalized seizures or diffuse macroscopic neocortical abnormalities may adversely affect a wider cortical network associated with the retrieval of episodic details and may have a cumulative impact on autobiographical recall over time. Therefore, the implementation of
interventions aimed at enhancing autobiographical retrieval may be warranted in children with epilepsy.

Acknowledgments
We would like to thank Ms. Chloe Gott from the University of Sydney for assisting with the CAI scoring and Dr. Jayne Antony at the Children’s Hospital at Westmead for assistance in recruiting patients. MG was supported by a postgraduate scholarship from The University of Sydney and the ARC-CCD PhD completion scholarship. Sunny Lah was in part supported by The University of Sydney Thompson Fellowship. Finally, we would like to express our gratitude to all participants and their parents for taking part in this study.

References


CHAPTER 8: General Discussion
The primary aim of this thesis was to examine long-term memory ability in children with epilepsy, accomplished by assessing recall of a newly-learned list of words and autobiographical memory performance. Compared to controls, children with TLE recalled fewer words following a long (7-day) delay compared with a short (30-min) delay, while age was also negatively correlated with word recall after short and long delays within the TLE group. Children with IGE recalled fewer words after a long, but not short, delay relative to controls. Among children with IGE, greater epilepsy severity was also associated with poorer 7-day word recognition.

With respect to autobiographical memory, children with TLE recalled fewer episodic, but not semantic, details than controls. Unlike controls, episodic recall did not increase with age in the TLE group and was unrelated to epilepsy factors, such as side of seizure focus or the presence of structural hippocampal abnormalities. Children with IGE recalled fewer episodic details than controls while earlier age of seizure onset was associated with poorer episodic recall.

Taken together, the results of these studies provide the first evidence for accelerated long-term forgetting (ALF) and deficits in the recall of episodic aspects of personally-experienced past events in children with TLE and in those with IGE.

The fact that ALF was not related to the presence of hippocampal abnormalities in children with TLE but was also found in children with IGE who are free of macroscopic structural abnormalities suggests that disruption of the interaction within the network that is important for long-term memory formation, in addition to cortical lesions themselves, has the potential to interfere with the consolidation of long-term
memory. ALF also appears to be unrelated to initial learning efficiency, as both our TLE and IGE groups demonstrated this long-term memory deficit when patients who did not reach the learning criterion were removed from the sample. Overall our findings are consistent with Classic Consolidation Theory (CCT) of long-term memory formation that requires information to be transferred from the hippocampus to neocortical long-term storage sites via the process of consolidation.

The association between ALF with either the laterality of seizure focus and hippocampal integrity remains unclear, as our relatively small sample of patients with TLE did not provide sufficient statistical power to fully assess the impact of these variables. The impact of these factors needs to be examined in a study involving a larger sample of children with TLE and quantified structural and/or functional imaging data.

Although our studies provided evidence of ALF for verbal information, no long-term memory deficit was found for visual information, at least for patients with TLE. This may be due to the possibility that our newly-developed tool used to assess recall of visual information after long delays did not appear sensitive to deficits in visual memory in general, as no difference between TLE and control groups was found on any of the scores obtained on this task. Future studies may be able to assess ALF for visual material by developing a measure that has a greater capacity to detect long-term loss of visual information.

Both of the ALF studies within this thesis assessed seizure severity and frequency with a composite measure based on a variety of epilepsy-related factors. Both seizure
Previous ALF studies have attempted to assess seizure activity during retention periods with a range of measures, including seizure diaries (Muhlert et al., 2011; Wilkinson et al., 2012). However, even very accurate seizure diaries, will not provide accurate information about subclinical seizure activity, which in a recent study that used ambulatory EEG was found to be associated with ALF in patients with partial seizures (Fitzgerald, Thayer, Mohamed, & Miller, 2013).

Particularly intriguing are our findings that revealed evidence of impaired recall of autobiographical episodic information not only in children with TLE, but also in children with IGE relative to control participants. We have not examined a temporal gradient of retrograde memory deficits, but the presence of deficits in children with IGE (who are free of hippocampal pathology) would not be predicted by Multiple Trace Theory, which points out that the hippocampus is involved in maintenance and retrieval of autobiographical episodes indefinitely. If maintenance of autobiographical episodes, however, requires interaction between the hippocampus and the neocortex (proposed by CCT) then disruption of this consolidation process could compromise recall of episodes encountered in the past. Consistent with this conclusion are our findings in children with TLE, where the presence of hippocampal lesions was not associated with deficits in the recall of episodic details.

The findings of some of the studies within this thesis provided further insight into the development of memory ability. Unlike controls, the free recall of episodic autobiographical details did not increase with age among patients with TLE or those
with IGE. Furthermore, among children with TLE, both short- and long-term recall ability for newly-learned information also appeared to decline with age. These findings suggest that, among children with TLE, seizures may have a gradual but cumulative adverse impact on the ability to recall newly-learned information and to freely recall episodic autobiographical details. However, as our studies relied on cross-sectional data, future research that adopts a longitudinal design may be able to provide direct evidence of this apparent developmental hindrance in children with TLE.

The findings of our study are of high clinical relevance. Notably, autobiographical memory deficits and ALF remain undetected by standardised tests which typically require learning and recall of information after short (30-min) delays. Given the apparent shortcomings of currently used standardized memory tools, the development of new instruments that will enable accurate diagnosis of these new forms of memory disorders is paramount. Finally, in addition to accurate diagnosis, it is vital to develop and validate treatment strategies for a range of memory deficits experienced by children with epilepsy.

References


APPENDIX A: Human Ethics Research Approval
24 June 2009

Dr Sunny Lah
School of Psychology
Mungo McCallum (F17)
Locked Bag 4001
Camperdown NSW 2006

Dear Dr Lah,

HREC reference number: HREC/08/CHW/119
SSA reference number: SSA/09/CHW/85
Project title: Everyday memory in children with Idiopathic Generalised Epilepsy; Relationship with autobiographical memory and long-term consolidation

Thank you for submitting an application for authorisation of this project. I am pleased to inform you that authorisation has been granted for this study to take place here at The Children’s Hospital at Westmead.

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and which are submitted to the lead HREC for review, are copied to the research governance officer;

2. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project are to be submitted to the research governance officer.

Yours sincerely,

[Signature]

Mr James Cokayne
Research Governance Officer
Ref: MC/KR

8 April 2009

Dr Sunny Lah
Room MM422
Brennan MacCallum Building – A18
The University of Sydney

Dear Dr Lah

Title: Everyday memory in children with Idiopathic Generalised Epilepsy; Relationship with autobiographical memory and long-term consolidation (Ref. No.11739)

DCP Student: Mr Michael Gascoigne

Your application was reviewed by the Executive Committee of the Human Research Ethics Committee (HREC), and in doing so has ratified your study to include the DCP student – Mr Michael Gascoigne.

The Executive Committee acknowledges your right to proceed under the authority of The Children's Hospital at Westmead Ethics Committee.

Please note, this ratification has been given only in respect of the ethical content of the study.

Any modifications to the study must be approved by The Children's Hospital at Westmead Ethics Committee before submission to the University of Sydney Human Research Ethics Committee.

Yours sincerely

Marietta Coutinho
Deputy Manager
Human Research Ethics Administration

cc Mr Michael Gascoigne, School of Psychology, Mungo McCallum – F17, The University of Sydney
27 April 2011

Dr Suncica Lah
Psychology, University of Sydney

Dear Dr Lah,

Project Title: Everyday memory in children with Epilepsy
Project No: 08/CHW/119

Parent / Guardian Information Sheet: as attached

At its meeting on 1 April 2011 the Human Research Ethics Committee approved amendments to this project for the inclusion of children with Temporal Lobe Epilepsy aged 6-16 and a matched control group, inclusion of additional tasks in the neuropsychological battery, amendment of the project title and updates to the information sheet and consent form.

We wish you well with your project. Please contact us should you have any queries.

Yours sincerely,

Karen Steinhoff
Secretary, Human Research Ethics Committee
Mutual Data/Biological Sample Transfer Agreement ("Agreement")
Research Use of Personal Health Information

BETWEEN:

The Hospital for Sick Children ("HSC")
556 University Avenue
Toronto, ON, M5G 1X8

AND

The University of Sydney ("UoSy")
School of Psychology
Rm MM422, Brennan MacCallum Building – A18
Sydney, NSW 2006 Australia
("Institution")

SickKids Investigator:
Dr. Mary Lou Smith
(together with HSC = "SickKids")

Institution Investigator:
Dr. Suncica Lah
(together with UoSy = Sydney)

Name of Study ("Study"): Long-term Memory in Children with Temporal Lobe Epilepsy

SickKids REB Study Number(s): To be finalised
Institution IRB Study Number: University of Sydney Ref No: 11739

Data and/or biological samples, as applicable, to be provided ("Data/Samples"): As per the REB/IRB approved Study Protocol, incorporated herein by reference.

This Agreement, effective as of the last date of signature below, is entered into between the parties to govern the transfer of the Data/Samples mutually between SickKids and Sydney to be used for the purposes of the Study in accordance with this Agreement. The party providing the Data/Samples is the "PROVIDER" and the party receiving the Data/Samples is the "RECIPIENT." PROVIDER retains the right to refuse transfer of the Data/Samples requested.

PROVIDER will prepare and furnish to RECIPIENT the Data/Samples (as applicable) in accordance with applicable laws, and specifically warrants that transfer of the Data/Samples by PROVIDER will be in compliance with IRB approved subject Informed consent forms ("ICFs") provided by the individuals from whom the Data/Samples were collected, or terms of an IRB Waiver of Consent, as applicable. Data/Samples will not be transferred until each party’s IRB/REB provides written approval for the Study.

RECIPIENT shall use the Data/Samples in compliance with all applicable laws; and shall specifically only use or disclose the Data/Samples for the conduct of the Study in accordance with the permitted uses of the Data/Samples specified in the applicable ICFs or IRB Waiver of Consent, or otherwise as required by law.

No right, title or interest in and to the Data/Samples is granted or implied to the RECIPIENT hereunder.

RECIPIENT shall have the right to use (1) the analyzed, de-identified data derived from the use of the Data/Samples, and (2) de-identified information and results arising out of analysis of the Data/Samples, as part of a publication or presentation of the results of the Study, and shall own such de-identified, analyzed data and results. RECIPIENT shall not include any personally identifying information in any publication or presentation. Provider's contribution to the Study shall be acknowledged appropriately in any such publication or presentation in accordance with academic standards.

RECIPIENT shall use appropriate safeguards to prevent any unauthorized use or disclosure of the Data/Samples and shall report to the PROVIDER any unauthorized use or disclosure of which RECIPIENT becomes aware, or of any breach of this Agreement. RECIPIENT shall not use the Data/Samples to identify or contact the individuals from whom such Data/Samples were collected. RECIPIENT shall securely destroy the Data/Samples as required by the Protocol or PROVIDER and provide a written confirmation of the manner of destruction in a form acceptable to PROVIDER. PROVIDER may conduct audits of the RECIPIENT concerning the maintenance of appropriate security safeguards to ensure compliance with this Agreement.

RECIPIENT shall give access to the Data/Samples only to its staff with a need to know for the purpose of conducting the Study, and who are bound by RECIPIENT to comply with the terms of this Agreement.

Sydney will reimburse SickKids for expenses related to the Study in accordance with Appendix A attached herein.

This Agreement may be signed in counterparts, and each counterpart may be delivered by facsimile or signed PDF by email. Each counterpart shall constitute an original, and when taken together, shall constitute one and the same instrument.
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I have authority to bind the organization.

Date: 28/04/11
Research Ethics Board (REB)

The Research Ethics Board for The Hospital for Sick Children is organized and operates according to the principles and practices outlined in the Tri-Council Policy Statement, the ICH Harmonized Tripartite Guidelines: Good Clinical Practice, and Division 5 and the Medical Devices Regulations of the Food and Drug Act as well as the Natural Health Products Regulations of Health Canada. This signed document is in lieu of the Health Canada Research Ethics Board Attestation Form.

Approval & Terms of Agreement

Investigators: Dr. Mary Lou Smith, S.Lah, M.Gascoigne

Study Title: Long-Term Memory in Children with Temporal Lobe Epilepsy

REB File number: 1000026003 Level of Continuing Review: II C

Protocol Version Date: April 5, 2011

Consent & Assent Form Version Date(s): Participants with Epilepsy for self; Parents of participants with Epilepsy; Control Participants for self; Parents of Control participants; Audiotaping consent for parents of participants; Audiotaping consent for participants (May 26, 2011); Child Assent for Participants with Epilepsy; Child Assent for Control Participants (June 9, 2011)

Investigator's Brochure Version Date: n/a

Other Approved Recruitment Document Dates: Everyday memory Questionnaire (Kadis et al 2004); Child Behaviour Checklist (Achenbach, 1991); Quality of Life questionnaire (Koren 2003) (modified); Recruitment advertisement (April 5, 2011); recruitment letter (March 23, 2011)

I agree to carry out the proposed research involving human subjects in accordance with the above-noted guidelines and regulations (as applicable) and using only the REB-approved study protocol and consent/assent form(s). I shall notify the division/department head and the REB prior to implementing any amendments in the protocol and consent/assent forms and of any deviations or any changes in study activity. I shall also notify the REB of any unexpected adverse events as per REB guidelines. As applicable, I certify that the research contract and corresponding protocol are consistent and will inform the contract manager of any protocol amendments as required.

I agree that, in accordance with the Personal Health Information Protection Act of Ontario, I am responsible for adhering to all conditions and restrictions imposed by the REB governing the use, security, disclosure, return and disposal of the research subjects' personal health information. I am also responsible for reporting immediately any privacy breach to the REB Chair and to Janice Campbell, the Sick Kids privacy officer. I will ensure that the personal health information is used, only as necessary, to fulfill the specific research objectives and related research questions described in this application and approved by the REB.

Signature of Principal Investigator

May 26, 2011

I approve of this research protocol, agree to share responsibility for its proper conduct, and will ensure that the REB is notified of concerns, as appropriate.

Signature of Division/Department Head

June 19, 2011

The REB of the Hospital for Sick Children has reviewed and approved the above-named research study.

Mr. Richard Sugarman, REB Chair
555 University Avenue, Toronto, Ontario, M5G 1X8
Tel: 416-813-6152 Fax: 416-813-6085 Email: richard.sugarman@sickkids.ca

Date of Approval: June 16, 2011 Expiry Date: June 2012
APPENDIX B: Participant Consent and Information Sheets
Parent/guardian consent form

Everyday memory in children with epilepsy

Investigators:
Dr Sunny Lah, Senior Lecturer, School of Psychology, The University of Sydney (Usyd) (Ph: 02 9351 2648);
Dr Richard Webster, Paediatric Neurologist, Children’s Hospital Education Research Institute (CHERI), The Children’s Hospital at Westmead (CHW) (Ph: 02 9845 0418);
Dr Belinda Barton, Head, CHERI, CHW (Ph: 02 9845 0415);
Mr Michael Gascoigne, Doctoral Candidate, School of Psychology, Usyd (Ph: 0418 241 008);
Dr Deepak Gill, Paediatric Neurologist, Neurology Department, CHW (Ph: 02 9845 2657).

I have read and have understood the parent/guardian information sheet, and give my consent for my child to participate in this research project:

________________________________________________________

I understand that I am free to withdraw my child from this project at any time and this decision will not otherwise affect my child’s treatment at the Hospital.

Name of child: ____________________________________________

Name of parent/guardian: __________________________________

Signature of parent/guardian: ____________________________ Date: __________

Name of witness: _________________________________________

Signature of witness: ________________________________ Date: __________
Everyday memory in children with epilepsy

What is the study about?
Memory problems are common in epilepsy patients. Even though children with epilepsy may seem to perform well on standard memory tasks that require recall after a short delay, there is evidence that they have difficulties recalling the same material after a long delay (i.e. after a day or a week). It is unknown whether this problem influences children’s recall of events from their past and affects their performance in everyday memory tasks.

The aim of this study is to determine whether the everyday memory of children with epilepsy is different from children without epilepsy. Comparing these two groups will allow us to detect differences in their everyday memory that are more likely to be due to epilepsy. We will also examine the relationship between forgetting, memories for the past and performance in day-to-day tasks in children with epilepsy. We hope that the results from this study will allow us to accurately monitor children with epilepsy and, if needed, to develop specific interventions.

Who can participate in the study?
Children with epilepsy who meet the following criteria are invited to participate:

- Aged between 6 and 14 years of age
- Are fluent in the English language. The child’s parent/guardian must also be fluent in the English language.
- Have a full scale IQ above 79. A brief IQ test will also be conducted prior to the assessment to determine if he or she is suitable for the study.
What will the study involve?
If you agree to participate, the study will involve you and your child either coming to The Children’s Hospital at Westmead or the Psychology Clinic at The University of Sydney for an assessment. You will also be asked to complete some questionnaires.

Child’s Assessment
The assessment will take approximately 2 hours (including a short break) and will be organised at a time convenient to you. We would prefer the assessment to be in the morning, as most children find it easier to work and concentrate at this time. Before the assessment your child will do a brief IQ test to determine if he or she is suitable for the study. If your child’s full scale IQ is below 79 he or she will not undergo further assessment.

During the assessment your child will be asked to answer some questions, complete some puzzles and memory tasks. Parents don’t have to be present during the assessment. We will also contact you and your child by phone the following week after the appointment at a mutually convenient time. This telephone conversation is likely to take 5 to 10 minutes.

Parent Questionnaires
While your child is being assessed, we will ask you to complete two questionnaires about your child’s behaviour and everyday memory which will take approximately 15-20 minutes to complete.

Are there any benefits for my child participating in the study?
Each parent or guardian will receive a brief report which will summarise and interpret the results of your child’s assessment and may include recommendations. If you would like to send a copy of the report to your child’s teacher or doctor, we will be happy to provide you with multiple copies.

Members of the research team will be happy to be contacted if you would like to discuss assessment results further. We may also recommend a referral to a specific service for further treatment and/or assessment, if needed.

The results of this assessment may give parents a better understanding of any memory difficulties that your child may have.

You should not expect your child’s medical condition to improve as a result of participating in this study.

Are there any side effects and risks associated with this study?
There are no known side effects or risks arising from this study. Your child will be asked to complete various cognitive and memory tasks during the assessment. Some of the tasks will be easy while others may be more difficult.

If your child becomes concerned or distressed in any way during an assessment, the session will be stopped and you will be consulted. The psychologists involved in this study who will assess your child have experience in working with children of all ages. Before the assessment is given, they will talk to you and your child and make sure your child feels relaxed and comfortable.
Other information
All data will be stored in locked filing cabinets at the University of Sydney Psychology Department for a minimum of 15 years. After this period, the assessment forms will be shredded.

Electronic data stored on a computer database will be accessible only to investigators on the study with an appropriate security protected password.

Your child will be assigned a coded number so no identifying information will be used in the database. Results from this study may be published in scientific journals, but at no time will any information or data be used that will identify you or your child.

Participation in this study is voluntary, and if you and your child decide not to take part, or decide to withdraw at any time, this will in no way affect your child’s care at The Children’s Hospital at Westmead or at the Psychology Clinic at the University of Sydney.

If you have any questions about this study, please do not hesitate to discuss these with Miss Jasmin Grayson-Collins, University of Sydney Psychology Department (Ph: 0478 418 814), Mr Michael Gascoigne, University of Sydney Psychology Department (Ph: 0418 241 008) or Dr Sunny Lah, University of Sydney Psychology Department (Ph: 02 9351 2648).

This project has been approved by The Children’s Hospital at Westmead Ethics Committee. If you have any concerns about the conduct of this study, please do not hesitate to contact Ms Eleanor Thackray, Secretary of the Ethics Committee, (Ph: 02 9845 3017).

This information sheet is for you to keep. We will also provide you with a copy of the signed consent form for your child’s participation in the research study.

Please complete and return the preference slip in the supplied reply-paid envelope or email Jasmin Grayson-Collins at jgra3716@uni.sydney.edu.au or Michael Gascoigne at michaelg@psych.usyd.edu.au to indicate whether you are willing to participate.

Preference Slip

I would like to be contacted regarding the memory in children with epilepsy study

☐ YES  ☐ NO

Signed: __________________________________________

Name: _________________________________________

Date: __________________________________________

Contact detail(s) (if willing to be contacted, please tick which method you would prefer):

☐ Home telephone number: __________________________

☐ Business telephone number: _______________________

☐ Email address: _________________________________
Parent/guardian information sheet

Everyday memory in children with epilepsy

Investigators:
Dr Sunny Lah, Senior Lecturer, School of Psychology, The University of Sydney (Usyd) (Ph: 02 9351 2648);
Dr Richard Webster, Paediatric Neurologist, Children’s Hospital Education Research Institute (CHERI), The Children’s Hospital at Westmead (CHW) (Ph: 02 9845 0418);
Dr Belinda Barton, Head, CHERI, CHW (Ph: 02 9845 0415);
Mr Michael Gascoigne, Doctoral Candidate, School of Psychology, Usyd (Ph: 0418 241 008);
Dr Deepak Gill, Paediatric Neurologist, Neurology Department, CHW (Ph: 02 9845 2657);
Miss Jasmin Grayson-Collins, Doctorate of Clinical Psychology Candidate, School of Psychology, Usyd (Ph: 0478 148 814).

We would like you and your child to consider participating in a research study currently being conducted by the School of Psychology at The University of Sydney in conjunction with the Children’s Hospital Education Research Institute (CHERI) and the Neurology Department at The Children’s Hospital at Westmead.

This study is examining memory in children with epilepsy. Both children with and without epilepsy will be recruited for this study. This information sheet is for parents of children who do not have epilepsy.

What is the study about?
Memory problems are common in epilepsy patients. Even though children with epilepsy may appear to perform well on standard memory tasks that require recall after a short delay, there is evidence that they have difficulties recalling the same material after a long delay (i.e. after a day or a week). It is unknown whether this problem influences children’s recall of events from their past and affects their performance in everyday memory tasks.

The aim of this study is to determine whether the everyday memory of children with epilepsy is different from children without epilepsy. Comparing these two groups will allow us to detect differences in their everyday memory that are more likely to be due to epilepsy. We will also examine the relationship between forgetting, memories for the past and performance in day-to-day tasks in children with epilepsy. We hope that the results from this study will allow us to accurately monitor children with epilepsy and, if needed, to develop specific interventions.

Who can participate in the study?
Children without epilepsy who meet the following criteria are invited to participate:
• Aged between 6 and 14 years of age
• Are fluent in the English language. The child’s parent/guardian must also be fluent in the English language.
• Have a full scale IQ above 79. A brief IQ test will also be conducted prior to the assessment to determine if he or she is suitable for the study.

What will the study involve?
If you agree to participate, the study will involve your child being seen for a cognitive assessment at the school (if approved by your child’s school) or at The Children’s Hospital at Westmead or the Psychology Clinic at the University of Sydney. You will also be asked to complete some questionnaires.

Child’s Assessment
The assessment will take approximately 2 hours (including a short break) and will be organised at a time convenient to you. We would prefer the assessment to be in the morning, as most children find it easier to work and concentrate at this time. Before the assessment your child will do a brief IQ test to determine if he or she is suitable for the study. If your child’s full scale IQ is below 79 he or she will not undergo further assessment.

During the assessment your child will be asked to answer some questions, complete some puzzles and memory tasks. Parents do not need to be present during the assessment. We will also contact you and your child by phone on the following day and one week after the appointment at a mutually convenient time. This telephone conversation is likely to take 5 to 10 minutes.

Parent Questionnaires
While your child is being assessed, we will ask you to complete two questionnaires about your child’s behaviour and everyday memory which will take approximately 15-20 minutes to complete.

Are there any benefits for my child participating in the study?
Each parent or guardian will receive a brief report which will summarise and interpret the results of your child’s assessment and may include recommendations. If you would like to send a copy of the report to your child’s teacher or doctor, we will be happy to provide you with multiple copies.

Members of the research team will be happy to be contacted if you would like to discuss assessment results further. In addition, we may recommend a referral to a specific service for further treatment and/or assessment, if needed. The results of this assessment may give parents a better understanding of any memory difficulties that your child may have.

Are there any side effects and risks associated with this study?
There are no known side effects or risks arising from this study. Your child will be asked to complete various cognitive and memory tasks during the assessment. Some of the tasks will be easy while others may be more difficult.

If your child becomes concerned or distressed in any way during an assessment, the session will be stopped and you will be consulted. The psychologists involved in this study who will assess your child have experience in working with children of all ages. Before the assessment is given, they will talk to you (if available) and your child and make sure your child feels relaxed and comfortable.
Other information
All data will be stored in locked filing cabinets at the University of Sydney Psychology Department for a minimum of 15 years. After this period, the assessment forms will be shredded.

Electronic data stored on a computer database will be accessible only to investigators on the study with an appropriate security protected password.

Your child will be assigned a coded number so no identifying information will be used in the database. Results from this study may be published in scientific journals, but at no time will any information or data be used that will identify you or your child.

Participation in this study is voluntary, and if you and your child decide not to take part, or decide to withdraw at any time, this will in no way affect any future care your child’s may need at The Children’s Hospital at Westmead or at the Psychology Clinic at the University of Sydney.

If you have any questions about this study, please do not hesitate to discuss these with Miss Jasmin Grayson-Collins, University of Sydney Psychology Department (Ph: 0478 148 814), Mr Michael Gascoigne, University of Sydney Psychology Department (Ph: 0418 241 008) or Dr Sunny Lah, University of Sydney Psychology Department (Ph: 02 9351 2648)

This project has been approved by The Children’s Hospital at Westmead Ethics Committee. If you have any concerns about the conduct of this study, please do not hesitate to contact Ms Eleanor Thackray, Secretary of the Ethics Committee (Ph: 02 9845 3017).

This information sheet is for you to keep. We will also provide you with a copy of the signed consent form for your child’s participation in the research study.

Please complete and return the preference slip below in the supplied reply-paid envelope or email Jasmin Grayson-Collins at jgra3716@uni.sydney.edu.au or Michael Gascoigne at michaelg@psych.usyd.edu.au to indicate whether you are willing to participate.

Preference Slip
I would like to be contacted regarding the memory in children with epilepsy study

☐ YES  ☐ NO

Signed: ____________________________________________

Name: ____________________________________________

Date: ____________________________________________

Contact detail(s) (if willing to be contacted, please tick which method you would prefer):
☐ Home telephone number: ____________________________

☐ Business telephone number: ____________________________

☐ Email address: ____________________________
Participant information sheet

Everyday memory in children with epilepsy

Who is doing the study?

Investigators:
Dr Sunny Lah, Senior Lecturer, School of Psychology, The University of Sydney (Usyd) (Ph: 02 9351 2648);
Dr Richard Webster, Paediatric Neurologist, Children’s Hospital Education Research Institute (CHERI), The Children’s Hospital at Westmead (CHW) (Ph: 02 9845 0418);
Dr Belinda Barton, Head, CHERI, CHW (Ph: 02 9845 0415);
Mr Michael Gascoigne, Doctoral Candidate, School of Psychology, Usyd (Ph: 0418 241 008);
Dr Deepak Gill, Paediatric Neurologist, Neurology Department, CHW (Ph: 02 9845 2657);
Miss Jasmin Grayson-Collins, Doctorate of Clinical Psychology Candidate, School of Psychology, Usyd (Ph:0478148814).

What is the study about?
This study is looking at everyday memory in children. Memory problems are common in people of all ages. These problems can include forgetting things that you have learned more quickly than usual or having difficulty recollecting events that happened in the past. We hope to learn more about how these difficulties may be related to everyday memory performance. Specifically, we will see if everyday memory in children with epilepsy is different from children without epilepsy. If needed, we will use this information to develop teaching programs that will assist in overcoming everyday memory problems.

Who can participate in the study?
Both children with and without epilepsy will participate in this study. All children will be between the ages of 6 and 14, will be fluent in the English language and have an IQ score above 79.

What will the study involve?
If you agree to participate, we will ask your parents/carer to fill out a questionnaire about your everyday memory abilities. We will also do a brief IQ test with you to see if you are able to complete the tasks in the study. Following this we will look at your memory and thinking skills either at your school, the Children’s Hospital at Westmead or at the University of Sydney Psychology Clinic. This will take about two hours, along with a short break. We will also talk to you briefly over the phone the next day and the following week.
Do I have to take part in the research?
No you don’t. If you don’t want to take part in the research, that is OK. Even if you start to take part, if you don’t like it, you can change your mind. All you need to do is let the researcher or your parents know that you don’t want to take part in the research any more.

Will I be given something for taking part?
No, you will not be given anything for participating in the research. We hope that the results for this study will increase our understanding and knowledge about memory in children with epilepsy. We also hope that you enjoy the program and find it helpful.

Are there any side effects or risks associated with the study?
We do not expect anything in the program to upset you. However, sometimes looking at a person’s memory problems might upset them. If this happens, the researcher will be happy to stop the program and you can talk to him or your parents/carers. All the researchers in this project are trained psychologists and health professionals.

Other information
Any information about you and your family will remain confidential. This means that the information could be used in reports about the research, but your name will not be used in these reports, so you will not be identified. Once the study is completed the information from this study will be stored in a locked room on a password protected computer and will be destroyed after 15 years.

Participation in this project is voluntary and if you decide not to take part or decide to withdraw at any time this will not otherwise affect your care at the Children’s Hospital at Westmead.

If you want to talk to us about the research project please call us. You can reach us on:
- Mr. Michael Gascoigne (0418 241 008)
- Miss. Jasmin Grayson-Collins (0478 148 814)
- Dr. Sunny Lah (02 9351 2648)
- Eleanor Thackray (02 9845 3017) who is the Secretary of the Ethics Committee who has approved this project.

This information sheet is for you to keep. We will also give you a copy of the signed consent form.
APPENDIX C: Experimental Materials
**Name:_____________________________**

**Years 9 and older**

<table>
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<th>Long Delay: 7 days</th>
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Immediate Recall: Bananas
Short Delay: 30mins
Long Delay: 7 days

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**Under 9 Years of age**

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- 木: 木头
- 月: 月亮
- 司: 司令
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APPENDIX D: Published Manuscripts
Accelerated long-term forgetting in children with idiopathic
generalized epilepsy

*Michael B. Gascoigne, †Belinda Barton, ‡Richard Webster, ¶Deepak Gill, ‡Jayne Antony, and
*Suncica Sunny Lah

*School of Psychology, and ARC Centre of Excellence in Cognition and its Disorders, The University of Sydney, Sydney, Australia; †CHERI, The Children’s Hospital at Westmead and Discipline of Paediatrics and Child Health, Faculty of Medicine, University of Sydney, Sydney, New South Wales, Australia; and ‡T.Y. Nelson Department of Neurology and Neurosurgery, The Children’s Hospital at Westmead, Sydney, New South Wales, Australia

SUMMARY

Purpose: The rapid forgetting of information over long (but not short) delays (accelerated long-term forgetting [ALF]) has been associated with temporal lobe epilepsy but not idiopathic generalized epilepsy (IGE). Long-term memory formation (consolidation) is thought to demand an interaction between medial temporal and neocortical networks, which could be disrupted by epilepsy/seizures themselves. The present study investigates whether ALF is present in children with IGE and whether it relates to epilepsy severity.

Methods: Sixty-one children (20 with IGE and 41 healthy controls [HC]) of comparable age, sex, and parental socioeconomic status completed neuropsychological tests, including a measure of verbal learning and recall after, short (30-min) and long (7-day) delays, and recognition. Epilepsy severity was rated by treating neurologists.

Key Findings: A two-way repeated measures analysis of covariance (ANCOVA) found a significant Group x Delay interaction; the children with IGE recalled (and recognized) significantly fewer words after a long, but not short (2- and 30-min) delay relative to the HC children. Moreover, greater epilepsy severity was associated with poorer recognition.

Significance: This study demonstrates, to our knowledge for the first time, that children with IGE present with ALF, which is related to epilepsy severity. These findings support the notion that epilepsy/seizures themselves may disrupt long-term memory consolidation, which interferes with day-to-day functioning of children with IGE.

KEY WORDS: Idiopathic generalized epilepsy, Accelerated forgetting, Memory, Recall, Consolidation.
could be found in patients with generalized seizures who have no detectable cortical pathology: idiopathic generalized epilepsy (IGE; Davidson et al., 2007).

To date, two studies have examined ALF in IGE populations: one involved adults (Muhlert et al., 2011) and another children (Davidson et al., 2007). The former found no evidence of memory deficits on short (30-min) and long delays (3 weeks) in patients with IGE. Findings of adult studies, however, should not be automatically generalized to children, as children’s cognitive skills and functional brain organization are still developing. Indeed, in children with IGE Davidson et al. (2007) found evidence of ALF, but attributed this finding to poor initial learning efficiency. Although seizures were proposed to play a critical role in long-term consolidation, 24% of the sample of Davidson et al. had been seizure free for 2 years, and the adult study did not state whether seizure-free participants were included. Inclusion of seizure-free participants could have reduced the likelihood of finding ALF in these studies. Nevertheless, adult TLE studies have yielded inconsistent findings on the role of seizures in ALF: two studies found significant associations between seizures and rate of forgetting over long delays (Mameniskiene et al., 2006; Wilkinson et al., 2012), and one study did not (Blake et al., 2000).

It is possible that instead of a single factor, a combination of epilepsy-related factors play a significant role in ALF, which could account for inconsistent findings. For example, greater seizure severity (Mameniskiene et al., 2006), longer duration of epilepsy disorder (Blum, 2001; Nolan et al., 2004; Wang et al., 2011), and the use of poly-pharmacy (Alessio et al., 2004) were all found to be associated with poor learning and recall after short delays. Therefore, a measure that considers overall epilepsy severity, rather than epilepsy factors separately, could be related to the rate of long-term forgetting.

This study aimed to examine long-term verbal memory formation in children with IGE and determine whether it relates to epilepsy severity and day-to-day memory difficulties. To overcome the shortcomings of previous studies we included only children who had experienced at least one overt seizure in the last 2 years and examined the relationship between epilepsy and long-term memory formation using a validated epilepsy severity scale. We hypothesized that children with IGE will have poorer recall and recognition of verbal information after long, but not short delays, and that poorer long-term memory will be associated with more severe epilepsy and everyday memory complaints.

**Methods**

**Sample**

There were 20 children diagnosed with IGE and 41 healthy control (HC, free of epilepsy history) participants aged 6–16 years, fluent in English, with Full Scale Intelligence Quotient (FSIQ) >79, and free of preexisting diagnoses of major: sensory, neurodevelopmental [but not Attention Deficit Hyperactivity Disorder (ADHD) or learning difficulties] and other neurological disorders. Children with IGE were recruited through the neurology department, The Children’s Hospital at Westmead (CHW). Medical history, electroencephalography, and imaging data were reviewed by treating neurologists according to the International League Against Epilepsy (ILAE) criteria for IGE (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Only children who had experienced at least one seizure in the 2-year period before the assessment and whose clinical magnetic resonance imaging (MRI) scans (when available, n = 14) were free of structural abnormalities were considered for the study; 27 (87%) of 31 consented. Seven were excluded because subsequent findings disqualified IGE diagnosis (n = 6), or long-term verbal memory materials were noted and rehearsed, invalidating the test (n = 1). Control participants were recruited via word-of-mouth (snowball recruitment), through the peer networks of both IGE and other control participants.

**Materials**

**Socioeconomic status (SES)**

Daniel’s Scale of Occupational Prestige (Daniel, 1983) rates parental occupation on a seven-point scale, with higher scores reflecting lower SES. Mean parental occupation scores were used, except for single-parent families.

**Neuropsychological measures**

Clinical neuropsychological instruments are summarized in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Clinical neuropsychological instruments</th>
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<tr>
<td><strong>Domain</strong></td>
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<tr>
<td>Intelligence</td>
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<tr>
<td>Everyday memory</td>
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<tr>
<td>Working memory</td>
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<td></td>
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<tr>
<td>Short-term memory</td>
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WASI, Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999); EMQ, Everyday Memory Questionnaire (Kadis et al., 2004); WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition (Wechsler, 2003); WMTB-C, Working Memory Battery for Children (Pickering & Gathercole, 2001); WRAML2, Wide Range Assessment of Memory and Learning, Second Edition (Sheslow & Adams, 2003); CMS, Children’s Memory Scale (CMS) (Cohen, 1997).
Accelerated Long-Term Forgetting in Children

Experimental verbal memory measure

Word lists were derived from the California Verbal Learning Test – Children’s Version (CVLT-C, Delis et al., 1994), which has been shown to have acceptable reliability (coefficient alpha ranging from 0.72 to 0.85; Delis et al., 1994) and construct validity (Griffiths et al., 2006) in children with epilepsy. A 9- and 12-word list was devised for children <9 and ≥9 years of age, respectively. First, this list (A) was read until all words were recalled on two consecutive trials or 12 learning trials (two IGE participants) were completed. Second, list B (interference) was read and recalled once. Third, a recall of list A was requested following two short (2- and 30-min) and one long (one week) delay, without forewarning. Fourth, on completion of the long delay recall, a recognition list was presented. Long delay recall and recognition were conducted via telephone. The following scores were used: (1) number of learning trials (learning efficiency), (2) percentage of words recalled (max 100%) relative to last learning trial (recall), and (3) d prime (d’, recognition), which takes into account the proportion of correctly and incorrectly recognised words (Macmillan & Creelman, 1991).

Epilepsy severity

The Global Assessment of Severity of Epilepsy (GASE, Speechley et al., 2008) rates overall epilepsy severity on a scale from 1 (Not at all severe) to 7 (Extremely severe). It considers the frequency and intensity of seizures, injuries during seizures, severity of postictal period, number and side effects of antiepileptic drugs, and interference of epilepsy or drugs with daily activities. This scale has good construct validity as well as high interrater (weighted $\kappa = 0.85$) and test–retest (weighted $\kappa = 0.90$) reliability.

Procedure

The study was approved by the CHW and University of Sydney Ethics Research Committees. Parents gave informed consent and children were tested individually over one 90-min session and contacted 7 days later via phone. Memory questionnaires were completed by parents. Developmental history, SES, and information about relevant epilepsy variables were gathered via parental interview. Information about epilepsy was verified by treating pediatric neurologists and review of medical records. Neurologists, who were blinded to children’s scores on neuropsychological measures, completed the GASE scale.

Statistical analysis

All tests were two-tailed, with $\alpha < 0.05$. Groups were compared using independent $t$-tests and chi-square tests on background variables, and ANCOVA (with centered FSIQ as a covariate) on other measures. Spearman’s rho ($r_s$) was used to assess strengths of correlations between epilepsy severity and everyday memory with long-term and short-term memory measures.

Scores obtained on the experimental measure of verbal memory were analyzed using a two-way (Group × Delay) repeated measures ANCOVA, followed by Sidak post hoc tests. A priori hypotheses concerning ALF were assessed with the following planned contrasts; the 30-min and 7-day, and the 2- and 30-min delays.

Results

IGE participants were diagnosed at a mean age of 6.09 (standard deviation, SD 3.25) years and had experienced epilepsy for an average of 4.54 (SD 2.18) years (Table S1). All IGE children were taking antiepileptic drugs (AEDs): 18 monotherapy and 2 polytherapy. The mean epilepsy severity score (M 2.17, SD 1.69) corresponded to a rating between “A little severe” and “Somewhat severe.” The IGE and control groups did not differ in age, SES, sex distribution, and frequency of ADHD or learning difficulties diagnosis (see Table 2). Mean FSIQ of the IGE group was significantly lower than that of the control group.

On the Everyday Memory Questionnaire (EMQ) ANCOVA revealed significantly lower parental ratings in the IGE compared to the control group (Table 3). No significant differences were found between the groups on tests of working or visual memory. However, on the verbal memory test (WRAML2: Story Memory) the IGE children recalled a significantly fewer details immediately after the presentation and on 30-min delay relative to the control group.

Experimental measure of verbal memory

ANCOVA yielded no significant difference between the IGE (M 6.57, SD 2.59) and control (M 5.85, SD 2.15) groups in the number of trials needed to reach the learning criterion ($F_{1,60} = 0.39, p = 0.54$).

Recall and recognition data are presented in Fig. 1A,B, respectively. A two-way repeated-measures ANCOVA found a significant interaction between Group and Delay ($F_{2,116} = 8.39, p < 0.01$). Planned contrasts revealed that, compared to the control group, the IGE group recalled significantly fewer words from 30 min to 7 days ($F_{1,58} = 9.89$, $p = 0.002$).

### Table 2. Demographic and intelligence variables

<table>
<thead>
<tr>
<th>Group</th>
<th>IGE (n = 20)</th>
<th>Control (n = 41)</th>
<th>Test of significance</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>10.76 (2.47)</td>
<td>11.23 (2.63)</td>
<td>$t_{59} = -0.68$</td>
<td>0.50</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>10/10</td>
<td>21/20</td>
<td>$\chi^2 = 0.01$</td>
<td>0.93</td>
</tr>
<tr>
<td>SES</td>
<td>4.08 (1.31)</td>
<td>3.70 (1.08)</td>
<td>$t_{59} = 1.13$</td>
<td>0.27</td>
</tr>
<tr>
<td>FSIQ</td>
<td>102.00 (10.60)</td>
<td>111.32 (11.22)</td>
<td>$t_{59} = -3.10$</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Comorbid</td>
<td>1/0</td>
<td>0/0</td>
<td>$\chi^2 = 2.10$</td>
<td>0.15</td>
</tr>
<tr>
<td>ADHD/LD</td>
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IGE, idiopathic generalized epilepsy; SES, socioeconomic status; FSIQ, Full-Scale Intelligence Quotient; ADHD, attention deficit hyperactivity disorder; LD, learning difficulty.
p = 0.003), but not from 2 to 30 min (F \(1,58 = 0.74, p = 0.39\)). In addition, a main effect of Delay (F \(2,116 = 81.08, p < 0.001\)), but not Group (F \(1,58 = 1.36, p = 0.25\)) was evident. No significant difference in recall was found between the 2- and 30-min delays. However, participants recalled fewer words from the 30-min to 7-day delay (p < 0.001). Finally, the ANCOVA indicated that IGE participants had significantly poorer verbal recognition (d\(^c\)) compared to control participants (F \(1,60 = 17.82, p < 0.001\)).

Is ALF related to incomplete learning and poor verbal memory (story memory)?

To address this question, a repeated-measures ANCOVA that only included participants who learned all words (IGE, n = 18; HC, n = 41) was rerun, with Story Memory (immediate and delayed) and FSIQ as covariates. This ANCOVA again yielded a significant interaction between Group and Delay (F \(2,108 = 7.96, p = 0.001\)) and a significant main effect of Delay (F \(2,108 = 74.84, p < 0.001\)), but not Group (F \(1,54 = 2.60, p = 0.11\)). Planned contrasts showed that the IGE group recalled significantly fewer words from 30-min to 7-day delay (p < 0.001). Finally, the ANCOVA indicated that IGE participants had significantly poorer verbal recognition (d\(^c\)) compared to control participants (F \(1,56 = 17.82, p < 0.001\)).

Relations between experimental memory measure, epilepsy severity, and everyday memory

A significant negative correlation was found between epilepsy severity ratings on the GASE scale and long-term
verbal recognition accuracy (d': $r_s = -0.49$, $p < 0.05$); greater epilepsy severity was associated with worse long-term verbal recognition. However, epilepsy severity did not correlate with recall of information at any delay (2-min: $r_s = -0.10$; 30-min: $r_s = -0.18$; 7-days: $r_s = -0.21$; all $p$'s $> 0.05$).

Significant correlations were found between the EMQ scores and recall of words on 7-day ($r_s = 0.33$, $p < 0.05$), but not 2- ($r_s = 0.02$) and 30-min ($r_s = 0.09$; all $p$s $> 0.05$) delays and 7-day recognition accuracy (d': $r_s = 0.44$, $p < 0.001$); better everyday memory was associated with higher recall and better recognition accuracy.

**DISCUSSION**

This study found evidence of ALF in children with IGE. Moreover, children with more severe epilepsy had poorer long-term recognition of newly learned verbal materials. Memory problems displayed in day-to-day life were greater in IGE than in control children and were significantly associated with poorer recall and recognition after long, but not short, delays.

We found that children with IGE had difficulties with recall of information after long, but not short delays, which is typical of ALF. In our study (unlike in Davidson et al., 2007) ALF was not explained by reduced learning efficiency as (1) there was no between-group difference in the number of learning trials, (2) exclusion of participants who did not learn materials to criterion did not eliminate ALF, and (3) on the long delay the IGE participants had deficits not only in recall, but also in recognition of previously learned words. Taken together, our findings suggest that IGE participants have impaired long-term retention and impoverished long-term memory stores.

It is important to note that all IGE children in our study were still being treated for epilepsy and had experienced at least one overt seizure in the last 2 years, whereas 24% of children in the Davidson et al. (2007) study were in remission. Furthermore, we found that greater epilepsy severity was associated with worse long-term recognition. Therefore, the between-study difference in epilepsy status may, in part, explain why the ALF was found only in our study. Nevertheless, whether seizures themselves (or a combination of epilepsy factors) compromised long-term memory formation is difficult to ascertain, as in our study seizure activity was not monitored during the retention period, and several studies of TLE patients (except Jokeit et al., 2001 and Mameniskiene et al., 2006) found comparable forgetting rates during retention periods, regardless of seizure activity (Bergin et al., 1995; Blake et al., 2000; Muhlert et al., 2011). In patients with IGE, ALF may also be secondary to the reduced capacity of neocortical storage sites (critical for long-term memory) due to diffuse neocortical abnormalities beyond the resolution of structural brain scans (Woermann et al., 1998). In addition, AEDs could have contributed to ALF, although most patients were taking monotherapy, which is less deleterious to cognitive functions than polytherapy (Jokeit et al., 2005).

In our study, parental ratings of children’s everyday memory were related to long-term (but not short-term) recall and recognition. This is consistent with previous adult studies that involved patients with left-hemisphere epilepsy focus (Blake et al., 2000) and patients with TEA (Butler et al., 2009). These findings are not surprising, as in everyday life, information frequently needs to be retained and recalled after long periods of time (i.e., days or months, rather than minutes). This pattern also testifies to the ecological validity of paradigms that require recall of information after long delays, and suggests that parental memory questionnaires may be used to screen for ALF.

Notably, prevalence of ADHD in our IGE sample was lower than in previous studies that involved children with epilepsy (Dunn et al., 2003; Dunn & Kronenberger, 2005; Hermann et al., 2007). This was possibly due to a reliance on preexisting diagnoses, rather than formal diagnostic assessments being conducted, which represents a limitation of our study. At present, however, there is no evidence that ADHD increases a risk of ALF.

In conclusion, this study provided evidence of ALF in patients with epilepsy who do not have a temporal lobe seizure focus/pathology: in children with IGE. Our findings are consistent with the consolidation theory, and suggest that factors other than a temporal lobe seizure site, such as epilepsy severity, may play significant roles in consolidation of memories into long-term stores. Clinically, it is important to note that (1) parental reports of everyday memory difficulties are related to long-term (but not short-term) memory recall, and (2) scores obtained on standardized memory tests that require recall of information after short delays do not account for deficits in long-term memory formation. Specifically, children with more severe epilepsy whose parents report higher levels of memory difficulties in day-to-day life are at risk of ALF, which can remain undetected on standardized testing. Given that standardized instruments do not capture this phenomenon, the development of appropriate clinical assessment tools is essential to improve diagnosis and develop treatments.

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The authors thank the children and parents for their participation, Dr. Margaret Charles for her data analysis assistance, and acknowledge a University of Sydney scholarship awarded to Mr. Michael Gascoigne.

**Disclosure**

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.
SYMPOSIUM

Autobiographical Memory in Children with Temporal Lobe Epilepsy

Michael B. Gascoigne,1,2 Mary Lou Smith,3 Richard Webster,4 Belinda Barton,5 Deepak Gill,4 AND Suncica Lah1,2

1School of Psychology, The University of Sydney, Australia
2Australian Research Council Centre of Excellence in Cognition and Its Disorders, Sydney, Australia
3The University of Toronto and The Hospital for Sick Children, Toronto, Canada
4T.Y. Nelson Department of Neurology and Neurosurgery, The Children’s Hospital at Westmead, Sydney, Australia
5Children’s Hospital Education Research Institute, The Children’s Hospital at Westmead and Discipline of Paediatrics and Child Health, Faculty of Medicine, The University of Sydney, Australia

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Abstract

Autobiographical memory involves the recall of personal facts (semantic memory) and re-experiencing of specific personal events (episodic memory). Although impairments in autobiographical memory have been found in adults with unilateral temporal lobe epilepsy (TLE) and attributed to compromised hippocampal integrity, it is not yet known whether this occurs in children with TLE. In the current study, 21 children with TLE and 24 healthy controls of comparable age, sex, and socioeconomic status were administered the Children’s Autobiographical Interview. Compared to controls, children with TLE recalled fewer episodic details, but only when no retrieval prompts were provided. There was no difference between the groups for semantic autobiographic details. Interestingly, the number of episodic details recalled increased significantly from 6 to 16 years of age in healthy control children, but not in children with TLE. Exploratory analyses revealed that, within the group of children with TLE, epilepsy factors, including presence or absence of structural hippocampal abnormalities, did not relate to the richness of episodic recall. Our results provide first evidence of autobiographical episodic memory deficits in children with TLE. (JINS, 2013, 19, 1–11)

Keywords: Episodic memory, Long-term memory, Hippocampus, Seizures, Remote memory, Memory disorder

INTRODUCTION

Temporal lobe epilepsy (TLE) often has onset in childhood and persists into adulthood. Interestingly, distinct neurological and neuropsychological features of this type of epilepsy are not apparent in infants and preschool children, but gradually emerge, as the brain matures and a range of physiological and behavioral manifestations develop. For example, in adults with TLE, memory deficits (learning and/or retention of information over 20- to 30-min delays) are often found to be material-specific. Impaired memory for verbal materials is evident in patients with a left temporal lobe seizure focus (Bell, Fine, Dow, Seidenberg, & Hermann, 2005; Frisk and Milner, 1990; Hermann, Wyler, Richey, & Rea, 1987; Jones-Gotman et al., 1997; Seidenberg et al., 1996). Impaired memory for visual materials tends to be found (albeit less consistently) in patients with a right hemisphere seizure focus (Bell et al., 2005; Chiaravalloti, Tulsky, & Glosser, 2004; Jones-Gotman, 1986; Jones-Gotman et al., 1997; Pillow et al., 1999; Smith and Milner, 1989). Memory deficits are also evident in children with TLE, but the findings relating to material-specificity tend to differ from the findings in the adult literature. In children, verbal memory deficits are often found to be unrelated to laterality of seizure focus (Gonzalez, Anderson, Wood, Mitchell, & Harvey, 2007; Lendt et al., 2002; Mabbott & Smith, 2003; but see: Cohen, 1992; Gleissner et al., 2002), whereas visual memory deficits have been found in children with right hemisphere seizure focus in some (i.e., Beardsworth & Zaidel, 1994; Nolan et al., 2004), but not in other studies (e.g., Gonzalez et al., 2007). Interestingly, a recent longitudinal study revealed a change in the pattern of memory deficits from childhood to adolescence/young
adulthood (Gonzalez, Mahdavi, Anderson, & Harvey, 2012). Initially, verbal memory deficits in children were unrelated to the laterality of seizure focus, but lateralized verbal memory deficits were evident at follow-up, during adolescence or young adulthood. Similarly, in a large cross-sectional study examining verbal memory across a wide age-span (6–68 years) impact of laterality was not evident in children, but was apparent in adolescence/early adulthood (Helmstaedter & Elger, 2009). Inspection of verbal memory scores across childhood and adolescence/early adulthood was indicative of a developmental hindrance (rather than cognitive decline) in patients with epilepsy relative to healthy participants. This hindrance resulted in a gap that widened from childhood to adolescence/early adulthood. Interestingly, the emergence of lateralized verbal memory deficits coincides with the endpoint of functional cerebral plasticity and increased hippocampal activation as children move into adolescence (Ghetti, DeMaster, Yonelinas, & Bunge, 2010). Importantly, for our study, the hippocampus is also proposed to be critical for recollection of past autobiographical memories irrespective of their distance from the present (Nadel & Moscovitch, 1997). Moreover, adults with unilateral TLE have been found to experience difficulties in autobiographical recall (Addis, Moscovitch, & McAndrews, 2007; Viskontas, McAndrews, & Moscovitch, 2000). It is not known, however, whether children with TLE experience similar difficulties.

Autobiographical memory is a complex, uniquely human memory system that contains semantic and episodic components. While the semantic component involves recall of factual autobiographical information, the episodic component relates to the ability to recollect personally experienced events of a known temporality that are rich in contextual details (Tulving, 2002). Moreover, recalled episodes (but not semantic details) are often emotionally salient (Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003), vivid, and associated with the sense of re-experiencing (Hassabis & Maguire, 2007). These two components of autobiographical memory were proposed to be supported by different neural networks (but see Squire, Cohen & Nadel, 1984) and to have different developmental trajectories. While the semantic memories can be supported by neocortical structures, the retrieval and re-experiencing of autobiographical episodes require hippocampal involvement. With respect to developmental trajectories, marked improvements have been documented in the recall of episodic details from childhood to adolescence in the general population (Picard, Reuffueve, Eustache, & Piolino, 2009; Picard, Cousin, Guillery-Girard, Eustache, & Piolino, 2012; Piolino et al., 2007; Willoughby et al., 2012), while increases in the recall of semantic details over the same developmental period have either been small (Willoughby, Desrocher, Levine, & Rovet, 2012) or insignificant (Piolino et al., 2007).

Given the role of the hippocampus in autobiographical memory, studies of TLE patients are particularly relevant, as seizures often (but not always (Cascino, 1992)) emanate from the hippocampus within this patient group (Spencer, Williamson, Spencer, & Msattson, 1987; Spencer, Spencer, Williamson, & Mattson, 1990). Several recent studies of adults with TLE [but not all, (Upton, Corcoran, Fowler, & Thompson 1992)], have found evidence of impaired autobiographical memory, but the patterns of impairments differed. Impairments have been found in the recall of (i) semantic, but not episodic, memories (Barr, Goldberg, Wasserstein, & Novelly, 1990; Lah, Grayson, Lee, & Miller, 2004); (ii) episodic (O’Connor et al., 1999; Noulhiane et al., 2007; Voltzenlogel, Despres, Vignal, Kehrl, & Manning, 2007), but not semantic memories (Addis et al., 2007; St-Laurent, Moscovitch, Levine & McAndrews, 2009; Viskontas et al., 2000; Volzenlogel et al., 2006), and (iii) both episodic and semantic memories (Herfurth, Kasper, Schwarz, Stefan, & Pauli, 2010; Lah, Lee, Grayson, & Miller, 2006). Although it is possible that these inconsistencies are partly due to variations in methods, test protocols, or sample characteristics, they may also be due to between-study differences in hippocampal status, as functional neuroimaging studies have found that the activity of the residual hippocampal tissue was significantly reduced in an autobiographical memory task relative to a control task in pre-surgical patients (Addis et al., 2007). Furthermore, it has been found that the volumes of residual mesial temporal structures were correlated with episodic autobiographical memory scores (Noulhiane et al., 2007). Finally, regional cerebral blood flow in the medial temporal lobe, including the hippocampus, has also been associated with the recall of episodic events from all stages of life (Piolino et al., 2008), providing further support for the notion that the hippocampus is necessary for re-experiencing episodic memories, irrespective of their age (Steinvorth, Levine, & Corkin, 2005).

In addition to hippocampal integrity, other clinical variables (i.e., laterality of seizure focus and epilepsy treatment) have also impacted autobiographical memory recall in adults with TLE, although findings have been inconsistent. Deficits in episodic recall were found to be more severe in patients with a seizure focus in the left (Barr et al., 1990; Leeman, Macklin, Schomer, & O’Connor, 2009; Volzenlogel et al., 2006) or in the right (Lah et al., 2006) temporal lobe. Moreover, in patients who underwent temporal lobectomy, the absence of seizures and being off anti-epileptic drugs was associated with better semantic recall (Lah et al., 2004). In pre-surgical patients with TLE, those on polytherapy have exhibited poorer episodic recall than those on monotherapy (Lah et al., 2006). Finally, as the hippocampus is purported to be critical for both new learning and recall of past personally experienced episodes, it was expected that the correlations between scores obtained on these two types of memory tests will be high. Instead, significant correlations have been found between new learning and semantic autobiographical details (Lah et al., 2006), but not between new learning and recall of personally experienced episodes (Herfurth et al., 2010; Lah et al., 2004, 2006). Finally, seizures themselves may interfere with consolidation (in adults: Blake, Wroe, Breen, & McCarthy, 2000; Mameniskiene, Jatruzis, Kaubrys, & Budrys, 2006; Muhlert et al., 2011; in children: Gascoigne et al., 2012), which in turn could compromise autobiographical memory.
To our knowledge, no study has systematically examined autobiographical memory in children with TLE, although Smith, Elliot & Lach (2006) noted that children with epilepsy (among whom were a large proportion with TLE) reported difficulties recalling events from their lives. This lack of research represents a notable gap, as these children are likely to be at risk of autobiographical memory impairments, which is of clinical significance. In addition, studies involving children with TLE may offer further insight into the role of the hippocampus in autobiographical memory. Of relevance are studies involving patients with developmental amnesia (DA) arising from early bilateral hippocampal damage (e.g., from perinatal hypoxia or ischemia). The memory impairment in these patients is characterized by severely impaired new learning and recall of this newly learned information after short delays (Vargha-Khadem et al., 1997) and poor everyday memory (Gadian et al., 2000; Vargha-Khadem et al., 2003), but relatively preserved semantic knowledge (Gardiner, Brandt, Vargha-Khadem, Baddeley, & Mishkin, 2006). As young adults, these patients tended to recall significantly fewer episodic details, but not semantic details relative to healthy controls on autobiographical memory tasks (Kwan, Carson, Addis, & Rosenbaum, 2010; Rosenbaum et al., 2011). Moreover, in a recent study that examined 24-hr recall of staged events typically encountered during a neuropsychological assessment, Cooper, Vargha-Khadem, Gadian, and Maguire (2011) found that, relative to controls, school-aged children with DA exhibited poorer recall of spatiotemporal and episodic information (while being able to recall the gist of the event). Additionally, within the DA group, smaller hippocampal volume (both right and left) was associated with poorer episodic recall (Cooper et al., 2011).

This study aimed to examine autobiographical memory in children with TLE. We hypothesized that, in a test of autobiographical recall, children with TLE would recall fewer episodic details relative to their healthy control peers. Further exploratory analyses were conducted to investigate potential relationships between performance on the autobiographical memory task, tests of new learning and short-term memory, chronological age, and relevant epilepsy variables (presence of hippocampal abnormality, laterality of seizure focus, surgical treatment, mono versus poly-therapy, epilepsy severity, age at diagnosis, and proportion of life with epilepsy).

**METHOD**

**Participants**

Twenty-four healthy children (the control group) and 21 children with TLE were recruited for the present study. Inclusion criteria were: aged 6 to 16 years at the time of assessment and fluency in English. Exclusion criteria were: (i) Full Scale Intelligence Quotient (FSIQ) < 80; (ii) presence of a major sensory deficit; (iii) significant neurodevelopmental disorder (e.g., autism, but not learning disability or ADHD), or (iv) the presence of another neurological disorder.

TLE participants were recruited from specialist epilepsy programs within three children’s hospitals: The Children’s Hospital at Westmead (Sydney, Australia) and The Hospital for Sick Children (Toronto, Canada) and McMaster Children’s Hospital (Hamilton, Canada). The study was approved by ethics committees of participating hospitals and The University of Sydney. Potential participants with TLE (pre-surgical, post-surgical, and non-surgical) were identified by review of patient files. Electroencephalography (EEG) records, medical history, and imaging data (where available) were reviewed by the treating pediatric neurologists, and only children who met the International League Against Epilepsy criteria for TLE (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) were invited to participate. Clinical data for all TLE participants are summarized in Supporting Table 1.

Of the 21 children with TLE, 13 had seizures emanating from the left temporal lobe (including six postoperative patients), six from the right temporal lobe (including one postoperative patient) while the laterality of seizure focus could not be satisfactorily determined in two participants. A total of six participants who had not undergone surgery had MRI evidence of a hippocampal abnormality, involving either hippocampal sclerosis (n = 2), tumor (n = 1), dysplasia (n = 2), and gliosis (n = 1). Of the seven postoperative TLE patients, six had undergone a resection that involved the hippocampus, as a result of mesial temporal gliosis (n = 3), sclerosis (n = 1), microcortical dysgenesis (n = 1), and dysplasia (n = 1). One patient with TLE underwent a left anterior lateral temporal lobectomy (due to ganglioglioma), which spared the hippocampus. One participant was left-handed. Complex partial seizures were the most common seizure type. Seventeen participants experienced only one seizure type, while four experienced a combination of seizure types. Two participants were not taking any anti-epileptic drugs (AEDs). Twelve were on monotherapy and seven on polytherapy. Six different AEDs were represented within the TLE patient group. One TLE participant was reported to have a diagnosed learning disability; however, no control participant was diagnosed with a comorbid developmental disorder.

Control participants were recruited via word-of-mouth through the peer networks of both TLE and control participants (snowball recruitment). Only children who met inclusion/exclusion criteria, and were free of a history of epilepsy, as per intake interviews with the parents/guardians, were invited to be control participants.

**Measures**

Socioeconomic status (SES) was measured by average years of parent/guardian education. Intelligence (FSIQ; M = 100; SD = 15) was assessed with the two-subtest version (Vocabulary and Matrices) of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler 1999). New learning and short-term memory were evaluated with the Dot Location subtest from the Children’s Memory Scale (CMS; Cohen, 1997) and the Story Memory subtest from the Wide Range
Table 1. Demographic, cognitive, and clinical data

<table>
<thead>
<tr>
<th></th>
<th>Left TLE (n = 13)</th>
<th>Right TLE (n = 6)</th>
<th>Test of significance</th>
<th>TLE (n = 21)</th>
<th>Control (n = 24)</th>
<th>Test of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>12.97 (5.57)</td>
<td>11.26 (5.21)</td>
<td>U = 28</td>
<td>12.29 (2.78)</td>
<td>12.16 (2.80)</td>
<td>t(43) = 0.16 .88</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>7/6</td>
<td>4/2</td>
<td>X^2 = 0.32</td>
<td>0.85</td>
<td>11/10</td>
<td>0.16 .69</td>
</tr>
<tr>
<td>SES (years)</td>
<td>13.50 (15.50)</td>
<td>14.00 (4.88)</td>
<td>U = 37</td>
<td>10.95 (6.45)</td>
<td>10.11 (7.14)</td>
<td>t(43) = 0.41 .68</td>
</tr>
<tr>
<td>FSIQ</td>
<td>94.00 (16.50)</td>
<td>99.00 (27.25)</td>
<td>U = 22.5</td>
<td>95.81 (12.09)</td>
<td>106.46 (10.05)</td>
<td>t(43) = -3.23 .002</td>
</tr>
<tr>
<td>WRAML2 Story Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>7.00 (2.50)</td>
<td>9.50 (4.75)</td>
<td>U = 22</td>
<td>8.76 (2.51)</td>
<td>11.92 (2.15)</td>
<td>t(43) = -4.55 &lt;.001</td>
</tr>
<tr>
<td>Delayed Recall (30 min)</td>
<td>7.00 (3.00)</td>
<td>9.50 (4.00)</td>
<td>U = 19</td>
<td>8.52 (2.44)</td>
<td>11.67 (2.16)</td>
<td>t(43) = -4.58 &lt;.001</td>
</tr>
<tr>
<td>CMS Dot Locations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>9.00 (6.00)</td>
<td>9.50 (7.75)</td>
<td>U = 38</td>
<td>9.48 (3.41)</td>
<td>10.21 (3.49)</td>
<td>t(43) = -0.71 .48</td>
</tr>
<tr>
<td>Delayed Recall (30 mins)</td>
<td>7.00 (5.00)</td>
<td>9.50 (6.00)</td>
<td>U = 27</td>
<td>9.05 (2.97)</td>
<td>10.33 (3.32)</td>
<td>t(43) = -1.36 .18</td>
</tr>
<tr>
<td>Mean number of AEDs</td>
<td>2.00 (1.00)</td>
<td>1.00 (0.00)</td>
<td>U = 24</td>
<td>1.19 (0.75)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age diagnosed (years)</td>
<td>4.00 (4.69)</td>
<td>6.99 (4.70)</td>
<td>U = 22.5</td>
<td>6.21 (3.70)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Proportion of life with epilepsy</td>
<td>68.21% (55.00%)</td>
<td>45.73% (42.00%)</td>
<td>U = 20</td>
<td>0.11 47.88% (29.71%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Comorbid LD (Yes/No)</td>
<td>1/12</td>
<td>0/6</td>
<td>X^2 = 0.5</td>
<td>0.49</td>
<td>1/18</td>
<td>—</td>
</tr>
<tr>
<td>Surgery (Yes/No)</td>
<td>6/7</td>
<td>1/5</td>
<td>X^2 = 1.5</td>
<td>0.32</td>
<td>7/12</td>
<td>—</td>
</tr>
<tr>
<td>Epilepsy severity rating</td>
<td>2.00 (2.00)</td>
<td>3.50 (3.00)</td>
<td>U = 32</td>
<td>2.57 (1.25)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hippocampal abnormality (Yes/No)</td>
<td>9/4</td>
<td>3/3</td>
<td>X^2 = 0.7</td>
<td>0.52</td>
<td>12/7</td>
<td>—</td>
</tr>
</tbody>
</table>

AED: anti-epileptic drug; CMS: Children’s Memory Scale; FSIQ: Full Scale Intelligence Quotient; IQR: Inter-Quartile Range; LD: learning disability; SES: Socioeconomic status; TLE: temporal lobe epilepsy; WRAML2: Wide Range Assessment of Memory and Learning, Second Edition.

Assessment of Memory and Learning: Second Edition (WRAML2; Sheslow & Adams 2003). Age scaled scores were used (M = 10; SD = 3).

Epilepsy Severity

Treating pediatric neurologists completed the Global Assessment of Severity of Epilepsy (Speechley et al., 2008), an instrument which has high test–retest (weighted j = 0.90) and inter-rater reliability (weighted j = 0.85), in addition to good construct validity. When giving a severity rating, neurologists considered the frequency and intensity of seizures, severity of postictal period, injuries during seizures, number and side effects of antiepileptic drugs, and interference of epilepsy or drugs with daily activities. Epilepsy severity was rated from 1 (Not at all severe) to 7 (Extremely severe).

Children’s Autobiographical Interview

The Children’s Autobiographical Interview (CAI; Willoughby et al., 2012) is an adapted version of the Autobiographical Interview (AI; Levine, Svododa, Hay, Winocur, & Moscovitch, 2002), which was originally developed for adults. Children were asked to recall two separate events (specific to a time and place) which they were personally involved in from any period during their lives, except for the preceding month. To aid the selection of appropriate memories, all children were provided with a list containing examples of 18 different life events (such a birthday party or school excursion), but reminded that they were free to recall any event, irrespective of the suggestions contained in the list.

The CAI involved administration of three conditions: Free Recall, General Probe, and Specific Probe. In the Free Recall condition, which was administered first, participants were given up to five minutes to recall as much information as possible about a specific event without any interruptions or prompting from the interviewer. In the General Probe condition, administered immediately after the Free Recall of an event, participants were either given (i) a general prompt to recall any additional details or (ii) to choose and clarify the event if multiple or non-specific events had been recounted during Free Recall. The Specific Probe condition was the final stage of the CAI, administered only once the Free Recall of an event if multiple or non-specific events had been recounted during Free Recall. The Specific Probe condition was the final stage of the CAI, administered only once the Free Recall of an event if multiple or non-specific events had been recounted during Free Recall. The Specific Probe condition was the final stage of the CAI, administered only once the Free Recall of an event if multiple or non-specific events had been recounted during Free Recall.

The recall of both memories was recorded and transcribed (see example in Figure 1). Each memory was scored according to the AI scoring manual (Levine et al., 2002). Two main types of details were identified within each memory: (i) episodic details, that pertain directly to the main episode and (ii) semantic details, representing general autobiographical information that is not integral to the main event. The average score of the two recalled memories was obtained separately for episodic and semantic details for each of the three conditions: (i) Free Recall, (ii) General Probe (Free Recall + General Probe), and (iii) Specific Probe (Free Recall + General Probe + Specific Probe). See Figure 1 for a scored example of a transcribed memory.
Each transcribed memory was initially scored by one experimenter (MG) who had previously completed training by scoring a practice set of memories provided with the AI scoring manual (Levine et al., 2002), achieving correlations ranging from 0.89 to 0.99 with the practice set. Another trained staff member independently scored ten randomly selected memories. Intra-class inter-rater correlations for the composite scores obtained on the CAI were (i) Free Recall: 0.77 and 0.71 for episodic and semantic details, respectively; (ii) General Probe: 0.82 and 0.88 for episodic and semantic details, respectively; and (iii) Specific Probe: 0.98 and 0.75 for episodic and semantic details, respectively.

Procedure

Parents gave informed consent and children gave informed assent for participation in the study. Medical records were reviewed to obtain relevant medical information, which was verified by treating pediatric neurologists. Parents of control and TLE participants were interviewed regarding their child’s developmental and medical history, relevant epilepsy and SES variables, and completed questionnaires about their child. All children underwent a 90-min assessment, conducted by a psychologist, which included a battery of intelligence and memory tests, administered in a set order. The CAI, administered at the end, took approximately 25 min to complete. One interviewer (M.G.) conducted 33 (73%) of the interviews, while the remaining 12 (27%) were conducted by another psychologist (M.L.S.) and other trained support staff. Treating neurologists assessed epilepsy severity in the children with TLE.

RESULTS

Background Demographic, Cognitive and Clinical Variables

The left- and right-TLE groups did not differ on any demographic variables, including: age, sex distribution, and SES (see Table 1). Similarly, scores obtained by left- and right-TLE groups on Story Memory (WRAML2) and Dot Location (CMS) were comparable. Furthermore, the left- and right-TLE groups did not differ on clinical variables, including age of epilepsy diagnosis, proportion of life spent with epilepsy, mean number of prescribed AEDs, surgical history, epilepsy severity rating, presence of hippocampal abnormality or presence of a comorbid neurodevelopmental disorder.

As the left- and right-TLE groups were comparable on all background variables, and to increase statistical power, the two TLE groups, and two TLE participants in whom the laterality of seizure focus could not be satisfactorily determined, were merged into a single patient group and compared to the control group in subsequent analyses. No differences
were found between the TLE and control groups for age, sex, and SES. However, the TLE group had significantly lower FSIQ than the control group. Moreover, the TLE group obtained significantly lower scores than the control group on immediate and delayed recall on Story Memory (WRAML2), but not on Dot Location (CMS; see Table 1).

Although the FSIQ of the TLE group was significantly below that of the control group, FSIQ was unrelated to the recall of autobiographical memory details within the TLE group during either the Free Recall (Episodic: \( r_s = 0.28; p = .22 \); Semantic: \( r_s = 0.07; p = .76 \)), General Probe (Episodic: \( r_s = 0.31; p = .17 \); Semantic: \( r_s = -0.10; p = .68 \)), and Specific Probe (Episodic: \( r_s = 0.27; p = .23 \); Semantic: \( r_s = -0.38; p = .87 \)) conditions. Additionally, Dennis et al. (2009) pointed out that when a clinical group is significantly different from the control group on a variable that is integral to the condition, it is not necessary to control for this variable. Low FSIQ had previously been found to be an integral part of TLE (Hermann, Seidenberg, Schoenfeld, & Davies, 1997); FSIQ < 85 was found in approximately 30% of TLE patients (Helmstaedter & Kockelmann, 2006). Moreover, in our study, the between-group difference in FSIQ could not be attributed to differences in the demographic variables, such as SES, as our groups were well matched on these variables. For these reasons, FSIQ was not used as a covariate in the subsequent analyses.

**Children’s Autobiographical Interview (CAI)**

Total episodic and semantic scores obtained by two groups on the CAI across the three recall conditions are presented in Figure 2. Mann-Whitney U tests revealed that the TLE group recalled significantly fewer episodic details (median = 16; interquartile range (IQR) = 11.00) than the control group (median = 21.8; IQR = 20.88) in the Free Recall condition \( (p = .02; d = 0.67) \). However, no between-group differences in the recall of episodic details were found during either the General Probe \( (p = .07; d = 0.61) \) or Specific Probe conditions \( (p = .46; d = 0.47) \). Furthermore, no between-group differences were found for the recall of semantic details during the Free Recall \( (p = .62; d = 0.03) \), General Probe \( (p = .44; d = 0.09) \), or Specific Probe stages \( (p = .43; d = 0.07) \).

Post hoc calculations indicated that to detect a significant statistically difference between the TLE and Control groups at the General and Specific probe stages of the CAI, with power of 0.80 and \( \alpha \) at 0.05, a total of 36 TLE participants and 59 TLE participants, respectively, would be required.

![Fig. 2. Children’s Autobiographical Interview: number of episodic and semantic details by group and recall condition.](image)

\* \( p < 0.05 \); TLE: Temporal Lobe Epilepsy. Boxes represent the Inter-Quartile Range, which contains data between the 25th and 75th percentiles. The median is represented by a horizontal line within each box. Whiskers represent minimum and maximum values.
Similarly, no differences between the TLE and control groups were found in the proportion of episodic details, relative to semantic details, recalled during either the Free Recall (median = 81.3%; IQR = 27.0% vs. median = 88.0%; IQR = 14.0%, respectively; \( p = .13 \)), General Probe (median = 82.1%; IQR = 27.0% vs. median = 87.5%; IQR = 15.0%, respectively; \( p = .10 \)), or Specific Probe (median = 85.5%; IQR = 11.0% vs. median = 90.6%; IQR = 10.0%, respectively; \( p = .32 \)) conditions.

Due to the absence of between-group differences in the recall of semantic details in all conditions, and episodic details in the General and Specific Probe conditions, and to minimize the number of comparisons, we only undertook further analyses for episodic scores obtained in the Free Recall condition. Given the small sample sizes in these analyses, they should be considered as exploratory.

**Exploratory Analyses**

**Relations with chronological age**

Relations between chronological age and recall of episodic details were separately examined in the TLE and control groups (see Figure 3). A significant correlation was found in the control group (\( r_s = 0.45; p < .05 \)); that is, older children recalled more episodic details. There was no significant correlation for the TLE group (\( r_s = 0.34; p = .11 \)).

**Relations with tests of new learning and short-term memory**

Within the TLE group, relations were examined between the Free Recall of episodic details and scores on standardized tests that required new learning and short-term memory on which significant between-group differences were found. Correlations with Story Memory (WRAML2): immediate (\( r_s = 0.08; p = .72 \)) and delayed (\( r_s = 0.15; p = .50 \)) recall, and Dot Location (CMS): immediate recall (\( r_s = 0.08; p = .72 \)) were small and non-significant.

**Hippocampal abnormality**

To explore the potential relationship between hippocampal integrity and the recall of episodic details in the Free Recall condition of the CAI, TLE patients with an intact hippocampus (\( n = 9; \) median = 16; IQR = 7.50) were compared with those whose hippocampus was abnormal (\( n = 12; \) median = 15.5; IQR = 19.63). A Mann-Whitney \( U \) test showed that the two groups did not differ significantly in the number of episodic details recalled (\( p = .97; d = 0.23 \)).

**Other epilepsy variables**

Mann-Whitney \( U \) tests revealed no significant differences between right-TLE (\( n = 6; \) median = 24; IQR = 22) and left-TLE (\( n = 13; \) median = 13.5; IQR = 9.25, \( p = .11 \); \( d = 0.97 \)) children in the Free Recall of recall of episodic details. Inspection of boxplots and scores for individual participants in Figure 3 suggests that laterality played little role in recall of autobiographical memory. Moreover, correlations between episodic recall and age at diagnosis (\( r_s = 0.20; p = .39 \)), proportion of life with epilepsy (\( r_s = -0.07; p = .39 \)), and epilepsy severity ratings (\( r_s = 0.03; p = .90 \)) were small and not significant.

**Epilepsy treatment**

Children who underwent surgical treatment (\( n = 7; \) median = 17.5; IQR = 11.5) did not differ significantly (\( p = .91 \); \( d = 0.09 \)) from children who did not undergo surgery (\( n = 14; \) median = 16; IQR = 13.38) in the number of episodic details recalled. Finally, no significant difference (\( p = .15 \); \( d = 0.33 \)) was found between children who were on monotherapy (\( n = 12; \) median = 16; IQR = 15.38) compared to those on polytherapy (\( n = 7; \) median = 17.5; IQR = 13).

**DISCUSSION**

In this, to our knowledge, first study of autobiographical memory in children with TLE, significant deficits were evident in the free recall of episodic (but not semantic) autobiographical details. Exploratory analysis suggested that hippocampal abnormalities may not appear to be associated with worse recall of episodic details in the TLE group. Moreover, epilepsy variables (seizure laterality, duration, and severity of epilepsy disorder), treatment variables (surgery, drug polytherapy), and scores on standardized memory tests were not associated with episodic recall. The richness of episodic recall did not improve with age in children with TLE, unlike the healthy control group.

Interestingly, the between-group difference in recall of autobiographical events was not present when children were prompted. This raises a possibility that, within the TLE group, impairments in episodic recall were largely due to...
retrieval difficulties, rather than memory storage. Moreover, episodic recall was not associated with standardized memory test scores, even though it has been proposed that episodic recall and recall of newly learned material are both related to hippocampal integrity. While puzzling, this is consistent with other adult studies that have not reported a significant association between autobiographical recall and standardized memory test scores (Herfurth et al., 2010; Lah et al., 2004, 2006). Moreover, and again contrary to our expectations, no between-group difference in episodic recall was found when children with a hippocampal abnormality were compared with children without a hippocampal abnormality. Together, our findings raise a possibility that other cognitive deficits, such as executive dysfunction, contribute to impaired episodic recall in patients with TLE and/or that contralateral or surrounding ipsilateral brain regions support the functions of the abnormal hippocampus in children with unilateral TLE.

Other epilepsy variables, such as epilepsy severity ratings, lifetime duration of active epilepsy, and age at diagnosis were also unrelated to episodic recall in children with TLE. It is possible that these factors may have a cumulative, but gradual impact on formation and retrieval of autobiographical memories. Thus the effect of these factors may not become apparent until adulthood.

The relationship between chronological age and number of episodic details recalled was somewhat different in children with TLE and control children. Like previous developmental studies (Picard et al., 2009, 2012; Piolino et al., 2007; Willoughby et al., 2012), we found that, within the control group, the richness of episodic recall appeared to increase in older children. While in children with TLE the same trend was observed, the strength of the association between the richness of episodic recall and age was slightly weaker, and did not reach statistical significance. This correlation, however, was medium in size ($r = 0.34$), which suggests that the relation between chronological age and richness of episodic recall needs to be explored in larger samples of children with TLE. Although based on a small number of participants and related to recall of memories from the past, however, our findings are consistent with a large cross-sectional study that compared learning and word recall between patients with chronic TLE ($n = 1156$, aged 6 to 68 years) with control subjects ($n = 1000$, aged 6 to 80 years) (Helmstaedter & Elger, 2009). Patients made much smaller gains in recall of newly learned material during childhood and adolescence in particular, as learning peaked at an earlier age in patients (16–17 years) compared to controls (23–24 years). In addition, lack of significant developmental gains in memory for arbitrarily related word pairs from childhood to adolescence was also evident in another longitudinal study (Gonzalez et al., 2012). Together, these findings suggest that children with TLE “grow into their deficits.” This suggestion raises a possibility that in our study, the lack of between-group differences in episodic recall, despite retrieval support, was due to participants being rather young. This conclusion, however, seems at odds with findings of studies involving patients with DA, where memory deficits were evident in childhood rather than appearing in teenage years (Vargha-Khadem et al., 1997, 2003). Nevertheless, while patients with DA had severe episodic memory deficits arising from bilateral hippocampal pathology, children in our study had mild episodic memory deficits arising from unilateral temporal lobe abnormalities/seizure foci. These milder episodic deficits may not be evident early but are likely to come to light gradually, over the course of episodic memory development, which unlike semantic memory, continues to develop into adolescence.

Our study has several limitations. First, the heterogeneity of the TLE sample is acknowledged. A more homogenous sample of TLE participants would have been preferable, as those in the current study varied with respect to surgical history, laterality of seizure focus and presence of hippocampal lesions. Second, the analyses of the relationship between hippocampal integrity and episodic recall relied on visual inspection by experienced neuroradiologists of clinically obtained MRI rather than quantified structural or functional neuroimaging data, which would provide more precise information about this relationship. It is also possible that the comparatively lower episodic recall scores within the TLE group could be due subtle hippocampal structural or functional abnormalities that could not be detected by visual inspection of the clinical scans. Third, our clinical sample was too small to undertake statistical analyses (such as regression) that would allow us to concurrently examine contribution of different variables on episodic memory. Fourth, it is acknowledged that our findings are based on cross-sectional data, which address the relationship between age and memory development only indirectly. Accordingly, longitudinal studies are needed to yield more precise data about episodic memory development, and factors that may interfere with its development in children with TLE. Fifth, it is unclear whether difficulties in episodic recall were secondary to poor executive or reduced naming skills, which were not measured in our study, but were previously found to contribute to recall of event details in typically developing children (e.g., Piolino et al., 2008). Sixth, while the CAI protocol does not require memories to be dated this information would be useful to further examine the relationship between seizure onset and episodic recall. Seventh, it is acknowledged that some of our null findings should be treated with caution, as the modest sample size limited statistical power to detecting large effect sizes. Replication of our findings in a large sample is warranted. Eighth, our patients were recruited from specialized, tertiary health care facilities, which limits generalizability of our findings. Nevertheless, it is important to note that in patients with TLE seizures are more likely to be difficult to control with medication than in patients with other types of epilepsy. Hence patients with TLE are often referred to specialized tertiary epilepsy facilities. Thus participants of our study may not be dissimilar to other children with TLE. Finally, future studies could examine the impact of other potentially important epilepsy-related factors such as seizure frequency, which has been associated with a decline in hippocampal volume (Fuerst, Shah, Shah, & Watson, 2003) and could
thereby lead to deficits in the recall of autobiographical events (Addis et al., 2007; Noulhiane et al., 2007).

Although with limitations, our study has provided novel findings that are theoretically intriguing and clinically relevant. Theoretically, our findings raise a possibility that the nature of autobiographical memory deficits changes in children with unilateral TLE with age, in a similar manner to changes in memory for new verbal materials previously demonstrated in this patient population (Gonzalez et al., 2012; Helmstaedter & Elger, 2009). Our findings raise a possibility that the contralateral hippocampus or temporal structures that surround the abnormal hippocampus, support autobiographical memory in children, but not in adolescents with unilateral TLE. This issue warrants further examination, ideally using functional neuroimaging. The findings of our study are also of clinical significance. They suggest that older children/adolescents with TLE are at risk of episodic autobiographical memory deficits, which has not been recognized until now. This risk is important, as autobiographical memory has been found to play a significant role in everyday life and adaptive functioning. For example, in adults with TLE poor recall of past autobiographical event details was associated with reduced social problem solving (Sheldon, McAndrews, & Moscovitch, 2011). Thus early diagnosis and intervention that enhances retrieval of memories is likely to be important for children with TLE.

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Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S1355617713000970

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