Memory in Paediatric Temporal Lobe Epilepsy

Sarah Buck

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UCL Great Ormond Street Institute of Child Health

Declaration

I, Sarah Buck, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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“In the garden of memory,

In the palace of dreams…

That is where you and I shall meet”

Mad Hatter

Alice Through the Looking Glass

Abstract

Temporal lobe epilepsy (TLE) is a common form of epilepsy and is frequently associated with memory and learning impairments. Medically intractable and lesion-based TLE occurs in 20-30% of the patients, in which case a surgical intervention is proposed. However, there is a clear gap in knowledge about pre-operative memory status in children undergoing surgery and post-operative memory outcome. It is unclear whether paediatric patients show material-specific memory impairments associated with side of pathology and whether specific memory processes are affected more than others, *i.e*. learning, recall and recognition. Lastly, as opposed to language lateralisation, the neural representation of memory is unknown and memory fMRI has never been explored in paediatric TLE.

The aim of this project is therefore to investigate the hippocampal-neocortical network that is at risk of compromise given learning and recall deficits in paediatric TLE at the pre-operative level in order to contribute to the prediction of outcome after surgery. I developed a neuropsychological protocol and a neuroimaging protocol for the investigation of pre-operative memory functions. The neuropsychological protocol is a tablet-based version of a paired-associate learning paradigm that allows comparisons between verbal and non-verbal memory. I validated this protocol in normally-developing children (N=130, 8-18 years). The neuroimaging protocol is a combined language and memory fMRI task that allows the investigation of the interaction between the two networks within one scanning session. This protocol was also validated in normally-developing children (N=28, 8-18 years). The feasibility of these protocols for clinical assessments was explored in a representative sample of children with TLE who were being considered for surgery (N=6, 12-18 years).

These protocols add value to the diagnosis of memory impairments associated with paediatric TLE and provide a better understanding of pre-operative memory profile at the individual level. The findings also contribute towards the use of memory fMRI in the surgical decision-making process. Combining information from these protocols could provide prognostic indicators of outcome after surgery.

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List of Abbreviations

AED	Anti-epileptic drug
ANCOA	Analysis of covariance
ANOVA	Analysis of variance
ATL	Anterior temporal lobe
BOLD	Blood-oxygenated-level-dependent
CI	Confidence interval
CMS	Children's Memory Scale
DNET	Dysembryoplastic neuroepithelial tumour
EPI	Echo planar imaging
FCD	Focal cortical dysplasia
FIACH	Functional Image Artefact Correction Heuristic
fMRI	Functional magnetic resonance imaging
FSIQ	Full Scale Intelligence Quotient
FWE	Family-wise error
GLM	General Linear Model
GOSH	Great Ormond Street Hospital
HRF	Haemodynamic response function
HS	Hippocampal sclerosis
IFG	Inferior frontal gyrus
IQ	Intelligence Quotient
LI	Laterlisation index
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe
PFC	Prefrontal cortex
PIQ	Performance Intelligence Quotient
ROI	Region of interest
SD	Standard deviation
SNR	Signal-to-noise ratio
SPM	Statistical Parametric Mapping
STG	Superior temporal gyrus
TLE	Temporal lobe epilepsy
VG	Verb generation
VIQ	Verbal Intelligence Quotient
WASI-IV	Wechsler Abbreviated Scale of Intelligence – Fourth Edition
WMS-IV	Wechsler Memory Scale – Fourth Edition

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Chapter 1

Introduction

This chapter provides an overview of the theoretical framework leading up to the current research project. I will first describe the taxonomy of long-term memory and the progressive development of episodic memory. The second part will focus on the effects of early-acquired brain pathology, and more specifically temporal lobe epilepsy, on the development of episodic memory. Neurocognitive impairments and changes in neural representation as a function of brain plasticity will be discussed.

1 Long-Term Memory

"Memory is a gift of nature, the ability of living organisms to retain and to utilise acquired information or knowledge" (Tulving, 1995). Advances have been made over the last hundred years to understand the mechanism of memory and the distinction between multiple memory systems. It is now well understood that memory is not a unitary system and instead is composed of multiple subsystems. Much of the evidence comes from patients with brain damage who exhibit *selective* memory impairment. The taxonomy of long-term memory (Squire, 1987) is displayed in Figure 1.1.

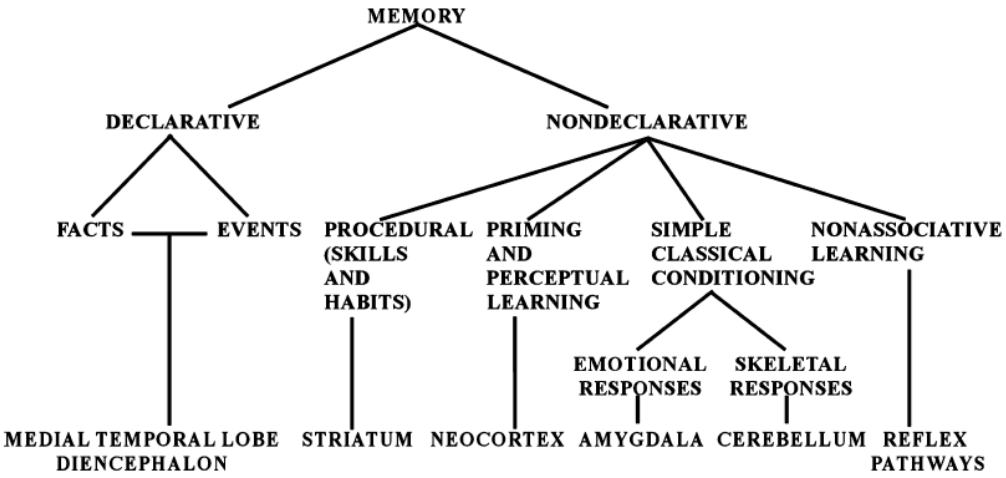


Figure 1.1 Taxonomy of long-term memory (Squire et al., 1987).

1.1 Declarative *versus* Non-Declarative Memory

A major distinction is between declarative and non-declarative memory (Cohen & Squire, 1980). Declarative memory relates to conscious recollection about facts and events, whereas non-declarative is expressed through performance rather than recollection and occurs as unconscious modification of the performance system, such as skill learning.

Evidence from patients with brain pathology has shed light on the fundamental distinction between distinct memory systems. The first evidence came from the famous case of patient H.M. Patient H.M. underwent bilateral removal of the medial temporal lobes to relieve epilepsy after which he exhibited profound

amnesia in the context of preserved intellectual and perceptual abilities (Scoville & Milner, 1957). In addition, Milner demonstrated that patient H.M. was able to learn mirror drawing (a hand-eye coordination skill) in the absence of recollection of having practiced the task (Milner, 1962). This seminal research demonstrated dissociation between procedural (non-declarative) and declarative memory systems. Subsequently, other relevant work emerged on patients with amnesia who exhibit intact priming in the absence of conscious memory (Hamann & Squire, 1997; Stark & Squire, 2000). Priming reflects the facilitation in processing of a stimulus due to its prior encounter and is devoid of intentional and conscious recollection (Graf & Schacter, 1985). As such, priming is a form of non-declarative memory and is not affected in amnesia, contrary to declarative memory. Together, these patient studies shed light on the mechanisms of memory and on the dissociations between declarative and non-declarative memory systems.

1.2 Semantic *versus* Episodic Memory

Tulving's theory of memory draws a distinction between two forms of declarative memory: episodic and semantic memory (Tulving, E, 1972); see Squire & Zola, 1998 for an alternative view). Semantic memory refers to knowledge of facts about the world (*e.g*. the capital of Belgium is Brussels). It allows the acquisition of factual information that are essential for cognitive operations beyond immediate perception and this form of memory is necessary for the use of language (Tulving, 1984). Episodic memory relates to the ability to remember personal past experiences (*e.g*. my 28th birthday in the park with my colleagues), through conscious awareness of recollection of the past.

Evidence from patient studies demonstrates the division of memory systems in the healthy brain. Vargha-Khadem and colleagues described several patients who became amnesic as a result of neonatal hypoxia/ischaemia that produced selective bilateral hippocampal pathology. These patients show great difficulty recalling personal past experiences, but are nonetheless able to acquire large amounts of semantic knowledge (Vargha-Khadem et al., 1997). Evidence from

patients with developmental amnesia therefore demonstrates the distinction between episodic and semantic memory systems.

According to the hierarchical organisation of memory posited by Tulving (1995), cognitive memory (*i.e*. declarative memory) is hierarchically organised into four systems (perceptual memory, semantic memory, working/short-term memory and episodic memory; Table 1.1). Tulving posited that these systems are organised in a hierarchical manner, whereby each system is supported by the operation of the previous systems. As such, episodic memory is dependent on, and support by, the operation of the semantic memory system, whereas semantic memory can operate independently of episodic memory. Tulving's model suggests that despite the fact that these forms of memory are distinct, they are interdependent and relations between and among these cognitive memory systems exist.

Table 1.1 Major categories of human learning and memory (Tulving, 1995).

Major categories of human learning and memory

System	Other terms	Subsystems	Retrieval
Procedural	Nondeclarative	Motor skills Cognitive skills Simple conditioning Simple associative learning	Implicit
PRS	Priming	Structural description Visual word form Auditory word form	Implicit
Semantic	Generic Factual Knowledge	Spatial Relational	Implicit
Primary	Working Short-term	Visual Auditory	Explicit
Episodic	Personal Autobiographical Event memory		Explicit

Tulving's hierarchical organisation of memory maps onto the neural-based model of memory proposed by Mishkin (Mishkin et al., 1997). According to this model, the hippocampus sits at the top of the hierarchy, supporting episodic but not semantic memory, whereas surrounding cortical areas contribute to both (Figure 1.2). As such, selective damage to the hippocampus compromises episodic memory, sparing semantic memory, as shown in patients with developmental amnesia. The model of hierarchical organisation of memory, supported by

neuroanatomical and neurobehavioural studies, suggests distinct neural mechanism supporting episodic and semantic memory systems.

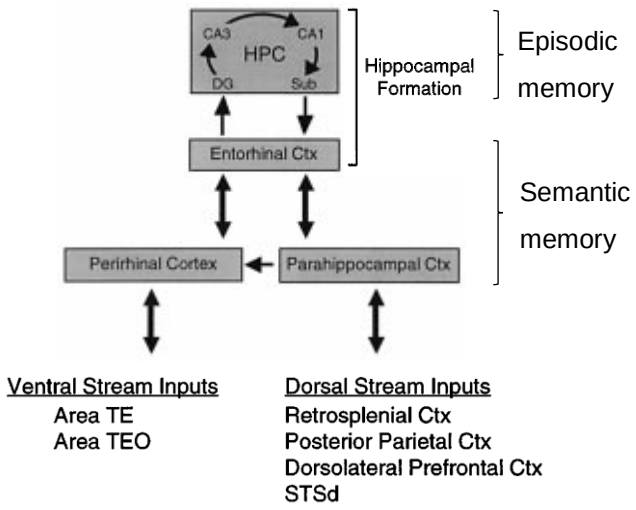


Figure 1.2 Connections of the hippocampal system illustrating its hierarchical organisation, adapted from Mishkin et al. (1997).

2 Episodic Memory

2.1 Stages of Memory

Episodic memory involves the ability to encode, consolidate and retrieve an event with its contextual details. The present thesis focuses on memory acquisition and retention, but not on remote memory or the semanticisation of episodic memory with time.

2.1.1 Encoding

The first stage of memory is encoding, whereby the information is perceived and transformed into a mental representation. According to the encoding specificity principle suggested by Tulving and Thomson, specific encoding operations determine what is stored and influence effective retrieval (Tulving & Thomson, 1973). Craik and Lockhart studied effective encoding operations and

demonstrated that depth of processing at encoding influences subsequent retrieval of information (Craik & Lockhart, 1972). According to this levels-of-processing effect, deep processing of information (*e.g*. encoding the meaning of the item) leads to better subsequent retrieval than shallow processing (*e.g*. encoding the perceptual features of the item). The underlying mechanisms of the superiority of deep over shallow encoding for memory are not fully understood. Generally, studies converge towards the observation that shallow encoding is associated with weaker activation in similar brain regions than deep encoding. Otten and colleagues, for example, showed activation related to deep-encoding in bilateral inferior frontal gyrus and left anterior and posterior hippocampus, whereas shallow encoding was associated with activation in the anterior hippocampus only and in the left inferior frontal gyrus (Otten & Rugg, 2001). Thus, encoding strategies are likely to have an impact on normative memory performance in childhood.

2.1.2 Storage/Consolidation

After the information has been processed and encoded, it is stored for subsequent retrieval through a process of memory consolidation, whereby memory traces are strengthened and stabilised (McGaugh, 2000). New memory traces consolidate slowly over time (Müller & Pilzecker, 1900) and become less vulnerable to interference (Davis & Squire, 1984).

2.1.3 Retrieval

Retrieval is the process by which information that is stored in memory is re-accessed. Tulving first described two processes that accompany retrieval of information: recollection and familiarity (Tulving, 1985). Recollection refers to the reliving of episodes with vivid and detailed retrieval of memories, whereas familiarity is associated with a sense that an item was previously encountered but is devoid of its contextual details. Recollection and familiarity are functionally separate, in that when a person does not remember an event, they may still know something about it (Yonelinas, 1997). It is possible that familiarity and recollection are dependent on different encoding strategies. For example, normal aging is associated with recollection, but not familiarity difficulty, which is related to

diminished use of elaborative and associative encoding strategies (Yonelinas, 2002).

On a neuropsychological perspective, it is difficult to tap into the processes of recollection and familiarity, and instead neurocognitive tools provide measures of recall and recognition to assess these processes, respectively. Recall is necessary for recollection tests, while for recognition, familiarity is sufficient even if recall can occur.

2.2 Psychological Processes of Learning and Memory

Despite clear understanding of the different phases involved in episodic memory, from a neuropsychological perspective it is difficult to tease apart each phase, and instead, cognitive tools often measure the processes learning, recall and recognition. Whereas neuropsychological tools are intrinsically not episodic in nature, they tap into the *features* of episodic memory by assessing the mnemonic processes involved.

2.2.1 Learning

Learning is the improvement of performance with practice (Woodrow, 1946). The question of how we learn has been speculated on for a long time, with Hull and Ebbinghaus as some of the pioneers in the quest for a better understanding. Hull postulated that learning is the acquisition of knowledge through the strengthening of associations (Hull, 1943), and similarly, one basic assumption for Ebbinghaus is that repetition is essential for learning (Ebbinghaus, 1964). Repetition improves memory whereby repeated presentation of information leads to strengthening of its memory trace and allows the participant to recall the information. This is shown in research experiments, with improvement in performance across learning trials, demonstrating a strengthening of the memory traces with repetition of presentation (*e.g.* Roediger & Nestojko, 2015).

2.2.1.1 The Testing Effect

Memory tests assess the level of learning but also improve later retention, a phenomenon known as the testing effect. This effect is observed even when tests

do not involve feedback and thus is not simply a product of re-exposure. In an experiment conducted by Roediger & Karpicke (2006), students who were able to re-study the materials, but who were not being tested, showed poor long-term retention compared to students who were tested (Roediger & Karpicke, 2006b). Such testing effect is thought to be related to practice of the skills that are required for retrieval and thus enhances long-term retention. Whereas re-studying allows re-exposure to the material, testing allows the practice of the skills during learning. As such, according to McDaniel & Fisher, testing improves learning by strengthening the mnemonic traces (McDaniel & Fisher, 1991). In addition, testing can also influence subsequent learning through metacognitive awareness (Yang & Shanks, 2017) whereby participants pay more attention and commit more effort to encoding new information (see Yang et al., 2018 for a review). Together, these studies indicate that retrieval practice clearly influences learning.

2.2.1.2 Paired-Associate Learning

In the experimental and clinical settings, the ability to learn arbitrary associations is often assessed. Associate learning reflects the ability to form new associations between items and bind features into an integrated percept, which is essential to the acquisition of knowledge in children. Moreover, paired-associate learning is involved in everyday ecological scenarios and is representative of the type of learning children face on a daily basis. Associative learning is related to children's experiences of learning, and more specifically to their reading-related skills through the ability to establish links between written and spoken features of information (Mourgues et al., 2016). As such, paired-associate learning, and more specifically, cross-modal association of auditory and visual (and/or spatial) information, is implicated in the binding of disparate elements of classroom teaching/learning and has a role as predictor of learning ability in the educational setting.

In addition, whereas paired-associate learning of semantic items (*e.g*. words and objects) allows semantic linking that facilitates learning, items that are devoid of semantic knowledge (*e.g*. pseudowords and abstract shapes) require the formation of new representations and hence push the limits of new learning. In

this respect, paired-associate learning of non-semantic items may be more closely related to academic achievement. In fact, performance on such test is related to reading skill in school-age children, especially in those with reading difficulties (Li et al., 2009; Warmington & Hulme, 2012). Such paired-associate learning test may be particularly useful in predicting academic achievement in children with learning difficulties, and warrants further investigation.

2.2.2 Recall and Recognition

Information that has been learnt and stored in memory is accessible for later retrieval and children generally exhibit resilience to forgetting (Gordon et al., 2016). After learning has taken place, maintenance of representation occurs as a function of elapsed time (short and long delay) and consolidation. “Episodic” information about the event might be lost at short delays (Ebbinghaus, 1880; Hardt et al., 2013), whereas the “gist” of learnt information (*i.e*. the semantic content) may improve through consolidation and integration into the semantic network (Darby & Sloutsky, 2016; Newell et al., 2009).

Retrieving information from memory can occur through the processes of recall and recognition. Recall refers to the ability to bring back to mind consolidated representations whereas recognition reflects the ability to identify presented items as familiar. Recognition is generally easier than recall, and items that are recallable are intrinsically recognisable (Watkins & Todres, 1978). According to the strength theory, recognition is superior than recall because recalling an item requires stronger memory traces than recognising it (Postman, 963). Similarly, the generate-recognise theory suggests that recall is more difficult because it requires the retrieval of candidate items from memory through recollection followed by a familarity decision, whereas recognition memory only requires the familiarity decision (Hollingworth, 1913).

From an experimental perspective, one can assess the amount of information that is available to recall and to recognition, a short delay after learning. When recall fails, the ability to recognise information may shed light on the mechanism of retrieval, whereby the information is not accessible (recall fails) but is available (the information is recognised). In such event, information is recognisable in the absence of recall. The memory processes of recall and recognition are related

(Watkins & Todres, 1978) although independent, and as such, can be impaired independently of one another (see section 3.3.2, page 15) providing evidence that memory is not a unitary process and is instead composed of multiple memory processes.

2.3 Neural Substrates Subserving Learning and Memory

As mentioned above, memory is not a unitary process and instead comprises of different sub-processes, namely learning, recall and recognition. Episodic memory is supported by a distributed network involving the medial temporal lobe (MTL), but the subregions of the MTL are thought to subserve distinct memory processes. The MTL is composed of the hippocampus, and perirhinal, entorhinal, and parahippocampal cortices (Figure 1.3).

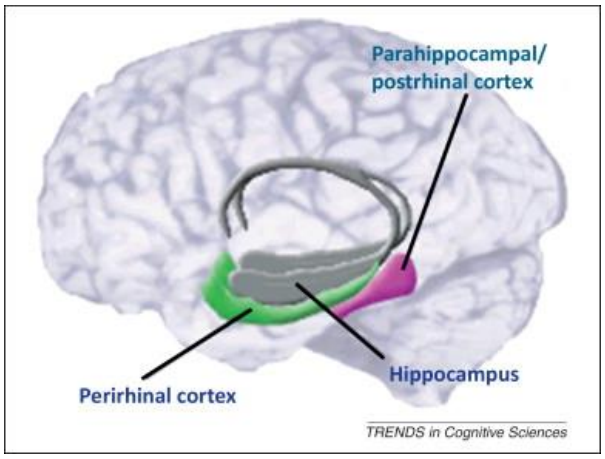


Figure 1.3 MTL regions supporting learning and memory. Image created by Dr Andrew Doherty, Centre for Synaptic Plasticity, University of Bristol, Bristol, UK.

It is well recognised that the hippocampus is critical for the binding of information into a representation for later retrieval, as required in paired-associate learning tasks (Brown & Aggleton, 2001; Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 1994; Hannula et al., 2006; Manns & Eichenbaum, 2006). Patient studies have demonstrated that the effects of lesion to the hippocampus are selective to specific forms of learning/memory, and are apparent on tasks of arbitrary paired-associates (Scoville & Milner, 1957), in which association between the items of a pair is necessary for successful performance. More specifically, the hippocampus

plays a critical role in encoding trial-unique events by binding spatial and temporal features of an episode to form an integrated representation. In this respect, it is involved in forming and retrieving novel associations (Konkel & Cohen, 2009) and allows new memory traces to be processed and consolidated for long-term storage.

2.3.1 Learning – Complementary Learning Systems

According to the complementary learrning systems theory, there are separate and complementary cortical and hippocampal learning systems (McClelland et al., 1995). The cortex is involved in a slow learning system and requires multiple exposures whereby memories gradually integrate in the cortex through repeated encodings, whereas the hippocampal learning system is involved in rapid integration of arbitrary new information. The hippocampal learning system has been demonstrated in animal studies showing the involvment of the hippocampus in rapid encoding of single trials (Bast et al., 2005; Steele & Morris, 1999).

These complementary learning systems are responsible for long-term storage of information in the neocortex through neocortical-hippocampal interaction. Information is initially stored in the hippocampal memory system at the time of initial memory formation and is gradually integrated in the neocortical system through the process of consolidation (Squire, 1992). As such, consolidation occurs as a result of strengthening of memory traces in the hippocampus (Hardt et al., 2013) and of interaction between information presented in the hippocampus and the neocortex (McClelland et al., 1995; Nadel et al., 2012). Temporally-graded retrograde amnesia in patients with hippocampal damage shows evidence of a temporary circumscribed role of the hippocampus in memory retrieval, whereby memory for recent events is worse than for older events (Squire et al., 1975; Sutherland et al., 1987). Representations of events stored in the neocortical system consist in widely distributed patterns of neural activity, and newly acquired information is transferred between the hippocampal system and the neocortical system, promoting learning.

2.3.2 Recall and Recognition

During recall, a fragment of the pattern representing the event from the neocortical system triggers the retrieval of the whole representation via pattern completion supported by the hippocampal system (Rolls, 2016). The hippocampus is therefore also involved in memory reactivation until the representation is fully established in the neocortical system, through repetitive learning (Wickelgren, 1979). In order to recall an event (to bring back to mind a specific past episode), the different features of the event must be processed and bound together. Successful recall therefore requires the use of associative mechanisms, which depend on the hippocampus.

As mentioned above, the dual-process models of memory posit that two distinct processes support memory retrieval, namely recollection and familiarity (Yonelinas, 2002). These processes are anatomically distinct and are supported by different regions in the medial temporal lobe (see Yonelinas, 2002, for a review). Whereas the hippocampus is involved in recollection processes, it is thought that familiarity processes rely on other medial and inferior temporal regions such as the perirhinal and parahippocampal cortices (Eichenbaum et al., 2007; Davachi et al., 2003; Diana et al., 2007).

Studies on patients with focal brain damage demonstrate selective impairment in separate domains, providing evidence of structural and functional dissociation. Patients with developmental amnesia who sustained selective early onset bilateral hippocampal pathology (Vargha-Khadem et al., 1997) exhibit severe and selective impairment in recall memory, in the context of relatively well-preserved recognition memory (Adlam et al., 2009; Baddeley et al., 2001; Patai et al., 2015). The distinction between these memory processes has also been documented in neuroimaging studies, whereby familiarity is associated with parahippocampal activation, and recollection with activity in the hippocampus (*e.g*. Daselaar et al., 2006; Ranganath et al., 2003). These studies therefore document the role of the hippocampus for recall and the involvement of parahippocampal and perirhinal cortices for recognition.

3 Development of Episodic Memory

3.1 Infantile Amnesia

Infantile amnesia, first identified by Freud, refers to the inability to remember personal experiences that occurred during infancy and early childhood (Hayne, 2004; Pressley & Schneider, 1997). As such, young children have very little explicit memory before the age of 2 years. During the second to third year of life, infants begin to encode information at a higher speed thereby creating richer mnemonic representations (Rovee-Collier et al., 1989). In addition, the encoded information decays at a slower rate and remains available for retrieval for a longer period of time (Hartshorn et al., 1998; Herbert & Hayne, 2000). It is thought that during infancy, mnemonic traces decay within days or weeks, whereas older children are able to retrieve memory representations over longer delays. The phenomenon of infantile amnesia raises questions regarding the emergence and the developmental trajectory of episodic memory across the lifespan.

Whereas the neural substrates supporting episodic memory are formed perinatally, they still undergo protracted structural maturation, and particularly, the hippocampus undergoes protracted postnatal structural development (Josselyn & Frankland, 2012). During infancy, these structures therefore lack functional competence until early childhood (Dumas & Rudy, 2010; Nelson, 2000), leading to infantile amnesia. Patient studies provide evidence of late emergence of declarative memory. For example, patients with developmental amnesia sustain hippocampal pathology perinatally but the severe recollection impairments only become apparent in early childhood (Gadian et al., 2000). In typically-developing infants, the structure is formed but the function emerges later. As such, the functionality of explicit memory emerges with experience later in life and becomes superimposed on the neural structure.

3.2 Emergence of Declarative Memory

Tulving proposed a cognitive model to describe the ontogenic development of memory (Table 1.1, page 4) with the emergence of separate forms of memory at different stages of life (Tulving, 1995). According to this model, the cognitive action system (*i.e.* the procedural memory system) evolves first in early infancy followed by cognitive representation system with episodic memory evolving last and developing in later childhood. More specifically, the ontogenic development of semantic memory precedes development of episodic memory.

Within the episodic memory system, distinct emergence of specific memory processes is observed. Whereas visual recognition memory is evident from early infancy (Rose et al., 2004), young children around the age of 2 years begin to form and verbally recall declarative memory which gradually emerges as a function of maturation and experience (Eisenberg, 1985; Hudson, 1991; Peterson, 2002). However, at this stage, these memories remain inaccessible for retrieval at adulthood. The ability to form stable and enduring memories gradually emerges across the preschool years (see Peterson, 2002 for a review), through the development of autobiographical memory. Autobiographical memory refers to the explicit memory of a personal event within the temporal and spatial context (Tulving, 2002) and contributes to one's personal life story, contrary to other episodic memory. Whereas young children show evidence of episodic memory, they do not yet have autobiographical memory.

The gradual emergence of autobiographical memory is related to the skills through the ability to tell others about their experiences thereby reinforcing these mnemonic traces. Language provides an organisational structure in narrative form of personal experiences. This representational function of language appears towards late pre-school years (Nelson, 1993) and contributes to the establishment of autobiographical memory. In the first instant, it is the engagement of parents in talking about the past, or even in talking during the ongoing experience, that contributes to autobiographical memory by aiding the child to organise the representation (see Nelson, 1993 for a review). Another way language contributes to memory is through the effects of reinstatement, which refer to the preservation of memory through re-experiencing parts of the context

within a given period of time. Overall, it is understood that language contributes to the emergence and development of autobiographical memory, by sharing and retaining the memory for personal events.

3.3 Age-Related Changes in Episodic Memory

After the emergence of episodic memory, the function is not fully established and instead developmental changes persist throughout childhood and adolescence.

3.3.1 Learning

Associative learning is fundamental to the acquisition of knowledge in children and has an important role in the educational setting. The ability to learn information over repetitive trials undergoes developmental changes, possibly reflecting the extension of the semantic system with age and the maturation of hippocampal-neocortical interactions. In addition, it is thought that age-related improvement is related to the development of executive functions and working memory through increased efficiency in information encoding (Baddeley & Hitch, 1974; Baddeley, 2000; Baddeley et al., 2011; Harel et al., 2014).

3.3.2 Recall and Recognition

There are distinct developmental trajectories for distinct sub-processes of memory retrieval, namely recall and recognition. Several studies have demonstrated that familiarity judgement is age-invariant after the age of eight onward (*e.g*. Naus et al., 1977, although see Davidson & Hoe, 1993; Newcombe et al., 1977). On the other hand, recollection shows more developmental changes throughout childhood and adolescence (*e.g.* Bjorklund et al., 2009; Ghetti & Angelini, 2008; Jabes & Nelson, 2015), with age-related improvements in recall of contextual details (*e.g.* Ghetti & Angelini, 2008; Ghetti et al., 2011). The maturation of the recollection process is thought to be intrisically related to the development of the ability to bind features of a representation, known to be dependent on the hippocampal system.

3.4 Neural Development of Structures supporting Episodic Memory

Despite early structural maturation of neural substrates, their functional specialisation develops as a function of age and experience, paralleling the protracted developmental trajectory of learning and memory.

The neural basis supporting memory undergoes structural and functional development mediating the development of episodic memory (Sowell et al., 2001). Developmental studies have shown cortical maturation to support learning, and more specifically, cortical thickness across the temporal lobe undergoes protracted changes, with increases then decreases until adolescence (Gogtay et al., 2004; Sussman et al., 2016). In addition, the MTL develops with age, but it is thought that subregions within the MTL develop at different rates (Bachevalier, 2014). Structural differences of the hippocampus are observed until the age of 25 years (Gogtay et al., 2006), however, some substructures of the hippocampus (*e.g.* the CA1) are mature by the age of 2 years. These studies document protracted development of the structure supporting learning and memory until adolescence and adulthood.

The extended trajectory of these neural changes is intrinsically linked to the development of learning and memory in children. For example, Riggins et al. (2015) showed that episodic memory is related to hippocampal volume in normally developing 6-year old children, but not in 4 year olds, suggesting that changes in hippocampal structure may contribute to age-related episodic memory ability (Riggins et al., 2015). In addition, Ghetti et al. (2010) showed stronger correlation between activity in the hippocampus and memory performance in older compared to younger children (Ghetti et al., 2010). Regions of the prefrontal cortex (PFC) also have a particular role in episodic memory (Khul et al., 2008), through the implementation of mnemonic strategies at encoding and retrieval (Blumenfeld & Ranganath, 2007). Structural and functional development in the PFC account for episodic memory improvement (Newcombe et al., 2007), through improvements in strategic processes that support episodic memory (Bjorklund et al., 2009). Together, structural and functional development of these

regions may mediate the development and maturation of episodic memory across childhood and adolescence.

4 Paediatric Temporal Lobe Epilepsy

Temporal lobe epilepsy (TLE) is the most frequent form of focal onset epilepsy, with medial TLE being more prevalent than neocortical TLE (Williamson et al., Epilepsy: a comprehensive textbook). The overall incidence of epilepsy in children ranges between 33 to 82 per 100,000 children per year (Blom et al., 1978; Wirrell et al., 2011), although the incidence of TLE specifically is not clear.

4.1 Aetiology

Paediatric TLE is relatively less clinically and pathologically homogeneous than the syndromes observed in adult TLE, and, for example, mesial pathology is often accompanied with cortical pathology (Bocti et al., 2003; Lee et al., 2010). In children, the most frequent aetiology of TLE are malformation of cortical development (*e.g*. cortical dysplasia), hippocampal sclerosis, and low-grade tumours (Franzon & Guerreriro, 2006). Hippocampal sclerosis affects 10 to 20% of children with TLE and is considered the most frequent lesion in children with refractory TLE (Bourgeois, 1998; Grattan-Smith et al., 1993; Mizrahi et al., 1990). However, other authors claim that focal cortical dysplasia in the temporal lobe is the most common cause of refractory childhood TLE (Bocti et al., 2003; Duchowny et al., 1992).

4.2 Neurocognitive Impairments

The most important cognitive comorbidity of TLE is impairment in episodic memory. Given that the hippocampus plays a major role in the generation and spread of temporal lobe seizures (McIntyre & Racine, 1986) and it is also a critical structure serving long-term memory, including episodic memory (Squire & Zola-Morgan, 1991), impairments in memory and learning are frequently reported in TLE patients. In adults, approximately 70 to 80% of TLE patients exhibit episodic memory deficits related to temporal lobe pathology. In childhood TLE,

episodic memory impairments are also documented (Jambaque et al., 1993), however, studies are lacking. These impairments impede on quality of life of these children and impact daily functioning (Smith & Lah, 2011) and are particularly vulnerable in cases of mesial pathology, such as hippocampal sclerosis, compared to lateral temporal lesions, such as cortical dysplasia (Cormack et al., 2012). The effects of unilateral pathology on lateralisation of memory impairments will be discussed in section 5.2.2.1 (page 31).

Although semantic memory has been poorly studied in childhood TLE, several studies demonstrate that children with TLE are at risk of semantic memory deficits (Cormack et al., 2012; Rzezak et al., 2011; Smith & Lah, 2011). In adults, semantic memory deficits are associated with poor integrity of lateral temporal structures (Koylu et al., 2006) and hippocampal integrity (Davies et al., 1998; Messas et al., 2008), suggesting a role of hippocampal-neocortical interactions for the retrieval of semantic information stored in cortical structures. Impairments in semantic memory include difficulty in category fluency, object naming, word definition, and sentence repetition, some of which may also be associated with language deficits. Language difficulty is sometimes documented in children with TLE, particularly in those with left-side pathology. These difficulties include naming difficulties, limited vocabulary and reading abilities (Jambaque, 2001).

Overall, greater cognitive impairments are documented than in adult TLE (Hermann et al., 2002) and intractable seizures in the developing brain are often associated with neurocognitive impairments beyond the temporal lobe functions. For example, executive dysfunction is also documented in childhood TLE, which may also contribute to memory impairment (Rzezak et al., 2012). These cognitive difficulties contribute to academic underachievement and learning difficulties (Fastenau et al., 2004; Schouten et al., 2002).

4.3 Neurosurgical Intervention for Drug-Resistant Epilepsy

Medically intractable, and lesion-based TLE occurs in 20-30% of the patients (Engel, 1998), in which case a surgical intervention is proposed for the resection of the temporal lobe lesion and the epileptogenic zone which usually encroaches

on the hippocampus (Clusmann, 2008; Radhakrishnan et al., 1998). The purpose of neurosurgical intervention for epilepsy is two-fold: 1) alleviate seizures, and 2) halt cognitive decline associated with ongoing seizures. In paediatric TLE, early surgery is particularly encouraged to halt the cognitive decline over time (Wyllie et al., 1993). Neurosurgical intervention yields seizure freedom in 73 to 100% of children one-year post-surgery (Blume, 1997), and in about 62% of the cases, 5 years post-surgery (Tellez-Zenteno et al., 2005). However, despite favourable impact on seizure control (Clusmann et al., 2004), surgical procedure carries a risk of cognitive deterioration.

4.4 Post-Operative Cognitive Outcome

4.4.1 Cognitive Decline

In adults, left-sided temporal surgery is typically associated with decline in verbal memory (Shermann et al., 2011), as well as in naming (Hermann et al., 1994) and semantic memory (Lambon et al., 2012), whereas right-sided surgery is more frequently associated with non-verbal memory deficits (Vaz, 2004). High inter-individual variability in post-operative memory outcome are documented (Sherman et al., 2011). Greater memory decline is associated with older age at time of surgery, older age at seizure onset (Andersson-Roswall et al., 2010), left-sided surgery, extensive resections (Helmstaedter et al., 2002), ipsilesional memory and language dominance (Binder et al., 2008), and higher pre-operative functions (Gleissner et al., 2002; Miranda & Smith, 2001; Rausch et al., 2003; Szabo et al., 1998; Westerveld et al., 2000).

In children, the effects of temporal lobe surgery on cognitive outcome are less extensively studied. Several studies have documented vulnerability of verbal memory after left temporal resections (Jambaque et al., 2007; Lah, 2004; Szabo et al., 1998), but not others (Gonzalez et al., 2012; Helmstaedter & Elger, 1998; Mabbott & Smith, 2003). It is therefore of great importance to examine cognitive impairments associated with unilateral pathology, as well as the effects of temporal lobe resection on cognitive functions.

4.4.1.1 Functional Reserve and Functional Adequacy

Two models of memory function aim to account for post-surgical cognitive deterioration. According to the *functional reserve* model, memory loss is a function of the capacity of the contralateral temporal lobe to support memory after surgery. The *functional adequacy* model posits that post-surgical memory loss is dependent on the functional integrity of the resected tissue, whereby more deterioration is observed if the resection encroaches on functional tissues.

Both models are supported by neuropsychological findings. However, Chelune posited that the functional adequacy model has a greater role in predicting post-operative memory loss compared to the functional reserve model (Chelune, 1995). Greater cognitive deterioration after surgery is observed in patients with more neurocognitive and structural adequacy prior to surgery than those whose hippocampi are less functional.

4.4.2 Cognitive Recovery

After surgical intervention, seizure cessation and medication reduction can lead to cognitive improvement. Greater functional recovery after temporal lobe surgery is documented in childhood TLE than in adult TLE (Gleissner et al., 2005). After an initial post-operative decline, paediatric patients are reported to recover from their memory deficits and reach pre-operative performance standards by one year after surgery (Gleissner et al., 2005). There is however a big variability in verbal memory outcome, which is related to the integrity of the left temporal lobe.

It appears that recovery in cognitive functions may not be apparent before several years after surgical intervention. Skirrow et al. (2011) demonstrated improvement in intellectual functioning 10 years following surgery in children with TLE, with a gain of about 10 IQ points in 41% of surgical patients compared to relatively unchanged scores in non-surgical patients (Skirrow et al., 2011). This cognitive improvement was associated with seizure cessation and was only seen 6 years after surgery, suggesting a prolonged period for cognitive recovery after temporal lobe surgery.

Subsequently, Skirrow et al. (2015) also reported recovery of memory functions after surgery in the temporal lobes in the same patient cohort as reported in

2011. Interestingly, the improvement was observed in the memory functions subserved by the un-operated temporal lobe, with improvements in visual memory after left-sided resections and improvement in verbal memory after right-sided resections. This phenomenon, known as the “release effect”, relates to the release of cognitive functions which were suppressed by seizures (Helmstaedter et al., 2003). This release effect was observed as a function of post-operative seizure freedom, shorter duration of seizures, and less extensive resections. The former indicates that post-operative recovery is limited by the integrity of the ipsilesionnal temporal lobe which continues to support memory functions (Bonelli et al., 2013). These findings suggest the importance of tailored resection of the temporal lobes and leaving intact critical brain structures that contribute to post-operative recovery of memory functions.

4.5 Assessing Memory for Pre-Surgical Decision-Making

Assessment of cognitive abilities is important for surgical decision-making to predict the potential surgical risks. Such assessment is typically done through a combination of behavioural and neuroimaging investigations and requires specific and developmentally-adapted protocols.

4.5.1 Behavioural Investigation

Neuropsychological assessment includes age-appropriate standardised tests and assesses multiple cognitive domains, including intelligence, language, memory, attention, problem-solving/executive function, visuospatial, and academic skills. These assessments identify relevant cognitive strengths and weaknesses of an individual, provide indication on the lateralisation of language and memory functions, and provide guidance for the prediction of cognitive deficits after surgical intervention.

Neuropsychological evaluation contributes to surgical decision-making in paediatric TLE in several ways. First, it allows characterising the status of memory and learning in relation to different aspects of cognitive function to identify the selectivity of impairment *versus* a global pattern of cognitive dysfunction, including intellectual disability. Second, it establishes the pattern of

lateralisation of function vis-à-vis the focus of seizures and/or locus of lesion. A common interest amongst researchers and clinicians relates to the lateralisation of memory. Clinicians investigate a patient's performance depending on the nature of the material to be learned and memorised. This approach aims to compare how well a patient encodes and retrieves verbal material compared to visual material, and to identify material-specific impairment. Third, the assessment relates selective deficits in learning and memory to the neural systems subserving the mnemonic functions. The association of cognitive domains to specific brain correlates provides indication of the cause of observed cognitive impairments and allows clinicians and researchers to relate cognitive symptoms to underlying brain pathology. Fourth, it permits to identify risks to memory and learning in the presence of unilateral *versus* bilateral disease. In the case of unilateral pathology, neuropsychological assessment provides indication on the functionality of the hemisphere contralateral to the lesion, and can detect possible dysfunction contralateral to the primary seizure focus (Jones-Gotman et al., 2000). Fifth, the assessment predicts learning and memory outcome post-surgery. In addition to contributing to surgical decision-making, early neuropsychological assessment can guide neurocognitive rehabilitation.

4.5.2 Neuroimaging Investigation

Pre-surgical investigation of a patient's functional anatomy surrounding the brain lesion is critical for the surgical approach. As a result of brain pathology, an individual's functional organisation may be atypical and can therefore not be inferred on the basis of typical functional organisation observed in healthy individuals. Brain mapping at the individual-level is therefore critical (Bates et al., 2003; Duffau, 2005).

Intracarotid sodium amobarbital testing (also known as the Wada test) has been used for many years to determine hemispheric dominance for language and verbal memory and to predict post-operative outcome (Wada & Rasmussen, 1960). The Wada test involves injecting amobarbital into the internal carotid artery ipsilateral to the seizure focus to anesthetise one brain hemisphere. After the injection, cognitive functions of both hemispheres are tested to lateralise

functions. This procedure requires full cooperation and causes stress, particularly for children (de Ribaupierre et al., 2012).

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive alterative approach to examine hemispheric dominance (Binder, 2011). Task-based fMRI techniques measure changes in Blood Oxygenated-Level Dependent (BOLD) signal induced by a specific cognitive task. In 1993, it was estimated that over 95% of epilepsy surgery centres were performing the Wada test (Rausch et al., 1993), whereas centres have started to replace this technique with fMRI for the past 20 years (Baxendale et al., 2008). The aim of fMRI is to determine the territories of eloquent tissue that serve the critical functions of memory and language prior to surgical intervention to guide surgical decision-making (Lindquist, 2008).

4.5.2.1 Strengths of fMRI for pre-surgical assessment

In addition to being non-invasive, fMRI holds several strengths for pre-surgical assessment. In contrast to the Wada test, which only provides indication on functional lateralisation, fMRI investigation also provides information regarding intra-hemispheric localisation of critical language and memory sites, and thus identifies all brain regions associated with the performance of a specific task.

For language lateralisation, there are strong correlations between results obtained with the Wada test and fMRI (Binder, 2011). Several studies have demonstrated that fMRI is reliable for language lateralisation, with high sensitivity and specificity, in patients with typical (Bauer et al., 2014) and atypical (Dym et al., 2011) language lateralisation. Detre et al (1998) showed 100% concordance between fMRI and the Wada test in nine patients (Detre et al., 1998). Janececk et al. (2013) showed that when the results is not concordant, fMRI is superior for the prediction of language outcome (Janecek et al., 2013). These findings suggest that fMRI is superior to invasive gold-standard brain mapping techniques.

fMRI is a useful pre-surgical diagnostic tool that can help predict post-operative cognitive outcome. Several studies support the functional adequacy model which suggests that patients with greater ipsilateral than contralateral mesial temporal activation are at greater risk of memory decline after temporal surgery (Binder et

al., 2008; Bonelli et al., 2010; Dupont et al., 2010; Powell et al., 2008). Moreover, when fMRI is conducted, the Wada test does not provide additional predictive value (Binder et al., 2008). As such, the prognostic accuracy of fMRI for the prediction of cognitive outcome is better than with the Wada test (Limotai & Mirsattari, 2012).

4.5.2.2 Limitations of fMRI for pre-surgical assessment

Despite great advances in the technique, fMRI faces several limitations. fMRI detects changes in neural signal which can be as small as 1-5%. Data quality can therefore be reduced due to high levels of "noise" (Parrish et al., 2000) which may depend on several factors including paradigm design and task selection, data acquisition and analysis. In addition, decreases in Signal-to-noise ratio (SNR) are observed as a result of susceptibility artefact which is particularly prominent in the inferior temporal and inferior medial frontal regions (Ojemann et al., 1997). Moreover, fMRI is susceptible to motion artefact as a result of long acquisition time. fMRI detects signal changes in an image over time (*i.e.* changes in neural activity), but head motion can be misinterpreted as relevant change. It has been shown that patients (Seto et al., 2001) and children (Afacan et al., 2016) have particular difficulty remaining still inside the scanner, for whom motion artefacts are therefore particularly susceptible.

As mentioned above, fMRI identifies all brain regions associated with a specific task. However, it is unable to distinguish between essential and participating areas, of which the former are the most important to preserve during surgery. Surgical removal of essential areas, but not necessarily participating areas, will lead to neurological impairments. Limitations related to memory fMRI specifically relate to the lack of robust paradigms with high sensitivity and specificity, and as such, brain activation can vary depending on the nature of the memory task and other cognitive demands related to the task.

fMRI brain mapping is therefore limited by several factors which alter interpretation of fMRI findings. However, in spite of the limitations, fMRI is increasingly used as a clinical tool for the pre-surgical assessment of cognitive functions to locate eloquent tissues and predict outcome. In addition, careful

considerations related to data acquisition and data processing can be implemented to reduce or counteract these limitations.

4.5.3 Identifying Functionality of the Contralateral Temporal Lobe

Global amnesia is documented in a small number of patients after temporal lobe surgery and is associated with undetected contralateral damage to the hippocampus. In those cases, surgical removal of the damaged hippocampus produces bilateral hippocampal damage, therefore causing amnesia.

Pre-surgical assessment of memory is therefore particularly critical to identify covert pathology, for example in the hemisphere contralateral to the seizure focus. Evidence of cognitive impairment may indicate covert pathology that can be related to the neural systems subserving the functions, and in turn provide evidence of the underlying neuropathology. Cases where the assessment points to a locus of pathology that is different from the locus of surgery run a higher risk of suffering from amnesia post-surgery. This observation points to the value of pre-operative neuropsychological assessment to guide identification of locus of pathology and predict outcome after surgery.

fMRI can also provide indication on the functionality of the contralateral temporal lobe by showing evidence of brain activation in the hemisphere contralateral to the structures subserving the function. It is possible, for example, that patients showing greater evidence of functional reorganisation of memory may be at lesser risk of memory impairment after surgery. In this respect, hemispheric specialisation should be investigated.

5 Hemispheric Specialisation

Since Brenda Milner's seminal study in 1971, it is understood that verbal and visual memory depend on left and right temporal lobe regions, respectively (Milner, 1971). This division of labour leads to material-specific impairments after unilateral pathology, with verbal and visual memory dysfunction after left and right temporal lobe pathology, respectively. However, in childhood TLE, the lateralisation of memory impairments is not as clear, which may be understood with respect to the emergence of hemispheric specialisation.

Hemispheric specialisation has been recognised for over a century and consists in the functional specialisation of the left and right hemisphere to subserve verbal and visual functions, respectively. Evidence of such hemispheric specialisation resides in complementary impairments resulting from unilateral brain damage in the mature brain, with drastic impairments in speech and language following left hemisphere damage surrounding the perisylvian areas, and visuospatial dysfunction arising after right-sided damage. However, the emergence of this hemispheric specialisation is not fully understood.

There is evidence to suggest that such hemispheric specialisation is not present from birth and does not appear before the age of 5 years (Vargha-Khadem et al., 2000). Whereas the left hemisphere may be predisposed to subserve language skills, this specialisation is not apparent at birth and instead develops with age, providing evidence of ontogenetic rather than early specialisation (Vargha-Khadem et al., 1994). Ontogenetic specialisation suggests gradual emergence of hemispheric specialisation during development. With this view, language is represented bilaterally in the infant brain, and progressively lateralises to the left with reduced contribution from the right hemisphere.

The emergence of visuospatial abilities, however, may follow a different trajectory. Gingras et al., (2018) demonstrated that prenatal unilateral cortical lesion to the right hemisphere consistently and robustly led to lower visuospatial compared to verbal abilities, suggesting that visuospatial abilities may be prenatally right-lateralised (Gingras & Braun, 2018). The asymmetry in the emergence of hemispheric specialisation for verbal and visuospatial functions possibly resides in the ontogenetic development. As such, infant and young children rely on visuospatial processing in the absence of speech, whereas language develops and matures with experience.

5.1 Factors affecting Hemispheric Specialisation

5.1.1 Brain Plasticity – Functional Reorganisation

With sufficient neural plasticity, additional neural resources in other brain regions, for example in the contralateral hemisphere, will allow the brain to sustain the

compromised functions. Such functional reorganisation is related to greater potential for plasticity following an injury in younger patients. Earlier onsets of seizures can result in the compensatory reorganisation of functions, thereby impeding the normal hemispheric lateralisation process.

According to Lashley (1922), and in accordance with the equipotentiality theory, one hemisphere can compensate for damage in the other regarding specific skills; for example, the right hemisphere can mediate language functions in the event of left hemisphere damage (Lashley, 1922). Similarly, early lesion to the left hemisphere can result in the reorganisation of verbal memory to the right hemisphere at the expense of other cognitive functions. This can result in verbal and visual memory being mediated by a common brain network, thereby causing crowding of functions within the right hemisphere (Lansdell, 1969; Lidzba et al., 2006; Strauss et al., 1990; Teuber, 1967) and in turn resulting in poor performance for both verbal and visual memory.

5.1.2 Effects of Age at Injury

When pathology arises before the age of 5 years, the predisposed hemispheric specialisation will be overridden by extensive lesion and high levels of brain plasticity. Division of labour is therefore not observed, and the damaged brain aims to preserve the functions that are most essential for social and environmental demand, *i.e.* language skills. Early onset pathology and efficient neural plasticity therefore result in a non-specialised hemispheric organisation, and instead, a diffuse representation of cognitive functions (Vargha-Khadem et al., 2000).

5.1.3 Stage of Development at the Time of Pathology

Similar to the effects of age at injury, the stage of functional development that has been reached at the time of pathology plays a role in the pattern of cognitive dysfunction. If a child has already reached a level of hemispheric specialisation once the brain pathology occurs (with verbal and visual memory lateralised to the left and right temporal lobes, respectively), the profile will be lateralised impairment based on the side of pathology. On the other hand, if the pathology occurs prior to the normal emergence of hemispheric specialisation, this will

result in widespread impairment. Early brain insult therefore overrides hemispheric specialisation, depending on the stage of development when the pathology is acquired.

5.1.4 Extent of Neuropathology

TLE is a network disease and epileptogenic activity may affect both sides of the temporal lobe. As such, unilateral mesial TLE is often associated with additional pathology in the contralateral hippocampus (Quigg et al., 1997), and the aetiology of TLE can be seen as manifestation of bilateral disease even in the presence of focal signs restricted to one temporal lobe (Babb, 1991; Halasz, 2016; Quigg et al., 1997).

Moreover, greater extent of neuropathology may be observed in childhood compared to adult TLE. The absence of clear lateralised memory dysfunction in childhood TLE could reflect more extensive neuropathology caused by seizures during early brain development. Grey matter abnormality is in fact observed in extra-hippocampal regions bilaterally in paediatric patients with hippocampal sclerosis and TLE (Cormack et al., 2005). Early onset of TLE can therefore be associated with network dysfunction rather than focal pathology per se.

5.2 Evidence of Hemispheric Specialisation in TLE

The question of hemispheric specialisation emerges in the context of focal epilepsy, whereas non-focal epilepsy affects neural networks globally and in which case the question of hemispheric specialisation is not relevant. In adult TLE, the pattern of complementary impairments caused by unilateral lesions reflects hemispheric specialisation of functions and provides strong clues about the organisation of memory in the healthy mature brain. On the other hand, early onset seizures interfere with the normal process of hemispheric lateralisation (Willment & Golby, 2013) and may result in the reorganisation of memory functions to a larger extent than in older patients (Helmstaedter & Elger, 1998; Gleissner et al., 2005; Willment & Golby, 2013).

5.2.1 Language

5.2.1.1 Behavioural Evidence

For language functions, there is behavioural evidence of hemispheric specialisation in adult TLE who tend to exhibit language impairments, including naming objects, word finding difficulties and auditory comprehension, after left-sided pathology (Bartha-Doering & Trinka, 2014; Mesulam et al., 2013). These deficits arise as a result of a strongly left lateralised language network for verbal concepts and pathology encroaching on the left anterior temporal lobe and left hippocampus (Davies et al., 1998; Drane et al., 2008; Hamberger et al., 2007). Language impairments in adults with TLE in the right hemisphere are less frequent and less severe (Bartha et al., 2004; Bartha et al., 2005; Bell et al., 2003; Field et al., 2000; Hamberger & Seidel, 2003; Oddo et al., 2003; Trebuchon-Da Fonseca et al., 2009), providing evidence of hemispheric specialisation and lateralised impairments associated with unilateral pathology in adult TLE.

In children, however, early unilateral damage usually does not result in severe language impairments. Even though left sided seizures can cause transient speech arrest (Nickels et al., 2012), children with TLE are rarely aphasic (Gleissner et al., 2005). Aphasia is only observed in Landau-Kleffner syndrome, whereby children have developed language functions normally before exhibiting aphasia as a result of continuous bilateral epileptic activity (Landau & Kleffner, 1957). Naming difficulties are, however, sometimes documented in children with left sided-TLE, similarly to the adult TLE cohort, but the severity of deficits appears lesser, and instead children with TLE exhibit a more widespread pattern of cognitive dysfunction. Difficulties in reading skills are also observed, although no difference between left and right TLE is reported (see Lah et al., 2017 for a review).

Other studies have shown no significant language impairments compared to healthy children. Datta et al. (2013) demonstrated no significant difference in language performance in children with and without epilepsy in the temporal lobes (age range 7 and 13 years) on tasks of language production and comprehension. Similarly, Mankinen et al. (2014) showed no significant language impairment in

childhood TLE compared to a group of healthy children (age range 8-15 years) (Mankinen et al., 2014). Together, these findings suggest that early-acquired left-sided pathology does not result in severe language deficits, unlike in adult-onset TLE, providing little evidence of hemispheric specialisation.

5.2.1.2 Neuroimaging Evidence

fMRI studies have shown atypical distribution patterns of language activation (right lateralisation or bilateral representation of language) in about 20 to 33% of adult TLE cases (Adcock et al., 2003; Gaillard et al., 2007; Vingerhoets et al., 2004). However, several others have shown left lateralisation of language in adult TLE similarly to healthy controls (Friedman et al., 1998; Rutten et al., 2002; Cousin et al., 2008), suggesting hemispheric specialisation.

In children with TLE, language activation is weaker and less strongly left lateralised than in healthy children (Yuan et al., 2005). Several fMRI studies provide neuroimaging evidence of functional reorganisation in children with TLE who show atypical language lateralisation. More specifically, Yuan et al. (2005) showed that cortical representation of language is atypical when pathology is acquired before the age of five. Everts et al. (2010) investigated language lateralisation using fMRI in children with and without focal epilepsy (not specific to the temporal lobe) between the ages of 7 and 18 years (Everts et al., 2010). Whereas every child without epilepsy showed left lateralisation, 30% of children with epilepsy showed atypical lateralisation. In addition, the researchers demonstrated no difference in language dominance between children with seizures occurring in the left *versus* right hemisphere. Similarly, Yuan and colleagues documented atypical lateralisation in 78% of children with TLE compared to only 11% in age-matched controls (Yuan et al., 2006). Datta et al. (2013) showed that despite differences in language laterality, children with and without epilepsy do not significantly differ on measures of language abilities, suggesting efficient compensatory reorganisation to support language performance (Datta et al., 2013). Datta et al. (2009) pointed out that typical development of language is hampered in the context of childhood TLE (Datta et al., 2009). These findings demonstrate that children with TLE may show less

evidence of hemispheric specialisation and more occurrence of atypical language lateralisation compared to adults with TLE.

5.2.2 Memory

5.2.2.1 Behavioural Evidence

Behavioural evidence of hemispheric specialisation for memory relies on lateralisation of impairments. In adult TLE, material-specific memory impairments are often reported, with verbal memory deficits in patients with left TLE and visual memory deficits in patients with right TLE (Helmstaedter et al., 2003; Jones-Gotman et al., 2000; Jones-Gotman et al., 2010). However, verbal memory deficits are generally more prominent than visual memory deficits. In addition, standardised tests of visual memory do not always reliably distinguish between left and right TLE (Lee et al., 2002; McConley et al., 2008). Despite methodological limitations, neuropsychological studies demonstrate material-specific memory impairments in adults with TLE, consistent with the side of pathology.

In contrast to adult-onset TLE, material-specific deficits are not as clearly side-dependent in paediatric TLE, and studies show inconsistent findings. Within-group comparisons in two studies show that the left TLE groups are more impaired in verbal compared to visual memory, and the right TLE groups are more impaired in visual compared to verbal memory (Kar et al., 2010; Kibby et al., 2014). Between-group comparisons with healthy controls show that left TLE groups are significantly impaired on verbal memory tasks compared to controls (Cohen, 1992; Engel, 1998; Kibby et al., 2014), and the right TLE groups show significant impairments in visual memory (Cohen, 1992; Engle & Smith, 2010; Kibby et al., 2014). Several studies do not compare patients' performances to a control group (Mabbott & Smith, 2003; Gonzalez & Anderson, 2007; Kar et al., 2010). When comparing the two patient groups together, some studies report more visual memory deficits in the right TLE group compared to the left TLE group for dot location (Kibby et al., 2014) and face recognition (Mabbott & Smith, 2003; Gonzalez & Anderson, 2007; Kibby et al., 2014). However, no differences between the two patient groups are reported for verbal memory. A recent study

by Cormack and colleagues reported a bigger effect of aetiology than side of lesion, where hippocampal sclerosis (HS), but not dysembryoplastic neuroepithelial tumours (DNT), was associated with impairments in delayed story recall tasks regardless of the side of lesion (Cormack et al., 2012).

Few studies control for IQ making it difficult to know whether the memory and learning difficulties reflect global cognitive impairments or selective memory deficits in the presence of preserved intelligence. Whereas studies investigating long-term memory in childhood TLE suggest a tendency for lateralised deficits, more widespread memory impairments are reported than in adults, as both verbal and visual memory are impaired.

5.2.2.1.1 Problems with Standardised Tests

Studies examining material-specific impairments in unilateral brain pathology show inconsistent findings. These inconsistencies could be related to the imperfection of the tests designed to measure lateralised effects, which may not be sensitive enough to the specialisation of the left and right temporal lobes. Several confounds in the memory processes that these tests assess, as well as in the nature of items to remember, may hamper clear comparison between verbal and visual tests.

First, standardised verbal and visual memory tasks often assess distinct cognitive processes, wherein verbal memory is usually being tested through recall and non-verbal (*i.e*. visual) memory through recognition. As previously discussed, recognition and recall are separate memory processes subserved by distinct substructures of the MTL. Second, differences in the modality of presentation of verbal and non-verbal materials could also contribute to inconsistent findings. Verbal tasks are usually presented in the auditory modality (*e.g.* spoken words); whereas non-verbal tasks are presented in the visual modality (*e.g.* designs). Information in the auditory modality is received in temporal order, whereas the visual modality is more prone to configural organisation. With this respect, it is important that stimuli in both tasks are presented in the same sensory modality by, for instance, assessing verbal memory in the visual modality for better comparisons with non-verbal memory tasks. In addition, differences in task difficulty between input modality may hamper clear investigation of lateralisation

of memory dysfunction. Third, studies often compare verbal *associative* memory (*i.e.* word pairs) to *single* item visual memory (*e.g*. complex figures). Distinct neural mechanisms subserve these processes, whereby the hippocampus contributes to associative memory, and other non-hippocampal medial temporal regions contribute to single-item memory (Henke et al., 1999; Eichenbaum et al., 1994; Brown & Aggleton, 2001). The nature of unbalanced standardised tests has made it difficult to investigate lateralisation of dysfunction associated with unilateral pathology. More balanced and controlled paradigms are required to investigate this further.

5.2.2.2 Neuroimaging Evidence

fMRI studies in adults demonstrate functional reorganisation of memory functions, with activation contralateral to the seizure focus (Golby et al., 2002; Powell et al., 2005; Sidhu et al., 2013). However, it has been shown that contralateral reorganisation of memory is an inefficient process which does not allow preservation of memory performance (Powell et al., 2005). On the other hand, Sidhu et al. (2013) demonstrated that ipsilateral reorganisation to posterior portions of the hippocampus successfully supports memory performance (Sidhu et al., 2015). However, contralateral reorganisation can become efficient as a long-term process after surgery. Sidhu et al. (2016) demonstrated that engagement of the contralateral hippocampus 12 months after surgery is associated with better memory performance. These studies demonstrate functional reorganisation (ipsilateral or contralateral) of memory in adult TLE, and indicate that fMRI can be used as a tool to provide evidence of hemispheric specialisation. In addition, there is evidence of relationship between language and verbal memory lateralisation. Sepeta and colleagues (2016) demonstrated that Broca's area and the MTL are co-lateralised in adults with and without TLE. Similarly, Everts and colleagues (2010) showed that language lateralisation is related to verbal memory performance in patients with left TLE. Such co-lateralisation of language and verbal memory provides valuable information regarding hemispheric specialisation.

For childhood TLE, however, there are no fMRI studies investigating memory networks and therefore no neuroimaging evidence of hemispheric specialisation.

It has been shown in adult studies that stronger functional reorganisation of memory is associated with earlier age at onset of seizures (Mechanic-Hamilton et al., 2009; Sidhu et al., 2015), providing assumptions that functional reorganisation may be prominent in childhood TLE. In addition, there is no indication regarding co-lateralisation of language and verbal memory in childhood TLE. This co-lateralisation of functions should therefore be investigated to examine the extent of memory reorganisation and its relation to language laterality. This would provide useful information for the prediction of language and memory outcome after surgery.

These findings from language and memory studies suggest that functional deficits are less lateralised in childhood TLE than in adult TLE, providing less evidence of hemispheric specialisation in the paediatric cohort. In addition, atypical language representation is more prominent in children compared to adults with TLE, however there is a dearth of information regarding functional representation of memory in childhood TLE and its relation to language laterality.

6 Current Research

6.1 Aims

The current study arose from the breadth of research discussed above. The main aim of the current research was to develop experimental tools to provide better investigation of hemispheric specialisation of memory in childhood TLE to optimise surgical decision-making and decrease the risk of memory impairment after temporal lobe surgery. Particularly, the aim was to develop two protocols: a behavioural protocol and an fMRI protocol.

The first aim was therefore to develop a behavioural protocol to assess lateralisation in paediatric TLE, using knowledge of neurobiology of the memory system and respecting models of processes of memory. Such experimental protocol would refine identification of side-dependent impairment in relation to material type, levels of semantic access and input modality in childhood TLE.

The second aim was to develop an fMRI protocol to assess localisation of verbal memory circuits in relation to language laterality. More specifically, the aim was to design a memory paradigm that taps into the hippocampal-neocortical network that is at risk of compromise given learning and recall deficits. Together, these protocols may improve interpretation of findings and optimise clinical applications.

6.2 Overview of Thesis

- Chapter 1 was the introductory chapter that laid the groundwork for the subsequent chapters.
- Chapter 2 will describe the development of the behavioural protocol (the Pair Games) to assess lateralisation of memory.
- Chapter 3 will discuss the findings in a large cohort of typically-developing children who were administered the Pair Games.
- Chapter 4 will discuss the pilot findings in a sample of six young patients with TLE who were candidates for surgery.
- Chapter 5 will describe the development of the fMRI protocol to examine language and verbal memory representations.
- Chapter 6 will discuss the findings in a cohort of typically-developing children who were administered the fMRI protocol.
- Chapter 7 will discuss the pilot findings in a sample of five young patients with TLE who were candidates for surgery.
- Chapter 8 is the final chapter that provides a general discussion about the overall thesis.

Chapter 2

The “Pair Games”: A Test of Learning and Memory

Children with Temporal Lobe Epilepsy often exhibit learning and memory impairments. Neuropsychological assessment characterises and quantifies the extent of these cognitive impairments, however, quantifying memory deficits has been compromised by a lack of adequate instruments. The aim of the present chapter was therefore to develop a diagnostic tool to refine diagnosis of memory impairment and help predict outcome after surgery in the temporal lobe.

1 Introduction

Memory deficits are frequently reported in patients with Temporal Lobe Epilepsy (TLE). Medically intractable, and lesion-based TLE occurs in 20-30% of the patients (Engel, 1998). In such cases, a surgical intervention is proposed for the resection of the temporal lobe lesion and the epileptogenic zone which usually encroaches on the hippocampus (Radhakrishnan et al., 1998). TLE and surgical intervention in the temporal lobe are associated with cognitive impairments, most prominent in the domains of learning and memory. Such cognitive dysfunctions are pervasive and debilitating in childhood TLE and impact the quality of life of these patients.

Neuropsychological assessment characterises and quantifies the extent of cognitive dysfunction associated with TLE, and evaluation of learning and memory is particularly important in this context due to the prominence of memory impairment associated with seizures and/or presence of a lesion in the temporal lobe. As mentioned in Chapter 1 (section 4.5.1, page 21), the contribution of neuropsychological evaluation to surgical decision-making in paediatric TLE is to: 1) characterise the status of memory and learning in relation to different aspects of cognitive function, 2) establish the pattern of lateralisation of function vis-à-vis the focus of seizures and/or locus of lesion, 3) relate selective deficits in learning and memory to the neural systems subserving the mnemonic functions, 4) identify risks to memory and learning in the presence of unilateral *versus* bilateral disease, and 5) predict learning and memory outcome post-surgery. In addition, neuropsychological assessment provides indication on the functionality of the hemisphere contralateral to the lesion, and can detect possible dysfunction contralateral to the primary seizure focus (Jones-Gotman et al., 2000).

These goals are achieved in adults with TLE who most often show a specialised and lateralised pattern of brain organisation (Bell & Davies, 1998; Hermann et al., 1997; Jones-Gotman, 1993; Zhao et al., 2014). On the other hand, focal representation of function and overall pattern of brain organisation is often disrupted in children with early onset of seizures, even in those patients who present with seizures/lesions involving the temporal lobe, leading to a more generalised pattern of cognitive and learning deficits (Cohen, 1992; Cormack et

al., 2005; Cormack et al., 2012; Engle & Smith, 2010; Golouboff et al., 2012; Rzezak et al., 2009).

Such generalised patterns of deficits are caused by multiple factors, including 1) early onset of TLE as a reflection of network dysfunction rather than focal pathology per se (Cormack et al., 2005; Doucet et al., 2015), 2) aetiology of TLE as manifestation of bilateral disease even in the presence of focal signs restricted to one temporal lobe (Babb, 1991; Halasz, 2016; Quigg et al., 1997), 3) the trajectory of learning and memory development may differ based on the involvement of cortical *versus* subcortical mesial temporal lobe pathology (Bell et al., 2013; Mueller et al., 2012).

To overcome some of these issues, and to achieve the goals of an informed and effective neuropsychological assessment outlined above, tests that measure different components of learning and memory in relation to their neural structures are needed. There is a need for the development of assessment tools that are consistent with theoretical concepts of memory processes. In addition, such tools should cater to the age range of the clinical population being investigated, and be sensitive to detecting variations in age differences at test and/or age at onset of the seizure-inducing pathology. More specifically, there is a need to construct tests that address several memory processes and that use measures that tap into these processes. These variables are described below.

1.1 Processes of Learning and Memory

Although epilepsy is a disease of cortical organisation (Kramer & Cash, 2013), it invariably affects subcortical as well as cortical interactions. When epilepsy affects the temporal lobes, targeted and sensitive tests are required to investigate how much of the hippocampal-cortical network is compromised, and, in relation to this, identify which aspects of the memory and learning system subserved by this network are impaired prior to surgical decision-making.

1.1.1 Learning

Paired-associate learning paradigms assess the ability to bind information into a mental representation for later retrieval. The hippocampus plays a critical role in

the binding of disparate elements. More specifically, it encodes trial-unique events by binding spatial and temporal features of an episode to form an integrated representation (Cohen & Eichenbaum, 1993). Supporting this idea, patients with hippocampal damage exhibit impairments in tasks that require relational binding of information (Watson et al., 2013).

1.1.2 Recall and Recognition

Successful retrieval requires the use of associative mechanisms, and in that respect, it relies on the structural and functional integrity of the hippocampal formation (Eichenbaum et al., 1994; Kesner et al., 2005; Konkel & Cohen, 2009; Morris, 2006). Successful recognition in the absence of recall suggests that the information has been encoded and consolidated, and is available for retrieval, but is not accessible through recall (Tulving, 1991). The processes of recall and recognition are supported by distinct neural substrates, with the hippocampal formation supporting recall (Patai et al., 2015) and the parahippocampal and perirhinal cortices supporting recognition (Davachi et al., 2003; Diana et al., 2007; Henke et al., 1999). Testing the processes of recall *versus* recognition in childhood TLE can result in dissociations, and shed light on the cognitive profile of patients and provide information related to the localisation of brain dysfunction. More specifically, this can shed light on the territory of damage to the cortical *versus* subcortical structures.

The intrinsic role of the hippocampus in learning and retrieval and its vulnerability to insults (Lowenstein et al., 1992) reflects the wide range of individual variation both in typical and clinical populations. Moreover, the extended developmental trajectory of hippocampal formation is related to later emergence of episodic memory difficulties in clinical populations, with difficulties sometimes only recognised in school age years (Gadian et al., 2000). The developmental nature of learning and the effects of elapsed time and consolidation on retrieval suggest the importance of characterising impairments related to the distinct processes of learning and recall as a function of age in childhood TLE.

1.2 Measures of Learning and Memory

Adequate measures are necessary to assess how learning and memory processes are affected in patients.

1.2.1 Material Type

Material-specific memory deficits have been reported in imaging and lesion studies (Dalton et al., 2016; Milner, 1971; Golby et al., 2001; Golby et al., 2002; Willment & Golby, 2013), demonstrating that verbal and non-verbal memory systems are functionally separate but interconnected.

Numerous observations in patients with unilateral lesions of the medial temporal lobe (MTL) indicate that memory processes are lateralized according to content. Left-sided lesions interfere with verbal memory processes, whereas right-sided lesions interfere with non-verbal memory processes. However, paediatric TLE studies often investigate lateralisation of memory deficits where verbal memory is tested through recall and non-verbal memory is tested through recognition (*e.g.* Engle & Smith, 2010; Kibby et al., 2014). As mentioned above, distinct neural substrates subserve recall and recognition, hampering the comparison between verbal and non-verbal memory reported in those studies.

Saling introduced the notion of task-specificity which suggests that different memory processes (*e.g.* recall and recognition) assessed with different tasks might be differentially affected in TLE (Saling, 2009), and suggests the need to assess and compare memory processes using comparable tests that are equated in difficulty, each tested in the same modality. Because of the distinct neural substrates subserving the processes of recall and recognition, comparing verbal recall to non-verbal recognition results in different systems being inappropriately compared and compromises the investigation of lateralisation of memory. It is clinically critical to distinguish between recognition and recall-based tasks, and because of the hippocampal involvement frequently associated with TLE, the particular aspects of memory that are at risk may be better assessed with recall tasks. This shows the importance of assessing verbal and non-verbal memory within the same memory process, *e.g.* recall.

1.2.2 Input Modality

In addition, the investigation of lateralisation of memory deficits in paediatric TLE may have been hampered by the confounding effects of input modality. Verbal memory tasks are usually presented in the auditory modality (*e.g*. stories or words read to the patients), whereas non-verbal memory tasks are presented in the visual modality (*e.g*. designs) (Cohen, 1992; Cormack et al., 2012; Engle & Smith, 2010; Kar et al., 2010; Kibby et al., 2014; Mabbott & Smith, 2003).

Words presented in the visual and auditory modalities are processed in separate streams (Penney, 1989), and distinct strategies may be used for the processing of auditory and visual words. Left and right hemispheres use qualitatively different strategies to process words, and sensory modalities may play different roles in conceptual representations (Gainotti, 2014). Information in the auditory modality is received in temporal order, whereas the visual modality is more prone to configural organisation. In this respect, it is important that stimuli in both tasks are presented in the same sensory modality by, for instance, assessing verbal memory in the visual modality for better comparisons with non-verbal memory tasks.

1.2.3 Levels of Semantic Structure

The levels of semantic structure of information have an impact on how well the material is learned and memorised. Pre-existing representations of individual items allow the support of a dual-coding strategy whereby both verbal and non-verbal systems are engaged which enhances the memory trace (Silverberg & Buchanan, 2005). Semantic items are better learned and memorised as a result of more exposures and easier access to pre-existing representations.

Examination of lateralisation of memory impairment in paediatric TLE has been hindered by the confounding effects of levels of semantic structure, whereby standard tests are often composed of items that can be coded both verbally and visually. Standardised non-verbal memory tests may be insensitive to right hemisphere pathology, which generally allow some level of verbal labelling of pictures. Patients with right hemisphere damage may automatically activate the verbal system for the encoding of pictorial information thereby compensating for a

non-verbal memory deficit. The impurity of non-verbal stimuli may therefore hinder the test’s ability to capture impairment in visual memory. Comparing memory performance for non-semantic non-verbal information and verbalisable images may tease apart the nature of impairment in right hemisphere damaged patients. Tests of memory for non-semantic items may be more sensitive to capture lateralised impairment in unilateral brain damage.

In addition, performance on verbal memory tests composed of semantic stimuli is often compared to performance on non-verbal memory tests composed of abstract shapes that provide limited access to semantic representations (Cohen, 1992; Cormack et al., 2012; Kar et al., 2010). Moreover, memory for non-semantic items pushes the boundaries of new learning and, in that respect, may be better predictors of post-operative learning ability.

1.3 A “Purer” Measure of Memory

Paediatric TLE is often associated with a generalised pattern of cognitive dysfunction, involving impairments in learning and episodic memory, but also in semantic memory, intellectual abilities and executive function (Cohen, 1992; Cormack et al., 2005; Cormack et al., 2012; Engle & Smith, 2010; Golouboff et al., 2012; Rzezak et al., 2009). This generalised pattern of impairment may result from a network dysfunction associated with early onset of pathology (Cormack et al., 2005; Doucet et al., 2015). Because of this pattern of dysfunction, clinical tools assessing memory without controlling for the effects of other cognitive processes may have led to an inappropriate designation of impairment in children with TLE. Tests that are highly influenced by the level of general intellectual functioning may have difficulty capturing memory impairments in isolation from other cognitive impairments.

In healthy children, executive function contributes to performance in episodic memory, particularly for recall rather than recognition (Rajan et al., 2014), reflecting the use of strategic processes required to encode and retrieve episodic traces (Schneider & Pressley, 1997). As a result of this contribution, memory impairments in childhood TLE are partially explained by executive dysfunction (Rzezak et al., 2012). This suggests the importance of using tools that enable a

better isolation of learning and memory impairments in order to identify the extent of hippocampal involvement in the cognitive profile of TLE for a better prediction of memory outcome after surgery in the temporal lobe.

1.4 Aims

The aims of the present chapter are to:

a) Develop a diagnostic tool that incorporates the critical domains discussed above by designing a paired-associate learning test for the assessment of hippocampal learning and memory systems that is consistent with theoretical knowledge of neural substrates of recall *versus* recognition and is sensitive to the lateralisation of memory deficits in childhood TLE.
b) Examine the contribution of intellectual functioning in performance on the Pair Games.
c) Examine test validity and reliability of the construct.
d) Standardisation of raw scores in order to provide normative data.

2 Methods

2.1 Participants

One hundred and thirty typically-developing children and adolescents between the ages of 8 and 18 years were recruited for the study (*M*=13 years, *SD*=3). These children were approached through East London schools, and were all English-speaking with no history of psychiatric or neurological disorder. These exclusion criteria were identified with a screening questionnaire completed by parents. Participants were not excluded based on learning disabilities, such as dyslexia or ADHD, in order to provide a better representation of the general population. In the full cohort, 5 children had learning difficulties (attention difficulties, N=2 and dyslexia, N=3), but nonetheless had normal IQ. Informed written consent was obtained from parents for participants under 18 years old, and from participants themselves if they are 18 years old. The cohort was composed of 30 males and 100 females. There was generally more interest from

females than males in participating in the study, and obtaining a balanced sample was difficult.

2.2 Socio-Economic Status

Socio-economic status was determined based on the participants’ postcode using The Index of Multiple Deprivation from the UK Department for Communities and Local Government . Deprivation deciles range from most deprived (score of 1) to least deprived (score of 10). Participants in the present cohort had SES scores across the whole range (*M*=4, *SD*=2, *min*=1, *max*=10).

2.3 Neuropsychological Assessment

General intellectual functioning was assessed using the Wechsler Abbreviated Scale of Intelligence – Fourth Edition (WASI-IV).

Memory ability was assessed using the Children’s Memory Scale (CMS), which is a widely used standardised diagnostic tool for children. This test is composed of several subtests and provides measures of verbal and non-verbal learning and memory. For the purpose of this study, only two subtests were administered: The Dot Locations and Word Pairs. The Word Pairs subtest assesses the ability to learn a list of pairs of words over three consecutive trials, whereby the examinee is presented with the first word of each pair and is asked to recall the second word (cued recall). In the delayed test, following a 30-minute delay, the participant is asked to retrieve as many pairs as possible through free recall, and is then asked to make yes/no recognition judgments to word pairs to indicate whether they were part of the list that was learned earlier. The Dot Locations subtest evaluates the ability to learn the spatial location of several dots over three consecutive trials. After a 30-minute delay, the participant is asked to recall those locations again by placing the tokens in the grid.

In this chapter, the neuropsychological properties of the Pair Games paradigm are compared with those obtained from the subtests of the CMS.

2.4 Development of the Pair Games

2.4.1 Paired-associate Learning

The paired-associate paradigm adopted here compares the learning and recall of pairs of items presented in the auditory or visual modality across three learning trials. The paired-associate learning paradigm along with retrieval through recall (rather than recognition) is considered to be dependent on the integrity of the hippocampus (see Chapter 1, section 2.3.2, page 12). The Pair Games is composed of five subtests, controlling for several variables to allow systematic comparisons between them (Table 2.1). These variables are material (verbal *versus* non-verbal), modality of presentation (auditory *versus* visual), and conceptual component of items (semantic *versus* non-semantic). The five subtests consist of paired-associate learning of Spoken Words, Written Words, Objects, Abstract Designs, and Pseudowords. The remainder of the stimulus categories from Table 2.1 were not developed because of the difficulty retrieving sounds through the process of recall. Sounds that can be labelled are not remembered by their modality of input (*i.e*. audition). A sound that does not have a label, or cannot be repeated (backward speech which cannot be articulated by the human vocal chords) cannot be easily remembered. However, the five stimulus categories selected for the development of the Pair Games allow comparison between the three variables of interest.

Table 2.1 Overview of the experimental paradigm.

			Material	
		Concept	Non-verbal	Verbal
Modality	Visual	Semantic	Objects	Written words
		Non-semantic	Designs	Written pseudowords
	Auditory	Semantic	Meaningful sounds	Spoken words
		Non-semantic	Non-meaningful sounds	Spoken pseudowords

2.4.2 Stimulus Material

The stimuli with access to semantic labels (*i.e*. objects and written words) were selected from the MRC Psycholinguistic Database (Wilson, 1988), and are matched to each other on age of acquisition (Kuperman et al., 2012), verbal frequency (Brown, 1984), word length, concreteness, familiarity and imageability.

A total of 120 word stimuli were selected for the word tasks; 60 stimuli were used for the Spoken Words task and 60 others were used for the Written Word task.

For the Object task, 60 object stimuli were selected from Snodgrass’ original dataset (1980) based on concept familiarity and visual complexity. For these stimuli, concept familiarity ranged from 1.4 to 4.95 and visual complexity ranged from 1.10 to 3.90 on a 5-point rating scale (where 1 indicates simple and 5 indicates very complex).

The pseudoword items are composed of monosyllabic and bi-syllabic pronounceable non-words and are matched to the words in terms of the number of syllables. The design stimuli are composed of black and white abstract, but reproducible, line drawings.

The stimuli which compose each subtest of the Pair Games (versions A and B) are presented in Appendix A (page 311). Each task is composed of 30 stimuli, 20 of which were used to create 10 pairs, and the remaining 10 used as distractors for the recognition task (see section 2.7.3, page 49). Amongst the 10 pairs, 8 are composed of unrelated items (hard pairs) and 2 are composed of related items (easy pairs).

2.5 Two Parallel Versions

For each of these subtests, two versions were created using different stimuli to enable administration of parallel versions to the same participants at two different time points (*e.g.* before and after surgery). The stimuli selected for Spoken Word, Written Word, and Object subtests are equivalent across the two versions. No significant difference in performance between the versions (A *versus* B) was

observed, $F_{(1,49)}$=0.337, p=0.564, thus allowing for a comparable assessment across two time points.

2.6 Tablet-based Application

An application was developed using the MIT App Inventor 2 software for the presentation of the stimuli and the recording of the responses. Administering the memory subtests with a tablet makes the testing procedure more engaging and child-friendly, and also allows a more controlled administration process.

2.7 Learning and Memory Processes

2.7.1 Learning

The list of 10 stimulus pairs was presented to the participants who were asked to listen/look carefully to remember the pairings. The participants were then presented with the first item of each pair and were asked to try and remember the item that went with it. Each pair was presented individually for 5 seconds during which the participants were asked to click on the stimulus that they preferred (Figure 2.1A). This was to ensure the encoding of each pair within each subtest, and to use the same procedure across the 5 subtests. After the last pair of the list was presented, the participant was immediately presented with the stimulus appearing on the left hand side of the screen for each pair and asked to recall by drawing (for non-verbal items) or writing (for verbal items) the stimulus that was paired with it (Figure 2.1B). This encoding-cued recall cycle is repeated 3 times in a row for each subtest to establish a learning curve for each participant on that subtest. No feedback was given on their performance.

A pseudo-random response order was used to avoid a recency effect, whereby last items of the list are better retrieved. To achieve this, the items that were presented last during encoding were not presented at the beginning of the retrieval phase. This way, immediate recall of the last items of the list is prevented.

The paradigm involves two measures of learning: learning average and learning gain. The learning average score in the Pair Games is measured by averaging performance from the three consecutive trials. It has been argued that learning should be measured as a gain score from initial to last performance (Woodrow, 1946). In that respect, we define the learning gain as the extent of increase in the acquisition of stimulus pairings over consecutive trials. This learning curve is thought to be affected by testing, wherein testing studied items after each learning phase increases later delayed recall, compared to repeated study without testing (Potts & Shanks, 2012; Roediger III & Arnold, 2012). The gain in learning refers to the increase in performance from the first to the third trial and is measured by subtracting performance at trial 1 from performance at trial 3.

2.7.2 Delayed Recall

A final cued recall trial is administered after a 15-minute delay, where participants are presented with a cue, *i.e.* the first stimulus item of the pair, and are asked to remember the item that was paired with it. This is performed for each pair of each subtest. During this delay period, the learning phase of another task takes place.

The measure of delayed recall refers to the amount of learned information at trial 3 that is forgotten after a delay, and is measured by subtracting performance at the delayed trial from performance at trial 3. A negative score therefore indicates a loss of information. This score is therefore computed with consideration of prior learning by taking into account how much information was previously learned in order to fully characterise delayed recall ability.

2.7.3 Delayed Recognition

In the forced-choice recognition stage, participants are presented with the first stimulus of each pair (*i.e.* the cue) and asked to pick from 3 choices the target associate that was paired with the cue (Figure 2.1C). Amongst the 3 choices, there are 2 distractors: 1 new stimulus and 1 familiar stimulus that was among the list to be remembered, as part of a different pair. With this paradigm, the distractors cannot be rejected purely on the basis of familiarity, and recall of the association is required to make recognition judgments. Such associate-recognition tasks are thought to rely on both familiarity and recollection processes

(Yonelinas, 2001), and in that respect, are more sensitive to the functionality of the MTL than standard item-recognition tasks.

Because of the response options, recognition is easier than cued recall by its very nature. Examining recognition after recall therefore allows the investigation of retrieval of information that is encoded and available but that was not previously accessible through recall. The measure of recognition accuracy refers to the amount of information that is successfully recognised after accounting for false alarms. This measure is obtained by subtracting familiar and intrusion errors from the correctly identified targets. With these three response options, chance recognition accuracy is 33%.

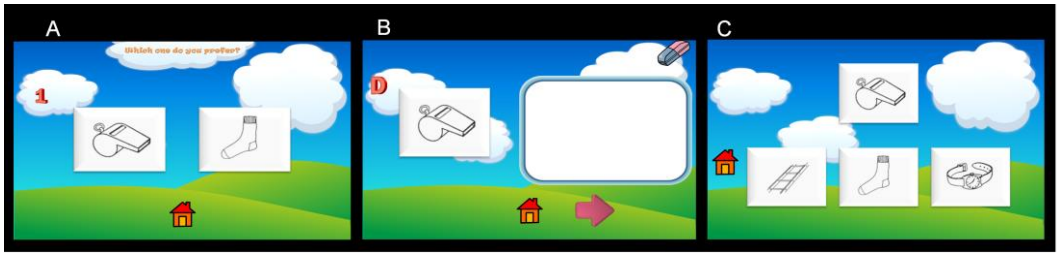


Figure 2.1 A. Encoding. B. Cued Recall. C. Recognition.

2.8 Procedure of Administration

The administration of the 5 subtests is counterbalanced between and within material type (verbal and non-verbal) in order to prevent interference, and the order of administration of the tasks was randomised between participants.

The administration of the whole paradigm took about 1 ½ hours and took place either at the UCL Great Ormond Street Institute of Child Health or at the participant’s school.

2.9 Statistical Analyses

Statistical analyses are carried out to investigate the psychological properties of the Pair Games, in comparison to the standardised measure of memory *i.e.* the CMS. This includes examination of validity and reliability of the paradigm.

Analyses of variance with repeated measures were performed, with a 5 (subtest: Spoken Words, Written Words, Objects, Designs, Pseudowords) x 3 (trial: one to three) design. Other statistical analyses in this section include partial Pearson correlations, factor analysis, and Cronbach’s alpha. Analyses are adjusted for age and intellectual functioning FSIQ, where appropriate.

Performances on the CMS were examined with repeated measures ANOVAs, with a 2 (subtest: Dot Locations and Word Pairs) x 3 (trial: one to three) design. Analyses are performed on raw data, rather than on age-controlled standard scores, in order to be able to capture age-related differences.

3 Results

3.1 Neuropsychological Assessment

The WASI-IV provided measures of intellectual ability for full scale IQ (*M*=104, *SD*=10), verbal IQ (*M*=106, *SD*=10), and performance IQ (*M*=100, *SD*=11). No participants had standard scores below 70. Memory ability, assessed using the CMS, provide measures of verbal learning (*M*=92, *SD*=17), verbal delayed recall (*M*=96, *SD*=15), non-verbal learning (*M*=103, *SD*=15) and non-verbal delayed recall (*M*=104, *SD*=14). The range of memory scores is larger than for IQ scores, as illustrated in Figure 2.2.

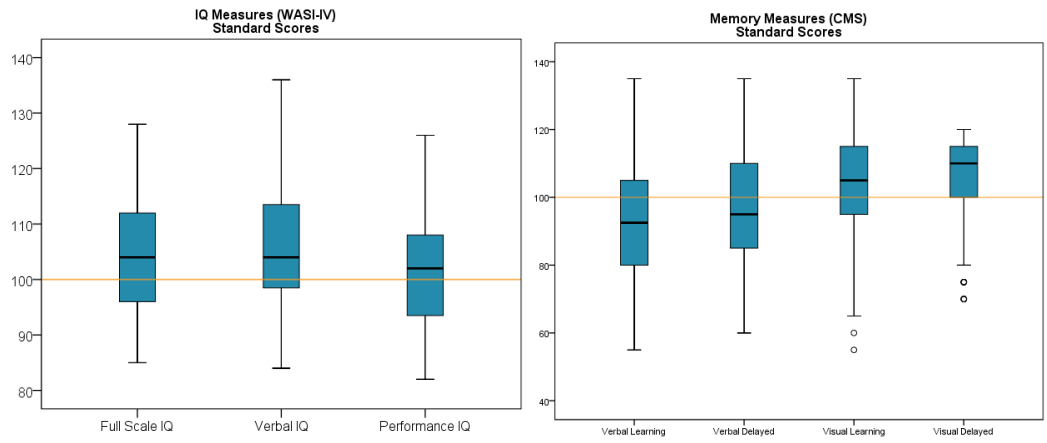


Figure 2.2 Standard scores on measures of IQ and memory.

All children successfully completed all subtests from the Pair Games, as well as the two subtests selected from the CMS. Table 2.2 illustrates memory performances for each subtest as the average percentage correct recall over the three trials. Figure 2.3 is a boxplot representation of the distribution of performance for each subtest and illustrates large variability across individuals.

Table 2.2 Descriptive statistics for memory scores across subtests (%).

	Subtests	Mean	SD	Min	Max
Pair Games	Spoken words	61	21	10	100
	Written words	66	25	7	100
	Objects	65	23	0	100
	Designs	47	20	7	93
	Pseudowords	41	23	0	97
CMS	Dots	85	13	25	100
	Word Pairs	56	18	0	93

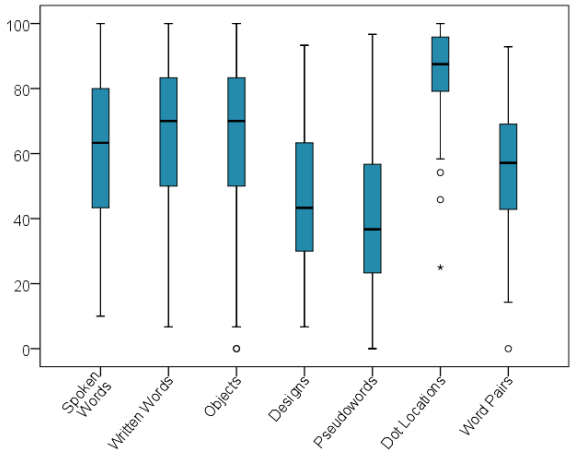


Figure 2.3 Boxplot of distribution of performance across subtest (%).

3.2 Capturing a Wide Range of Abilities

The ability of the Pair Games to capture a wide range of abilities was verified by calculating the percentage of participants with floor and ceiling performances in each subtest of the Pair Games.

A floor performance is when the score achieved at the third trial is 0%, in which case the task is too difficult. A ceiling performance is when the performance at the first trial is 100%, in which case the task is too easy. Table 2.3 illustrates the percentages of participants who demonstrate these effects for each subtest, and suggests that these extreme scores are relatively infrequent. This finding indicates that the Pair Games is able to capture a wide range of abilities and can reflect the high variability in performances across patients.

Table 2. Proportion of floor and ceiling effects for each subtest of the Pair Games (%).

Task	Floor effect	Ceiling effect
Spoken words	0	0.8
Written words	0.8	5.5
Objects	2.3	2.3
Designs	0	0
Pseudowords	3.2	0

Similar analyses were conducted for the subtests of the CMS. There seems to be a high percentage of participants obtaining a ceiling effect on the Dot Locations subtest, with 22% of children obtaining 100% correct performance at the first trial. This finding suggests that the task may be too easy (Table 2.4A). This ceiling effect was further explored in different age groups, and results suggest that the percentage of participants obtaining at or near ceiling scores is high even in younger children (Table 2.4B).

Table 2.4 A. Percentage of floor and ceiling effects for each subtest of the CMS (%). B. Percentage of ceiling effects for Dot Locations in three age groups (%).

A

Task	Floor effect	Ceiling effect
Dot Locations	0	22.2
Word Pairs	0.8	0

B

Age group	Ceiling effect
8-11 years	15.8
12-15 years	14.3
16-18 years	37.2

3.3 Test Validity

3.3.1 Concurrent validity

Concurrent validity is the correlation between a test and a validated tool that measures a different but related construct. Performance on the Pair Games was compared to intellectual functioning measured by WASI-IV. Correlation analyses with measures of general cognitive ability provide an estimate of the degree that intellectual functioning accounts for memory and learning ability in typically-developing children.

Table 2.5 illustrates the correlations between the learning scores of the Pair Games subtests and WASI-IV measures. The findings indicate that learning and memory skills are positively correlated with intellectual functioning. However, these correlations are low to moderate, suggesting that intelligence has a small to moderate impact on children’s memory ability.

The subtest learning scores from the CMS were also compared to IQ scores. Fisher’s tests were computed to compare correlations between the subtests of the Pair games and the CMS’s Word Pairs task with FSIQ. Results show that the Word Pairs scores are more strongly correlated with FSIQ than the Pair Games is (p<0.06), suggesting that the CMS subtest is more closely related to intelligence than the Pair Games is. Performance on that subtest may be more dependent on intellectual functioning than the comparable subtests of the Pair Games.

Table 2.5 Correlation coefficients between learning and intelligence scores.

		Verbal IQ	Performance IQ	Full Scale IQ
Pair Games	Spoken words	0.20*	0.21*	0.24**
	Written words	0.21*	0.18*	0.23**
	Objects	0.16	0.26**	0.25**
	Designs	0.21*	0.24**	0.28**
	Pseudowords	0.23*	0.28**	0.31**
CMS	Dots	0.12	0.30**	0.25**
	Word Pairs	0.40**	0.38**	0.47**

** Correlation is significant at the 0.01 level (2-tailed)
* Correlation is significant at the 0.05 level (2-tailed)

3.3.2 Convergent Validity

Convergent validity is the degree to which two measures that are assumed to measure the same construct are related. We can explore convergent validity between the CMS and the Pair Games tests and assess to what extent they measure the same construct of learning and memory. Correlation analyses were computed between the tests, with FSIQ partialled out (Table 2.6). Moderate correlations are found between the subtest scores involving cued recall from the Pair Games and Word Pairs from the CMS (p<0.001). Low correlations were found between the subtest scores of the Pair Games and Dot Locations from the CMS (p<0.030).

Fisher’s tests were computed to compare coefficient correlations and demonstrate that the results of the Pair Games are more strongly correlated with those of the Word Pairs subtest than those of the Dot Locations subtest (p<0.08). This is found for all subtest scores of the Pair Games apart from the Objects (p=0.47) and Pseudowords (p=0.68) subtest scores. Higher correlations with the Word Pairs subtest than with the Dot Locations subtest may be related to the fact that the latter is a measure of spatial memory. In addition, the memory load is greater in the paired-associate tests, wherein each item is paired with another item requiring the binding of the two items. On the other hand, the Dot Location test requires the binding of the same items with a different location, thereby reducing the load. These correlations indicate convergent validity with the CMS, particularly for measures that involve cued recall.

Table 2.6 Correlation coefficients between Pair Games and CMS scores.

	Dot Locations	Word Pairs
Spoken Words	0.22*	0.39**
Written Words	0.19*	0.46**
Objects	0.29**	0.36**
Designs	0.27**	0.44**
Pseudowords	0.35**	0.31**

** Correlation is significant at the 0.01 level (2-tailed)
* Correlation is significant at the 0.05 level (2-tailed)

3.4 Test reliability

Reliability analysis was computed on the Pair Games paradigm to determine how closely related the subtests are and how strongly each subtest is associated with the memory component that the paradigm measures. An exploratory factor analysis was performed to understand the structure of the subtests from the two paradigms. Cronbach’s alpha was then calculated on the Pair Games paradigm to assess internal consistency of the construct.

Exploratory factor analysis consists of separating the variables into factors based on statistical measures. A factor loading is produced for each subtest of the two paradigms, *i.e.* the Pair Games and the CMS, as an indication of how strongly each subtest is associated with the factor. The principal-axis factoring method was used with direct oblimin rotation to assess the factor structure. Eigenvalues greater than one were used as a threshold to determine the number of factors to retain. The analysis yielded only one factor with 53.35% of total variance explained. Sampling adequacy measured by the Kaiser-Meyer-Olkin (KMO) index was 0.86, and Bartlett’s Test of Sphericity was significant ($p<0.001$), both indicating the appropriateness of interpreting factor analysis. Table 2.7 presents the factor loadings on the factor for each subtest, and demonstrates that the factor loadings for the subtests of the CMS are lower than for the subtests of the Pair Games. Only 19% of variance in Dot Locations can be explained by the factor, whereas much higher variance in all subtests of the Pair Games can be explained by the factor.

Table 2.7 Factor analysis on memory scores.

		Factor loadings	% of Variance explained
Pair Games	Spoken words	0.68	46
	Written words	0.74	54
	Objects	0.74	55
	Designs	0.74	55
	Pseudowords	0.72	52
CMS	Dots	0.44	19
	Words	0.64	41

Cronbach’s alpha was calculated as a measure of internal consistency of the Pair Games paradigm. The results indicate Cronbach’s α = 0.84, demonstrating high reliability as values above 0.8 are considered as acceptable for cognitive tests (Kline, 1999). Table 2.8 shows how Cronbach’s α would change if specific items were removed from the analysis. None of the subtest would increase reliability of the paradigm if deleted from the analysis, suggesting that they each contribute to the reliability of the paradigm.

Table 2.8 Cronbach’s α for each subtest from the Pair Games.

	Cronbach’s α if item deleted
Spoken words	0.82
Written words	0.81
Objects	0.80
Designs	0.81
Pseudowords	0.81

3.5 Standardisation of Raw Scores

The final aim was to compute standardised scores for clinical purposes. For each subtest of the Pair Games, standardisation of raw scores was performed for five separate age groups (group 1: 8-9, group 2: 10-11, group 3: 12-13, group 4: 14-15, group 5: 16-18 years old). Standardisation was conducted on 5 age groups from 8 to 18 years old to account for changes in cognitive developmental profiles as a function of age. The division into five age bands allows a balanced composition of groups with equivalent number of individuals in each age group. This standardisation of scores was computed for each measure (section 2.7, page 48), allowing meaningful comparison between them, as well as with other standardised tools used clinically. The standardisation tables are illustrated in Appendix C (page 316).

Raw scores were converted to z-scores by subtracting the mean and dividing by the standard deviation for each age group separately. Those scores were then multiplied by 15, and 100 was added to compute scores analogous to Wechsler scores with a mean of 100 and a standard deviation of 15. A score of 100 therefore reflects the average performance of a given age group. The few

missing scores were replaced with the mean standard score (100) to create representative standard scores.

3.5.1 Combination of Subtests for Index Scores

Index Scores were derived from the average of each participant’s standard scores on the relevant subtests (Table 2.9). The derivation of Index Scores allows the investigation of different variables of interest, *i.e.* material type, access to semantic label, and modality of presentation. These index scores can be investigated for all four measures of learning and memory. For example, for the measure of delayed recall, one can investigate verbal materials specifically, which comes down to a “verbal delayed recall” score referring to the average delayed recall scores of Written Words and Pseudowords.

In addition, despite not being Index Scores per se, performance on the Spoken Words and Written Words tasks can be compared to provide indication of modality differences (auditory modality for the former and visual modality for the latter).

Table 2.9 Index Scores and the subtests they comprise.

Index Scores	Subtests that the index comprises
Verbal material	Written Words and Pseudowords
Non-verbal material	Objects and Designs
Semantic	Written Words and Objects
Non-Semantic	Pseudowords and Designs

3.5.2 Differences between Index Standard Scores

An important consideration for interpreting the performances across domains is the amount of difference between different standard scores, *e.g*. difference between Verbal Learning and Non-verbal Learning. The minimum difference between any pair of scores required for statistical significance was computed. Because very small variance is observed between the different age groups, the values are shown for all age groups combined. To obtain those values, the first step was to calculate the standard deviation of the scores’ paired difference (SD_y), for a measure of variability. Correlation between the two scores ($r_{y.x}$) was then calculated, for a measure of reliability. The standard error of measurement

of the difference was then calculated using the formula below (Harvil, 1991), where N =130.

$$SE_{Mdiff} = SD_{x.y}\sqrt{(1 - r^2)\frac{N - 1}{N - 2}}$$

Those values were then multiplied by a factor of 1.96 to yield the amount of difference that is statistically significant at $p \leq 0.05$. In addition, the frequency of the difference in the standardisation sample is represented in separate tables to provide an indication of how frequently such discrepancy is observed in the general population. Appendix D (page 360) contains the tables with differences between Index Scores required to reach significance and the frequency of those differences. With these scores, differences between standardised domains can be better interpreted.

3.6 Summary of Results

This chapter had several aims regarding the development of the memory protocol. Table 2.10 provides a summary of the findings corresponding to each aim.

Table 2.10 Summary of aims and the results.

Aims		Results
1	Develop a diagnostic tool to assess hippocampal learning and memory systems with theoretical knowledge of neural substrates of recall *versus* recognition and is sensitive to the lateralisation of memory deficits	The tool is a paired-associate paradigm of learning, recall and recognition, controlling for material (verbal *versus* non-verbal), modality of presentation (auditory *versus* visual), and conceptual component of items (semantic *versus* non-semantic).
2	Examine the contribution of intellectual functioning in performance on the Pair Games	Intellectual functioning had only a small contribution in performance on the Pair Games ($r<0.23$ across subtests, with correlations either non-significant or significant at the 0.05 level)
3	Examine test validity and reliability of the construct	Moderate correlations were found between the subtests of the Pair Games and Word Pairs from the CMS (r=0.31-0.46). Low correlations were found between the subtest of the Pair Games and Dot Locations from the CMS (r=0.19-0.35). Exploratory factor analysis yielded only one factor with 53.35% of total variance explained. The factor loadings for the subtests of the CMS (19-41%) were lower than for the subtests of the Pair Games (46-55%). Internal consistency of the Pair Games indicated Cronbach’s α = 0.84, demonstrating high reliability.
4	Standardisation of raw scores in order to provide normative data	For each subtest of the Pair Games, standardisation of raw scores was conducted for five separate age groups from 8 to 18 years old. In addition, the minimum difference between any pair of scores required for statistical significance was calculated.

4 Discussion

There has been growing interest in examining learning and memory abilities in children with TLE, particularly in the context of pre-operative assessments for the prediction of outcome. Current measures that are available to assess memory are vulnerable to the effects of confounding variables, such as input modality and dual-coding, influencing performance on the tests and hindering the examination of lateralisation and selective impairments in memory function. In addition, these measures do not provide a comprehensive, balanced and systematic approach to memory assessment, hampering the ability to compare performances across tests and identify specific memory impairments. The Pair Games was developed to overcome these issues.

4.1 Construction of the Pair Games

This novel paradigm is a paired-associate learning paradigm devised to counter the shortcomings in the literature, and add to improved understanding of the neurobiology of learning and memory. The paradigm provides measures of learning and retrieval of learnt information, both assessed through cued recall, as well as a measure of delayed recognition. In order to understand the mechanisms underlying an impairment in delayed recall, we can investigate whether the information was not properly encoded or stored in long-term memory, or whether the information is available in long-term memory but simply not accessible through recall.

Recognition memory is based on two separate sub-processes, namely recollection and familiarity, which are functionally distinct and depend on different brain regions. Recollection processes involve the retrieval of rich contextual details, whereas familiarity reflects a general feeling about previous encounters without specific details (Eichenbaum et al., 2007; Yonelinas, 2002). Recollection is generally more impaired than familiarity after hippocampal pathology; it is therefore useful to assess recognition memory through recollection rather than through familiarity, otherwise intact recognition may simply reflect preserved familiarity. Because the response options in the Pair Games recognition task include familiar distractors, successful recognition is performed with reduced involvement of familiarity. Reducing involvement of familiarity-based retrieval is

possibly more likely to capture the functionality of the hippocampus, as opposed to other regions of the MTL. In addition, the inclusion of familiar distractors makes the recognition task more challenging and reduces the risk of ceiling effects. Recognition tasks that are too easy are not sensitive enough to capture subtle deficits, and make interpretation of performance difficult.

Epilepsy is a disorder of cortical organisation but it interferes with the network as a whole rather than the cortex alone. By designing the Pair Games, we are able to evaluate different aspects of this network. The balanced nature of the instrument allows for adequate comparison between tests, such as verbal and non-verbal tests, providing indication of lateralisation of memory function, relevant to patients with TLE. The variables of input modality and levels of semantic structure were also taken into account, allowing 1) the examination of the effects of these variables on learning and memory, and 2) controlled and adequate comparison between verbal and non-verbal memory. The Pair Games could be clinically useful for the assessment of the integrity of the medial temporal lobe regions, and the hippocampal region in particular, at the pre-operative level, and in turn, it could provide input to surgical decision-making and prediction of memory outcome.

4.2 A “Purer” Measure of Memory

The findings suggest that whereas intellectual status contributes to learning and memory functioning in typically-developing children, the influence is moderate and the level of intellectual ability cannot fully predict memory capacity. The factor analysis shows that the yielded factor explained higher variance in all subtests of the Pair Games than in the subtests of the CMS. This suggests that the Pair Games provides a purer assessment of memory, whereas the CMS reflects the contribution of additional factors, such as intellectual ability and/or executive function. In accordance with the hypothesis that the CMS assesses broader cognitive abilities than the Pair Games, the present findings show that the CMS, and more particularly the Word Pair subtest, is more closely related to intellectual functioning than the Pair Games.

In addition, the Pair Games involves deep encoding whereby the participants are asked to make a preference judgment for each pair, minimising inter-individual

variability in executive functions, such as attention or concentration (Baumeister et al., 2007). The use of such judgement at encoding may help them focus on the pairs and control for potential concentration difficulties.

This has clinical relevance as it is important to examine memory impairments in isolation of other cognitive processes, such as general cognitive ability or executive functioning. The clinical assessment should disentangle impairments in different cognitive processes and identify specific deficits by understanding whether poor performances on memory tests reflect intrinsic memory deficits or low general cognitive abilities/executive functioning. This has implication both in terms of cognitive intervention and in the prediction of memory impairments after surgery for TLE. Whereas neuropsychological tasks are never process-pure, using instruments that limit the involvement of other cognitive processes may provide better indication of the functionality of the memory process and of the extent of hippocampal involvement in the cognitive profile. The limited involvement of other cognitive processes in addition to the balanced design of the paradigm minimises differences due to factors such as concentration between tasks and makes the subtests more equivalent, thereby allowing better comparison between, for example, verbal and non-verbal memory.

4.3 Validity and Reliability

The present chapter demonstrated evidence of validity and reliability by evaluating psychometric properties of the instrument (Pawlowski et al., 2013; Urbina, 2004). Test validity was verified with correlations with other standardised tests, namely with the WASI-IV for a measure of intellectual functioning and the CMS for a measure of memory, and confirmed that the test measures what it intends to measure (Westen & Rosenthal, 2003). Test reliability was verified by examining internal consistency using Cronbach’s alpha, as well as examining factor structure and dimensionality of the instrument using factor analysis (Embretson, 2007; Schmitt et al., 2010).

4.4 Standardised Scores

Comprehensive normative data were collected and are now available, providing a standard against which the performance of patients with TLE can be compared (Cohen & Swerdlik, 2005; Franzen & Wilhelm, 1996). The instrument was standardised across a large age range of typically-developing children to take into account the developmental trajectory of learning and memory.

4.5 Additional Advantages of the Pair Games

The Pair Games is able to measure performance across a broad range of learning and memory abilities without leading to floor or ceiling effects, permitting its use with both low and high functioning patients. Moreover, this tool could be used to provide valuable information and identify patients’ strengths to use for remedial programs and compensate for weaknesses.

In addition, the parallel versions of the paradigm allow systematic comparisons between performances across two time points. For example the Pair Games can be administered before and after clinical intervention (*e.g.* surgery) and such clinical follow-up can provide indication on the impact of surgery on cognitive outcome and on the trajectory of learning and memory.

Finally, the computerised characteristic of the Pair Games has multiple advantages associated with the optimisation of test administration. First, using a tablet-based application allows for a more controlled administration process with, for example, standardised presentation of pairs. Second, a portable neuropsychological tool reduces the amount of materials usually involved in standardised tests, and facilitates administration in different contexts. Last, the utilisation of the interactive platform allows for a child-friendly psychological assessment, allowing examinees to be more engaged and more highly motivated.

5 Conclusions

The present chapter described the development of the Pair Games, a paired-associate learning paradigm assessing learning, delayed recall and recognition for different types of information (verbal *versus* non-verbal materials, auditory

versus visual input modalities, and semantic *versus* non-semantic information). The balanced nature of the Pair Games tests allows comparing different subtests and capturing specific memory impairments. Examining subtests in isolation does not permit clear understanding of the deficit, whereas direct comparison between subtests of the Pair Games can shed light on the underlying impairment. For example, reporting impairment in the Object subtest in isolation cannot distinguish between non-verbal memory impairment and semantic deficit. Comparing this subtest with Written Words can provide indication of material-specific impairment. Similarly, comparing Objects with Designs can provide indication of semantic deficit. Without these comparisons, conclusions are difficult. The Pair Games therefore allows the investigation of memory profiles beyond material-specificity and provides a better understanding of the nature of the impairments.

In addition, the contribution of intellectual functioning to learning and memory performance was investigated. Whereas standard memory tools possibly assess broader cognitive abilities beyond memory functioning leading to performance being mediated by other cognitive processes and being influenced by, for example, attentional difficulties, the Pair Games provides a purer measure of memory, reducing the contribution of general cognitive ability and/or executive functioning. In that respect, the Pair Games may be more specific to temporal lobe pathology than standard tools which are more dependent on intellectual functioning. Finally, normative scores were derived from raw scores; useful for clinical practice. The instrument should now be validated among typically-developing children in order to establish a profile of learning and memory in children before the tool can be used clinically (see Chapter 3).

6 Future Directions

The next step will be to examine the behavioural data acquired with the Pair Games in a sample of healthy children to identify the profile of learning and memory in typically-developing children and to define developmental changes in mnemonic functions. These investigations will offer a baseline against which comparisons to the neuropsychological profile in children with epilepsy can be made.

Chapter 3

Paired-associate Learning and Memory in Children and Adolescents Using the Pair Games

The “Pair Games”, which was developed and described in Chapter 2, was administered on a large sample of typically-developing children and adolescents. This chapter discusses the findings regarding the developmental trajectory of learning and memory and the performance for different material types. Documenting developmental effects on performance establishes a baseline to which performance from paediatric TLE patients of various ages can be compared, and from which the effects of age at seizure onset on learning and memory can be better understood.

1 Introduction

The full description of the Pair Games designed for the assessment of learning and memory in childhood Temporal Lobe Epilepsy (TLE) was provided in the previous chapter (Chapter 2). This new measure was developed to improve the diagnosis of learning and memory problems at baseline, and help with prediction of outcome after surgery. Before this experimental paradigm can be translated into clinical application, it is necessary to establish its relevance to charting the typical development of learning and memory from childhood to adolescence in healthy controls, thereby providing a standard against which the performance of patients with TLE can be evaluated. This chapter will present the learning and memory performance of a group of healthy children and adolescents using the five subtests of the Pair Games.

1.1 Theoretical Framework

1.1.1 Neocortical and Hippocampal Learning Systems

As discussed in Chapter 1, the complementary learning systems theory posits separate but complementary cortical and hippocampal learning systems (McClelland et al., 1995). Whereas the neocortical learning system is involved in slow learning and requires multiple exposures, the hippocampal learning system has a role in rapid encoding and integration of new information. These complementary learning systems are responsible for long-term storage of information in the neocortex through neocortical-hippocampal interaction. In this framework, information is initially stored in the hippocampal memory system and is gradually integrated in the neocortical system through the process of consolidation (Squire, 1992). In this respect, the hippocampus is also involved in memory retrieval until the representation is fully established in the neocortical system (Wickelgren, 1979).

1.1.2 Subregions of the MTL - Recall versus Recognition

The Medial Temporal Lobe (MTL) plays a crucial role in episodic memory, but the subregions of the MTL are thought to subserve distinct memory processes. As discussed in Chapter 1, a consensus has emerged over the functional

dissociation between recollection and familiarity (Eichenbaum et al., 2007), typically assessed with measures of recall and recognition, respectively. Whereas the hippocampus is involved in recollection processes, familiarity processes are reported to rely on the perirhinal cortex (Davachi et al., 2003; Diana et al., 2007). Lesion studies have provided evidence of these distinct memory processes. Patients with developmental amnesia (DA) who sustained selective early onset bilateral hippocampal pathology (Vargha-Khadem et al., 1997) exhibit severe and selective impairment in recall memory, in the context of relatively well-preserved recognition memory (Adlam et al., 2009; Baddeley et al., 2001; Patai et al., 2015). Based on these models of learning and memory, it is assumed that *learning* is dependent on hippocampal-neocortical interactions, *recall* is predominantly mediated by hippocampal retrieval mechanisms, and *recognition* is primarily dependent on parahippocampal and perirhinal cortices.

In that respect, it is important to study different aspects of memory processes in relation to the brain anatomy and the organisation of the medial temporal memory system. However, it is difficult to tease apart the psychological processes of recollection and familiarity on the basis of behavioural data, and few studies tap into the neural substrate of recollection. Instead, we can address the question of how children and adolescents learn and retrieve learnt information from memory through tests of recall and recognition. Whereas recognition reflects the contribution of both processes, *i.e.* recollection and familiarity, recall can only be achieved through recollection of information.

1.2 Developmental Trajectory of Learning and Memory

1.2.1 Ontogeny of Learning and Memory

Neurodevelopmental studies demonstrate that different learning and memory processes come online at different stages of development. Studies in young monkeys and preverbal human infants have provided evidence of early emergence of recognition memory, through preferential viewing paradigms which measure the tendency to fixate longer on novel stimuli compared to familiar ones. In humans, evidence of this type of recognition memory is present in the first few weeks of life (Fagan, 1970; Pascalis & de Schonen, 1994). On the other hand, the ability to learn relational associations between stimuli develops somewhat

later in life, around the ages of 5 and 6 years (Rudy et al., 1993). Similarly, the ability to form and bring back to mind episodic memory emerges in early childhood, and as a result, impairment in the system subserving the ability to recall events does not become apparent until this age. Consistent with this hypothesis, children with DA do not show signs of recall impairments until early childhood, when recall ability typically emerges (Gadian et al., 2000). These findings indicate that some memory processes, such as recognition memory, are present early in life, whereas other processes, such as recall and learning that require more complex cognitive demands, emerge later in life.

1.2.2 Neural Development of Structures supporting Learning and Memory

As discussed in Chapter 1, evidence suggests that the protracted course of neural development of regions subserving memory may be related to the developmental trajectory of learning and memory ability. The neural basis supporting these functions undergoes structural and functional development across childhood and adolescence (Sowell et al., 2001), including changes in hippocampal volume and cortical thickness of the temporal lobe (Gogtay et al., 2004; Sussman et al., 2016). The extended trajectory of these neural changes parallels the development of learning and memory in children, with the age-related emergence of functional relationship between these structures and memory performance (Blumenfeld & Ranganath, 2007; Ghetti et al., 2010; Khul et al., 2008; Newcombe et al., 2007; Riggins et al., 2015). Together, structural and functional development of these regions may mediate the development and maturation of learning and memory functions across childhood and adolescence.

1.2.3 Age-Related Changes in Learning and Memory

Age-related increases in learning and memory are documented across childhood and adolescence (Pirogovsky et al., 2009; Litt et al., 2013), however, the developmental trajectory for distinct learning systems is not fully understood and developmental changes in memory are much better documented for aspects of semantic memory, such as vocabulary development (Henderson et al., 2013; Wojcik, 2013) and concept formation (Favarotto et al., 2014; Robertson & Kohler, 2007), than for episodic memory.

1.2.3.1 Neocortical Learning System – Repetitive Learning

Associative learning is the process by which information is integrated and encoded into memory such that exposure to one component of the mnemonic trace elicits retrieval of other components (Mayes et al., 2007; Pirogovsky et al., 2009; Postma et al., 2008). Studies that have examined the developmental trajectory of learning have generally focused on verbal memory or on memory for easily verbalised items (common objects) (Beuhring & Kee, 1987; Hund et al., 2002; Jansen-Osmann & Heil, 2007; Pentland et al., 2003; Shing et al., 2008), and may have thus captured the maturation of memory as well as language abilities. The development of non-verbal paired-associate learning is less understood and researched. Harel et al. (2014) studied learning of pattern-location associations in school-age children (5-10 years old) and demonstrated learning improvement with age that was attributed to the development of executive functions (Harel et al., 2014). These developmental studies document age-related improvements in associative learning, for either verbal or non-verbal materials, but comparison of different processes enabling such learning has not been investigated.

Information about the developmental process of learning across childhood and adolescence remains sparse and further research is needed across a large age range. More specifically, research is needed not only to chart the maturation of different learning processes (verbal and non-verbal), but also to conduct direct and balanced comparisons between these processes for a more concise examination of the development of learning abilities.

1.2.3.2 Hippocampal Learning System – Recall

The process of recollection is thought to improve gradually throughout childhood and adolescence (Bjorklund et al., 2009), with age-related improvements in recall of contextual details from 8 to 24 years (*e.g.* Ghetti & Angelini, 2008; Ghetti et al., 2011). The maturation of the recollection process, known to be dependent on hippocampal retrieval mechanisms, is thought to be intrisically related to the development of the ability to bind features of a representation. In several studies, age-related improvement was associated with binding abilities, and was apparent in tests of item combination but not in tests of single item memory (Lloyd et al., 2009; Sluzenski et al., 2006). These findings indicate that age-related

improvement of recollection may be linked to maturation of the hippocampal-dependent binding process.

However, it is unclear whether these age-related changes reflect changes in the ability to form strong mnemonic traces or the ability to bring information back to mind. Previous studies have often examined recall as a measure of delayed retention without controlling for prior encoding levels. There is therefore a need to investigate age-related changes in the ability to bring previously learnt information back to mind in order to disentangle age-related changes in memory formation and recall. Helmstaedter and Elger (2009) used this approach to examine recall and demonstrated age-related decreases in number of forgotten words over time between the ages of 10 and 20 years. Further research is required to study age-related changes as a function of type of material (*e.g.* verbal *versus* non-verbal).

1.2.3.3 Perirhinal-dependent memory – Recognition

Recognition memory also improves with increasing age, although there are distinct developmental processes for familiarity- and recollection-based recognition, possibly reflecting distinct maturation trajectory for perirhinal *versus* hippocampal regions. Age-related changes are documented for recollection-based recognition across childhood and adolescence (between the ages of 8 and 18 years), whereas familiarity-based recognition reaches its peak during middle childhood (*e.g*. Naus et al., 1977) and remains relatively stable across this time span (Billingsley et al., 2002; Ghetti & Angelini, 2008).

Overall, age-related changes are documented in learning and memory, however, many developmental studies have focused on the preschool age, and less is known about changes in school-age children and adolescents (although see (Billingsley et al., 2002 and Ghetti & Angelini, 2008). Moreover, there is a dearth of knowledge regarding the developmental trajectory of learning and memory as a function of type of information, and previous studies have often investigated performance using one task only (a verbal or non-verbal memory test).

1.3 Variables Influencing Learning and Memory

1.3.1 Material Type

1.3.1.1 Verbal and non-verbal materials are processed and learned differently

Whereas there is evidence for age-related improvement in learning and memory abilities across childhood and adolescence (*e.g*. Pirogovsky et al., 2009; Litt et al., 2013), less is known about the differences in learning abilities for different material types (*e.g.* verbal *versus* non-verbal). Verbal and non-verbal materials are processed differently (Paivio, 1971), whereby pictorial information is configural and holistic, whereas verbal information is associated with sequential modes of processing. Differences in cognitive processing of verbal and non-verbal information may be associated with differences in learning and memory ability for these two types of information.

1.3.1.2 Visual Superiority Effects in Adults

Paivio postulated a dual-code model whereby verbal and visual systems are specialised for the processing of verbal (*e.g*. words) and visual (*e.g*. pictures) information, respectively (Paivio, 1971). Paivio also demonstrated that visual stimuli are more likely to be encoded in both verbal and visual representations relative to verbal stimuli, leading to better memory for visual information compared to verbal information (Paivio, 1991). This visual superiority effect has been shown in adults for associative memory, providing evidence for mnemonic advantage for the association of non-verbal information (Hockley, 2008), possibly as a result of higher likelihood to verbalise pictures than to visualise words (Snodgrass et al., 1974) and, in that respect, making use of the dual-coding system. These studies suggest visual superiority effects in adults, but such effects are less known in children.

1.3.1.3 Children: verbal PA associated with reading/writing abilities

In children, acquisition of verbal paired-associates (PA) is related to orthographic learning (Wang et al., 2017) and reading ability (Litt et al., 2013) through the ability to form links between phonological and visual (orthographic) features of words. Such links were not observed with visual paired-associate learning (Wang et al., 2017), suggesting that the relationship between paired-associate learning

and reading/spelling is not driven by the overall associative learning ability, but rather by the ability to link phonological and orthographic forms together (Elbro & Jensen, 2005; Litt et al., 2013; Messbauer & de Jong, 2006). These studies suggest distinct material-specific processes for verbal and non-verbal modes of learning and memory. Whereas verbal paired-associate learning may be enhanced or further mediated by reading/writing abilities, non-verbal paired-associate learning may not be influenced in this way, and therefore may be less cognitively demanding.

1.3.1.4 The right hippocampus is functional earlier than the left

From a neuronal perspective, material-specific memory is an indirect reflection of hemispheric specialisation (left *versus* right) and neuroimaging studies have documented the specific role of the right hippocampus in children to support visuo-spatial memory. Prabhakar et al. (2018) studied hippocampal activation associated with memory for object-location in toddlers and demonstrated stronger right than left hippocampal activation (Prabhakar et al., 2018). However, this study focused on spatial memory rather than cognitive episodic memory. The putative roles of the hippocampus in spatial memory *versus* that in cognitive non-verbal memory are distinct and can be dissociated even though they can be both subserved by the right hemisphere. It is possible that the right hippocampus may be functional earlier than the left hippocampus, possibly to sustain visuo-spatial abilities (Burgess et al., 2002) which may be more important than linguistic abilities in early childhood. In that respect, young children may exhibit higher learning and memory for non-verbal, compared to verbal information.

1.3.2 Input Modality

The ability to learn new words is a fundamental characteristic of linguistic development, and requires the establishment of new representations. The separate stream hypothesis posits that verbal information presented in the auditory and visual modality are processed in separate streams (Penney, 1989). The two modalities also differ in their linguistic form, whereby orthographic information is presented in the visual modality, while phonological information is delivered through the auditory modality (Rummer et al., 2013). Differences in memory performance between the two modalities can relate to the properties of these streams.

Several studies document the asymmetry between the two modalities with better learning of written compared to spoken words in adults. Fueller et al. (2013) used a paired-associate learning paradigm to compare immediate recall of words in spoken and written forms presented either orally or visually. The authors reported better recall for words retrieved through the visual modality, irrespective of the input modality and attributed their finding to the superiority of written representations at the time of retrieval (Fueller et al., 2013). The superiority of written words over spoken words can possibly be explained by reduced cognitive load of maintaining temporal representations and therefore by reduced effort (Janczyk, et al., 2018). Similarly, Nelson et al (2005) demonstrated that written training of rare words leads to better representation than phonological training (Nelson et al., 2005). These authors also demonstrated that phonological recoding of written words is more readily available than orthographic recoding of spoken words, essentially leading to stronger mnemonic traces of written words. Differences in the ability to learn spoken and written words therefore appears to be related to the quality of phonological and orthographic representations.

The indication that written words establish traces that are more accessible than spoken words, possibly as a result of variable quality of phonological representations, is supported by neuropsychological evidence. Children with dyslexia tend to have underspecified phonological representations (Elbro & Jensen, 2005) and also show impairment on paired-associate learning of auditory verbal information, but not when verbal stimuli are presented in the visual modality. This finding suggests the influence of phonological processing skills in auditory verbal paired-associates (de Jong et al., 2000; Windfurh, 2001), and contributes to the observation that phonological representations may be less stable or less well-specified.

Together, these studies converge on the idea of superiority of the visual modality to learn words, as a result of reduced effort and stronger representations; however less is known about the persistence of this asymmetry between the two modalities after memory consolidation. More research is needed to study modality-specific asymmetry in word recall after a delay, to examine the extent to which the visual superiority persists after learning.

1.3.3 Levels of Semantic Structure – effects of IQ

Learning and memory depend on the availability of information, and higher performance is therefore shown for information that allows access to conceptual representations (Elbro & Jensen, 2005; Messbauer & de Jong, 2006). Non-semantic verbal (*i.e.* pseudowords) and visual (*i.e*. abstract shapes) information requires forming the fully specific phonological/configural representation before the material can be learned and memorised, and in this respect, task demand is increased. The ability to form and retain in memory such phonological/configural representations for non-semantic information may be related to other higher cognitive functions.

For the verbal domain, it has been shown that language abilities improve with age and influence associative learning (Luciana, 2003), particularly through the development of reading abilities (Litt et al., 2013; Hulme et al., 2007; Windfurh, 2001). The development of verbal learning and memory may therefore be intrinsically related to the maturation of language (Hund & Plumert, 2003; Shing et al., 2008). Consistent with this hypothesis, Hulme et al. (2007) demonstrated that paired-associate learning is associated with irregular word reading abilities, through the binding of phonology and orthographic representations (Hulme et al., 2007). More specifically, the most robust relationship with reading ability has been consistently reported for paired-associate learning of pseudowords, compared to real words (Clayton et al., 2018; Elbro & Jensen, 2005; Hulme et al., 2007; Mayringer & Wimmer, 2000). These findings indicate that non-semantic verbal paired-associate learning and memory are intrinsically related to language abilities. The underlying mechanisms of non-verbal paired- associate learning are however less understood and most studies have focused on verbal paired-associate learning and its contribution to language abilities. Following the identified relationship between paired-associate learning of novel words and language abilities, it is possible to generalise this link and predict that paired-associate learning of non-semantic information (pseudowords and abstract shapes) is related to general intellectual ability.

1.4 Aims and Hypotheses

Despite substantial progress towards an understanding of the processes supporting memory and the developmental changes occurring in childhood and adolescence, there remain major gaps in our knowledge about the nature of these changes. New research is needed to gain an in depth understanding of memory development, particularly the ways in which children acquire and retrieve learnt information, and more specifically the variables that influence performance.

The aims of the present study are to:

1. Chart the developmental trajectory and performance changes in learning, recall and recognition during childhood. The following hypothesis was formulated:
    a. Given the rapidly developing learning ability of healthy children and adolescents, paired-associate learning performance, as well as subsequent recall and recognition of learnt material will improve with age.
2. Compare learning, forgetting and recognition for different types of information. Based on theoretical frameworks about emerging specialisation of function in children (*i.e*. verbal *versus* non-verbal), the temporal versus configural nature of input modality (*i.e* auditory *versus* visual), and access to conceptual representations (*i.e*. semantic *versus* non-semantic), the following hypotheses were formulated:
    a. Better learning and memory performance for non-verbal compared to verbal materials.
    b. Better learning and memory performance will be demonstrated for verbal information presented in the visual, compared to the auditory modality.
    c. Higher levels of IQ will be associated with better learning and memory for non-semantic, but not for semantic information.

2 Methods

2.1 Participants

The participant sample included in this chapter is the same as the one reported in the previous chapter (Chapter 2). Briefly, the sample consisted of 130 healthy children and adolescents between the ages of 8 and 18 years (*M*=13 years, *SD*=3).

2.2 Pair Games

The Pair Games paradigm which was developed for the investigation of learning, recall and recognition was described in Chapter 2. The score of forgetting was used to account for learning capacity (how much is learned before the delay period) to provide a measure of retention, whereby negative scores indicate that information was forgotten after a delay. In the results section, I therefore refer to scores of *forgetting*, but for the sake of consistency with previous studies, I refer to the term *retention* or *recall* in the discussion section.

The paradigm is composed of balanced subtests allowing comparison between different variables, namely material type (verbal *versus* non-verbal), semantic structure of information (semantic *versus* non-semantic content) and input modality (auditory *versus* visual). There are two versions of the same paradigm, as described in the previous chapter (Chapter 2, section 2.5, page 47)

2.3 Statistical Analyses

Analyses of variance using a repeated measures design were computed, exploring different variables of interest, *i.e.* material type (verbal *versus* non-verbal), lexical access (semantic *versus* non-semantic content), and modality of presentation (auditory *versus* visual). For the investigation of the first two variables, a 2 (concept: semantic, non-semantic) x 2 (material: verbal, non-verbal) design was employed. For the investigation of modality of presentation, modality (auditory, visual) was the within-subject factor. The analysis of 'modality' was separate from the analysis of 'material' and 'access to semantics' because

the paradigm is not fully balanced. For example, a task using auditory presentation of non-verbal information, such as the sound of a train, was not included in the design of the Pair Games (see Chapter 2, section 2.4.1, page 46 for more detail).

These analyses of within-subject effects were carried out separately for the different measures, thus giving rise to four measures, namely, learning, gain in learning, forgetting, and recognition. Statistical analyses were carried out on the raw scores (percentages) in each case. In addition, the influence of intellectual status and age on performance was controlled with Pearson partial correlations.

3 Results

3.1 Learning

3.1.1 Measure

As stated above, two measures were investigated in this section: learning and learning gain. The measure of learning was explored by averaging performance across three trials. The gain in learning was explored by measuring the increase in performance from the first to the third trial to have a measure of how much is gained over repetitive trials.

3.1.2 Learning Performance

Table 3.1 and Figure 3.1 illustrate the descriptive statistics and distribution of learning and learning gain, respectively. For the gain in learning, a negative score indicates that previously correct recall of pairs (*i.e.* on trial 1) was erroneous on trials 2 or 3. This decrease in performance with repeated trials was of no more than two items and occurred in less than 1% of the participants' responses for each subtest. Overall, the results demonstrate that a large proportion of information across all subtests was successfully learned. In addition, there was a significant learning curve with improvement in performance over consecutive trials (Figure 3.2).

In order to test whether higher learning gain was related to lower initial acquisition due to greater opportunity for improvement, a correlation analysis was computed between learning gain and performance at trial 1. Analysis of the composite score (all subtests) demonstrates no relationship between initial acquisition and learning gain (r=0.16 p=0.078). However, separate analyses on each subtest indicate a significant relationship for performance on the subtests with semantic content, wherein lower initial acquisition was related to higher learning gain (Spoken Words r=-0.40, Written Words r=-0.50, and Objects r=-0.29). This relationship was not observed for subtests without semantic content (Pseudowords r=0.02 and Designs r=0.06). Additional correlations were computed for those composite scores (semantic and non-semantic content) and these confirm a negative relationship between initial acquisition and learning gain for semantic items (r=-0.259, p=0.003), whereby higher initial acquisition was associated with lower learning gain. On the other hand, a positive relationship was shown between initial acquisition and learning gain for non-semantic items (r=0.25 p=0.007), whereby higher initial acquisition was associated with higher learning gain.

Table 3.1 Descriptive statistics for learning and learning gain (%).

Learning

Subtests	M	SD	Min	Max
Spoken words	61	21	10	100
Written words	66	25	7	100
Objects	65	23	0	100
Designs	47	20	7	93
Pseudowords	41	23	0	97
Overall	56	18	13	89

Learning gain

Subtests	M	SD	Min	Max
Spoken words	37	18	-20	80
Written words	35	24	-10	100
Objects	33	19	-20	80
Designs	26	17	-10	70
Pseudowords	32	21	-10	80
Overall	33	11	2	56

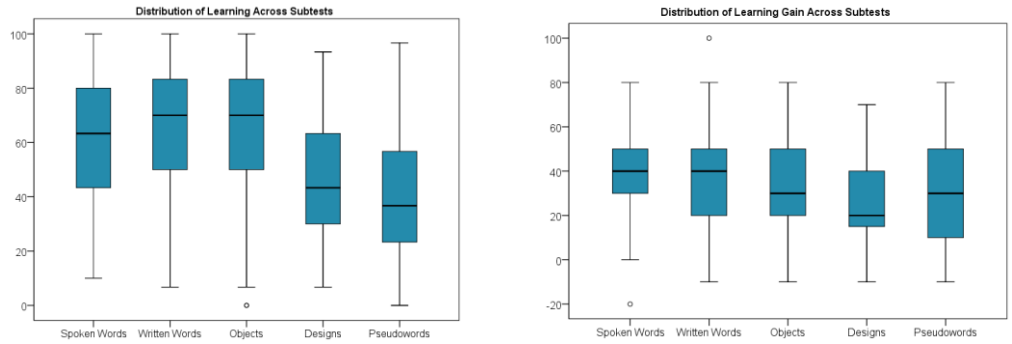


Figure 3.1 Boxplot illustrating the distribution of learning and learning gain across subtests.

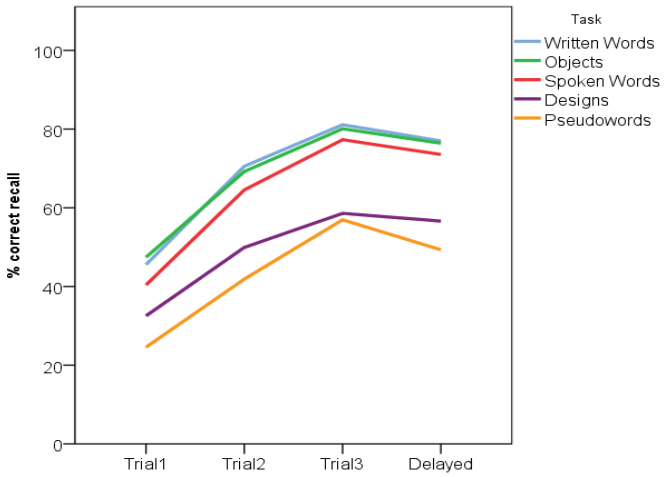


Figure 3.2 Learning curve and loss after a delay for each subtest of the Pair Games.

3.1.3 Relationship to Intellectual Status

Confirming one of the postulated hypotheses, both measures of learning (learning and learning gain) across tasks were significantly related to the level of intellectual abilities (r=0.43, p<0.001 and r=0.22, p=0.018, respectively). Average learning in each individual subtest is significantly related to intellectual abilities, with higher IQ associated with better learning (Table 3.2). Investigation of correlations at every trial shows significant relationship between intelligence and performance at every step of the learning process (trial 1: r=0.40, trial 2: r=0.40, trial 3: r=0.43, all p<0.001).

Table 3.2 also illustrates that the influence of intellectual ability on learning gain is observed for Designs and Pseudowords, but not for Objects and Words.

Table 3.2 Pearson's correlations, and *p* values, between learning scores (learning and learning gain) of each subtest and intellectual abilities, with age partialed out.

A. Learning

Subtests	*r*	*p*
Spoken words	0.28	0.018
Written words	0.30	0.003
Objects	0.32	0.001
Designs	0.35	0.001
Pseudowords	0.37	<0.001
Overall	0.43	<0.001

B. Learning Gain

Subtests	*r*	*p*
Spoken words	0.01	0.931
Written words	-0.12	0.864
Objects	-0.12	0.843
Designs	-0.22	0.022
Pseudowords	-0.41	<0.001
Overall	0.22	0.018

3.1.4 Developmental Trajectory of Learning

Partial Pearson correlations show that average learning across subtests was significantly related to age (r=0.53 p<0.001), with better learning in older children (Table 3.3). However, this relationship was not observed for the gain in learning across subtests (r=0.16 p=0.092). Figure 3.3 illustrate the developmental trajectory for these two measures.

Table 3.3 Pearson's correlations, and *p* values, between learning scores (learning and learning gain) of each subtest and age, with FSIQ partialed out.

A. Learning

Subtests	*r*	*p*
Spoken words	0.27	0.002
Written words	0.40	<0.001
Objects	0.45	<0.001
Designs	0.53	<0.001
Pseudowords	0.43	<0.001
Overall	0.53	<0.001

B. Learning Gain

Subtests	*r*	*p*
Spoken words	-0.01	0.921
Written words	-0.11	0.236
Objects	0.07	0.447
Designs	0.26	0.005
Pseudowords	0.29	0.002
Overall	0.16	0.092

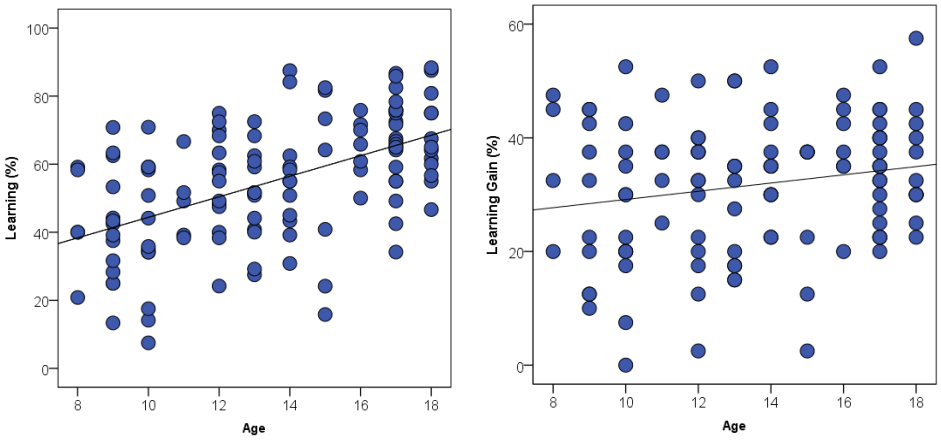


Figure 3.3 Influence of Age on Learning and Learning Gain.

3.1.5 Effect of Semantics

There was a significant main effect of semantics on learning ($F_{(1,124)}$=227.467, p<0.001), where semantic items were better learned than non-semantic items (65% and 44%, respectively), irrespective of material type (Table 3.4 and Figure 3.4). There was also an effect of semantics on learning gain ($F_{(1,114)}$=7.905,

p=0.006), where higher learning gain was observed for semantic items (34%) compared to non-semantic items (29%) (Figure 3.4).

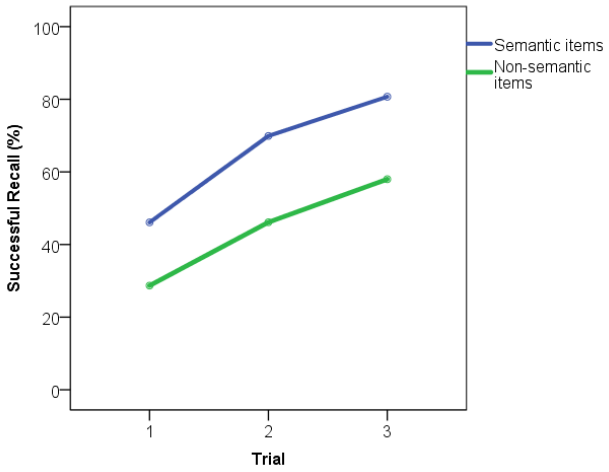


Figure 3.4 Effect of semantics for Learning and Learning Gain.

Table 3.4 Descriptive statistics for learning of semantic and non-semantic items (%).

	Learning		Learning gain	
Conceptual Level	M	SD	M	SD
Semantic	65	24	34	22
Non-semantic	44	22	29	19

Correlations between FSIQ and learning gain indicate that non-semantic items were better learned by those who have higher intellectual functioning (*r*=0.41, *p*<0.001), whereas this relationship was not found for semantic items (*r*=-0.03, *p*=0.749) (Figure 3.5).

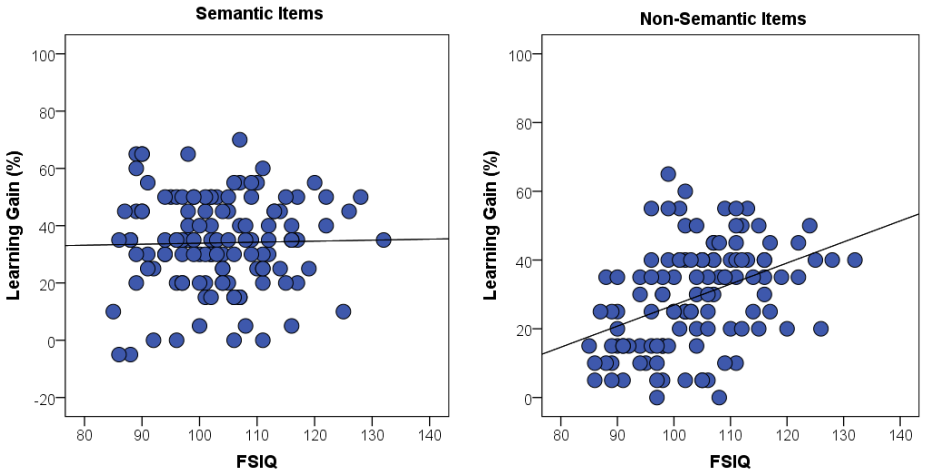


Figure 3.5 Correlations between FSIQ and learning gain for semantic and non-semantic items.

Another significant correlation between age and learning gain indicates that non-semantic items were better learned by older children compared to younger children (r=0.36, p<0.001), whereas this relationship was not found for semantic items (r=-0.04, p=0.682) (Figure 3.6).

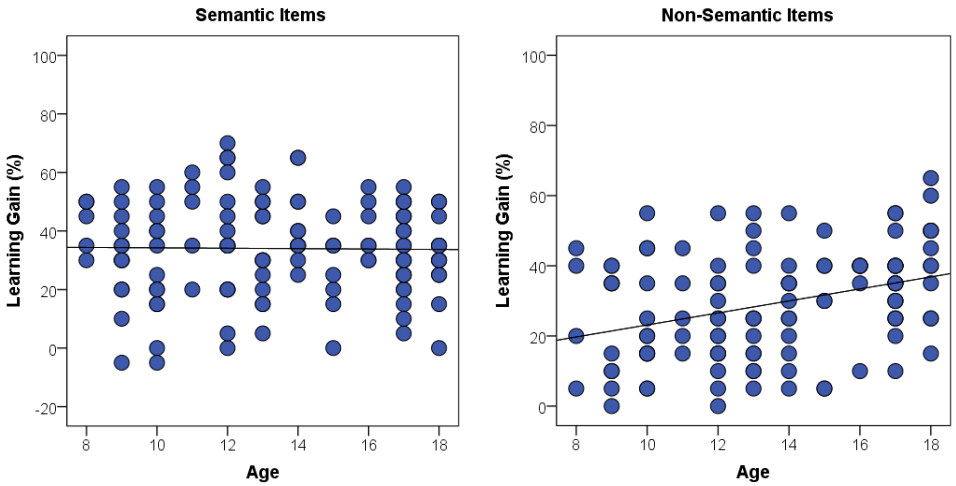


Figure 3.6 Correlations between age and learning gain for semantic and non-semantic items.

3.1.6 Effect of Material Type

There was an effect of material type on learning ($F_{(1,124)}$=4.811 p=0.030), as well as an interaction between material and semantics ($F_{(1,124)}$=7.968 p=0.006) (Figure 3.7). Post-hoc paired sample t tests showed that the effect of material type was only significant for non-semantic items ($t_{(125)}$=3.79, p<0.001), and non-verbal items were learned better than verbal items (47% and 41%, respectively). Semantic items did not show an effect of material type ($t_{(127)}$=0.079, p=0.937). The descriptive statistics are displayed in Table 3.5.

Table 3.5 Descriptive statistics for learning and learning gain of verbal and non-verbal materials, for non-semantic items only (Pseudowords and Designs) (%).

	Learning		Learning gain	
Material Type	M	SD	M	SD
Verbal	41	23	32	21
Non-Verbal	47	20	26	17

In addition, there was a significant effect of material type for learning gain ($F_{(1,114)}$=4.856, p=0.030), where performance was higher for verbal compared to non-verbal items (34% and 30%, respectively). No significant interaction was shown.

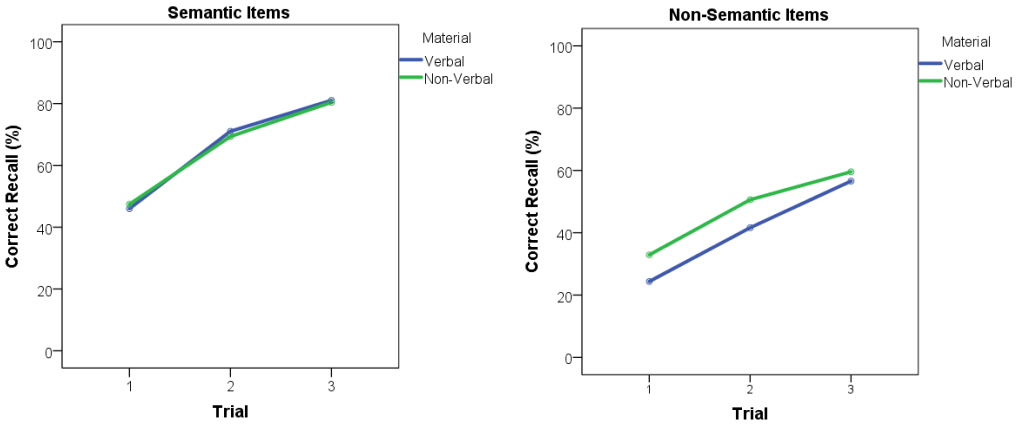


Figure 3.7 Recall performance across three learning trials depending on material and levels of semantic structure.

3.1.7 Modality effect

There was a significant effect of modality of presentation on learning ($F_{(1,128)}$=5.351, p=0.022) whereby the performance was higher for information presented in the visual modality compared to the auditory modality (66% and 61%, respectively). However, the learning gain was similar for information presented in either modality ($F_{(1,124)}$=0.008, p=0.927). As illustrated in Table 3.6, llearning gain was 37% for auditory information and 36% for visual information.

Table 3.6 Descriptive statistics for learning and learning gain of auditory and visual items (%).

	Learning		Learning gain	
Modality	Mean	SD	Mean	SD
Auditory	61	21	37	18
Visual	66	25	36	24

3.2 Forgetting

3.2.1 Measure

The measure investigated in this section is the amount of learnt information that was lost after a delay, which was constant across subtests (*i.e*. 15 minute delay). This provides an indication of forgetting as a function of delay.

3.2.2 Forgetting Score

Table 3.7 illustrates the descriptive statistics for forgetting. Negative scores indicate loss of learnt information after a delay, whereas positive scores indicate an increase in performance after a delay. The boxplot (Figure 3.8) illustrates the distribution of forgetting across participants, for each subtest. For all subtests, the majority of participants retained learnt information after a delay (0% loss), but some forgot and others remembered more after a delay. One-sample *t* tests showed significant forgetting in all subtests (p<0.001), apart from Designs (p=0.103).

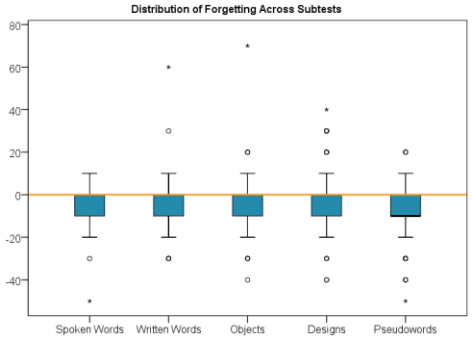


Figure 3.8 Boxplot illustrating the distribution of forgetting accuracy for each subtest.

Table 3.7 Descriptive statistics for level of forgetting of learned material (%).

Subtests	M	SD	Min	Max
Spoken words	-4	9	-50	10
Written words	-4	11	-30	60
Objects	-4	12	-40	70
Designs	-2	14	-40	40
Pseudowords	-7	13	-50	20
Overall	-4	6	-20	16

3.2.3 Relationship with Intellectual Abilities

Partial correlations were computed to examine the relationship between intellectual abilities and forgetting (Table 3.8), but no relationship was found (r=-0.10 p=0.270) (Figure 3.9).

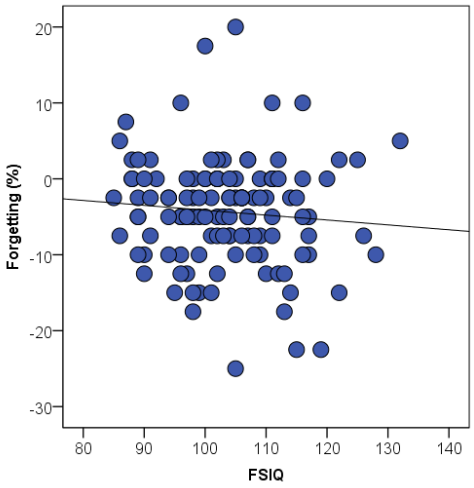


Figure 3.9 Correlations between FSIQ and forgetting.

Table 3.8 Correlations between forgetting in each subtest and FSIQ.

Subtests	*r*	*p*
Spoken words	-0.05	0.627
Written words	0.04	0.708
Objects	-0.04	0.718
Designs	-0.09	0.358
Pseudowords	-0.12	0.211
Overall	-0.10	0.270

3.2.4 Developmental Trajectory of Forgetting

Similarly, a partial Pearson correlation controlling for FSIQ showed an overall weak effect (r=0.19 p=0.033), driven by the effect found in the Spoken Word subtest, suggesting that, overall, forgetting is only weakly age-related (Table 3.9

and Figure 3.10). Ad hoc investigation of each subtest separately showed a significant relationship between age and the Spoken Word subtest only (r=0.18 p=0.046), whereby older children retained slightly more than younger children.

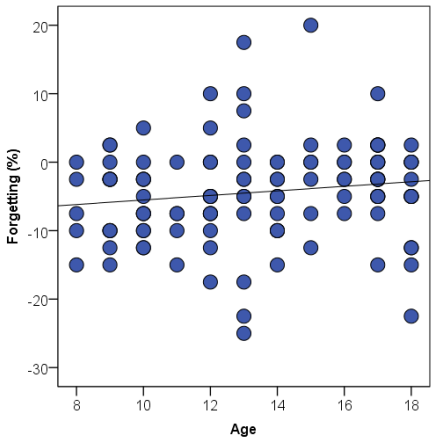


Figure 3.10 Correlations between Age and forgetting.

Table 3.9 Correlations between forgetting in each subtest and age.

Subtests	*r*	*p*
Spoken words	0.18	0.046
Written words	0.17	0.065
Objects	0.12	0.188
Designs	0.07	0.450
Pseudowords	-0.01	0.970
Overall	0.19	0.033

3.2.5 Effect of semantics

There was no evidence of an effect of semantics on forgetting ($F_{(1,120)}$=0.544, p=0.462) and, as illustrated in Table 3.10, a similar amount of information was forgotten after a delay whether it was semantic or non-semantic (-4 and -5%, respectively).

Table 3.10 Descriptive statistics for forgetting of semantic and non-semantic items (%).

Conceptual Level	Mean	SD
Semantic	-4	12
Non-semantic	-5	14

3.2.6 Effect of material type

There was a significant effect of material type found for the measure of forgetting ($F_{(1,120)}$=9.954, p=0.002), suggesting that the loss of retained information after a delay was greater for verbal compared to non-verbal items (-6% and -3%, respectively, Table 3.11). There was also a significant interaction between

material and semantics ($F_{(1,120)}$=6.767, p=0.010) (Figure 3.11). A post-hoc paired t test suggests that this effect of material type was only shown for non-semantic items (t(122)=3.616, p<0.001), where there was a greater loss of verbal (-7%) compared to non-verbal (-2%) information after a delay. No effect of material type was found for semantic items (Paired t test, t(125)=-0.422, p=0.674).

Table 3.11 Descriptive statistics for forgetting of verbal and non-verbal items (%).

Material	Mean	SD
Verbal	-6	12
Non-verbal	-3	13

In addition to the amount of information that was lost, the frequency of forgetting also differed. Indeed, 23% of participants showed a spontaneous increase in performance for non-verbal material, compared to 9% for verbal material.

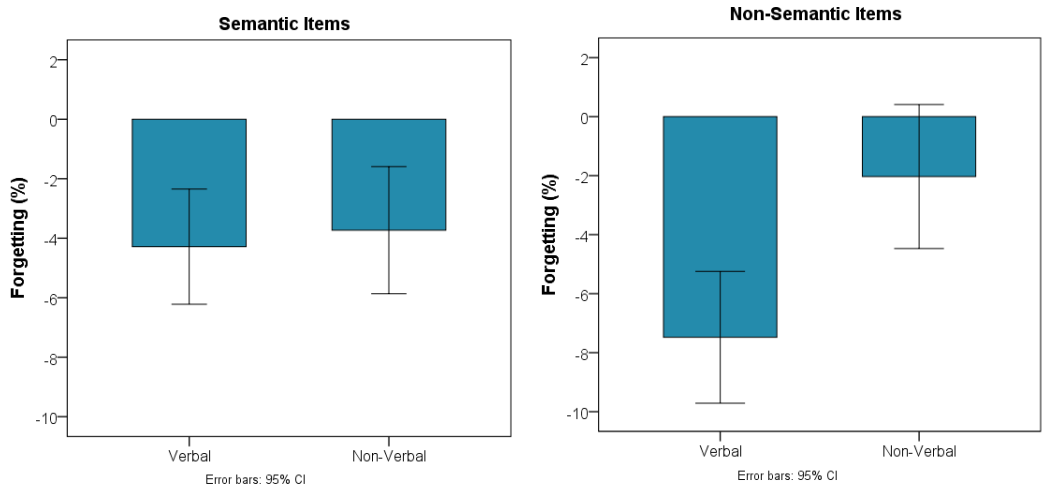


Figure 3.11 Interaction between Material and Semantics.

3.2.7 Modality Effect

There was no significant effect of modality of presentation on the amount of forgetting after a delay (-4% in both modalities, Table 3.12) ($F_{(1,126)}$=0.177, p=0.675). Figure 3.12 illustrates that the amount of information that was lost after a delay was similar whether the information was presented in the auditory or visual modality.

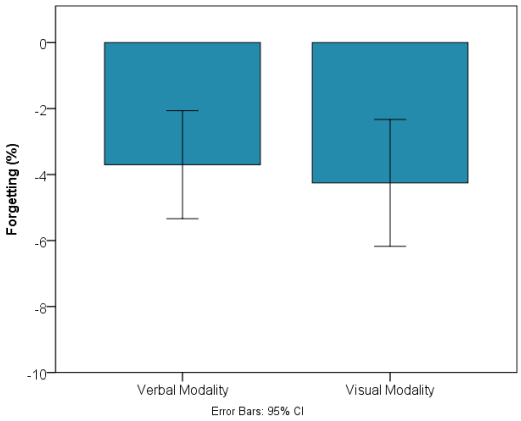


Figure 3.12 No Effect of Modality on Forgetting.

Table 3.12 Descriptive statistics for forgetting of auditory and visual items (%).

Modality	Mean	SD
Auditory	-4	9
Visual	-4	11

3.3 Recognition

3.3.1 Measure

The measure of recognition accuracy was computed by subtracting intrusion errors and familiar errors from correct recognition of target items [Target - (Intrusion + Familiar error)]. Intrusion errors consisted of selecting a new item that was not part of the studied list, and familiar errors consisted in selecting a familiar stimulus that was among the list to be remembered, but part of a different pair. A negative score indicates that more errors were made relative to correct performance (*i.e.* target).

3.3.2 Recognition Performance

Table 3.13 illustrates the descriptive statistics for recognition. The boxplot (Figure 3.13) illustrates the distribution of recognition accuracy across participants, for each subtest. A repeated ANOVA, with a 2 (concept: semantic, non-semantic) x 2 (material: verbal, non-verbal) design was computed to explore familiarity errors. A significant effect of semantics was shown ($F_{(1,120)}$=40.23, p<0.001), with more familiarity errors made for non-semantic items (10%) than semantic items (5%).

Table 3.13 Descriptive statistics for recognition scores (%).

Subtests	Target	Intrusion error	Familiar error	Recognition accuracy	SD	Min	Max
Spoken words	94	1	5	87	25	0	100
Written words	94	1	5	88	24	-40	100
Objects	95	1	4	90	21	0	100
Designs	88	1	11	76	30	-40	100
Pseudowords	88	3	9	76	35	-80	100
Overall	91	1	7	83	20	4	100

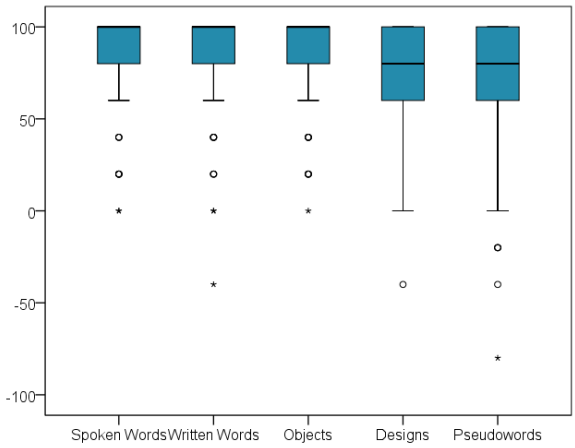


Figure 3.13 Boxplot illustrating the distribution of recognition accuracy for each subtest.

3.3.3 Relationship with Intellectual Abilities

A partial correlation, controlling for the effect of age, showed that FSIQ was significantly related to recognition accuracy across subtests (r=0.22, p=0.015), where those with higher FSIQ had better recognition scores (Figure 3.14). Investigating each subtest individually showed a significant correlation with recognition accuracy for Pseudowords only (r=0.26, p=0.005), and not for the other subtests (Table 3.14).

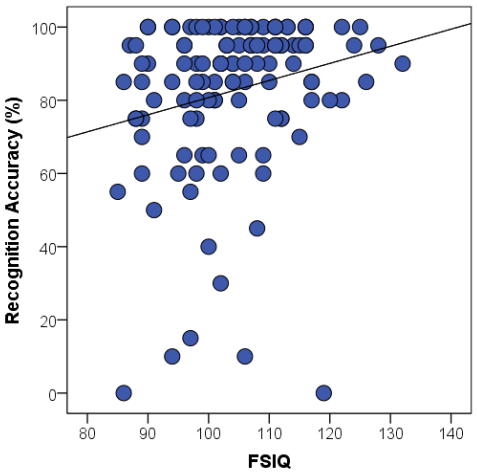


Figure 3.14 Correlations between recognition in each subtest and FSIQ.

Table 3.14 Correlations between FSIQ and recognition scores.

Subtests	*r*	*p*
Spoken words	0.12	0.186
Written words	0.09	0.313
Objects	0.17	0.075
Designs	0.16	0.097
Pseudowords	0.26	0.005
Overall	0.22	0.015

3.3.4 Developmental Trajectory of Recognition

A partial correlation, controlling for the effect of FSIQ, showed a relationship between age and recognition (r=0.34, p<0.001), whereby older children had better recognition scores than younger children (Figure 3.15 and Table 3.15). This was observed across all subtests, apart from the Spoken Words which did not reach acceptable levels of statistical significance (r=0.164 p=0.078).

In addition to recognition accuracy, familiar errors were also investigated as these indicate familiarity-based retrieval of information. A significant negative correlation was observed with age, after controlling for FSIQ (r=-0.39, p<0.001), where older children produced less familiar errors than younger children.

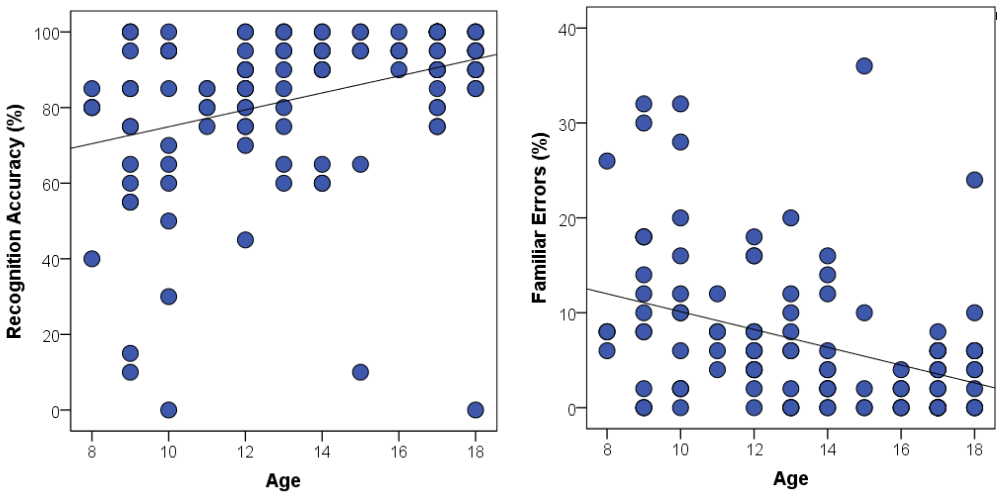


Figure 3.15 Correlations between age and recognition accuracy/familiar errors.

Table 3.15 Correlations between age and recognition accuracy/familiar errors.

A. Recognition Accuracy

Subtests	*r*	*p*
Spoken words	0.16	0.078
Written words	0.24	0.010
Objects	0.29	0.002
Designs	0.31	0.001
Pseudowords	0.25	0.008
Overall	0.34	<0.001

B. Familiarity Error

Subtests	*r*	*p*
Spoken words	-0.19	0.032
Written words	-0.30	0.001
Objects	-0.26	0.006
Designs	-0.31	0.001
Pseudowords	-0.25	0.006
Overall	-0.39	<0.001

3.3.5 Effect of Semantics

A significant main effect of semantics ($F_{(1,119)}$=44.074, p<0.001) indicates that semantic items were better recognised than non-semantic items (89% and 76%, respectively) (Table 3.16 and Figure 3.16).

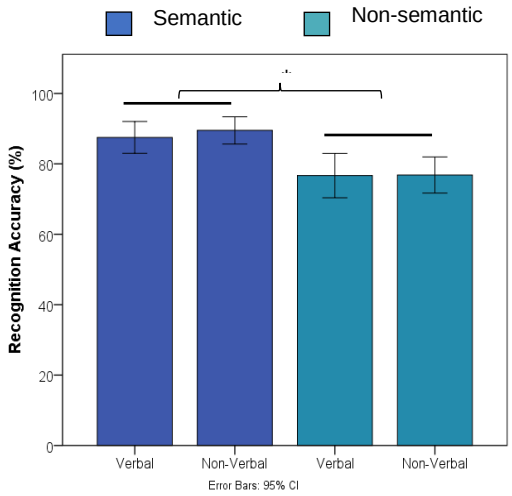


Figure 3.16 Effect of semantics on recognition.

Table 3.16 Descriptive statistics for recognition of semantic and non-semantic items (%).

Conceptual Level	Mean	SD
Semantic	89	23
Non-semantic	76	33

Partial Pearson correlations demonstrate that recognition accuracy was related to intellectual abilities for non-semantic items (r=0.26, p=0.005), but not for semantic items (r=0.14 p=0.129) (Figure 3.17). Log transformation was applied on the recognition scores of semantic items in order to account for ceiling effects. Correlation analysis on the transformed scores showed significant relation with FSIQ (r=0.24, p=0.008).

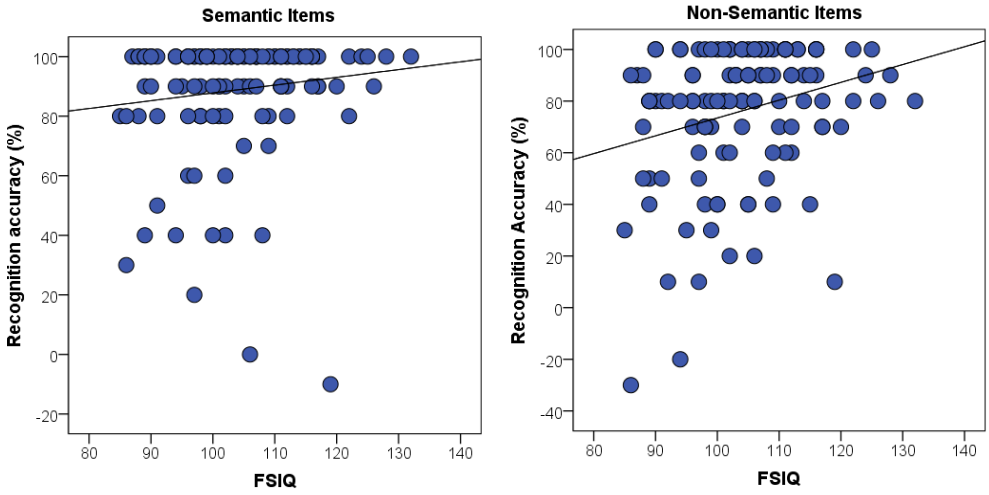


Figure 3.17 Correlations between FSIQ and recognition for semantic and non-semantic items.

3.3.6 Effect of material type

There was no evidence of effect of material type on recognition ($F_{(1,119)}$=0.335, p=0.564), indicating that verbal (82%) and non-verbal (83%) materials were similarly recognised (Table 3.17 and Figure 3.18).

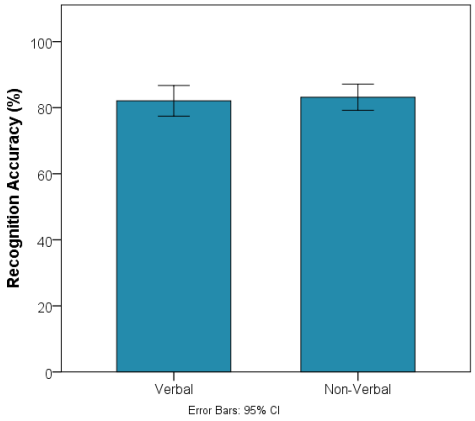


Figure 3.18 No material-effect on recognition.

Table 3.17 Descriptive statistics for recognition of verbal and non-verbal (%).

Material	Mean	SD
Verbal	82	25
Non-Verbal	83	23

3.3.7 Modality Effect

There was no evidence of a modality effect on recognition ability ($F_{(1,123)}$=0.096, p=0.758). Table 3.18 and Figure 3.19 illustrate that information presented in the auditory (87%) or visual modality (88%) were similarly recognised.

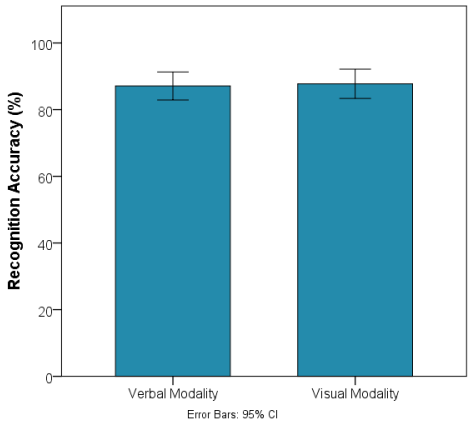


Figure 3.19 No modality-effect on recognition.

Table 3.18 Descriptive statistics for recognition of auditory and visual items (%).

Modality	Mean	SD
Auditory	87	25
Visual	88	24

3.4 Summary of Findings

Several hypotheses were generated based on the theoretical framework and current literature on learning and memory in children. Table 3.19 provides a summary of the findings corresponding to each hypothesis.

Table 3.19 Summary of generated hypotheses and the results

Hypotheses		Results
1	Paired-associate learning, as well as subsequent recall and recognition of learnt material will improve with age	Age-related improvement was observed for learning (r=0.53 p<0.001) and recognition (r=0.34 p<0.001), but less so for recall (r=0.19 p<0.033) where the correlation was driven by the Spoken Words subtest. The same pattern of results was found for intellectual status, whereby higher IQ was associated with better learning (r=0.43 p<0.001) and recognition (r=0.22 p=0.015), but not with recall (r=-0.10 p=0.270)
2	Better learning and memory will be shown for non-verbal compared to verbal materials	Better learning (47% *versus* 41%, p<0.001) and less forgetting (-2% *versus* -7%, p<0.001) was found for non-verbal compared to verbal materials, but only for non-semantic information (Designs *versus* Pseudowords). No material-specific effect was shown for recognition (82% *versus* 83%, p=0.564).
3	Better learning and memory will be observed for verbal information presented in the visual, compared to the auditory modality	Better learning (p=0.022) was shown for written words (66%) compared to spoken words (61%). However, no difference was shown for recall (-4% in both modalities, p=0.675) or recognition (87% and 88%, p=0.758).
4	High IQ will be associated with better learning and memory for non-semantic, but not for semantic information	High IQ was associated with greater gain in learning for non-semantic items (r=0.41 p<0.001), but not for semantic items (r=-0.03 p=0.749). Similarly, high IQ was associated with better recognition for non-semantic items (r=0.26, p=0.005), but not for semantic items (r=0.14 p=0.129). The effect of IQ on semantic *versus* non-semantic items was not observed in scores of learning and forgetting.

4 Discussion

4.1 Development of Learning and Memory

The findings from the present study demonstrate distinct age effects for learning/recognition and recall. Whereas learning and recognition improved with increasing age (consistent with the first hypothesis), recall remained constant across the age range (inconsistent with predictions from the first hypothesis). These findings can shed light on the developmental trajectory of neocortical and hippocampal learning systems.

4.1.1 Learning and Recognition Abilities have a Developmental trajectory

The results documented in this study suggest age-related differences in learning and recognition, whereby improvement in performance was associated with increasing age. This finding is consistent with various studies investigating the development of long-term memory (Alexander & Smales, 1997); Baddeley et al., 2011; Harel et al., 2014; Ghetti & Bunge, 2012). For example, Helmstaedter and Elger (2009) documented age-related improvement in verbal learning (word list learning), from age 5 until about 22 years (Helmstaedter & Elger, 2009). The results from the current study corroborate the findings from previous developmental studies and demonstrate increasing capacity for learning as the ability for binding increases. The development of episodic memory may therefore be a result of increased efficiency with which information is processed and retained in long-term memory.

Despite a significant age effect in the present study, the results show only subtle developmental changes in learning and recognition. The moderate age effects on learning and recognition performance are consistent with the observation that these processes emerge in early infancy (Fagan, 1970; Pascalis & de Schonen, 1994; Rudy et al., 1993). The pillars for learning and recognition processes are therefore established early in life, and age-related changes in performance possibly reflect specialisation of these processes and access to a larger pool of strategies and knowledge. As they get older, children have increasing access to semantic knowledge and to mnemonic strategies that may be useful for learning arbitrary pairs of items.

In this respect, age-related changes in learning and recognition may be a result of the use of more elaborate strategies (Bjorklund et al., 2009). In the present study, high IQ was also associated with increased learning and recognition performance. Parallel relationships with intellectual abilities are therefore consistent with this hypothesis, whereby higher intellectual functioning may be associated with the use of strategies to process information (Kron-Sperl et al., 2008). Moreover, putative neocortical networks become more differentiated as semantic categories expand and differentiate, and generalisations across and within conceptual categories emerge.

4.1.2 Recall Ability does not Show a Developmental Trajectory

Whereas the ability to learn and recognise previously learnt information was age-dependent, the ability to bring back to mind the same information was not. The present study showed age-invariant ability for the recall of learnt information, after the level of prior learning was taken into account. Despite late emergence of the recollective process, the present findings suggest that once established, the capacity is age-invariant.

This finding is inconsistent with age-related improvement in recall reported in previous studies (Bjorklund et al., 2009; Ghetti & Angelini, 2008; Ghetti et al., 2011; Lloyd et al., 2009; Sluzenski et al., 2006). However, previous studies that have shown improvement in recall with age have not accounted for prior learning. Age-related changes reported in those studies could therefore be due to changes in learning as well as retention abilities. Helmstaedter et al. (2009) used a similar score to the one used in the present study to take account of learning capacity, and also showed age-related improvement. However, in contrast to the present study which included five subtests, these authors examined auditory verbal memory only, and it is possible that age-related improvement in retention may be a characteristic that is specific to the auditory modality. This will be discussed in section 4.3. The present finding therefore indicates that retention remains the same across the age range if learning capacity is controlled for, and suggests the importance of accounting for learning capacity when studying development of retention. In addition, the paradigm used by Helmstaedter and colleagues was not paired-associate, but instead supra span learning of categorisable single

items. As such, the recall (after 5 repetitions) is more neocortically mediated than in the Pair Games. to

The present study indicates a finite age-invariant capacity to bring back to mind information that is bound as a paired-associate, after a short delay. This interpretation is also supported by the absence of a relationship between recall and IQ, suggesting that recall ability does not change as a function of intellectual ability. In addition, similar levels of recall were shown for different types of information (temporal *versus* configural nature of input modality and semantic *versus* non-semantic representations), indicating that recall ability is not influenced by modality and representational content of the stimuli. Age-invariant recall ability may indicate that the hippocampal learning system is memory pure, independent of other cognitive factors that instead influence the neocortical learning system.

Whereas there is evidence of developmental changes in the structure of the hippocampus until the age of 25 (Gogtay et al., 2006), it has been shown that the hippocampus develops rapidly in the first few years of life, but with slow increases after that. In this respect, a relationship between hippocampal volume and memory ability would have been predicted in early childhood and less so in older children. Yet, hippocampal-dependent episodic memory does not appear to emerge until later in childhood. However, studies show similar relationships between hippocampal volume and memory in children and young adults, but a diminished relationship during adulthood (see Van Petten, 2004, for a review).

It is understood that a) learning is dependent on hippocampal-neocortical interactions, b) recall is predominantly mediated by hippocampal retrieval mechanisms, and c) recognition is primarily dependent on the parahippocampal cortices. Based on the above theoretically-guided framework, it is possible that different developmental changes for learning/recognition and recall reflect distinct maturation of neocortical and hippocampal systems. The neocortical learning system may show functional maturation across childhood and adolescence, mirroring the protracted neurodevelopment of cortical areas, such as cortical thickness of the temporal lobe (Gogtay et al., 2004; Sussman et al., 2016), as well as the interaction between the hippocampus and the temporal and prefrontal cortices (Bachevalier & Vargha-Khadem, 2005; Mishkin et al., 1997; Mishkin et al., 1998). On the other hand, the hippocampal learning system may be more

age-invariant. Whereas hippocampal volume develops across childhood and adolescence (Gogtay et al., 2006), it is established that subfields of the hippocampus may develop at different rates, with for example the CA1 reaching structural maturity by the age of 2 years. Distinct maturation for subregions of the hippocampus may contribute to the observation that not all functions of the hippocampus develop at the same rate (Bachevalier & Vargha-Khadem, 2005). More research is required to investigate the mechanisms underlying recall ability and its development before it reaches maturity, as well as to reconcile the current behavioural observations with neurodevelopmental findings on the maturation of the hippocampus.

4.2 Superiority of the Visuo-spatial System for Learning and Recall

The balanced nature of the Pair Games allows for adequate comparison between subtests, such as verbal and non-verbal subtests, allowing direct comparison between verbal and non-verbal memory systems. Whereas pictorial information is configural, verbal information is temporal and sequential; therefore it is assumed that verbal and non-verbal materials are processed differently.

Consistent with the second hypothesis, non-verbal materials were better learned and were less susceptible to forgetting after a delay than verbal materials, suggesting that once non-verbal information is learned, the memory traces are well-retained after a delay. This could suggest better encoding and consolidation of non-verbal, compared to verbal material over time; thereby making those memory traces more resistant to interference. This is consistent with adult studies which demonstrated superiority of non-verbal over verbal learning and memory, with better learning and slower decay of non-verbal representation of information compared to verbal representation (Hockley, 2008; Stenberg & Radeborg, 1995). Interestingly, this effect of material type is not observed in recognition, possibly reflecting an effect of accessibility rather than availability of information. The present study therefore demonstrated better non-verbal than verbal learning and memory, extending adult findings to children and adolescents.

An interesting finding is that the material effect reported here was only observed for non-semantic items, and no difference was shown for semantic materials.

Non-semantic items were developed with the aim of minimising the effects of the dual route to learning and retention, whereby pseudowords are visualised with more difficulty than words, and designs are verbalised with more difficulty than objects. This was verified with participants' debriefs wherein they reported less dual encoding for non-semantic items. However, it is possible that a dual-route strategy was more accessible for designs than for pseudowords, with verbalisation of designs easier than visualisation of pseudowords. This could contribute to the effect of material type shown for non-semantic items. The absence of an effect of material type for semantic items may suggest that these items are processed with multiple semantic associations, whereby both verbal and non-verbal information are encoded and stored visually and verbally through a dual-process. On the other hand, it is also possible that the two systems actually differ in their mnemonic efficacy, with mnemonic superiority of the visual code over the verbal code (Stenberg & Radeborg, 1995). This material-effect for non-semantic items is consistent with the theory of mnemonic superiority of the non-verbal memory system, with better learning and retention of non-verbal compared to verbal items indicating stronger visuospatial representations. An important note to consider relates to the difference between 2- versus 3-dimensional visuo-spatial abilities. The latter is truly spatial in that it externalises the representation from within self to the external space outside of one's own. The pattern of results obtained with the Pair Games may therefore be specific to 2-dimensional visuo-spatial ability.

Disparity in the mnemonic performance across materials may be related to differences in cognitive processes. On the assumption that configural processing is less cognitively demanding than orthographic processing, participants may have more possibility to explicitly engage in elaborate processing of non-verbal materials. Distinct mnemonic strategies may be employed at encoding, with subvocal rehearsal of verbal information, and more elaborate strategies for non-verbal information, such as the binding of individual items of a pair, leading to better performance. This hypothesis is consistent with the strategies reported by participants when debriefed on the tasks. In addition, whereas verbal paired-associate learning is influenced by reading/writing abilities (Elbro & Jensen, 2005; Litt et al., 2013; Messbauer & de Jong, 2006; Wang et al., 2017; Windfurh, 2001), the present finding suggests that non-verbal paired-associate is less cognitively demanding than verbal paired-associate learning. The superiority of non-verbal

over verbal learning and memory may therefore reflect reduced cognitive load and more elaborate mnemonic strategies.

From a neurobiological point of view, the superiority of the visuo-spatial system mirrors neurodevelopmental findings. Several studies suggest that the right hippocampus is functional earlier than the left hippocampus, through higher activation (Prabhakar et al., 2018) and higher volume (Thompson et al., 2009; Uematsu et al., 2012) to support early visuo-spatial abilities (Burgess et al., 2002). Whereas the present study did not show material-specific effects of age, it is possible that these would have been observed in a younger sample (below 8 years old), with possibly stronger age-related changes in verbal compared to non-verbal learning and memory. Despite similar rates of development for verbal and non-verbal materials, it is possible that visuo-spatial memory emerges earlier and remains better than verbal memory across childhood and adolescence, as a result of early functionality of the right hippocampus.

4.3 Modality Differences for Learning

This study allowed delineation of two separate modalities (auditory and visual modalities) for the processing of verbal material. Consistent with the third generated hypothesis, words presented in the visual modality were better learned than words presented in the auditory modality. Differences in performance based on the input modality were observed for learning but not retrieval (recall and recognition scores), implying that performance equalised during consolidation. In addition, age-related improvement was observed in the retention of spoken words, but not of other information type, suggesting that it is a characteristic specific to auditory verbal memory.

4.3.1 Better Learning for Written than Spoken Words

The modality asymmetry, with better learning of written compared to spoken words reported here is consistent with adult studies (Fueller et al., 2013; Janczyk et al., 2018; Nelson et al., 2005), and may be associated with differences in the quality of phonological and orthographic representations. Moreover, an ERP study showed longer processing time for temporal analysis of auditory information compared to visual information (Kayser et al., 2003), providing

evidence that the superiority of the visual modality may result from reduced cognitive load of maintaining temporal representations. Overall, the visual modality system appears to be more efficient for the initial processing and memory trace formation of words.

4.3.2 Performance Equalises over Consolidation

Whereas differences between the two modalities were observed for learning, performance equalised during consolidation, and no modality effect was shown for subsequent recall and recognition. One possible explanation is that the graphic and phonological mnemonic traces are strengthened with repeated presentations, and repeated learning allows for the establishment of decontextualized representations, creating stronger traces and reducing effects of input modality after a delay.

This finding has important clinical implications, as it is possible that children with learning difficulty do not reach a level of learning that is sufficient for establishing robust and decontextualized representations and may show persistence of modality asymmetry after a delay. Strengthening memory traces by encouraging a combination of orthographical and phonological representations of words could help enhance retention. However, this is also related to IQ in that with patients who are of low ability, graphic and orthographic representations may not be able to rise to the level required to enhance retention. This finding warrants further investigation and more research is required to examine the utility of using orthographical representations as a mnemonic strategy in cognitive intervention.

4.3.3 Increased retention of auditory verbal information with age

Whereas no overall age-related changes were shown for retention (discussed in section 4.1.2, page 98), improvement was nevertheless found for the Spoken Words subtest, whereby verbal retention increased with increasing age. This finding replicates the findings of Helmstaedter's study which also demonstrated age-related effects of verbal retention. Because this age-related effect was only found for that subtest, and not for the other four, it is assumed that age-related changes in retention are specific to auditory memory. Evidence from animal studies raises the possibility that auditory memory in the service of verbal learning and retention may be related to the human-specific ability of speech. In

Fritz and colleagues' study (2016), monkeys were trained on auditory memory and although they showed evidence of visual and tactile memory, they exhibited great difficulty with auditory memory (Fritz et al., 2016), possibly as a result of lack of speech (Fritz et al., 2005). Monkeys are able to hold auditory information in working memory but not in long-term memory because this needs to ride on a sensory system for storage; which in the case of audition means auditory-motor links. For humans, the phonological subvocal reverberations when we perceive verbal information provide us with that auditory/motor link up. However, in the absence of such a link up, the monkey can only hold on to auditory traces for brief periods of time in working memory. This therefore suggests that long-term auditory memory is related to speech, and in that respect, development in auditory memory may mirror the development of language skills in children (Schulze et al., 2012). This finding may have important implication in the clinical context, in that it is possible that children who present with language impairments may also exhibit auditory long-term memory deficits.

4.4 Effect of IQ on Non-Semantic Learning Gain and Recognition

The present study showed that information containing semantic representations showed higher gain in learning and better subsequent recognition than non-semantic information, but no effect of semantic content was observed for retention. The levels of semantic structure of information to be encoded have an impact on how well it is learned and recognised, with better performance for semantic items as a result of more exposures and of easier access to pre-established representations. In a paired- associate task, semantic items of a pair need to be bound at encoding for later retrieval, but non-semantic items require the establishment of semantic representations before the items of a pair can be bound into a holistic representation. Whereas semantic items allow semantic linking to facilitate learning, non-semantic items reduce this possibility and, in this respect, push the limits of new learning.

Consistent with the fourth hypothesis, the effect of semantics on learning gain and recognition was found to be IQ-dependent. This finding is consistent with another study which demonstrated that individual differences in learning of a

complex video game are mediated by differences in fluid intelligence (Lee et al., 2015). In the present study, children with higher IQ showed higher performance for non-semantic information than children with lower IQ, possibly as a reflection of the efficiency of encoding strategies (Bjorklund et al., 2009; Cusack et al., 2009; Kron-Sperl et al., 2008). For example, deep-encoding strategies may be employed by children with higher intellectual status, whereas those with lower IQ might process the perceptual components of the paired items. Easy items (*i.e.* semantic items in the present study) are processed through the use of similar strategies (or different strategies of the same efficiency) across IQ levels, whereas difficult items (*i.e.* non-semantic items in the present study) are processed differently based on IQ levels. The finding therefore shows that non-semantic learning and recognition are mediated by variations in IQ, whereas recall is not.

Intellectual ability is a function of the cortical network and age-related improvements are mediated by cortical maturation, such as cortical thickness, as well as access to more extensive neuronal networks and higher levels of semantic categorisation (Burgaleta et al., 2014; Shaw et al., 2006). The neuroanatomical correlates of intellectual ability and their relation with the cortical learning system (learning and recognition), but not with the hippocampal learning system (recall), provide added evidence of the two the separate systems (cortical *versus* hippocampal). Whereas knowledge of words is dependent on the neocortical system (Marslen-Wilson, 1984; Tranel et al., 2001), learning new material is dependent on hippocampal-neocortical interactions (Davis et al., 2009). Neuropsychological evidence suggests that initial processing of new words (pseudowords) is supported by the hippocampal learning system (Gooding et al., 2000; Vergaellie et al., 1995), and gradually becomes integrated into the neocortical learning system, through hippocampal-neocortical interactions as novel words become familiar (Davis et al., 2009). This suggests that non-semantic learning could be a marker for the ability of hippocampal-neocortical interactions in children with TLE. Together, these findings support the complementary learning systems theory which posits separate cortical and hippocampal learning systems (McClelland et al., 1995).

The influence of IQ on the ability to learn new information may have important clinical implications. On the basis of the present findings, it may be possible to

address individual differences in cognitive rehabilitation and help design and implement more effective training programmes. Patients with lower IQ may benefit from deep processing of information and explicit training instructions, and may require more guided intervention to improve cognitive rehabilitation success. It is possible that these patients will benefit from strengthening of the habit learning system which is slow in contrast to the hippocampal cognitive learning system which is fast and trial unique. Moreover, tests of non-semantic items showed that higher initial acquisition (at trial 1) was associated with *higher* learning gain. On the other hand, in tests of semantic items, higher initial acquisition was associated with *lower* learning gain due to lower opportunity for improvement or possibly effects of proactive interference. This observation suggests that non-semantic paired-associate learning tests may be more sensitive for the assessment of learning gain than tests of semantic items. In order to assess whether a patient may benefit from repetitive learning in the educational setting for example, non-semantic paired-associate learning tests may be more appropriate. These findings provide important clinical implications.

5 Limitations

The measures obtained in this study are based on accuracy of responses. It is possible that some more subtle effects were not captured with this methodology and could be captured using methods such as reaction time. In addition, the Pseudowords and Designs subtests were developed with the aim of minimising dual-encoding strategies in order to reflect purer measures of verbal and non-verbal memory compared to words and objects. However, complete abolishing of a dual-route strategy is not possible and it could be argued, for example, that some level of verbalisation is still possible for the abstract shapes, allowing verbal labelling in addition to the visual code. Nonetheless, this verbal coding of shapes did not seem to occur frequently and when debriefed on the task, participants reported encoding the visual properties of the shapes. This observation was similar for the Pseudowords.

6 Conclusions

The aim of the present chapter was to characterise the profiles of learning and memory in a large sample of children across a wide age range, documenting

developmental changes. Four main findings were discussed. First, increasing age across childhood and adolescence was related to improved learning and recognition. However, the ability to recall learnt information from long-term storage was not age-dependent. From a methodological point of view, this finding indicates that it is crucial for memory tests to employ a scoring system that accounts for such distinct age-related effects. A delayed recall score which does not take prior learning into account will provide a misinterpretation of age-effects. The present findings therefore highlight the advantage of a "forgetting" score over a stand-alone "delayed recall" score. Second, lower performance was shown for verbal compared to non-verbal memory, providing evidence of the superiority of visuo-spatial representations. Third, lower learning was shown for auditory compared to visual memory indicating modality differences at the initial acquisition, although performance equalised after consolidation. Fourth, levels of semantic structure of information had an impact on how well the relevant material was learned and memorised in children and this effect was dependent on IQ levels. Overall, the present study provides evidence for distinct developmental trajectory of the hippocampal *versus* neocortical learning systems, and characterises learning and memory performance for different types of materials, shedding light on the underlying mechanism of these functions.

7 Future Directions

The clinical utility of the Pair Games paradigm will be assessed by collecting data on different clinical groups with known or suspected MTL pathology. Administering this paradigm to a group of patients with TLE would provide more refined measures than currently available to detect learning and memory impairments in patients with damage to regions critical for these functions. Comparison with standardised diagnostic measures would shed light on the added value of the Pair Games for the identification of specific impairments.

Chapter 4

Pilot of the “Pair Games” in Childhood TLE

In the present chapter, the Pair Games was piloted in a small sample of paediatric patients with TLE who were candidates for surgery. Performance of patients on this novel protocol was compared with performance on standardised tests. The aim was to assess whether the Pair Games could reveal the status of lateralisation in individual patients with unilateral pathology in the temporal lobe, and characterise any selective deficits consistent with the underlying neuropathology. More specifically, the added clinical value of the Pair Games over the standardised tests was investigated.

1 Introduction

Temporal lobe epilepsy (TLE) is a common form of seizure disorder. Given that the hippocampus plays a major role in the generation and spread of temporal lobe seizures (McIntyre & Racine, 1986) and is also a critical structure serving long-term memory, including episodic memory (Squire & Zola-Morgan, 1991), impairments in memory and learning are frequently documented in patients with TLE. The effects of TLE on cognitive function can be quite different in children compared to adults. The present chapter focuses the review of the literature on TLE in paediatric cases.

In such patients, identification of specific learning and memory impairments is critical, particularly in MR-negative cases where a structural lesion is not visible. Evidence of cognitive impairment may indicate covert pathology, with specific neuropsychological deficits related to compromised neural systems. This type of brain-behaviour-dependent information can in turn identify the territory of covert brain pathology and inform surgical decision-making.

Evidence suggests that in patients with epilepsy, particularly in those with early onset of seizures, the extent of cognitive impairment may be often greater than the territory of the lesion (Cormack et al., 2005). For example, Hippocampal Sclerosis (HS) is frequently associated with a more extensive pattern of extra-temporal lesion than other types of epileptogenic lesions. Patients with HS thus present with greater functional and structural alterations in brain organisation than those with mesial TLE associated with other lesions such as tumours (Wei et al., 2016).

Evidence of wider cognitive impairment was also put forward by Skirrow et al. (2015), who identified “release effects”. The authors showed that, after surgery for TLE, children showed improvement in memory functions typically subserved by the unoperated temporal lobe (Skirrow et al., 2015). As such, improvements in verbal memory were observed after right temporal lobe surgery, and improvements in non-verbal memory were observed after left temporal lobe surgery. This release phenomenon is a reflection of the combined effects of reduction of seizures, cessation of drug therapy, as well as the release of the functions of the unoperated side from the spill over of seizures from the damaged

side. These release effects suggest that unilateral seizures have noxious effects on the memory function subserved by the contralateral side, which may not be consistently identified pre-operatively. The cognitive profile may therefore be more severe than the visible lesion. In view of these considerations, neuropsychological tests based on knowledge of structure/function relationships within and beyond the MTL system are required to ascertain the status of memory and learning in relation to other aspects of cognitive function to help with surgical decision-making.

1.1 Lateralisation of Memory Deficits

In adults, unilateral temporal lobe lesions result in material-specific memory deficits, wherein left and right temporal lesions are associated with verbal and visual memory deficits, respectively (Jones-Gotman et al., 2000; Golby et al., 2002; Milner, 1966; Willment & Golby, 2013), however inconsistencies have also been reported (see Saling, 2009, for a review). These side-dependent dissociations in memory are interpreted in terms of the underlying hemispheric specialisation of function that is normally well established in adults and is compromised after unilateral temporal lobe seizures/lesions.

In children, long-term memory and learning deficits are frequently reported, but material-specific deficits are not as clearly side-dependent as in adults, and studies show inconsistent findings. Several studies have documented verbal memory impairment in left TLE (Cohen, 1992; Engel, 1998; Kibby et al., 2014; Kar et al., 2010) and non-verbal memory impairment in right TLE (Cohen, 1992; Engle & Smith, 2010; Kibby et al., 2014). However, when comparing the performance of left and right TLE patients directly, some studies reported more non-verbal memory deficits in the right TLE group compared to the left TLE group for dot location (Kibby et al., 2014) and face recognition (Mabbott & Smith, 2003; Gonzalez & Anderson, 2007; Kibby et al., 2014), but no difference was observed between the two patient groups on measures of verbal memory. Other studies showed no difference between the two groups on any measure of verbal and non-verbal memory (Cohen, 1992; Engle & Smith, 2010).

The argument for this pattern of finding may also relate to the observation that the net effect of a unilateral lesion sustained in childhood is impairment in non-

verbal functions, including non-verbal memory. A left-sided lesion often leads to reorganisation of language along with verbal memory to the right hemisphere thus “crowding out” visuospatial functions of the right side. At the same time, a lesion of the right hemisphere impairs non-verbal functions of that side. In this respect, impairment in non-verbal memory is observed irrespective of side of pathology. Moreover, a generalised pattern of dysfunction may be related to several factors including age at onset of epilepsy and the manifestation of bilateral disease despite focal signs (see Chapter 1, section 5.1, page 26). In addition, inconsistent findings across studies may be related to the insensitivity of neuropsychological tools to measure lateralisation of cognitive deficits.

1.1.1 Standardised tests are not sensitive enough to detect anomalous patterns of cerebral lateralisation

Whereas there is some evidence of material-specific deficits in the literature, the findings are inconsistent across studies and reports have been confounded by unbalanced tests and the lack of test sensitivity to measure laterality effects. The inadequacy of the tests is even more striking in paediatric studies wherein the patterns of impairment are more varied and less clear-cut than those in adults. These tests may not be sensitive enough to capture the processes dependent on the mesial *versus* the lateral cortical regions, or the specialisation of the left and right temporal lobes.

Investigation of laterality effects in memory has been confounded by several factors. First, verbal memory has been typically assessed through recall whilst non-verbal memory has been assessed through recognition. Such comparisons are problematic because the processes of recall and recognition are dependent on distinct subregions of the temporal lobe (Diana et al., 2007; Patai et al., 2015). In addition, recognition is easier than recall, making a balanced comparison more difficult to achieve. Second, access to semantic representations has not been balanced in verbal and non-verbal memory tests. Thus, verbal memory tests commonly use words, which have a semantic representation, whilst non-verbal memory tests often use abstract designs which do not carry representational content. Third, the input modality (auditory *versus* visual) has been confounded whereby verbal memory tests are often presented in the auditory modality whilst non-verbal memory tests are presented in the visual modality. In addition, ceiling

effects shown in some subtests (*e.g*. Dot Locations from the CMS) may not capture any underlying impairment.

These considerations raise the need for directly comparable measures to assess and contrast verbal and non-verbal memory performance and to capture any laterality effects. The difficulty in addressing the question of memory lateralisation in childhood TLE also relates to the age at onset of seizures and the status of hemispheric specialisation prior to the insult (see Chapter 1, section 5.1, page 26).

1.2 Compromised Memory Processes

In addition to the effects of side of temporal lobe pathology, the pattern of learning and memory dysfunction in TLE may be related to the involvement of cortical *versus* mesial temporal lobe structures. Different functional roles of cortical *versus* mesial structures have been put forward in animal and adult studies (Cohen & Eichenbaum, 1993; Eichenbaum et al., 1992; Murre, 1996; Saling et al., 2002; Squire, 1992; Squire et al., 1993), whereby mesial temporal lobe structures mediate retrieval processes of new information and cortical structures store long-term memories. Adult patients with pathology in these specific structures show distinct memory profiles, whereby deterioration in delayed recall is related to mesial pathology and impairment in learning and recognition are often associated with pathology in temporolateral structures (Bugerman et al., 1995; Helmstaedter et al., 1997; Helmstaedter et al., 1996).

In childhood TLE, the influence of mesial *versus* cortical temporal lobe pathology is less understood. Several studies have shown that mesial pathology is particularly susceptible to impairments in delayed recall (Law et al., 2017; Ljung et al., 2017; Rzezak et al., 2014; Zhao et al., 2014). Cormack and colleagues showed a larger effect of aetiology than side of lesion, where hippocampal sclerosis (HS), but not dysembryoplastic neuroepithelial tumours (DNET), was associated with impairments in delayed recall regardless of the side of lesion (Cormack et al., 2012). As mentioned above, MTS is more bilateral and extends beyond the MTL by virtue of its nature whereas DNET has a more restricted effect, often sparing the hippocampus and showing a more selective side-dependent effect.

However, the specific memory processes (*e.g*. recall *versus* recognition) impaired in TLE with cortical pathology has not been extensively studied. Nolan and colleagues directly compared mesial and cortical TLE paediatric groups but no difference was found between the memory performance of the two groups (Nolan et al., 2004). Gonzalez and colleagues demonstrated higher memory impairment in mesial than cortical TLE, particularly for measures of delayed recall of paired-associates (Gonzalez & Anderson, 2007). Neuropathology does not neatly occur in TLE making it difficult to separate how much is cortical *versus* mesial and how this variable relates to recognition *versus* recall. However, the clinical tools may not have provided adequate comparison between memory processes.

Investigations of mnemonic processes have been confounded in the literature, and methodological considerations of standardised tests may hinder the ability to compare learning, recall and recognition processes. First, the delayed recall score may not fully take account of the underlying process it intends to measure. Some patients may find it difficult to learn new information, but could nevertheless be able to maintain the learnt information over a delay. Such a profile of performance cannot be fully documented based on scores that are computed irrespective of prior learning, as for example in the CMS wherein the delayed recall score refers to the amount of information recalled after a delay. Second, whereas learning is assessed through cued recall in the CMS, retrieval after a delay is assessed using a free recall test, and the comparison between these two scores may therefore be confounded by the effects of distinct cognitive mechanisms involved in cued and free recall. Third, recognition tests that require a yes/no judgment may not be sensitive enough to capture impairment. This characteristic also affects chance level performance, which is reduced when more response options are available (*i.e*. chance=50% in the CMS, and 33% in the Pair Games). The standardised tests may therefore not provide adequate comparison between memory processes, thus impeding the accuracy of diagnostic assessments.

1.3 The Pair Games

The Pair Games was developed for the assessment of learning and memory, based on knowledge of the neurobiology of memory functions. This paradigm allows direct comparisons between verbal and non-verbal mnemonic functions,

and between separate memory processes (*i.e*. learning, recall and recognition). A full description of the development of the Pair Games can be found in Chapter 2, and normative data on a large sample of typically-developing children were described in Chapter 3. The construct of the Pair Games may provide an improved detection of specific learning memory impairments in patients with TLE.

1.4 Aims and Hypotheses

The aim of the present chapter is to pilot the Pair Games in a small sample of paediatric patients with TLE and evaluate the face validity of the novel instrument. The present chapter will present the pattern of performance across all cases, using both the standardised tests and the Pair Games. It is predicted that the overall pattern of performance will be better differentiated with the Pair Games than with standardised tests. More specifically, the Pair Games will more clearly identify:

a) The presence of verbal *versus* non-verbal impairments in relation to side of pathology (left *versus* right).
b) Different components of psychological processes (*i.e*. learning, recall and recognition) that may be compromised.

The patients involved in the current study presented as candidates for temporal lobectomy to the epilepsy surgery service at Great Ormond Street Hospital for Children NHS Foundation Trust. They were not selected to address specific questions relating to hemispheric side, site, and extent of pathology affecting the temporal lobe. Rather, these cases were representative of candidates for temporal lobe surgery. As such, they provide the opportunity to evaluate the clinical relevance and applicability of the Pair Games over and above the standardised protocols routinely used for pre-surgical evaluation of memory in our paediatric patient population. Isolating the mnemonic processes that may be compromised in these cases will inform surgical decision-making, and guide prognosis of memory outcome after surgery.

2 Methods

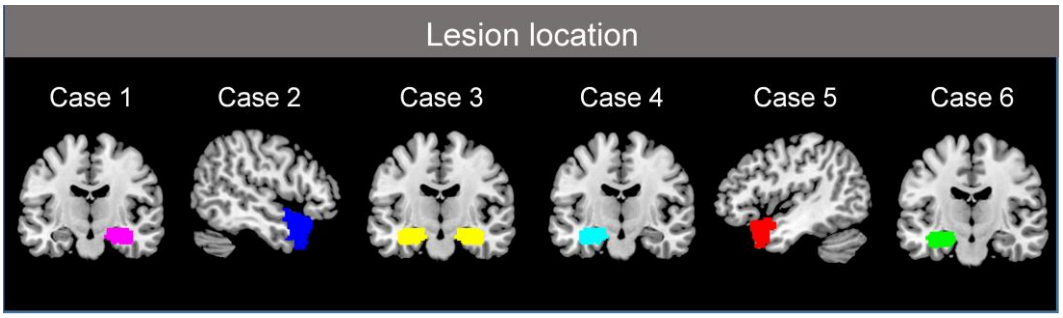
2.1 Participants

Six children with TLE were recruited from Great Ormond Street Hospital (GOSH) in London, UK for the purpose of this study. All patients were diagnosed with intractable epilepsy and had been on multiple anticonvulsant medication for a number of years. The sample is composed of three children with left-sided pathology, two with right-sided pathology, and one with bilateral pathology. The aetiology is varied, with four patients diagnosed with Hippocampal Sclerosis (HS) and two with pathology sparing the mesial structures on MRI (one with a porencephalic cyst and one with Dysembryoplastic Neuroepithelial Tumour (DNET) in the temporal lobe). one patient showed additional extra-temporal pathology, with Focal Cortical Dysplasia (FCD) in the parietal lobe. The age at onset of seizures ranges from 1 to 10 years, and the patients were aged between 12 and 18 years at the time of testing. Clinical characteristics of the patients are reported in Table 4.1 and a representation of the lesion location for each case is illustrated in Figure 4.1. Appendix F (page 365) provides the structural MRI scans (coronal and sagittal views) for each patient.

Table 4.1 Clinical Characteristics of Patients.

	Side of pathology	Aetiology	Seizure onset (age in years)	Age	Gender
Case 1	Right	HS	2	16	F
Case 2	Right	Porencephalic cyst in temporal lobe	9	16	F
Case 3	Bilateral	HS	9	16	M
Case 4	Left	HS	8	12	F
Case 5	Left	DNET in temporal lobe	11	16	F
Case 6	Left	HS and FCD in parietal lobe	1	18	F

Figure 4.1 Representation of the six cases' lesion location.



2.2 Standardised Neuropsychological Tests

All patients underwent a full neuropsychological assessment of language, memory and intellectual ability using standardised clinical protocols. Intellectual abilities were assessed using the Wechsler Intelligence Scale for Children 4th UK Edition, which provides standard scores for Full Scale IQ (FSIQ), Perceptual Reasoning (PSI), Verbal Comprehension (VIQ), and Working Memory (WMI). VIQ and PIQ scores for each case are presented in Table 4.2.

Table 4.2 VIQ and PIQ scores for each case.

	Side of pathology	VIQ	PIQ
Case 1	Right	96	102
Case 2	Right	99	94
Case 3	Bilateral	83	110
Case 4	Left	91	115
Case 5	Left	104	121
Case 6	Left	85	77

Patients aged below 18 (N=5) were administered the Children's Memory Scale which provides measures of verbal and non-verbal learning and memory. The verbal subtests of the CMS consist of story recall (Stories) and paired-associate learning (Word-Pairs). For the Stories subtest, the patient listens to a story and is asked to recall the contents from memory, immediately and after a 30 minute filled delay. The Word Pairs test consists of a list of pairs of words to be learned over three consecutive trials, through cued recall. A free recall test is then administered after a 30 minute delay, followed by a yes/no recognition test. The

non-verbal subtests of the CMS are Dot Locations and Faces. The former subtest evaluates spatial memory, whereby the patient is asked to learn the location of dots over three consecutive trials, then again after a delay of 30 minutes. The Face subtest consists of yes/no recognition judgments to a series of previously studied faces, assessed both immediately after exposure and after a 30-minute delay.

One patient who was above the age limit to be administered the CMS for clinical assessment (>16 years old) was instead administered the Wechsler Memory Scale 4th UK Edition (WMS-IV), which provides a comparable measure of verbal and non-verbal immediate and delayed memory.

2.3 The Pair Games

The Pair Games paradigm was developed for the assessment of learning and memory through recall to provide assessment of the functional integrity of the left and right hippocampus in patients with known or suspected pathology of this structure. The paradigm is composed of 5 subtests assessing verbal and non-verbal learning and memory. These subtests are Spoken Words, Written Words, Written Pseudowords, Objects and Designs. These subtests assess cued recall over three consecutive learning trials, as well as delayed cued recall and recognition after a 15 minute delay. The recognition tests involve multiple choice answers (1 target and 2 distractors), amongst which one distractor is a familiar item that belongs to another pair (familiar item) and another distractor is completely new to the test (new item). This method measures intrusion errors and false alarms and provides a more stringent evaluation of recognition.

The Pair Games provides measures of learning, delayed recall and recognition. The measure of learning is the average performance over the three consecutive trials. The measure of delayed recall is computed based on the amount of previously learnt information that is remembered after a delay, and in that respect, takes the level of prior learning into account. The measure of recognition is computed based on the number of target items that are successfully recognised, minus intrusion and familiar errors (refer to Chapter 2 for a more detailed description of these measures). Standard scores were computed from a sample of 130 typically-developing children.

2.4 Analyses

For the standardised tests, performance was examined using the scaled scores and standard scores. Results from the Pair Games paradigm are reported using standard scores, derived from raw scores using the standardisation tables reported in Appendix C (page 316). Standard scores from the standardised memory tests and the Pair Games are reported in Appendix E (page 362) for each patient separately.

A standard score of 100 reflects average performance of a given age-group, and scores of 85 and 115 are 1 standard deviation (*SD*) below and above the mean, respectively. Similarly, scores of 70 and 130 are 2 *SD*s from the mean, respectively. In that respect, scores of 70 or below reflect significant impairment. The full classification of standard scores is presented in Appendix B (page 315).

2.4.1 Lateralisation of Memory

Discrepancies between verbal and non-verbal scores were investigated to assess material-specific impairments. These discrepancy scores were examined using the CMS and the Pair Games, thereby comparing the two test instruments. In the CMS, verbal memory scores are composed of scores from the Word Pairs and Stories subtests, and non-verbal memory scores are composed of scores from Dot Locations and Faces subtests. Discrepancies between verbal and non-verbal scores were examined for immediate recall and delayed recall. The significance of discrepancies between these scores was evaluated using the CMS manual. Discrepancy between verbal and non-verbal immediate recall was not computed for one patient (Case 1), because this patient was assessed with another standardised test (WMS-IV) which does not provide computed measures of verbal and non-verbal immediate recall.

The Pair Games can determine how well a patient learns and remembers verbal material (Written Words and Pseudowords), compared to non-verbal material (Objects and Designs). Discrepancies between verbal and non-verbal memory were examined for learning, recall and recognition. For better comparison with the CMS, the effect of material type was investigated in the Pair Games separately for semantic items (Written Words *versus* Objects) and non-semantic items (Pseudowords *versus* Designs). Discrepancies between verbal and non-

verbal materials are presented in Appendix D, Table D.5 (page 361) for learning, delayed recall and recognition scores.

2.4.2 Compromised Memory Processes

With the CMS, measures of learning, recall and recognition were compared for the Word Pairs subtest only, as this is the only subtest that provides all the relevant measures. The significance of discrepancies between these scores was evaluated using the CMS manual. A measure of learning could not be computed for one patient (Case 1), because this patient was assessed with another standardised test (WMS-IV) which does not provide a measure of learning.

The Pair Games enables assessment of how well a child is able to learn *versus* how well he/she can recall the learnt information, as well as how well a child recalls *as opposed to* recognises newly learnt information. Discrepancies between learning and recall, and between recall and recognition were examined for each subtest separately.

3 Results

3.1 Lateralisation of Memory Deficits

3.1.1 CMS

Discrepancy between verbal and non-verbal scores was investigated for the measures of immediate recall and delayed recall across patients (Table 4.3). For the measure of immediate recall, 5/5 cases showed lower verbal compared to non-verbal scores. However, significant discrepancy was shown in only one patient (Case 3 with bilateral pathology), with higher verbal compared to non-verbal deficits. For delayed recall, the discrepancies were small, and in the expected direction based on the side of pathology in only 1/5 unilateral cases. Case 3 with bilateral pathology showed lower verbal compared to non-verbal delayed recall. None of the discrepancy scores between verbal and non-verbal delayed recall reached significance.

The directions of the discrepancies were generally not in accordance with the side of pathology. The test did not capture stronger non-verbal compared to

verbal learning/memory deficit in any of the six patients, even in the right-sided cases.

Table 4.3 Discrepancy between verbal and non-verbal scores for immediate recall and delayed recall, for the CMS (standard scores). Positive values indicate lower scores for non-verbal compared to verbal performance, and negative scores indicate the opposite. Based on the predictions, left TLE cases are expected to show negative scores (stronger verbal than non-verbal deficit), whereas right TLE cases are expected to show positive score (stronger non-verbal than verbal deficit). Numbers in red indicate significant discrepancy between verbal and non-verbal scores.

	Side of pathology	Immediate Recall	Delayed Recall
Significance threshold		18	19
Case 1	Right	NA	2
Case 2	Right	-4	-3
Case 3	Bilateral	-28	-6
Case 4	Left	-10	6
Case 5	Left	-9	3
Case 6	Left	-7	3

3.1.2 Pair Games

3.1.2.1 Semantic Subtests

Discrepancy between verbal and non-verbal scores was investigated for the Pair Games, for semantic and non-semantic subtests separately. The thresholds for significant discrepancy between scores for learning, recall and recognition are indicated in Table 4.4.

Within the right TLE group (N=2), lower non-verbal compared to verbal scores would be predicted based on the right-sided pathology. This was confirmed in 2/2 cases for learning, 2/2 for recall, and 1/2 for recognition. The discrepancies reached significance in one patient, for learning and recognition scores. Within the left TLE group (N=3), lower verbal compared to non-verbal scores was predicted. This was shown in 2/3 cases for learning, 3/3 cases for recall, and 1/3 cases for recognition for which the discrepancy reached significance. The patient with bilateral pathology (Case 3) showed a similar profile to the left-sided cases with verbal recall impairment. Figure 4.2 illustrates discrepancy between verbal and non-verbal scores for the CMS and the Pair Games (semantic subtests).

Table 4.4 Discrepancy between verbal and non-verbal scores for learning, recall and recognition, for semantic subtests of the Pair Games (Written Words *versus* Objects, standard scores). Positive values indicate lower scores for non-verbal compared to verbal

performance, and negative scores indicate the opposite. Based on the predictions, left TLE cases are expected to show negative scores (stronger verbal than non-verbal deficit), whereas right TLE cases are expected to show positive score (stronger non-verbal than verbal deficit). Numbers in red indicate significant discrepancy between verbal and non-verbal scores.

	Side of pathology	Learning	Recall	Recognition
Significance threshold		28	38	18
Case 1	Right	13	26	-4
Case 2	Right	38	1	25
Case 3	Bilateral	9	-36	1
Case 4	Left	-9	-15	-74
Case 5	Left	2	-20	1
Case 6	Left	-23	-18	12

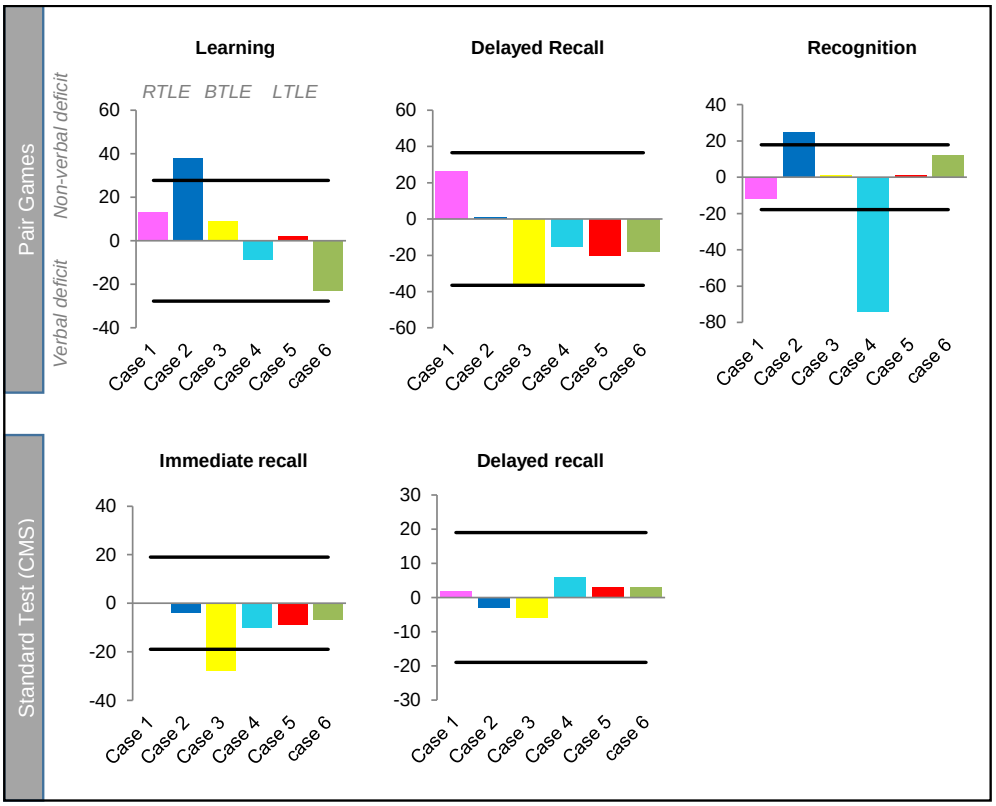


Figure 4.2 Material-specific impairment for learning, recall and recognition (for immediate and delayed recall for the standard test), within subtests composed of semantic items (Written Words and Objects). The bars represent verbal performance minus non-verbal performance, with positive values indicating higher non-verbal relative to verbal deficit, and negative values indicating the opposite pattern. Values close to 0 indicate little difference between verbal and non-verbal scores. The black lines indicate the threshold at which differences between scores are significant, based on data from the sample of typically-developing children.

3.1.2.2 Non-Semantic subtests

Material-specific effects were then investigated for non-semantic items, and the discrepancies between verbal and non-verbal scores are illustrated in Table 4.5. Within the right TLE group (N=2), lower non-verbal compared to verbal scores was shown in 1/2 cases for learning, 0/2 for recall, and 2/2 for recognition, but none of these discrepancies reached significance. Within the left TLE group (N=3), lower verbal compared to non-verbal scores were shown in 1/3 cases for learning, 2/3 cases for recall, and 2/3 cases for recognition. Amongst these discrepancies, 2 reached significance. Figure 4.3 illustrates discrepancies between verbal and non-verbal scores for the non-semantic subtests of the Pair Games.

Table 4.5 Discrepancy between verbal and non-verbal scores for learning, recall and recognition, for non-semantic subtests of the Pair Games (Pseudowords *versus* Designs, standard scores). Positive values indicate lower scores for non-verbal compared to verbal performance, and negative scores indicate the opposite. Based on the predictions, left TLE cases are expected to show negative scores (stronger verbal than non-verbal deficit), whereas right TLE cases are expected to show positive score (stronger non-verbal than verbal deficit). Numbers in red indicate significant discrepancy between verbal and non-verbal scores.

	Side of pathology	Learning	Recall	Recognition
Significance threshold		28	36	32
Case 1	Right	-15	-4	2
Case 2	Right	1	-30	7
Case 3	Bilateral	8	-5	13
Case 4	Left	10	-15	-19
Case 5	Left	-28	8	-15
Case 6	Left	5	-21	17

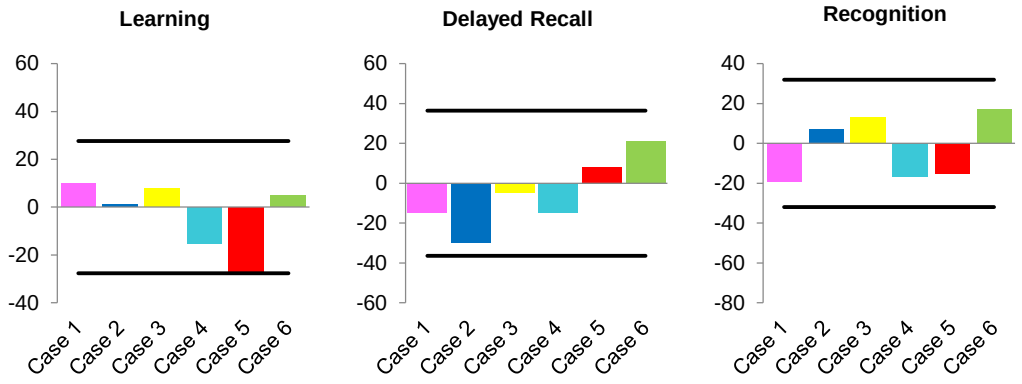


Figure 4.31 Material-specific impairment for learning, recall and recognition (for immediate and delayed recall for the standard test), within subtests composed of non-semantic items (Pseudowords and Designs). The bars represent verbal performance minus non-verbal performance, with positive values indicating higher non-verbal relative to verbal deficit, and negative values indicating the opposite pattern. Values close to 0 indicate little difference between verbal and non-verbal scores. The black lines indicate the threshold at which differences between are significant, based on data from the sample of typically-developing children.

Table 4.6 provides an overview of the discrepancies captured with the CMS and the Pair Games. With the CMS, all patients had lower verbal than non-verbal scores, therefore the discrepancy was consistent with the side of pathology only in left TLE cases. Within the semantic subtests of the Pair Games, material-specific impairments were observed in accordance with the side of pathology in all cases and reached significance in 3/6 of them. Within the non-semantic subtests, the pattern of discrepancies was less conclusive. In addition to the large ranges within which discrepancies are considered non-significant, reflecting high variability among the normative sample, the direction of discrepancy was not always consistent with the prediction based on side of pathology.

Table 4.6 Discrepancy between verbal and non-verbal scores as a function of side of pathology, captured with the CMS, the semantic subtests of the Pair Games (Written Words *versus* Objects) and the non-semantic subtests of the Pair Games (Pseudowords *versus* Designs). The ticks indicate when the direction of discrepancy between verbal and non-verbal learning/memory is consistent with the side of pathology (left *versus* right), irrespective of whether it is significant or not. Double ticks indicate that the discrepancy reached significance.

	Side of pathology	CMS	Pair Games Semantic items	Pair Games Non-Semantic items
Case 1	Right		√	
Case 2	Right		√√	
Case 3	Bilateral	√√	√√	
Case 4	Left	√	√√	√
Case 5	Left	√	√	√√
Case 6	Left	√	√	

3.1.2.3 Influence of IQ on Semantic and Non-Semantic Learning

In the present cohort, the patients with IQ scores below 100 showed lower learning gain for non-semantic than semantic information, whereas the other patient who did not show this pattern of impaired performance had a high IQ (Table 4.7).

Table 4.7 Discrepancy between learning gain scores for semantic (S) and non-semantic (NS) information.

	VIQ	PIQ	Discrepancy between S and NS	Stronger impairment
Significance threshold			28	
Case 1	96	102	15	NS
Case 2	99	94	26	NS
Case 3	83	110	24	NS
Case 4	91	115	14	NS
Case 5	104	121	-15	S
Case 6	85	77	22	NS

3.2 Compromised Memory Processes

3.2.1 CMS

The comparisons between recall and learning/recognition were investigated for scores obtained from the standardised test for each case (Table 4.8). Lower learning compared to recall scores was observed across patients (5/5), but the discrepancy reached significance in only 1/5 cases. Similarly, the discrepancy between recall and recognition scores reached significance in only 1/5. Apart from case 6 (scale score=3), the recognition scores were very similar across participants (scaled scores between 10 and 11).

Table 4.8 Discrepancy between learning, recall and recognition scores, for the Word Pairs subtest of the CMS (scaled scores). Positive scores indicate lower recall compared to learning/recognition scores. Numbers in red indicate significant discrepancy between verbal and non-verbal scores.

	Pathology	Side of pathology	Learning *versus* recall	Recall *versus* recognition
Significance threshold			4	4
Case 1	Mesial	R	NA	NA
Case 2	Cortical	R	-2	3
Case 3	Mesial	B	-2	2
Case 4	Mesial	L	-4	2
Case 5	Cortical	L	-3	-2
Case 6	Mesial	L	-2	-5

3.2.2 Pair Games

Tables 4.9 and 4.10 illustrate the discrepancies between learning and recall, and between recall and recognition, respectively, for each subtest of the Pair Games. Across the two comparisons (learning *versus* recall and recall *versus* recognition) and across all subtests, discrepancy reached significance in 4/6 cases (Cases 1-4) and almost reached significance in the remaining two cases.

Table 4.9 Discrepancy between learning and recall for each subtest of the Pair Games (standard scores). Positive scores indicate lower recall compared to learning scores. Numbers in red indicate significant discrepancy between learning and recall scores, numbers in orange indicate that the discrepancy is within 3 points of reaching significance.

	Pathology	Side of pathology	Spoken Words	Written Words	Pseudo-words	Objects	Designs
Significance threshold			35	38	42	41	44
Case 1	Mesial	R	16	0	-11	7	0
Case 2	Cortical	R	17	-25	8	-62	-23
Case 3	Mesial	B	-73	52	19	7	6
Case 4	Mesial	L	54	9	10	3	-15
Case 5	Cortical	L	11	13	6	-9	42
Case 6	Mesial	L	-12	-20	-39	-15	-23

Table 4.10 Discrepancy between recall and recognition for each subtest of the Pair Games (standard scores). Positive scores indicate lower recall compared to recognition scores. Numbers in red indicate significant discrepancy between recall and recognition scores.

	Pathology	Side of pathology	Spoken Words	Written Words	Pseudo-words	Objects	Designs
Significance threshold			38	39	40	39	41
Case 1	Mesial	R	24	5	13	43	7
Case 2	Cortical	R	32	-1	22	-25	-15
Case 3	Mesial	B	-43	58	26	21	8
Case 4	Mesial	L	-20	-45	-6	14	-12
Case 5	Cortical	L	0	-1	-4	-22	19
Case 6	Mesial	L	24	5	-18	-25	-14

Table 4.11 provides an overview of the discrepancies between recall and learning/recognition scores captured with the CMS and the Pair Games.

Table 4.11 Significant discrepancy between recall and learning/recognition captured with the CMS and the Pair Games.

	Pathology	Side of pathology	CMS	Pair Games				
			Word Pairs	Spoken Words	Written Words	Pseudo-words	Objects	Designs
Case 1	Mesial	R	NA				√	
Case 2	Cortical	R					√	
Case 3	Mesial	B		√	√			
Case 4	Mesial	L	√	√	√			
Case 5	Cortical	L						√
Case 6	Mesial	L	√			√		

3.2.3 Auditory Verbal Memory

For the auditory verbal subtests, performance was particularly susceptible to impaired recall across patients, and low-to-impaired recall scores were identified in 4/6 cases with the Pair Games and in 3/6 cases with the CMS (Table 4.12). Similarly, learning performance was susceptible to impairment as captured with both tools, but recognition impairments were captured in only 1/6 cases with either protocols.

Table 4.12 Low performance (standard score<85, √) and deficits (standard score<70, √√) in auditory verbal memory captured with the Pair Games (PG) and the standardised test (CMS).

	Side of pathology	Learning		Recall		Recognition	
		PG	CMS	PG	CMS	PG	CMS
Case 1	Mesial			√			
Case 2	Cortical	√	√√	√√	√√		
Case 3	Mesial	√	√√				
Case 4	Mesial		√√	√√	√	√√	
Case 5	Cortical						
Case 6	Mesial	√	√√	√	√		√√

3.3 Summary of Findings

It was predicted that the overall pattern of dysfunction would be better differentiated with the Pair Games than with standardised tools. Table 4.13 provides a summary of the findings corresponding to each hypothesis.

Table 4.13 Summary of formulated hypotheses and results.

Hypotheses		Results
1	The Pair Games will more distinctively identify the presence of verbal *versus* non-verbal impairments in relation to side of pathology (left *versus* right)	Significant discrepancy between verbal and non-verbal memory was identified in 3/6 patients with the Pair Games. These material-specific impairments were consistent with the side of pathology. The other patients showed non-significant discrepancy in line with the side of pathology. The CMS identified significant discrepancy in only 1/6 patient (Case 3 with bilateral pathology). Memory for non-semantic items (Pair Games) and auditory verbal memory (Pair Games and CMS) were not side-dependent.
2	The Pair Games will more distinctively identify the different components of compromised memory processes (learning, recall and recognition)	Discrepancy between learning/recognition and recall was identified in 4/6 patients with the Pair Games and in 2/6 with the CMS. Auditory verbal recall was particularly susceptible to impairment.

4 Discussion

4.1 Lateralisation of Memory Deficits

Investigation of material-specific impairments with standardised tools is generally confounded by the effects of input modality (auditory *versus* visual) and access to semantic structure (semantic *versus* non-semantic). Lateralisation of memory deficits was investigated in the present cohort of children with TLE using a standardised test (*i.e*. CMS) and the novel test of Pair Games.

4.1.1 CMS versus Pair Games

In the present cohort of patients, the CMS captured significant discrepancies between verbal and non-verbal scores in one patient only. In addition, for the remainder of the patients, the discrepancies were generally not consistent with the side of pathology. More importantly, the CMS did not capture material-specific impairment in patients with right-sided pathology, suggesting that this paradigm captures material-specific deficits only for verbal functions and may not be sensitive enough to reveal hippocampal-dependent dysfunction occurring as a result of right-sided TLE. In addition, the CMS provides a measure of recognition only for verbal material, reducing the possibility of highlighting deficits in patients with right-hemisphere damage.

The inconsistencies in the literature pertaining to material-specific impairments in childhood TLE could be the result of methodological shortcomings of the standardised tests which may be insensitive to distinctions between the functions of the mesial temporal structures, or to their associated memory processes. Assumptions that left TLE is associated with more straightforward verbal memory deficits than right TLE (*e.g*. Alessio et al., 2004; Hermann et al., 1997) may result from the inability of standardised tools to successfully capture non-verbal memory deficits. This finding has clinical implications for the validity of the standardised non-verbal memory tests, and may suggest impoverished sensitivity of these tests.

The Pair Games, on the other hand, controls for several variables and allows more direct comparisons between verbal and non-verbal mnemonic functions. Significant discrepancies consistent with the side of pathology were identified in 3/6 cases. These discrepancies reflected both verbal-specific impairments and non-verbal-specific impairments and are consistent with the side of pathology, whereby left- and right-sided lesions were associated with verbal and non-verbal memory impairments, respectively. The other three patients showed discrepancy scores in the expected direction, but these did not reach significance.

4.1.2 Effects of Age at Onset of Epilepsy

A standardised test should be sensitive to variations in age, such as differential memory profiles depending on the age at which the pathology occurred. The present pilot study showed evidence of distinct memory profiles as a function of

age at onset of seizures. All patients with evidence of material-specific impairments had seizure-onset during middle to late childhood (after the age of 8 years), whereas other patients who did not show material-specific deficits had considerably earlier onset of seizures (before the age of 2). These findings are compatible with the effects of age at onset of epilepsy on patterns of lateralisation of memory impairment (Mechanic-Hamilton et al., 2009; Sidhu et al., 2015).

This effect of age at onset of pathology is related to the specialisation of cognitive abilities and the division of labour between the cerebral hemispheres as a function of the developmental process (Satz & Strauss, 1990; Vargha-Khadem et al., 1997). In this context, seizures in early life interfere with the normal emergence of hemispheric specialisation (Vargha-Khadem et al., 1994). An early onset of pathology may therefore lead to alterations in patterns of brain organisation resulting in the lowering of cognitive abilities and generalised impairments across cognitive domains (Vargha-Khadem, 2002). Thus, early lesions take maximum advantage of brain plasticity and reorganizational capacity of the immature brain by rescuing high priority cognitive functions, but in the process sacrifice hemispheric specialisation and focal representation of function. Children with early onset of epilepsy may therefore show a less lateralised pattern of memory dysfunction. By contrast, pathology acquired later in life may impair aspects of function selectively depending on the site of damage.

4.1.3 Performance on the Auditory Verbal Memory subtest is not Sensitive to Hemispheric Side of TLE

Standardised tests, such as the CMS, often assess verbal memory through auditory input. However, auditory verbal memory may be particularly susceptible to disruption in TLE, irrespective of hemispheric side of pathology (see 4.2.2 for a discussion). In the present cohort, 4/6 patients presented with low to impaired recall in the Spoken Word subtest across both left and right TLE, whereas 2/6 showed lateralised deficits on the equivalent Written Words subtest. This finding raises the possibility that studies demonstrating verbal memory deficits using auditory input in patients with left or right TLE (Cormack et al., 2012; Engle & Smith, 2010; Mabbott & Smith, 2003; Nolan et al., 2004) may in fact be reporting on the confounded effects of input modality and material specificity.

4.1.4 Non-Semantic Subtests do not show Lateralised Deficits

Side-dependent material-specific impairments were initially predicted to be more easily documented using subtests composed of non-semantic items inasmuch as these items do not allow dual-encoding (Silverberg & Buchanan, 2005). Contrary to predictions, however, material-specific impairments related to side of pathology were mostly observed for semantic rather than non-semantic items (*e.g*. words and objects *versus* pseudowords and designs). However, these subtests may provide valuable clinical information not captured with semantic subtests as discussed below.

4.1.4.1 Ability for New Learning to Predict Outcome

The non-semantic subtests may play an important role in predicting the limits of cognitive capacity by testing the ability to form links between novel items not present in the mental lexicon. Thus, pseudowords and design pairs push the limits of new learning. As such, these measures can prove valuable not only in determining the status of patients' ability in relation to healthy controls, but also in predicting the capacity for new learning after surgery for TLE. Consistent with this reasoning, patients in the present cohort exhibit increased difficulty learning non-semantic than semantic paired-associates relative to controls. The Pair Games was previously administered to a large sample of typically-developing children and the results were discussed in Chapter 3. An important finding that resulted from that study demonstrated that the effect of semantics on learning gain was IQ-dependent. Thus, healthy controls with higher IQ learned non-semantic information better over consecutive trials than those with lower IQ (Chapter 3, section 4.4, page 104). The scores of patients with TLE, who generally exhibit lower IQ, should therefore be interpreted within the context of the findings reported for healthy controls. In the present cohort, 5/6 patients showed lower learning gain for non-semantic than semantic information, and all 5 patients had IQ scores below 100, whereas the one patient who did not show this pattern of impaired performance had a high IQ (see Table 4.12). These findings provide evidence that whereas the non-semantic subtests of the Pair Games do not capture material-specific impairment, they contribute to the diagnostic assessment by identifying difficulties with learning of novel verbal and non-verbal

information. This learning difficulty may be a reflection of memory problems in the educational setting which requires acquisition of novel information.

4.2 Compromised Memory Processes

Compromised memory processes were assessed with the CMS and the Pair Games and specific impairments and discrepancies between learning, recall and recognition scores were examined with both paradigms.

4.2.1 CMS versus Pair Games

Overall, the CMS captured significant discrepancy between impaired memory processes in 2/6 patients. However, these discrepancy scores were small and fell just short of significance. In addition, all patients showed a comparable pattern of recognition abilities, coupled with lower learning compared to recall performance. In this respect, distinct patterns of compromised memory processes were not identified across patients. On the other hand, the Pair Games did distinguish between learning and recall performance, and between recall and recognition performance in 5/6 patients.

The Pair Games may therefore be useful in identifying the specific memory process(es) that are compromised, thereby implicating the neural substrates underlying specific aspects of memory. To the extent that recall is dependent on the hippocampus whereas recognition is not (Patai et al., 2016), with the latter more likely served by the cortical parahippocampal and lateral temporal regions, relative deficits in one or the other mnemonic abilities may serve as a guide as to the structures and/or areas that may be compromised by TLE. For example, Case 6 with HS shows a general pattern of lower learning and recognition scores compared to recall scores, which may be consistent with the additional adverse effects of focal cortical dysplasia in the left parietal lobe. Similarly, Case 4 showed lower learning/recognition compared to recall scores, possibly reflecting cortical pathology. Overall, the Pair Games identified more clearly than the CMS the different components of mnemonic processes affected.

4.2.2 Susceptibility of Auditory Memory to Forgetting

As previously indicated, standardised tests of learning, delayed recall and recognition for verbal information are usually presented in the auditory modality. Findings from the present study demonstrate the susceptibility of auditory verbal information to forgetting as a function of elapsed time. This is attributed, at least in part, to the limited capacity of the auditory system for temporal order (Janczyk et al., 2018), irrespective of the underlying site of neuropathology (mesial *versus* cortical) and side of pathology (left *versus* right). In contrast to the other subtests of the Pair Games, the Spoken Words subtest did not reveal a clear pattern of discrepancy scores as a function of side and site of neuropathology. Several factors may account for reasons why auditory memory is susceptible to forgetting in paediatric TLE.

First, age-related effects in auditory memory shown in typically-developing children (see Chapter 3, section 4.3.3, page 103) may implicate the contribution of other cognitive skills which develop with age. An age-related effect of delayed recall was shown only for the Spoken Words subtest, whereby older children recalled more words than younger children after a delay. Memory for auditory verbal information may be particularly susceptible to the influence of other factors, such as levels of late-emerging executive functioning, and variations in attention (Chang et al., 2010; Vanderploeg et al., 1994). These considerations raise the possibility that auditory verbal input may not be as process-pure as those that are less influenced by temporal order. Discrepancy scores between mnemonic processes may therefore be influenced by other cognitive factors in tests of auditory verbal memory.

Second, typically-developing children showed modality-specific differences with lower performance in auditory compared to visual learning, but performance equalised after a delay (see Chapter 3, section 4.3, page 102). As such, children learn visually-presented words better than orally-presented words, but they show similar delayed retention abilities for both input modalities. It was postulated that through repetitive learning trials, children were able to establish decontextualized representations which were then no longer dependent on the input modality. It is possible that children with TLE, who exhibit learning difficulty, do not reach a learning standard that is sufficient for robust representations to be formed, and

therefore they continue to show better performance during delayed recall for information presented in the visual modality compared to the auditory modality.

Third, long-term auditory memory is related to speech (Fritz et al., 2005), therefore children who present with language impairments, as often reported in childhood TLE (Zhao et al., 2014), may also be vulnerable to auditory memory deficits. Together, these observations suggest that children with TLE are susceptible to forgetting auditory verbal information after a delay, irrespective of side and site of neuropathology.

5 Limitations

The present study contains only six patients and is therefore a pilot study to test the face validity of the Pair Games. Such a small sample size limits conclusions, and instead, provides preliminary findings that await more rigorous and systematic examination using a much larger sample tested both pre- and post-operatively. A second limitation relates to the difficulty of assessing the consequences of developmental pathology in a heterogeneous patient group. In addition, children with TLE, and more specifically, those with HS, often show extensive functional abnormality beyond what is visible on MRI.

6 Conclusions

Overall, the Pair Games provided finely grained analyses of memory performance compared to the standardised test (*i.e*. the CMS). Compared to standardised tests, the Pair Games provides refined identification of learning and memory impairments. This novel tool identifies non-verbal memory deficits, which are captured with difficulty using standardised instruments. This suggests that the Pair Games is a useful tool to assess the functionality of the left and right hippocampi. However, even with the Pair Games, material-specific impairments are not as clear and consistent in young TLE patients as what is reported in the adult literature, and may be related to age at onset of seizures.

The non-semantic subtests of the Pair Games did not identify patterns of lateralised deficits but may instead provide information regarding the ability to learn new information, irrespective of material type. The present findings also suggest susceptibility of auditory memory to forgetting after a delay in childhood

TLE. Auditory verbal memory was susceptible to forgetting after a delay, irrespective of the side and site of neuropathology. Verbal memory tests composed of auditory items may therefore not be suitable for the investigation of discrepancies between scores. This may provide important methodological and clinical implications considering that standardised tests of verbal memory are typically auditory.

Overall, the Pair Games has the potential to be a useful clinical tool to provide behavioural evidence of the integrity of the hippocampi and its interaction with the neocortical learning system. The present findings suggest that this novel tool provides more specific and sensitive assessment of learning and memory impairments than standardised instruments, thereby providing a better understanding of the cognitive profile and delineating the specific nature of impairment. In conjunction with other standardised measures, this tool could provide valuable information in clinical populations, and may even be used to investigate the functionality of the hippocampi in other clinical populations.

7 Future Directions

Following the pilot of this Pair Games in a small sample of children with TLE, confirmation of the findings are necessary by administering the protocol to a larger patient sample. Moreover, in order to verify the pattern of lateralised dysfunction as identified with the Pair Games, this novel tool could be administered in a sample of adult patients with TLE who generally show clearer patterns of lateralised dysfunction. More specifically, it would be relevant to test whether semantic and non-semantic subtests provide distinct profiles of lateralisation, similarly to children with TLE.

In addition, further work is required to validate the ability of the protocol to predict memory outcome after surgery by administering the protocol to the same patients after surgical intervention. Such a follow-up study would allow the identification of specific subtests that best predict memory outcome. For example, non-semantic subtests push the limits of new learning, and as such, may best predict academic achievement.

Chapter 5

Development of a Combined Language/Memory fMRI Paradigm

Functional Magnetic Resonance Imaging (fMRI) is a technique frequently used to determine the territories of eloquent tissue that serve critical functions, such as language. This can be particularly useful as part of the pre-surgical assessment for TLE in order to predict cognitive outcome and guide surgical decision-making. Whereas language fMRI is widely used, memory fMRI is less frequently employed in adult TLE, and lacking in childhood TLE. The aim of the present chapter was to develop a combined language/memory fMRI paradigm that would be suited for children, to provide clinically useful information for surgical planning in paediatric TLE.

1 Introduction

1.1 Learning and Memory Deficits after Temporal Lobe Surgery for Epilepsy

Focal surgery for intractable epilepsy aims to halt or decrease the frequency of seizures (Sherman et al., 2011). However, children with Temporal Lobe Epilepsy (TLE) are at risk of verbal learning and memory deficits after resection of the temporal lobe (Adams et al., 1990; Gleissner et al., 2002; Szabo et al., 1999; Williams et al., 1998). The major cognitive complaint of patients who undergo surgery in the temporal lobe is difficulty with learning and memory demonstrated through a failure to recall the relevant memoranda (Baxendale et al., 2007; Bowles et al., 2010; Manns & Eichenbaum, 2006; Helmstaedter & Elger, 1993; Khalil et al., 2016; Mueller et al., 2012). There is growing interest in using functional imaging as a pre-operative tool with the aim to evaluate the risk of, and possibly reduce, such post-operative cognitive impairments.

1.2 fMRI protocols to Predict Memory Outcome

Early onset seizures interfere with the normal process of hemispheric lateralisation (Willment & Golby, 2013) and may result in the reorganisation of memory functions to a larger extent than in older patients (Helmstaedter & Elger, 1998; Gleissner et al., 2005). In patients with TLE who have unilateral lesions, it is difficult to assess how much of the preservation is mediated by the unoperated side which can compensate for any failures of the operated side. It is therefore important to identify the lateralisation and localisation of these functions prior to surgical intervention to test the ability of non-damaged tissue to support memory and evaluate the risk of major post-operative memory deficits. Functional magnetic resonance imaging (fMRI) is a potentially useful pre-surgical diagnostic tool of memory lateralisation, and can help predict post-operative learning and memory performance. The aim of fMRI is to determine the territories of eloquent tissue that serve the critical functions of memory and language prior to surgical intervention to guide surgical decision-making (Lindquist, 2008).

FMRI is widely used for language mapping in adults and children; however memory fMRI is more seldom employed with limited published studies in children (Mankinen et al., 2015). The present chapter discusses the development of a novel fMRI protocol for the pre-operative functional mapping of language and memory to guide surgical decision-making and help with predictions of outcome.

1.2.1 Language fMRI to Predict Memory Outcome

Information obtained from language fMRI is sometimes used to predict memory outcome in TLE, due to Medial Temporal Lobe (MTL) activation during language tasks (Sepeta et al., 2016). Binder and colleagues demonstrated that language lateralisation was predictive of verbal memory change from pre- to post-surgery in adult patients with left TLE (Binder et al., 2008; Binder et al., 2010). They showed that stronger left lateralisation of language was associated with stronger verbal memory decline after surgery. Language fMRI has also been used in paediatric patients to infer the relationship between memory ability and the functions of the language network. Everts and colleagues showed an association between language lateralisation and verbal memory in patients with left TLE (Everts et al., 2010). However, neuropsychological evaluation of memory is not predictive of post-operative outcome (Lah, 2004); therefore such relationship as identified at the pre-operative level in Everts and colleagues' study does not necessarily contribute to the prediction of memory outcome after surgery. These studies suggest that whereas language fMRI can possibly provide useful information regarding memory outcome after surgery in adult TLE, it is not sufficiently robust in paediatric TLE, and targeted memory fMRI paradigms should be developed.

Using language fMRI to predict memory outcome assumes co-lateralisation of these functions. Co-lateralisation of language and memory functions has previously been studied (Cai & Van der Haegen, 2015); however, dissociating these domains of function can be difficult due to overlapping and/or interconnectivity of regions involved during cognitive processing, such as the prefrontal and parietal cortex. Similarly, the left hippocampus is activated in a verbal fluency task as well as in an auditory word recognition task (Pirmoradi et al., 2015). Moreover, Sepeta and colleagues demonstrated that Broca's area and the MTL are not co-lateralised in children (Sepeta et al., 2016), suggesting that

language fMRI is not a viable substitute to predict memory outcome. Indeed, language fMRI remains an indirect marker of memory function, whilst information obtained from memory fMRI, such as memory lateralisation (Bonelli et al., 2010; Sidhu et al., 2015)(), are regarded as better predictors of memory outcome after surgery than language fMRI. These findings not only indicate the need for developing suitable memory fMRI paradigms, as opposed to relying on language fMRI, for the prediction of memory outcome particularly in paediatric patients, but also suggest the importance of examining the relationship between language and memory lateralisation.

1.2.2 Memory fMRI to Predict Memory Outcome

1.2.2.1 Memory Encoding

Memory fMRI is employed in adult TLE studies to investigate neural subtrates related to encoding and/or retrieval processes. Memory fMRI studies often evaluate the encoding phase, with retrieval assessed after the scanning (Bonelli et al., 2010; Golby et al., 2002; Rabin et al., 2004; Sidhu et al., 2013; Sidhu et al., 2015a; Sidhu et al., 2015b). In these studies, images are acquired during the presentation of information, when participants encode items in the scanner, with retrieval of information occuring after the scanning session. This provides information about the neural network associated with the encoding phase of memory, but not the network that is involved in storage and/or retrieval of mnemonic information.

1.2.2.2 Memory Retrieval

1.2.2.2.1 Recognition

fMRI studies investigating retrieval-related activations often use a recognition task (*e.g.* Kennepohl et al., 2007), and examine MTL activity during successful recognition. The old/new paradigm which is often used compares brain activation during retrieval of studied items (“old”) and new items (“new”). With these paradigms, brain activation during retrieval of studied items could reflect retrieval associated with either familiarity or recollection processes, leading to confusion regarding the differential role of subregions engaged within the MTL. As discussed in Chapter 1 (section 2.1.3, page 6), recollection refers to the reliving of vivid and detailed episodes, whereas familiarity is associated with a sense that

information was previously encountered but without any contextual detail. These two processes are thought to be mediated by distinct subregions of the MTL, with recollection supported by the hippocampus and familiarity relying on perirhinal cortex (Aggleton & Brown, 1999; Eichenbaum et al., 2007; Yonelinas, 2002).

Surgical intervention for TLE usually involves the removal of variable portions of the hippocampus depending on the extent of the lesion (Radhakrishnan et al., 1998), as well as surrounding perirhinal and temporal neocortex. In cases of cortical damage, whereby the hippocampus may not have a major role in the seizure onset and/or progression, it is still critical to test the functionality of this structure considering its major role in initial memory formation (McClelland et al., 1995). In this respect, cortical damage may still hamper the hippocampal-neocortical network of memory, leading to apparent learning and memory deficits. Pre-operative examination of the integrity of the hippocampal-neocortical network that is at risk of compromise is therefore particularly relevant.

Examination of hippocampal activity requires memory fMRI tasks that engage the recollection process. This can be achieved using the Remember/Know paradigm (*e.g.* Giovanello et al., 2006; Henson et al., 1999; Smith et al., 2011; Wais et al., 2010) for which the responses are thought to reflect recollection/familiarity processes, respectively (Tulving, 1985). However, this paradigm may be too complex for young children and patient populations. In addition, familiarity and recollection may differ along a continuum depending on response confidence, and the imaging contrasts may therefore not be totally process-pure (Eichenbaum et al., 2007). In that respect, brain activation during a so-called "recollection" contrast (*i.e*. "Remember>Know") may also include some activity related to familiarity; which may lead to differences in findings between fMRI studies. As a result, fMRI recognition tasks that only address the neocortical network may not be optimal for the investigation of the hippocampal-neocortical network in TLE.

1.2.2.2.2 Recall

An alternative is to employ recall paradigms to investigate memory networks. However, fMRI studies that use such paradigms usually involve covert responses, with additional verbal recall after the scanning session to measure performance (*e.g.* de Zubicaray et al., 2007; Reas et al., 2011). A potential issue

with this approach is that performance may differ between the two retrieval periods, and the fMRI data may therefore not fully represent activation related to successful performance. In this respect, in-scanner overt recall may be more valid.

For clinical purposes, it may be useful to acquire data related to separate phases of the memory process, *i.e.* encoding and retrieval. For example, patients with TLE may have particular difficulty retrieving information from memory, with relatively normal encoding performances, in which case identifying the underlying mechanism of retrieval may be useful, whereas other patients may show the opposite pattern. The development of new memory fMRI paradigms is needed in order to better characterise the neural substrates subserving memory and better predict memory outcome after surgery in paediatric TLE.

1.3 Problems with Scanning the Medial Temporal Lobe

Heterogeneous findings across fMRI studies investigating memory-related MTL activations may relate to methodological considerations, both in terms of the memory task itself and of data analysis. This is observed in the failure to replicate results from previous studies and to report significant activation in the hippocampus. fMRI images are sensitive to distortions in regions where the magnetic field is particularly non-homogeneous, such as in the MTL. Susceptibility artefacts are prominent in the MTL and can lead to image distortion and signal loss in Echo-Planar Imaging (EPI) images (Figure 5.1) (Olman et al., 2009), making it difficult to obtain reliable signal and, in turn, hampering interpretation. For these reasons, methodological considerations need to be rigorously applied in fMRI studies that have a particular interest in the MTL.

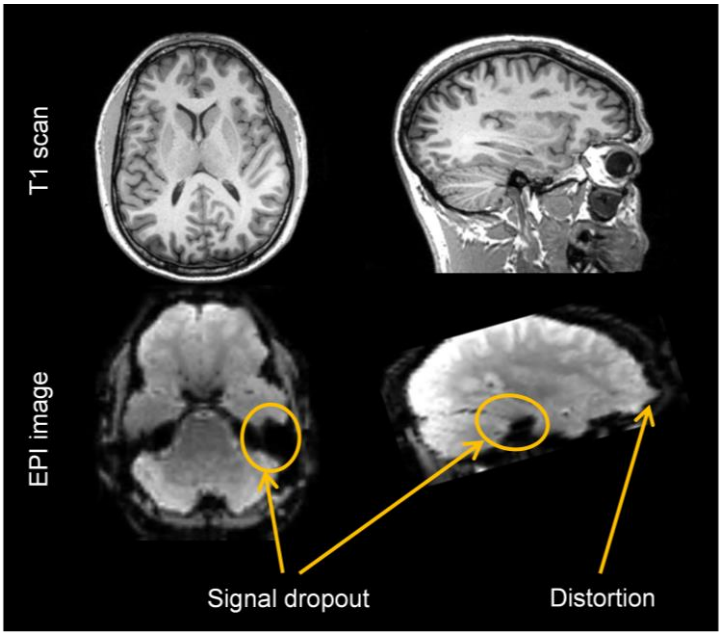


Figure 5.1 Signal Dropout and Distortion in EPI images.

1.4 Single-Subject Level *versus* Group-Level Analyses

Single-subject analyses of fMRI data are critical for clinical decisions on individual patients. Potential diagnostic use of fMRI tools, for example to guide surgical planning in TLE patients, is only possible if it is valid at the single-subject level. However, there has been little focus on single-subject fMRI, mainly due to difficulty in producing reliable findings at the individual level (Fadiga, 2007), and further research is required to assist single-subject fMRI.

1.5 Aims

Overall, it may be more suitable to use recall-based memory paradigms that tap into the hippocampal-neocortical network that is at risk of compromise given that the phenotype is failure to learn and recall new information. As mentioned above, previous paradigms may be insensitive to recall-based activation or to online performance (overt responses). In addition, paradigms used in adult studies involving multiple levels of answers, such as the Remember/Know paradigm, may be too complex for the paediatric population.

The present fMRI protocol was developed with understanding of neuropsychological theories of memory in order to guide experimental design,

improve interpretation of findings and optimise clinical applications. The development of this protocol had several aims which will be described in the methods section of the present chapter:

a) Develop a combined language/memory fMRI paradigm to examine the networks of both functions within one scanning session, providing a cost- and time-effective approach and, most importantly, permitting investigation of the interaction between the two circuits.
b) Design a protocol that examines brain activity related to both memory encoding and retrieval.
c) Develop a paradigm sensitive to MTL function because of its known involvement in memory and its susceptibility to pathology in TLE.
d) Construct a paradigm to investigate brain activation at the single-subject level, to guide clinical decisions on individual patients.

Several variables related to the experimental fMRI protocol will be specifically investigated in the results section: 1) test validity, 2) data quality, and 3) reproducibility of the protocol.

2 Methods

2.1 Participants

Twenty-eight normally developing children and adolescents were recruited for this study; one participant was excluded from further analyses due to high level of in-scanner movement. These participants also took part in the study reported in Chapters 2-3 (see Chapter 2, section 2.1, page 44). The sample in this study includes 11 males and 17 females, aged between 8 and 18 years (*M*=14, *SD*=3).

2.2 Socio-Economic Status

Socio-economic status was determined for each participant with deprivation deciles ranging from most deprived (score of 1) to least deprived (score of 10). SES deciles in the present cohort ranged from 2 to 10 (*M*=5, *SD*=2).

2.3 General Intellectual Functioning

General intellectual functioning was assessed using the Wechsler Abbreviated Scale of Intelligence – Fourth Edition (WASI-IV). This tool provides measures of full scale IQ (*M*=107, *SD*=9), verbal IQ (*M*=107, *SD*=9), and performance IQ (*M*=106, *SD*=10). The group-level scores on these measures are illustrated in Figure 5.2.

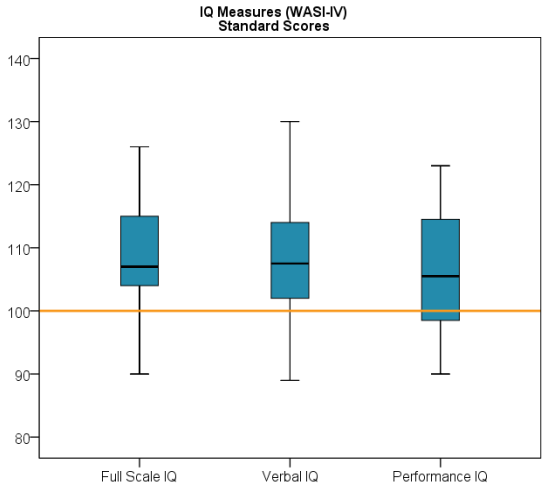


Figure 5.2 Standard scores for Full Scale IQ, Verbal IQ, and performance IQ.

2.4 Memory

Memory ability was assessed using the Children's Memory Scale (CMS), which provides measures of verbal and visual learning and memory. These measures are described in Chapter 2 (section 2.3, page 45). The group-level scores on these measures are illustrated in Figure 5.3.

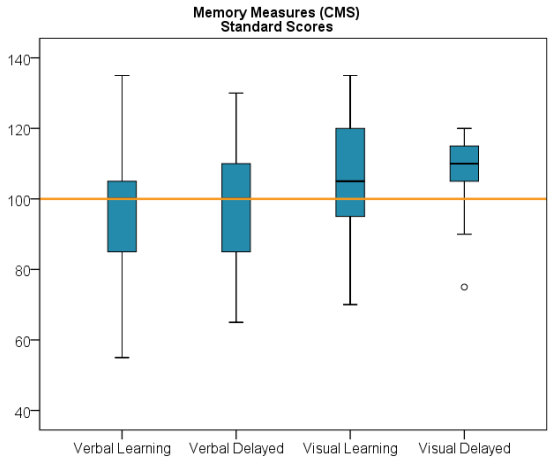


Figure 5.3 Standard scores for learning and memory measures obtained from the CMS.

2.5 Development of the fMRI protocol

2.5.1 Language Task: Verb Generation (VG)

A verb generation task (VG), which consists in generating verbs that correspond to a given noun, is currently being used clinically at Great Ormond Street Hospital as part of the pre-surgical evaluation of expressive language (Petersen et al., 1988). A similar task has been employed in neuroimaging studies to examine neural substrates supporting retrieval of semantic knowledge (*e.g.* Holland et al., 2001; Kurland et al., 2014), generating strong and consistent lateralised activation in the left hemisphere language network. The specific regions that are activated during this task include Broca's area, Wernicke's area, the middle frontal gyrus, dorsolateral prefrontal cortex, cingulate cortex, supplementary motor area, and right cerebellum (Brennan et al., 2016; Gaillard et al., 2000; Holland et al., 2001; Pang et al., 2011).

In the present study, the same VG paradigm was employed, whereby participants were presented with nouns one at a time, and were asked to overtly generate a verb for each noun (for example they hear "cake" and generate the verb "eating"). There were a total of 60 nouns, divided into 6 lists of 10.

2.5.2 Memory Task: Cued Recall

The memory task involves remembering the nouns that were presented during the language task. In that respect, the language block involves the encoding of

words, and the memory block involves the retrieval of words. Cues are presented to the participants to guide recall of previously encoded words in order to compare correctly recalled *versus* forgotten words. These cues consist of two-phoneme word stems created from the studied words (for example “æn” as a cue for “animal”) and are pronounced slowly to ensure correct perception. Participants are presented with word stems, one at a time, and are asked to say the word it corresponds to if they remember it, or to say “pass” if a study word could not be retrieved. Each stem is unique in the full list of study words (60). The performance is calculated as percent correct recall.

Cued-recall using word stems has multiple advantages. First, it allows event-related investigation of fMRI data, as retrieval-related activation is time-locked to each cue. This permits investigation of brain activation related to successful memory specifically. Second, the performance reflects recall memory which is known to be dependent on the hippocampus (Patai et al., 2016), as opposed to recognition memory. This approach was adopted in a couple of studies which reported activation in the hippocampus during successful recall (Okada et al., 2013; Schott et al., 2005).

2.5.2.1 Accounting for Priming Effects

Priming is the facilitation in processing of a stimulus due to prior encounter with that stimulus. This implicit memory is devoid of intentional and conscious recollection (Graf & Schacter, 1985). The effect of priming has been widely studied using word-stem completion tasks whereby participants are presented with words, and are later asked to complete word stems with the first word that comes to mind. Word stems are more likely completed with previously presented words. In contrast to recall processes dependent on the hippocampal system, priming is cortically-mediated (Buckner et al., 1995; Squire, 1992; Wiggs & Martin, 1998).

The present paradigm aims to test the integrity of the memory network which consists of the interaction between the hippocampus and the MTL in TLE patients. These patients sustain unilateral damage with possible changes in the pattern of lateralisation, therefore the aim is to test the residual capacity of this network regardless of the side of damage. In this respect, even in the event that

word fragments may prompt priming, the paradigm would still test the integrity of the hippocampal-neocortical network.

However, several measures have been put in place to minimise this priming effect. First, stems for words that were not previously heard (foils) were inserted in the cued recall phase (15 words in each list: 5 foils and 10 target words), to which participants are expected to respond “pass” and not try to complete with a word. The stem of these foils do not match any studied word. With this approach, it is possible to have a measure of false alarms (stem completion with non-studied words). Second, the task instructions emphasised explicit recollection. Participants were instructed to give a word response only when certain of their prior presentation and to otherwise say “pass” in the event of uncertainty. This procedure resembles the Remember/Know procedure commonly used to dissociate recollection and familiarity processes; however, such procedure may have been too complicated for younger children in this study. Generally, it is understood that a task’s instructions heavily influence the form of memory used, *i.e.* implicit memory (priming) *versus* explicit remembering (Graf et al., 1984). Third, each of these unique 90 stems (from 60 studied words and 30 foils) is shared by at least 4 other common words. The number of words that share the same word stem refers to the lexical set size. The lexical set size affects word-stem completion and retention whereby larger set sizes lead to reduced target recovery (Nelson et al., 1987). Response alternatives may lead to a different word than the target word, therefore requiring conscious recollection to retrieve the correct word. With these methodological considerations, the risk of priming effects is minimised, and performance should primarly reflect conscious recall.

2.5.3 Baseline Task

The baseline task involves making an odd/even decision to numbers; for example, the participant is presented with the number “3” and has to say “odd”. The presentation of this number is similar to the presentation of words and word stems (every 4 seconds).

This baseline task has three purposes. First, it acts as a baseline to subtract from the active conditions (language and memory) to investigate activation contrasts. This task was selected because of its simplicity and accessibility to all ages and because of its motor processes. It is generally recommended to use an active

control task as baseline rather than passive rest for contrasting with an active cognitive task, as it can account for cognitive attentional and motor processes (Binder et al., 2008). In a study comparing several baseline tasks, Stark and Squire (2001) demonstrated higher activation in the hippocampal region associated with a memory task when the odd/even digits task was used as baseline, compared to when rest was used as baseline (Stark & Squire, 2001). This finding provides evidence that this baseline task is useful for the exploration of hippocampal activity in memory tasks. The second purpose of the baseline task is to introduce a short delay period between encoding and recall, and the third purpose is to prevent subvocal rehearsal and the maintenance of information in short-term memory storage during the delay. The selection of this baseline task therefore optimises investigation of brain activation during the language and memory tasks.

2.5.4 Stimulus Material

For the purpose of this study, stimuli were selected from the MRC Psycholinguistic Database and the word properties were compared with that of the stimuli from the clinical VG task. New words were selected for this experimental version in order to administer and compare the clinical and experimental versions in the same participants. The new stimuli matched the ones from the clinical version on several properties: word frequency (Brown, 1984), concreteness, familiarity, and imageability (Table 5.1). In addition, all of the words were acquired before the age of 8 (Kuperman et al., 2012) and were composed of 1 to 3 syllables, similar to the clinical version.

Table 5.1 Matched properties between the experimental and the clinical protocols.

	Clinical		Experimental		*t*	df	*p* value
	M	*SD*	*M*	*SD*			
Word frequency	12	3	13	3	0.299	138	0.765
Concreteness	600	3	594	3	1.489	131	0.139
Familiarity	578	5	568	5	1.641	136	0.103
Imageability	606	3	600	3	1.319	135	0.189

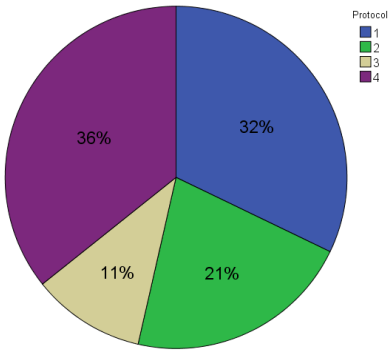
2.5.5 Overt Response

Whereas most fMRI studies involve covert verbal responses in order to avoid movement artifacts (Alessio et al., 2013; Barch et al., 1999), the present study involves overt responses. In addition to being easier for children, overt verbal

responses may be advantageous for clinical studies. Involving overt responses allows online measure of performance and this is beneficial as it makes it possible to explore specific brain activation associated with verbal output. This is particularly relevant for the interpretation of performance and the investigation of brain network in patients with cognitive impairment. Movement-related artifacts can be controlled for using image processing techniques (Birn et al., 2004). A couple of studies have employed overt cued recall paradigms and demonstrated significant activation in the MTL for successful recall (Hayama et al., 2012; Okada et al., 2012). In addition, overt responses also have the potential to reveal the interaction of two networks as cognitive memory is translated into a verbal output. For the purpose of this study, overt verbal responding was therefore used during fMRI scanning.

2.5.6 Previous Protocols Leading up to the Final Protocol

The fMRI protocol was developed while investigating different variables in order to optimise activation in the hippocampus. The protocol was therefore adapted along the recruitment period and not all 28 participants were administered the same version of the protocol. The pie chart below illustrates the distribution of protocol versions across participants (Figure 5.4).



Protocol 1	Two baseline tasks: counting task and rest	N=9
Protocol 2	Add visual cues on the screen and change baseline task into odd/even task	N=6
Protocol 3	Remove Rest Block to reduce delay between encoding and retrieval	N=3
Protocol 4	20 different words - replace the least remembered words with more memorable ones	N=10

Figure 5.4 Pie chart illustrating the distribution of protocol versions across participants.

The initial version (protocol 1) contained two baseline tasks: a rest and a counting task whereby participants had to count upward starting from a number provided to them *e.g.* count upward from 7. The first nine participants were administered this version of the protocol. Upon realisation that the stimuli were sometimes difficult to perceive due to high level of scanner noise, visual presentation of the stimuli was added to the auditory presentation. Combined visual and auditory presentation of stimulus ensured successful perception, *i.e*. they hear and see the words at the same time. In addition, the baseline task was replaced with the odd/even decision task to optimise hippocampal activation in the memory block. Six participants were administered this version 2 of the protocol.

In the third version, the rest block was removed as it did not provide significant additional information than the other baseline task and made the overall scanning session longer. Three participants were administered this version with the rest block removed. The last and final protocol version (4) was created to increase hippocampal activation at the individual level. Investigation of hippocampal activation in individual subjects showed that the presence of signal in the hippocampus was related to in-scanner memory performance and not to any other measure, *e.g*. movement parameters (Figure 5.5). In that respect, it was important to increase in-scanner memory performance to boost hippocampal activation. The twenty least remembered words from the list were therefore replaced with more memorable words which have the same properties discussed in section 2.5.4 (page 149). The last 10 participants recruited for this study were administered this protocol version.

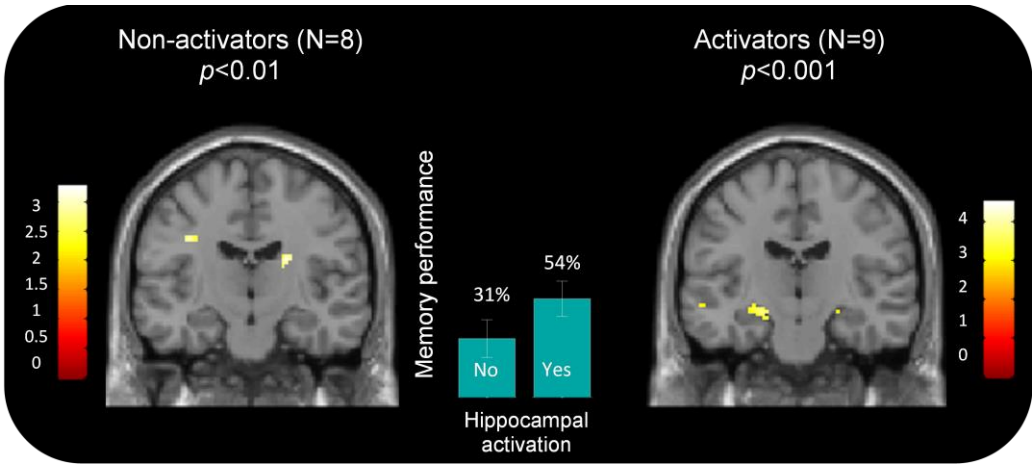


Figure 5.5 Presence of signal in the hippocampus is related to in-scanner memory performance.

Despite these slight modifications, the activation tasks (*i.e.* language and memory tasks) remained the same, and the analyses were therefore collapsed across protocol versions and all participants were included in the following analyses.

2.5.7 Procedure

Before the scanning session, participants completed a practice session during which they received instructions on how to perform the VG, baseline and cued recall tasks. The protocol was composed of a total of 6 lists of 10 words, with each list composed of different words. The scanning session was composed of 3 runs, each composed of two lists of words. Verbal responses were monitored via an MRI-compatible microphone.

Figure 5.6 illustrates the procedure of the fMRI protocol. Before the beginning of each block, a visual prompt was displayed on the screen for 5000ms in order to prepare the participants for the upcoming task. These prompts were [ACTION WORDS] for the VG block, [ODD OR EVEN?] for the baseline block, and [REMEMBER OR "PASS"] for the cued recall block (Figure 5.6).

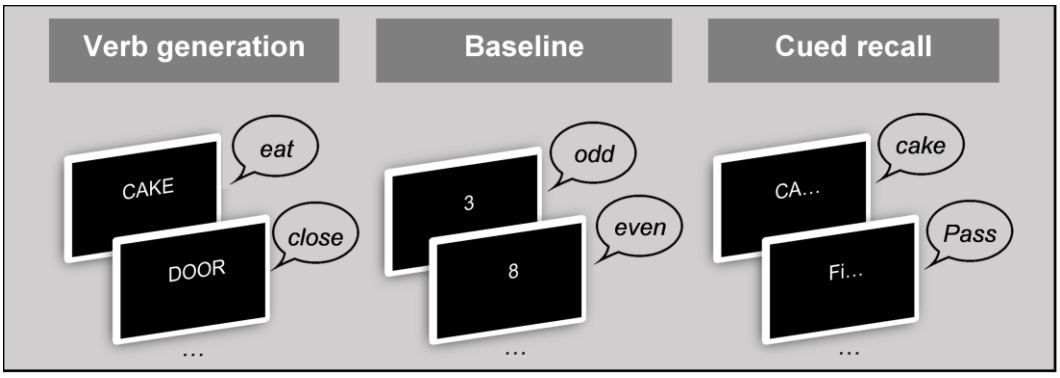


Figure 5.6 Procedure of fMRI protocol.

The stimuli were presented at a rate of one every 4 seconds. Each block of VG and baseline lasted for 40 seconds (10 x 4), whereas the cued recall block lasted for 60 seconds (15 x 4), and the whole protocol lasted for 16 minutes.

2.5.8 Two Parallel Versions

Two versions of this protocol were developed using different stimuli to allow administration to the same participants at two time points (*e.g.* before and after surgery) and compare findings.

2.6 Data Acquisition

Data were acquired on a 3T Siemens MRI system with a 20 channel head coil. Imaging parameters for multiband EPI images were the following: TR (repetition time) = 1250, TE (echo time) = 26ms, slice thickness 2mm, slice gap 1mm. A slice tilt was applied to align the scans perpendicular to the long axis of the hippocampus (Figure 5.7) and optimise the Blood Oxygenated Level Dependent (BOLD) sensitivity in medial temporal lobe regions (Weiskopf et al., 2006). For each functional scanning run, 270 images were acquired, with a total of 810 images across the 3 runs. In addition to the functional images, a T1-weighted magnetisation prepared rapid gradient-echo (MPRAGE) scan was acquired for anatomical localisation.

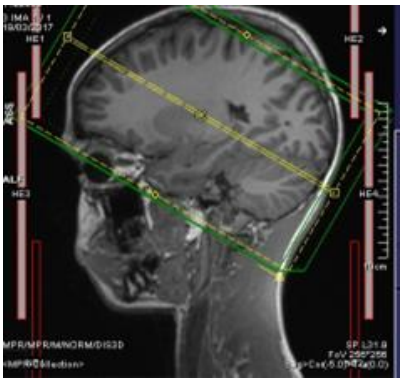


Figure 5.7 Functional Scans are aligned perpendicular to the long axis of the hippocampus.

The presentation of stimuli (every 4 sec) was purposely not locked to the TR (1.25 sec) in order to improve effective sampling of the signal. This way, data were sampled at different points on the canonical response, providing better estimation of the latency of response and quantifying the response shape (Figure 5.8). It has been shown that effective sampling is improved by staggering stimulus presentation relative to TR onset (Cabeza & Kingstone, 2006).

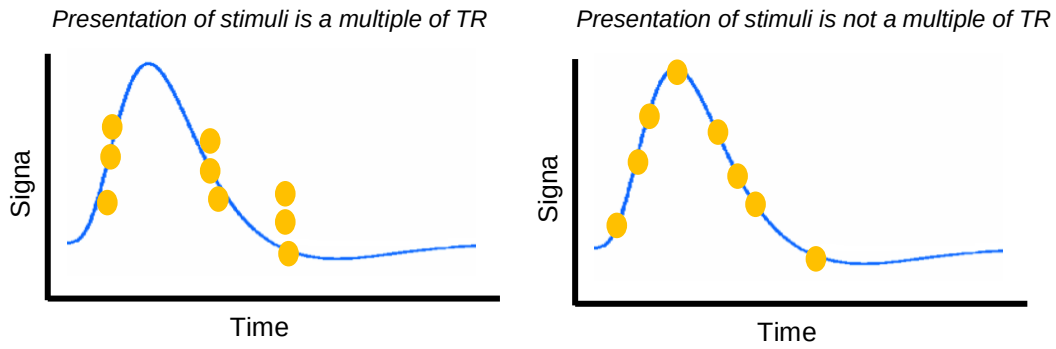


Figure 5.8 Presentation of stimuli not locked to the TR improves effective sampling of the signal.

2.7 Data Pre-Processing

The signal in raw fMRI data is influenced by many factors other than brain activity, such as heart beat, respiration and head movement. Whereas it is difficult to adjust for all factors, the signal undergoes pre-processing steps prior to data analysis in order to remove head motion artifacts and increase validity and sensitivity in group analyses. Figure 5.9 illustrates each step of data pre-processing.

The first step was spatial realignment of the images to account for head motion, using Statistical Parametric Mapping software (SPM12, Wellcome Department of Cognitive Neurology, London, UK: www.fil.ion.ucl.ac.uk/spm/). Retrospective motion correction is useful to reduce artifacts related to head movement during data acquisition. The second step was to unwarp the images in order to reduce spatial distortion. To achieve this, opposite phase encoded EPIs (blip-up and blip-down images) were acquired during scanning and the unwarping was performed using the TOPUP toolbox in FSL (Andersson et al., 2003).

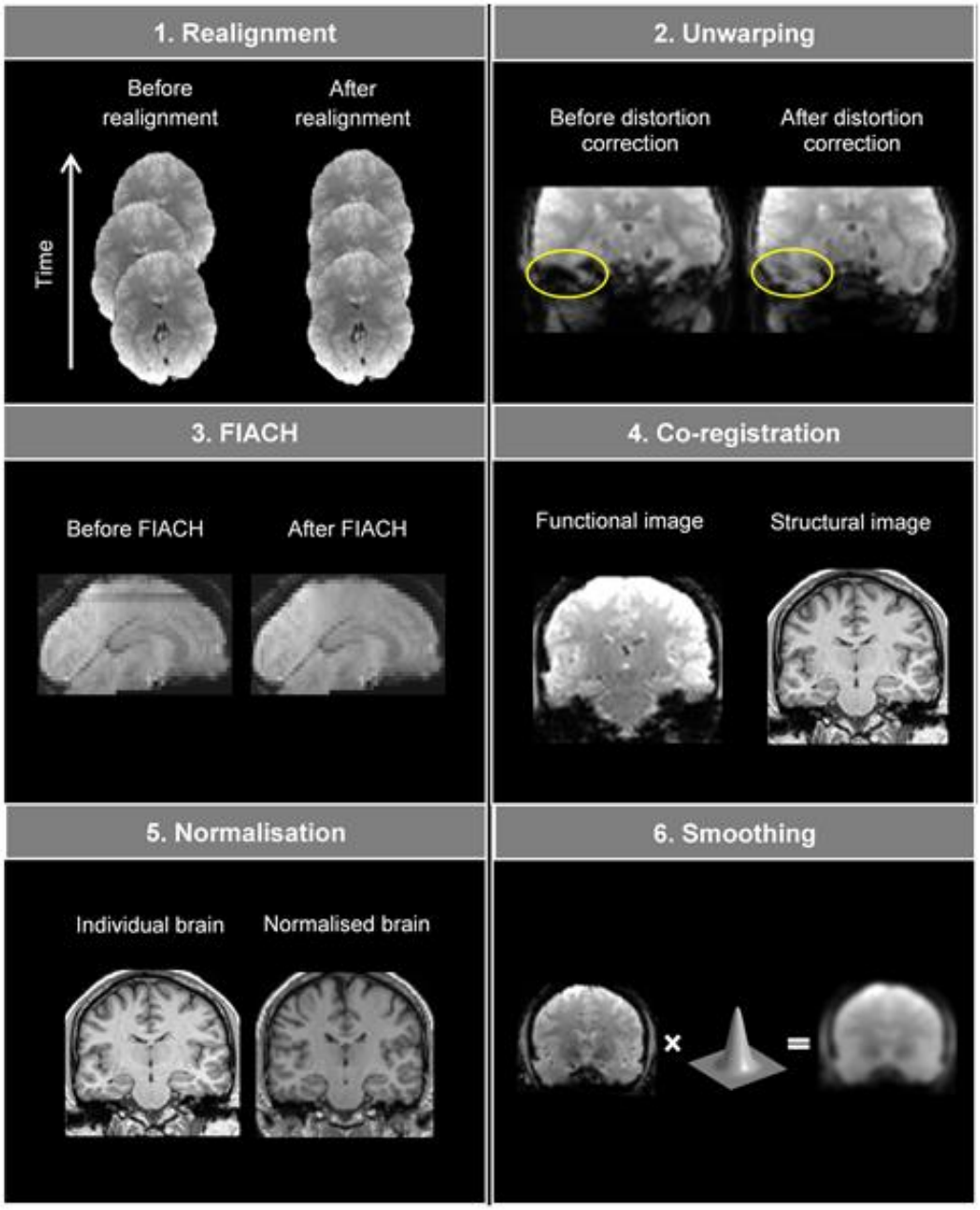


Figure 5.9 Illustration of each step of data pre-processing.

The third step, carried out in the R statistical programming language (R Core Team, 2013), involved additional retrospective motion correction using Functional Image Artefact Correction Heuristic (FIACH) which controls for physiological noise and corrects for large amplitude signal change (Tierney et al., 2015). FIACH has been shown to be particularly useful in cases of task-induced motion and improves signal to noise ratio in regions that are susceptible to field inhomogeneity, *e.g*. the inferior temporal lobe. Finally, the images were co-

registered, normalised to a standard MNI space for group analyses, and smoothed with a Gaussian kernel of 6 mm full width half maximum (Weiskopf et al., 2006).

2.8 Imaging Analyses

Functional MRI data captured changes in BOLD signal over time in each voxel during the experiment. The intensity of the signal in each voxel over time is called the time-series. Statistical analysis of functional images was conducted on SPM using a General Linear Model (GLM) to predict the time-series of each voxel using a linear combination of predictor variables (Friston et al., 1995). The movement parameters were included in the design matrix as covariates. For the purpose of this study, contrasted parameter estimate images were created for each participant, describing differences in brain activation between language and baseline tasks ("Language>Baseline") and between memory and baseline tasks ("Memory>Baseline").

The equation of the GLM is the following: $Y = X * \beta + \mathcal{E}$, where Y is the BOLD signal, X is the design matrix that contains the predictors that explain variance in Y, β is the beta values from each condition $[\beta_1X_1+ \beta_2X_2+ \beta_3X_3\ldots]$, and Ɛ is noise, or unexplained variance (Figure 5.10). In the equation, βX is the predicted effect of interest for each condition of the paradigm. In the design matrix, each column is a regressor and contains the beta values for the specific condition, and each row is a volume of fMRI data.

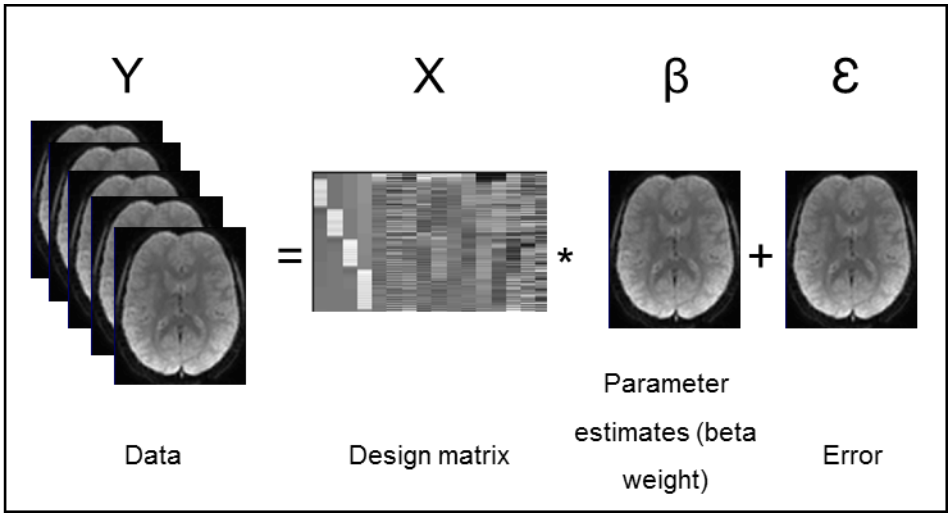


Figure 5.10 The General Linear Model (GLM).

A high-pass filter was applied to remove low frequency noise and the effects of scanner drifts (Lindquist, 2008). Temporal and dispersion derivatives were included in the GLM in order to model the onset and duration of the BOLD peak (Henson et al., 2001). The temporal derivatives slightly shift the signal and the dispersion derivatives change the width of the haemodynamic response.

For individual-subject analyses (1st level), the changes in BOLD signal over time was examined for each individual using fixed effect analysis across the three runs. For group analyses (2nd level), contrast estimates from each individual were entered into a GLM with individuals treated as a random factor. Random effect analyses were computed to identify patterns of task-related activation that are consistent across the group.

Whole brain analysis was performed, with independent *t* tests for each voxel in the brain. Statistical tests were carried out for each voxel to test how well the model predicts the observed data by determining whether activation in a specific voxel is systematically related to the task. SPM provides a statistical map showing the test statistics for each individual voxel. These statistical maps are overlaid onto structural images to display the activated voxels. The statistical parametric maps only display voxels whose *t*-values exceed a selected statistical threshold (α) and are therefore considered significant. Extend and height threshold were employed, and specified where appropriate.

2.8.1 Regions of Interest (ROIs)

Several regions of interest (ROIs) were created for the analysis of functional activation, using the Hammersmith atlas (Hammers et al., 2003) and the MarsBar software (Brett et al., 2002). ROIs were created around Broca's area for the investigation of language activation, and the hippocampus for the investigation of memory activation. Manual segmentation of the hippocampus ROI was performed along the anterior/posterior axis for further investigation of hippocampus subregions. In addition, the ROIs were divided into left/right ROIs to compare signal in left and right hippocampi. The whole temporal lobe was also investigated for both language and memory activations.

2.9 Test Validity

2.9.1 In- and Out-Scanner Memory Performance

Before inferring memory-related brain activity from this fMRI study, it is important to verify the nature of the memory task. To do this, performance on the memory task administered inside the scanner was compared to performance on a standardised tool assessing memory which was administered outside the scanner, *i.e.* learning and delayed recall of Word Pairs from the Children's Memory Scale (CMS).

2.9.2 Controlling for Priming Effects

The issue of priming effects in an explicit memory task has been described in section 2.5.2.1 (page 147). In addition to the methodological considerations to reduce the risk of a priming effect, investigation of performance was carried out to ensure that this effect was absent or minimal.

First, average intrusion (retrieval of a word that was not part of the list) was calculated. Second, a stem completion task was administered after the scanning session to measure the rate of word completion for the word stems. In the stem completion task, participants were presented with word stems other than the ones presented in the scanner and were instructed to say the first word that comes to mind. The participants who were administered version A inside the scanner were presented with the word stems from version B for the stem

completion task, and vice versa. The percentage of stem completion with the target word was calculated for each word stem and compared with memory performance for that word stem. This was done for the stems of the most remembered words (>90%). If performance was mediated by priming, we would predict the word stems generating the highest recall to also be associated with high completion with the target words.

2.10 Data Quality

Data quality in fMRI is typically measured using the signal-to-noise ratio (SNR) of the acquired data. Several types of SNR can be investigated in fMRI data: image SNR, temporal SNR (tSNR) and contrast-to-noise ratio (CNR).

2.10.1 Image SNR

Image SNR is the quality of data in a single fMRI volume and is quantified as mean signal value of voxels divided by the standard deviation of voxels (Bennett & Miller, 2010):

$$SNR_{image} = \frac{\mu_{image}}{\sigma_{image}}$$

SNR was measured in the mean EPI image in each individual (Welvaert & Rosseel, 2013) (Figure 5.11A). The image SNR was calculated in the hippocampus to measure data quality in the specific region of interest. The SNR was also tested in separate regions of the hippocampus, *i.e*. the anterior and posterior portions of the hippocampus (Figure 5.11B). Paired *t* tests were carried out between the signal intensity in different subregions of the hippocampus.

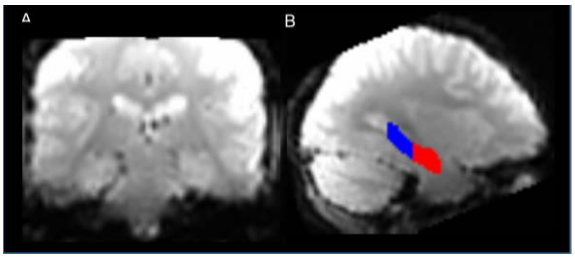


Figure 5.11 A. Example of an individual's mean EPI image, from which SNR was measured. B. SNR was calculated in different portions of the hippocampus: in the anterior hippocampus, shown in red, and in the posterior hippocampus, shown in blue.

2.10.2 Temporal SNR (tSNR)

The tSNR refers to the amount of raw (non-task specific) signal across time, and assesses data quality of fMRI time series (Welvaert & Rosseel, 2013). Voxel based time-series were extracted in two ROIs (Broca's area and the hippocampus), whereby one value was obtained for each scan for each participant, providing a time course of the signal. Paired *t* tests were carried out between the tSNR in different ROIs.

2.10.3 Contrast-to-Noise Ratio (CNR)

The CNR corresponds to the data quality based on a specific contrast and includes information related to the strength of the signal for a specific contrast. The CNR therefore can provide an indication of the ability to detect BOLD changes (Olman et al., 2009) and provides indication of how well the task-induced brain activation is detected (Welvaert & Rosseel, 2013). To calculate the CNR, beta values were extracted in ROIs (hippocampus and Broca's area) using MarsBar for the two contrasts of interest ("Memory>Baseline" and "Language>Baseline"):

$$CNR = \frac{\mu_{contrast}}{\sigma_{contrast}}$$

Paired *t* tests were carried out between the two contrasts of interest, in each ROIs separately.

2.10.4 Movement Artefacts

Movement parameters from FIACH were investigated to test whether they have an impact on EPI intensity in the hippocampus. In-scanner motion can degrade image quality and reduce SNR (Van Dijk et al., 2012). The effect of movement artefacts was therefore investigated in the hippocampus ROI due to its susceptibility to low SNR. Pearson's correlations were computed between signal intensity and FIACH TSNR, which is a measure of deviation of the realigned images (Tierney et al., 2015). The effect of movement artefact was investigated for the different types of data quality measures, namely image SNR, tSNR, and CNR.

2.11 Reproducibility of the Protocol

2.11.1 Memory Performance across Runs

The reproducibility of the protocol was determined based on the stability of the data across the three scanning runs, which were a few minutes apart. For this section, each run was analysed separately to investigate inter-run variability.

The consistency between performance across runs was measured using Intra Class Correlation (ICC), which is a measure of the ratio of between-subjects variance and between-tests variance. In this respect, the value approaches 1 if the variability across individuals is larger than the variability within individuals across repeated runs. The ICC was based on a mean-rating (*k*=3), absolute agreement, 2-way mixed-effects model.

2.11.2 Laterality Indices across Runs

Lateralisation indices (LI) assess hemispheric lateralisation for a specific cognitive function. This LI is calculated based on the sum of voxel value and takes the strength of a voxel's activation into consideration. For the present purpose, LIs were calculated in two ROIs; in Broca's area and in the hippocampus. These LIs were calculated using the LI toolbox (Wilke & Lidzba, 2007), where

$$\mathrm{LI} = \frac{\sum \mathrm{activation}_{left} - \sum \mathrm{activation}_{right}}{\sum \mathrm{activation}_{left} + \sum \mathrm{activation}_{right}}$$

Consistent with clinical studies, values above 0.2 are considered left lateralised, LIs below 0.2 are considered right lateralised, and values between -0.2 and 0.2 indicate bilateral representation. Language lateralisation was determined based on LI values in Broca's area during the VG task, and memory lateralisation was determined based on LI values in the hippocampus during the cued recall task. The consistency between LI values across runs was measured using ICC, based on a mean-rating (*k*=3), absolute agreement, 2-way mixed-effects model.

2.11.3 SNR in the Hippocampus across Runs

Signal intensity in the hippocampus was identified in each individual's EPI acquisitions (image SNR) and compared across scanning runs. ICC was

computed based on a mean-rating (*k*=3), absolute agreement, 2-way mixed-effects model.

3 Results

3.1 Test Validity

3.1.1 In- and Out-Scanner Memory Performance

As shown in Figure 5.12, learning scores on the standardised test (*i.e.* the CMS) and memory scores on the fMRI task are moderately related (*r*=0.39, *p*=0.042), suggesting that the memory fMRI task does reflect memory performance observed outside the scanner, but is also influenced by other factors inside the scanner. The delayed memory score on the Word Pair subtest of the CMS was not related to the in-scanner memory performance (*r*=-0.06, *p*=0.765), probably due to the longer delay interval, *i.e.* 20 minutes, as opposed to 1 minute in the scanner. In that respect, the in-scanner performance is more closely related to the CMS learning score than to the delayed memory score.

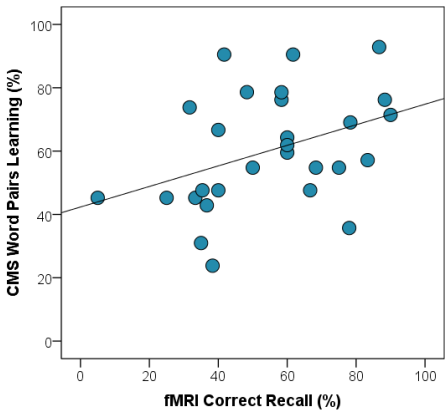


Figure 5.12 Significant positive correlation between in-scanner memory performance and performance on the standard memory test administered outside the scanner.

3.1.2 Controlling for Priming Effects

The priming effect was investigated by calculating the false alarm rate and investigating performance on the word-stem completion task. First, few false alarms were made, with an average intrusion of 4% (*SD*=6%) across participants. Second, the percentage of stem completion with the target word is presented in Table 5.2 for the best recalled words (>90%). For example, the word “ant” was part of the studied list in version A but not in version B, and half of the participants were administered version A and the others were administered version B. In version A, the word stem “An” led to the successful recall of the word “ant” 100% of the time. However, in version B, this word stem was completed with the word “ant” only 33% of the time. High prevalence of stem completion with the target word was observed in only one word that also had high recall prevalence (*i.e.* “table”). These findings suggest that recall performance cannot be fully explained by priming.

Table 5.2 Stem Completion and Recall Performances (%).

Word	Word stem	Correctly recalled	Stem completed with target word
Ant	An	100	33
Brain	Bra	100	33
Father	Fa	95	12
Leaf	Lea	100	42
Pocket	Po	100	0
Rat	Ra	95	0
Table	Ta	100	83
Team	Tea	100	0

3.2 Data Quality

3.2.1 Image SNR

The signal (mean signal intensity), noise (standard deviation of signal intensity) and SNR are reported in Table 5.3. A Paired sample *t* test shows no significant difference between the SNR of anterior and posterior hippocampi, $t(26)=-1.505$, $p=0.144$.

Table 5.3 Signal, Noise, and SNR in the hippocampus.

	Signal	Noise	SNR
Hippocampus	4740	372	6.8
Anterior hippocampus	4558	397	7.2
Posterior hippocampus	4979	375	7.7

3.2.2 Temporal SNR (tSNR)

The time-series in the two ROIs, averaged across participants, are illustrated in Figure 5.13. The intensity of the time-series in Broca's area (M=4.9 SD=0.02) was higher than in the hippocampus (M=4.5 SD=0.04), and a paired t test confirms significance of the difference ($t(26)$=4.966, p<0.001). The standard deviations suggest little difference in the variability across time (scans) in either of the two ROIs. However, the variability between voxels within a ROI is larger, and is particularly high in the hippocampus (mean variability across scans 22.1, compared to 1.49 in Broca's area).

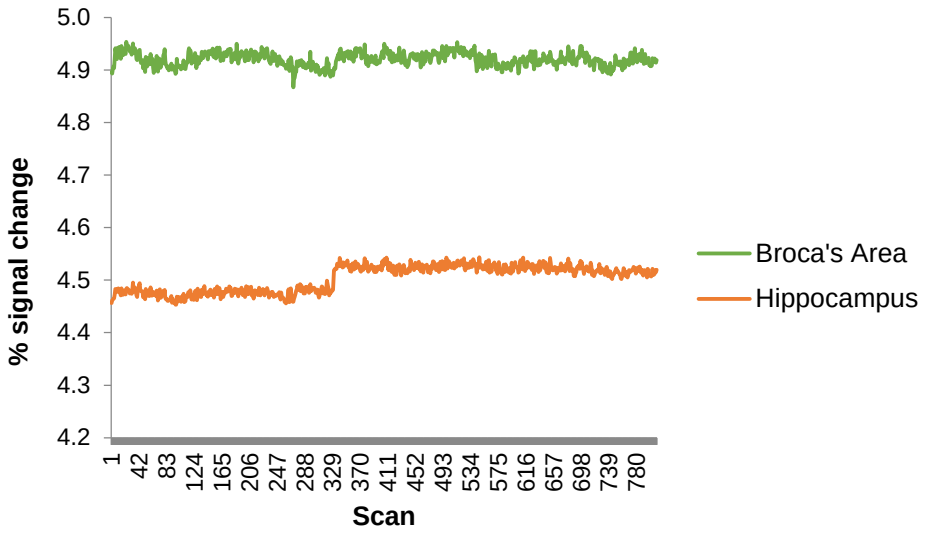


Figure 5.13 Time-series in Broca's area and the hippocampus, across participants.

3.2.3 Contrast-to-noise ratio (CNR)

The CNRs in both ROIs for both contrasts are illustrated in Figure 5.14. CNR in Broca's area was higher than in the hippocampus, for both contrasts. A paired-sample *t* test showed that CNR in Broca's area is higher for the contrast "Language>Baseline" (*M*=1.26 *SD*=0.49) than "Memory>Baseline" (*M*=0.80 *SD*=0.68), which is expected (*t*(26)=-3.114, *p*=0.004). However, CNR in the hippocampus was also higher in the contrast "Language>Baseline" (*M*=0.29 *SD*=0.79) compared to "Memory>Baseline" (*M*=-0.16 *SD*=0.87) (*t*(26)=-2.903, *p*=0.008).

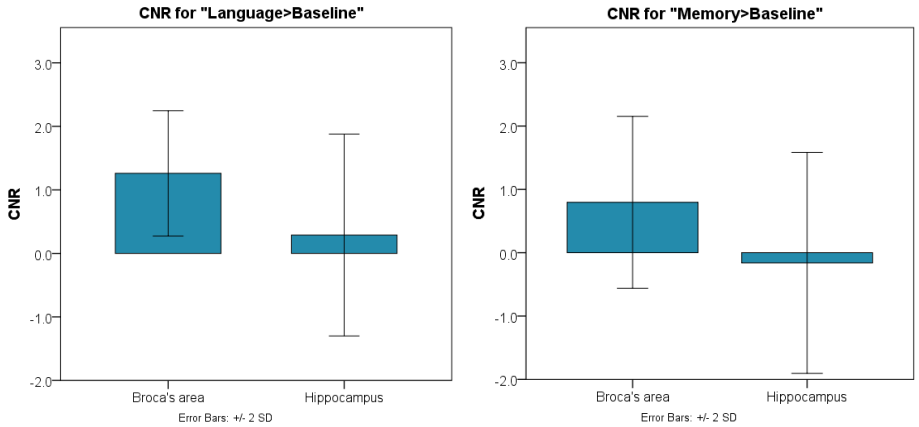


Figure 5.14 Mean CNR across participants for two contrasts of interest ("Language>Baseline" and "Memory>Baseline") in two ROIs (Broca's area and the hippocampus).

3.2.4 Effect of Movement Artefact

The relations between movement parameter and image SNR, tSNR, and CNR are illustrated in Figure 5.15. No significant relation was found between movement artifact and image SNR in the hippocampus (*r*=0.250, *p*=0.200). Correlation analyses were performed between FIACH TSNR and the time-series extracted in the hippocampus and showed no significant relation *(r*=0.273 *p*=0.160). Finally, the relation was tested for the CNR in the hippocampus, for the contrast Memory>Baseline, and showed no significant effect of movement artefact *(r*=-0.097 *p*=0.623).

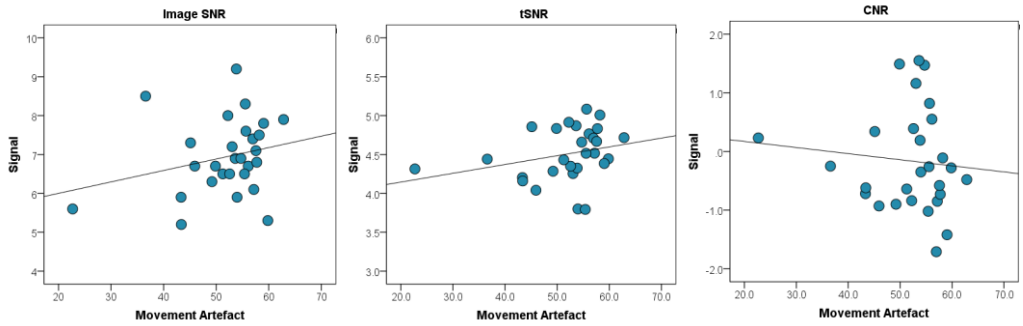


Figure 5.15 Correlations between movement artefact and measures of data quality in the hippocampus.

3.3 Reproducibility of the Protocol

3.3.1 Memory Performance across Runs

Memory performance across runs is illustrated in Figure 5.16. Performance was 58% (*SD*=24) in the first run, 53% (*SD*=21) in the second run, and 60% (*SD*=18) in the third run. ICC was 0.91, indicating stability of performance across runs. This implies that it is possible to collapse findings from across the runs and treat them as fixed effect in 1st level analyses.

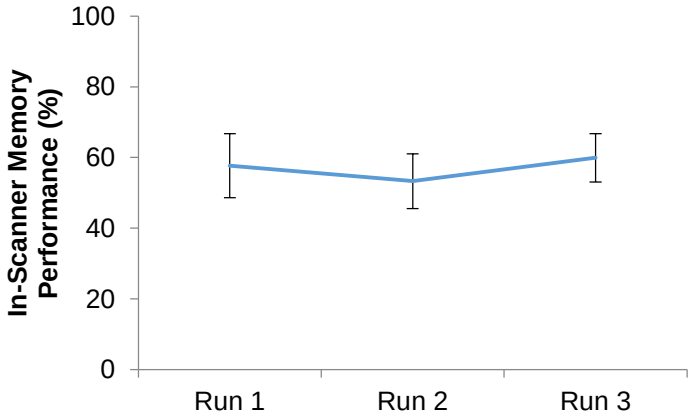


Figure 5.16 In-scanner memory performance across three scanning runs (95% CIs).

3.3.2 Laterality Indices across Runs

Group-level language and memory LIs across the three runs are reported in Figure 5.17. For language LIs, ICC was 0.45, indicating stability of values across

runs. For memory LIs, ICC could not be calculated because the between-subject variation is relatively small compared to the within-subject variation, indicating that the LIs are not stable across runs.

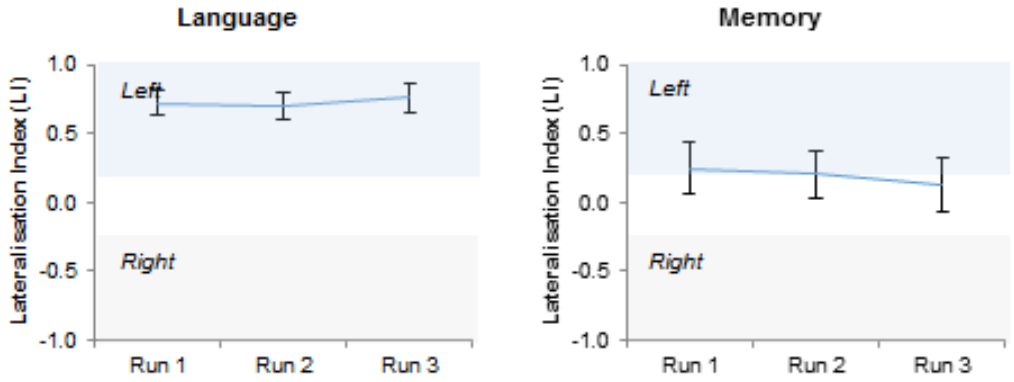


Figure 5.17 Group-Level Lateralisation Indices for Language and Memory in each run (95% CIs).

For the values of language lateralisation, only 3 out of 28 participants showed difference in the classification of LIs (*i.e.* left, right or bilateral) across runs, and the LIs vary between left and bilateral representations. Memory LIs show more variation across runs than language LIs. Some participants showed differences in the classification of values with the LIs varying from left to right representations across runs. However, memory LI is overall more bilateral than language LI; it is therefore not surprising that differences in the LI classification (left *versus* right) are more common for memory LI than for language LI.

3.3.3 SNR in the Hippocampus across Runs

Signal intensity in the hippocampus across scanning runs is represented in Figure 5.18. ICC was 0.98, indicating high reliability of intensity across runs.

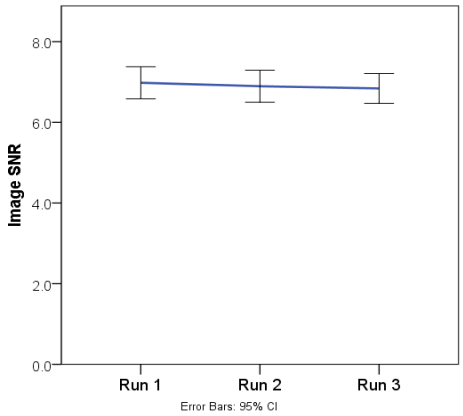


Figure 5.18 Mean image SNR in the hippocampus across runs.

3.4 Summary of Results

This chapter had several aims regarding the development of the fMRI protocol. Table 5.4 provides a summary of the findings corresponding to each aim.

Table 5.4 Summary of aims and results.

Aims		Results
1	Develop a combined language/memory fMRI paradigm	The paradigm involves a language task, *i.e.* verb generation task, and a memory task, i.e. cued recall task, allowing the investigation of both cognitive networks within one scanning session.
2	The protocol should allow to examine brain activity related to both memory encoding and retrieval	The language block acts also as the memory encoding phase, and the words are subsequently retrieved. This protocol design permits the investigation of both encoding- and retrieval-related brain activation.
3	The protocol should be sensitive to MTL function	The memory task consists in recall-based retrieval to increase hippocampal involvement.
4	The protocol should allow investigation of brain activation at the single-subject level	Although this is an intrinsic aim of the protocol, activation at the single-subject level was not explicitly investigated in the present chapter. Instead, this aim will be examined in the chapter related to patients with TLE (Chapter 7). However, it is important to note that low reliability of fMRI findings may hamper single-subject level analysis.

5	Examine test validity of the protocol	Learning scores on the standardised test (*i.e.* the CMS) and memory scores on the fMRI task were moderately related (r=0.39, p=0.042). False alarms (*i.e.* identifying a foil as "remembered") were shown in only 4%. In addition, the percentage of stem completion with the target word was not related to recall performance. These findings suggest little influence of priming on memory retrieval.
6	Examine data quality of the protocol	There was no significant difference between image SNR of anterior and posterior hippocampi (p=0.144). Regarding tSNR, intensity of the time-series was higher in Broca's area (M=4.9 SD=0.02) compared to the hippocampus (M=4.5 SD=0.04). The CNR in Broca's area and the hippocampus were higher for the contrast "Language>Baseline" (M=1.26 and M=0.29, respectively) compared to the contrast "Memory>Baseline" (M=0.80 and M=-0.16, respectively). Finally, there was no effect of in-scanner motion on any measure of data quality (p>0.160).
7	Examine the reproducibility of the protocol	The results showed stability of memory performance across runs (ICC=0.91). Language LIs were also stable (ICC=0.45), but the memory LI appeared less stable across runs (ICC could not be calculated). SNR in the hippocampus was stable across runs (ICC=0.98).

4 Discussion

4.1 Data Quality

4.1.1 SNR

The data quality of fMRI data was first investigated in terms of SNR. In EPI images, SNR has been used as a measure of signal dropout by Olman and colleagues (Olman et al., 2009), and was specifically investigated in the hippocampus in the present study due to its susceptibility to signal distortion.

Olman et al. (2009) calculated signal intensity in different MTL regions and reported a mean signal of 5662 averaged across seven ROIs, namely the anterior hippocampus, middle hippocampus, posterior hippocampus, entorhinal cortex, perirhinal cortex, posterior parahippocampal gyrus, and the amygdala.

The mean signal intensity in the hippocampus calculated in the present study (*i.e.* 4741) is similar to the one documented in Olman's study, although unfortunately the authors did not report signal intensity for separate ROIs, therefore a more specific comparison between hippocampal signals was not possible.

Whereas anterior regions of MTL are more prone to susceptibility-induced signal distortion than posterior regions (Olman et al., 2009), no difference in SNR was found between the different subregions of the hippocampus ROI in the present study. This finding indicates that the present protocol allows significant brain activation to be captured in the anterior hippocampus and that differences in activation between subregions of the hippocampus may be attributed to functional segregation of the hippocampus (*e.g.* Lepage et al., 1998; Paz-Alonso et al., 2008) rather than to signal dropout in the anterior hippocampus.

In addition, time-series extracted in Broca's area and the hippocampus showed higher raw (non-task specific) signal for the former ROI, which may be due to the magnetic susceptibility of the MTL region. Within the hippocampus ROI, variability in signal between voxels was particularly high. Several factors may contribute to this finding. First, it is possible that the hippocampus is more susceptible to non-task related variability which may be reflected in the variability of the time-series. Such variability may include movement artefacts (although this is not found in the present study), physiological noise or signal distortions,. Second, differences in signal intensity between left and right hippocampus may generate overall high variability in time-series within the hippocampus ROI. In addition, it is possible that this variability is actually related to the task, but is not captured by looking at raw signal activation. For example, it is possible that different voxels within the ROI are activated for successful memory compared to unsuccessful memory, leading to high variability when voxel activation is collapsed across performance (*i.e*. successful and unsuccessful). Task-related activation will be explored in Chapter 6. Similarly, low CNR in the hippocampus may reflect either high amount of non-task related variability (*i.e.* noise), or task-related differences (*i.e.* successful *versus* unsuccessful memory) in voxel activation within the ROI which is not captured using a block analysis contrast (*i.e*. "Memory>Baseline").

Generally, fMRI studies do not always report SNR or other measures of data quality. Signal loss in MTL regions lead to low SNR in those regions, making null

findings difficult to interpret as they may reflect signal loss as opposed to absence of brain activity in that region. Moreover, the studies that do present SNR of their data use different definitions and measurements of SNR, making comparison with other fMRI studies difficult (Welvaert & Rosseel, 2013).

4.1.2 In-Scanner Motion

In-scanner motion can be an issue in fMRI and may hamper data quality. Task-related motion, such as head movement related to speech, can cause signal changes which may be misinterpreted as brain activation (Friston et al., 1996). Negative effects of in-scanner motion are especially pronounced in paediatric populations (Engelhardt et al., 2017) and should particularly be taken into consideration in fMRI studies involving overt speech. It has been shown that image quality is specifically impeded in images with low SNR (Havsteen et al., 2017), therefore the effect of movement artefact on image quality in the present study was specifically investigated in the hippocampus due to its relatively lower SNR compared to Broca's area. However, in-scanner motion did not have a significant impact on fMRI data quality, providing evidence that overt verbal responses do not significantly impact on the fMRI signal and should be considered in future fMRI studies.

4.2 Reproducibility and Reliability

The reproducibility of the fMRI protocol was tested by investigating the stability of several variables across the three scanning runs. These variables were 1) memory performance, 2) language and memory LIs, and 3) EPI signal intensity (image SNR) in the hippocampus. First, memory performance was investigated across the three scanning runs. The average memory performance across the runs was 55% (*SD*=22), and the variability across runs was not significant. The consistency of performance across the runs indicates the reproducibility of the memory task.

Second, language and memory LIs were investigated across the scanning runs. Bennett and Miller suggested a range of ICC values between 0.33 and 0.66 within which fMRI studies are typically reliable (Bennett & Miller, 2010). In the present study, the ICC value for language LIs was 0.45 which therefore reflects

reliable results and indicates that language LI values were stable across runs. Memory LI values were less stable across runs, however, possibly as a result of noise in the data (*e.g.* physiological noise from the participants and system noise in the scanner) or subject variability in use of strategy (Bennett & Miller, 2010). It is possible that the changes in LI values in memory reflect changes in attention and arousal between runs which can modulate responses and influence brain activation (*e.g*. Sterr et al., 2007). These factors suggest that a considerable amount of trials may be needed to provide a measurable response, and it is possible that the number of trials in each run (10 for language and 15 for memory) prevents analysis of reliability across runs. Another possible influence is differences in cognitive strategies used during the memory task to retrieve the words (*e.g.* Miller et al., 2002) or differences in performance (*i.e.* successful *versus* unsuccessful memory). These results indicate that whereas the language LIs were stable across the three scanning runs, the memory LIs were less stable, which may be due to several factors and should be investigated further.

Reliability is the likelihood of obtaining the same results (*i.e.* brain activations) if the fMRI experiment is repeated. In this respect, reliability has usually been measured with separate scanning sessions (*e.g*. days apart), rather than with separate runs within a session as in the present study. Splitting the data into separate runs decreases the number of trials and may hamper the ability to examine reliability. Another study investigated reliability of brain activity in the amygdala during emotional face processing and reported poor reliability of activation in the amygdala, both between two runs (10 minutes apart) and between two scanning sessions (two weeks apart), whereas the reference regions (*i.e*. the fusiform face area) showed high reliability between runs and between sessions (Nord et al., 2017). Regions within the MTL are particularly susceptible to poor reliability of brain activation (Brandt et al., 2013), which has important implications with regards to interpreting fMRI results. Further investigation of reliability of hippocampal activation should therefore be conducted across different scanning sessions.

Brandt and colleagues investigated reliability of memory fMRI activation using data from two sessions, 1 month apart. The authors measured ICC for the degree of activation at each voxel of the brain and reported that despite reliability of memory activation at the group-level, activation was not stable within individuals

(Brandt et al., 2013). Overall, reliability of fMRI findings is rarely investigated, and those studies that do investigate it generally report poor reliability of brain activation (see Bennett & Miller, 2010, for a review). Several factors can however improve reliability of fMRI results, including increasing the size of the ROIs (Friedman et al., 2013), having additional runs (Friedman & Glover, 2006) and increasing the SNR by having additional scans (Bennett & Miller, 2010).

The reliability of fMRI should be a concern for researchers because without reproducible results, studies cannot effectively contribute to scientific knowledge. The issue of reliability is particularly important for clinical application of fMRI findings, whereby, for example, localisation of function is used to guide surgical planning. In the case of low reliability, single-subject fMRI analysis is hampered which reduces clinical validity of the paradigm as a diagnostic tool. In the future, it would therefore be important to measure reliability across separate scanning sessions in order to perform the reliability analysis.

4.3 Clinical Implications

This fMRI protocol has multiple advantages over current neuroimaging tasks. First, the combined language/memory aspect of the protocol offers pre-operative mapping of both networks in a time- and cost-effective manner. Memory fMRI administered in conjunction with language fMRI could provide a better guide for tailored resections, particularly in the temporal lobe, and help predict outcome. This protocol can be used to shed light on how the two systems interact in cases of early TLE abnormality, and explore whether lateralisation for memory and language are interdependent. This paradigm can provide additional information compared to other paradigms that investigate language and memory separately, by providing indication of the interaction between these two networks and of the status of functional organisation in the context of brain lesion.

Second, the protocol enables examination of fMRI activation related to both memory encoding and retrieval, providing a more robust mapping of memory-related networks, as both phases are dependent on hippocampal involvement (Saddiki et al., 2018; Spaniol et al., 2009). Moreover, obtaining robust activation in the hippocampus at the individual level has proven challenging across fMRI studies (Dupont et al., 2001; Saddiki et al., 2018), but a wider approach to

memory mapping involving two memory phases (encoding and retrieval) may increase the chances of capturing such an effect.

Third, this protocol investigates activity related to recall memory, as opposed to recognition, for a better examination of the hippocampal-neocortical network (Aggleton & Brown, 1999; Eichenbaum et al., 2007; Patai et al., 2016; Yonelinas, 2002). Failure to show robust activation in hippocamal regions in some fMRI studies may be due to the recognition nature of the tasks often employed, which may rely on other subregions of the MTL. Word-stem cued recall tasks have been used by previous fMRI studies and show activation in several regions which are associated with successful recall, namely bilateral parietal cortex, bilateral medial temporal lobe, including the hippocampi, and left temporal cortex in healthy adults (Hayama et al., 2012; Okada et al., 2012; Schott et al., 2005; Wimber et al., 2008). Patients with epilepsy are impaired in word-stem recall (Hudson et al., 2010), making this task potentially sensitive to the identification of network abnormalities.

Lastly, the design of the protocol permits investigation of fMRI data through both block-analyses and event-related analyses. Block analyses allow examination of brain activity related to memory effort, irrespective of performance, whereas event-related analyses examine successful memory specifically and are particularly relevant for predicting memory outcome in the clinical setting. Together, the features of this protocol make it particularly useful for the investigation of pre-operative memory networks and for the prediction of memory outcome in TLE.

5 Limitations

As mentioned above, the influence of priming has been controlled for in the memory test. However, it is possible that, despite efforts to reduce the effect of priming, the retrieval of words is still influenced by some level of automatic retrieval or echoic memory.

Another limitation relates to the short delay between encoding and retrieval phases (50 seconds). The attribution of long-term memory with such delay could be disputed, but methodological considerations were put in place to insure this. The baseline task involving active and overt response prevents subvocal

rehearsal and maintenance of information in working memory. It is possible that a longer delay between encoding and recall phases of memory is more sensitive for the investigation of hippocampal-related brain activation, but this comes with the pitfall of longer scanning time, especially with children.

As mentioned in section 4.3 (page 173), low reliability of fMRI findings may hamper single-subject level analysis which has crucial implications in the clinical context. Reliability of fMRI needs to be taken into consideration and confirmation of reliability may be difficult without additional scanning sessions.

6 Conclusions

A combined language/memory fMRI paradigm was developed to map critical functions in paediatric TLE prior to surgical intervention. The advantages of this paradigm are 1) the functional mapping of language and memory within one scan, 2) the investigation of encoding and retrieval neural networks, 3) recall-based retrieval to increase hippocampal involvement, and 4) overt verbal responses to monitor in-scanner memory performance.

In the present chapter, several variables related to the novel fMRI protocol were examined: 1) test validity, 2) data quality, and 2) reproducibility of the protocol. To examine test validity, behavioural performance was investigated and compared with out-of-scanner memory performance. To test data quality, SNR was investigated and the findings indicate no significant difference in signal quality in the anterior *versus* the posterior hippocampi. This finding has important implications considering the anterior hippocampus is generally susceptible to signal loss, hampering interpretation of findings. The present protocol therefore provides the ability to capture brain signal in different subregions of the hippocampus. In addition, because the present protocol involves overt speech, in-scanner motion was examined. The results showed that movement artefact does not have a negative impact on image quality, suggesting that overt verbal responses should be considered in future studies to monitor in-scanner performance. Lastly, the reproducibility of the protocol was investigated and the results showed stable image SNR in the hippocampus, as well as stable memory performance and language LI values across the three scanning runs. However, memory LIs were less stable across runs which may be attributed to several factors and should be investigated further across several scanning sessions

rather than scanning runs. Overall, this novel language/memory fMRI protocol was developed and examined as part of this thesis, and could provide clinically useful information for surgical planning in paediatric TLE.

7 Future Directions

The next step will be to investigate the imaging data acquired with this protocol in a sample of healthy children to identify the language and memory networks in typically-developing children. In addition, it will be relevant to characterise the relationship between language and memory lateralisation, and to define age-related changes in the memory network using the novel fMRI protocol. These investigations will offer a baseline against which comparisons to the network in children with epilepsy can be made.

Chapter 6

Language and Memory networks in Typically-Developing Children using a combined fMRI paradigm

In the present chapter, the language/memory fMRI paradigm, which was developed and described in Chapter 5, was administered to a sample of typically-developing children to define the typical networks engaged in language and memory processing. This chapter aims at characterising the development of the memory network and its relation to language lateralisation. This study has clinical implications regarding surgical decision-making in childhood TLE, by providing the opportunity to compare the networks activated in children with epilepsy to a typical network.

1 Introduction

When studying clinical populations, novel protocols should be validated in typically-developing children before they are used in a clinical setting. It is important to define the typical networks engaged in cognitive processing, in the case of this research those involved in memory, to which we can compare the networks activated in children with epilepsy, and from which predictions can be made about memory outcome after temporal lobe surgery. In children with epilepsy, different aspects of memory function can reorganise to other brain regions, similarly to what is reported for language reorganisation (de Ribaupierre et al., 2012; Yuan et al., 2006). Such shifts in reorganisation of cognitive functions must be identified at the pre-operative level as this information often aids surgical planning by mapping the territory of eloquent tissue, and also serve as a prognostic indicator of cognitive outcome after surgery.

Whereas the language network is routinely being investigated in the clinical workup of children with Temporal Lobe Epilepsy (TLE) who are candidates for surgery, there is a dearth of information about the status of the memory network in these children. In addition, there is little understanding regarding the relationship between the organisation or reorganisation of the language network and the memory network, and their respective lateralisation. The present chapter will therefore investigate the language and memory networks in typically-developing children using the novel functional Magnetic Resonance Imaging (fMRI) protocol.

1.1 Defining the Territory of the Language Network

As discussed in Chapter 1, the language network is often identified in both healthy children and patients with brain pathologies using a verb generation task. The verb generation task requires participants to generate a semantically appropriate verb for each noun presented (*e.g.* generate the verb “eat” for the noun “cake”). Activated regions typically associated with these tasks are illustrated in Figure 6.1, and include Broca’s area in the Inferior Frontal Gyrus (IFG), Wernicke’s area in the left superior temporal gyrus (STG), the cingulate gyrus, and the dorsolateral prefrontal cortex (Holland et al., 2001). This task

typically shows left lateralisation in frontal and temporal regions in children (Friedman et al., 1998; Gaillard et al., 2000; Holland et al., 2001).

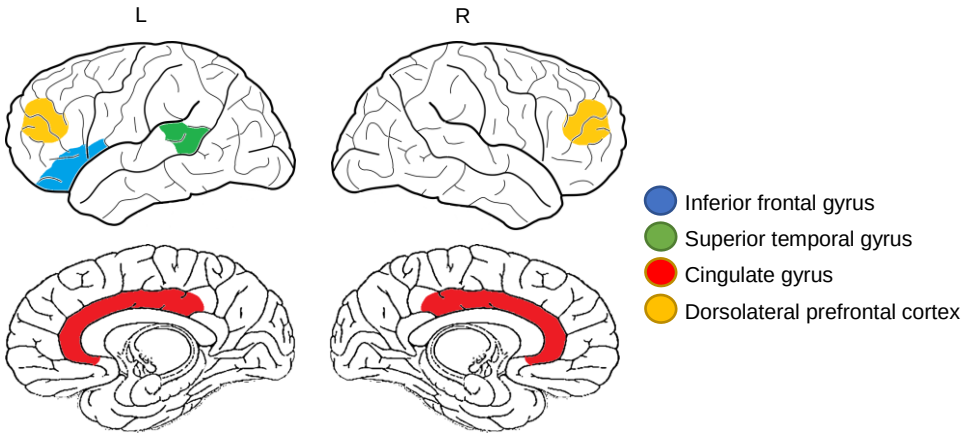


Figure 6.1 Summary of language-related brain activation reported in healthy children.

1.2 Defining the Memory network

1.2.1 Memory Encoding Network

Compared to the memory network in adults, the network in children remains relatively unexplored (see Chapter 1, section 5.2.2.2, page 33). However, the research that has been conducted to date indicates that the memory network changes over development until adolescence (Guler et al., 2013; Ofen et al., 2007; Maril et al., 2010). In one study relevant to the memory network in children, Maril and colleagues (2010) investigated verbal memory encoding-related activity using an incidental encoding task in children and adolescents (age range 7-19 years). Activity related to subsequent memory was shown in left hippocampus, left prefrontal cortex (PFC) and bilateral basal ganglia (Maril et al., 2010). Figure 6.2 illustrates the activated regions typically associated with memory.

The authors also documented age-related effects with reduced activation in the right inferior temporal lobe and right dorsolateral PFC, as well as reduced hippocampal activation with increasing age. Age-related changes in hippocampal activation are however not consistent across studies. As opposed to Maril and colleagues' study, Ghetti et al. (2010) documented increasing activation with age.

In the former study, the memory task consisted of phonological encoding with a surprise recognition task, whereas in the latter study, the memory task consisted of paired-associate learning of objects. Ofen et al. (2007) examined brain activation during scene encoding and showed no age-related effects in the MTL. Differences in the memory tasks between the studies make it difficult to make direct comparisons and may explain the mixed findings.

Another reason for mixed findings and inconsistent hippocampal effects across studies relates to the fact that the hippocampus is not a single homogeneous structure but instead contains several subregions that likely perform more than one memory-related function, and show different activation patterns depending on task demands. Several studies have documented differential roles of subregions of the hippocampus in adults (Lepage et al., 1998; Greicius et al., 2003). Similarly, the roles of hippocampal subregions have been investigated in children and there is evidence of a higher contribution of anterior compared to posterior hippocampus to memory encoding (Ghetti et al., 2010; Maril et al., 2010). However, functional segregation of the hippocampus is not consistently investigated in paediatric studies (*e.g*. Guler et al., 2013; Ofen et al., 2007) and is therefore not fully understood.

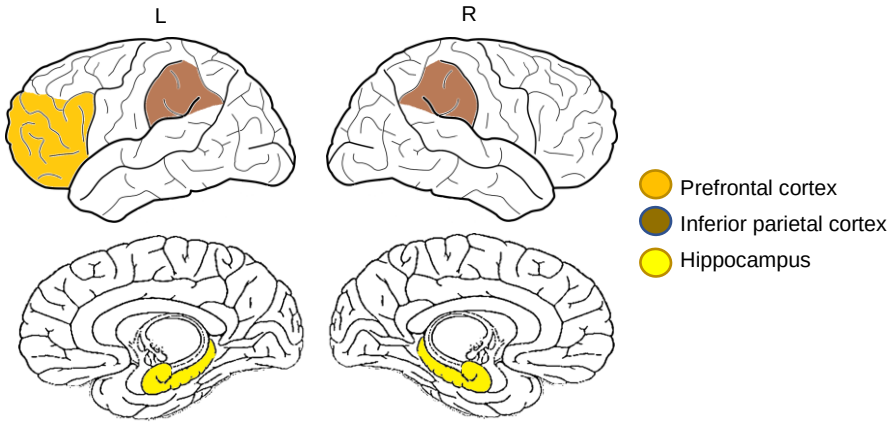


Figure 6.2 Summary of memory-related (encoding and retrieval) brain activation reported in healthy children.

1.2.2 Memory Retrieval Network

In children, less is known about the memory retrieval network than the encoding network.The research that has been conducted suggests that the memory

retrieval network in children is largely similar to that of adults (Guler and Thomas, 2013; Bauer et al., 2017). However, there is also evidence that the memory retrieval network changes over development. For example, Guler and Thomas (2013) showed that the left ventrolateral PFC and left inferior parietal cortex are activated during memory retrieval in older children but not in younger children. In addition, Bauer and colleagues documented age-related increases in activation in hippocampal and parahippocampal regions (Bauer et al., 2017). Figure 6.3 provides a visual summary of age-related changes in memory-related activation in healthy children. Further research needs to replicate these findings and establish the significance of the functional activation profiles that occur over the lifespan.

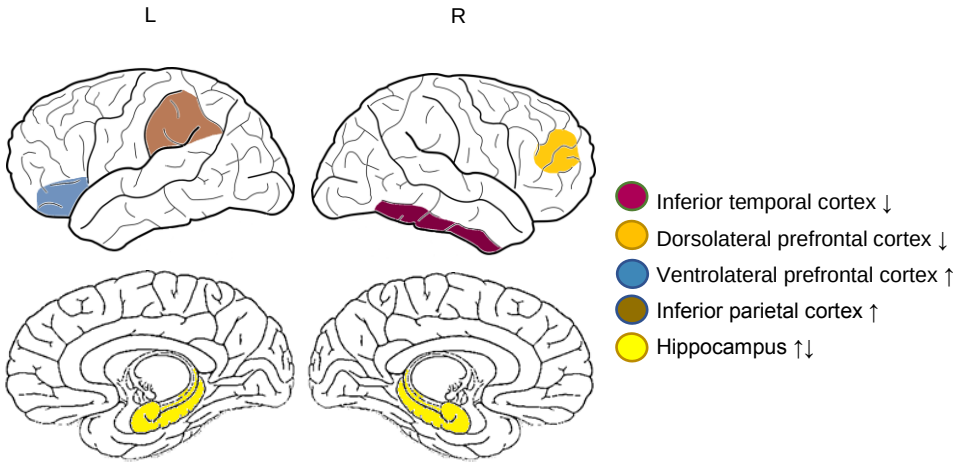


Figure 6.3 Summary of age-related changes in memory-related activation in healthy children.

Functional segregation of the hippocampus for memory retrieval has previously been documented, with different roles of the anterior and posterior subregions (Paz-Alonso et al., 2008), as being similar to encoding. In addition to the retrieval network being less investigated than the encoding network in children, brain activations related to retrieval have solely been investigated using recognition tasks. This is especially important to note because the hippocampus is thought to be more important for recall than for recognition (see Chapter 1, section 2.3.2, page 12). Patients with Developmental Amnesia (DA) who sustained neonatal hypoxia/ischaemia and consequently suffered selective bilateral hippocampal pathology (Vargha-Khadem et al., 1997) exhibit severe and selective impairment

in recall memory, in the context of relatively well-preserved recognition memory (Adlam et al., 2009; Baddeley et al., 2001; Patai et al., 2015). Based on these data, it appears that the hippocampus plays a critical role in recollection and recall, but less so in recognition which is mediated by the parahippocampal cortices.

1.3 Relationship between Language and Memory Networks

Numerous studies have demonstrated hippocampal activation during language processing, whereby this structure contributes to language function through the retrieval and binding of information across domains (see Duff & Brown-Schmidt, 2012 for a review). Milner and Rasmussen's study (1977) claimed that language reorganises only if one or both of the language areas are damaged. Contradicting this finding, Liegeois and colleagues showed that patients who had lesions far from the language areas reorganised, but those who had lesions encroaching language areas did not (Liegeois et al., 2004). Kneckt then surmised that those who reorganised had lesions encroaching the hippocampus (Knecht, 2004). These lesion studies suggest that hippocampal pathology influences language lateralisation, suggesting that the repesentation of langage might be different in the context of reorganisation of the memory system (Weber, 2005). Together, these findings suggest there may be a relation between memory and language lateralisation.

However, DA patients show good preservation of language skills, especially vocabulary and semantic memory, in the presence of severe bilateral hippocampal damage, indicating that the hippocampus is not crucial for language functions (and semantic memory) (see Elward & Vargha-Khadem, 2018 for a review). The relation between language and memory networks is therefore unclear at this stage, and may critically depend on long-term auditory verbal memory. Until this relationship is fully investigated, it will be difficult to take full account of any differences between the data in adults *versus* children.

Co-lateralisation of memory and language functions in healthy adults has been demonstrated, whereby those with language dominance in the left hemisphere also show left lateralisation for verbal memory and right lateralisation for faces

(Weber et al., 2007). A recent study by Sepeta and colleagues investigated lateralisation of MTL and language regions (Broca's and Wernicke's areas) during a language task in adults and children. The task consisted of an auditory description decision task whereby participants heard a sentence that described an object (*e.g.* "A long yellow fruit is a banana"), which was a correct definition in 70% of the time. Participants were asked to make a semantic decision on the accuracy of the sentence. The authors showed co-lateralisation of activation in Broca's area and the MTL in healthy adults (Sepeta et al., 2016). Left lateralised activation in the MTL was reported in those who showed left lateralised activation of language regions, whereas those with atypical language lateralisation activated right or bilateral MTL regions. These findings indicate co-lateralisation of activations in language regions and the MTL in right handed adults.

In children, however, this co-lateralisation of activations in Broca's/Wernicke's areas and MTL regions were not found. Sepeta and colleagues demonstrated increasing left lateralisation of MTL activation with age, but activations in Broca's area and medial temporal regions were less interrelated in paediatric cases compared to adults. Whereas the activations in both Broca's/Wernicke's areas and the MTL were examined during a language task, the findings could indicate more segregation between lateralisation of language and lateralisation of memory functions in healthy children. This could in turn have implications for the pattern of findings in the paediatric patient population with MTL pathology.

1.4 Aims

This study aims to:

a) Identify the typical network supporting language performance in children and adolescents.
b) Define the core network supporting verbal memory encoding and memory retrieval, to identify activity related to successful memory performance.
c) Characterise the relationship between language and memory lateralisation in children and adolescents.
d) Define age-related activity-dependent changes in the memory network.

2 Methods

2.1 Participants

The participant sample included in this chapter is the same as the one reported in Chapter 5. Briefly, the sample consisted of 27 healthy children and adolescents, 10 males and 17 females, between the ages of 8 and 18 years (*M*=14 years, *SD*=3).

Intellectual status was measured in each individual using the Wechsler Abbreviated Scale of Intelligence – Fourth Edition (WASI-IV), as described in Chapter 5 (section 2.3, page 145). The scale provides measures of Full Scale, Verbal and Performance Intelligence Quotients (FSIQ, VIQ and PIQ). Handedness was measured for each participant using the Edinburgh Handedness Inventory (Oldfield, 1971), providing a score between -100 (*i.e*. strongly left handed) and 100 (*i.e.* strongly right handed).

2.2 fMRI protocol

A full description of the fMRI protocol is provided in Chapter 5. Briefly, the language paradigm consists of a verb generation task, in which participants are presented with nouns and are asked to overtly produce a corresponding verb for each noun. The memory task requires recalling the nouns presented during the language task utilising word stems as cues to guide recall. The baseline task, to which both the language and memory tasks are compared, is an odd/even decision-making task with written numbers.

Verbal responses were monitored via an MRI-compatible microphone and accuracy was assessed for each participant to examine in-scanner performance. Percentage scores based on in-scanner performance were subsequently analysed.

2.3 Behavioural analyses

Behavioural performance was investigated for the language and memory tasks. For the language task, an incorrect response consisted of a failure to generate a verb. For the memory task, each response was classified as a 'hit' (correct recall), 'miss' (incorrect recall), 'correct rejection' (foils are correctly rejected) or 'false alarm' (foils are identified as being part of the studied list and completed with a word).

Pearson correlations were carried out between language and memory performances and demographic variables, including FSIQ, VIQ, handedness and age.

2.4 Imaging Analyses

2.4.1 Modelling

fMRI analyses were conducted using blocked and event related models. For block analyses, effects of interest were modelled by convolving block sequences (onset and duration *i.e*. 40 seconds for language and baseline blocks and 60 seconds for memory block) with a haemodynamic response function (HRF). For event-related analyses, effects of interests were modelled by convolving each trial onset with HRF. Within the language block, subsequent hits and subsequent misses were modelled separately. Similarly, within the memory block, hits, misses and correct rejections were modelled separately.

For individual subject analyses (1^{st} level), the changes in Boldl Oxygenation Level-Dependent (BOLD) signal over time was examined using fixed effects analysis across the three runs. For group analyses (2^{nd} level), contrast estimates from each subject were entered into a General Linear Model (GLM) with subjects treated as a random factor. Random effects analyses were computed to identify patterns of task-related activation that are consistent across the group.

Temporal and dispersion derivatives of the HRF were included in the model in order to model the onset and duration of the BOLD peak (Henson et al., 2001).

2.4.2 Block Analysis

In block analyses, the different conditions (*i.e.* language, baseline and memory) were separated into blocks of extended time intervals. Block analyses have high detection power for the difference in amplitude of brain activation using the HRF (Henson, 2004), meaning that it has good ability to differentiate between different conditions.

2.4.2.1 First Level

Three regressors of interest were created: Language (L), Baseline (B) and Memory (M) (Table 6.1). For each subject, contrasts were created for language [defined by (L)-(B)] and memory [defined by (M)-(B)]. These contrasts for each subject were used in the second level analysis.

Table 6.1 Description of each regressor.

Regressors	Description
Language (L)	Verb generation task
Baseline (B)	Baseline task: odd/even decision to numbers
Memory (M)	Cued recall task, irrespective of performance

2.4.2.2 Second Level

A single contrast image was entered for each subject into a one-sample *t* test (one-tailed) to examine the group effect of each contrast of interest. Language activations were investigated for the contrast “Language>Baseline”. Whole-brain analysis at the group level is reported at a height threshold of $p<0.05$, corrected for multiple comparisons (FWE).

Memory activations were investigated for the contrast “Memory>Baseline”. Whole-brain analysis at the group level is reported at a height threshold of $p<0.001$, uncorrected. Lower threshold is employed for the memory contrast compared to the language contrast for better investigation of smaller brain regions within the MTL.

2.4.3 Event-Related Analysis

In event-related analyses, the BOLD response is modelled to each trial within a block (Henson et al., 2001) and allows the separation of trials based on the

participant's performance (*e.g.* correct *versus* incorrect). It provides a better representation of the latency of brain response by providing a better characterisation of the shape and the onset of the HRF than block analyses (Mechelli et al., 2003).

2.4.3.1 First Level

Six regressors of interest were created (Table 6.2): Subsequent Hit (SH), Subsequent Misses (SM), Baseline (B), Hits (H), Misses (Mi) and Correct Rejections (CR).

Table 6.2 Description of each regressor of interest.

Regressors	Description
Subsequent Hits (SH)	Activation during the encoding of words that were later retrieved
Subsequent Misses (SM)	Activation during the encoding of words that were later forgotten
Baseline	Baseline task: odd/even decision to numbers
Hits (H)	Activation during the successful retrieval of words
Misses (Mi)	Activation during the unsuccessful retrieval of words
Correct rejection (CR)	Activation during correct rejections of words at retrieval

The encoding-related responses for words that were subsequently remembered (SH) were compared to words that were subsequently forgotten (SM). For each subject, contrast images were created for subsequent memory [defined by (SH)-(SM)] and memory retrieval [defined by (H)-(M+CR)]. In addition to brain activation, brain deactivation that predicts subsequent memory was also investigated. This was examined using the opposite contrast ("SM>SH"). These contrast images for each subject were used in the second level analysis. Table 6.3 provides the number of trials for each regressor.

Table 6.3 Average number of trials across participants for each regressor used in the event-related analyses.

Regressors	Number of Trials	SD	Min	Max
Subsequent Hits (SH)	33	13	8	54
Subsequent Misses (SM)	25	11	6	41
Hits (H)	33	13	8	54
Misses (Mi)	25	11	6	41
Correct rejections (CR)	30	2	24	30

2.4.3.2 Second Level

Second level analyses were computed to investigate the group effect of each contrast of interest, using one-sample *t* tests, one-tailed. Whole-brain analysis at height threshold of $p<0.05$ (FWE, corrected) did not yield significant activated voxels, and instead, a liberal threshold of $p<0.01$, uncorrected, was used to characterise trends in the data that are subthresholded. A lower threshold was employed for event-related analyses compared to block analyses to identify activation in specific subregions of the MTL.

2.4.4 Age-Related Effects

Age-related effects in memory activations were examined using age as a continuous regressor in an analysis of covariance (ANCOVA) against the whole brain event-related design retrieval activations.

2.4.5 Anterior versus Posterior Hippocampal Activation

Comparison between memory-related activation in the anterior and posterior hippocampus were investigated by extracting and comparing beta weights in different hippocampus ROIs, for memory encoding (contrast “SH>SM”) and memory retrieval (contrast “H>Mi+CR”). A beta weight is the estimated parameter value for a specific condition in the statistical model. Extracting beta weights from ROIs can provide a measure of parameter estimates which is not dependent on an arbitrarily defined threshold. Beta weights indicate the effect size and the direction of the signal in the specific ROI. They can be informative, especially in cases where activation in an ROI is not visible on the thresholded t-map, by providing numeric representation of the activation for each condition. In addition, beta weights can be useful for assessing individual differences.

2.4.6 Laterality Index (LI) Calculations

LIs were calculated to assess hemispheric lateralisation for language and memory, as described in Chapter 5 (section 2.11.2, page 161). LIs were determined at the individual level in separate ROIs for language and memory. Language LIs were determined based on LI values in Broca’s area during the VG task, and memory LIs were determined based on LI values in the hippocampus during the cued recall task.

To investigate the relationship between language and memory LIs, correlations were carried out between language LI in Broca's area and memory LIs in the hippocampus. In addition, language LI was also calculated in the hippocampus to have a comparison with memory LI in that same region.

3 Results

3.1 In-Scanner Behavioural Performance

3.1.1 Language Task

Participants had an average score of 91% (*SD*=9) on the VG task. An independent sample *t* tests showed no significant difference in performance between males (M=90% SD=12%) and females (M=91% SD=6%), *t*(25)=-0.249, *p*=0.805. Correlation analyses showed that performance was not related to FSIQ, after controlling for age (*r*=0.262, *p*=0.195), or to handedness (*r*=0.287, *p*=0.147). Partial correlations showed that the scores were correlated with age, controlling for FSIQ (*r*=0.376, *p*=0.058), where older children performed better than younger children (Figure 6.4A). The results were similar when VIQ was used as covariate instead of FSIQ.

3.1.2 Memory Task

The types of responses from the cued recall task are reported in Table 6.4. On average, over half of the words were successfully recalled (57%), and almost all lures were successfully rejected (96%).

Table 6.4 In-scanner memory performance (mean (M) and standard deviation (SD) expressed in percentage).

Performance	Mean	SD
Hits (H)	57	20
Misses (M)	43	20
Correct rejection (CR)	96	6
False alarms (FA)	4	6

An independent samples *t* tests showed no significant difference in performance between males (M=65% SD=20%) and females (M=51% SD=18%), $t(25)=1.845$, $p=0.077$. Memory scores were not related to FSIQ or VIQ, after controlling for age, or to handedness (Table 6.5). The scores were, however, significantly related to age, after controlling for FSIQ, with better performance with increasing age (Figure 6.4B).

Table 6.5 Correlations between demographic variables and in-scanner memory performance.

	Statistic
FSIQ	*r*=0.27 *p*=0.180
VIQ	*r*=0.03 *p*=0.894
Handedness	*r*=0.49 *p*=-0.139
Age	*r*=0.41 *p*=0.036

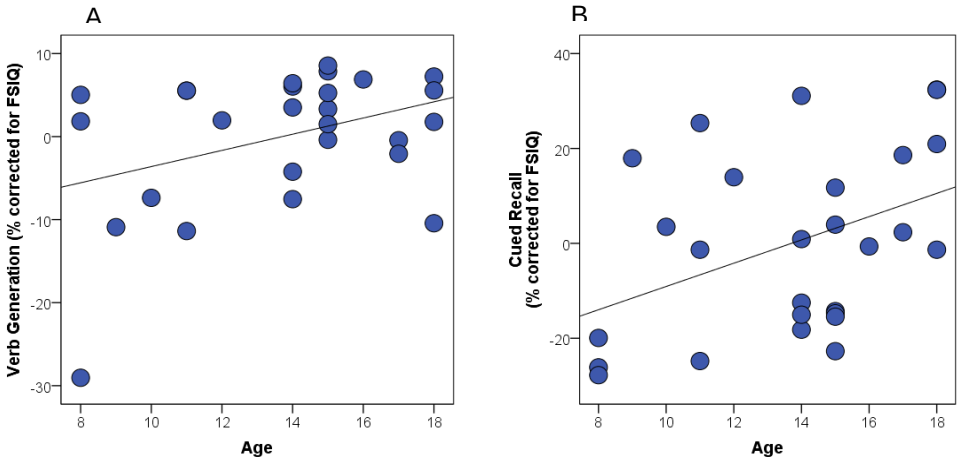


Figure 6.4 Relationship between age and performance on the language (A) and memory (B) tasks, corrected for FSIQ.

3.2 Block analyses

3.2.1 Language Activations

Activations were found in regions typically associated with language. Activation was found in left Broca's area, the left STG, bilateral dorsolateral prefrontal cortex (DLPFC), pre-supplementary motor area (pre-SMA), right cerebellum, left

thalamus, left anterior insula and bilateral middle cingulate cortex (MCC) (Figure 6.5). In addition, activation was also found in the left posterior hippocampus at a lower threshold (p<0.001) (Figure 6.6).

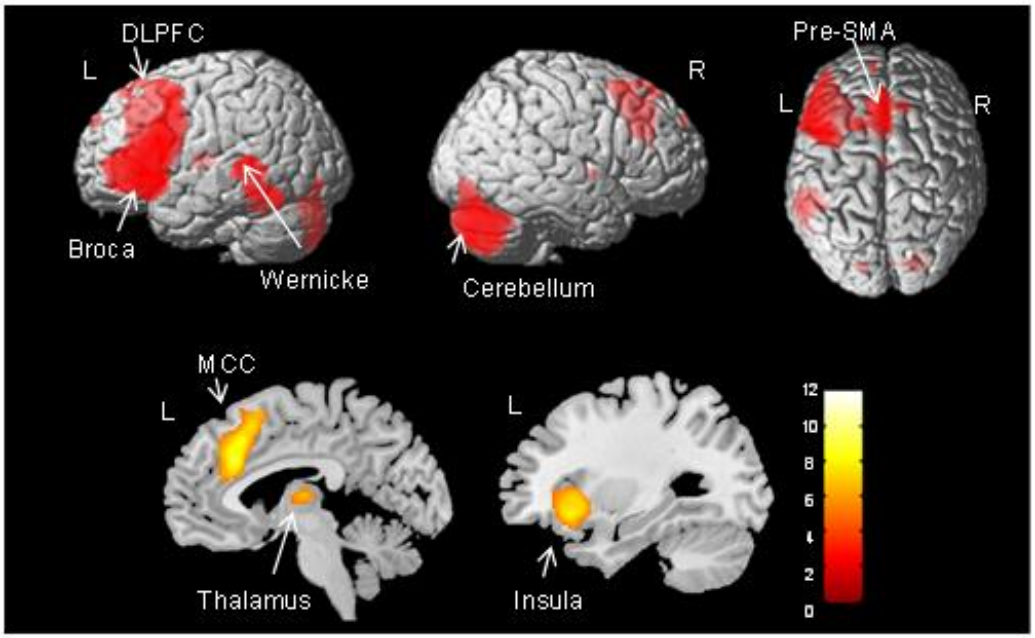


Figure 6.5 Group activation during verb generation task (p<0.05, FWE).

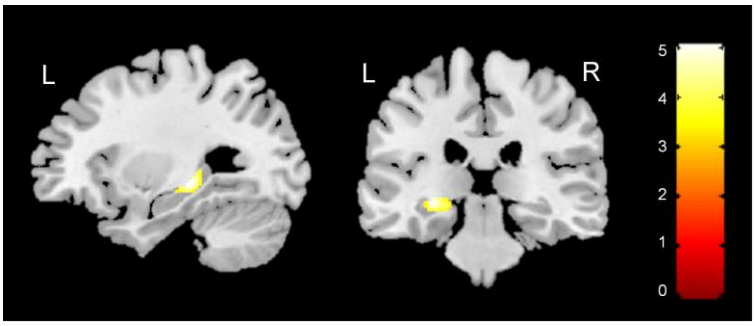


Figure 6.6 Group activation in the hippocampus during verb generation task (p<0.001, uncorrected). Whole brain analysis but masked to include only the hippocampal region for viewing purposes.

3.2.2 Memory Activations

Activations were found in left Broca's area, left dorsolateral PFC, bilateral cerebellum and bilateral posterior temporal lobes. Activations were also shown in bilateral anterior insula, bilateral pre-supplementary motor area (pre-SMA)

bilateral middle and posterior cingulate cortex (PCC & MCC), and bilateral caudate.

Because many of these activations overlap with those reported for language, another contrast was investigated ("Memory>Language") to identify activations that are specific to the memory task. Activations were shown in right dorsolateral PFC, right orbitofrontal PFC, bilateral posterior temporal lobes (right posterior middle temporal gyrus and left posterior superior temporal gyrus), right pre-SMA, and posterior cingulate cortex (p<0.001, uncorrected) (Figure 6.7).

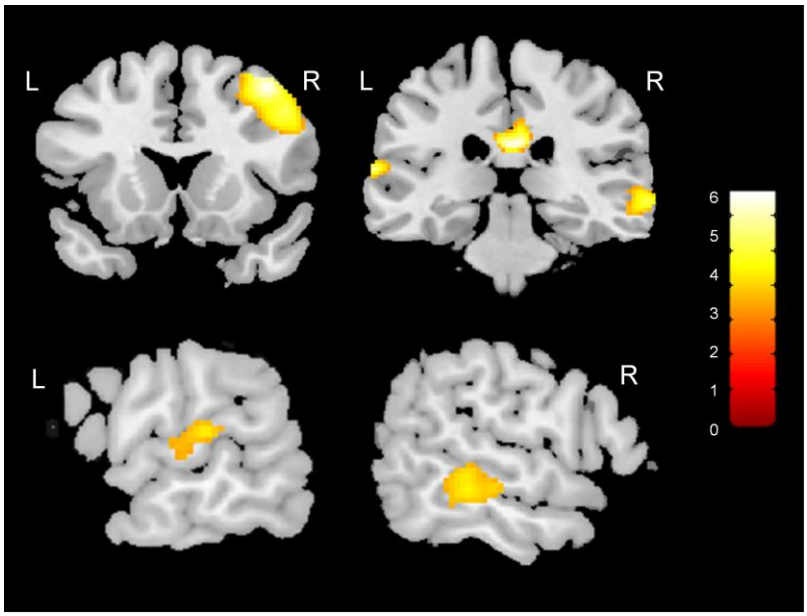


Figure 6.7 Group activation during cued recall task (p<0.001, uncorrected) (contrast "M>L").

3.3 Event-Related Analyses

3.3.1 Memory Encoding

Successful memory encoding was associated with activity in the left temporal pole and right posterior superior temporal lobe (Figure 6.8). Deactivations were found in bilateral parahippocampal gyrus, bilateral supramarginal gyrus, bilateral lingual gyrus, and left cerebellum.

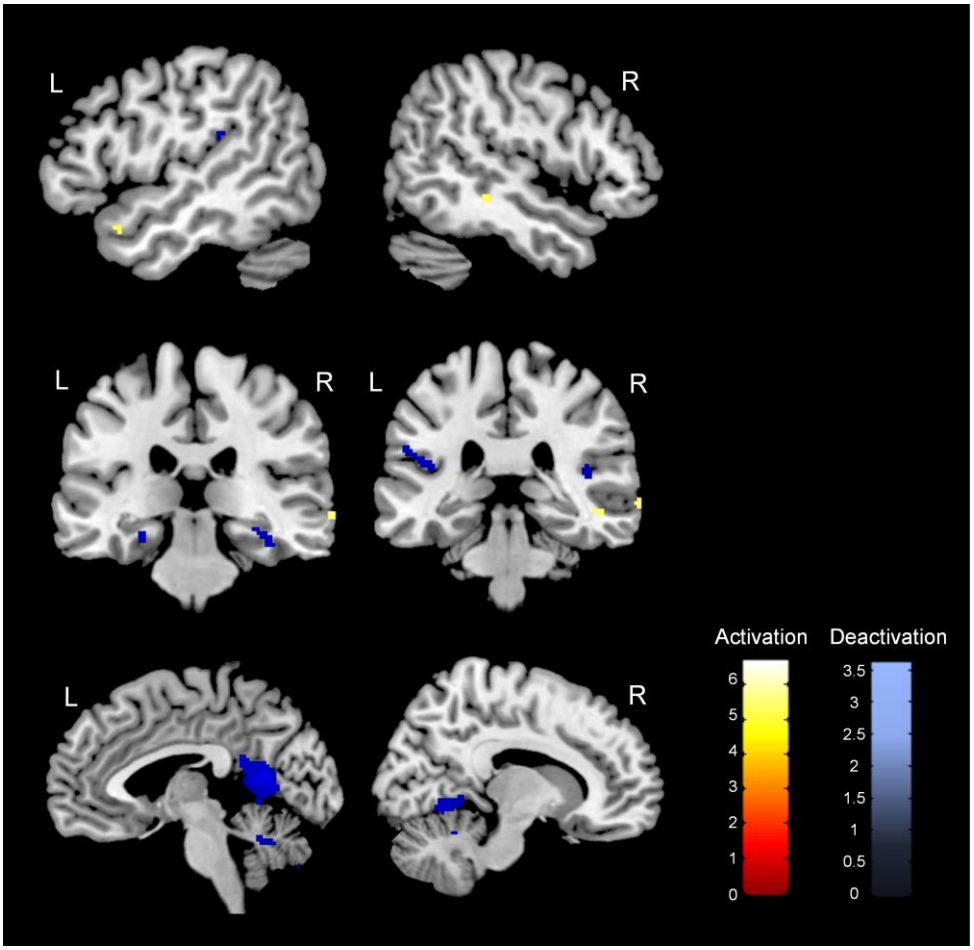


Figure 6.8 Group activation and deactivation for subsequent memory (p<0.01, uncorrected).

Beta weights were extracted from the hippocampus ROI for subsequent hits and subsequent misses (Table 6.6 and Figure 6.9). These values did not significantly differ from one another (paired *t*-test, $t(26)=-0.758$, $p=0.455$). The paired *t*-test was repeated in subregions of the hippocampus (anterior and posterior) separately in case an effect is specific to a subregion and not apparent in the averaged ROI. However, the subsequent hits and misses values did not significantly differ from one another, either in the anterior (paired *t*-test, $t(26)=-0.590$, $p=0.560$) or the posterior (paired *t*-test, $t(26)=-0.870$, $p=0.392$) hippocampus.

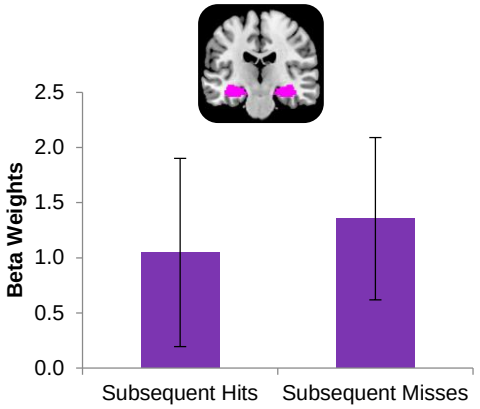


Figure 6.9 Mean beta weights for subsequent hits and misses extracted from hippocampus ROI. Displayed with confidence intervals.

Table 6.6 Mean beta weights for subsequent hits and misses extracted from hippocampus ROI.

Performance	Mean	SD
Subsequent Hits	1.05	2.26
Subsequent Misses	1.36	1.95

3.3.2 Memory Retrieval

Activity associated with successful memory retrieval was shown in bilateral hippocampi, left posterior superior temporal gyrus and left caudate (Figure 6.10). Deactivation was shown in right DLPFC, right ACC, bilateral insula, and right inferior anterior temporal gyrus.

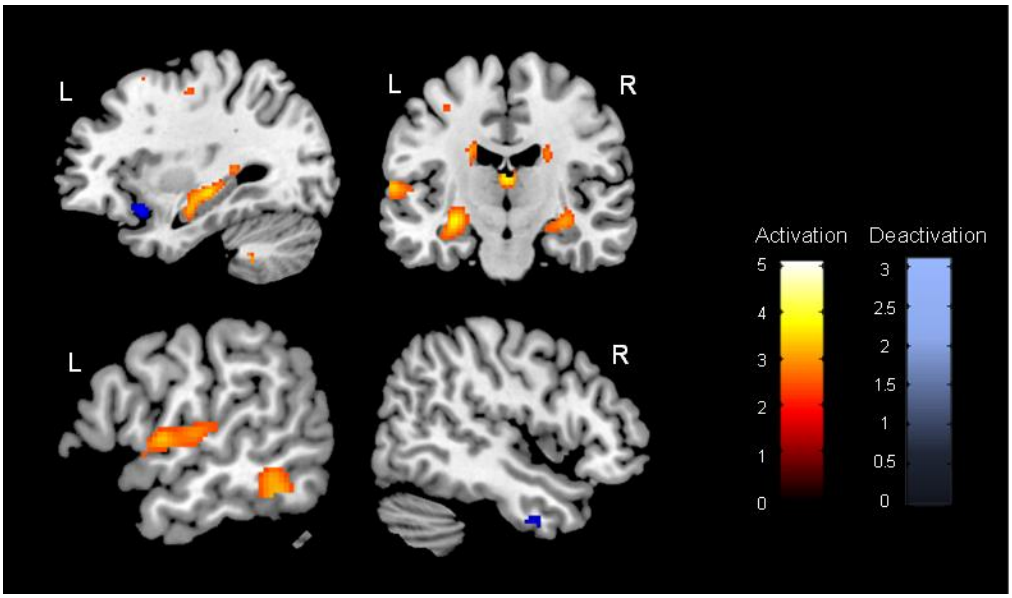


Figure 6.10 Group activation and deactivation for successful retrieval (p<0.01, uncorrected).

Figure 6.11 and Table 6.7 provides a visual representation of the mean beta weights extracted from a hippocampus mask, for each condition of memory retrieval (hits, misses and correct rejections). Paired *t*-tests show a trend towards higher beta weights for hits compared to misses ($t(26)=1.83$, $p=0.078$), and no significant difference between hits and correct rejections ($t(26)=1.30$, $p=0.206$) or between misses and correct rejections ($t(26)=0.43$, $p=0.67$).

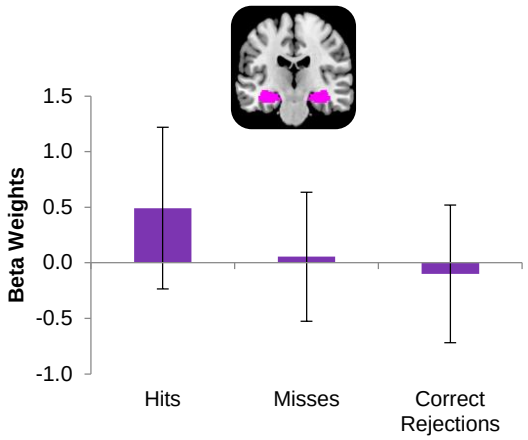


Figure 6.11 Mean beta weights for hits, misses and correct rejections extracted from hippocampus ROI. Displayed with confidence intervals.

Table 6.7 Mean beta weights for hits, misses and correct rejections extracted from hippocampus ROI.

Performance	Mean	SD
Hits	0.49	1.93
Misses	0.05	1.54
Correct rejections	-0.10	1.64

3.4 Age-Related Effects

The results show positive and negative correlations between memory retrieval activations and age. More specifically, age-related changes were observed in the hippocampus and the bilateral medial prefrontal cortex (mPFC). Activation in the right hippocampus increased with age, whereas activation in the mPFC decreased with age (Figure 6.12).

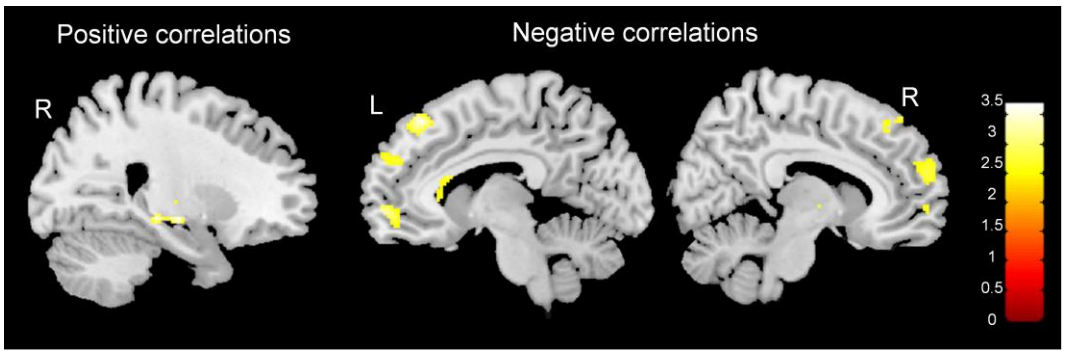


Figure 6.12 Positive and negative correlations between memory retrieval activation and age ($p<0.01$, uncorrected).

3.5 Anterior *versus* Posterior Activations

Beta weights were extracted from anterior and posterior hippocampus ROIs during memory encoding and retrieval and are displayed in Figure 6.13. Paired *t* tests were carried out to compare beta weights in the anterior and posterior hippocampi. For encoding, the values were not significantly different ($t(26)=0.32$, $p=0.750$). For retrieval, the values in the anterior hippocampi were significantly higher than those in the posterior hippocampi ($t(26)=2.20$, $p=0.037$). The paired *t*-tests were repeated in left and right hippocampus separately in case an effect is side-specific and not apparent in the averaged ROI. For encoding, the values in the anterior and posterior hippocampi were not significantly different in either the left ($t(26)=0.702$, $p=0.485$) or right ($t(26)=-0.335$, $p=0.740$) hippocampus. For retrieval, the additional analyses showed that the reported higher values in the anterior compared to the posterior portions was specific to the right hippocampus ($t(26)=2.602$, $p=0.015$). The values were not significantly different in the left hippocampus ($t(26)=1.556$, $p=0.132$).

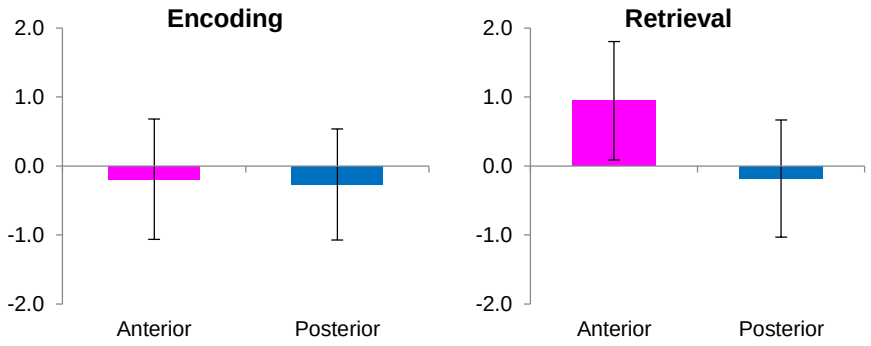


Figure 6.13 Beta weights extracted from anterior and posterior hippocampus ROIs during memory encoding and retrieval.

3.6 Memory Lateralisation

Functional lateralisation was investigated for memory retrieval, for block activations and event-related activations (Figure 6.14). For event-related analyses, there is a large variability in the memory LIs across the anterior and posterior hippocampi. For block analysis (activation irrespective of memory performance) the LI is also widespread in the posterior hippocampus. However, the group-level memory LI in the anterior hippocampus is more left lateralised

(*M*=0.45, *SD*=0.45) than in the posterior hippocampus (*M*=0.26, *SD*=0.51). In fact, the majority of participants show left lateralisation (N=22), and the others show either right lateralisation (N=3) or bilateral representation (N=2).

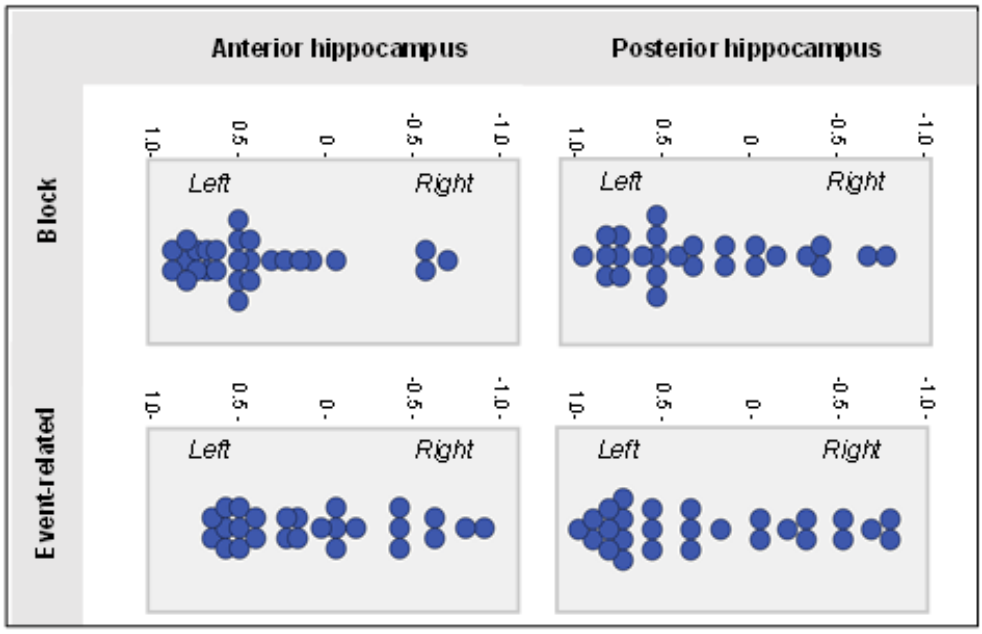


Figure 6.14 Memory retrieval LIs in the anterior and posterior hippocampi, for block and event-related analyses.

3.7 Relationship between Language and Memory Lateralisation

As illustrated in Figure 6.15, language was left lateralised in all participants (N=27, *M*=0.80, *SD*=0.18). Memory was less strongly left lateralised and more variable across individuals (*M*=0.31, *SD*=0.50). Whereas every subject showed left lateralisation for language, the distribution proved far more widespread for memory, with a range of LIs in participants (N left=17, *M*=0.64, *SD*=0.19, N right=5, *M*=-0.53, *SD*=0.16, N bilateral=5, *M*=0.01, *SD*=0.16).

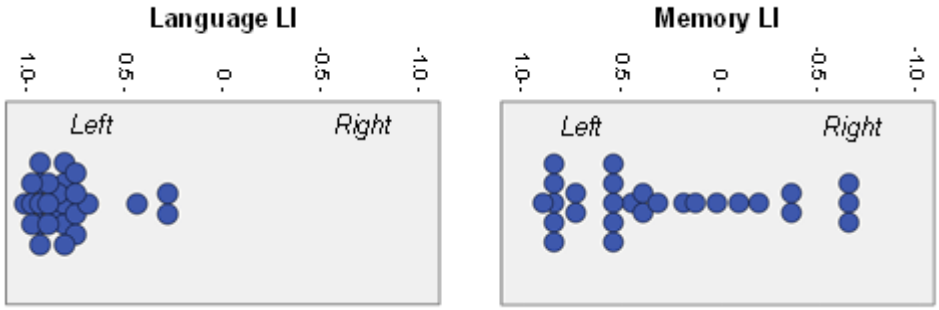


Figure 6.15 Distribution of language ("Language>Baseline") and memory ("Memory>Baseline") lateralisation across individuals.

Language and memory LIs were not significantly correlated (r=0.13, p=0.458). Correlations were also investigated with memory LIs in the different portions of the hippocampus but the results indicate no significant correlation between language LI and memory LI in the anterior hippocampus (r=0.06, p=0.760) or the posterior hippocampus (r=0.18, p=0.329). In addition, language and memory LI values were not significantly related to age, FSIQ, VIQ, or handedness (Table 6.8).

Table 6.8 Correlations between language and memory LIs and demographic variables.

	Demographic variables	Statistics
Language LI	Age	r=-0.18 p=0.363
	FSIQ	r=0.25 p=0.210
	VIQ	r=0.22 p=0.268
	Handedness	r=0.11 p=0.602
Memory LI	Age	r=-0.50 p=0.401
	FSIQ	r=0.23 p=0.245
	VIQ	r=0.34 p=0.079
	Handedness	r=0.08 p=0.691

As illustrated in Figure 6.16, for language, LIs in Broca's area and in the hippocampus were significantly and positively correlated (r=0.39, p=0.037).

However, language LI in the Broca's area was not correlated with memory LI in the hippocampus (r=-0.01, p=0.942).

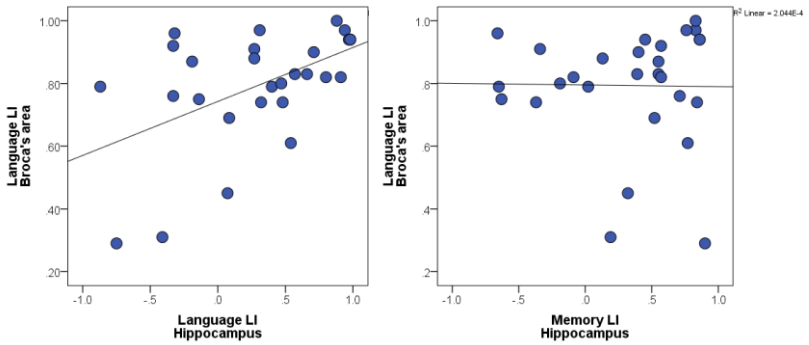


Figure 6.16 Correlations between language LI in Broca's area and memory LIs in the hippocampus.

3.8 Summary of Findings

This chapter had several aims regarding the mapping of language and memory networks in typically-developing children and adolescents. Table 6.9 provides a summary of the findings corresponding to each aim.

Table 6.9 Summary of aims and the findings

Aims		Findings
1	Identify the typical network supporting language performance in children and adolescent	Language-related activation was found in regions typically associated with verb generation tasks, namely Broca's area, Wernicke's area, the cingulate gyrus, left insula, left thalamus, left insula and the dorsolateral prefrontal cortex.
2	Define the core network supporting verbal memory encoding and memory retrieval	For memory encoding, hippocampal activation was shown, irrespective of subsequent performance. Successful memory encoding was associated with activity in the left temporal pole and right posterior superior temporal lobe. For memory retrieval, activations were found in left Broca's area, left dorsolateral PFC, bilateral cerebellum, bilateral posterior temporal lobes, bilateral anterior insula, bilateral pre-SMA, bilateral PCC & MCC, and bilateral caudate. Successful memory retrieval was associated with activity in bilateral hippocampi, left posterior superior temporal gyrus and left caudate.
3	Characterise the relationship between language and memory lateralisation	Language was left lateralised in all participants (M=0.80, SD=0.18). Memory was less strongly left lateralised and more variable across individuals (M=0.31, SD=0.50). Language and memory LIs were not significantly correlated (r=0.13, p=0.458).
4	Define age-related activity-dependent changes in the memory network	Activation in the right hippocampus increased with age, whereas activation in the mPFC decreased with age.

4 Discussion

This study investigated language and memory networks in children and had four primary aims: 1) identify the language network, 2) define the verbal memory network (encoding and retrieval), 3) characterise the relationship between

language and memory lateralisation, and 4) define age-related changes in the memory network. Figure 6.17 provides an illustration of activations and deactivations for memory encoding and retrieval.

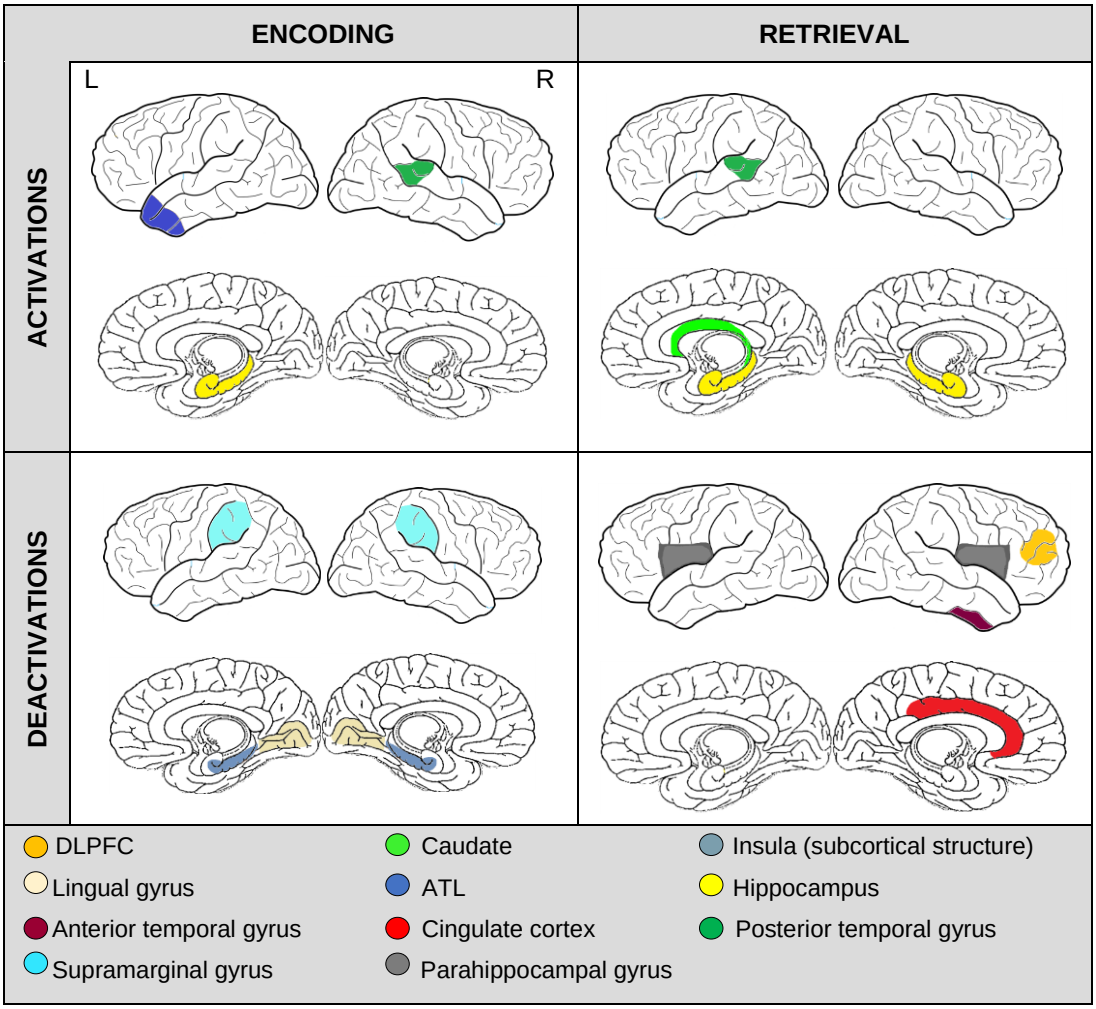


Figure 6.17 Illustration of activations and deactivations for memory encoding and retrieval.

4.1 Validating the Language Task

Language-related activation was found in regions typically associated with verb generation tasks, namely Broca's area, Wernicke's area, the cingulate gyrus, left insula, left thalamus and the dorsolateral prefrontal cortex (Holland et al., 2001). Activation in the left insula has previously been reported during verb generation (Rau et al., 2007), and is thought to mediate motor aspects of speech production

(Cereda et al., 2002; Oh et al., 2014; Van Turennout et al., 2003). The left insula may thus reflect overt speech in the present protocol. Moreover, the thalamus, sometimes shown in memory fMRI studies (Guler & Thomas, 2013), is involved in the manipulation of lexical information (see (Llano, 2013), for a review). Overall, the present study identifies language-related activation in regions previously documented as being associated with language tasks, and thereby replicates previous findings and validates the experimental language task.

4.2 Hippocampal Activation during Encoding, Irrespective of Retrieval Success

During memory encoding (*i.e.* the language block), activity was found in the left posterior hippocampus. Hippocampal activation has not previously been reported during verb generations tasks, and activation could instead reflect encoding of the words for subsequent retrieval. The participants were aware of the following memory task, and may have engaged strategies to encode the words. As such, hippocampal activation during the language task in the present study may be related to the encoding of words into memory storage.

However, whereas hippocampal activation was found during word encoding, activation did not predict memory retrieval. The beta weights extracted from the hippocampus ROI showed similar levels of activation for subsequent hits and misses. This indicates that the hippocampus was activated irrespective of whether the words were later remembered or forgotten. This finding replicates that observed in Sidhu and colleagues' study (2013) whereby left hippocampal activation was shown in healthy adults during word encoding, irrespective of later retrieval (as shown in block analysis). In the paediatric literature, there are mixed findings. Two studies found hippocampal activation during encoding which was predictive of later retrieval (Maril et al., 2010; Ofen et al., 2007). On the other hand, similarly to the present findings, Guler and Thomas (2013) did not find hippocampal activation that predicted recall, although they did not report whether activation was found with block analysis. Ghetti and colleagues (2010) found different patterns of activation in different age groups. Adults and 14 year olds activated the MTL during successful encoding, whereas encoding-related MTL activation did not predict subsequent retrieval in 10 year olds, suggesting

developmental changes in functional specialisation of the MTL. Overall, these studies demonstrate a clear role in the hippocampus for memory encoding in children. However, as with the present findings, it is unclear whether activation at encoding predicts later retrieval, and studies report mixed findings.

Differences in memory protocols may explain mixed findings across studies with regards to hippocampal activation during encoding. First, event-related analysis of successful encoding is dependent on the retrieval task, and the documented activation may therefore differ across studies depending on the paradigm. The above mentioned studies which documented hippocampal activation that was predictive of retrieval used a recognition task. On the other hand, the present study along with Thomas and Guler's study assessed retrieval with a recall task and did not find subsequent memory effects in the hippocampus. These findings suggest that subsequent memory effects in the hippocampus may differ between recognition and recall in children.

Second, the strategy at encoding may have an impact on hippocampal activation (Heckers et al., 2002). In Maril and colleagues' study, the encoding was phonological and incidental. Children were instructed to generate a new word from two presented words by replacing the first phoneme of the second word with the first phoneme of the first word (*e.g.* generate "pool" from "pen" and "tool"). In Ofen and colleagues' study, children were asked to make an indoor/outdoor decision to visually presented scenes. In the present study, however, the instruction encouraged binding of information through the generation of verbs that are semantically related to the nouns being presented. Similarly, Guler and Thomas' study involved paired-associate learning, encouring the binding of items into a holistic representation. This binding is known to be associated with hippocampal activation (Habib & Nyberg, 2008; Meltzer & Constable, 2005), and may be less involved in studies that instruct phonological processing or indoor/outdoor decision. Becker and colleagues (2017) directly compared incidental *versus* intentional encoding for subsequent retrieval and showed greater hippcampal activation for the latter compared to the former. The authors postulate that the intent to remember triggers the binding process supported by the hippocampus (Becker et al., 2017). It is therefore possible that whereas hippocampal activation is associated with subsequent recognition effects (Maril et al., 2010; Ofen et al., 2007), it is also associated with binding of information

irrespective of subsequent retrieval, as shown in the present study. Another interpretation for hippocampal activation observed in block but not event-related analyses resides in the large interindividual variability in hippocampal activation, which will be discussed below (section 4.4, page 206).

4.3 Anterior Hippocampus supports Memory Retrieval

4.3.1 Functional Segregation of the Hippocampus

Bilateral activation in the hippocampus was shown during successful retrieval of words (as shown in event-related analyses). Hippocampal activation is associated with the binding of information (Habib & Nyberg, 2008; Meltzer & Constable, 2005); as such, the word stem cues presented at retrieval may have triggered the retrieval of features that were bound together into a holistic representation at encoding, thereby rendering them dependent on hippocampal activation. More specifically, the anterior hippocampus appears to have a bigger role in memory retrieval than the posterior hippocampus. Functional segregation of the hippocampus was investigated in the present study by extracting beta weights in the anterior and posterior hippocampi. The findings showed higher beta weights in the anterior hippocampus compared to the posterior hippocampus for successful retrieval, providing evidence of functional segregation of the hippocampus.

The anterior-posterior functional segregation in the MTL has previously been documented in adults. The HIPER model described by Lepage and colleagues in 1998 postulated the role of anterior and posterior hippocampus in encoding and retrieval, respectively (Lepage et al., 1998). However, this functional segregation is not consistently reported. For example, Heckers and colleagues showed anterior hippocampal activation during successful retrieval (Heckers et al., 2002). Similarly, Greicius and colleagues showed anterior and posterior hippocampal activation during both encoding and retrieval (Greicius et al., 2003).

Although the posterior hippocampus may play a role in episodic memory in adults, there is evidence to suggest the role of anterior hippocampus in children. Moreover, the distinguishing feature of the anterior *versus* posterior hippocampus in humans is cognitive memory *versus* visuo-spatial navigation. The posterior

hippocampus subserves visuospatial navigation (Maguire et al., 2011), whereas the anterior hippocampus subserves cognitive memory, including episodic memory. Gogtay and colleagues (2016) documented structural changes in the anterior hippocampal region, with decrease in volume between the ages of 4 and 25 years. Although the significance of this structural development is not fully understood, it could reflect synaptic pruning (Johnson et al., 1996) and enhanced selectivity of this region to support cognitive memory (Ghetti & Bunge, 2013). In addition, Riggins and colleagues (2015 and 2016) showed significant correlation between anterior hippocampal volume and episodic memory in young children (Riggins et al., 2015; Riggins et al., 2016). Consistent with the present findings, several fMRI studies have shown evidence of the role of the anterior hippocampus in episodic memory development (Ghetti et al., 2010; Maril et al., 2010; Paz-Alonso et al., 2008). Whereas these previous studies documented anterior hippocampal activation during encoding (Ghetti et al., 2010; Maril et al., 2010) and recognition (Paz-Alonso et al., 2008), the present study extends the findings to recall memory. Overall, these studies along with the present findings show evidence of specialisation along the longitudinal axis of the hippocampus in children, with a clear role of the anterior region in cognitive memory.

The reason for differences in functional segregation of the hippocampus between children and adults is not fully understood. For an explanation, it would be pertinent to examine the trajectory of development of cognitive memory *versus* visuo-spatial memory in children *versus* adults. Anterior hippocampal activation in children could mirror structural development in subregions of the hippocampus (Gogtay et al., 2006) and, in this respect, reflect developmental changes. Alternatively, methodological considerations may have hindered the ability to observe activation in the anterior hippocampus in previous studies. Magnetic susceptibility is particularly prominent in the anterior hippocampus (Olman et al., 2009) reducing the possibility of capturing activation in that brain region. Prior studies that did not attempt to reduce signal loss in the anterior hippocampus (*e.g.* by applying a slice tilt, as in the present study) may have resulted in misconceptualised functional segregation of the hippocampus, providing more functional importance to the posterior portion. These interpretations warrant further investigation with, for example, more longitudinal studies examining hippocampal activation in a large age range that includes both children and adults, with methodological consistency across children and adults.

4.3.2 Left Lateralisation in the Anterior Hippocampus

Additional evidence supporting the role of the anterior hippocampus in memory retrieval resides in lateralisation indices. Investigation of memory LIs showed varied lateralisation across individuals in the posterior hippocampus, but left lateralisation in the anterior hippocampus during retrieval, irrespective of performance (as shown in block-analyses). Memory-related activation in the anterior hippocampus was robustly left lateralised in the control sample, providing additional evidence that the anterior hippocampus has a specific role in memory retrieval. This has important clinical implications, because it indicates that block-analysis can be used as a good marker for TLE by characterising changes in the lateralisation pattern of memory. Whereas typically-developing children show left lateralisation of memory in the anterior hippocampus during memory retrieval, irrespective of performance, children with TLE may show different lateralisation patterns as a result of brain injury and/or functional reorganisation. This lateralisation pattern may provide clinically useful information for the prediction of memory outcome after surgery.

4.4 Individual Differences in Memory Lateralisation

The present findings showed large variability in memory lateralisation across individuals, particularly for activation reflecting successful memory (as shown in event-related analyses). Interindividual variability in language lateralisation has been previously documented (see Josse & Tzourio-Mazoyer, 2004 for a review) and is influenced by factors such as manual preference, whereby right-handedness is associated with left hemispheric specialisation for language (Satz, 1979; Rasmussen & Milner, 1977). With regards to memory, the adult literature reports interindividual variability in the quantity and quality of memory, and in the mnemonic strategies employed (Jones et al., 2006; Kanai & Rees, 2011; Nyberg et al., 2003). Although individual differences in mnemonic performance have been documented, there are limited studies reporting individual differences in the neural substrates supporting memory in children (although see Prabhakar et al., 2018).

4.4.1 Developmental Changes

The interindividual variability in memory lateralisation can be related to several factors, such as developmental changes and/or differences in mnemonic strategies employed. The variability in lateralisation could reflect developmental changes in the lateralisation of the MTL, with stronger left lateralisation arising in older adolescents. There may be high inter-individual variability in memory representations before lateralisation is established. In typically-developing children, language lateralisation changes with age paralleling the development of language skills (Holland et al., 2007) and is emergent by the age of 5 (Hodgson et al., 2016; Weiss-Croft & Baldeweg, 2015). Similarly to language function, it is possible that the lateralisation of memory changes with age and parallels the development of mnemonic skills. In addition, several studies converge on the observation that the right hippocampus is functional earlier than the left hippocampus (Prabhakar et al., 2018; Thompson et al., 2009; Uematsu et al., 2012), which may be associated with age-related changes in hippocampal laterality. One could therefore assume that memory is initially associated with bilateral or right-sided hippocampal activation, with increasing left lateralisation with age concomitant with language learning, literacy skills and social interactions.

This interpretation could provide insight into the pattern of lateralised impairments shown in TLE, whereby less lateralised MTL function in children could explain why memory deficits are less clearly lateralised in paediatric compared to adult patients. However, the present findings do not suggest a developmental trajectory in memory lateralisation, and such functional development was not captured possibly due to the older age of participants (8 to 18). Similar to language, it is possible that memory lateralises early in life, before the age of 8. The present data are, however, not sufficiently powered to look at trajectories as a function of age groups' maturing specialised functions. Administering the memory paradigm in younger children (between 5 to 8 years old) could shed light on the developmental trajectory of memory lateralisation.

As an alternative and contradicting interpretation, several authors have postulated that adults show *higher* brain variability compared to children which reflects greater neural complexity and a higher cognitive ability such as cognitive flexibility (Hutchison & Morton, 2016; McIntosh et al., 2008). Similarily, Marusak

and colleagues (2017) demonstrated age-related increases in the variability of functional connectivity in children aged between 7 and 16 years old (Marusak et al., 2017). The present study did not elucidate developmental changes in inter-individual variability of brain activation. Whether increasing age is associated with *more* or *less* variability in memory-related brain activation remains unknown and more research is needed to characterise how functional representations of memory change over the course of development.

4.4.2 Visual Imagery

Alternatively, the reported varied memory lateralisation could reflect distinct mnemonic strategies employed. D'Argembeau and colleagues (2006) showed that mnemonic strategies influence the pattern of brain activation and contribute to interindividual differences in neural representation. Visual imagery is a common form of mnemonic strategy (Belardinelli et al., 2009; Bogousslavsky et al., 1987) and is supported by the right hippocampus (Ishai et al., 2002; Ghaem et al., 1997; Mellet et al., 2000). In the present study, right hippocampal activation was found in participants who may have explicitly applied imagery strategies to memorise the words.

Paivio described the Dual-Coding theory which postulated the superiority of high-imageability words in memory (Paivio, 1991). According to this theory, participants can memorise high-imageability words with two codes, the verbal and the visual codes. The latter consist in forming an image of the word to study. For low-imageability words, however, the verbal codes are most likely to be used. Consistent with this hypothesis, preventing visual imagery processing at retrieval reduces the ability to remember concrete but not abstract words from a studied list (Parker & Dagnall, 2009). These findings indicate that high-imageability words, as employed in the present study, may be processed via verbal and/or visual codes.

There is evidence to suggest that visual imagery of words may be processed by the right hippocampus. The Dual-Coding theory may show lateralisation effects in brain activation, whereby low-imageability words, amenable to verbal mediation, are left lateralised, whereas high-imageability words which can be processed via both codes show more bilateral representation. Patients with right-hippocampal damage reportedly show visual memory impairment, but verbal memory deficits

are sometimes documented as well (*e.g.* Engle & Smith, 2010), possibly as a result of impaired visual imagery of verbal information. In addition, lesion studies have documented hemispheric lateralisation of imageability whereby patients with right temporal lobe damage were impaired on memory for high- but not low-imageability words (Jones-Gotman & Milner, 1978; Villardita et al., 1988). However, neuroimaging studies have not been very conclusive regarding the lateralisation effect and do not always support the assumption that the right hemisphere is involved during the processing of high-imageability words (Fiebach & Friederici, 2004; Klaver et al., 2005; Scott, 2004). These imaging studies have not controlled for the participants' mnemonic strategies (verbal mediation *versus* visual imagery), however, and these could possibly affect lateralisation above and beyond word property (low- *versus* high imageability). Despite not being directly investigated in the present study, right-hippocampal activation during memory for words may provide neural evidence of lateralisation effects of mnemonic strategies for high-imageability words. Further research into the effect of visual imagery on memory lateralisation is needed to confirm this speculation.

Overall, the present set of results leads to the following formulation: whereas the left anterior hippocampus is consistently activated across individuals during memory retrieval irrespective of performance, inter-individual differences occur for activation that is specific to remembered words possibly as a result of differences in mnemonic strategies. Although the reason for right-sided hippocampal activation during verbal memory is not discernable from the present data, the assumption is that visual strategies may be used to support verbal memory.

4.4.3 Interpreting Interindividual Variability

With high variability in the pattern of brain activation, the question arises as to how a participant's memory activation can be interpreted. Multivariate Pattern Analysis (MVPA) can be carried out on fMRI data to examine the distributed pattern of activation across voxels at the individual-subject level. MVPA exploits voxel-level variability within subjects and neutralises the effects of subject variability, and is therefore more sensitive to neural differences at the individual level than univariate analyses. Morcom and Henson (2017) used MVPA to study memory representation in healthy older adults. Whereas prefrontal activation

during memory was previously documented in healthy aging, Morcom and Henson were able to demonstrate that this activation was not compensatory and therefore non-specific in that it did not carry information about memory outcomes. The authors postulated that brain activation in the prefrontal cortex becomes less specific with age (Morcom & Henson, 2018). Similarly to adults, MVPA could be applied to healthy children to examine the functional role of each hippocampus to sustain memory, and, whether the left and/or the right hippocampus contains differential mnemonic traces. The finding from Morcom and Henson's study, along with the large variability in hippocampal activation found in the present study, suggest that there may not be a single typical memory network, and instead, different regions support memory in different ways across the early age spectrum, and indeed across the lifespan.

To understand the pattern of activation in children with epilepsy, it is important to compare the pattern of activation typically observed in children at the same age. However, the large variance in memory representation in the typical population may suggest that it is not clinically feasible to compare a single TLE patient against a common average. In addition, because memory representations are so varied in children, it is especially important to better understand whether the network of memory representations is focal or more diffuse, and consider the implications on other aspects of cognition, before decisions are made for surgical resection of temporal lobe structures.

4.4.4 Relationship between Language and Memory Lateralisation

With the present paradigm, it was possible to investigate the interaction of hemispheric lateralisation for language and memory functions. The findings showed that whereas every participant was strongly left lateralised for language, there was high inter-individual variability in lateralisation for memory. In addition, correlation analyses indicated that language and memory LIs were not related. These findings demonstrate that memory-related hippocampal lateralisation does not parallel language-related Broca's lateralisation in children.

The lack of co-lateralisation of cognitive functions in typically-developing children is in line with the study from Sepeta et al. (2016) which documented a lack of co-lateralisation in Broca's area and the MTL during a language task. In that study, in contrast to evidence of co-lateralisation in adults, in children there was left

lateralisation in Broca's area, but bilateral activation in the MTL within the same task. The present study expands this finding by demonstrating a lack of co-lateralisation between language and verbal memory functions.

Whereas a relationship between language and verbal memory lateralisation is documented in the adult literature, the present finding does not show such a relationship in children and adolescents. The findings might therefore suggest a developmental shift in the relationship between memory and language lateralisation. However, hippocampal lateralisation was not related to age in the present study, which is inconsistent with previous findings that showed increasing left lateralisation in the MTL (Sepeta et al., 2016). However, differences between the studies might explain distinct findings. First, in their study, MTL lateralisation was examined during a language task, whereas in the present study hippocampal lateralisation was examined during a memory task. Second, the cohort was younger (6-13 years old) than in the present study (8-18 years old), and this difference might indicate that developmental changes occur before the age of 8. To explore this further, age-related changes in memory-related MTL lateralisation should be further explored in children below the age of 8 years, particularly if different aspects of cognitive memory emerge at different stages of development.

Characterising memory networks and the relationship with language lateralisation provides a baseline against which the network in children with epilepsy can be compared. The present findings showed that language and memory networks are not co-lateralised in typically-developing children, underlining the importance of examining both networks in the patient population for the prediction of cognitive outcome.

4.5 Age-Related Effects

4.5.1 Core Recollection Network is Stable across the Lifespan

Despite the individual differences in memory activation, there is a "core recollection network" that showed consistent memory activation in the present study and appears to be stable across childhood and adolescence. This recollection network comprises the left hippocampus, left temporal lobe and left

caudate. Similarly, the adult literature described the core recollection network comprising the hippocampus, parahippocampal, posterior cingulate cortex, left angular gyrus and mPFC which is stable across the adult lifespan (de Chastelaine et al., 2016). Together, these findings document brain activation related to memory retrieval which is stable across childhood and adulthood, particularly in the left hippocampus.

Age-related effects were however found in two brain regions in the present study, whereby activation in the right hippocampus increases and activation in the mPFC decreases with age. In adults, these brain regions do not show age-related effects, but instead the magnitude of hippocampal and prefrontal activation is associated with memory performance (de Chastelaine et al., 2016). Both the MTL and PFC have consistently been described has playing a critical role in episodic memory in adults (Blumenfeld & Ranganath, 2007; Staresina & Davachi, 2006) and children (Ghetti et al., 2010; Guler & Thomas, 2013; Ofen et al., 2007; Maril et al., 2010). Both of these regions undergo structural changes throughout childhood and adolescence. Hippocampal volume increases with age (Durston et al., 2001), and this is particularly documented in the posterior hippocampus (Gogtay et al., 2006) which continues to grow until adolescence (Insausti et al., 2010). The anterior hippocampus on the other hand decreases in volume with age (Gogtay et al., 2006), possibly as a result of pruning. Similarly, the prefrontal cortex undergoes protracted development until late adolescence (Casey et al., 2000). Functional development of these regions is however less clear.

4.5.2 Increase in Right Hippocampal Activation

Functional development of the hippocampus might parallel the structural maturation documented across childhood. Age-related effects in the hippocampus were previously documented by Ghetti et al. (2010). Their study examined age-related differences in hippocampal activation during encoding of arbitrary associations between objects and colours in four groups of participants (8-year-olds, 10–11-year-olds, 14-year-olds, and young adults). The authors documented increased functional selectivity in the hippocampus whereby younger children recruit the hippocampus for item recognition (*i.e*. objects), but from the age of 14 years old, the hippocampus is selectively activated during the

retrieval of previously learnt associations (*i.e.* objects-colours). Their findings, along with the current finding, converge toward the interpretation that increases in hippocampal activation with age may reflect increased recruitment of binding strategies for memory (Davachi, 2006; Konkel & Cohen, 2009; Moscovitch, 2008).

However, other studies showed different age-related effects in the hippocampus. Maril et al. (2010) examined hippocampal activation with a word encoding task in participants aged between 7 and 19 years and showed decreases in hippocampal activation as age increased. As mentioned above, in their study, words were phonological and incidentally encoded, and retrieval was tested with a surprise recognition task. This study therefore tested item recognition and did not involve the binding of information, contrary to Ghetti and colleagues' study and to the present study where semantic association at encoding was likely to have occurred. Ofen et al. (2007) studied participants aged between 8 and 24 years and found strong hippocampal activation during global scene encoding, but did not find age-related effects in the hippocampus. Methodological differences across studies may explain the mixed findings observed.

It is possible that age-related increases in hippocampal activation are less likely to be observed in tasks that involve global (Ofen et al.) or phonological (Maril et al.) processing of information rather than associative integration of information (Maril et al, and the present study). In addition, previous studies assessed retrieval with recognition tasks whereas the present study employed a recall task. Recall-based memory is more effortful and shows a more protracted development than recognition memory (Perlmutter & Lange, 1978). It is therefore possible that hippocampal activation shows distinct age-related effects for recognition and recall. Hippocampal activation related to recognition may *decrease* with age as a result of increased functional selectivity in the hippocampus whereby this structure becomes more specialised for the retrieval of associations rather than item recognition which is likely to be cortically mediated (*e.g.* Barker et al., 2007). On the other hand, activation related to recall may *increase* with age through the elaboration of binding and mnemonic strategies.

More specifically, in the current study, age-related increases were particularly observed in the right hippocampus. Whereas the left hippocampus is recruited

across childhood and adolescence, the role of the right hippocampus may arise as children get older. As discussed above, we postulated that visual imagery may play a role in remembering words, and may be associated with right hippocampal activation. It is possible that such a mnemonic strategy is particularly developed in older children who may then process words via both codes (verbal mediation and visual imagery). On the other hand, younger children might rely solely on verbal mediation dependent on the left hippocampus. The present study therefore documents age-related changes in hippocampal activation, specific to the right side, which may reflect increases in visual imagery with age. In addition, whereas developmental changes have been demonstrated for encoding-related activation, the present study demonstrates age differences in retrieval-related hippocampal activation.

4.5.3 Decrease in mPFC Activation

The specific roles of subregions within the PFC are still under investigation, but it is assumed that the lateral PFC guides cognitive control processes at encoding and contributes to the elaboration of mnemonic strategies at retrieval (Badre & Wagner, 2007; Blumenfeld & Ranganath, 2007) which are known to develop with age (Durston et al., 2001). On the other hand, the medial PFC contributes to one's own cognitive or affective state (Dobbins & Han, 2006; Simons et al., 2005).

Previous studies have demonstrated increase in lateral PFC activation with age. Several studies have demonstrated increase in activation during memory encoding, which was also associated with increased memory performance (Ghetti et al., 2010; Ofen et al., 2007; Wendelken et al., 2011). Similalry, increase in lateral PFC activation with age was also shown during memory retrieval (Guler et al., 2013; Paz-Alonso et al., 2008). Together, these findings converge on the idea that functional development of the lateral PFC contributes to age-related improvement in memory, possibly through the elaboration of strategic processes.

The present study, however, showed decrease in bilateral mPFC activation with increasing age. Age-related effects in the mPFC are seldom documented, but Guler et al. showed the opposite effect with activation increase in older children, which they attributed to increased metamemory abilities. Instead, age-related decrease in mPFC activation shown in the present study may be attributable to

other factors. The mPFC has a role in the representation of emotions (Ochsner & Gross, 2014) and developmental studies have shown age-related changes in the contribution of mPFC to aversive stimuli across childhood and adolescence (Cohen et al., 2016; McRae et al., 2012; Silvers et al., 2017). It is possible that older children show decreased mPFC activation during the retrieval of neutral words for which an emotional response is not necessary, whereas older children show mPFC activation for both neutral and aversive stimuli. Cassidy et al. (2014) showed age-related differences in mPFC activation in adults, where older adults showed increased activation during encoding compared to young adults. The authors attributed this effect to increased focus on the emotional aspect of the material in older adults. Similarly, age-related decrease in mPFC activation shown in the present study may reflect reduced focus on emotional aspects of information during word retrieval. However, this interpretation remains weak considering the studied list did not contain emotional words.

Another interpretation relates to the self-referential role of episodic memory, which relies on the mPFC (Denny et al., 2012; Martinelli et al., 2013; Northoff & Bermpohl, 2004). Self-referential processing at encoding consists of linking the items to be learned with personal information or knowledge, for example retrieving an autobiographical memory related to a word presented. Self-referential processing enhances memory retrieval (Serbun et al., 2011) and its influence on memory is shown across the adult lifespan (Kalenzaga et al., 2015). In children, self-referential processing at encoding also enhances memory retrieval (Cunningham et al., 2014; Sui & Zhu, 2010) but it is unclear whether this strategy is applied spontaneously and if so, whether there are developmental changes in its spontaneous usage. Children's memories are more self-referential than memories in adolescents, and have more references to children's cognitive and affective state (Fivush & Zaman, 2014). In this respect, whereas in younger children, word retrieval might spontaneously trigger self-reference context associated with the words learned at encoding, older children might show reduced self-referencing. In other words, decreased mPFC activation with age might reflect a decrease in the contribution of self-related processes during memory and an objective retrieval of words.

These interpretations remain speculative at this point, and warrant further investigation. However, age-related functional changes may indicate more

selective recruitment of the PFC and reflect a shift from diffuse to focal activation with age (Durston et al., 2006). Younger children show activation throughout the lateral and medial PFC, but older children show more focal activation with activation in the DLPFC only.

4.6 Additional Clinical Implications for Paediatric TLE

Identifying a typical network of memory encoding and retrieval offers a baseline against which comparisons to the network in patients with TLE (who are candidates for surgery) can be made. The present study demonstrates deactivation of the primary hub of the Default Mode Network (DMN). Encoding-related deactivation was found in the parahippocampal gyri bilaterally and retrieval-related deactivation was found in the PFC and the right inferior temporal cortex. These regions are part of the DMN (Ward et al., 2014; Uddin et al., 2013), and it is thought that the suppression of the DMN is functionally important for goal-directed cognition (Anticevic et al., 2012). Task-induced deactivation of the DMN enables allocation of resources for successful encoding of information, and is associated with memory formation (Chai et al., 2014). For example, deactivation of the PFC is associated with successful retrieval in healthy adults (*e.g.* Balardin et al., 2015; Otten & Rugg, 2001) and children (Guler & Thomas, 2013). Identifying the pattern of deactivation related to successful memory is critical as it suggests the ability to deactivate specific brain regions for successful encoding and retrieval of information.

Failure to deactivate regions that form the DMN may be associated with poor memory performance (Anticevic & al., 2010). It has been shown that epileptic discharges affect the DMN (Fahoum et al., 2013) and, more specifically, TLE with HS is associated with decreased functional connectivity within the DMN (Liao et al., 2011). Such abnormalities in DMN may contribute to cognitive deficits in children with epilepsy (Wang et al., 2017). Compared to healthy controls, patients with TLE have different patterns of activation and/or deactivation and this has been documented both in adult TLE (Stretton et al., 2012), and paediatric TLE (Mankinen et al., 2015). The absence of deactivation in specific regions may serve as a possible predictor of post-operative memory impairment. These patterns may be associated with their memory impairments, providing predictions of memory outcome after surgery. This novel fMRI protocol is therefore able to

define activation and deactivation related to memory in typically-developing children and can be applied in clinical settings to guide surgical decision-making.

5 Limitations

Overt responses were used in the present paradigm in order to monitor performance and conduct event-related analyses. Whereas this has advantages in terms of identifying neural correlates that are specific to successful memory, it may come at the cost of speech-related artefacts. However, pre-processing steps were implemented (*e.g.* FIACH, see Chapter 5, section 2.7, page 154) in order to reduce these artefacts. In addition, Chapter 5 investigated the impact of such motion related artefact on fMRI signal and did not show significant detrimental effects.

Low statistical thresholds (p<0.01) were used to look for trends that are non-significant, but may be promising indicators for future work. Such low threshold produces large clusters of activation over multiple anatomical regions and runs the risk of leading to false positives (Cremers et al., 2017; Woo et al., 2014). However, whereas the thresholded *t* maps were used to display whole brain activations, statistical analyses were carried out on ROIs independent of an arbitrarily defined thresholds. In view of the *a priori* hypothesis, LI calculations and beta extractions were carried out in the hippocampus, limiting the number of statistical tests (Poldrack, 2007). This study was the first to investigate hippocampal activation related to recall memory in children and remains exploratory. The findings should therefore be interpreted with caution and additional research with bigger sample sizes are now needed to confirm the preliminary findings, possibly using a more stringent statistical threshold.

6 Conclusions

The present study is the first to investigate language and memory networks within one paradigm in children and adolescents. The study demonstrated several interesting findings. First, hippocampal activation was shown during word encoding irrespective of memory retrieval, possibly reflecting the binding of information irrespective of subsequent retrieval. Second, the trends observed in this study may indicate functional segregation of the hippocampus with a role of the anterior region in memory retrieval. Third, there was a large variability in

memory lateralisation across individuals, which may be attributable to distinct mnemonic strategies employed. This finding has particular clinical implication as it indicates that it is critical to examine how a patient represents memory before surgical decision-making for the resection of the temporal lobe. In addition, as a result of this large interindividual variability in memory lateralisation, there was no significant relation with language lateralisation which was strongly left lateralised across individuals. Similarly, this finding holds important clinical relevance by indicating that the neural representation of the two functions should be examined prior to surgery and that memory lateralisation cannot be predicted based on language lateralisation. Finally, despite individual differences in memory activation, the present study demonstrated a core recollection network that appears to be stable across childhood and adolescence. Age-related changes were however shown in some brain regions, namely increases in right hippocampal activation and decreases in mPFC activation with age. Together, these findings provide interesting theoretical implications regarding the development of the memory network and its relation to language lateralisation, as well as clinical implications regarding surgical decision-making in childhood TLE.

7 Future Directions

The clinical utility of the combined language/memory fMRI protocol will be verified by administering the paradigm to children with TLE. The ability of children with cognitive impairments to perform the tasks inside the scanner will be tested, as this has an impact on the possibility to conduct event-related analyses. In addition, the ability of the fMRI protocol to identify eloquent cortex subserving critical functions at the individual level will be verified.

Chapter 7

Pilot of the Language/Memory fMRI in Childhood TLE

In the present chapter, the language/memory fMRI paradigm was piloted in a sample of paediatric patients with TLE who were candidates for surgery. The clinical aim of this protocol is to improve pre-surgical mapping of cognitive functions and improve prognostication of verbal memory outcome after surgery for TLE. In order to test face validity of this paradigm before it can be used clinically, several hypotheses were postulated on the basis of adult fMRI studies and knowledge on the effects of early age at onset of epilepsy, and examined in the present chapter.

1 Introduction

As discussed in Chapter 1 (section 4.5.2, page 22), functional MRI (fMRI) is a useful pre-surgical tool for language and memory mapping to guide surgical decision and predict cognitive outcome in patients with Temporal Lobe Epilepsy (TLE) (Bonelli et al., 2010; Janszky et al., 2005; Sidhu et al., 2015; Rabin et al., 2004). Memory fMRI has been used for surgical decision-making in adult TLE, but not yet for paediatric TLE. As discussed in Chapters 5 and 6, I developed a combined language/memory fMRI protocol which was validated in a sample of typically-developing children aged 8-18 years. The aim of this chapter was to pilot the protocol in a sample of paediatric patients with TLE who are candidates for surgery. Verbal memory is particularly vulnerable in patients with TLE (as opposed to non-verbal memory) (Baxendale et al., 2007; Gleissner et al., 2002; Helmstaedter & Elger, 1993; Khalil et al., 2016; Mueller et al., 2012), although see Chapter 4 for a discussion. In addition, one of the aims of the protocol is to characterise co-lateralisation of language and memory functions. For these reasons, verbal memory will be the focus of the present chapter.

1.1 Mapping of Memory Functions in Adult TLE

1.1.1 Contralateral Reorganisation

Numerous studies have shown evidence of functional compensation in the context of unilateral brain pathology, leading to bilateral representations of cognitive functions. Functional correlates of verbal memory are often bilaterally activated in TLE (Towgood et al., 2015). Patients with right TLE have more bilateral representations of language and memory functions than left TLE and healthy controls (Sidhu et al., 2015; Sidhu et al., 2016), although patients with left TLE can show bilateral activation (Koylu et al., 2006; Milian et al., 2015; Sidhu et al., 2015). Bilateral activations documented in these studies indicate that functional representations are less lateralised in patients with TLE.

Similarly to contralateral reorganisation of language (Hamberger & Cole, 2011), inter-hemispheric reorganisation of memory can occur in TLE with activations in homologous regions in the right hemisphere (Powell et al., 2007). Patients with

left TLE often show greater right hippocampal activation compared to the left, for verbal memory (Jokeit et al., 2001; Richardson et al., 2003; Golby et al., 2002; Powell et al., 2007). Strandberg and colleagues investigated verbal memory activations in left and right TLE patients and demonstrated a greater proportion of right-sided Medial Temporal Lobe (MTL) activation for verbal memory in patients with left TLE (N=6/8) compared to right TLE (N=2/6) (Strandberg et al., 2017). This difference in the laterality of memory impairments suggests functional reorganisation of verbal memory to the right hemisphere in left TLE cases.

Contralesional lateralisation of memory can indicate functional reorganisation (Richardson et al., 2003) or simply reduced activation ipsilateral to the seizure onset (Detre et al., 1998; Golby et al., 2001; Janszky et al., 2005). Nonetheless, localising and lateralising critical cognitive functions before surgical intervention can spare essential brain regions and limit detrimental effects on language and memory functions.

1.1.2 Ipsilateral Reorganisation

In addition to contralateral reorganisation of memory, ipsilateral reorganisation is observed in adult patients with left TLE (Bonelli et al., 2013; Sidhu et al., 2015; Sidhu et al., 2016). A shift of activation to posterior portions of the hippocampus is associated with early onset of seizures (Sidhu et al., 2015), and may therefore be commonly observed in paediatric patients. Such ipsilateral reorganisation of memory is protective of memory impairment after anterior temporal lobe resection, more so than contralateral reorganisation (Sidhu et al., 2015). These findings indicate that distinct patterns of functional reorganisation may occur in the context of TLE and that ipsilateral reorganisation may be more benefitial for the preservation of functions than contralateral reorganisation.

1.1.3 Co-Lateralisation of Language and Memory

As discussed in Chapter 6, co-lateralisation of language and verbal memory functions is often documented in healthy adults reflecting lateralisation of verbal functions to the left hemisphere (*e.g* Weber et al., 2007). Numerous studies have demonstrated hemispheric specialisation for language processing in healthy adults, with language lateralising to the left hemisphere (Josse & Tzourio-Mazoyer, 2004; Knecht, 2000; Springer et al., 1999). Similarly, material-specificity

in the medial temporal lobe (MTL) is documented for memory processing, with verbal and visual memory surbserved by the left and right MTL, respectively (Golby et al., 2001; Kelley, 1998; Shallice, 1994). Despite high occurrence of concordance between language and verbal memory lateralisation in healthy adults, discrepancies are sometimes documented. For example, an MEG study demonstrated co-lateralisation of language and verbal memory in 6 of the 10 controls (60%) (Pirmoradi et al., 2016), with the remaining showing atypical (bilateral or right) lateralisation of language. These findings indicate a clear relationship between language dominance and material-specific lateralisation in the MTL in healthy adults, although discrepancies are sometimes shown.

In adult TLE, whereas reorganisation of language and verbal memory often occurs jointly, discrepancy of lateralisation is sometimes shown, with only one function reorganising. Strandberg and colleagues (2017) documented a considerable proportion (N=5/8) of left TLE patients who showed left lateralisation of language in Broca's area but right lateralisation of verbal memory in the MTL. Golby and colleagues documented language and memory lateralisation in adult patients with TLE, with 7 out of 9 patients showing discrepancy of lateralisation (Golby et al., 2002). Similarly, Pirmoradi et al. (2016) demonstrated co-lateralisation of language and verbal memory in only 5 out of 13 adult TLE patients (38%). Interestingly, there is evidence to suggest that the relation between language and memory lateralisation may depend on the underlying pathology. Kovac et al. (2009) demonstrated that patients with hippocampal damage showed less correspondence between language and memory lateralisations than patients with cortical damage (Kovac et al., 2009). Similarly, patients with hippocampal pathology show higher occurrence of atypical language organisation (Knecht, 2004; Jansky et al., 2003; Liegeois et al., 2004; Weber et al., 2006). These findings suggest that language and memory may reorganise independently, and even in cases where language remains left-lateralised, verbal memory can reorganise to the contralateral hemisphere (Strandberg et al., 2017). Investigating the neural correlates for both functions is therefore critical prior to surgical intervention.

1.1.4 Effect of Mesial Pathology

Evidence suggests the role of the underlying neuropathology in the functional reorganisation of memory. Functional reorganisation of memory to the contralateral hippocampus is documented in patients with Hippocampal Sclerosis (HS) (Richardson et al., 2003; Sidhu et al., 2013; Sidhu et al., 2015). Similarly, Richardson and colleagues documented more left hippocampal activation during word encoding in patients with less severe left hippocampal pathology (Richardson et al., 2004). Moreover, significant relations between hippocampal volume and fMRI activations indicate that the degree of functional reorganisation is proportional to the extent of hippocampal damage (Powell et al., 2007). The latter study demonstrated this observation in both left and right TLE patients for verbal and visual memory, respectively. These findings indicate that the underlying brain pathology has a role in the functional reorganisation of memory, with mesial pathology associated with greater functional reorganisation of memory than cortical pathology. TLE with HS is associated with earlier age at onset than TLE without HS (Engel, 1993; Weiser et al., 1993); the presence of hippocampal pathology (*i.e.* HS) may therefore be associated with greater functional reorganisation as a result of early age of brain insult.

1.2 Mapping of Memory Functions in Children

Investigation of the effect of hippocampal damage on functional representation of memory in children is limited. In paediatric epilepsy, functional MRI studies have not yet investigated memory organisation, and have instead focused on the representation of language processing. Atypical language lateralisation is relatively frequent in children with TLE. For example, Yuan and colleagues documented atypical lateralisation in 78% of children with TLE compared to only 11% in age-matched controls (Yuan et al., 2006). It is possible that reorganisation of memory function may also occur, as documented in adult TLE, and should be investigated alongside language lateralisation.

Compared to adults with TLE, children with TLE may be prone to greater bilateral representation of functions as a result of greater potential for brain plasticity and/or more extensive brain pathology. It has been shown that children with TLE show greater occurrence of atypical language lateralisation compared to adults

with TLE (de Ribaupierre et al., 2012). The same pattern may be true for memory. Sidhu and colleagues demonstrated that early age at onset of seizures (age range 3-25 years) was associated with bilateral verbal memory representation in the temporal lobes in adults with left TLE (Sidhu et al., 2015). Such a pattern of activation may be specifically associated with early onset of pathology. Children with hippocampal damage as a result of congenital hypothyroidism recruit additional bilateral hippocampus to maintain memory (Wheeler et al., 2011). The authors showed that the volume of the left hippocampus is correlated with visual memory and the volume of the right hippocampus is correlated with verbal memory. Similarly, patients with developmental amnesia who have selective bilateral hippocampal damage sustained by perinatal hypoxic-ischemic events show bilateral activations for memory retrieval. These patients show similar memory-related activations as healthy controls but also show additional activations in homologuous regions in the right hemisphere (Maguire et al., 2001). As such, it is possible that children with TLE exhibit stronger bilateral representation of memory, as a result of early acquired pathology/onset of seizures. Children with TLE may develop mnemonic strategies to support memory, reflecting plastic changes in response to early acquired pathology in the hippocampus, to counteract the noxious effects of early hippocampal damage. From a clinical perspective, it is important to assess the ability of the contralateral hippocampus to sustain memory, as this has implications for the prediction of memory outcome after surgery.

Whereas contralateral reorganisation of verbal memory is more frequent in adults with left compared to right TLE, consistent with material-specific deficits, the pattern of functional reorganisation may be different in paediatric TLE. Material-specificity of memory impairments is not always documented in children with hippocampal damage (Engle & Smith, 2010; Gold & Trauner, 2014) and Saling suggested that verbal and non-verbal memory are not entirely lateralised (Saling, 2009). As such, lateralisation of verbal memory in children with TLE may be less dependent on the side of pathology than in adult TLE. If bilateral representation of verbal memory is to be found in paediatric TLE irrespective of lesion side, this can explain the finding that material-specific memory impairments are less pronounced in the younger population. Contralateral reorganisation of memory in paediatric TLE as a function of side of pathology should therefore be investigated.

In addition to contralesional hippocampus subserving memory, the contribution of the damaged hippocampus to memory retrieval has previously been investigated in children. Maguire et al. assessed the functionality of the remaining hippocampal tissue and its contribution to memory retrieval in a patient with developmental amnesia. This patient, Jon, has severe episodic memory impairments in the context of good general knowledge. Despite great bilateral volume reduction in the hippocampus, Jon showed hippocampal activation during autobiographical retrieval (Maguire et al., 2001). This finding provides evidence of the functionality of the damaged hippocampus and its contribution to memory retrieval. It is possible that in children with TLE, functional activation in the damaged hippocampus occurs to sustain memory retrieval, reflecting some functionality remaining in the residual hippocampal tissue. This would have critical implication as, in such cases, surgical removal of the damaged hippocampus may cause memory impairment. It is therefore of importance to examine the functional capacity of the remnant tissue of the damaged hippocampus in children with TLE prior to surgical intervention.

1.3 Predicting Cognitive Outcome

A goal of this language/memory fMRI protocol is to provide useful information regarding memory localisation prior to surgery in order to guide surgical decision and help predict cognitive outcome, and identify those patients who will be at risk of severe memory impairment after temporal lobectomy. Verbal memory decline is often reported after surgery in the left temporal lobe (see (Lah, 2004) for a review). However, after an initial post-operative decline, paediatric patients are reported to recover from their memory deficits and reach pre-operative performance standards within one year (Gleissner et al., 2005). Gleissner and colleagues however showed a big variability in verbal memory outcome, which is associated with the integrity of the left temporal lobe. This suggests the need for tailored resection of the structures that are critical to memory. Identifying functional organisation prior to surgical intervention could therefore guide tailored resection and limit detrimental loss of memory after surgery.

The present protocol identifies prominent activations in temporal lobes, both in the MTL and lateral regions (Chapter 6). More specifically, activations in the anterior temporal lobes are related to successful memory and are known to have

a role in semantic integration. Surgical intervention for TLE often involves resection of the anterior temporal lobes; for that reason, functional representation in those regions may provide crucial clinical information prior to surgery. This protocol therefore has the potential to provide useful clinical information for predicting outcome after surgery in the temporal lobe in TLE.

Numerous studies have demonstrated the utility of memory fMRI to predict memory outcome in adult TLE after surgery (see (Binder, 2012) for a review). Binder and colleagues demonstrated that verbal memory fMRI paradigms, as used by Bonelli, Powel and Richardson, have higher predictive value for verbal memory outcome than the scene encoding tasks used by Binder, Frings and Rabin (Binder et al., 2010; Bonelli et al., 2010; Frings et al., 2008; Rabin et al., 2004; Richardson et al., 2004; Powell et al., 2008). Bonelli and colleagues showed particularly promising findings (Bonelli et al., 2010). These authors used MTL activation asymmetry during word encoding and predicted about 20% of the variance in memory changes from pre- to post-surgery. They showed greater verbal memory decline associated with greater pre-operative asymmetry to the left anterior MTL. Moreover, they showed that less decline was associated with greater asymmetry to the left posterior MTL, suggesting that ipsilateral reorganisation to posterior portions of the hippocampus is protective of memory decline. Similarly to the adult patient population, memory fMRI may prove itself useful in determining the risks of surgery and predicting outcome in children with TLE, but this has not yet been applied to children.

1.4 Aims and Hypotheses

The aim of this chapter is to pilot the language/memory fMRI protocol, described in the previous chapter, in a representative sample of paediatric patients with TLE who are candidates for surgery. The language/memory fMRI protocol was discussed in Chapter 5, and the neural network associated with word recall in typically-developing children was demonstrated in Chapter 6.

Healthy children aged 8-18 years performed well in both tasks inside the scanner regardless of age (Chapter 6, section 3.1, page 189). Children with intractable epilepsy are at risk of cognitive deficits (Bailet & Turk, 2000), and may find the protocol challenging. Poor in-scanner performance reduces the number of “hits”

relative to “misses” and impedes the ability to investigate brain activation using event-related analyses. The first aim of this chapter was therefore to determine whether children with TLE could perform the task to provide enough hits and misses trials for event-related analyses to be powered.

The language task of the protocol was validated against the clinical verb generation protocol currently used at Great Ormond Street Hospital by examining correspondence between the language networks and the language lateralisations across the experimental and clinical protocols. The ability of the protocol to show hippocampal activation at the individual-level was also investigated. In addition, several hypotheses regarding memory activations were generated for the current paediatric sample:

a) Co-lateralisation of language and memory functions: functional organisation of memory will not necessarily be related to language lateralisation in all patients.
b) Lateralisation of verbal memory based on side of pathology: memory lateralisation will not be related to side of pathology.
c) Anterior *versus* posterior hippocampal activation: posterior hippocampal activation is expected to be found in both left and right TLE patients.
d) Functional reorganisation as a function of type of pathology: there will be more contralateral reorganisation in cases where the lesion encroaches on mesial regions (*i.e.* MTL), and less in cases of damage to lateral temporal lobes.

2 Methods

2.1 Participants

Five patients with intractable TLE were recruited from Great Ormond Street Hospital for Children in London, UK, and were administered the language/memory fMRI protocol. These patients were diagnosed with left (N=2), right (N=2) or bilateral (N=1) TLE with various aetiologies, and were candidates for surgical intervention. Clinical characteristics of these patients are reported in Table 7.1. The participants were aged between 12 to 18 years and were part of

the sample investigated in Chapter 4 regarding their performance on the Pair Games.

Appendix F (page 365) provides the structural MRI scans (coronal and sagittal views) for each patient.

Table 7.1 Clinical Characteristics of Patients.

	Side of pathology	Aetiology	Seizure onset (age in years)	Age	Gender
Case 1	Right	HS	2	16	F
Case 2	Right	Porencephalic cyst in temporal lobe	9	16	F
Case 3	Bilateral	HS	9	16	M
Case 4	Left	HS	8	12	F
Case 5	Left	DNET in temporal lobe	11	16	F

For comparison purposes, data related to functional lateralisation from these patients were compared to that from typically-developing children documented and discussed in Chapter 6. The sample of controls consisted of 27 children and adolescents aged between 8 and 18 years (see Chapter 6, section 2.1, page 184). Due to the slightly older age of the patient cohort compared to the control cohort, the patient data was also compared to that of an age-matched subsample of the control group (age 12-18 years) but did not yield different results. In addition, it was shown in Chapter 6 that memory lateralisation was not age-dependent.

2.2 fMRI Protocol

The fMRI protocol was fully described in Chapter 5. Figure 7.1 illustrates the procedure, which involves a verb generation task, a baseline task and a cued recall task. Functional images were acquired and pre-processed as per Chapter 5 (sections 2.6 and 2.7, page 153).

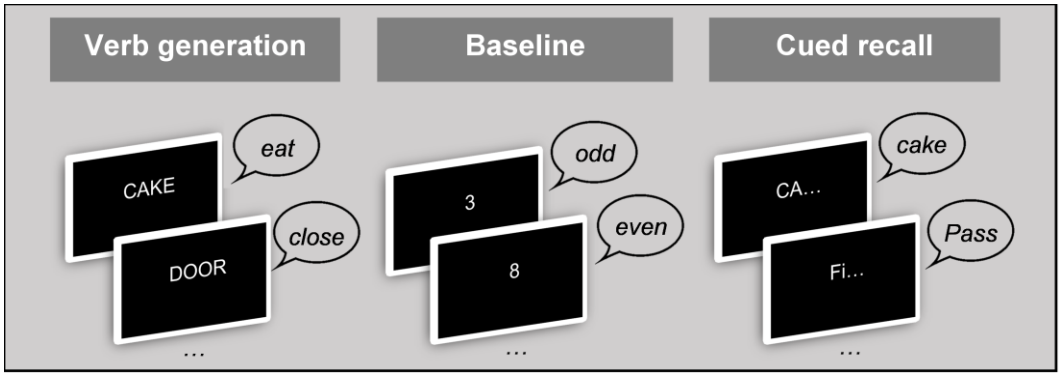


Figure 7.1 Procedure of fMRI protocol.

2.3 Imaging Analyses

Imaging analyses were carried out as per chapter 6 (section 2.4, page 185). Language-related activations were investigated using block analyses with 2 regressors of interest (Table 7.2). Memory-related activations were investigated using event-related analyses with 5 regressors of interest (Table 7.3). Due to the small sample size (N=5), no statistical analyses were carried out and instead, observational analyses were conducted.

Table 7.2 Description of each regressor in block-analyses.

Regressors	Description
Language (L)	Verb generation task
Baseline (B)	Baseline task: odd/even decision to numbers
Memory (M)	Cued recall task, irrespective of performance

Table 7.3 Description of each regressor in event-related analyses.

Regressors	Description
Subsequent Hits (SH)	Activation during the encoding of words that were later retrieved
Subsequent Misses (SM)	Activation during the encoding of words that were later forgotten
Baseline	Baseline task: odd/even decision to numbers
Hits (H)	Activation during the successful retrieval of words
Misses (Mi)	Activation during the unsuccessful retrieval of words
Correct rejection (CR)	Activation during correct rejections of words at retrieval

2.3.1 Clinical versus Experimental Language Protocols

To validate the language task, the brain activation from the language task in the experimental protocol was compared to that of the clinical protocol. Both of these

protocols involve overt language tasks allowing direct comparisons. Three patients out of the sample of five were administered both protocols, in separate scanning sessions, for whom comparison of language-related activation was made possible. Language LIs were calculated in Broca's area for each patient in both protocols and lateralisation indices (LIs) were calculated and compared between the two protocols for each patient.

A height threshold of $p<0.05$ (FWE), corrected, was used for the experimental protocol, and a lower threshold ($p<0.01$, uncorrected) was used for the clinical protocol in order to obtain activation in language brain regions.

2.3.2 Individual-Level Hippocampal Activation

The ability of the fMRI paradigm to show individual-level activation in the hippocampus was investigated for both encoding-related ("SH>SM") and retrieval-related contrasts ("H>Mi+CR"). Whole-brain analyses are reported at height threshold $p<0.05$, uncorrected, for each individual patient separately.

2.3.3 Co-Lateralisation of Language and Memory Functions

To test co-lateralisation of functions, LIs were calculated for language and memory in several Regions of Interest (ROIs), namely Broca's area, the temporal lobe and anterior and posterior hippocampi. The LIs were calculated using the LI toolbox (Wilke & Lidzba, 2007), where:

$$\mathrm{LI} = \frac{\sum \mathrm{activation}_{left} - \sum \mathrm{activation}_{right}}{\sum \mathrm{activation}_{left} + \sum \mathrm{activation}_{right}}$$

Values above 0.2 represent left lateralisation, LIs below 0.2 represent right lateralisation and values between -0.2 and 0.2 indicate bilateral representation. The categorisation of LI values (left, right, bilateral) was compared between language and memory for each patient.

Language and memory LIs were calculated for the contrasts "L>B" and "M>B", respectively. Memory LIs were investigated for block-analyses rather than event-related analyses 1) for better comparison with language LIs, and 2) because typically-developing children were more left lateralised in block- compared to event-related contrasts (Chapter 6) making it a better investigation of changes in memory lateralisation in children with TLE.

2.3.4 Lateralisation of Verbal Memory based on Side of Pathology

Memory LIs were calculated in several hippocampus ROIs (full, anterior and posterior hippocampus) as described in Chapter 6 (section 2.4.6, page 188). The LIs were investigated for memory retrieval (contrast "M>B"). LI values were investigated with the block contrast since this is the one that is the most lateralised in the typically-developing sample (see Chapter 6, section 3.6, page 196). LI values for event-related contrasts were varied and all over the spectrum, making it difficult to interpret values from TLE patients.

These LI values were investigated in light of side of pathology (left *versus* right). The proportion of cases showing left, right or bilateral activations for verbal memory was compared to the proportion documented in healthy controls (Chapter 6, section 3.6, page 196).

2.3.5 Anterior versus Posterior Hippocampal Activation

Beta weights related to memory retrieval were extracted from anterior and posterior hippocampus masks, as described in Chapter 6 (section 2.4.5, page 188), for the contrast "H>Mi+CR" because typically-developing children show stronger anterior than posterior hippocampal activation for that specific contrast (Chapter 6). For visual purposes, values from the posterior hippocampus were subtracted from values from the anterior hippocampus to indicate, for each patient, in which portion (anterior *versus* posterior) memory shows the highest beta values. These individual values were compared to the control group's value.

2.3.6 Effect of Type of Pathology on Functional Reorganisation

Memory LI values (for the contrast M>B) were investigated for each patient in several masks, namely the hippocampus (full, anterior and posterior) and the temporal lobe. These values were investigated in light of the underlying pathology (mesial *versus* cortical). The proportion of patients with mesial pathology showing contralateral reorganisation of memory will be compared to that of patients with cortical pathology.

3 Results

3.1 Behavioural Performance

Despite lower cognitive abilities than controls on measures of memory and intellectual functioning, all patients were able to perform the tasks inside the scanner. For the language task, they successfully generated a verb for 72 to 92% of the nouns heard (Table 7.4). For the memory task, they successfully remembered between 45% and 87% of the words and successfully rejected 100% of the foils.

Table 7.4 In-scanner language and memory scores, expressed in percentages.

	Verb generation	Hits	Correct rejections
Case 1	77	78	100
Case 2	75	77	100
Case 3	72	87	100
Case 4	83	45	100
Case 5	92	70	100

3.2 Language Activation in Clinial *versus* Experimental Protocol

Table 7.5 provides language LIs calculated in Broca's area in the clinical and experimental protocols. The classification of LIs (left/right/bilateral) is consistent between protocols for each patient.

Table 7.5 Language LI in Broca's area during clinical and experimental VG tasks.

	Clinical protocol	Experimental Protocol	LI classification
Case 3	-0.73	-0.98	Right
Case 4	0.57	0.90	Left
Case 5	0.40	0.93	Left

Thresholded SPM maps are illustrated in Figure 7.2. The VG task from the experimental protocol activated similar regions to the language task from the clinical protocol, namely Broca's area, Wernicke's area and the cingulate gyrus.

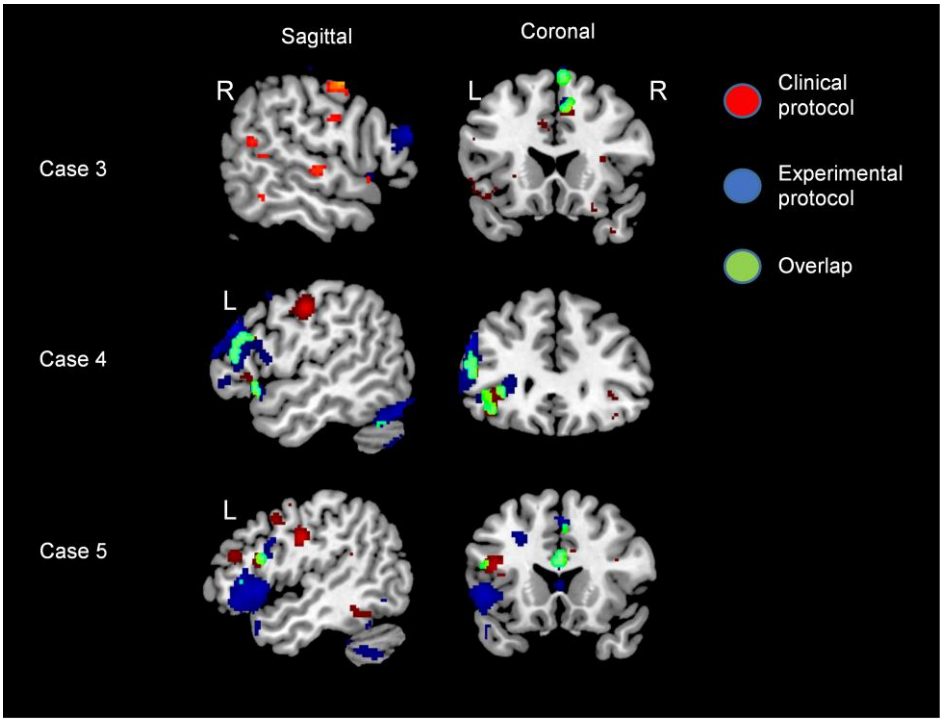


Figure 7.2 Correspondence of language activations with the clinical and experimental protocols. SPM maps for clinical protocols are displayed at $p<0.01$, uncorrected, and for experimental protocols at $p<0.05$(FWE), corrected.

3.3 Individual-Level Hippocampal Activation

Figure 7.3 illustrates encoding-related and retrieval-related hippocampal activation for each case separately. The results show encoding-related activation in 4/5 cases and retrieval-related activation in 4/5.

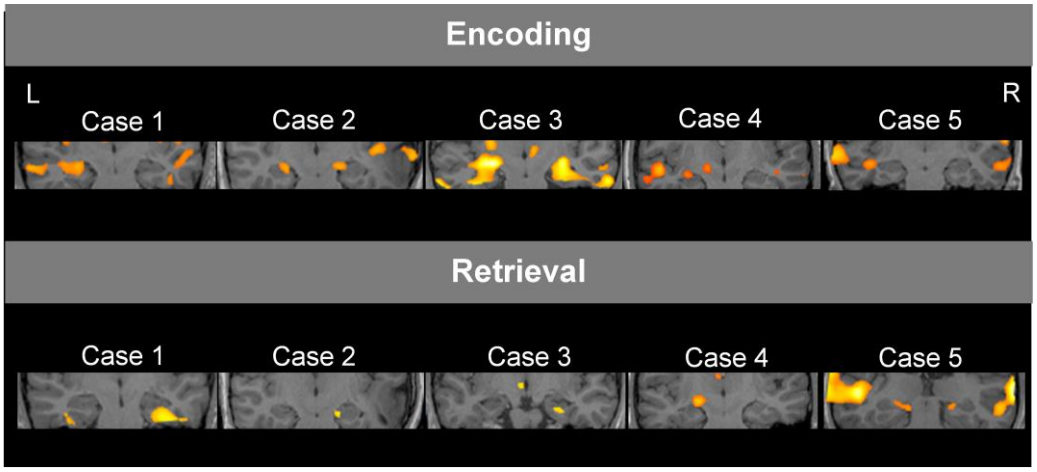


Figure 7.3 Encoding- and retrieval-related hippocampal activation for each case at $p<0.05$, uncorrected.

3.4 Co-Lateralisation of Language and Memory Functions

Language and memory LI values are displayed in Table 7.6 for each case. Language was left lateralised for 4/5 TLE patients. Case 3, who had bilateral TLE, showed right lateralisation in Broca's area. For memory, laterality was varied across patients in both the hippocampus and the temporal lobe. Three out of four cases with left lateralisation of language showed bilateral or right lateralisation of memory in the hippocampus, and only case 4 demonstrated co-lateralisation language and memory patterns. The pattern of lateralisation is different between the anterior and posterior hippocampus ROI and will be investigated further below. Figure 7.4 illustrates language and memory LIs for each individual patient, colour-coded for lesion location.

Table 7.6 Categorisation of LI values for language (L>B) and memory (M>B) in several ROIs (Broca's area, temporal lobe (TL), hippocampus (H)).

		Language		Memory			
	Side of pathology	Broca's	TL	H	Anterior H	Posterior H	TL
Healthy controls		0.79	0.64	0.32	0.46	0.28	0.37
Case 1	Right	0.87	0.87	-0.78	-0.64	-0.77	0.67
Case 2	Right	0.98	0.64	0.22	.08	.88	.68
Case 3	Bilateral	-0.8	0.38	-.12	.01	-.60	-.09
Case 4	Left	0.90	0.80	.56	-.52	.65	.63
Case 5	Left	0.93	0.75	-0.5	-.56	.85	-.05

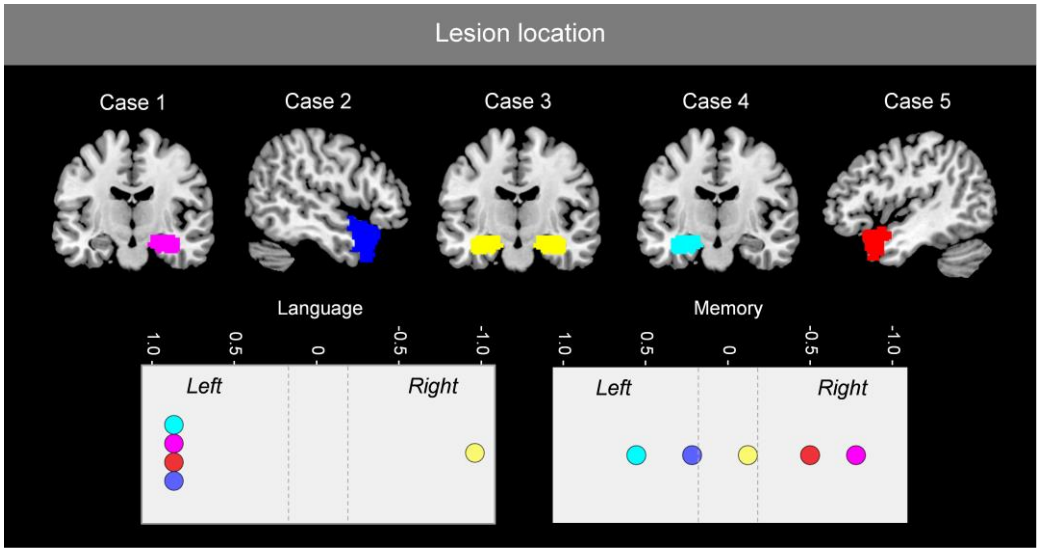


Figure 7.4 Language (contrast "L>B") and memory (contrast "M>B") LIs for each individual case, colour-coded for lesion location. Language and memory LIs were calculated in Broca's area and the hippocampus, respectively.

3.5 Lateralisation of Verbal Memory based on Side of Pathology

In the typically-developing sample (Chapter 6), the majority of children were left lateralised in the anterior hippocampus for memory (N=22), with some showing right lateralisation (N=3), and other bilateral representations (N=2). Three out of five patients with TLE (left and right TLE), however, showed right lateralisation for memory. Cases 2 and 3 (right and bilateral TLE, respectively) showed symmetric bilateral activations of memory. Figure 7.5 provides an illustration of the memory LI for each case, colour-coded for the lesion location.

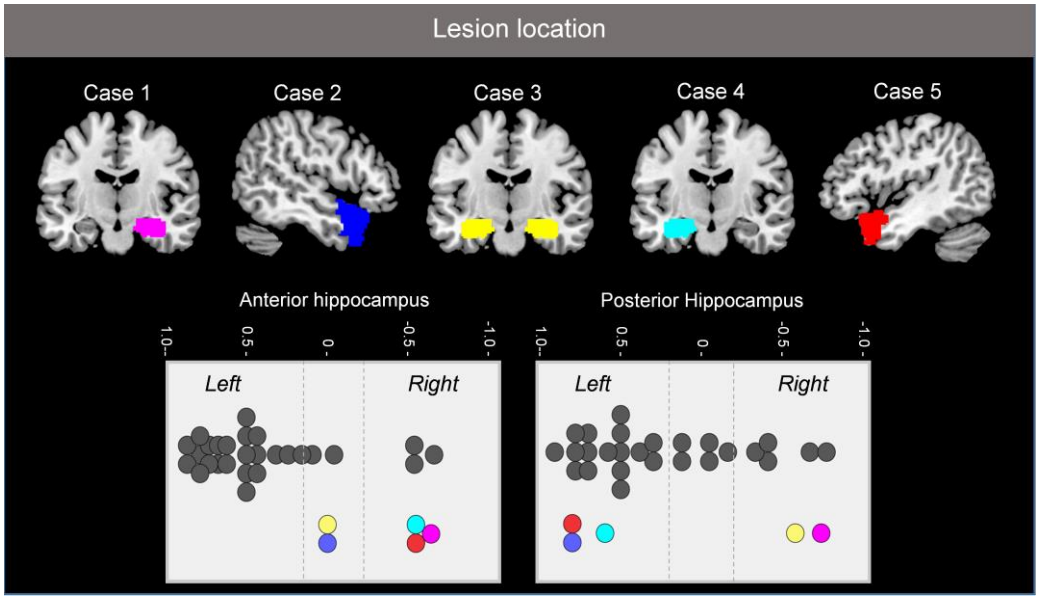


Figure 7.5 Distribution of memory LIs for controls (grey) and TLE patients (colour-coded based on lesion location), for memory retrieval (contrast "M>B").

In the posterior hippocampus, the LI values in the typically-developing sample were more varied and spreadout along the spectrum. In the clinical sample, three patients showed left lateralisation (cases 2, 4 and 5), whereas the other two (cases 1 and 3) showed right lateralisation. None of the patients showed symmetric bilateral activations in the posterior hippocampus.

3.6 Anterior *versus* Posterior Hippocampal Activation

The difference between anterior and posterior hippocampus beta weights provides an indication of anterior *versus* posterior activation for each case. Positive values indicate higher betas in anterior compared to posterior hippocampus. Figure 7.6 illustrates difference in beta weights between anterior and posterior hippocampi for each case.

The grey line represents the value from healthy controls and indicates stronger anterior than posterior hippocampal activation. All but one patient showed less anterior hippocampal activation compared to controls. Cases 4 and 5, with left TLE, showed particularly stronger activation in the posterior compared to the anterior hippocampus. Case 3 who has bilateral HS, on the other hand, showed stronger activation in the anterior compared to the posterior hippocampus.

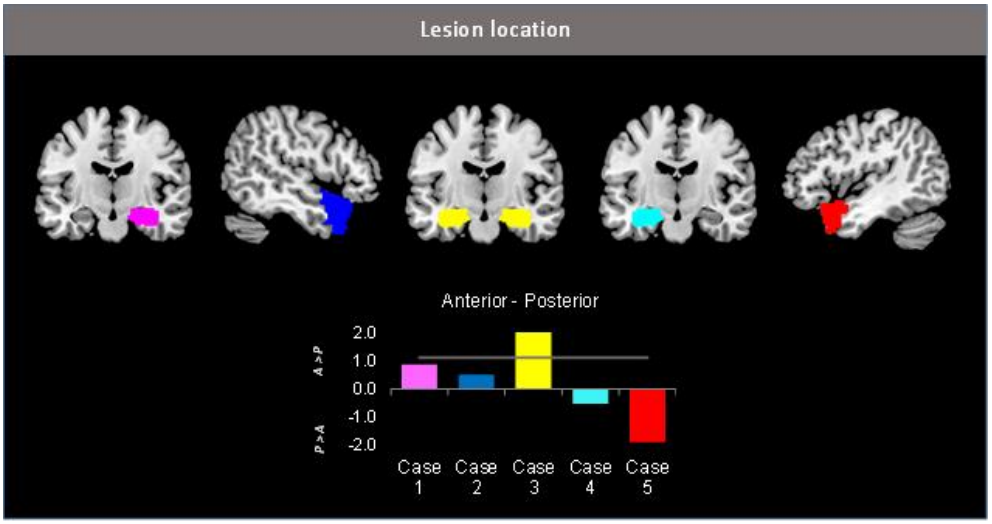


Figure 7.6 Beta weights related to successful memory retrieval for each TLE case. Beta weights were extracted from anterior and posterior hippocampi ROIs. The grey line indicates the mean beta weights from healthy controls. Positive values indicate higher betas in anterior (A) compared to posterior (P) hippocampus ROI.

3.7 Memory Reorganisation as a Function of Type of Pathology

One of the hypotheses postulated functional reorganisation particularly in cases where the lesion encroaches on the MTL, and less in cases of damage to cortical regions. Cases 1, 3 and 4 have HS, whereas cases 2 and 5 have damage to cortical regions of the temporal lobe. Apart from case 4, cases with HS show right lateralisation in the posterior hippocampus, whereas the two cases with cortical damage show left lateralisation in the posterior hippocampus (Table 7.7). The pattern of functional reorganisation as a function of pathology is not as clear in the anterior hippocampus.

Table 7.7 Classification of memory LIs (left, right, bilateral) in the anterior and posterior hippocampi for memory retrieval (contrast M>B), for each case

	Pathology	Anterior hippocampus (LI)	Posterior hippocampus (LI)
Case 1	Mesial	-0.64	-0.77
Case 2	Cortical	.08	.88
Case 3	Mesial	.01	-.60
Case 4	Mesial	-.52	.65
Case 5	Cortical	-.56	.85
NCs		0.46	0.28

3.8 Summary of Findings

Several hypotheses regarding memory activations were generated for the paediatric sample. Table 7.8 provides a summary of the findings corresponding to each hypothesis.

Table 7.8 Summary of formulated hypotheses and results.

Hypotheses		Results
1	Functional organisation of memory will not necessarily be related to language lateralisation in all patients	Whereas language was left lateralised for 4/5 TLE patients, memory laterality was varied across patients in both the hippocampus and the temporal lobe.
2	Memory lateralisation will not be related to side of pathology	In the anterior hippocampus, 3/5 patients with TLE (left and right TLE), showed right lateralisation for memory. In the posterior hippocampus, 3/5 patients (left and right TLE) showed left lateralisation, whereas the other two showed right lateralisation.
3	Posterior hippocampal activation is expected to be found in both left and right TLE patients	All patients with unilateral TLE showed less anterior hippocampal activation compared to controls. The two patients with left TLE showed stronger activation in the posterior compared to the anterior hippocampus. The patient with bilateral HS showed stronger activation in the anterior compared to the posterior hippocampus.
4	There will be more contralateral reorganisation in cases where the lesion encroaches on mesial regions and less in cases of damage to lateral temporal lobes	Two out of three cases with HS showed right lateralisation in the posterior hippocampus, whereas the two cases with cortical damage showed left lateralisation.

4 Discussion

4.1 Activations at the Individual Level

In the normal brain, heterogeneity of activation patterns is observed between individuals as a result of variability in functional organisation (see Chapter 6 for a discussion), but the heterogeneity may be even higher in the clinical population. Gupta and colleagues identified neural correlates for a language and a motor task in children with epilepsy and in typically-developing children. The authors showed that the activation pattern associated with the language task, but not with the motor task, was more heterogeneous across paediatric patients than across typically-developing children (Gupta et al., 2014). The authors attribute the heterogeneity to impaired language functions and to functional compensation for neural disturbances (Eliasen et al., 2008; Vlooszijk et al., 2010). Spatial heterogeneity in patients makes it difficult to draw conclusions at the group-level. From a clinical perspective, characterising brain activations at the individual subject level is most relevant for diagnosis and prognosis.

The present memory protocol captured MTL activation in each of the five TLE cases. Despite considerable efforts to document neural correlates of memory in adult TLE, report of memory network at the individual-level is lacking. Group-level analyses are useful to understand differences in activation patterns related to TLE, based on the spatial overlap of brain regions being activated among individuals of the sample (Haxby et al., 2001). However, the heterogeneity of clinical variables (*e.g.* underlying pathology, age at onset of seizures, and duration of epilepsy) across patients may influence neural networks (Sidhu et al., 2015). For this reason, group-level analyses may fail to capture clinically relevant patterns of activation at the individual level. In the present study, individual subject MTL activation was detected in all five patients, providing useful clinical information.

4.2 Correspondence between Clinical and Experimental Language Tasks

To validate the experimental language task against the well-validated clinical task, the language networks were compared between the two protocols. Three patients (2 left TLE and 1 bilateral TLE) were administered both protocols in separate scanning sessions allowing within-subjects comparisons. In all three cases, there was a clear overlap between the language activations of the two protocols. In addition, language LI values were calculated for each protocol, and provide the same categorisation (left, right, bilateral) for the three patients. This is particularly relevant for case 3 who shows atypical language lateralisation and for whom this is reflected with both protocols. The correspondence of language activations between the clinical and experimental tasks demonstrates the validity of the experimental verb generation task for the investigation of the language network related to verb generations.

4.3 Lack of Co-Lateralisation of Language and Memory

Atypical functional organisation has been documented in adult TLE for both language (Benke et al., 2006; Miro et al., 2014) and memory (Richardson et al., 2003; Towgood et al., 2015), and functional reorganisation of language and verbal memory often occurs jointly (*e.g*. Golby et al., 2002). In childhood TLE, atypical language organisation is also shown (Gaillard et al., 2007; Maulisova et al., 2016 (Yuan et al., 2006) but memory fMRI has never been investigated, and more specifically, co-lateralisation of language and memory had never been studied until the present study. The combined language/memory fMRI protocol offers the possibility of investigating lateralisation of both functions.

The findings from a recent study implied lack of co-lateralisation of language and memory functions in paediatric TLE. During a language task, Sepeta and colleagues demonstrated left lateralisation in Broca'a area, but age-dependent laterality of the MTL, with stronger left lateralisation with increasing age and therefore stronger independence of Broca's area and MTL lateralisation in children compared to adults (Sepeta et al., 2016). This finding suggested that language areas and the MTL do not necessarily co-lateralise, and children, both

with and without TLE, show more bilateral activation within the MTL despite left lateralisation within language areas. In fact, typically-developing children presented in Chapter 6 showed variable memory lateralisation in the hippocampus indicating that verbal memory laterality is not related to language dominance. Similarly, the present chapter shows varied memory laterality across patients in both the hippocampus and the temporal lobe, despite left lateralisation for language. Only one patient from the present sample showed co-lateralisation of language and memory (to the left). Together, these findings indicate a lack of co-lateralisation of language and memory in children, both typically-developing and with TLE.

The pattern of activation in children suggests that language and memory are two structurally-independent systems, at least during childhood and adolescence. In addition, the findings from the present chapter indicate that early damage associated with TLE alters the functional organisation of memory but overall does not substantially modify the language network. In the adult TLE literature, there is higher evidence of contralateral reorganisation of memory compared to language. In a study by Strandberg et al. (2017), 5 out of 8 (62%) patients showed left lateralisation for language but right lateralisation for memory. Similarly, Golby et al. (2002) showed that 5 out of 9 (56%) patients with language lateralised to the left and memory to the right, compared to 2 out of 9 (22%) with the opposite pattern. Moreover, even healthy children show less lateralised MTL activation (discussed in Chapter 6) which could also contribute to a lack of lateralised memory deficits in young patients with epilepsy (Cormack et al., 2012). Whereas language lateralisation is established by the age of 5 (Weiss-Croft & Baldeweg, 2015), it is possible that hemispheric specialisation for memory is a slower process, leading to non-lateralised memory impairments in the occurrence of early onset pathology. These findings converge on the idea that contralateral reorganisation is more frequent for memory than for language.

It was previously assumed that atypical language lateralisation in children occurs when lesions encroach on language areas (*e.g*. Lazar et al., 2000). However, Liegeois et al. (2004) showed that it is lesions to the MTL region rather than to the language regions that influence language reorganisation to the right hemisphere. Contralateral reorganisation of language was observed in only one case from the present sample (case 3 with bilateral TLE) which may be related to

bilateral hippocampal damage. The other patients with unilateral damage do not show atypical language representation. This observation is consistent with Liegeois et al's findings and suggests the influence of bilateral hippocampal damage on language reorganisation to the right hemisphere.

Overall, the findings suggest that lateralisation patterns of language and memory functions are independent in paediatric TLE. Temporal lobe seizures and/or pathology arising in adulthood reportedly alter the functional organisation of language and memory. Laterality information gathered from language fMRI is therefore sometimes used to estimate memory lateralisation, and hence predict memory outcome after surgery in adult TLE. However, the lack of co-lateralisation of functions in children has implications for surgical decision and prediction of outcome, and indicates that for paediatric TLE, language lateralisation cannot be used to predict memory outcome.

4.4 Evidence of Contralateral Reorganisation in the Anterior Hippocampus

Adult patients with TLE often show contralateral reorganisation of memory, particularly verbal memory reorganisation to the right hemisphere in left TLE (Jokeit et al., 2001; Richardson et al., 2003; Golby et al., 2002). Such right hippocampal recruitment for verbal memory is shown in the present paediatric sample whereby both left TLE cases show right lateralisation of verbal memory in the anterior hippocampus, but not in the posterior hippocampus. This finding indicates distinct patterns of functional reorganisation in different portions of the hippocampus, with contralateral reorganisation of verbal memory in the anterior hippocampus as a function of side of pathology.

This pattern of functional reorganisation based on side of pathology is not as clear in the posterior hippocampus and both left TLE cases are left lateralised. Two cases (1 and 3, with left and bilateral TLE, respectively) in the present sample show right lateralisation in the posterior hippocampus. Right lateralisation of verbal memory in right TLE (case 1) suggests memory lateralisation ipsilateral to seizure focus. Although this may seem counterintuitive, memory lateralised to the side of seizure onset has previously been documented where patients with right medial TLE show a reduced left hemisphere activity compared to controls

and to left medial TLE (Detre et al., 1998). Golby and colleagues also documented one patient with right MTL atrophy and right lateralisation of memory (Golby et al., 2002). Similarly, Dupont and colleagues described altered neural networks supporting verbal memory in patients with right medial TLE, where these patients exhibit global decreased activation in the left hemisphere compared to left TLE patients and healthy controls (Dupont et al., 2002). Alternatively, right lateralisation of verbal memory could simply reflect inter-individual variability in memory lateralisation which is also reflected in the normative sample. Overall, these findings suggest that whereas memory lateralisation in the anterior hippocampus is somewhat related to the side of pathology, memory lateralisation in the posterior hippocampus may depend on other clinical factors.

The recruitment of contralateral homologous areas may be related to greater potential for brain plasticity in children (Mundkur, 2005) or to a halt in the hemispheric specialisation process as a result of early onset pathology (Vargha-Khadem et al., 2000). Distinct patterns of reorganisation in the anterior and posterior hippocampi may be related to distinct age-related structural changes in these regions. Gogtay et al. (2016) showed age-related *decrease* in anterior hippocampal volume, possibly reflecting pruning, but *increase* in posterior hippocampal volume. Contralateral activation in the anterior hippocampus specifically may therefore be shown as a result of early onset pathology. In addition, as described and discussed in Chapter 6, the anterior hippocampus seems to have a particular role in memory in healthy children and adolescents. The anterior hippocampus may therefore be more susceptible to functional reorganisation in the context of pathology. These interpretations remain speculative, and more research is required to investigate the differential patterns of memory reorganisation in the anterior and posterior hippocampus.

Regardless of the underpinning factors driving memory organisation, pre-operative memory lateralisation in the hemisphere ipsilateral to the seizure focus has important clinical implications as it tends to suggest high likelihood of post-operative impairments. Sidhu and colleagues demonstrated that adult patients with left TLE who showed pre-operative memory activation in the left anterior hippocampus exhibited greater memory decline after anterior temporal lobectomy. Similarly, right TLE patients who showed pre-operative activation in

the right anterior hippocampus exhibited greater memory decline after surgery (Sidhu et al., 2015). Patients who show memory lateralised to the side of seizure onset are therefore at higher risk of memory impairment following surgery.

Whereas interhemispheric functional reorganisation is sometimes associated with recovery of cognitive function (Weiller et al., 1995; Blasi et al., 2002), other studies have shown that contralateral reorganisation of functions is associated with poor recovery (Johansen-Berg et al., 2002; Ward et al., 2003). Powel et al. (2007) demonstrated that compensatory contralateral hippocampal activation in adults with unilateral HS is an inefficient process in that it does not allow the preservation of memory function. In children, it is not clear whether contralateral reorganisation of memory reflects an efficient mechanism to preserve memory function, and further investigation is required in paediatric TLE.

4.5 Evidence of Ipsilateral Reorganisation to the Posterior Hippocampus

In addition to contralateral reorganisation of memory, ipsilateral reorganisation can occur. This pattern of memory organisation has been documented in adult TLE and is associated with early onset of seizures (Sidhu et al., 2015). In the present study, whereas typically-developing children showed greater anterior than posterior hippocampal activation, both left TLE patients showed stronger posterior compared to anterior hippocampal activation. This shift of hippocampal activation along the anterior-posterior axis may reflect functional reorganisation to compensate for memory loss. Several studies have documented stronger posterior hippocampal activation in older individuals in order to maintain memory performance (Blum et al., 2014; Wang et al., 2010). Similarly, in a recent study, Li et al. (2017) investigated resting state functional connectivity in adult TLE and showed reorganised patterns of intra-hemispheric connectivity across the anterior and posterior hippocampal networks. The authors suggested that this pattern of connectivity strengthens the communication between bilateral posterior hippocampi and may compensate for the detrimental effects of seizures on memory performance (Li et al., 2017). These findings, along with the present study, suggest that the posterior hippocampi play a role in a compensatory mechanism to support memory.

Conversely, both right TLE patients showed stronger activation in the anterior compared to posterior hippocampi, similarly to controls, and case 3 with bilateral TLE showed an even higher proportion of anterior hippocampal activation than controls and left TLE cases. This finding therefore indicates a shift of memory activation to posterior hippocampi in left, but not right and bilateral TLE cases. However, only verbal memory was investigated in the present study, and it is possible that a posterior shift in hippocampal activation would be observed in right TLE cases if visual memory was assessed. Nevertheless, this finding suggests ipsilateral reorganisation to posterior hippocampi as a function of side of pathology.

Powel et al. (2007) showed that memory performance in adult TLE was associated with ipsilateral activation, and for example in left TLE patients, verbal memory scores were correlated with activation in the damaged left hippocampus (Powell et al., 2007). Similarly, other authors demonstrated that ipsilateral, but not contralateral reorganisation of memory is associated with less memory decline after surgery (Bonelli et al., 2010; Sidhu et al., 2015). Similarly to adults, it is possible that ipsilateral rather than contralateral reorganisation of memory may be more beneficial in children. This finding has clinical relevance as it may suggest the importance of targeted anterior temporal lobe resection with the sparing of posterior hippocampi, especially in left TLE cases. Such surgical procedure may prove itself effective in sparing memory functions after surgery and reducing memory deterioration. This assumption warrants further investigation to verify to what extent sparing the posterior hippocampus in the surgical intervention helps the preservation of memory.

4.6 Effect of Type of Pathology on Memory Reorganisation

The present study showed memory lateralisation in the posterior hippocampus related to the type of pathology. Two out of the three patients with mesial pathology showed right lateralisation, whereas the two patients with cortical pathology showed left lateralisation. Memory lateralisation as a function of the type of pathology was however specific to the posterior hippocampus and was not shown in the anterior hippocampus. This finding suggests contralateral

reorganisation of verbal memory in the posterior hippocampus only in patients with mesial pathology. In addition, language was represented in the right hemisphere only in the case of bilateral hippocampal damage. These findings are consistent with the observation that reorganisation of language function in children is related to lesion in the MTL (Liegeois et al., 2004). Language lateralisation depends on the integrity of the hippocampus, suggesting a role of the hippocampus in language reorganisation (Knecht, 2004).

It appears therefore that hippocampal damage is associated with contralateral reorganisation of memory in the posterior hippocampus. Additional research is however needed to confirm this, by comparing memory organisation between mesial *versus* cortical damage in a larger sample. Patients with temporal lesions are often excluded from studies (*e.g.* Gargaro et al., 2013), making it difficult to study the underlying factors associated with functional reorganisation. Together, these findings suggest stronger reorganisation in cases with hippocampal damage, compared to cases with cortical damage.

5 Limitations

The present study contains only five patients and is therefore a pilot study to test the clinical value of the fMRI protocol. Small sample sizes in neuroscience research may lead to reduced chances of detecting true effects and to low reproducibility of the findings (Button et al., 2013; Turner et al., 2017). Such sample size limits statistical power and inferences, and instead, provides preliminary conclusions; confirmation of the findings will require larger sample sizes. In addition, because examination was carried out at the individual-level for clinical purposes, a low statistical threshold (p<0.05, uncorrected) was used to visualise brain activation in subregions of the MTL. Whereas components above such low threshold might be labelled as noise, the findings were consistent with prior hypotheses. In addition, beta extraction and LI calculation were carried out independent of an arbitrarily defined threshold. The objective at this stage was to pilot the experimental fMRI protocol to examine its feasibility and provide a first examination of memory fMRI in the pre-surgical setting. Despite the small sample size and the low statistical threshold, the findings are consistent with hypotheses postulated on the basis of adult studies, and provide valuable first insight into the neural correlates of memory in children with TLE.

Another limitation from the present study relates to the fact that only verbal (not visual) memory was investigated. It is possible that similar patterns of brain activation would have been shown in right TLE patients if visual memory were also assessed. Investigating verbal and visual memory together would provide insight into material-specific lateralisation of memory in left and right TLE patients. However, the present study focused on verbal memory 1) to directly compare with language laterality, and 2) because verbal memory impairment is the main complaint after temporal lobe surgery. This protocol might therefore be more informative for left TLE cases, although verbal memory impairments are sometimes documented in right TLE patients, in which case this protocol would provide useful clinical information.

6 Conclusions

The language/memory fMRI protocol was designed for the investigation of both language and memory networks and therefore addresses two clinical questions within one scanning. This time- and cost-effective protocol was previously tested in a sample of healthy controls (Chapter 6), and now piloted on a small sample of paediatric patients with TLE. Findings from the present chapter suggest that this protocol provides successful mapping of language and memory networks in children with TLE, in accordance with hypotheses postulated on the basis of adult fMRI studies and knowledge on the effects of early age at onset of epilepsy.

This study also provides preliminary findings regarding the lateralisation of verbal memory as a function of side and type of pathology. Patients with left TLE were left lateralised in the posterior hippocampus and right lateralised in the anterior hippocampus for verbal memory, possibly indicating ipsi- and contralateral functional reorganisation, respectively. In addition, left TLE patients showed overall greater posterior compared to anterior hippocampal activation. Whereas the pattern of activation in the anterior hippocampus was related to the side of pathology, with left TLE patients showing right lateralisation and right/bilateral TLE patients showing bilateral activation, lateralisation in the posterior hippocampus was related to the underlying pathology. Apart from one patient, those with mesial pathology showed right lateralisation of memory in the posterior hippocampus, whereas those with cortical pathology showed left lateralisation.

Further investigation on a larger patient sample should be carried out to confirm these preliminary findings.

This pilot study demonstrates the feasibility of the language/memory fMRI protocol to investigate language and memory networks in paediatric patients with TLE. The protocol provides additional information on hippocampal and temporal lobe activations which cannot be addressed with language fMRI alone. In addition, this protocol produces activation in those specific regions at the individual level and is therefore useful for clinical purposes. In this respect, this combined language/memory fMRI paradigm could improve prognostication of verbal memory outcome after surgery for TLE, at the individual level.

7 Future directions

Following the successful pilot of this protocol in a small sample of children with TLE, confirmation of the findings are required by administering the protocol to a larger patient sample. In addition, correlation analyses between the amount of brain activation and memory scores would elucidate whether functional reorganisation reflects an efficient mechanism to preserve memory function. For example, if functional reorganisation is associated with preserved memory performance, the neuro-cognitive plasticity is considered efficient. Moreover, comparing ipsilateral and contralateral reorganisation in terms of memory decline after surgery will indicate whether, similarly to the adult population, ipsilateral reorganisation is more efficient than contralateral reorganisation. Overall, with a larger sample size, correlational analyses could be carried out with memory scores providing evidence of the efficiency of memory lateralisation.

Further work is required to validate the ability of the protocol to predict memory impairments after surgery by investigating long-term post-surgical outcome. In addition, a follow-up study would allow the identification of the pre-operative variables that best predict memory outcome, such as memory LIs in the anterior *versus* the posterior hippocampus. Furthermore, following the present findings regarding the role of posterior hippocampi to subserve memory in paediatric TLE, further work is needed to test whether sparing this structure during surgery limits memory decline.

Chapter 8

General Discussion

This final chapter will provide a summary of the main findings from the present study (section 1). The clinical implications of these findings will then be discussed (section 2), wherein I will describe and document the relevance of the results for patients and the implication for ongoing assessments of memory function in TLE patients. I will close this chapter with methodological critiques (section 3), suggestions for further research (section 4), and final conclusions (section 5).

1 Summary of Findings

1.1 Paediatric Temporal Lobe Epilepsy

Temporal Lobe Epilepsy (TLE) is a common form of epilepsy in children and is characterised by poor learning and memory abilities. Surgical intervention involving the removal of the temporal lobe structural lesion and variable portions of the hippocampus is often proposed in cases of intractable focal TLE. Such intervention is associated with memory decline post-surgery, more particularly in verbal learning and memory, as a result of the removal of critical regions subserving these functions.

Pre-operative behavioural and neuroimaging assessments are critical to provide a focused diagnosis of the status of memory function and to identify the risks of such intervention on cognitive outcome. More specifically, the contribution of these assessments to surgical decision-making in paediatric TLE is to 1) characterise the status of learning and memory functions in relation to broader cognitive functions, such as intellectual status, 2) establish the pattern of lateralisation of language and memory functions, and 3) predict cognitive outcome post-surgery.

Unfortunately, such assessments are hampered by a lack of adequate tests available. The complexity of childhood TLE, as opposed to adult TLE, is related to the more widespread cognitive dysfunction often seen in patients with early onset of epilepsy, less evidence of material-specific memory impairments, as well as the greater potential for reorganisation of function afforded by brain plasticity in the younger brain. These observations suggest that the nature of impairments cannot be inferred from adult models, and instead, adequate tests and paradigms (both neuropsychological and neuroimaging) should be employed for a comprehensive assessment of the patient's profile prior to surgical intervention.

1.2 Aims

The research reported in this thesis arose from a lack of adequate measures (behavioural and neuroimaging) for the clinical assessment of memory in children with TLE, as well as from a limited understanding of the developmental trajectory of learning in typically-developing children, and of the associated neural network supporting memory in children. The latter is important in the clinical setting for establishing a standard against which performance of patients can be compared to.

The main aims of this thesis were: 1) to develop behavioural protocols for the assessment of learning and memory (Chapter 2), to administer the said protocols to a large sample of typically-developing children (N=130; Chapter 3) to provide an indication of the normal developmental trajectory of verbal and non-verbal learning and memory, and to compare the performance of a small group of patients with TLE with that of the healthy controls using the same protocols (N=6; Chapter 4), and 2) to develop an fMRI paradigm for the investigation of language and memory networks (Chapter 5), to administer this protocol to a group of healthy children and adolescents to identify the neural network supporting memory (N=27; Chapter 6), and to pilot this same fMRI protocol in the small group of patients (N=5) who were candidates for temporal lobe surgery (Chapter 7).

1.3 Development of Protocols

1.3.1 Behavioural: The Pair Games

The ability to identify and characterise specific memory impairments in TLE is dependent upon the sensitivity and specificity of the neuropsychological instruments. Investigation of memory impairments as a function of side of pathology provides an indication of lateralisation of memory impairments (verbal *versus* non-verbal memory) associated with unilateral pathology in the left *versus* the right temporal lobe. Unfortunately, many of the standardised memory tools do not allow delineation of memory impairments and are confounded by the effects of 1) input modality (auditory *versus* visual), levels of semantic structure

(semantic *versus* non-semantic), and 3) memory processes (recall *versus* recognition).

In order to provide an improved assessment of the lateralisation of memory impairments, a novel verbal and non-verbal memory test (The Pair Games) was designed based upon theoretical models of memory (Chapter 2). Several variables that were potentially confounded, were controlled for in the development of the Pair Games, permitting balanced comparisons between the subtests. For each subtest containing different types of information, the paired-associate paradigm was used to assess learning over three consecutive trials, followed by delayed recall and recognition after a 15-minute delay. The five subtests consist of: Spoken Words, Written Words, Pseudowords, Objects, and Designs.

Few tests provide pure measures of memory and performance of participants usually depends on multiple processes. Attentional deficits, for example, can contribute to low performance on a memory test. However, the Pair Games was designed to be a balanced paradigm controlling for the effects of factors, such as attention, by encouraging deep-encoding processes. The Pair Games therefore aims to distinguish selective memory impairments from global cognitive and learning deficits, and provides a purer measure of memory and learning than currently available.

In addition, the Pair Games has the potential to provide an indication of lateralised memory impairments within the context of input modality, and access to semantic *versus* non-semantic representations. In these respects, the Pair Games offers a more controlled assessment to identify specific memory impairments leading to a clearer diagnosis of the patient's memory profile than currently available prior to surgery, and a quantifiable prognosis of outcome post-surgery.

1.3.2 Neuroimaging: Combined Language/Memory fMRI Protocol

Pre-operative functional mapping is performed in patients with TLE using functional Magnetic Resonance Imaging (fMRI) in order to determine the territories of eloquent tissue subserving critical cognitive functions prior to surgical intervention. Language mapping is widely carried out in adult and

paediatric patients, whereas to this day, memory mapping has been performed only in adults. Memory fMRI protocols developed for adults that assess recognition-based memory may not be sensitive enough to capture the processes dependent on the hippocampus *versus* the parahippocampal regions, whilst other paradigms, such as the Remember/Know paradigm, may not be suitable for children due to their complexity.

A combined language and memory fMRI protocol was developed as part of this research (Chapter 5) in order to map the critical regions subserving both language and verbal memory within one scanning session. This time-, and cost-effective protocol investigates the neural networks of both functions and sheds light on how the two systems interact. The language task consists of an overt verb generation test whereby participants are asked to generate a verb for each noun heard over the headphone. This noun/verb generation phase also provides a measure of encoding the nouns into memory. The memory task entails recall-based retrieval of the nouns presented during the language task. This retrieval is guided by word-stem cues to allow event-related examination of the neural network specific to successful memory.

As a result of the language task serving the encoding stage of memory formation, this protocol enables the examination of neural correlates of both memory encoding and memory retrieval networks. Together, the features of this combined language/memory fMRI protocol are particularly relevant for the clinical setting and the prediction of cognitive outcome after surgery in paediatric patients with TLE.

Two versions of the behavioural and fMRI protocols allow investigation of patients at two time points (*i.e*. pre- and post-operative) to investigate the potential impact of surgery on cognitive and neural changes, and on the trajectory of behavioural and functional changes that occur with age.

1.4 Memory in Typically-Developing Children

These novel behavioural and neuroimaging protocols were administered to typically-developing children to examine the trajectory of learning and memory (Chapter 3) and the neural network supporting memory (Chapter 6).

1.4.1 Behavioural Assessment

1.4.1.1 Developmental Trajectory

The developmental trajectory of learning and memory was examined across the wide age range (8 to 18 years old). The study demonstrated increases in learning performance with increasing age, across all subtests of the Pair Games. Age-related improvement in learning gain (increases in performance from the first to the third learning trial) was shown for non-semantic subtests only (Pseudowords and Designs), possibly reflecting an increase in the usage or efficacy of mnemonic strategies with age (*e.g*. deep encoding strategies).

Increases in scores of delayed recall were demonstrated only for the Spoken Words subtest, thus providing evidence of age-related recall abilities specific to auditory verbal memory. However, there was no age-related difference in recognition scores for that subtest, indicating that the age-effect reflects a difference in accessibility, but not availability of the relevant auditory verbal information. For the other subtests, improvement in recognition was observed with increasing age, and this improvement paralleled age-related decreases in "familiar errors" (familiar items that are paired with another item from the list – *i.e*. lures). This finding indicates age-related improvement in recollection-based recognition specifically, and reduced reliance on familiarity.

These findings suggest that the Pair Games paradigm captures age-related differences and documents developmental changes in learning and memory. These findings highlight the clinical relevance of the paradigm by revealing the developmental trajectory of learning and memory and interpreting deficits in TLE. Moreover, different memory profiles emerge depending on the age at which the pathology first occurred and the stage of development reached prior to the onset of pathology. The protracted development of the hippocampus and its functions, and the relatively late emergence of episodic memory in childhood, suggest that the above variables need to be taken into account to guide the formulation and the risks to memory and learning in TLE candidates for surgery.

1.4.1.2 Information Processing

The balanced nature of the Pair Games permits comparison between different subtests and examination of the influence of specific variables on learning and

memory. The variables of interest are material type, input modality, and level of semantic structure.

Non-verbal materials were better learned and were less susceptible to loss after a delay than verbal materials, providing evidence of greater strength of memory traces for configural information. However, this was dependent on the level of semantic access such that learning and memory for designs was better than that for pseudowords (*i.e.* comparison of performance within non-semantic items), but there was no difference between learning and memory for objects *versus* written words (*i.e.* comparison of performance within semantic categories). These discrepant results may possibly reflect access to dual-coding processes, and reliance on both verbal and visual coding of semantic items.

Similarly, verbal information presented in the visual modality (Written Words) was better learned than that presented in the auditory modality (Spoken Words). However, this discrepancy was not present for delayed recall and recognition, suggesting that performance became more balanced during the period of consolidation.

Significant discrepancy was also exhibited for learning and recognition performance on semantic (Written Words and Objects) and non-semantic subtests (Pseudowords and Designs). The discrepancy for learning was greater than that shown for recognition, again suggesting that the differences diminished over the consolidation process.

These findings indicate that different types of information are processed differently in typically-developing children, and that behavioural differences are mainly observed at the early stage of memory formation with reduced differences after consolidation.

1.4.2 Neuroimaging Assessment

1.4.2.1 Memory Network

Neural correlates of the memory encoding network irrespective of performance (investigated with block analysis) involved the left posterior hippocampus, reflecting the binding of information. Successful encoding (investigated with event-related analysis) was associated with activation in semantic-related brain

regions (*i.e*. right posterior superior temporal lobe and left anterior temporal lobe) and deactivation of regions supporting phonological processing of words (*i.e*. right supramarginal gyrus), providing evidence of the benefits of deep-encoding for later retrieval. Such semantic processing at encoding for subsequent retrieval was previously postulated with regards to the behavioural findings for items that push the boundaries of new learning (*i.e.* Pseudowords and Designs) (Chapter 3, section 4.4, page 104) and for which performance is particularly dependent on the efficacy of mnemonic strategies, such as deep encoding.

For memory retrieval (investigated with event-related analysis), activation was found in the left temporal lobe and in the hippocampus bilaterally. This protocol identifies memory-related activation in the mesial and neocortical regions of the temporal lobes, and thus provides critical information for the prediction of memory outcome after surgery in TLE.

1.4.2.2 Age-Related Effects in the Hippocampus

The study demonstrated an age-related effect in the hippocampus for retrieval, whereby older children recruited the right hippocampus more than younger children during successful retrieval of words. This observation possibly reflects age-related improvement in binding processes which are dependent on the hippocampus.

Different levels of recruitment of the hippocampus across the age range can be indicative of developmental changes in the use of mnemonic strategies or of functional development and the recruitment of different brain regions with increasing age. Such age-related effects can have implications for the neural representation of memory in children with TLE, depending on the age at seizure onset.

1.4.2.3 Relationship between Memory and Language Lateralisation

Lateralisation indices (LI) were calculated to provide measures of hemispheric lateralisation for language and memory, enabling direct comparison between these functions. Language is typically lateralised to the left hemisphere and it is generally assumed that language and verbal memory are co-lateralised, although this is rarely examined.

In the present study, co-lateralisation of function was directly investigated. Whereas left lateralisation for language was observed in every child, lateralisation for memory was more varied across individuals with some children showing left lateralisation, others showing right lateralisation, and some demonstrating bilateral representation. Correlational analyses between language and memory LI demonstrated the absence of a relationship between the two, suggesting that these functions are not co-lateralised in typically-developing children.

More specifically, whereas LI in Broca's area was significantly and positively related to LI in the hippocampus during the language task, language LI in Broca's area was not related to memory LI in the hippocampus. Moreover, these lateralisation indices were not significantly related to other variables such as IQ, handedness and age.

Together, these findings suggest independence of language and memory lateralisation and indicate that information related to language lateralisation cannot be used to predict memory lateralisation. Instead, memory fMRI should be carried out in the clinical setting alongside language fMRI.

1.5 Memory in Paediatric TLE

The behavioural and fMRI protocols developed as part of this thesis were also piloted in a small sample of children with TLE who were candidates for surgery (N=6 for the behavioural protocol and N=5 for the fMRI protocol). Out of the 6 patients, 3 were diagnosed with left TLE, 2 with right TLE, and 1 with bilateral TLE. The underlying aetiology varied between mesial and predominantly cortical pathology; 4 patients were diagnosed with Hippocampal Sclerosis (HS) and 2 with primarily neocortical pathology (1 with a porencephalic cyst and 1 with Dysembryoplastic Neuroepithelial Tumour (DNET) in the temporal lobe).

1.5.1 Behavioural Assessment

The applicability of the Pair Games in the clinical setting was verified by testing the ability of the Pair Games to provide a refined identification of learning and memory impairments (Chapter 4). The overall pattern of dysfunction was better differentiated with the Pair Games than with standardised tests of memory.

Lateralisation of memory impairments were investigated in relation to the side of pathology. Previous researchers have struggled to document lateralisation of memory deficits in childhood TLE, possibly as a result of several confounding factors. First, early onset seizures may be related to more widespread pathology affecting both verbal and non-verbal memory functions. Second, the immature brain is associated with more efficient neural plasticity possibly leading to reorganisation of high-priority functions, such as speech and language, at the expense of other cognitive functions, a phenomenon referred to as the "crowding effect". Third, early pathology may cause a change and/or an arrest in the trajectory of development of hemispheric specialisation. Mindful of the fact that previous investigations have converged on reduced material-specificity of impairments in childhood compared to adult TLE, but cognisant of the need to control for factors that influence the pattern of memory lateralisation, the Pair Games was designed to provide a balanced test of memory and learning for paediatric patients undergoing evaluation for epilepsy surgery.

Results from a pilot study on paediatric patients with TLE indicated that the Pair Games was able to identify material-specific deficits in 4 out of 6 patients, consistent with the side of pathology. Thus, patients with left-sided TLE showed verbal memory deficits, whilst those with right-sided TLE showed non-verbal memory impairments. This finding provides evidence of the utility of the Pair Games for investigations of lateralised memory deficits associated with unilateral TLE. However, despite the sensitivity of the Pair Games to detect material-specific deficits, memory and learning patterns were not as clear and consistent in young patients with TLE as in adult patients. Furthermore, factors such as age at onset of seizures, and status of cognitive development prior to onset of brain insult were found to influence memory profiles.

Comparison between distinct memory processes, namely, learning, recall and recognition, provides behavioural evidence pointing to the underlying neuropathology. The ability of the Pair Games to identify restrictions in different aspects of memory was put to test in a small group of patients. Overall, the Pair Games identified deficits in memory and learning more often and more clearly than the standardised test of memory currently available for children.

Methodological caveats cannot be completely ruled out however. Although the design of the Pair Games was based on a theoretical framework to balance the

subtests as much as possible, these were nevertheless not equated for difficulty level, nor for variations in conceptual modes of processing. Given this caveat, it is possible that some of the differences in performance may have been influenced by the absence of equal weighting of the subtests in terms of difficulty. This is in contrast to other tests of memory, such as the Doors and People Test, wherein the processes of recognition and recall are equated in terms of difficulty (Baddeley et al., 1994). However, standardised scores reduce the effects of this limitation to some extent. In addition, material-specific effects in patients were investigated by comparing the discrepancy between verbal and non-verbal scores with the discrepancy observed in the normative sample. This approach also accounted for differences in difficulty levels between subtests.

Together, the findings reported in this thesis provide support for face validity of the Pair Games for diagnosis of specific memory and learning deficits in children with TLE. In addition to improved identification of material-specific memory deficits compared to standardised tests, the results of the pilot patient study of Pair Games highlighted the effects of age at onset of seizures on learning and memory profiles. However, these observations remain speculative at this stage and further investigation on larger sample sizes is necessary to confirm these results.

1.5.2 Neuroimaging Assessment

To test the clinical utility of fMRI protocols for identifying memory networks in TLE patients, hypotheses were based in part on the adult TLE literature, but also on our understanding of the effects of early brain injury on brain organisation for language and memory (Chapter 7).

Consistent with our prior hypotheses, children with TLE exhibited more bilateral representation of language and memory compared to their typically-developing controls. In addition, language and memory functions were not co-lateralised to one hemisphere, and right-sided lateralisation for memory was observed in some cases even when language was lateralised to the left hemisphere. This finding highlights the need to administer memory fMRI for the prediction of memory outcome rather than extrapolating the status of memory lateralisation from language fMRI.

Another finding related to the site of hippocampal activation, whereby compared to healthy controls, patients with left-sided TLE activated a more posterior region of the hippocampus, possibly as a result of intra-mesial temporal reorganisation for memory processes. This finding is consistent with that reported in adult TLE studies (Bonelli et al., 2013; Sidhu et al., 2015; Sidhu et al., 2016) and with reports of the influence of early onset seizures on posterior hippocampal activation during memory tasks (Sidhu et al., 2015). The present study also demonstrated contralateral reorganisation of verbal memory retrieval as a function of side of pathology, whereby patients with left TLE showed right lateralisation and those with right or bilateral TLE showed symmetric bilateral activation in the anterior hippocampus.

Moreover, the findings suggest contralateral reorganisation of verbal memory from left to right medial temporal regions. In cases with left or bilateral Mesial Temporal Sclerosis (MTS), memory activation is predominantly in the right MTL, whereas in cases with left neocortical abnormality, the memory activation remains in the left side. This observation is consistent with the suggested role of hippocampal pathology in the reorganisation of cognitive functions (Liegeois et al., 2004; Knecht, 2004).

This combined language/memory fMRI protocol provides successful mapping of language and memory networks in children with TLE and, more specifically, identifies prominent activations in temporal lobes, both in the MTL and lateral regions, and thus provides useful clinical information for predicting outcome after surgery in the temporal lobe.

2 Clinical Implications

2.1 Improved Diagnosis

The Pair Games designed as part of this research was based on theoretical models of memory and the existing literature (Chapter 2). The balanced nature of the Pair Games provides a refined diagnosis and identification of specific impairments in patients with TLE for an improved understanding of their cognitive profiles. The development of the Pair Games may have clinical implications for

assessment of memory and learning in patient groups with known or suspected MTL pathology beyond those with TLE, for example patients with Alzheimer's Disease.

2.1.1 Implications for Cognitive Intervention

A better understanding of the memory profile of each individual patient can provide useful information about their strengths and weaknesses, which can in turn inform methods of cognitive intervention. The aim of cognitive rehabilitation for memory is not to restore, but to compensate for the deficits (Farina et al., 2015) in order to improve everyday functioning. In this respect, precise diagnosis is essential for the implementation of an individualised cognitive intervention programme. Compensatory strategies based on preserved cognitive abilities may be particularly useful to reduce the adverse effects of temporal lobe surgery on memory outcome (Mosca et al., 2014), with this being particularly relevant to children who have greater adaptive capabilities compared to adults. For example, visual strategies (*e.g.* visual imagery) can be implemented to support verbal memory in cases where non-verbal memory is preserved. Similarly, a patient who exhibits specific impairments in auditory verbal memory, but not in verbal memory for information presented in the visual modality, can learn to encode verbal information via the visual coding system to improve performance. Likewise, because patients with hippocampal damage tend to have better recognition than recall memory, recognition-based training could be applied as cognitive remediation. These techniques would be most relevant to children and adolescents who are in the education system and benefit from consistent exposure to the learning environment. Unfortunately, the evidence in paediatric TLE for effective improvement of memory is sparse (see Joplin et al., 2018 for a review) and rehabilitation methods warrant further investigation.

2.2 Improved Prediction of Cognitive Outcome

Improved diagnosis has implications for accurate prognosis of cognitive outcome after surgery. Memory fMRI carried out in adult TLE predicts the risk of cognitive impairments post-surgery (Bonelli et al., 2010; Powell et al., 2008b; Richardson et al., 2004). In childhood TLE, verbal memory decline is often reported after surgery, particularly when surgery is in the left temporal lobe (see Lah, 2004 for a

review). However, there is high variability in verbal memory outcome, and this could be related to the integrity of the left temporal lobe and the extent of surgical removal. Memory fMRI can therefore be useful in identifying eloquent regions within the temporal lobes and the potential for memory support (Gleissner et al., 2005).

The combined language/memory fMRI protocols (Chapter 5) identify neural activity at the individual level in surgical candidates. The findings from the present study, both in typically-developing children (Chapter 6) and in children with TLE (Chapter 7), demonstrated that in contrast to adults, language and memory functions are not co-lateralised in children. This finding is important inasmuch as it demonstrates that prediction of memory outcome cannot be extrapolated from language fMRI, but needs to be based on memory fMRI protocols that engage the specialised functions of the MTL.

Combined neuroimaging assessments in the form of activation asymmetries, and pre-operative neuropsychological evaluations of memory have proved effective in predicting memory decline after temporal lobe resection in adult TLE (Baxendale et al., 2006; Bonelli et al., 2010; Lineweaver et al., 2006). It is anticipated that administering both the Pair Games and the combined fMRI protocols at the pre-operative level will provide improved diagnosis of language and memory status in individual patients, and also provide prognostic indicators of outcome after temporal lobe surgery in paediatric TLE. Table 8.1 provides a representation of information gathered from both protocols for each patient. Together, the behavioural and fMRI protocols can identify those who are at particular risk of learning and memory decline after surgery, which has critical implications for surgical decision-making. In this respect, Case 3 seems at particular risk of decline due to bilateral damage, bilateral activation on memory fMRI, and most importantly, because this patient already exhibits verbal memory impairments at the pre-operative level, without enough tissue on the right temporal lobe to salvage verbal memory. The data reported in Table 8.1 indicates that early pathology, even when it is unilateral, has seemingly bilateral effects and cognition in general is reduced.

Table 8.1 Information gathered from behavioural and neuroimaging protocols for each patient.

	Side of pathology	Verbal memory lateralisation left *versus* right	Memory deficit verbal *versus* non-verbal	Contralateral deficit
Case 1	Right	Right	Non-verbal	
Case 2	Right	Bilateral	Non-verbal	Verbal
Case 3	Bilateral	Bilateral	Verbal	
Case 4	Left	Right	Verbal	
Case 5	Left	Right	Verbal	
Case 6	Left	N/A	Verbal	Non-verbal

A recent study demonstrated higher risk of post-operative memory decline in adult patients who show limited pre-operative cognitive reserve (*i.e.* significantly low non-verbal memory in the left TLE group) (Baxendale & Thompson, 2018). In the present cohort, two patients showed additional contralateral memory deficit (Cases 2 and 6). Similarly to adults, this profile could be indicative of greater risk of post-operative memory decline as a result of reduced functional reserve (Chelune, 1995); this should be taken into consideration when predicting post-operative memory deterioration. However, a cautionary note pertains to the difficulty to make such comparisons between adult and child studies and make predictions in children based on adult data. More paediatric research studies are critical for the advancement of prediction of cognitive outcome.

A further cautionary note relates to the role of intellectual status in paediatric patients, particularly those with early onset of pathology. These protocols are most informative when used for the pre-surgical assessment of memory in children who exhibit IQ levels within the normal range. Patients with low IQ show a more distributed pattern of neural activation, in which case such predictions are less pertinent. Ojemann and colleagues conducted intracranial stimulation during object naming in high and low functioning participants and showed more widespread activations in low functioning compared to higher functioning individuals (Ojemann, 1991). A similar relationship may hold between ability and the neural organisation of memory, with less focal memory network integrity in those with lower intellectual status. The current protocols are therefore pertinent to focal pathology that has not interfered with network establishment and is associated with some evidence of hemispheric specialisation. It is in this specific

context of focal pathology that it is important to predict which specific aspect of memory is at risk of impairment.

2.3 Lateralisation of Memory

The Pair Games provides a better investigation of lateralisation of memory function, and as demonstrated in this thesis (Chapter 4), is able to identify material-specific impairments not captured with standardised tests.

As mentioned above, irrespective of side of pathology, there are complaints about verbal learning and memory problems in childhood TLE. Several factors may contribute to this observation. First, these complaints may be the result of the vulnerability of the auditory-verbal system (discussed in section 2.4, page 265), which is also demonstrated in typically-developing children in the present research (Chapter 3). Second, the susceptibility of acoustic verbal information to forgetting (discussed in section 2.5, page 265) makes auditory memory tests non-comparable to non-verbal memory tests (Chapters 3 and 4). Whereas the Spoken Words subtest of the Pair Games does not provide an indication of deficits related to left-sided pathology specifically, the Written Word subtest provides more evidence of material-specificity of impairment and may therefore be better suited for such investigation. Third, this observation may be a result of insensitivity of tests to capture material-specific impairments. As discussed above, comparison between verbal and non-verbal memory has been hampered by confounding effects. Diagnostic tools are generally not sensitive to capture non-verbal memory impairments and are not sensitive to right-sided pathology (Jones-Gotman et al., 1993), misleading the interpretation of lateralisation of memory dysfunction. For example, non-verbal memory is often assessed through recognition which is considerably easier than recall, reducing the ability to capture non-verbal memory impairments.

In contrast, as a result of its balanced nature, the Pair Games was able to identify non-verbal memory impairments in patients with right-sided pathology and captured material-specific deficits in both left and right TLE (Chapter 4). Despite less clear lateralisation of memory dysfunction in children compared to adult TLE as a result of early onset of seizures, the pattern of memory impairments may be less sporadic than reported in the literature. In addition, with the standardised

tests, clear predictions cannot be drawn from the non-verbal memory subtests whereas the Pair Games provides tables of verbal and non-verbal memory outcome predictions *versus* IQ. These clinical values highlight the strengths of the Pair Games over standardised tests.

2.4 Vulnerability of Verbal Memory to Temporal Lobe Pathology

The literature suggests behavioural differences in verbal and non-verbal memory abilities. Verbal memory is intrinsically related to academic attainment and intellectual status in children (Catroppa & Anderson, 2007; Hainlen, 1995). In addition, visuospatial memory shows a higher peak during adolescence than verbal memory (Murre et al., 2013). Consistent with these findings, the present study showed poorer verbal compared to non-verbal learning scores in typically-developing children (Chapter 3). It is possible that verbal learning is dependent on other cognitive abilities more so than non-verbal learning, especially during school-age years.

Considering the higher incidence of verbal over non-verbal memory complaints in childhood TLE (Fuentes & Smith, 2015; Law et al., 2017), examination of the profile of verbal memory in the typically-developing population is critical for a better understanding of dysfunctions, particularly in patients. As such, the lower efficiency of the verbal memory system in typically-developing children may indicate that this aspect of memory is more vulnerable in patients with temporal lobe pathology than non-verbal memory. This finding also underlines the value of standard scores in the investigation of material-specific impairments in order to account for lower verbal memory baseline. Examining raw scores, as opposed to standard scores, may contribute to null findings regarding material specificity of dysfunction as a result of inadequate comparisons between verbal and non-verbal memory.

2.5 Auditory Verbal Memory: Susceptibility to Forgetting

In typically-developing children, retention of auditory verbal information is age-dependent whereby younger children forget more auditory information after a

delay than older children (Chapter 3). In addition, children with TLE are susceptible to forgetting auditory verbal information after a delay, irrespective of side and site of neuropathology (Chapter 4). This susceptibility of auditory memory to forgetting is observed in young healthy children and in children with TLE, and may provide an indication of characteristics that are specific to auditory memory.

Because of the acoustic and temporal characteristics of auditory stimuli, storage of their representations requires the transformation of the acoustic sequence into a subvocal motor sequence. Long-term auditory memory requires subvocal reproduction of speech sounds by means of the oromotor system and, in this respect, is closely related to speech (Schulze et al., 2012). It is possible that the development of long-term auditory memory parallels speech development, and early onset of seizures impedes the development of these functions, leading to impairments in both language abilities and auditory verbal memory. An implication of the above is that younger children and children with TLE may find it difficult to store lasting representations of auditory information. The relationship between the development of speech and auditory verbal memory warrants further investigation. As a result of these acoustic and temporal characteristics, tests of auditory verbal memory are not comparable to those of non-verbal memory which are presented in the visual modality, and may not be suitable for the examination of lateralisation of memory function.

2.6 Advantages of Non-Semantic Subtests

Whereas memory for familiar stimuli (words and objects) can rely on previously stored representations, memory for non-semantic stimuli (pseudowords and designs) must rely on newly established representations. In this respect, non-semantic subtests push the boundaries of new learning. The establishment of these new representations may depend on mnemonic strategies at encoding. As such, age-related improvement in learning gain for non-semantic subtests observed in typically-developing children may reflect the development of mnemonic strategies with age (Chapter 3).

In addition, tests of non-semantic items show an association between learning gain and intellectual status in typically-developing children. This finding has

clinical relevance in that a patient with high IQ might be at risk of deficits in new learning; a risk not picked up with tests of semantic items (*i.e*. most standardised tests). In that respect, non-semantic tests may serve as more sensitive indicators of damage to critical regions subserving memory.

2.7 Separate Learning/Recognition from Recall Abilities

The findings from Chapter 3 suggest that learning and recognition memory are distinct from the recall memory process. Learning and recognition are intrinsically related to age, and similar effects of intellectual status indicate that learning and recognition are related to the maturation and acquisition of knowledge that increases with age. As children develop, they learn and form new semantic associations. Similarly, age-related effects shown for recognition can be understood as stronger associations made at encoding which influence recognition performance at retrieval.

On the other hand, recall (the ability to bring back to mind something that is no longer present) does not vary with age across childhood and adolescence. In addition, once it is established the ability to recall is not dependent on item features. As such, children and adolescents recall the same amount of information irrespective of the input modality (auditory *versus* visual) and of the degree of semantic access (semantic *versus* non-semantic). The distinction between the processes of recall and recognition has implication for the design of memory research studies and suggests the importance of using recall memory tasks. Recognition tasks are often employed to assess memory impairments in children with TLE in the clinical setting whereas recall memory is often ignored. Without testing recall, researchers only have a partial understanding of the memory system, and are neglecting what is arguably the most relevant aspect of memory for epileptic patients. In this respect, the fMRI protocol developed and discussed in Chapter 5 investigated neural correlates of recall.

2.8 Material-specific Asymmetry of the Hippocampal Learning System

The left hemisphere mediates verbal memory and the right hemisphere visuospatial memory (Milner, 1971; Saykin & Robinson, 1992). The findings from the present study suggest, however, that the hippocampal learning system may not be as clearly lateralised as the neocortical learning system as previously reported, at least in the case of paediatric cohorts. This may explain why neuroimaging findings are not always consistent regarding lateralisation of hippocampal activation. Casasanto et al. (2000) posited that whereas hemispheric laterality for memory appears material-dependent in other regions of the MTL, the hippocampus may show less lateralised activation (Casasanto et al., 2000). The findings from the present study are consistent with this notion. In Chapter 6, the results showed high inter-individual variability in lateralisation of hippocampal activation in typically-developing children (for event-related analyses), whereas the lateralisation of activation in other brain regions was more consistent. Further research on factors affecting hemispheric specialisation of the hippocampus may help reconcile neuropsychological findings that support the material-specific role of the hippocampal system, with conflicting neuroimaging findings.

The specialisation of the hippocampus may depend on the ease of access to semantic representations. As such, during memory processing, semantic materials (*e.g*. words and objects) may be integrated into material-specific representations stored in neocortical regions, whereas non-semantic materials (*e.g.* pseudowords and abstract designs) may struggle to become associated with cortical representations, and instead may rely on both hippocampi for processing. The findings reported in Chapter 4 showed material-specific impairments in children with TLE well-characterised with the semantic subtests of the Pair Games (Written Words and Objects), but not with the non-semantic subtests (Pseudowords and Designs). The ability to form representations of new material (*i.e*. non-semantic items) is a putative property of the hippocampus. With repeated exposures, these new representations gradually become integrated into the neocortical system through hippocampal-neocortical interactions (Davis et al., 2009). It is possible that, at least in children and adolescents, the hippocampal learning system has not yet acquired a clear asymmetry, and that representations

of new material (*e.g.* pseudowords and designs) have not yet become anchored as material-specific. The material-specific process of these representations may arise once they are integrated into the neocortical learning system through hippocampal-neocortical interactions.

The present findings therefore suggest lateralisation of the neocortical learning system and/or hippocampal-neocortical interactions for semantic items in children with TLE, but an absence of lateralisation of the hippocampal learning system for non-semantic items. This interpretation remains speculative at this stage and warrants further research.

2.9 Emerging Co-Lateralisation of Function with Age

Models of hemispheric specialisation posit that language and verbal memory functions are co-lateralised to the left hemisphere (*e.g.* Milner, 1971). However, the trajectory of the emergence of hemispheric specialisation for distinct cognitive functions is not well-established and it is possible that different functions may show lateralisation at different stages of development, thereby influencing the emergence of co-lateralisation of functions.

Whereas co-lateralisation of verbal memory and language is reported in adults (*e.g*. Pirmoradi et al., 2016; Sepeta et al. 2016), the same pattern was not found in patients or indeed in typically-developing children (Chapters 6 and 7). It is possible that co-lateralisation of language and memory gains strength across development. Whereas there is no evidence of developmental trajectory of hippocampal lateralisation in the present cohort, it is possible that the age range (8 to 18 years) does not cater to the slow process of hemispheric specialisation. Therefore the process may be slow for some functions but not for others. It may be that recollective processes that are dependent on the hippocampus are slow to develop, in contrast to speech and language. This has implications for the understanding of material-specific impairments in patients with brain damage acquired early in life. The little evidence of material-specific impairments in children with unilateral brain damage may be associated with the observation that MTL functions are not clearly lateralised in the immature brain. Further investigation into the development of co-lateralisation of functions would shed light on the underlying mechanisms of material-specificity of dysfunction.

2.10 Ipsilateral Functional Reorganisation

Consistent with the adult TLE literature, the present findings demonstrated an intrahemisphere posterior shift in hippocampal activation in children with left TLE (Chapter 7) compared to anterior hippocampal activation in typically-developing children (Chapter 6). This posterior hippocampal activation shift may be compensatory to protect against deficits in delayed recall. In the present cohort, the two patients with left TLE showed posterior hippocampal activation, whereas similar to the controls, the two patients with right TLE showed anterior hippocampal activation. The patient with bilateral TLE showed increased anterior hippocampal recruitment compared to controls and showed significant impairment in verbal delayed recall, to a greater extent than the other patients (Chapter 4). This observation may be attributable to bilateral pathology of the hippocampus severely affecting delayed recall, in conjunction with absence of functional reorganisation to support the function. This finding warrants further investigation, and larger patient cohorts are needed to further examine the compensatory value of posterior hippocampal activation to guard against impaired delayed recall at the pre-operative level.

Although the assessment in the present study was carried out at the pre-operative level only, this finding is in line with the functional adequacy model. This model posits that the capacity of the ipsilateral MTL regions to support memory predicts memory outcome following temporal lobectomy (Chelune, 1995). Adult TLE studies have supported this model (Baxendale et al., 2000; Bonelli et al., 2010; Helmstaedter et al., 2011b), and the present work suggests similar observations in the paediatric population. Post-operative evaluation is needed to adequately assess this hypothesis. If the finding is upheld, then there would be a strong argument for tailoring the temporal lobe resections to spare the posterior portion of the hippocampus.

This finding also indicates the importance of examining ipsilateral reorganisation alongside contralateral reorganisation to investigate the mechanisms that support memory in the injured brain and to address the question of memory outcome and the factors that influence it. For example, it is possible that a shift in activation to posterior portions of the hippocampus occurs as a consequence of disconnections from the anterior temporal lobe. Functional connectivity analysis

of fMRI data identifies brain regions that are temporally correlated and, as such, examines connectivity between regions within a functional network. Examining changes in ipsilateral functional connectivity might help us understand the mechanism underlying functional reorganisation of the memory network, and possibly shed light on the posterior shift in hippocampal activation in children with TLE.

2.11 Hippocampal Activation in fMRI Studies

Assessing fMRI of MTL functions has been more difficult than other cognitive functions. Whereas fMRI paradigms are very efficient at localising language and motor functions, localising memory function is more challenging. Several neuropsychological and technical factors contribute to this difficulty. The nature of the study material influences which cortical areas are recruited, however, the functional integrity of the MTL, and the hippocampus in particular, is crucial for episodic memory regardless of which type of material is being recalled. Based on the theoretical assumption, and evidence from patients with bilateral hippocampal damage of early onset (Patai et al., 2016) that the hippocampus supports recall processes and is involved in the relational binding of information, researchers who are particularly interested in assessing the functionality of the hippocampus should consider tasks involving recall and/or those that encourage binding (see Chapter 6, section 4.2, page 202). This can be achieved through the use of strategy at encoding, such as relational binding, which influences hippocampal activation (Becker et al., 2017; Heckers et al., 2002).

In the present study, the auditory verbal recall task was selected due to its applicability to ecological memory functioning, even though other tasks may have shown more robust hippocampal activation. Towgood et al. (2015) compared seven memory fMRI protocols in TLE, and demonstrated that the “hometown walking” paradigm, which requires imagining a familiar route, produced the best reliability of magnitude of activation.The selection of the task must be pertinent to the clinical aim of the study. If the aim is to assess the functionality of the hippocampus, then a task like the hometown walking paradigm may be pertinent. However, if the aim is to assess the ability of the hippocampus to support memory, then a verbal memory paradigm involving recall, as in the present study, is better suited.

Localisation of memory function is also made difficult due to technical factors, such as susceptibility artefacts. These artefacts are particularly prominent in the anterior temporal lobe, producing detrimental effects on MTL activation (see Chapter 1, section 4.5.2.2, page 24). The negative effects of these technical factors can be overcome (or at least accounted for) by adjusting the sequence parameters and optimising data collection (Chapter 5, section 2.6, page 153), such as applying a slice tilt which optimises the BOLD sensitivity in the MTL (Weiskopf et al., 2006). These technical considerations should be taken into account in combination with the task selection that is critical for MTL activation.

2.12 Inter-individual Variability in Memory LI: Implications for TLE

In Chapter 6, the results yielded large inter-individual variability in memory lateralisation in healthy children, particularly for activation reflecting successful memory (as shown in event-related analyses). This inter-individual variability might reflect that there is not a clear "typical" pattern of hippocampal memory activity to which a patient case might be compared to assess pathology. On the other hand, activation yielded from block-analyses showed less inter-individual variability and the majority of healthy controls were left lateralised. Such block-related activation in TLE may therefore be more suited for comparison to a "typical" network. Block analyses may be more informative for the comparison to controls, in order to capture the large reorganisation patterns in patients, whereas event-related analyses may be too "focal" to be able to compare to a control group. However, it is important to note that the questions that are pertinent to hemispheric specialisation (left *versus* right) and functional segregation of the hippocampus (anterior *versus* posterior), as well as the application of event-related analyses, are driven by intellectual ability levels. In cases of low intellectual ability, these questions and sophisticated analyses are not pertinent.

Alternatively, within-subject analyses of fMRI data, such as MVPA which examines the distributed pattern of activation across voxels, may provide important information regarding each patient's pattern of activation, without the necessity to compare to a "typical" network. This would provide more information

on each individual's memory representation, providing crucial clinical information before temporal lobe resection.

3 Limitations

3.1 Sample Selection

Children from the normative sample were recruited through East London schools and may therefore not be fully representative of the general population. However, measures of Socio-Economic Status (SES) were obtained and these showed that the current sample ranged across the whole spectrum of SES (from 1 to 10).

All six TLE patients included in the pilot cohort were under medication at the time of the study. In addition to the seizures, antiepileptic drugs (AEDs) interfere with normal brain development and alter cognitive profiles in a heterogeneous manner across individuals (Marsh et al., 2006). It is therefore difficult to rule out the effects of medication and other clinical factors on the behavioural and neuroimaging analyses conducted in the present work. It would be relevant to validate these novel protocols in adult patients who tend to demonstrate clearer cognitive profiles, and material-specific impairments. In addition, comparison between paediatric and adult patients would shed light on the impact of age at seizure onset on the behavioural profiles and neural networks associated with TLE.

Overall, the ultimate impetus of the present work is to improve diagnosis and prediction of outcome at the individual level. Presenting data from individual patients to show clinical validity is therefore critical at this stage. It would, however, also be informative to provide group-level findings in order to draw inferences and apply findings to other cases. Group analyses on larger cohorts with these protocols would shed light on the behavioural and neural mechanisms affected in TLE and in turn contribute to advances in epilepsy research.

3.2 Additional Neuropsychological Tests

Including additional neuropsychological tests would have been useful to test the influence of executive functions, such as attention, on performance on the Pair Games *versus* standardised tests. Additional cognitive tests would have been of interest, however, this would have considerably extended the length of testing which would have made it difficult to conduct the testing on school premises. The main focus of this thesis was on memory and priority was therefore given to the assessment of memory and intellectual functioning.

3.3 Technical Limitations in fMRI

Technical limitations often occurring in memory functional imaging studies include signal dropout of the MTL as a result of magnetic inhomogeneity. However, sequence parameters were adapted to improve signal in the MTL and data quality in those specific regions was tested (Chapter 5). In addition, overt speech is associated with motion artefact inside the scanner which may impede signal quality. Overt response in the present study has the strong advantage that in-scanner memory performance can be recorded for event-related analyses. Retrospective motion correction (*i.e*. FIACH) was applied to the data in order to remove such artefact, but it would be useful to consider methods of online motion correction and reduce speech-related artefacts for future studies involving overt responses. Moreover, low statistical thresholds were used for analyses due to the nature of individual-level analyses and the difficulty obtaining robust activation in the MTL. Whereas such low thresholds may be problematic for interpretation (*e.g*. false positives), this study remains exploratory and the preliminary findings may be promising indicators for future work.

4 Directions for Future Research

4.1 Memory Reorganisation as an Efficient Mechanism?

Correlation analyses between functional reorganisation (ipsilateral and contralateral) and memory scores would elucidate whether such reorganisation

reflects an efficient mechanism to preserve memory function in the context of brain pathology. Is the increased posterior hippocampal activation observed in paediatric TLE an efficient mechanism to help preserve memory? Several adult studies have reported such findings, supporting the functional adequacy model, whereby greater activation in ipsilateral MTL was correlated with better memory performance (Bigras et al., 2013; Bonelli et al., 2013; Limotai et al., 2018; Vannest et al., 2008). For example, greater left hippocampal activation was associated with better verbal memory in left TLE patients. Future research to examine the efficiency of such adaptive recruitments, particularly in the paediatric population, is necessary.

4.2 Long-Term Post-Operative Outcome

The ultimate goal of this research is to reduce the risks of cognitive decline after temporal lobe surgery in children with TLE. Two protocols were developed for this purpose, and further work is now required to test the predictive value of these protocols, by assessing long-term cognitive outcome in patients who have undergone surgery. This work is currently being undertaken by a PhD student, Dr Filipa Bastos. Filipa is increasing the sample size of epilepsy patients and is conducting a follow-up evaluation with both protocols in patients who have now undergone surgery. Post-operative assessment is carried out 4 months- and 12-months post-surgery in order to capture the trajectory of behavioural and neural changes. The ability of the Pair Games and the novel fMRI protocol to predict these changes will be investigated and compared to standardised measures.

When conducting these analyses on changes between pre- and post-operative performance, it is important to take into account any development that would have happened within that elapsed period of time. It is therefore crucial to have good measure of the patients' baseline performance prior to surgical intervention, because their post-operative profile will depend on their baseline performance prior to surgery.

4.3 Influence of Hippocampal Volume

Relating functional MRI and behavioural findings to hippocampal volume measurements would provide an indication of the structure-function relationship of hippocampal development and on the contribution of hippocampal volume to memory performance in both typically-developing children and paediatric TLE. For example, correlations between left/right hippocampal volume and verbal/non-verbal memory performances would shed light on the contribution of structural measures to performance. Such analyses would be pertinent in the TLE cohort in order to identify the influence of ipsilesional and contralesional hippocampal volume in the lateralisation of hippocampal activation. Additionally, it would be interesting to correlate the degree of hippocampal volume loss to the degree of memory impairment in these patients, as well as identifying the pattern of memory impairment (*e.g*. verbal *versus* non-verbal) based on the side of hippocampal volume loss.

5 Final Conclusions

As a result of the detrimental effects of temporal lobe seizures on the protracted development of the neural systems subserving learning and memory, children with TLE are particularly susceptible to learning and memory impairments. In paediatric TLE, the profile of cognitive dysfunction is not very clear due to several factors, one of which being early onset seizures interfering with the normal hemispheric specialisation process. Given the heterogeneity of profiles in paediatric TLE and the differences with adult TLE, diagnosis, surgical decision-making, and prediction of outcome cannot be extrapolated from adult studies and should instead rely on paediatric studies and the use of neuropsychological and fMRI tools developed for that purpose.

Two novel protocols were developed as part of this thesis: a behavioural protocol (the “Pair Games”) and a neuroimaging protocol. The Pair Games provides better informed neurocognitive diagnosis than standardised tests with better understanding of the nature of the memory deficit and the underlying processing impairment. Specific learning and memory deficits can be related to the neural systems subserving the functions, and in turn provide evidence of the underlying neuropathology which is critical for surgical decision-making. The advantages of

the Pair Games are 1) a balanced paradigm allowing comparison between verbal and non-verbal learning and memory, 2) assessment of learning, delayed recall and recognition within one protocol, 3) paired-associate learning paradigm to assess cognitive processes that are dependent on the hippocampal network, and 4) the use of a tablet-based application permitting controlled administration process and child-friendly approach to cognitive testing.

The combined language/memory fMRI also provides crucial information regarding the lateralisation and localisation of language and memory functions, as well as the interaction between them. The advantages of this fMRI protocol are 1) functional mapping of language and memory within one scanning, 2) assessment of both encoding- and retrieval-related neural networks, 3) the use of recall-based retrieval to increase hippocampal recruitment, and 4) overt responses allowing the investigation of neural networks that support successful memory specifically. Together, these protocols provide more precise information on the cognitive profile of surgical candidates and on the neural networks subserving functions at risk, and hence offer better guide for surgical decision-making.

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Appendix

Table A.1 Objects subtest version A

Pair 1	Pair 2	Pair 3	Pair 4	Pair 5
Pair 6	**Pair 7**	**Pair 8**	**Pair 9**	**Pair 10**

Table A.2 Objects subtest version B

Pair 1	Pair 2	Pair 3	Pair 4	Pair 5
Pair 6	**Pair 7**	**Pair 8**	**Pair 9**	**Pair 10**

Table A.3 Designs subtest version A

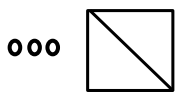
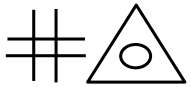
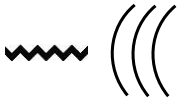
Pair 1	Pair 2	Pair 3	Pair 4	Pair 5
				
Pair 6	**Pair 7**	**Pair 8**	**Pair 9**	**Pair 10**
				

Table A.4 Designs subtest version B

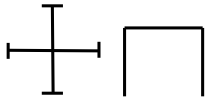
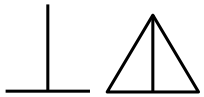
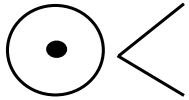
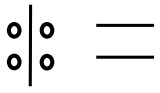
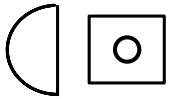
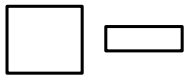
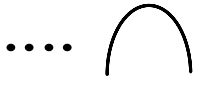
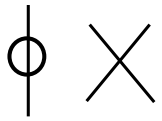
Pair 1	Pair 2	Pair 3	Pair 4	Pair 5
				
Pair 6	**Pair 7**	**Pair 8**	**Pair 9**	**Pair 10**
				

Table A.5 Pseudowords subtest version A

Pair 1	Pair 2	Pair 3	Pair 4	Pair 5
bame ree	wime lim	dif daf	figo dod	bollan bab
Pair 6	**Pair 7**	**Pair 8**	**Pair 9**	**Pair 10**
bumi mima	mulo soto	pag pam	peton lass	sarb sib

Table A.6 Pseudowords subtest version B

Pair 1	Pair 2	Pair 3	Pair 4	Pair 5
bepa chessa	wike nim	vot fot	nissa sus	fing bib
Pair 6	**Pair 7**	**Pair 8**	**Pair 9**	**Pair 10**
woot dep	cugo boko	tav vav	teson russ	corb roo

Table A.7 Written Words subtest version A

Pair 1	Pair 2	Pair 3	Pair 4	Pair 5
dress ocean	thumb squirrel	drink straw	driver bath	pet island
Pair 6	**Pair 7**	**Pair 8**	**Pair 9**	**Pair 10**
bridge orange	cake soap	music piano	home jaw	ship arm

Table A.8 Written Words subtest version A

Pair 1	Pair 2	Pair 3	Pair 4	Pair 5
hill bed	waist road	lemon fruit	soldier noodle	boat honey
Pair 6	**Pair 7**	**Pair 8**	**Pair 9**	**Pair 10**
frost picture	knee pot	coach van	dummy pocket	breakfast stone

Table A.9 Spoken Words subtest version A

Pair 1	Pair 2	Pair 3	Pair 4	Pair 5
bag pin	uncle square	knife fork	face jacket	pool wood
Pair 6	**Pair 7**	**Pair 8**	**Pair 9**	**Pair 10**
garbage market	teacher bubble	fox rabbit	girl barrel	turtle smoke

Table A.10 Spoken Words subtest version A

Pair 1	Pair 2	Pair 3	Pair 4	Pair 5
cousin egg	flame queen	koala mouse	towel school	valley pound
Pair 6	**Pair 7**	**Pair 8**	**Pair 9**	**Pair 10**
shirt water	forest plug	aunt woman	cream page	park head

Table A.11 Standard Scores and their Classifications

Standard score	Classification
130 or above	Exceptionally high
120 -129	High
110 – 119	High average
90 – 109	Average
80 – 89	Low average
71 – 79	Low
70 or below	Exceptionally low

Raw scores to standard scores Ages 8 through 9					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
1	58	67	61	62	81
2	59	68	61	63	82
3	60	69	62	64	82
4	61	69	63	65	83
5	61	70	63	66	84
6	62	71	64	67	84
7	63	72	65	68	85
8	64	72	66	70	86
9	64	73	66	71	87
10	65	74	67	72	87
11	66	74	68	73	88
12	67	75	68	74	89
13	68	76	69	75	89
14	68	76	70	76	90
15	69	77	71	77	91
16	70	78	71	78	91
17	71	78	72	79	92
18	72	79	73	81	93
19	72	80	74	82	94
20	73	80	74	83	94
21	74	81	75	84	95
22	75	82	76	85	96
23	75	82	76	86	96
24	76	83	77	87	97
25	77	84	78	88	98
26	78	84	79	89	99
27	79	85	79	90	99
28	79	86	80	92	100
29	80	86	81	93	101
30	81	87	81	94	101

Raw scores to standard scores Ages 8 through 9					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
31	82	88	82	95	102
32	83	88	83	96	103
33	83	89	84	97	103
34	84	90	84	98	104
35	85	91	85	99	105
36	86	91	86	100	106
37	86	92	86	101	106
38	87	93	87	103	107
39	88	93	88	104	108
40	89	94	89	105	108
41	90	95	89	106	109
42	90	95	90	107	110
43	91	96	91	108	111
44	92	97	91	109	111
45	93	97	92	110	112
46	94	98	93	111	113
47	94	99	94	112	113
48	95	99	94	114	114
49	96	100	95	115	115
50	97	101	96	116	115
51	98	101	97	117	116
52	98	102	97	118	117
53	99	103	98	119	118
54	100	103	99	120	118
55	101	104	99	121	119
56	101	105	100	122	120
57	102	105	101	123	120
58	103	106	102	125	121
59	104	107	102	126	122
60	105	108	103	127	123

Raw scores to standard scores Ages 8 through 9					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
61	105	108	104	128	123
62	106	109	104	129	124
63	107	110	105	130	125
64	108	110	106	131	125
65	109	111	107	132	126
66	109	112	107	133	127
67	110	112	108	134	127
68	111	113	109	136	128
69	112	114	109	137	129
70	112	114	110	138	130
71	113	115	111	139	130
72	114	116	112	140	131
73	115	116	112	141	132
74	116	117	113	142	132
75	116	118	114	143	133
76	117	118	115	144	134
77	118	119	115	145	135
78	119	120	116	147	135
79	120	120	117	148	136
80	120	121	117	149	137
82	122	122	119	151	138
83	123	123	120	152	139
84	123	124	120	153	139
85	124	124	121	154	140
86	125	125	122	155	141
87	126	126	122	156	142
88	127	127	123	158	142
89	127	127	124	159	143
90	128	128	125	160	144
91	129	129	125	161	144

Raw scores to standard scores Ages 8 through 9					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
92	130	129	126	162	145
93	131	130	127	163	146
94	131	131	127	164	147
95	132	131	128	165	147
96	133	132	129	166	148
97	134	133	130	167	149
98	134	133	130	169	149
99	135	134	131	170	150
100	136	135	132	171	151

Raw scores to standard scores Ages 8 through 9					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-30	36	53	60	51	59
-29	37	54	61	52	60
-28	38	55	61	53	61
-27	39	55	62	54	61
-26	39	56	63	55	62
-25	40	57	63	56	63
-24	41	57	64	57	64
-23	42	58	65	58	64
-22	43	59	65	59	65
-21	44	59	66	60	66
-20	45	60	67	61	67
-19	46	61	68	61	67
-18	47	61	68	62	68
-17	48	62	69	63	69
-16	49	63	70	64	69
-15	50	63	70	65	70
-14	51	64	71	66	71
-13	52	65	72	67	72
-12	53	65	73	68	72
-11	54	66	73	69	73
-10	54	67	74	70	74
-9	55	67	75	71	75
-8	56	68	75	72	75
-7	57	69	76	73	76
-6	58	70	77	74	77
-5	59	70	77	75	78
-4	60	71	78	76	78
-3	61	72	79	77	79
-2	62	72	80	78	80
-1	63	73	80	79	81

Raw scores to standard scores Ages 8 through 9					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
0	64	74	81	80	81
1	65	74	82	81	82
2	66	75	82	82	83
3	67	76	83	83	84
4	68	76	84	84	84
5	69	77	85	85	85
6	70	78	85	86	86
7	70	78	86	86	86
8	71	79	87	87	87
9	72	80	87	88	88
10	73	80	88	89	89
11	74	81	89	90	89
12	75	82	89	91	90
13	76	82	90	92	91
14	77	83	91	93	92
15	78	84	92	94	92
16	79	84	92	95	93
17	80	85	93	96	94
18	81	86	94	97	95
19	82	86	94	98	95
20	83	87	95	99	96
21	84	88	96	100	97
22	85	88	96	101	98
23	85	89	97	102	98
24	86	90	98	103	99
25	87	90	99	104	100
26	88	91	99	105	100
27	89	92	100	106	101
28	90	92	101	107	102
29	91	93	101	108	103

Raw scores to standard scores Ages 8 through 9					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
30	92	94	102	109	103
31	93	94	103	110	104
32	94	95	104	111	105
33	95	96	104	111	106
34	96	96	105	112	106
35	97	97	106	113	107
36	98	98	106	114	108
37	99	98	107	115	109
38	100	99	108	116	109
39	100	100	108	117	110
40	101	100	109	118	111
41	102	101	110	119	112
42	103	102	111	120	112
43	104	102	111	121	113
44	105	103	112	122	114
45	106	104	113	123	115
46	107	104	113	124	115
47	108	105	114	125	116
48	109	106	115	126	117
49	110	106	115	127	117
50	111	107	116	128	118
51	112	108	117	129	119
52	113	108	118	130	120
53	114	109	118	131	120
54	115	110	119	132	121
55	115	110	120	133	122
56	116	111	120	134	123
57	117	112	121	135	123
58	118	112	122	136	124
59	119	113	123	136	125

Raw scores to standard scores Ages 8 through 9					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
60	120	114	123	137	126
61	121	114	124	138	126
62	122	115	125	139	127
63	123	116	125	140	128
64	124	116	126	141	129
65	125	117	127	142	129
66	126	118	127	143	130
67	127	118	128	144	131
68	128	119	129	145	132
69	129	120	130	146	132
70	130	121	130	147	133
71	130	121	131	148	134
72	131	122	132	149	134
73	132	123	132	150	135
74	133	123	133	151	136
75	134	124	134	152	137

Raw scores to standard scores Ages 8 through 9					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-50	12	43	39	38	45
-49	14	45	40	40	46
-48	16	46	41	41	47
-47	18	47	43	42	49
-46	20	49	44	44	50
-45	22	50	45	45	51
-44	25	52	47	46	52
-43	27	53	48	48	54
-42	29	54	49	49	55
-41	31	56	51	50	56
-40	33	57	52	52	57
-39	35	59	53	53	58
-38	37	60	54	54	60
-37	39	62	56	56	61
-36	41	63	57	57	62
-35	43	64	58	58	63
-34	45	66	60	60	65
-33	47	67	61	61	66
-32	49	69	62	62	67
-31	51	70	64	64	68
-30	53	72	65	65	70
-29	55	73	66	66	71
-28	57	74	68	67	72
-27	59	76	69	69	73
-26	61	77	70	70	74
-25	63	79	72	71	76
-24	65	80	73	73	77
-23	67	82	74	74	78
-22	69	83	76	75	79
-21	71	84	77	77	81

Raw scores to standard scores Ages 8 through 9					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-20	73	86	78	78	82
-19	75	87	80	79	83
-18	77	89	81	81	84
-17	79	90	82	82	86
-16	81	91	84	83	87
-15	83	93	85	85	88
-14	85	94	86	86	89
-13	87	96	87	87	90
-12	89	97	89	89	92
-11	91	99	90	90	93
-10	93	100	91	91	94
-9	95	101	93	93	95
-8	97	103	94	94	97
-7	99	104	95	95	98
-6	101	106	97	96	99
-5	103	107	98	98	100
-4	105	109	99	99	102
-3	107	110	101	100	103
-2	109	111	102	102	104
-1	111	113	103	103	105
0	113	114	105	104	106
1	115	116	106	106	108
2	117	117	107	107	109
3	119	118	109	108	110
4	121	120	110	110	111
5	123	121	111	111	113
6	125	123	113	112	114
7	127	124	114	114	115
8	129	126	115	115	116
9	131	127	116	116	118

Raw scores to standard scores Ages 8 through 9					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
10	133	128	118	118	119
11	135	130	119	119	120
12	137	131	120	120	121
13	139	133	122	122	122
14	141	134	123	123	124
15	143	136	124	124	125
16	145	137	126	125	126
17	147	138	127	127	127
18	149	140	128	128	129
19	151	141	130	129	130

Raw scores to standard scores Ages 8 through 9					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-30	52	47	29	60	66
-29	53	48	30	60	67
-28	53	48	31	61	67
-27	54	49	31	61	68
-26	54	49	32	62	68
-25	55	50	32	62	68
-24	55	50	33	62	69
-23	55	51	34	63	69
-22	56	51	34	63	69
-21	56	52	35	64	70
-20	57	52	36	64	70
-19	57	53	36	65	70
-18	58	53	37	65	71
-17	58	54	38	65	71
-16	58	55	38	66	71
-15	59	55	39	66	72
-14	59	56	39	67	72
-13	60	56	40	67	72
-12	60	57	41	68	73
-11	61	57	41	68	73
-10	61	58	42	68	74
-9	62	58	43	69	74
-8	62	59	43	69	74
-7	62	59	44	70	75
-6	63	60	45	70	75
-5	63	60	45	71	75
-4	64	61	46	71	76
-3	64	61	46	71	76
-2	65	62	47	72	76
-1	65	62	48	72	77

Raw scores to standard scores Ages 8 through 9					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
0	66	63	48	73	77
1	66	63	49	73	77
2	66	64	50	74	78
3	67	64	50	74	78
4	67	65	51	75	78
5	68	65	52	75	79
6	68	66	52	75	79
7	69	66	53	76	79
8	69	67	53	76	80
9	70	67	54	77	80
10	70	68	55	77	81
11	70	68	55	78	81
12	71	69	56	78	81
13	71	69	57	78	82
14	72	70	57	79	82
15	72	70	58	79	82
16	73	71	59	80	83
17	73	71	59	80	83
18	74	72	60	81	83
19	74	72	60	81	84
20	74	73	61	81	84
21	75	73	62	82	84
22	75	74	62	82	85
23	76	75	63	83	85
24	76	75	64	83	85
25	77	76	64	84	86
26	77	76	65	84	86
27	77	77	66	84	87
28	78	77	66	85	87
29	78	78	67	85	87

Raw scores to standard scores Ages 8 through 9					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
30	79	78	67	86	88
31	79	79	68	86	88
32	80	79	69	87	88
33	80	80	69	87	89
34	81	80	70	87	89
35	81	81	71	88	89
36	81	81	71	88	90
37	82	82	72	89	90
38	82	82	73	89	90
39	83	83	73	90	91
40	83	83	74	90	91
41	84	84	74	90	91
42	84	84	75	91	92
43	85	85	76	91	92
44	85	85	76	92	93
45	85	86	77	92	93
46	86	86	78	93	93
47	86	87	78	93	94
48	87	87	79	93	94
49	87	88	80	94	94
50	88	88	80	94	95
51	88	89	81	95	95
52	89	89	81	95	95
53	89	90	82	96	96
54	89	90	83	96	96
55	90	91	83	96	96
56	90	91	84	97	97
57	91	92	85	97	97
58	91	92	85	98	97
59	92	93	86	98	98

Raw scores to standard scores Ages 8 through 9					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
60	92	94	87	99	98
61	93	94	87	99	98
62	93	95	88	100	99
63	93	95	88	100	99
64	94	96	89	100	100
65	94	96	90	101	100
66	95	97	90	101	100
67	95	97	91	102	101
68	96	98	92	102	101
69	96	98	92	103	101
70	97	99	93	103	102
71	97	99	94	103	102
72	97	100	94	104	102
73	98	100	95	104	103
74	98	101	96	105	103
75	99	101	96	105	103
76	99	102	97	106	104
77	100	102	97	106	104
78	100	103	98	106	104
79	100	103	99	107	105
80	101	104	99	107	105
81	101	104	100	108	106
82	102	105	101	108	106
83	102	105	101	109	106
84	103	106	102	109	107
85	103	106	103	109	107
86	104	107	103	110	107
87	104	107	104	110	108
88	104	108	104	111	108
89	105	108	105	111	108

Raw scores to standard scores Ages 10 through 11					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
1	65	69	67	72	72
2	66	70	67	73	73
3	66	70	68	74	74
4	67	71	69	75	75
5	68	72	69	75	76
6	68	72	70	76	77
7	69	73	70	77	77
8	70	73	71	78	78
9	70	74	72	79	79
10	71	75	72	80	80
11	72	75	73	81	81
12	72	76	74	82	82
13	73	76	74	82	83
14	73	77	75	83	84
15	74	78	76	84	85
16	75	78	76	85	85
17	75	79	77	86	86
18	76	80	78	87	87
19	77	80	78	88	88
20	77	81	79	88	89
21	78	81	79	89	90
22	79	82	80	90	91
23	79	83	81	91	92
24	80	83	81	92	93
25	81	84	82	93	93
26	81	84	83	94	94
27	82	85	83	95	95
28	83	86	84	95	96
29	83	86	85	96	97
30	84	87	85	97	98

Raw scores to standard scores Ages 10 through 11					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
31	84	87	86	98	99
32	85	88	87	99	100
33	86	89	87	100	101
34	86	89	88	101	101
35	87	90	88	101	102
36	88	91	89	102	103
37	88	91	90	103	104
38	89	92	90	104	105
39	90	92	91	105	106
40	90	93	92	106	107
41	91	94	92	107	108
42	92	94	93	107	109
43	92	95	94	108	109
44	93	95	94	109	110
45	93	96	95	110	111
46	94	97	96	111	112
47	95	97	96	112	113
48	95	98	97	113	114
49	96	98	97	114	115
50	97	99	98	114	116
51	97	100	99	115	117
52	98	100	99	116	117
53	99	101	100	117	118
54	99	102	101	118	119
55	100	102	101	119	120
56	101	103	102	120	121
57	101	103	103	120	122
58	102	104	103	121	123
59	102	105	104	122	124
60	103	105	105	123	125

Raw scores to standard scores Ages 10 through 11					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
61	104	106	105	124	125
62	104	106	106	125	126
63	105	107	106	126	127
64	106	108	107	127	128
65	106	108	108	127	129
66	107	109	108	128	130
67	108	109	109	129	131
68	108	110	110	130	132
69	109	111	110	131	133
70	110	111	111	132	133
71	110	112	112	133	134
72	111	113	112	133	135
73	111	113	113	134	136
74	112	114	114	135	137
75	113	114	114	136	138
76	113	115	115	137	139
77	114	116	115	138	140
78	115	116	116	139	141
79	115	117	117	140	141
80	116	117	117	140	142
81	117	118	118	141	143
82	117	119	119	142	144
83	118	119	119	143	145
84	119	120	120	144	146
85	119	120	121	145	147
86	120	121	121	146	148
87	120	122	122	146	149
88	121	122	123	147	149
89	122	123	123	148	150
90	122	124	124	149	151

Raw scores to standard scores Ages 10 through 11					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
91	123	124	124	150	152
92	124	125	125	151	153
93	124	125	126	152	154
94	125	126	126	152	155
95	126	127	127	153	156
96	126	127	128	154	157
97	127	128	128	155	157
98	128	128	129	156	158
99	128	129	130	157	159
100	129	130	130	158	160

Raw scores to standard scores Ages 10 through 11					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-30	56	56	62	38	62
-29	57	56	62	39	62
-28	57	57	63	40	63
-27	58	58	64	42	64
-26	59	58	64	43	64
-25	59	59	65	44	65
-24	60	60	66	45	65
-23	61	60	66	46	66
-22	62	61	67	48	67
-21	62	62	68	49	67
-20	63	62	69	50	68
-19	64	63	69	51	69
-18	64	64	70	52	69
-17	65	64	71	54	70
-16	66	65	71	55	71
-15	66	65	72	56	71
-14	67	66	73	57	72
-13	68	67	73	58	73
-12	69	67	74	60	73
-11	69	68	75	61	74
-10	70	69	75	62	75
-9	71	69	76	63	75
-8	71	70	77	64	76
-7	72	71	77	66	77
-6	73	71	78	67	77
-5	73	72	79	68	78
-4	74	73	79	69	79
-3	75	73	80	70	79
-2	76	74	81	72	80
-1	76	75	81	73	80

Raw scores to standard scores Ages 10 through 11					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
0	77	75	82	74	81
1	78	76	83	75	82
2	78	77	83	76	82
3	79	77	84	78	83
4	80	78	85	79	84
5	80	79	85	80	84
6	81	79	86	81	85
7	82	80	87	82	86
8	83	81	87	84	86
9	83	81	88	85	87
10	84	82	89	86	88
11	85	83	89	87	88
12	85	83	90	88	89
13	86	84	91	90	90
14	87	85	91	91	90
15	88	85	92	92	91
16	88	86	93	93	92
17	89	87	93	94	92
18	90	87	94	96	93
19	90	88	95	97	94
20	91	89	96	98	94
21	92	89	96	99	95
22	92	90	97	100	96
23	93	91	98	102	96
24	94	91	98	103	97
25	95	92	99	104	97
26	95	93	100	105	98
27	96	93	100	106	99
28	97	94	101	108	99
29	97	95	102	109	100

Raw scores to standard scores Ages 10 through 11					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
30	98	95	102	110	101
31	99	96	103	111	101
32	99	97	104	112	102
33	100	97	104	114	103
34	101	98	105	115	103
35	102	99	106	116	104
36	102	99	106	117	105
37	103	100	107	118	105
38	104	101	108	120	106
39	104	101	108	121	107
40	105	102	109	122	107
41	106	102	110	123	108
42	106	103	110	124	109
43	107	104	111	126	109
44	108	104	112	127	110
45	109	105	112	128	111
46	109	106	113	129	111
47	110	106	114	130	112
48	111	107	114	132	112
49	111	108	115	133	113
50	112	108	116	134	114
51	113	109	116	135	114
52	113	110	117	136	115
53	114	110	118	138	116
54	115	111	118	139	116
55	116	112	119	140	117
56	116	112	120	141	118
57	117	113	120	142	118
58	118	114	121	144	119
59	118	114	122	145	120

Raw scores to standard scores Ages 10 through 11					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
60	119	115	122	146	120
61	120	116	123	147	121
62	121	116	124	148	122
63	121	117	125	150	122
64	122	118	125	151	123
65	123	118	126	152	124
66	123	119	127	153	124
67	124	120	127	154	125
68	125	120	128	156	126
69	125	121	129	157	126
70	126	122	129	158	127
71	127	122	130	159	127
72	128	123	131	160	128
73	128	124	131	162	129
74	129	124	132	163	129
75	130	125	133	164	130
76	130	126	133	165	131
77	131	126	134	166	131
78	132	127	135	168	132
79	132	128	135	169	133
80	133	128	136	170	133
81	134	129	137	171	134
82	135	130	137	172	135
83	135	130	138	174	135

Raw scores to standard scores Ages 10 through 11					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-50	17	37	58	28	44
-49	18	38	59	30	45
-48	20	39	60	31	47
-47	22	41	61	33	48
-46	24	42	62	34	49
-45	26	44	63	36	51
-44	27	45	64	37	52
-43	29	47	65	39	54
-42	31	48	66	40	55
-41	33	50	67	41	57
-40	35	51	68	43	58
-39	36	52	69	44	60
-38	38	54	70	46	61
-37	40	55	71	47	63
-36	42	57	72	49	64
-35	43	58	73	50	66
-34	45	60	73	52	67
-33	47	61	74	53	69
-32	49	63	75	55	70
-31	51	64	76	56	72
-30	52	65	77	58	73
-29	54	67	78	59	75
-28	56	68	79	61	76
-27	58	70	80	62	78
-26	60	71	81	63	79
-25	61	73	82	65	81
-24	63	74	83	66	82
-23	65	76	84	68	84
-22	67	77	85	69	85
-21	68	78	86	71	87

Raw scores to standard scores Ages 10 through 11					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-20	70	80	87	72	88
-19	72	81	88	74	90
-18	74	83	89	75	91
-17	76	84	90	77	93
-16	77	86	91	78	94
-15	79	87	92	80	96
-14	81	89	92	81	97
-13	83	90	93	83	99
-12	85	91	94	84	100
-11	86	93	95	85	102
-10	88	94	96	87	103
-9	90	96	97	88	105
-8	92	97	98	90	106
-7	93	99	99	91	108
-6	95	100	100	93	109
-5	97	102	101	94	111
-4	99	103	102	96	112
-3	101	105	103	97	114
-2	102	106	104	99	115
-1	104	107	105	100	117
0	106	109	106	102	118
1	108	110	107	103	120
2	110	112	108	105	121
3	111	113	109	106	123
4	113	115	110	107	124
5	115	116	111	109	126
6	117	118	112	110	127
7	118	119	112	112	129
8	120	120	113	113	130
9	122	122	114	115	132

Raw scores to standard scores Ages 10 through 11					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
10	124	123	115	116	133
11	126	125	116	118	135
12	127	126	117	119	136
13	129	128	118	121	138
14	131	129	119	122	139
15	133	131	120	124	141
16	135	132	121	125	142
17	136	133	122	127	144
18	138	135	123	128	145
19	140	136	124	129	147
20	142	138	125	131	148
21	143	139	126	132	150
22	145	141	127	134	151
23	147	142	128	135	153
24	149	144	129	137	154
25	151	145	130	138	156

Raw scores to standard scores Ages 10 through 11					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-30	42	42	36	63	68
-29	42	43	37	63	69
-28	43	43	38	64	69
-27	43	44	38	64	69
-26	44	44	39	65	70
-25	44	45	39	65	70
-24	45	45	40	66	70
-23	45	46	40	66	71
-22	46	46	41	66	71
-21	46	47	42	67	71
-20	47	47	42	67	72
-19	47	48	43	68	72
-18	48	48	43	68	72
-17	48	49	44	69	73
-16	49	49	44	69	73
-15	49	50	45	69	73
-14	50	50	45	70	74
-13	51	51	46	70	74
-12	51	51	47	71	74
-11	52	52	47	71	75
-10	52	52	48	72	75
-9	53	53	48	72	75
-8	53	53	49	73	76
-7	54	54	49	73	76
-6	54	54	50	73	76
-5	55	55	51	74	77
-4	55	55	51	74	77
-3	56	56	52	75	77
-2	56	56	52	75	78
-1	57	57	53	76	78

Raw scores to standard scores Ages 10 through 11					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
0	57	57	53	76	78
1	58	58	54	76	79
2	58	59	55	77	79
3	59	59	55	77	79
4	60	60	56	78	80
5	60	60	56	78	80
6	61	61	57	79	80
7	61	61	57	79	81
8	62	62	58	79	81
9	62	62	59	80	81
10	63	63	59	80	82
11	63	63	60	81	82
12	64	64	60	81	82
13	64	64	61	82	83
14	65	65	61	82	83
15	65	65	62	82	83
16	66	66	62	83	84
17	66	66	63	83	84
18	67	67	64	84	84
19	67	67	64	84	85
20	68	68	65	85	85
21	69	68	65	85	85
22	69	69	66	85	86
23	70	69	66	86	86
24	70	70	67	86	86
25	71	70	68	87	87
26	71	71	68	87	87
27	72	71	69	88	87
28	72	72	69	88	88
29	73	72	70	89	88

Raw scores to standard scores Ages 10 through 11					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
30	73	73	70	89	88
31	74	73	71	89	89
32	74	74	72	90	89
33	75	75	72	90	89
34	75	75	73	91	90
35	76	76	73	91	90
36	76	76	74	92	90
37	77	77	74	92	91
38	77	77	75	92	91
39	78	78	76	93	91
40	79	78	76	93	92
41	79	79	77	94	92
42	80	79	77	94	92
43	80	80	78	95	93
44	81	80	78	95	93
45	81	81	79	95	93
46	82	81	79	96	94
47	82	82	80	96	94
48	83	82	81	97	94
49	83	83	81	97	95
50	84	83	82	98	95
51	84	84	82	98	95
52	85	84	83	98	96
53	85	85	83	99	96
54	86	85	84	99	96
55	86	86	85	100	97
56	87	86	85	100	97
57	88	87	86	101	97
58	88	87	86	101	98
59	89	88	87	101	98

Raw scores to standard scores Ages 10 through 11					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
60	89	88	87	102	98
61	90	89	88	102	98
62	90	89	89	103	99
63	91	90	89	103	99
64	91	91	90	104	99
65	92	91	90	104	100
66	92	92	91	105	100
67	93	92	91	105	100
68	93	93	92	105	101
69	94	93	93	106	101
70	94	94	93	106	101
71	95	94	94	107	102
72	95	95	94	107	102
73	96	95	95	108	102
74	97	96	95	108	103
75	97	96	96	108	103
76	98	97	96	109	103
77	98	97	97	109	104
78	99	98	98	110	104
79	99	98	98	110	104
80	100	99	99	111	105
81	100	99	99	111	105
82	101	100	100	111	105
83	101	100	100	112	106
84	102	101	101	112	106
85	102	101	102	113	106
86	103	102	102	113	107
87	103	102	103	114	107
88	104	103	103	114	107
89	104	103	104	114	108

Raw scores to standard scores Ages 10 through 11					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
90	105	104	104	115	108
91	106	104	105	115	108
92	106	105	106	116	109
93	107	105	106	116	109
94	107	106	107	117	109
95	108	107	107	117	110
96	108	107	108	117	110
97	109	108	108	118	110
98	109	108	109	118	111
99	110	109	110	119	111
100	110	109	110	119	111

Raw scores to standard scores Ages 12 through 13					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
1	55	60	59	61	72
2	56	61	60	61	73
3	56	61	61	62	74
4	57	62	61	63	75
5	58	63	62	64	76
6	59	63	63	65	76
7	60	64	63	66	77
8	60	64	64	67	78
9	61	65	65	68	79
10	62	65	65	69	80
11	63	66	66	70	80
12	63	67	67	71	81
13	64	67	67	72	82
14	65	68	68	73	83
15	66	68	69	74	84
16	67	69	69	75	84
17	67	70	70	76	85
18	68	70	71	77	86
19	69	71	71	78	87
20	70	71	72	78	88
21	71	72	72	79	88
22	71	73	73	80	89
23	72	73	74	81	90
24	73	74	74	82	91
25	74	74	75	83	92
26	75	75	76	84	92
27	75	76	76	85	93
28	76	76	77	86	94
29	77	77	78	87	95
30	78	77	78	88	96

Raw scores to standard scores Ages 12 through 13					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
31	79	78	79	89	97
32	79	79	80	90	97
33	80	79	80	91	98
34	81	80	81	92	99
35	82	80	82	93	100
36	83	81	82	94	101
37	83	82	83	95	101
38	84	82	83	95	102
39	85	83	84	96	103
40	86	83	85	97	104
41	87	84	85	98	105
42	87	84	86	99	105
43	88	85	87	100	106
44	89	86	87	101	107
45	90	86	88	102	108
46	90	87	89	103	109
47	91	87	89	104	109
48	92	88	90	105	110
49	93	89	91	106	111
50	94	89	91	107	112
51	94	90	92	108	113
52	95	90	93	109	113
53	96	91	93	110	114
54	97	92	94	111	115
55	98	92	95	112	116
56	98	93	95	112	117
57	99	93	96	113	118
58	100	94	96	114	118
59	101	95	97	115	119
60	102	95	98	116	120

Raw scores to standard scores Ages 12 through 13					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
61	102	96	98	117	121
62	103	96	99	118	122
63	104	97	100	119	122
64	105	98	100	120	123
65	106	98	101	121	124
66	106	99	102	122	125
67	107	99	102	123	126
68	108	100	103	124	126
69	109	101	104	125	127
70	110	101	104	126	128
71	110	102	105	127	129
72	111	102	106	128	130
73	112	103	106	129	130
74	113	103	107	130	131
75	114	104	107	130	132
76	114	105	108	131	133
77	115	105	109	132	134
78	116	106	109	133	135
79	117	106	110	134	135
80	117	107	111	135	136
81	118	108	111	136	137
82	119	108	112	137	138
83	120	109	113	138	139
84	121	109	113	139	139
85	121	110	114	140	140
86	122	111	115	141	141
87	123	111	115	142	142
88	124	112	116	143	143
89	125	112	117	144	143
90	125	113	117	145	144

Raw scores to standard scores Ages 12 through 13					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
91	126	114	118	146	145
92	127	114	119	147	146
93	128	115	119	147	147
94	129	115	120	148	147
95	129	116	120	149	148
96	130	117	121	150	149
97	131	117	122	151	150
98	132	118	122	152	151
99	133	118	123	153	151
100	133	119	124	154	152

Raw scores to standard scores Ages 12 through 13					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-30	42	66	47	57	56
-29	43	66	48	58	57
-28	44	67	49	59	58
-27	45	68	50	59	58
-26	46	68	50	60	59
-25	47	69	51	61	60
-24	48	69	52	62	61
-23	48	70	53	63	62
-22	49	70	53	64	62
-21	50	71	54	64	63
-20	51	71	55	65	64
-19	52	72	56	66	65
-18	53	72	57	67	65
-17	54	73	57	68	66
-16	54	74	58	68	67
-15	55	74	59	69	68
-14	56	75	60	70	69
-13	57	75	60	71	69
-12	58	76	61	72	70
-11	59	76	62	73	71
-10	60	77	63	73	72
-9	60	77	64	74	72
-8	61	78	64	75	73
-7	62	78	65	76	74
-6	63	79	66	77	75
-5	64	80	67	77	76
-4	65	80	68	78	76
-3	66	81	68	79	77
-2	66	81	69	80	78
-1	67	82	70	81	79

Raw scores to standard scores Ages 12 through 13					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
0	68	82	71	81	79
1	69	83	71	82	80
2	70	83	72	83	81
3	71	84	73	84	82
4	72	84	74	85	83
5	72	85	75	86	83
6	73	86	75	86	84
7	74	86	76	87	85
8	75	87	77	88	86
9	76	87	78	89	86
10	77	88	78	90	87
11	78	88	79	90	88
12	79	89	80	91	89
13	79	89	81	92	90
14	80	90	82	93	90
15	81	90	82	94	91
16	82	91	83	95	92
17	83	92	84	95	93
18	84	92	85	96	93
19	85	93	85	97	94
20	85	93	86	98	95
21	86	94	87	99	96
22	87	94	88	99	97
23	88	95	89	100	97
24	89	95	89	101	98
25	90	96	90	102	99
26	91	96	91	103	100
27	91	97	92	104	100
28	92	98	93	104	101
29	93	98	93	105	102

Raw scores to standard scores Ages 12 through 13					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
30	94	99	94	106	103
31	95	99	95	107	104
32	96	100	96	108	104
33	97	100	96	108	105
34	97	101	97	109	106
35	98	101	98	110	107
36	99	102	99	111	107
37	100	103	100	112	108
38	101	103	100	113	109
39	102	104	101	113	110
40	103	104	102	114	111
41	103	105	103	115	111
42	104	105	103	116	112
43	105	106	104	117	113
44	106	106	105	117	114
45	107	107	106	118	114
46	108	107	107	119	115
47	109	108	107	120	116
48	109	109	108	121	117
49	110	109	109	122	118
50	111	110	110	122	118
51	112	110	110	123	119
52	113	111	111	124	120
53	114	111	112	125	121
54	115	112	113	126	121
55	115	112	114	126	122
56	116	113	114	127	123
57	117	113	115	128	124
58	118	114	116	129	125
59	119	115	117	130	125

Raw scores to standard scores Ages 12 through 13					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
60	120	115	118	130	126
61	121	116	118	131	127
62	121	116	119	132	128
63	122	117	120	133	128
64	123	117	121	134	129
65	124	118	121	135	130
66	125	118	122	135	131
67	126	119	123	136	132
68	127	119	124	137	132
69	128	120	125	138	133
70	128	121	125	139	134
71	129	121	126	139	135
72	130	122	127	140	135
73	131	122	128	141	136
74	132	123	128	142	137
75	133	123	129	143	138
76	134	124	130	144	139
77	134	124	131	144	139
78	135	125	132	145	140
79	136	125	132	146	141

Raw scores to standard scores Ages 12 through 13					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
1	60	53	55	69	77
2	60	54	56	70	77
3	61	54	56	71	78
4	62	55	57	71	78
5	62	55	57	72	79
6	63	56	58	73	79
7	63	57	59	73	80
8	64	57	59	74	80
9	64	58	60	75	81
10	65	58	61	75	81
11	66	59	61	76	82
12	66	59	62	77	83
13	67	60	63	77	83
14	67	61	63	78	84
15	68	61	64	79	84
16	69	62	65	79	85
17	69	62	65	80	85
18	70	63	66	81	86
19	70	63	66	81	86
20	71	64	67	82	87
21	71	65	68	82	87
22	72	65	68	83	88
23	73	66	69	84	88
24	73	66	70	84	89
25	74	67	70	85	89
26	74	68	71	86	90
27	75	68	72	86	91
28	76	69	72	87	91
29	76	69	73	88	92
30	77	70	73	88	92

Raw scores to standard scores Ages 12 through 13					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
31	77	70	74	89	93
32	78	71	75	90	93
33	78	72	75	90	94
34	79	72	76	91	94
35	80	73	77	92	95
36	80	73	77	92	95
37	81	74	78	93	96
38	81	74	79	94	96
39	82	75	79	94	97
40	83	76	80	95	97
41	83	76	80	95	98
42	84	77	81	96	99
43	84	77	82	97	99
44	85	78	82	97	100
45	85	79	83	98	100
46	86	79	84	99	101
47	87	80	84	99	101
48	87	80	85	100	102
49	88	81	86	101	102
50	88	81	86	101	103
51	89	82	87	102	103
52	90	83	88	103	104
53	90	83	88	103	104
54	91	84	89	104	105
55	91	84	89	105	105
56	92	85	90	105	106
57	92	86	91	106	107
58	93	86	91	106	107
59	94	87	92	107	108
60	94	87	93	108	108

Raw scores to standard scores Ages 12 through 13					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
61	95	88	93	108	109
62	95	88	94	109	109
63	96	89	95	110	110
64	97	90	95	110	110
65	97	90	96	111	111
66	98	91	96	112	111
67	98	91	97	112	112
68	99	92	98	113	112
69	99	92	98	114	113
70	100	93	99	114	113
71	101	94	100	115	114
72	101	94	100	116	115
73	102	95	101	116	115
74	102	95	102	117	116
75	103	96	102	118	116
76	103	97	103	118	117
77	104	97	104	119	117
78	105	98	104	119	118
79	105	98	105	120	118
80	106	99	105	121	119
81	106	99	106	121	119
82	107	100	107	122	120
83	108	101	107	123	120
84	108	101	108	123	121
85	109	102	109	124	121
86	109	102	109	125	122
87	110	103	110	125	123
88	110	103	111	126	123
89	111	104	111	127	124
90	112	105	112	127	124

Raw scores to standard scores Ages 12 through 13					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
91	112	105	112	128	125
92	113	106	113	129	125
93	113	106	114	129	126
94	114	107	114	130	126
95	115	108	115	131	127
96	115	108	116	131	127
97	116	109	116	132	128
98	116	109	117	132	128
99	117	110	118	133	129
100	117	110	118	134	129

Raw scores to standard scores Ages 12 through 13					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-30	15	-11	13	35	48
-29	16	-10	14	36	49
-28	16	-10	14	36	49
-27	17	-9	15	37	50
-26	18	-8	16	37	50
-25	19	-7	17	38	51
-24	19	-6	17	39	51
-23	20	-5	18	39	52
-22	21	-4	19	40	52
-21	21	-3	20	40	53
-20	22	-2	20	41	53
-19	23	-1	21	42	54
-18	24	0	22	42	54
-17	24	1	22	43	55
-16	25	1	23	43	55
-15	26	2	24	44	55
-14	27	3	25	44	56
-13	27	4	25	45	56
-12	28	5	26	46	57
-11	29	6	27	46	57
-10	30	7	28	47	58
-9	30	8	28	47	58
-8	31	9	29	48	59
-7	32	10	30	49	59
-6	32	11	31	49	60
-5	33	12	31	50	60
-4	34	13	32	50	61
-3	35	13	33	51	61
-2	35	14	34	52	62
-1	36	15	34	52	62

Raw scores to standard scores Ages 12 through 13					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
0	37	16	35	53	63
1	38	17	36	53	63
2	38	18	36	54	64
3	39	19	37	55	64
4	40	20	38	55	65
5	41	21	39	56	65
6	41	22	39	56	66
7	42	23	40	57	66
8	43	24	41	58	67
9	44	24	42	58	67
10	44	25	42	59	68
11	45	26	43	59	68
12	46	27	44	60	69
13	46	28	45	61	69
14	47	29	45	61	70
15	48	30	46	62	70
16	49	31	47	62	71
17	49	32	48	63	71
18	50	33	48	64	72
19	51	34	49	64	72
20	52	35	50	65	73
21	52	35	50	65	73
22	53	36	51	66	74
23	54	37	52	67	74
24	55	38	53	67	74
25	55	39	53	68	75
26	56	40	54	68	75
27	57	41	55	69	76
28	57	42	56	70	76
29	58	43	56	70	77

Raw scores to standard scores Ages 12 through 13					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
30	59	44	57	71	77
31	60	45	58	71	78
32	60	46	59	72	78
33	61	46	59	73	79
34	62	47	60	73	79
35	63	48	61	74	80
36	63	49	61	74	80
37	64	50	62	75	81
38	65	51	63	76	81
39	66	52	64	76	82
40	66	53	64	77	82
41	67	54	65	77	83
42	68	55	66	78	83
43	68	56	67	79	84
44	69	57	67	79	84
45	70	57	68	80	85
46	71	58	69	80	85
47	71	59	70	81	86
48	72	60	70	82	86
49	73	61	71	82	87
50	74	62	72	83	87
51	74	63	73	83	88
52	75	64	73	84	88
53	76	65	74	85	89
54	77	66	75	85	89
55	77	67	75	86	90
56	78	68	76	86	90
57	79	68	77	87	91
58	79	69	78	88	91
59	80	70	78	88	92

Raw scores to standard scores Ages 12 through 13					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
60	81	71	79	89	92
61	82	72	80	89	92
62	82	73	81	90	93
63	83	74	81	91	93
64	84	75	82	91	94
65	85	76	83	92	94
66	85	77	84	92	95
67	86	78	84	93	95
68	87	79	85	94	96
69	88	80	86	94	96
70	88	80	87	95	97
71	89	81	87	95	97
72	90	82	88	96	98
73	90	83	89	97	98
74	91	84	89	97	99
75	92	85	90	98	99
76	93	86	91	98	100
77	93	87	92	99	100
78	94	88	92	100	101
79	95	89	93	100	101
80	96	90	94	101	102
81	96	91	95	101	102
82	97	91	95	102	103
83	98	92	96	103	103
84	99	93	97	103	104
85	99	94	98	104	104
86	100	95	98	104	105
87	101	96	99	105	105
88	101	97	100	106	106
89	102	98	101	106	106

Raw scores to standard scores Ages 12 through 13					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
90	103	99	101	107	107
91	104	100	102	107	107
92	104	101	103	108	108
93	105	102	103	109	108
94	106	102	104	109	109
95	107	103	105	110	109
96	107	104	106	110	110
97	108	105	106	111	110
98	109	106	107	112	110
99	110	107	108	112	111
100	110	108	109	113	111

Raw scores to standard scores Ages 14 through 15					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
1	63	61	67	65	75
2	64	61	67	66	76
3	64	62	68	66	77
4	65	63	68	67	77
5	66	63	69	68	78
6	66	64	70	68	78
7	67	64	70	69	79
8	68	65	71	70	80
9	68	66	71	70	80
10	69	66	72	71	81
11	70	67	72	72	81
12	70	67	73	72	82
13	71	68	74	73	83
14	72	68	74	74	83
15	72	69	75	75	84
16	73	70	75	75	84
17	74	70	76	76	85
18	74	71	76	77	86
19	75	71	77	77	86
20	76	72	78	78	87
21	76	73	78	79	87
22	77	73	79	79	88
23	78	74	79	80	89
24	78	74	80	81	89
25	79	75	80	81	90
26	80	75	81	82	90
27	80	76	82	83	91
28	81	77	82	83	92
29	82	77	83	84	92
30	82	78	83	85	93

Raw scores to standard scores Ages 14 through 15					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
31	83	78	84	85	93
32	84	79	85	86	94
33	84	80	85	87	95
34	85	80	86	87	95
35	86	81	86	88	96
36	86	81	87	89	96
37	87	82	87	89	97
38	88	82	88	90	98
39	88	83	89	91	98
40	89	84	89	91	99
41	90	84	90	92	99
42	91	85	90	93	100
43	91	85	91	93	101
44	92	86	91	94	101
45	93	86	92	95	102
46	93	87	93	96	102
47	94	88	93	96	103
48	95	88	94	97	104
49	95	89	94	98	104
50	96	89	95	98	105
51	97	90	96	99	105
52	97	91	96	100	106
53	98	91	97	100	107
54	99	92	97	101	107
55	99	92	98	102	108
56	100	93	98	102	108
57	101	93	99	103	109
58	101	94	100	104	109
59	102	95	100	104	110
60	103	95	101	105	111

Raw scores to standard scores Ages 14 through 15					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
61	103	96	101	106	111
62	104	96	102	106	112
63	105	97	102	107	112
64	105	98	103	108	113
65	106	98	104	108	114
66	107	99	104	109	114
67	107	99	105	110	115
68	108	100	105	110	115
69	109	100	106	111	116
70	109	101	106	112	117
71	110	102	107	112	117
72	111	102	108	113	118
73	111	103	108	114	118
74	112	103	109	114	119
75	113	104	109	115	120
76	113	105	110	116	120
77	114	105	111	117	121
78	115	106	111	117	121
79	115	106	112	118	122
80	116	107	112	119	123
81	117	107	113	119	123
82	117	108	113	120	124
83	118	109	114	121	124
84	119	109	115	121	125
85	119	110	115	122	126
86	120	110	116	123	126
87	121	111	116	123	127
88	121	111	117	124	127
89	122	112	117	125	128
90	123	113	118	125	129

Raw scores to standard scores Ages 14 through 15					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
91	123	113	119	126	129
92	124	114	119	127	130
93	125	114	120	127	130
94	125	115	120	128	131
95	126	116	121	129	132
96	127	116	122	129	132
97	127	117	122	130	133
98	128	117	123	131	133
99	129	118	123	131	134
100	129	118	124	132	135

Raw scores to standard scores Ages 14 through 15					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-30	47	62	47	55	51
-29	48	63	47	56	52
-28	49	63	48	57	53
-27	49	64	49	58	53
-26	50	64	50	59	54
-25	51	65	51	59	55
-24	52	65	52	60	56
-23	53	66	52	61	57
-22	53	67	53	62	57
-21	54	67	54	63	58
-20	55	68	55	64	59
-19	56	68	56	64	60
-18	57	69	57	65	60
-17	57	69	57	66	61
-16	58	70	58	67	62
-15	59	71	59	68	63
-14	60	71	60	69	64
-13	60	72	61	69	64
-12	61	72	62	70	65
-11	62	73	62	71	66
-10	63	73	63	72	67
-9	64	74	64	73	68
-8	64	74	65	74	68
-7	65	75	66	74	69
-6	66	76	67	75	70
-5	67	76	67	76	71
-4	68	77	68	77	72
-3	68	77	69	78	72
-2	69	78	70	79	73
-1	70	78	71	79	74

Raw scores to standard scores Ages 14 through 15					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
0	71	79	72	80	75
1	71	80	72	81	75
2	72	80	73	82	76
3	73	81	74	83	77
4	74	81	75	84	78
5	75	82	76	84	79
6	75	82	77	85	79
7	76	83	77	86	80
8	77	83	78	87	81
9	78	84	79	88	82
10	79	85	80	89	83
11	79	85	81	89	83
12	80	86	82	90	84
13	81	86	82	91	85
14	82	87	83	92	86
15	82	87	84	93	87
16	83	88	85	94	87
17	84	89	86	94	88
18	85	89	87	95	89
19	86	90	87	96	90
20	86	90	88	97	90
21	87	91	89	98	91
22	88	91	90	99	92
23	89	92	91	99	93
24	90	92	92	100	94
25	90	93	92	101	94
26	91	94	93	102	95
27	92	94	94	103	96
28	93	95	95	104	97
29	93	95	96	104	98

Raw scores to standard scores Ages 14 through 15					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
30	94	96	97	105	98
31	95	96	97	106	99
32	96	97	98	107	100
33	97	98	99	108	101
34	97	98	100	109	101
35	98	99	101	109	102
36	99	99	101	110	103
37	100	100	102	111	104
38	100	100	103	112	105
39	101	101	104	113	105
40	102	101	105	114	106
41	103	102	106	114	107
42	104	103	106	115	108
43	104	103	107	116	109
44	105	104	108	117	109
45	106	104	109	118	110
46	107	105	110	119	111
47	108	105	111	119	112
48	108	106	111	120	113
49	109	107	112	121	113
50	110	107	113	122	114
51	111	108	114	123	115
52	111	108	115	124	116
53	112	109	116	124	116
54	113	109	116	125	117
55	114	110	117	126	118
56	115	110	118	127	119
57	115	111	119	128	120
58	116	112	120	129	120
59	117	112	121	129	121

Raw scores to standard scores Ages 14 through 15					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
60	118	113	121	130	122
61	119	113	122	131	123
62	119	114	123	132	124
63	120	114	124	133	124
64	121	115	125	134	125
65	122	116	126	134	126
66	122	116	126	135	127
67	123	117	127	136	128
68	124	117	128	137	128
69	125	118	129	138	129
70	126	118	130	139	130

Raw scores to standard scores Ages 14 through 15					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-50	46	44	18	55	44
-49	47	45	20	56	46
-48	48	46	22	57	47
-47	49	47	23	58	48
-46	50	48	25	59	49
-45	51	50	27	60	50
-44	53	51	29	61	52
-43	54	52	31	62	53
-42	55	53	32	63	54
-41	56	55	34	64	55
-40	57	56	36	64	57
-39	59	57	38	65	58
-38	60	58	39	66	59
-37	61	60	41	67	60
-36	62	61	43	68	62
-35	63	62	45	69	63
-34	65	63	47	70	64
-33	66	64	48	71	65
-32	67	66	50	72	66
-31	68	67	52	73	68
-30	69	68	54	74	69
-29	71	69	56	75	70
-28	72	71	57	76	71
-27	73	72	59	77	73
-26	74	73	61	77	74
-25	75	74	63	78	75
-24	76	76	65	79	76
-23	78	77	66	80	78
-22	79	78	68	81	79
-21	80	79	70	82	80

Raw scores to standard scores Ages 14 through 15					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-20	81	81	72	83	81
-19	82	82	74	84	82
-18	84	83	75	85	84
-17	85	84	77	86	85
-16	86	85	79	87	86
-15	87	87	81	88	87
-14	88	88	82	89	89
-13	90	89	84	89	90
-12	91	90	86	90	91
-11	92	92	88	91	92
-10	93	93	90	92	94
-9	94	94	91	93	95
-8	95	95	93	94	96
-7	97	97	95	95	97
-6	98	98	97	96	98
-5	99	99	99	97	100
-4	100	100	100	98	101
-3	101	101	102	99	102
-2	103	103	104	100	103
-1	104	104	106	101	105
0	105	105	108	102	106
1	106	106	109	102	107
2	107	108	111	103	108
3	109	109	113	104	110
4	110	110	115	105	111
5	111	111	116	106	112
6	112	113	118	107	113
7	113	114	120	108	114
8	115	115	122	109	116
9	116	116	124	110	117

Raw scores to standard scores Ages 14 through 15					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
10	117	118	125	111	118
11	118	119	127	112	119
12	119	120	129	113	121
13	120	121	131	114	122
14	122	122	133	115	123
15	123	124	134	115	124
16	124	125	136	116	126
17	125	126	138	117	127
18	126	127	140	118	128
19	128	129	142	119	129

Raw scores to standard scores Ages 14 through 15					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-30	18	22	29	23	66
-29	19	23	29	24	67
-28	19	23	30	24	67
-27	20	24	30	25	67
-26	21	25	31	26	68
-25	21	25	32	26	68
-24	22	26	32	27	68
-23	23	27	33	28	69
-22	24	27	33	28	69
-21	24	28	34	29	69
-20	25	28	35	30	70
-19	26	29	35	30	70
-18	26	30	36	31	70
-17	27	30	36	32	71
-16	28	31	37	32	71
-15	28	32	38	33	71
-14	29	32	38	34	72
-13	30	33	39	34	72
-12	30	34	39	35	72
-11	31	34	40	36	73
-10	32	35	41	36	73
-9	32	36	41	37	73
-8	33	36	42	38	74
-7	34	37	42	38	74
-6	34	37	43	39	75
-5	35	38	44	40	75
-4	36	39	44	40	75
-3	36	39	45	41	76
-2	37	40	45	42	76
-1	38	41	46	42	76

Raw scores to standard scores Ages 14 through 15					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
0	39	41	47	43	77
1	39	42	47	44	77
2	40	43	48	44	77
3	41	43	48	45	78
4	41	44	49	46	78
5	42	44	50	46	78
6	43	45	50	47	79
7	43	46	51	48	79
8	44	46	51	48	79
9	45	47	52	49	80
10	45	48	53	50	80
11	46	48	53	50	80
12	47	49	54	51	81
13	47	50	54	52	81
14	48	50	55	52	81
15	49	51	56	53	82
16	49	52	56	54	82
17	50	52	57	54	82
18	51	53	57	55	83
19	52	53	58	56	83
20	52	54	59	56	83
21	53	55	59	57	84
22	54	55	60	58	84
23	54	56	60	58	84
24	55	57	61	59	85
25	56	57	62	60	85
26	56	58	62	60	85
27	57	59	63	61	86
28	58	59	63	62	86
29	58	60	64	62	86

Raw scores to standard scores Ages 14 through 15					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
30	59	61	65	63	87
31	60	61	65	64	87
32	60	62	66	64	87
33	61	62	66	65	88
34	62	63	67	66	88
35	62	64	68	66	88
36	63	64	68	67	89
37	64	65	69	68	89
38	64	66	69	68	89
39	65	66	70	69	90
40	66	67	71	70	90
41	67	68	71	70	90
42	67	68	72	71	91
43	68	69	72	72	91
44	69	69	73	72	91
45	69	70	74	73	92
46	70	71	74	74	92
47	71	71	75	74	92
48	71	72	75	75	93
49	72	73	76	76	93
50	73	73	77	76	93
51	73	74	77	77	94
52	74	75	78	78	94
53	75	75	78	78	94
54	75	76	79	79	95
55	76	77	80	80	95
56	77	77	80	80	95
57	77	78	81	81	96
58	78	78	81	82	96
59	79	79	82	82	96

Raw scores to standard scores Ages 14 through 15					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
60	80	80	83	83	97
61	80	80	83	84	97
62	81	81	84	84	97
63	82	82	84	85	98
64	82	82	85	86	98
65	83	83	86	86	98
66	84	84	86	87	99
67	84	84	87	88	99
68	85	85	87	88	100
69	86	86	88	89	100
70	86	86	89	90	100
71	87	87	89	90	101
72	88	87	90	91	101
73	88	88	90	92	101
74	89	89	91	92	102
75	90	89	92	93	102
76	90	90	92	94	102
77	91	91	93	94	103
78	92	91	93	95	103
79	92	92	94	96	103
80	93	93	95	96	104
81	94	93	95	97	104
82	95	94	96	98	104
83	95	94	96	98	105
84	96	95	97	99	105
85	97	96	98	100	105
86	97	96	98	100	106
87	98	97	99	101	106
88	99	98	99	102	106
89	99	98	100	102	107

Raw scores to standard scores Ages 14 through 15					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
90	100	99	101	103	107
91	101	100	101	104	107
92	101	100	102	104	108
93	102	101	102	105	108
94	103	102	103	106	108
95	103	102	104	106	109
96	104	103	104	107	109
97	105	103	105	108	109
98	105	104	105	108	110
99	106	105	106	109	110
100	107	105	107	110	110

Raw scores to standard scores Ages 16 through 18					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
1	50	45	7	49	62
2	51	46	8	50	63
3	52	46	10	51	64
4	52	47	11	52	64
5	53	48	12	53	65
6	54	49	13	54	66
7	55	49	14	54	67
8	55	50	16	55	67
9	56	51	17	56	68
10	57	52	18	57	69
11	57	52	19	58	70
12	58	53	20	59	70
13	59	54	21	60	71
14	60	55	23	61	72
15	60	55	24	61	72
16	61	56	25	62	73
17	62	57	26	63	74
18	63	57	27	64	75
19	63	58	29	65	75
20	64	59	30	66	76
21	65	60	31	67	77
22	65	60	32	68	78
23	66	61	33	69	78
24	67	62	34	69	79
25	68	63	36	70	80
26	68	63	37	71	81
27	69	64	38	72	81
28	70	65	39	73	82
29	70	66	40	74	83
30	71	66	42	75	83

Raw scores to standard scores Ages 16 through 18					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
31	72	67	43	76	84
32	73	68	44	77	85
33	73	69	45	77	86
34	74	69	46	78	86
35	75	70	47	79	87
36	75	71	49	80	88
37	76	71	50	81	89
38	77	72	51	82	89
39	78	73	52	83	90
40	78	74	53	84	91
41	79	74	54	84	91
42	80	75	56	85	92
43	81	76	57	86	93
44	81	77	58	87	94
45	82	77	59	88	94
46	83	78	60	89	95
47	83	79	62	90	96
48	84	80	63	91	97
49	85	80	64	92	97
50	86	81	65	92	98
51	86	82	66	93	99
52	87	83	67	94	100
53	88	83	69	95	100
54	88	84	70	96	101
55	89	85	71	97	102
56	90	85	72	98	102
57	91	86	73	99	103
58	91	87	75	100	104
59	92	88	76	100	105
60	93	88	77	101	105

Raw scores to standard scores Ages 16 through 18					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
61	93	89	78	102	106
62	94	90	79	103	107
63	95	91	80	104	108
64	96	91	82	105	108
65	96	92	83	106	109
66	97	93	84	107	110
67	98	94	85	107	111
68	99	94	86	108	111
69	99	95	87	109	112
70	100	96	89	110	113
71	101	97	90	111	113
72	101	97	91	112	114
73	102	98	92	113	115
74	103	99	93	114	116
75	104	100	95	115	116
76	104	100	96	115	117
77	105	101	97	116	118
78	106	102	98	117	119
79	106	102	99	118	119
80	107	103	100	119	120
81	108	104	102	120	121
82	109	105	103	121	121
83	109	105	104	122	122
84	110	106	105	123	123
85	111	107	106	123	124
86	111	108	108	124	124
87	112	108	109	125	125
88	113	109	110	126	126
89	114	110	111	127	127
90	114	111	112	128	127

Raw scores to standard scores Ages 16 through 18					
Learning Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
91	115	111	113	129	128
92	116	112	115	130	129
93	116	113	116	130	130
94	117	114	117	131	130
95	118	114	118	132	131
96	119	115	119	133	132
97	119	116	121	134	132
98	120	116	122	135	133
99	121	117	123	136	134
100	122	118	124	137	135

Raw scores to standard scores Ages 16 through 18					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-30	39	53	42	46	50
-29	40	54	43	47	51
-28	41	55	44	48	52
-27	42	56	45	49	52
-26	43	56	46	49	53
-25	44	57	47	50	54
-24	45	58	48	51	55
-23	46	59	48	52	55
-22	47	59	49	53	56
-21	47	60	50	54	57
-20	48	61	51	54	57
-19	49	61	52	55	58
-18	50	62	53	56	59
-17	51	63	54	57	60
-16	52	64	55	58	60
-15	53	64	56	59	61
-14	54	65	57	60	62
-13	55	66	57	60	62
-12	55	67	58	61	63
-11	56	67	59	62	64
-10	57	68	60	63	64
-9	58	69	61	64	65
-8	59	69	62	65	66
-7	60	70	63	66	67
-6	61	71	64	66	67
-5	62	72	65	67	68
-4	63	72	66	68	69
-3	64	73	67	69	69
-2	64	74	67	70	70
-1	65	75	68	71	71

Raw scores to standard scores Ages 16 through 18					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
0	66	75	69	72	72
1	67	76	70	72	72
2	68	77	71	73	73
3	69	77	72	74	74
4	70	78	73	75	74
5	71	79	74	76	75
6	72	80	75	77	76
7	73	80	76	78	76
8	73	81	77	78	77
9	74	82	77	79	78
10	75	83	78	80	79
11	76	83	79	81	79
12	77	84	80	82	80
13	78	85	81	83	81
14	79	85	82	84	81
15	80	86	83	84	82
16	81	87	84	85	83
17	81	88	85	86	84
18	82	88	86	87	84
19	83	89	87	88	85
20	84	90	87	89	86
21	85	91	88	90	86
22	86	91	89	90	87
23	87	92	90	91	88
24	88	93	91	92	89
25	89	93	92	93	89
26	90	94	93	94	90
27	90	95	94	95	91
28	91	96	95	96	91
29	92	96	96	96	92

Raw scores to standard scores Ages 16 through 18					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
30	93	97	97	97	93
31	94	98	97	98	93
32	95	99	98	99	94
33	96	99	99	100	95
34	97	100	100	101	96
35	98	101	101	101	96
36	98	101	102	102	97
37	99	102	103	103	98
38	100	103	104	104	98
39	101	104	105	105	99
40	102	104	106	106	100
41	103	105	107	107	101
42	104	106	107	107	101
43	105	107	108	108	102
44	106	107	109	109	103
45	107	108	110	110	103
46	107	109	111	111	104
47	108	109	112	112	105
48	109	110	113	113	105
49	110	111	114	113	106
50	111	112	115	114	107
51	112	112	116	115	108
52	113	113	117	116	108
53	114	114	117	117	109
54	115	115	118	118	110
55	116	115	119	119	110
56	116	116	120	119	111
57	117	117	121	120	112
58	118	118	122	121	113
59	119	118	123	122	113

Raw scores to standard scores Ages 16 through 18					
Learning gain Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
60	120	119	124	123	114
61	121	120	125	124	115
62	122	120	126	125	115
63	123	121	127	125	116
64	124	122	127	126	117
65	124	123	128	127	117
66	125	123	129	128	118
67	126	124	130	129	119
68	127	125	131	130	120
69	128	126	132	131	120
70	129	126	133	131	121

Raw scores to standard scores Ages 16 through 18					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-50	-9	7	-4	40	44
-49	-7	9	-2	41	46
-48	-4	11	0	43	47
-47	-2	13	2	44	48
-46	0	15	4	45	50
-45	3	17	7	46	51
-44	5	19	9	48	52
-43	7	21	11	49	54
-42	9	23	13	50	55
-41	12	25	15	51	56
-40	14	27	17	52	58
-39	16	29	19	54	59
-38	18	31	22	55	60
-37	21	33	24	56	61
-36	23	35	26	57	63
-35	25	37	28	58	64
-34	27	39	30	60	65
-33	30	41	32	61	67
-32	32	43	35	62	68
-31	34	44	37	63	69
-30	36	46	39	65	71
-29	39	48	41	66	72
-28	41	50	43	67	73
-27	43	52	45	68	75
-26	45	54	48	69	76
-25	48	56	50	71	77
-24	50	58	52	72	79
-23	52	60	54	73	80
-22	54	62	56	74	81
-21	57	64	58	76	82

Raw scores to standard scores Ages 16 through 18					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-20	59	66	60	77	84
-19	61	68	63	78	85
-18	64	70	65	79	86
-17	66	72	67	80	88
-16	68	74	69	82	89
-15	70	76	71	83	90
-14	73	78	73	84	92
-13	75	80	76	85	93
-12	77	82	78	87	94
-11	79	84	80	88	96
-10	82	86	82	89	97
-9	84	88	84	90	98
-8	86	89	86	91	100
-7	88	91	88	93	101
-6	91	93	91	94	102
-5	93	95	93	95	103
-4	95	97	95	96	105
-3	97	99	97	97	106
-2	100	101	99	99	107
-1	102	103	101	100	109
0	104	105	104	101	110
1	106	107	106	102	111
2	109	109	108	104	113
3	111	111	110	105	114
4	113	113	112	106	115
5	116	115	114	107	117
6	118	117	117	108	118
7	120	119	119	110	119
8	122	121	121	111	120
9	125	123	123	112	122

Raw scores to standard scores Ages 16 through 18					
Delayed recall Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
10	127	125	125	113	123
11	129	127	127	115	124
12	131	129	129	116	126
13	134	131	132	117	127
14	136	133	134	118	128
15	138	134	136	119	130
16	140	136	138	121	131
17	143	138	140	122	132
18	145	140	142	123	134
19	147	142	145	124	135

Raw scores to standard scores Ages 16 through 18					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
-30	12	20	-53	37	-4
-29	13	21	-52	37	-3
-28	13	22	-51	38	-2
-27	14	22	-50	38	-2
-26	15	23	-48	39	-1
-25	15	24	-47	39	0
-24	16	24	-46	40	1
-23	17	25	-45	40	2
-22	18	26	-44	41	3
-21	18	26	-42	42	4
-20	19	27	-41	42	5
-19	20	27	-40	43	5
-18	21	28	-39	43	6
-17	21	29	-38	44	7
-16	22	29	-36	44	8
-15	23	30	-35	45	9
-14	23	31	-34	45	10
-13	24	31	-33	46	11
-12	25	32	-32	46	12
-11	26	33	-30	47	12
-10	26	33	-29	48	13
-9	27	34	-28	48	14
-8	28	35	-27	49	15
-7	28	35	-26	49	16
-6	29	36	-24	50	17
-5	30	37	-23	50	18
-4	31	37	-22	51	19
-3	31	38	-21	51	20
-2	32	38	-20	52	20
-1	33	39	-18	53	21

Raw scores to standard scores Ages 16 through 18					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
0	34	40	-17	53	22
1	34	40	-16	54	23
2	35	41	-15	54	24
3	36	42	-14	55	25
4	36	42	-12	55	26
5	37	43	-11	56	27
6	38	44	-10	56	27
7	39	44	-9	57	28
8	39	45	-8	57	29
9	40	46	-6	58	30
10	41	46	-5	59	31
11	42	47	-4	59	32
12	42	47	-3	60	33
13	43	48	-2	60	34
14	44	49	0	61	35
15	44	49	1	61	35
16	45	50	2	62	36
17	46	51	3	62	37
18	47	51	4	63	38
19	47	52	6	64	39
20	48	53	7	64	40
21	49	53	8	65	41
22	49	54	9	65	42
23	50	55	10	66	42
24	51	55	12	66	43
25	52	56	13	67	44
26	52	57	14	67	45
27	53	57	15	68	46
28	54	58	16	68	47
29	55	58	18	69	48

Raw scores to standard scores Ages 16 through 18					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
30	55	59	19	70	49
31	56	60	20	70	49
32	57	60	21	71	50
33	57	61	22	71	51
34	58	62	24	72	52
35	59	62	25	72	53
36	60	63	26	73	54
37	60	64	27	73	55
38	61	64	28	74	56
39	62	65	30	75	57
40	62	66	31	75	57
41	63	66	32	76	58
42	64	67	33	76	59
43	65	68	34	77	60
44	65	68	36	77	61
45	66	69	37	78	62
46	67	69	38	78	63
47	68	70	39	79	64
48	68	71	40	80	64
49	69	71	42	80	65
50	70	72	43	81	66
51	70	73	44	81	67
52	71	73	45	82	68
53	72	74	46	82	69
54	73	75	48	83	70
55	73	75	49	83	71
56	74	76	50	84	71
57	75	77	51	84	72
58	75	77	52	85	73
59	76	78	54	86	74

Raw scores to standard scores Ages 16 through 18					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
60	77	78	55	86	75
61	78	79	56	87	76
62	78	80	57	87	77
63	79	80	58	88	78
64	80	81	60	88	79
65	81	82	61	89	79
66	81	82	62	89	80
67	82	83	63	90	81
68	83	84	64	91	82
69	83	84	66	91	83
70	84	85	67	92	84
71	85	86	68	92	85
72	86	86	69	93	86
73	86	87	70	93	86
74	87	88	72	94	87
75	88	88	73	94	88
76	89	89	74	95	89
77	89	89	75	95	90
78	90	90	76	96	91
79	91	91	78	97	92
80	91	91	79	97	93
81	92	92	80	98	94
82	93	93	81	98	94
83	94	93	82	99	95
84	94	94	84	99	96
85	95	95	85	100	97
86	96	95	86	100	98
87	96	96	87	101	99
88	97	97	88	102	100
89	98	97	90	102	101

Raw scores to standard scores Ages 16 through 18					
Recognition Raw	Spoken Words	Written Words	Objects	Designs	Pseudo-words
90	99	98	91	103	101
91	99	98	92	103	102
92	100	99	93	104	103
93	101	100	94	104	104
94	102	100	96	105	105
95	102	101	97	105	106
96	103	102	98	106	107
97	104	102	99	106	108
98	104	103	100	107	108
99	105	104	102	108	109
100	106	104	103	108	110

Table D.1 Ability-Memory Discrepancies: Differences between IQ and Index Scores Required For Statistical Significance at *p*=0.05

	VIQ	PIQ
General Memory	26.38	28.91
Learning	22.87	22.83
Learning gain	21.12	23.56
Delayed recall	24.68	26.88
Recognition	26.44	28.36
Verbal Learning	25.80	26.64
Non-verbal Learning	26.23	24.90
Verbal Learning Gain	24.22	26.59
Non-verbal Learning Gain	25.69	27.26
Verbal Delayed recall	29.48	31.10
Non-verbal Delayed recall	28.25	31.24
Verbal Recognition	28.59	28.92
Non-verbal Recognition	30.41	31.57

Table D2 Ability-Memory Discrepancies: frequency of statistical differences in the standardisation sample (%)

	VIQ	PIQ
General Memory	9.23	6.92
Learning	12.31	6.15
Learning gain	9.23	6.15
Delayed recall	8.46	3.08
Recognition	4.62	3.08
Verbal Learning	8.46	8.46
Non-verbal Learning	8.46	7.69
Verbal Learning Gain	12.31	4.62
Non-verbal Learning Gain	8.46	6.92
Verbal Delayed recall	9.23	2.31
Non-verbal Delayed recall	8.46	5.38
Verbal Recognition	5.38	3.85
Non-verbal Recognition	6.15	3.08

Table D3 Memory Process Discrepancies: Differences between Index Scores of Different Memory Domains Required For Statistical Significance at *p*=0.05

	Verbal items	Non-verbal items
Learning *vs* Delayed recall	32.02	32.49
Delayed recall *vs* Recognition	29.35	32.37

Table D4 Memory Process Discrepancies: frequency of statistical differences in the standardisation sample (%)

	Verbal items	Non-verbal items
Learning *vs* Delayed recall	5.38	6.92
Delayed recall *vs* Recognition	5.38	4.62

Table D5 Material Discrepancies: Differences Between Verbal and Non-verbal Index Scores Required For Statistical Significance at *p*=0.05

	All items	Semantic items only	Non-semantic items only
Learning	19.62	27.74	27.65
Learning gain	25.37	37.61	36.38
Delayed recall	25.06	36.56	36.43
Recognition	16.18	17.86	31.95

Table D6 Material Discrepancies: frequency of statistical differences in the standardisation sample (%)

	All items	Semantic items only	Non-semantic items only
Learning	9.23	8.46	6.15
Learning gain	5.38	6.92	5.38
Delayed recall	6.15	6.92	4.62
Recognition	13.08	14.62	10.00

Table D7 Semantic Discrepancies: Differences Between Semantic and Non-Semantic Index Scores Required For Statistical Difference at *p*=0.05

	All items	Verbal items only	Non-verbal items only
Learning	17.54	24.96	26.88
Learning gain	27.55	35.20	41.33
Delayed recall	29.51	37.79	41.51
Recognition	16.60	31.27	25.30

Table D8 Semantic Discrepancies: frequency of statistical differences in the standardisation sample (%)

	All items	Verbal items only	Non-verbal items only
Learning	10.77	9.23	5.38
Learning gain	3.85	3.85	3.08
Delayed recall	6.15	4.62	4.62
Recognition	13.85	6.15	11.54

Table D9 Modality Discrepancies: Differences Between Auditory and Non-verbal Scores Required For Statistical Significance at *p*=0.05

Learning	26.11
Learning gain	35.47
Delayed recall	42.14
Recognition	24.97

Table D10 Modality Discrepancies: frequency of statistical differences in the standardisation sample (%)

Learning	7.69
Learning gain	6.15
Delayed recall	6.15
Recognition	14.62

Table E1 Summary of case 1 performance on the WMS-IV

Case 1		Immediate recall	Delayed recall
Scaled scores	Logical Memory	5	7
	Word Pairs	11	11
	Designs	7	6
	Visual Reproduction	12	8
Standard scores	Verbal material		91
	Non-verbal material		89
	Overall	91	86

Table E2 Summary of case 1 performance on the Pair Games (Standard scores)

Case 1		Learning	Learning gain	Delayed recall	Delayed recognition
Separate tasks	Spoken words	98	111	82	106
	Written words	86	97	86	91
	Pseudowords	86	93	97	110
	Objects	73	106	60	103
	Designs	101	80	101	108
	Overall	89	97	85	104
Material	Verbal	86	95	91	101
	Non-verbal	87	93	81	105
Concept	Semantic	80	101	73	97
	Non-semantic	94	86	99	109
Modality of presentation	Auditory	98	111	82	106
	Visual	86	97	86	91

Table E3 Summary of case 2 performance on the CMS

Case 2		Immediate recall	Learning	Delayed recall	Delayed recognition
Scaled scores	Word Pairs	5	5	7	11
	Stories	8		8	8
	Dots	5	5	7	
	Faces	9		9	
Standard scores	Verbal material	78		85	97
	Non-verbal material	82		88	
	Overall		69		

Table E4 Summary of case 2 performance on the Pair Games (Standard scores)

Case 2		Learning	Learning gain	Delayed recall	Delayed recognition
Separate tasks	Spoken words	76	93	59	91
	Written words	80	119	105	104
	Pseudowords	79	93	71	93
	Objects	42	97	104	79
	Designs	78	72	101	86
	Overall	71	95	88	91
Material	Verbal	80	106	88	98
	Non-verbal	60	84	102	85
Concept	Semantic	61	108	104	92
	Non-semantic	78	82	86	89
Modality of presentation	Auditory	76	93	59	91
	Visual	80	119	105	104

Table E5 Summary of case 3 performance on the CMS

Case 3		Immediate recall	Learning	Delayed recall	Delayed recognition
Scaled scores	Word Pairs	7	7	9	11
	Stories	6		5	6
	Dots	8	8	7	
	Faces	14		9	
Standard scores	Verbal material	78		82	91
	Non-verbal material	106		88	
	Overall		85		

Table E6 Summary of case 3 performance on the Pair Games (Standard scores)

Case 3		Learning	Learning gain	Delayed recall	Delayed recognition
Separate tasks	Spoken words	76	102	149	106
	Written words	98	104	46	104
	Pseudowords	103	100	84	110
	Objects	89	124	82	103
	Designs	95	80	89	97
	Overall	92	102	90	104
Material	Verbal	101	102	65	107
	Non-verbal	92	102	85	100
Concept	Semantic	93	114	64	104
	Non-semantic	99	90	86	104
Modality of presentation	Auditory	76	102	149	106
	Visual	98	104	46	104

Table E7 Summary of case 4 performance on the CMS

Case 4		Immediate recall	Learning	Delayed recall	Delayed recognition
Scaled scores	Word Pairs	4	4	8	10
	Stories	8		8	7
	Dots	5	5	5	
	Faces	10		9	
Standard scores	Verbal material	75		88	91
	Non-verbal material	85		82	
	Overall		66		

Table E8 Summary of case 4 performance on the Pair Games (Standard scores)

Case 4		Learning	Learning gain	Delayed recall	Delayed recognition
Separate tasks	Spoken words	96	128	42	22
	Written words	89	110	80	35
	Pseudowords	98	103	88	82
	Objects	98	110	95	109
	Designs	88	110	103	101
	Overall	94	108	82	70
Material	Verbal	94	106	84	58
	Non-verbal	93	100	99	105
Concept	Semantic	94	110	88	72
	Non-semantic	93	96	95	92
Modality of presentation	Auditory	96	128	42	22
	Visual	89	110	80	35

Table E9 Summary of case 5 performance on the CMS

Case 5		Immediate recall	Learning	Delayed recall	Delayed recognition
Scaled scores	Word Pairs	12	10	13	11
	Stories	11		11	10
	Dots	13	14	12	
	Faces	13		11	
Standard scores	Verbal material	109		112	103
	Non-verbal material	118		109	
	Overall		112		

Table E10 Summary of case 5 performance on the Pair Games (Standard scores)

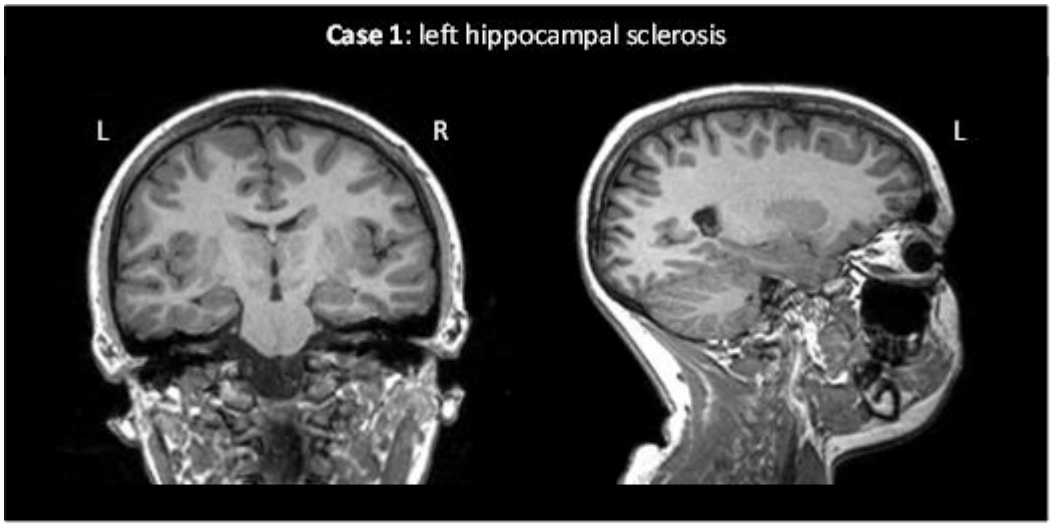
Case 5		Learning	Learning gain	Delayed recall	Delayed recognition
Separate tasks	Spoken words	117	84	106	106
	Written words	118	75	105	104
	Pseudowords	103	114	97	93
	Objects	116	69	125	103
	Designs	131	89	89	108
	Overall	117	86	104	103
Material	Verbal	110	95	101	98
	Non-verbal	123	79	107	105
Concept	Semantic	117	72	115	104
	Non-semantic	117	101	93	100
Modality of presentation	Auditory	117	84	106	106
	Visual	118	75	105	104

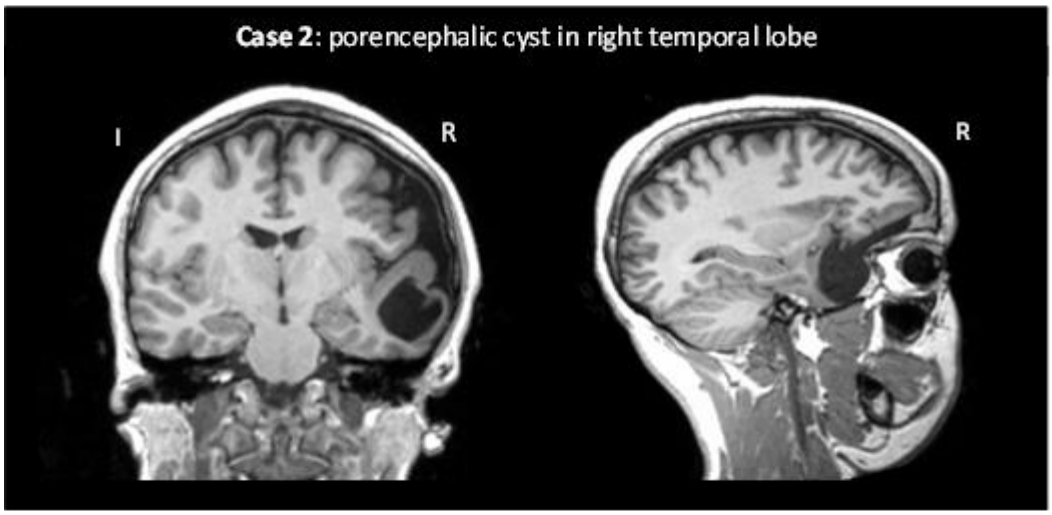
Table E11 Summary of case 6 performance on the CMS

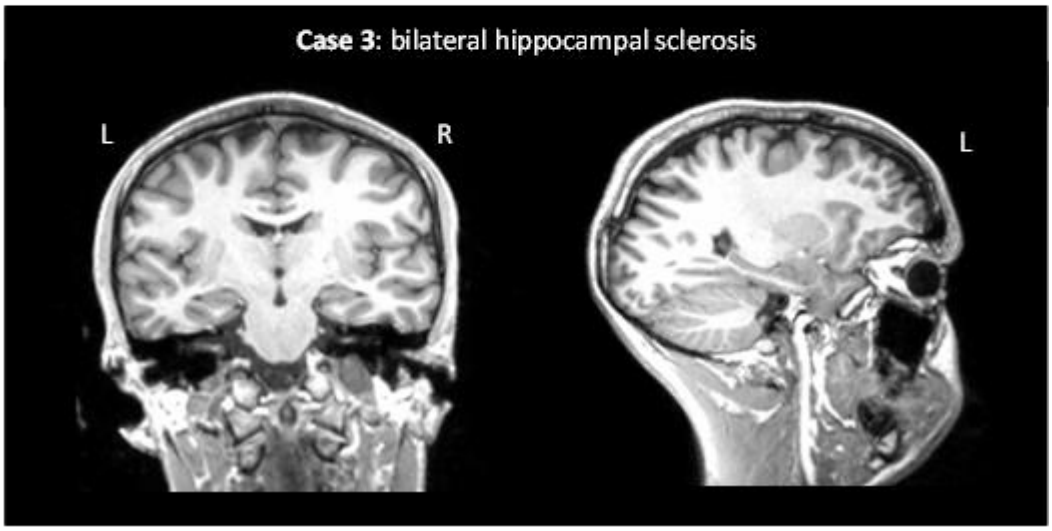
Case 6		Immediate recall	Learning	Delayed recall	Delayed recognition
Scaled scores	Word Pairs	6	6	8	3
	Stories	6		9	9
	Dots	7	8	7	
	Faces	7		9	
Standard scores	Verbal material	75		91	75
	Non-verbal material	82		88	
	Overall		82		

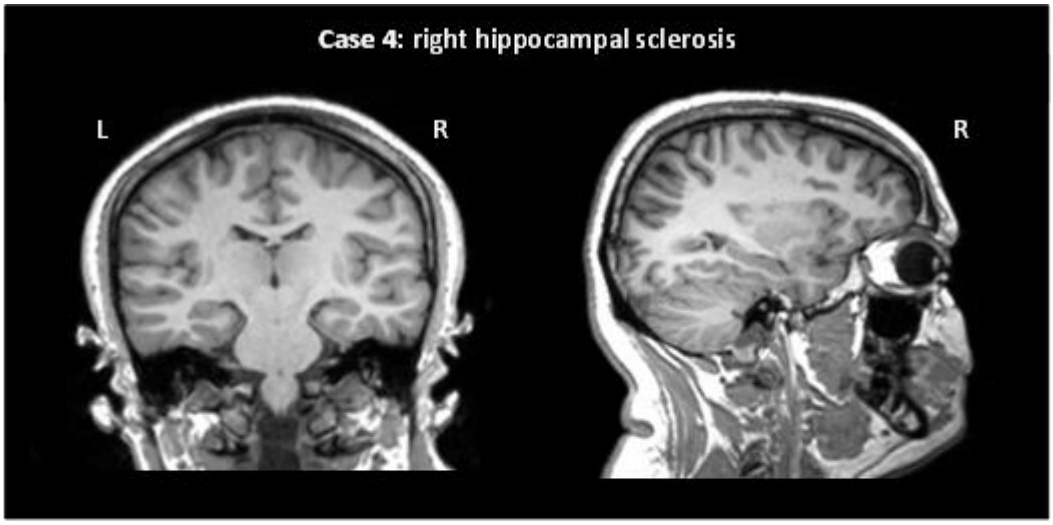
Table E12 Summary of case 6 performance on the Pair Games (Standard scores)

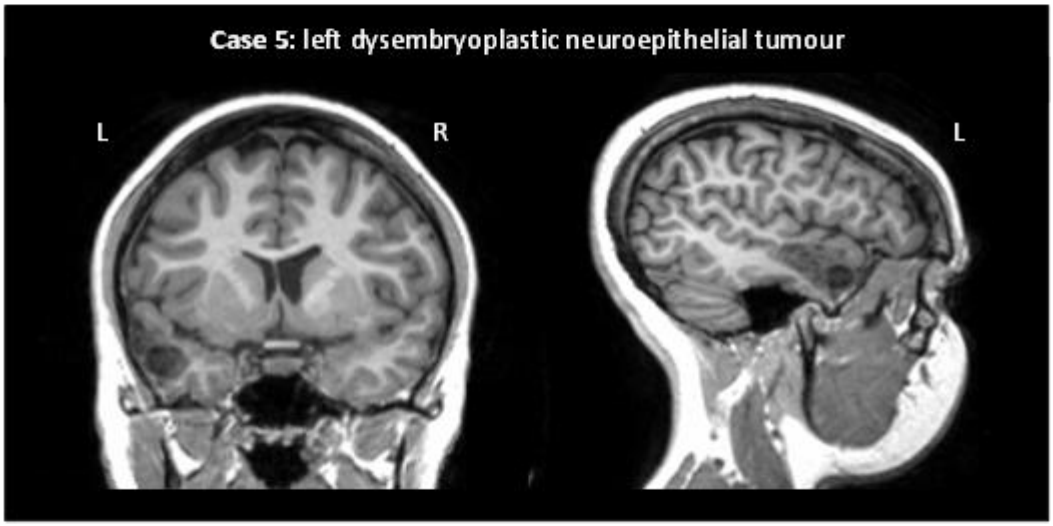
Case 6		Learning	Learning gain	Delayed recall	Delayed recognition
Separate tasks	Spoken words	76	102	82	106
	Written words	66	97	86	91
	Pseudowords	71	79	110	92
	Objects	89	115	104	79
	Designs	66	89	89	75
	Overall	74	96	94	89
Material	Verbal	69	88	98	92
	Non-verbal	77	102	96	77
Concept	Semantic	78	106	95	85
	Non-semantic	69	84	99	84
Modality of presentation	Auditory	76	102	82	106
	Visual	66	97	86	91

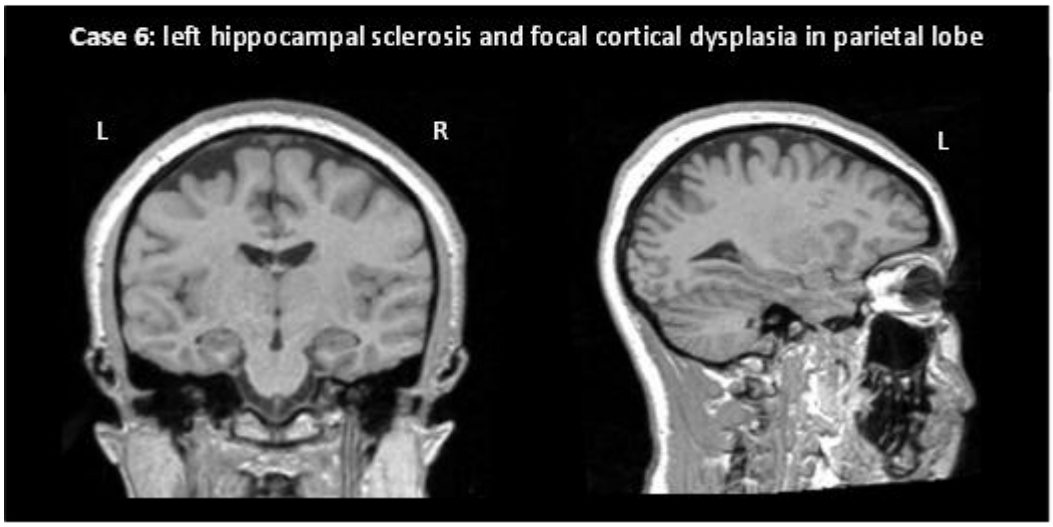

Case 1: left hippocampal sclerosis
L
R
L


Case 2: porencephalic cyst in right temporal lobe
I
R
R


Case 3: bilateral hippocampal sclerosis
L
R
L


Case 4: right hippocampal sclerosis
L
R
R


Case 5: left dysembryoplastic neuroepithelial tumour
L
R
L


Case 6: left hippocampal sclerosis and focal cortical dysplasia in parietal lobe
L
R
L