Autoimmune encephalitis and its implications for the neuroscience of remote memory

Submitted for the degree of Doctor of Philosophy in Clinical Neurosciences by
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Declaration of authorship and originality

I, Thomas David Miller, confirm that the work presented in this thesis is my own with the following exceptions:

Chapter 3: The 3D-FSE imaging parameters were developed by Dr. Clive Rosenthal and Professor Penny Gowland, with the hippocampal subfield segmentation protocol developed by Dr. Clive Rosenthal and myself.

Chapter 5: The Autobiographical Interview was double marked by Dr. Trevor Chong and myself.

Chapter 6: The foils for the new words were provided by the Oxford English Dictionary, according to the methods described in Chapter 2. Two undergraduate students collected the control data as part of their Final Honours School project, supervised by Dr. Clive Rosenthal and myself.

Dr. Thomas D. Miller

Table of contents

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* delete as applicable

To A:

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Lord, my first fruits present themselves to thee;
Yet not mine neither: for from thee they came,
And must return. Accept of them and me,
And make us strive, who shall sing best thy name.

George Herbert

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Abstract

Since the field-defining patient HM, consistent links have been made between a region of the brain called the hippocampus and memories that can be consciously declared – so called declarative memories. Declarative memories fall into two categories (1) episodic memories, memories that are highly detailed and re-experiential, and (2) semantic memories, fact-based memories for personal and public information but that have no sense of re-experiencing. It is believed that the intrinsic anatomy of the hippocampus supports episodic memory but not semantic memory. The hippocampus consists of five regions (cornu Ammonis, CA, 1-3, dentate gyrus, subiculum) with each purported to have a specific role in episodic memory acquisition and retrieval. However, controversy surrounds the temporal extent to which episodic memories rely on the hippocampus for retrieval: current consensus suggests the hippocampus supports these memories for five-10 years post-acquisition, but some suggest that it is required for retrieval across the lifetime. Voltage-gated potassium channel-complex antibody-mediated limbic encephalitis (VGKC-complex LE) is a recently described autoimmune disease that causes chronic hippocampal atrophy and mild amnesia on standardized neuropsychological assessment. Two subfields of the hippocampus – CA1 and CA3 – contain the antigenic targets of the disease but it is unknown if specific atrophy of these subfields underlies the hippocampal damage in humans. Here, the human hippocampal subfield volumes of VGKC-complex LE patients (n = 19, mean age: 64.0±2.55; range: 24-71) were investigated using ultra-high spatial resolution MRI at 7.0-Tesla. Assessment also included standardized neuropsychology to examine the impact of the pathology on hippocampal-dependent and –independent memory performance, as well as attention, language, executive function, and perception Declarative memory assessment measured semantic and episodic memory performance across the lifespan.

Manual segmentation detected lesions to just CA3, with no volume loss noted elsewhere in the hippocampus or brain. Patients were impaired on hippocampal-dependent memory domains but not the hippocampal-independent and non-memory domains. Notably, episodic memory assessment revealed episodic amnesia across the lifetime except for their earliest memories. This counters the received convention that the hippocampus has a temporally limited role in episodic retrieval. Conversely, the performance of the VGKC-complex LE patients for semantic memory, including a new test developed herein, was comparable to controls across the lifespan. It was then shown that CA3 volume predicted episodic memory performance across the lifetime. Together, the results suggest that VGKC-complex LE provides a novel model of human hippocampal subfield pathology, with which to explore the roles of hippocampal subfields in episodic memory acquisition and retrieval.

This thesis contains approximately 82,500 words.

Abbreviations

3D-FSE	three-dimensional fast spin echo
AA	anterograde amnesia
AC	anterior commissure
AD	Alzheimer's disease
AI	Autobiographical Interview
aMCI	amnesic mild cognitive impairment
AMI	Autobiographical Memory Interview
AMIPB	Adult Memory and Information Processing Battery
AMYG	amygdala
BIC	Bindings of Items and Context
BL	bilateral
BOLD	blood-oxygen-level dependent
CA	cornu Ammonis
CA1	cornu Ammonis 1
CA2	cornu Ammonis 2
CA3	cornu Ammonis 3
CA4	cornu Ammonis 4
Caspr2	contactin-associated protein-like 2
CVLT	California Verbal Learning Test
DG	dentate gyrus
DMN	default mode network
DTI	diffusion tensor imaging
EEG	electroencephalogram
ERC	entorhinal cortex
FBDS	faciobrachial dystonic seizures
FC-C	forced-choice corresponding
fMRI	functional magnetic resonance imaging
g	general intelligence factor
GK	general knowledge
GLM	general linear model
HM	Henry Molaison
HPC	hippocampus
ICC	intraclass correlation coefficient
L	left
LE	limbic encephalitis
Lgi1	leucine-rich glioma inactivated-1
LM1	Logical Memory 1
LM2	Logical Memory 2
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTL	medial temporal lobe
mTLE	medial temporal lobe epilepsy
MTT	multiple-trace theory
MVPA	multivariate pattern analysis
NMDAR	N-methyl-D-aspartate receptor
PC	posterior commissure
PCA	principal component analysis
PCC	posterior cingulate cortex
PDF	portable document format
PET	positron emission tomography
PFC	prefrontal cortex
PHC	parahippocampal cortex
PHG	parahippocampal gyrus
PIQ	processing intelligence quotient
PPVT	Peabody Picture Vocabulary Test
PRC	perirhinal cortex
R	right
RA	retrograde amnesia
RAVLT	Rey Auditory Verbal Learning Test
RBANS	The Repeatable Battery for the Assessment of Neuropsychological Status
RMT	Recognition Memory Test
ROCF	Rey-Osterreith Complex Figure
RSC	retrosplenial cortex
SAM	Survey of Autobiographical Memory
SD	standard deviation
SEM	standard error of the mean
SL	stratum lacunosum
SLRM	stratum radiatum, lacunosum, and moleculare
SM	stratum moleculare
SMC	standard model of consolidation
SP	stratum pyrimdale
SR	stratum radiatum
SSM	Survey of Semantic Memory
SUB	subiculum
TGA	transient global amnesia
TIV	total intracranial volume
TLE	temporal lobe epilepsy
TSS	toxic shock syndrome
UK	unknown

VBM	voxel-based morphometry	**WMS-III**	Wechsler Memory Scale 3rd Edition
VE	viral encephalitis	**WMS-IV**	Wechsler Memory Scale 4th Edition
VGKC	voltage-gated potassium channel-complex	**WMS-R**	Wechsler Memory Scale-Revised
VIQ	viusal intelligence quotient	**Y/N**	yes/no

List of Figures

List of Tables

Chapter 1

General introduction

For over 100 years, anecdotal associations between the structural integrity of the medial temporal lobe (MTL) and memory function have been made (e.g. von Bechterew, 1900). However, even into the 1950s formal links had not yet been made experimentally; this all changed with Henry Molaison, a case that would finally facilitate neuroscientific enquiries into the anatomical localization and characterization of human memory.

1.1. Henry Molaison

At the age of seven, Henry Molaison (later to become known as HM) was knocked off his bicycle and suffered a head injury. As a consequence he developed temporal lobe epilepsy (TLE) at the age of 10, eventually becoming severe and intractable by the age of 16. Despite escalating dosages of antiepileptic medications in 1953, and at the age of 27, he sought the help of the neurosurgeon William Scoville in an attempt to lead a normal life. Henry underwent a bilateral medial temporal lobe resection that brought about a resolution to his epilepsy (Squire, 2009). However, his surgery had unintended consequences for both Henry and the neuroscience of memory.

In 1952, Brenda Milner had already encountered two patients (PB and FC) who had become severely amnesic following unilateral resections of the left medial temporal lobe, a finding wholly unexpected at the time (Penfield and Milner, 1958). (It has subsequently been suggested that these patients had lesions to their right medial temporal lobes and so removal of the left, in effect, produced a bilateral lesion. This was proven

for PB on post-mortem examination). When she first visited Henry she was struck by the severity of his amnesia, worse than either PB or FC (Squire, 2009). She observed that Henry forgot daily events almost as quickly as they appeared, apologizing for forgetting names, and forgetting his own age, all without any apparent diminution in his general intellect, perceptual or language abilities. This contradicted the consensus view that damage to specific parts of the cerebrum would not only impair information processing for the modality supported by that cortical region (e.g. verbal, visual, auditory), but that this would also impair the specific memory for that modality (Eichenbaum, 2013; Squire, 2009).

Henry's case was eventually published alongside other patients who had suffered similar problems in their seminal 1957 paper *"Loss of recent memory after bilateral hippocampal lesions"* (Scoville and Milner, 1957). This paper is often erroneously cited as the first to link the hippocampus *per se* to mnemonic function, an impossibility given the nature of resection that included the hippocampus and medial temporal lobe structures (Scoville and Milner, 1957); however, it is certainly the paper that launched investigations into the neural basis of memory centred on the MTL structures.

1.1.1. What could HM learn?

Several articles have been written on the vast array of neuropsychological experiments conducted on HM after his operation (see, for instance, Corkin, 2002; Eichenbaum, 2013), and is explored in Chapter 4. As such a brief outline of these results will be given.

Despite his lesions it was noted that HM had a remarkable capacity for sustained attention as demonstrated by long conversations, the ability to repeat strings of numbers forwards and backwards and even remembering a three-digit number for as long as 15 minutes by various rehearsal strategies (Squire, 2009). If his attention was diverted to another topic, the previously retained information was lost. His memory for these tasks was also reduced by increasing the complexity of the thing to be remembered such as with non-verbal stimuli like faces or designs (Squire, 2009). The key determinant for this memory was not time but rather attention or the informational limits of what attention may hold.

HM's amnesia was initially thought to be dense across every testable modality (e.g. visual, verbal, short-delay, long-delay), but eventually it was discovered that HM could acquire visuomotor skills (e.g. drawing the outline of a star in a mirror and retaining it across several days, for review see (Corkin, 2002)). At no stage though could HM ever remember acquiring the skill. These findings were later broadened to a wide-range of procedural skills including word stem completion, conditional eye blink and priming tasks (for a review, see Corkin, 2002). Despite being able to learn these skills HM remained without an ability to remember any of the learning events. This dissociation led to an early formulation of two independent types of memory: declarative and procedural (Cohen and Squire, 1980). Declarative memories are referred to as knowledge of facts and events conscious declared with procedural memories being those skill-based knowledge gradual learned and with no conscious report being available. HM was critically impaired in declarative memory processes and hence the MTL system was critically linked to this type of memory (Squire, 2009).

With time more non-conscious memory types were discovered (such as skill learning, simple conditioning, priming and emotional and perceptual learning; Squire, 2009), and the term procedural memory was altered to non-declarative memory to encapsulate their relative differences from each other and declarative memory. Critically, these memories also had there own specific neuroanatomical circuits underlying their acquisition and retrieval (such as the basal ganglia, cerebellum, amygdala and neocortex; Squire, 2009). Following HM, therefore, it became clear that there were multiple parallel memory systems within the mammalian brain.

1.1.2. Declarative memory

The key finding for this thesis arising from HM and others was the development of what would be termed declarative memory, broadly the conscious retrieval of facts and events. In 1972, Tulving proposed a fractionation of memory at variance with a influential process-based approach (Craik and Lockhart, 1972). He proposed recollection based on conscious retrieval could be subdivided into two separate types: semantic memory and episodic memory (Tulving, 1972). Semantic memory:

> *"…allows the individual to construct mental models of the world… It makes possible the cognitive representation of objects, situations, facts and events"* (Tulving, 1985)

and so provides the knowledge of an event, but without any re-experiencing of the event itself. Conversely, episodic memory was described as:

> *"temporally dated episodes or events and* [have] *temporal-spatial relations"* (Tulving, 1972)

Episodic memories allow us to re-experience an event in the space-time in which it occurred and to know that we were agents within the event (so-called autonoesis, self-knowledge). More recently this definition has been extended to include a conscious state of recollection of these contextual details and a sense of self across time (i.e. *knowing* that this event happened to *me*), so called autonoetic consciousness (Tulving, 2002; Wheeler et al., 1997).

1.1.3. HM's legacy

Whilst not being the best example of focal hippocampal lesions studied in experiments of human memory, HM was certainly the most well-described experimentally and anatomically. It was these early descriptions of HM that inaugurated the modern era of memory research, the utmost of which was that declarative memory is a distinct, anatomically and behaviourally, cerebral function and that the medial temporal lobe is the critical locus for that memory type. It is this type of memory that forms the basis of the work presented in Chapters 4-7.

1.2. Anatomy and function of the medial temporal lobe

Given the centrality of the MTL structures to the investigations of declarative memory, it is important to consider the anatomy and connectivity of these regions in order to then understand the different types of memory and their anatomical localization with the MTL. Furthermore, particular importance surrounds the consideration of the type and origin of information that arrives at these central mnemonic structures and how

they might ultimately influence the type of information integrated into memory. The data that will be presented and discussed will arise largely from the comparative anatomy literature of rodents and primates. However, given the relative phylogenic preservation of these structures across mammalian species (Manns and Eichenbaum, 2006), the conclusions reached help provide an anatomical framework for the investigation of memory.

1.2.1. The medial temporal lobe

Traditionally, the MTL is formed by the amygdala, the allocortical areas of the hippocampal formation and the allocortical and periallocortical areas of the parahippocampal gyrus (Van Hoesen, 1995). The parahippocampal formation refers to the subicular cortices including the parasubiculum, presubiculum and subiciulum, the hippocampus proper (with the cornu Ammonis (CA) 1-3 fields) and the dentate gyrus (Van Hoesen, 1995). For the purposes of this thesis, the hippocampus will refer those five subfields as a single unit, unless otherwise specified. The anteromedial portion of the MTL is formed by the superficial nuclei of the amygdala that includes the cortical and medial nuclei. The lateral border of the parahippocampal gyrus is formed by the perirhinal cortex (Van Hoesen, 1995).

1.2.1.1. Hippocampal afferents

Informational access to the hippocampus arises from three main MTL structures: the perirhinal cortex, the parahippocampal cortex in primates, and the entorhinal cortex. These bidirectional connections with the hippocampus receive their own specific inputs from several cortical association areas suggesting that, hierarchically, the hippocampus receives highly integrated information from many different sensory modalities. This discussion will begin with these three cortical regions.

1.2.1.1.1. The perirhinal and parahippocampal cortices

1.2.1.1.1.1. The perirhinal cortex

The macaque perirhinal cortex (PRC, Brodmann areas, BA, 35 and 36 in humans; Ding and Van Hoesen, 2010) receives unimodal inputs arising from the superior temporal gyrus (conveying auditory information), TE/TEO (visual information) and the insular cortex (somatosensory information; Lavenex and Amaral, 2000). Multimodal inputs arise from the orbitofrontal cortex, the dorsal superior temporal sulcus, the parahippocampal cortex and the cingulate cortex. The projections from area TE carry information about objects originating from posterior cortical areas such as V4 and the posterior parietal cortex (Lavenex and Amaral, 2000; Suzuki and Amaral, 1994a). The caudal-most extent of the PRC is medially adjacent to the intermediate and caudal divisions of the entorhinal cortex (areas EI and EC, see below) and bounded laterally by the rostral portion of area TF of the parahippocampal cortex (Lavenex and Amaral, 2000).

1.2.1.1.1.1.1. The perirhinal cortex and cognition

Primate work demonstrates that lesions to the PRC also produced deficits in visual discrimination learning tasks (Buckley and Gaffan, 1997, 1998), and the anatomy of the ventral visual stream places the PRC at the apex of the "what" pathway (Bussey and Saksida, 2002; Murray and Bussey, 1999; Ungerleider and Mishkin, 1982), suggesting that the PRC functions, in a broad sense, in object identification (Buckley and Gaffan, 1998).

1.2.1.1.1.2. The parahippocampal cortex

The parahippocampal cortex (PHC) is caudally adjacent to the PRC and is comprised of a smaller medial area TH and larger laterally situated TF (subsequently subdivided into areas TFm and TFl; (Suzuki and Amaral, 2003)). Area TF receives input from caudal visual areas V4, TEO, Te and polymodal association cortices including the retrosplenial cortex and the superior temporal sulcus. TF also receives input from areas 7a and LIP (both from the posterior parietal cortex), insular cortex and areas 46, 13, 45 and 9 of the frontal cortex. Area TH also receives projections from auditory association areas of the superior temporal gyrus. The direction and neuronal polarity of these connections suggests that the PRC is at a higher level than the PHC in the hierarchy of

associational cortices. Both the PRC and PHC can project polymodal associational information to the CA1 region of the hippocampus (Suzuki and Amaral, 1990), although between them, the PHC and PRC provide almost two thirds of the neocortical input into the ERC, the central nexus through which information enters the hippocampus proper (Insausti et al., 1987).

1.2.1.1.1.2.1. The parahippocampal cortex and cognition

Episodic memory requires the association of objects, relations, places, sounds, emotions and thoughts into a single construct (Chadwick et al., 2014), and memories requiring this binding together of several features that appears to preferentially activate the PHC (Davachi et al., 2003; Duzel et al., 2003; Eacott and Gaffan, 2005; Hales et al., 2009; Henke et al., 1999; Kirwan and Stark, 2004; Tendolkar et al., 2008; Yang et al., 2008), especially to its surrounding context (and not the target alone; Davachi et al., 2003; Hayes et al., 2007; Wang et al., 2013). This contextual information may help provide the hippocampus with source memory details, the specific details about the episode (Davachi et al., 2003; Diana et al., 2010; Staresina et al., 2011). Damage to the PHC in animals and humans produce significant impairments in associative memories (Eacott and Gaffan, 2005; Malkova and Mishkin, 2003; Ploner et al., 2000; Zola-Morgan et al., 1989). Whilst the associative role has been seen prototypically in spatial tasks (Brewer et al., 1998; Staresina et al., 2011), it has also shown activation during non-spatial tasks (Hales et al., 2009; Henke et al., 1999; Wagner et al., 1998).

This evidence suggests that the key feature of stimuli reliably shown to utilize the PHC are those which require contextual association processing (Aminoff et al., 2013), and as such present highly processed contextual information to the hippocampus such that it might then bind together other processed information originating from the PRC and ERC (Ranganath, 2010).

1.2.1.1.1.3. Perirhinal and parahippocampal cortices: summary

The discussion above details how the PRC and PHC are integral for, though not limited to, the presentation of highly processed visual information to the hippocampus. It also suggests that under the right conditions the PRC, more so than the PHC, is capable of supporting object recognition memory. Overall, the anatomical and behaviour

data from above suggest that it is possible to conceptualize the PRC as being critical for object representation and the PHC as being central to spatial representation.

1.2.1.1.2. The entorhinal cortex

The entorhinal cortex (ERC; area 28) is the largest cortical field of the parahippocampal gyrus and is continuous with the subicular portion of the hippocampal formation. Given its anatomical position, it is the principal bidirectional gateway for communication between the neocortex and the hippocampus (Lavenex and Amaral, 2000). The ERC is subdivided into six parts arranged rosto-caudally: EO, the olfactory division that receives direct input from the olfactory bulb; ER, this borders the EO laterally; EL borders the ER and is the lateral most subdivision of the ERC; EI that borders both the EO and ER caudally and is the intermediate subdivision of the ERC; the caudal-most portion of the entorhinal cortex is made up of a large caudal division (EC) and a smaller caudal divisions (ECL; Lavenex and Amaral, 2000).

1.2.1.1.2.1. Afferent projections to the entorhinal cortex

Input to the ERC arises from several sources, with approximately two-thirds of its inputs arising from the PRC and PHC (Suzuki and Amaral, 1994b). Projections from the PRC terminate in the rostral two-thirds of the ERC whereas the PHC projections terminate in the caudal two-thirds (Suzuki and Amaral, 1994b). This anatomical segregation does not translate to a functional one: information from the PRC can reach all levels of the ERC via a disynaptic connection with the PHC or through a trisynaptic connection with the PHC, back to the PRC and thence onto the ERC (Lavenex and Amaral, 2000). However, these inputs arising from the PRC and PHC by-and-large project to the lateral ERC and medial ERC respectively. The DG and CA3 combine the two streams of information from the medial and lateral ERC into a single entity and in turn send feedback projections to both of these structures, carrying the combined information (Witter et al., 2014). The lateral and medial ERC therefore receive highly processed reciprocal information containing both spatial and non-spatial information.

Other neocortical projections to the ERC arise from the cingulate and retrosplenial cortices, the insular and orbitofrontal cortices, the superior temporal gyrus and the olfactory bulb (Insausti and Amaral, 2008). These cortical projections often arise

themselves from several polymodal association areas that in turn provide highly processed sensory information to the ERC and thence the hippocampus (Lavenex and Amaral, 2000). The consequence of this widespread afferent network is that the hippocampus is ultimately linked to much of the processing that takes place within the neocortex (Lavenex and Amaral, 2000).

The ERC also receives several subcortical projections including: the amygdaloid complex (especially the lateral and basal nuclei), cholinergic projections from the septum (which are reciprocated), the thalamus (the nucleus reuniens, nucleus centralis medialis and the medial pulvinar), the supramammillary hypothalamus, dopaminergic projections from the ventral tegmental area, serotnergic input from the raphe nuclei and noradrenergic inputs from the locus coeruleus (Amaral and Lavenex, 2007).

1.2.1.1.2.2. The significance of differential entorhinal projections to the hippocampus

The lateral ERC receives its innervation from the PRC and in turn innervates the outer third of the molecular layer of the DG, and the medial ERC receives its efferent projections from the PHC and innervates the middle third of the DG. Moreover, as shown above there are also different patterns of innervation along the transverse axis of the CA1, with the lateral ERC innervating the distal CA1 and the medial ERC projecting to the proximal CA1. Finally, there are also electrophysiological differences between the CA1 cells receiving these differential projections: cells in the proximal CA1 receiving medial ERC afferents have a higher spatial specificity than neurons in the distal, and therefore lateral ERC-projecting CA1 cells (Henriksen et al., 2010), in keeping with similar electrophysiological differences in the lateral and medial ERC (Deshmukh et al., 2010; Hargreaves et al., 2005).

There is a general suggestion, therefore, of a segregation of function within this MTL system. The lateral ERC is considered to be an extension of the ventral visual stream relaying "what" information about an object through the temporal lobe, whereas the medial ERC has been considered an extension of the dorsal visual stream carrying "where" information about an object through the parietal lobe (Knierim et al., 2014). The conjunctive role preformed by the hippocampus therefore would be form flexible associations between these two streams to form a "what happened where" engram,

critical to the formation of episodic memory (Knierim et al., 2014). Of course, this is an over-simplification of the true state of information flow to the hippocampus, with at least three dorsal stream parallel pathways existing (Kravitz et al., 2011), and four for the ventral stream (Kravitz et al., 2013) and that some cross-over between the systems exist (Kravitz et al., 2011); however, this remains a generally useful heuristic for the purposes of this thesis.

1.2.1.1.2.3. Other projections to and from the ERC

The PRC and PHC receive efferent projections from the ERC in a fashion that largely reciprocates the input pathways. However, where the caudal ERC projects to the PHC, the relationship between the ERC-PRC connections vary according to the mediolateral position within the PRC (Suzuki and Amaral, 1994b; Van Hoesen, 1982). Therefore, medial portions of the PRC have a higher degree of reciprocity that the lateral portion (Lavenex, 2012). As a general rule though, the efferent projections from the ERC to the PRC and PHC follows a largely reciprocal pattern.

1.2.1.1.2.4. Role of the entorhinal cortex in cognition

It was the discovery of grid cells within the medial ERC that gives most credence to the "what-where" distinctions made in Section 1.2.1.1.2.2 (Fyhn et al., 2004; Hafting et al., 2005). This was then followed by findings suggesting that there were also head directions cells, speed-modulated cells, and border/boundary cells in the medial ERC helped to further this view of the medial ERC being central to a spatial-processing system (Sargolini et al., 2006; Savelli et al., 2008; Solstad et al., 2008). Such a spatial response was not observed in lateral ERC cells (Hargreaves et al., 2005); but what was observed was the activation of lateral ERC neurons when animals investigated new objects into an exploratory arena (Deshmukh and Knierim, 2011), findings in keeping with a more "what" function of these neurons. However, more recent work has found that lesions to the lateral ERC does affect object recognition but rather the ability for animals to recognize displaced objects or to recognize specific objects in specific locations (Van Cauter et al., 2013; Wilson et al., 2013). Another study found that medial ERC lesions caused weak non-spatial deficits and that lateral ERC lesions caused weak spatial deficits (Hunsaker et al., 2013). These results are not surprising given the interconnectedness of the MTL system and that the hippocampus sends feedback projections to the lateral and medial ERC after combining these two information streams

(Witter et al., 2014). This work has led to the development of a local versus global framework model, whereby the medial ERC establishes a global map generated to provide information about where an organism may be within an environment, and the lateral ERC in turn provides information about local cues and the content of experience, including spatial information, related to these local objects (Knierim et al., 2014; Lisman, 2007).

1.2.1.2. Medial temporal lobe anatomy: summary

What is clear from this preceding discussion is that the MTL structures (the ERC, PRC and PHC) are not passive relay stations for information flowing from the neocortical associations to the hippocampus. Significant modulation of that information is undertaken in these regions and each has their own significant role in cognition and memory.

1.2.2. Other inputs into the hippocampus

The DG receives few inputs from the subcortical structures but receives innervation from the septal nuclei arising from the medial septal nucleus and nucleus of the diagonal band of Broca (Amaral et al., 2007). These fibres innervate the polymorphic cell layer of the DG and are principally cholinergic fibres (Amaral et al., 2007). The supramammillary areas also projects to the superficial granule cell layer and are glutamatergic in nature. The DG also receives noradrenergic innervation from the locus coeruleus, dopaminergic fibres from the ventral tegemental area and serotonergic projection that originates from the median and dorsal divisions of the raphe nuclei (Amaral et al., 2007).

1.2.3. The intrinsic connectivity of the hippocampus proper

The hippocampus is divided into five distinct regions: DG, CA3, CA2, CA1 and SUB, anatomical structures that are readily visible with ultra-high field MR imaging (Wisse et al., 2014; Wisse et al., 2012), and structures that theoretically are most implicated following VGKC-complex LE (Irani et al., 2010). There is in general a unidirectional flow of information through the hippocampal circuits beginning with the DG, through to CA3, CA2, CA1 with the predominant output structure being the SUB.

1.2.3.1. Dentate gyrus

The DG consists of three layers: the relatively acellular molecular layer which contains the dendrites of the DG cells, interneurons and the perforant pathway fibres from the ERC terminating in the molecular layer; the granule cell layer containing the packed granule cells; and the polymorphic layer which predominantly contains mossy cells (Amaral and Lavenex, 2007). It is the granule cells which then project onwards to the CA3 region of the hippocampus via their efferent projections, the mossy fibres. In monkeys there are approximately 7.2 million granule cells which project to 1.3 million CA3 pyramidal cells, each CA3 cell receives inputs from 83 granule cells (Amaral and Lavenex, 2007). This pattern of connectivity contributes to one of the fundamental roles of the DG, pattern separation, and it is this ability that is able to encode similar patterns of activation into distinct, non-overlapping representations (Bakker et al., 2008; Morris, 2007).

1.2.3.2. CA3

The proximal part of the CA3 is enclosed within the limbs of the DG and is characterised by large pyramidal cells (Jabes et al., 2011) which receive input from both the mossy fibre pathway from the DG and ERC (which projects to the distal region of the CA3; Witter and Amaral, 1991). Both the DG and ERC project to the CA3 in a topographical fashion and there are numerous CA3-to-CA3 associational connections which travel along the longitudinal axis of the CA3, but these connections are fewer in number than CA3-CA1 projections (Kondo et al., 2009). Reciprocal connections also exist between the proximal portion of the CA3 and the DG (Buckmaster and Amaral, 2001).

1.2.3.3. CA2

The CA2 layer lacks input from the mossy fibre layer of the DG but does receive input from the ERC and from the posterior hypothalamus especially the supramammillary area and tuberomammillary nucleus. There are CA2-to-CA2 projections that are arranged longitudinally and the CA2 region does not project outside of the hippocampus (Lavenex, 2012).

1.2.3.4. CA1

The CA1 receives input directly from the CA3 pyramidal neurons via the Schaffer collaterals which terminate along the entire transverse extent of CA1, and have reciprocal connections with CA3 (Kondo et al., 2009). There are no CA1-to-CA1 associational connections. CA1 also receives prominent projections from the ERC (which again projects in a topographical fashion), PRC and the PHC (Suzuki and Amaral, 1990). CA1 also has a number of subcortical inputs (Lavenex, 2012). The CA1 has strong projections out of the hippocampus proper into the SUB as well as projecting back to the ERC (in contrast with CA3 and CA2; Lavenex, 2012).

1.2.3.5. Subiculum

CA1 neurons are the main input into the SUB. ERC neurons also send a significant projection into the SUB and both have a topographic organisation. The SUB is the main output structure of the hippocampal formation, including the subcortical brain regions especially towards the lateral septal nucleus, the nucleus accumbens and the mammillary nuclei (Amaral and Lavenex, 2007). The SUB is therefore placed to provide separate channels to distribute the information processed in the hippocampal formation to cortical regions (especially the ERC) or to subcortical regions.

The SUB has extensive reciprocal connections with the various hypothalamic nuclei including the ventral premammillary nucleus, the medial septum/nucleus of the diagonal band and the anteroventral and anteromedial nuclei of the thalamus (Canteras and Swanson, 1992; Kohler, 1990; Risold et al., 1997).

1.2.3.6. Hippocampal subfield functions in memory

The retrieval of episodic memories involves the linking together of a series of events into a single cohesive re-experiential event, one that usually involves placing a set of items together into a spatial context. Computational modeling suggests that the formation of associations between these stimuli relies principally upon the CA3 region (Rolls, 2013). Recalling an event is usually triggered by a partial cue of that event (i.e. where were you for dinner last night?) causing the full recollection of the event. This process of full recollection from a partial cue is referred to as pattern completion, once again a function believed to depend on the CA3 (Rolls, 2013). Finally, several events

separated in time might have many shared features (i.e. several birthday parties happening in the same house), making the distinction between them difficult. The successful encoding and storage of these overlapping events requires the orthogonalization of those events, a process thought to be dependent upon the DG and CA3 (Leutgeb et al., 2007; Leutgeb and Leutgeb, 2007; Rolls, 2013). Pattern separation and completion will not be formally explored in this thesis; however, its relevance to the anatomical and behavioural findings will be discussed in greater detail in subsequent chapters.

1.2.3.7. Hippocampal efferents

In those regions so far discussed the DG, CA3, or CA2 regions do not project towards cortical areas. The predominant output of the hippocampus arises in the form of CA1 and SUB projections to the ERC (Lavenex, 2012). However, the CA1 and SUB also send modest projections to the rostral PRC (Insausti and Munoz, 2001). The hippocampal formation has extensive feedback projections to the cortex that arise from the subicular and CA1 regions which terminate in the orbitofrontal, dorsolateral, medial frontal, anterior temporal and posterior temporal association cortices (Kosel et al., 1982; Morecraft et al., 1992). The hippocampus also has other back-projections via the ERC and a large white matter tract called the fornix, the mammillary bodies, the medial parietal regions, the amygdala, retrosplenial cortex and cingulate (Lavenex, 2012). The PRC sends feedforward projections to the rostral two-thirds of the ERC while the PHC innervates the caudal ERC with feedback connections. It is the ERC that forms the majority of efferent projections away from the hippocampal formation and towards other neocortical sites.

1.2.3.8. Hippocampal anatomy: summary

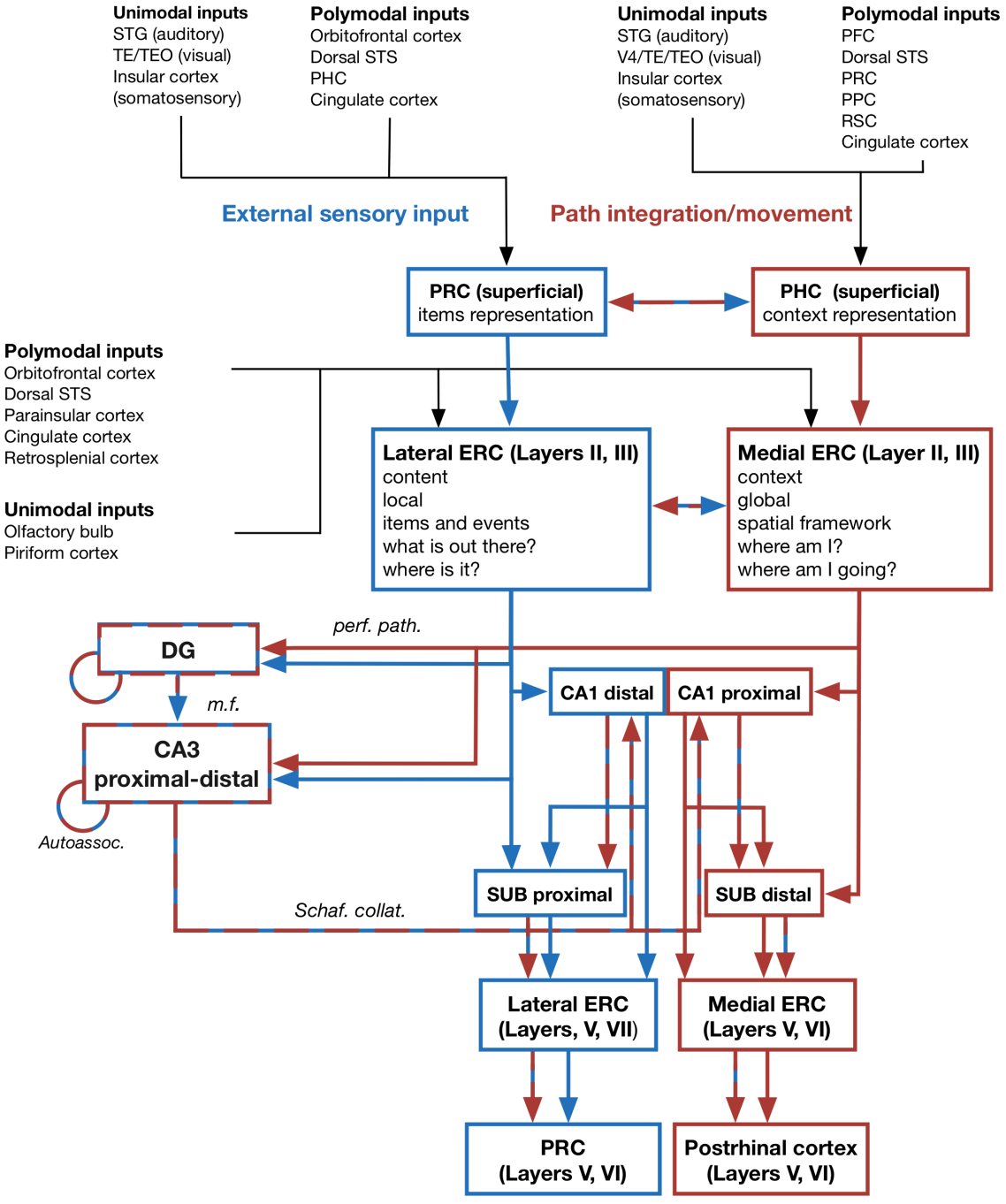
These data suggest that hippocampus is comprised of multiple functional units, each with a seemingly unique role within the representation of memory. These regions have specific predictions about the role they play within the acquisition and retrieval of memories (i.e. pattern separation and completion). The inherent anatomy of this region also lends itself to the establishment of complex associational memories primarily requiring the DG and CA3 for this role. However, what is also clear is that there are several areas outwith the hippocampi that have contributory roles to the establishment

and retrieval of complex memories. These primarily reside within the MTL (i.e. the PRC, PHC and ERC). The anatomical connectivity of the hippocampus described through section 1.2 is shown in Figure 1.1.

1.3. Regions critical to episodic memory outside the MTL

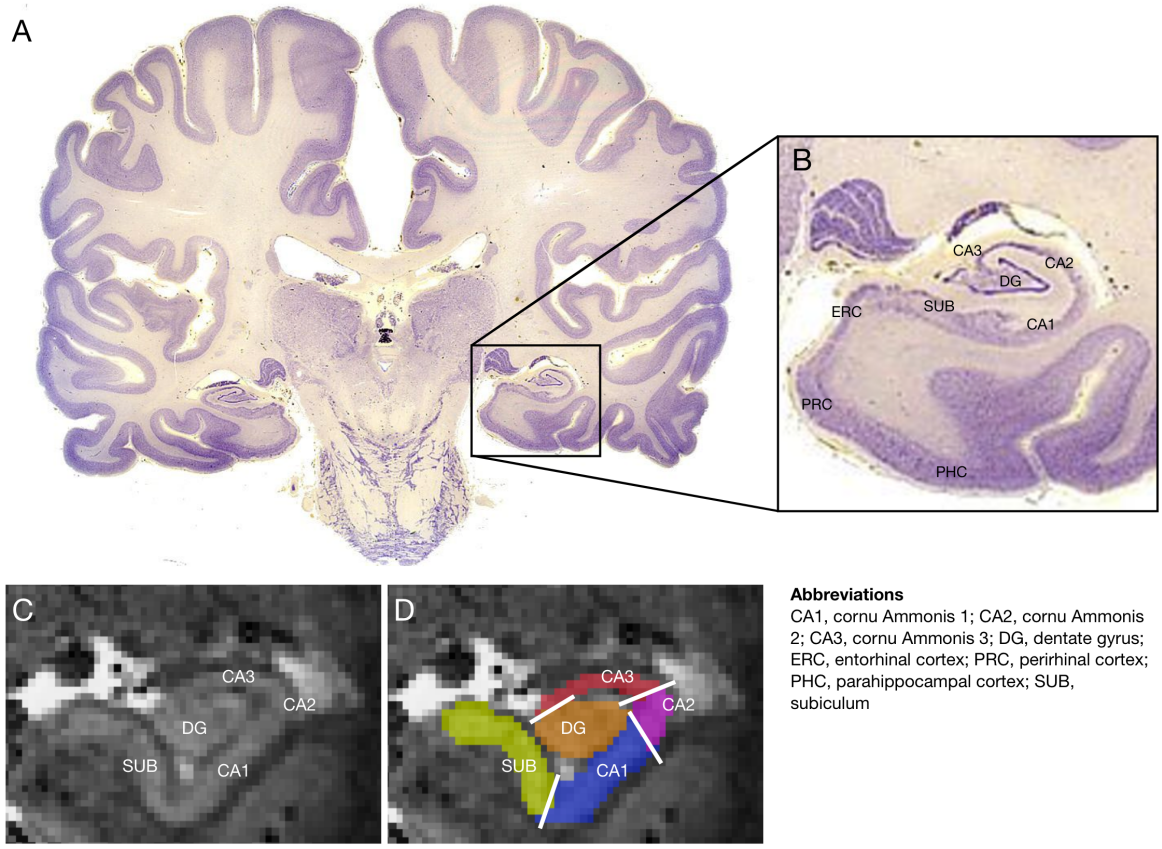
The anatomical, functional and network studies cited above suggest that the temporal lobes can no longer be considered, and the MTL specifically, as solely responsible for the behavioural manifestation of episodic memory. As such, it is worthwhile considering the functional contributions these extra-MTL regions (particularly the PFC, parietal lobe, precuneus and posterior cingulate cortex) make to episodic recall. The role of these regions in episodic memory retrieval will be discussed at length in Section 4.1.3.

Figure 1.1. The anatomy and connectivity of the mammalian hippocampus primarily focusing on the medial temporal lobe structures, but also wider cortical regions as arising from rat and primate work. This figure attempts to demonstrate the different pathways through which dorsal and ventral stream information arrives at the hippocampus, and thence is integrated into a single trace.



Abbreviations: *Autoassoc*., autoassociation reiprocal connections; CA1, cornu Ammonis 1; CA2, cornu Ammonis 2; CA3, cornu Ammonis 3; DG, dentate gyrus; ERC, entorhinal cortex; *perf. path.*, perforant pathway; PHC, parahippocampal cortex; RSC, retrosplenial cortex; PPC, posterior parietal cortex; PRC, perirhinal cortex; *Schaf. collat.*, Schaffer collaterals; STG, superior temporal gyrus; STS, superior temporal sulcus

Figure 1.2. Localization and intrinsic connectivity of the medial temporal lobe (MTL) complex within the human brain. (A). This panel demonstrates the location of the MTL complex within the human brain, on a coronal section, at the level of the hippocampal body. This Nissl stain demonstrates the cell bodies of the hippocampus and surrounding cortices, although cortical layers are not visualized at this magnification. (B). This panel shows demonstrates the *in vivo* location of the hippocampal subfields as well as the entorhinal, perirhinal, and parahippocampal cortices which provide the principal hippocampal afferent innervation. The neuroradiological appearance of these subfields at 7.0-Tesla is shown both before (C) and after (D) manual segmentation. Coronal section is from the National Museum of Health and Medicine (www.brainmuseum.org).



Abbreviations
CA1, cornu Ammonis 1; CA2, cornu Ammonis 2; CA3, cornu Ammonis 3; DG, dentate gyrus; ERC, entorhinal cortex; PRC, perirhinal cortex; PHC, parahippocampal cortex; SUB, subiculum

1.4. Human models of hippocampal dysfunction

What HM provided neuroscience with was a model of focal anterograde and retrograde amnesia following the focal resection of components of his MTL. This model led to many other patient-based studies of those who have had lesions restricted to the MTL structures. However, the anatomical model provided by HM has now become outdated, especially in the animal literature where focal lesions to subfields are now possible. Moreover, many subsequent patient studies suffer from their relatively low numbers (e.g., Bayley et al., 2005; Bayley et al., 2003; Cipolotti et al., 2001; Rosenbaum et al., 2005; Rosenbaum et al., 2008; Steinvorth et al., 2005), limited neuropsychological evaluation (e.g., Bayley et al., 2005; Bayley et al., 2003; Gold and Squire, 2005; Smith et al., 2013), limited anatomical descriptions both across the cerebrum and intra-hippocampally (e.g., Bayley et al., 2005; Rosenbaum et al., 2005; Rosenbaum et al., 2008), and varying aetiologies (e.g., viral encephalitis, Bayley et al., 2005; Rosenbaum et al., 2008; trauma, Rosenbaum et al., 2005; anoxia, Bayley et al., 2005; Cipolotti et al., 2001; temporal lobe epilepsy, Bayley et al., 2005).

1.4.1. VGKC-complex LE as a model of hippocampal dysfunction

Limbic encephalitis (LE) traditionally refers to the subacute onset of episodic memory impairment, disorientation and agitation (Brierley et al., 1960; Corsellis et al., 1968). This syndrome was also associated with seizures, hallucinations, and sleep disturbance. Early histopathological studies found inflammatory changes within the medial temporal lobes (MTL; Brierley et al., 1960), thereby suggesting the clinical syndrome of LE would only emerge with MTL pathology. These early cases were normally described in the context of solid organ tumours such as small-cell lung cancer (anti-Hu antibody; Dalmau et al., 1992; Alamowitch et al., 1997), testicular tumours (anti-Ma2 antibodies; Voltz et al., 1999), and thymomas (anti-CRMP5/CV2 antibodies; Antoine et al., 1995). Eventually non-paraneoplastic LE cases were described (Bien et al., 2000; Mori et al., 2002) but the immunological cause of such cases remained unclear. Eventually the pathogenic antibody associated with non-paraneoplastic limbic encephalitis was found to target the voltage-gated potassium channel complex (VGKC-complex) thus giving rise to the clinical syndrome of limbic encephalitis associated with voltage-gated potassium channel antibodies (VGKC-complex LE; Buckley et al., 2001;

Schott et al., 2003). VGKC-complex antibodies have been associated with three clinical syndromes (Irani et al., 2010):

1. Neuromyotonia – peripheral nerve hyperexcitability associated with muscle cramps and stiffness (Hart et al., 2002).
2. Morvan's syndrome – a combination of peripheral hyperexcitability alongside autonomic and central nervous system dysfunction and often insomnia (Josephs et al., 2004; Liguori et al., 2001).
3. Limbic encephalitis – the syndrome described above but often with an associated hyponatraemia in a pattern consistent with the syndrome of inappropriate anti-diuretic hormone (Graus et al., 2008; Vincent et al., 2004).

However, the clinical phenotype of VGKC antibodies continues to grow and these antibodies have been implicated in subacute idiopathic epilepsy (McKnight et al., 2005) and late-onset dystonic epilepsy (Barajas et al., 2010; Irani et al., 2008). In all these syndromes there is good response to immunotherapy (Buckley et al., 2001; Geschwind et al., 2008; Irani et al., 2008; Thieben et al., 2004; Vincent et al., 2004; Wong et al., 2010), although neuromyotonia and seizure syndromes may require only symptomatic treatment (Irani et al., 2010).

Since first being described, two principal antibodies have been discovered, each targeting different components of the VGKC-complex: leucine-rich glioma inactivated-1 (Lgi1) or contactin-associated protein 2 (Caspr2). VGKC-complex antibodies have been identified in 10% of unselected patients with late-onset refractory epilepsy (5,6). It appears that Lgi1 is more associated with LE than Caspr2 (Irani et al., 2010).

The typical presentation of VGKC-LE is usually a subacute amnesia and personality change and/or neuropsychiatric features alongside evidence of temporal lobe or faciobrachial seziures and a serum antibody tire >200pmol/l (Graus et al., 2004; Vincent et al., 2011). VGKC-complex LE has been well described for over a decade now and a substantial literature is now available describing the clinical presentation and course of this disease (Bataller et al., 2007; Bien et al., 2007; Buckley et al., 2001; Harrower et al., 2006; Irani et al., 2008; Jacob et al., 2008; Schott et al., 2003; Thieben et al., 2004; Vincent et al., 2004; Wong et al., 2010). Neuropsychological testing during the acute phase of disease shows global impairment across several domains including memory,

executive function and language (Buckley et al., 2001; Schott et al., 2003; Vincent et al., 2004). Studies that assessed the cognitive profile following resolution of the illness usually found that the executive function and language dysfunction largely resolved (Buckley et al., 2001; Vincent et al., 2004) but that patients showed residual anterograde or retrograde memory deficits (Addis et al., 2007; Buckley et al., 2001; Kartsounis and de Silva, 2011; Schott et al., 2003; Vincent et al., 2004).

Testing of retrograde episodic memory using the Autobiographical Memory Interview (AMI; see Chapter 4 for a discussion of its utility) have found deficits in recent but not remote episodic memories (Kartsounis and de Silva, 2011). Another study also found that impaired on measures of famous faces and famous news events and measures of anterograde paired-associate learning, with some improvement being observed after immunotherapy (although see Chapter 6 for a discussion of these results). Recognition memory and list-learning, however, were almost universally preserved following resolution of the illness (Addis et al., 2007; Kartsounis and de Silva, 2011; Vincent et al., 2004). Longitudinal studies have shown significant deficits in executive functioning, processing speed and verbal and visual memory at presentation (Butler et al., 2014; Frisch et al., 2013). At follow-up, after immunotherapies, there was a resolution in the dysexecutive features, but a significant deficit in visual and verbal memory persisted (Butler et al., 2014; Frisch et al., 2013). However, another study (Bettcher et al., 2014) found mild to moderate impairment on anterograde memory but also category fluency as well.

The majority of clinical MRI studies undertaken in acute VGKC-complex antibody LE demonstrate an active inflammatory process (as shown by high signal on T2 sequences and/or swelling) predominantly confined to the MTL structures (Bien et al., 2000; Bien et al., 2007; Thieben et al., 2004; Vincent et al., 2004). However, as a number of clinically distinctive features are being better characterized, there is increasing reported normality of MR imaging (Flanagan et al., 2010; Irani et al., 2013). Longitudinal scanning often demonstrates focal atrophy of the MTL structures in at least 48% of patients(Kotsenas et al., 2014). However, atrophy has been reported outside of the MTL (Irani et al., 2008; Jacob et al., 2008). Automated volumetric imaging (Finke et al., 2013; Wagner et al., 2014; although see Irani et al., 2013; Schott et al., 2003) demonstrates significant atrophy of the hippocampi. The antigenic targets of VGKC-LE, Lgi and

Caspr2, are also localized to DG and CA3 (Herranz-Perez et al., 2010; Irani et al., 2010; Irani et al., 2012). Pathological studies (Buckley et al., 2001; Khan et al., 2009; Park et al., 2007; Dunstan and Winer, 2006) show that VGKC-complex LE is confined to the hippocampus and amygdala. This evidence would suggest that, inasmuch as is possible without contemporaneous pathological studies, that VGKC-complex LE is a disease that produces focal MTL pathology and that it will tend to produce the same pathological patterns in all patients.

1.4.1.1. The use of VGKC-complex LE in cognitive neuroscience

The precedent of using VGKC-complex LE in studies of hippocampal function has also been established. For instance, three VGKC-LE patients have been used in a study of future imagining, a constructional process believed to be reliant upon the hippocampus and have been found to be impaired on this task (Hassabis et al., 2007), and a series of VGKC-complex LE patients were found to have deficits on a visual working memory task that required the binding of multiple items in space, a deficit not observed when patients had to remember the location of single items (Pertzov et al., 2013).

1.4.1.2. Criticisms of VGKC-complex LE

Criticisms have been raised concerning VGKC-complex LE in the Hassabis *et al.* study above (Squire et al., 2010). For instance:

> *"…patient P04 was described as having verbal and performance intelligence quotient (IQ) in the normal range but was considered to have some intellectual deficiency in view of his estimated high premorbid IQ."* (Squire et al., 2010)

This is a valid concern and speaks directly to the argument of hidden pathology. Briefly, structural scans cannot measure cortical activity on that are observable on functional scans (e.g. positron emission tomography or fMRI), and therefore structural scanning alone may not adequately describe diffuse cortical hypoactivty seen after some forms of brain injury (Markowitsch et al., 1997). However, this is normally observed in patients who have had anoxic damage and subsequent coma (Markowitsch et al., 1997). Critically, these patients usually have evidence of a global IQ drop and evidence of

widespread cortical and subcortical atrophy (Cipolotti et al., 2001). Therefore, these authors are right to raise concerns about the use of P04 in this study.

The principal complaint for these authors though was:

> *"Patients with limbic encephalitis can also perform poorly on tests of frontal lobe function. They may also confabulate, be confused, have seizures, manifest personality changes, and have EEG abnormalities in areas outside the medial temporal lobe. Patients with elevated serum VGKC-Abs can even present with frontotemporal-like dementia. These features of limbic encephalitis are associated mainly with its acute presentation. Nevertheless, because the condition presents initially with signs of broad cognitive impairment, it is possible that even patients who have stabilized with treatment can have persisting dysfunction in regions other than the medial temporal lobe."* (Squire et al., 2010)

As described above, and as acknowledged by the authors, these are the acute features of the disease, which resolve following treatment (Bataller et al., 2007; Bien et al., 2007; Buckley et al., 2001; Harrower et al., 2006; Irani et al., 2008; Jacob et al., 2008; Schott et al., 2003; Thieben et al., 2004; Vincent et al., 2004; Wong et al., 2010). Longitudinal neuropsychological studies likewise show this executive dysfunction during the acute stage but its resolution following treatment (Butler et al., 2014; Frisch et al., 2013; although see Bettcher et al., 2014). One of the studies cited by these authors for evidence of frontal dysexecutive features and electroencephalogram (EEG) changes outside the MTL, do later in their paper describe the resolution of the behavioural symptoms (Schott et al., 2003), although repeat EEG is not performed. Seizures are indeed a frequent feature of VGKC-complex LE, but they are localized to the temporal lobe and not generalized, in keeping with many other patients used in studies of declarative memory used by these authors (patients PH and LH, Bayley et al., 2005). The authors also cite a paper in which global atrophy was seen on long-term follow-up (Schott et al., 2003, see also Irani et al., 2013). The immediate resolution of this is not clear, although, as shown above, in a longitudinal study using age-matched controls, compared to the significantly younger controls compared to patients used by Irani *et al.*, and 15 patients found significant reductions in hippocampal and amygdalae volumes with all other MTL cortical regions unaffected (Wagner et al., 2014). Therefore, the

objections raised by (Squire et al., 2010) appear to be a conflation of the acute presentation with the post-treatment status of these patients.

1.4.1.3. Comparing VGKC-complex LE to other human models of MTL lesions

It is worthwhile briefly considering the appropriateness of VGKC-LE compared to two staple aetiologies used in memory research: viral encephalitis (Bayley et al., 2005; Rosenbaum et al., 2008), and anoxia (Bayley et al., 2005; Cipolotti et al., 2001).

1.4.1.3.1. Viral encephalitis

Viral encephalitis causes inflammation of the brain parenchyma and is generally characterized by an acute fever, altered mental status (i.e. confusion and disorientation), focal neurological symptoms, and generalized or focal seizures (Venkatesan et al., 2013). Severe disability is reported in up to 56% of survivors (Floret et al., 2007; Granerod et al., 2010; Thakur et al., 2013). In a large series of patients with encephalitis, 50.5% of patients with viral encephalitis had a good outcome at discharge compared with 40.5% of those with autoimmune encephalitis (collapsed across all forms including NMDA-receptor encephalitis which has a difficult outcome profile, Singh et al., 2014; Titulaer et al., 2013). Previous work has shown that the antigenic target of the virus is concentrated in the medial and inferior temporal lobes, the hippocampus, amygdaloid nuclei, olfactory cortex, insula and cingulate gyrus (Esiri, 1982) and pathological features are often found in the medial temporal lobes, orbitofrontal cortex and the anterior cingulate cortex (for review, Hokkanen and Launes, 2007). Moreover, viral encephalitis is often associated with a wide-range of cognitive impairment including amnesia, executive dysfunction, anomia, global cognitive decline, visuoperceptual dysfunction (Hokkanen and Launes, 2007; Hokkanen et al., 1996). Epilepsy is often observed following viral encephalitis (Hokkanen and Launes, 2007). The EEG findings in herpes simplex viral encephalitis (the most common aetiology used in cognitive neuroscience) typical show background slowing with periodic lateralized epileptiform discharge (Steiner et al., 2005). Acute MRI in herpes simplex encephalitis is usually associated with temporal lobe inflammation (i.e., not limited to the MTL) and inflammation of the cingulate gyrus is highly suggestive of this disease (Steiner et al., 2005). Generalised oedema is also observed (Steiner et al., 2005).

1.4.1.3.2. Anoxia

Global cerebral ischaemia and hypoxic-ischaemic injury are often seen after periods of cardiac arrest with patients frequently requiring intensive care support (Peskine et al., 2010). Imaging during the immediate perimorbid period is usually normal but can be associated with generalized swelling or basal ganglia changes (Peskine et al., 2010). It has generally been thought that the hippocampi are selectively vulnerable to hypoxia and therefore selective deficits in memory should be observed. However, growing consensus is that the basal ganglia and watershed – those areas that exist at the extremes of cerebral perfusion – cortical regions are the most susceptible structures to hypoxia (Caine and Watson, 2000). Moreover, clinical (Parkin et al., 1987), neuropathological (Grubb et al., 2000; Ng et al., 1989; Sevestre et al., 1988), and neuroimaging studies (Wallays et al., 1995) suggest that isolated hippocampal injury is an unusual consequence of cerebral anoxia (Caine and Watson, 2000). Therefore, the cognitive sequelae are frequently observed to be amnesia, executive dysfunction (Peskine et al., 2004; Tiainen et al., 2007), personality change, visuospatial deficits, and anomia (Peskine et al., 2010). Therefore even this well-established model of hippocampal damage has several caveats associated with the interpretation of the behavioural data associated with it.

1.4.1.4. The use of VGKC-complex LE in cognitive neuroscience: summary

The most parsimonious interpretation of this evidence is that both viral encephalitis and cerebral anoxia, on balance, appears to be associated with more widespread pathology as other aetiologies, and have a wider range of cognitive deficits postmorbidly than VGKC-complex LE. This is not to say that those cases reported as behaviourally and neuroradiologically focal should not be treated as an adequate lesion model, only that one cannot simply dismiss the use of VGKC-complex LE patients in cognitive neuroscience experiments on an *a priori* basis given that both viral encephalitis and cerebral anoxia are associated with much wider cognitive implications. (Squire et al., 2010) are right to suggest the clinical picture of VGKC-complex LE is complicated, because it is; however, it is no more complicated than either viral encephalitis or cerebral anoxia. This suggests that VGKC-complex LE is at least no worse a model of hippocampal dysfunction than viral encephalitis or anoxia, and is one that warrants

further characterization and assessment, especially given its predilection to produce CA specific pathology (see Chapter 3).

1.5. Structure of this thesis

This thesis will therefore attempt to characterize the *in vivo* hippocampal subfield pathology (Chapter 3), and neuropsychological phenotype (Chapter 4) of a large cohort of VGKC-complex LE patients, and use the observed data to try and determine how behaviourally specific VGKC-complex LE might be. This thesis will then explore retrograde declarative mnemonic performance for both episodic (Chapter 5), and semantic (Chapter 4 and 6) memories. Finally, relationships between hippocampal anatomy and behavioural performance will be examined in Chapter 7.

Chapter 2

Methods and participants

2.1. Chapter 3: *In vivo* quantification of hippocampal subfields in health and disease at 7.0-Tesla

2.1.1. Participants

All participants had no contraindications to MR imaging and reported no claustrophobia or any other reason for intolerance of MR imaging, and had no other neurological (except VGKC-complex LE), psychiatric or medial disorders. The 18 VGKC-complex LE participants (mean age: 64.0±2.55; range: 24-71) were recruited on the basis of having received a formal clinical diagnosis of a single aetiology known to be associated with anterograde amnesia (Irani et al., 2013). Patients were recruited if they were at least six months from the onset of the disease, and were considered clinically stable by their consultant neurologist. The average time from disease to screening was 4.32 years (range: six months to nine years). Informed written consent was obtained from 19 healthy participants (64.6±1.94; range: 22-76) and the participants with amnesia, in accordance with the approval of the Hammersmith and Queen Charlotte's & Chelsea Hospitals Research and Ethics Committee (REC No. 04/Q0406/147).

2.1.2. MRI Acquisition

All measurements were performed with a 7.0-Tesla whole body MR scanner (Achieva, Philips Healthcare, The Netherlands), based at the Sir Peter Mansfield Imaging Centre, University of Nottingham, operated with a volume-transmit 32-element receive coil array (Nova Medical, Inc., Wilmington, MA**,** USA). Each participant was placed head first and in the supine position into the magnet, and bilaterally braced with soft foam pads to minimize motion.

The MRI data acquisition involved the following three sequences: (1) a rapid whole head sagittal T1 weighted localizer images to verify head position and plan an oblique coronal volume of interest oriented perpendicular to the anterior-posterior axis of the hippocampus; (2) a three- dimensional T2-weighted fast spin-echo data set with the refocusing pulse adjusted to optimize contrast over the hippocampal region of the brain (0.39 mm × 0.39 mm × 1.0 mm resolution) in 52 contiguous oblique coronal sections acquired perpendicular to hippocampal axis, covering both hippocampi. T2-weighting provided the necessary contrast between white and grey matter to visualize the white matter bands between the CA1-3 and DG subfields; and, (3) a three-dimensional whole- brain T1-weighted Phase Sensitive Inversion Recovery sequence (Mougin et al., 2015) (0.6 mm × 0.6 mm × 0.6 mm resolution) with a tailored inversion pulse Tailored RF Pulse for Magnetization Inversion at Ultrahigh Field (Hurley et al., 2010), and providing inherent bias field correction. These sagittal T1- weighted images provided information on global brain morphology, and were used to derive intracranial volume (Mathalon et al., 1993; Nordenskjold et al., 2013). These three sequences took less than 30 min to acquire in total.

2.1.3. Manual hippocampal delineation and segmentation

Hippocampal delineation and segmentation were performed on the FSE images at native resolution (0.39 mm x 0.39 mm x 1 mm), in a coronal orientation and in the anterior-posterior direction. The acquisition of isotropic voxels would have required a reduction of in-plane resolution, in order to restrict the acquisition time to a reasonable duration, which would have made visualization of the subfields more difficult. Unlike prior studies, we elected not to resample the anatomical images to isotropic voxels, because the native resolution was adequate for the analysis consistent with our aims, and spatial interpolation cannot overcome the distortion introduced by non-isotropic voxels.

One rater (TDM) segmented bilateral SUB, CA1, CA2, CA3, and DG hippocampal subfields, using the freehand spline drawing and editing tools based manual segmentation tool in ITK-SNAP 3.2 (Yushkevich et al., 2006; http://www.itksnap.org). The segmentation of all hippocampi was repeated in full after at least one month. Three-dimensional rendering of the segmentation in ITK-SNAP 3.2 facilitated tracking of the borders of the subfields closely. The hippocampal subfields were traced in the following order: SUB, CA1, CA2, CA3, and DG.

2.1.3.1. Hippocampal delineation

Both hippocampi were identified in all participants as lobulated structures along the mesial temporal lobe, between the ambient cistern and temporal horn on the 3D-FSE images, guided by the EADC-ADNI Harmonized Protocol for Hippocampal Segmentation (Boccardi et al., 2015; Frisoni et al., 2015). The alveus and fimbria were not included because we were able to differentiate these white matter structures from the grey matter (GM) of the hippocampus. We also did not delineate the ERC, unlike the protocol by (Wisse et al., 2012).

Hippocampal delineation began anteriorly at the point where the CA1 and SUB subfields first became visible (Figure 2.1A), and proceeded from rostral to caudal on the coronal slices. Axial and sagittal planes were also checked frequently during hippocampal delineation and subfield segmentation. The superior border at this initial location was formed by the amygdala; the remaining borders were delineated by the white matter of the temporal lobe stem (Figure 2.1A). Occasionally, the lateral border was formed by the cerebrospinal fluid (CSF) in the temporal horn of the lateral ventricle. Moving posteriorly, the uncal sulcus could usually be visualized within 2.0 mm of the anterior-most slice. If the uncal sulcus could be followed from its fundus to the medial surface, the CSF in the cisterna ambiens defined the medial border of the hippocampus. When moving posteriorly, the region abutting the superior border of the hippocampus changed from the amygdala to either the CSF space or choroid plexus of the temporal horn of the lateral ventricle until the fimbria appeared; at this point, it was designated as the superior border of the hippocampus proper (Figure 2.1B). The superomedial border was defined as the CSF in the cisterna ambiens, where the uncus was no longer attached to the amygdala.

The border of the CA genu was defined superiorly as the border with the CSF space of the temporal horn of the lateral ventricle, around the curvature until it met the

parahippocampal gyrus inferiorly. At this point, a hypointense line between the two structures defined the inferior border of the hippocampus. The inferomedial border of the hippocampus was defined as the angle where the SUB met the ERC (Figure 2.1B), when following it along its medial traverse axis. An anterior-posterior hypointense line at this point usually signaled the transition from the SUB into the ERC; however, part of ERC may still have contributed towards SUB, because ERC can sometimes be found in the hippocampal fissure (Insausti et al., 1998).

All of these borders continued posteriorly, where the tail of the hippocampus began to angulate superiomedially, initially broadening until eventually thinning forming the fornix in the inferior floor of the atrium of the lateral ventricle. The anterior-posterior extent of the hippocampus was followed until it became too narrow to visualize (Figure 2.1F; Malykhin et al., 2010). The posterior-most aspect of the hippocampus was sought because the 3D-rendered images bore a noteworthy resemblance to the appearance of the hippocampus in anatomical models, suggesting that little or no distortion of the *in vivo* anatomy occurred with this technique.

2.1.3.2. Boundaries between head, body, and tail subregions

The boundary between the hippocampal head and body was defined as the first slice in which the uncal recess emerged on the superomedial surface of the hippocampus (Rajah et al., 2010), or where the medial extension of the uncal apex was seen (Malykhin et al., 2008). These structures were normally seen within the same slice (Figure 2.1D). The boundary between the hippocampal body and tail was defined at the first coronal slice in which the fornix was seen either in full profile (Malykhin et al., 2008), or, where the hippocampal grey matter appeared infero-medially to the trigone of the lateral ventricle or became separated from the wall of the lateral ventricle (Malykhin et al., 2008; Rajah et al., 2010). The tail was followed as posteriorly as the imaging allowed. The methods used to define the medial, inferior, lateral and superior boundaries of the hippocampus are described below.

2.1.3.3. Hippocampal subfield delineation and segmentation between SUB, CA1, CA2, CA3, and DG

The same hippocampal subfield segmentation protocol was followed in participants with chronic amnesia and healthy participants.

Manual segmentation of SUB, CA1, CA2, CA3, and DG hippocampal subfields

was guided by the (Duvernoy, 2013) hippocampus atlas and by the 7.0-Tesla manual subfield segmentation protocol of (Wisse et al., 2012), with support from the 4.7-Tesla protocols of (Malykhin et al., 2010) and 3.0-Tesla protocols of (Winterburn et al., 2013) and (Bonnici et al., 2012). The protocol reported by (Wisse et al., 2012) remains the only manual segmentation protocol conducted at 7.0-Tesla with sufficient detail to support systematic segmentation of SUB, CA1, CA2, CA3, and DG subfields.

In the same way as Wisse et al. (2012), we computed measures to describe intra-rater reliability, and additionally reported measures related to the distribution of each of the five subfields along the anterior-posterior axis, as a function of head, body, and tail subdivisions. Delineation was conducted on 52 slices and full segmentation took approximately 6-8 hours. Sulcal cavities, cysts and hypointense voxels consistent with CSF pools that occurred within the hippocampus were excluded from the segmentation. The most challenging areas to delineate were the transitions between subfields towards the head and the tail of the hippocampus.

The boundaries between the different subfields in the pyramidal cell layer of the cornu Ammonis (CA1, CA2 and CA3), as well as between CA1 and the subiculum, were visible and separation was made based on position, shape and intensity. In keeping with other studies, the anterior-most delineation between the CA1 and SUB fields was drawn along the widest medial-lateral line across the extent of the structure (Malykhin et al., 2010). However, in our images, a hypointense line was clearly visible across the extent of this line until the genu of the hippocampus became entirely CA1. This distinction was further aided by the differences in appearance of these histologically distinct regions (Figure 2.1A). Progressing posteriorly, the SUB extends along a more inferomedial path, whereas the CA1 moves in an inferior oblique fashion. When described alongside neighbouring regions – the presubiculum, parasubiculum, and entorhinal cortex, parahippocampal gyrus – and white matter layers, the SUB, also forms part of the extended hippocampal formation.

Wisse et al. (2012) extrapolated the border of the SUB and CA1 from the anterior subdivision along the length of the hippocampal axis according to a best-fit model. However, we were able to visualize the histological distinctions and hypointense border between the SUB and CA1 along the anterior-posterior axis of the hippocampus, so the border was followed as it moved medially into the head and eventually the body of the hippocampus (Wisse et al., 2012). The medial extent of the SUB was represented as a

hypointense line, where the SUB met the superiomedial extent of the parahippocampal gyrus (Figure 2.1A-F). Posteriorly, the SUB disappeared approximately 1.5-3.0 mm before the termination of the hippocampal tail (in keeping with Duvernoy, 2013). Posteriorly, the CA1 region underwent heavy folding to form the gyri of Andreas Retzius, and was, therefore, assigned to CA1 (Figure 2.1C).

The border between CA1 and CA2 became visible within 2.0-3.0 mm of the anterior-most appearance of the hippocampus (usually coinciding with the first appearance of the DG; Figure 2.1C). At this point, the CA2 tended to be either in the vertical segment of the CA genu or at its superior flexure. The CA1-CA2 border was visible as an anterior-posterior hypointense line from the lateral border of the hippocampus to the lateral border of the DG, and was usually found at the lateral most extent of the DG (Figure 2.1D). The CA2-CA3 border was seen as another hypointense line at a distance that was approximately 1-1.5 times the width of the entire CA2 region from the CA1-CA2 border. These borders were visible from their first anterior appearance to the tail of the hippocampus, where they usually disappeared <1 mm from the posterior-most extent of the hippocampus. Notably, these borders could not be seen anterior to their first appearance. By contrast, Wisse et al. (2012) defined CA2 as a square arising from the superior flexure of the hippocampus adjacent to CA3 and CA1, and segmented the CA2 region by extrapolating it along the length of the hippocampus, except for the posterior-most region of the hippocampus.

CA3 was considered to emerge when the CA2 region became visible. The lateral extent of CA3 began at the CA2-CA3 border, and its most medial border was the continuation of its structure to the uncinate gyrus. Although the CA3 region does not begin with such a sharp histological distinction, this method proved the most reliable in light of the anatomical features seen in the images (Figure 2.1D). However, the general shape and pattern of these regions were in general agreement with other recent studies (Winterburn et al., 2013; Wisse et al., 2012). Posteriorly, the CA1 and CA3 fields appeared to involute both the DG and CA2 regions, but there was a clear hypointense line distinguishing the two until the termination of the hippocampus.

The DG tended to appear within 2.0-3.0 mm of the anterior-most hippocampal slice, within the folds of the CA1 regions of the *digitationes hippocampi*, and appeared as contained structures, surrounded by a hypointense line representing the SLRM of CA and the dendrites of the molecular layer of the DG (Winterburn et al., 2013; Wisse et al.,

2012; see Figure 2.1C). These islands of tissue enlarged and coalesced into a single structure within 0.5-1.0 mm of their first appearance (Figure 2.1D). All borders of the DG were defined as the hypointense line of the stratum lacunosum-moleculare border. Moving posteriorly, the superomedial border of the DG became the CSF space of the temporal horn of the lateral ventricle, when the CA regions no longer enveloped it. Clear delineation of the DG usually ended approximately 1.5-3.0 mm from the posterior-most extent of the hippocampus (Figure 2.1F), and was enveloped once more by the CA regions (as shown in Duvernoy, 2013). The width of the CA fields was defined as tissue that ran from the outermost extent of the hippocampus (as detailed above) to the outermost extent of the stratum lacunosum-moleculare border of the DG. This formed a ribbon of CA tissue clearly distinct along the anterior-posterior axis of the hippocampus. The hyperintense band superior to the hippocampal sulcus is the stratum moleculare of the DG.

Mean subfield volumes for left and right hippocampi were derived from the results of the segmentation protocol implemented in ITK-SNAP 3.2 The percentage contributions of each subfield within head, body, and tail subdivisions, with data averaged and reported separately for left and right hippocampi.

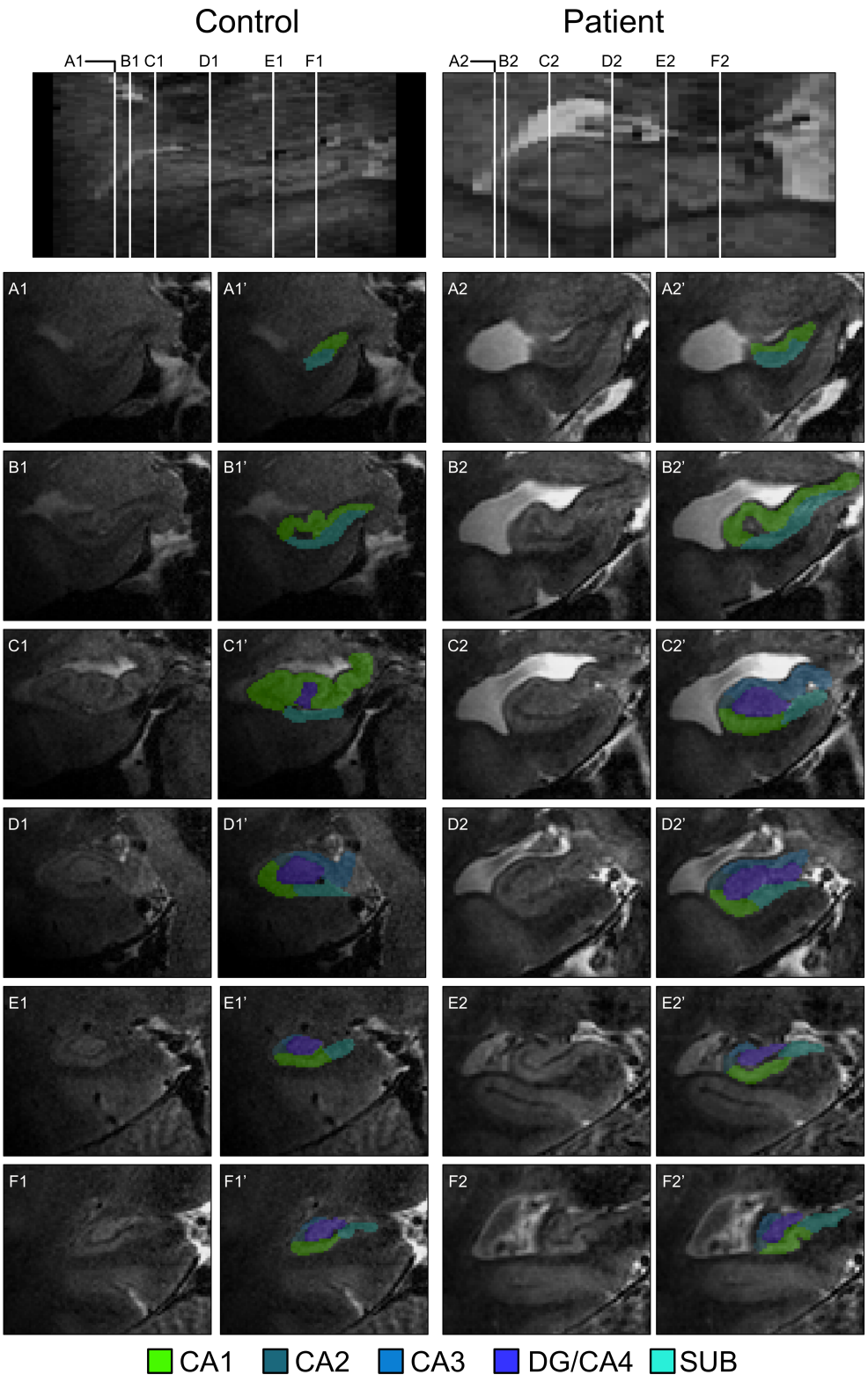
2.1.4. Intrahippocampal cysts

In both patients and healthy controls, intra-hippocampal cysts were occasionally observed. As discussed above, these structures were not included in the volumetric assessment. The hippocampal subfield segmentation protocol was followed in patients in similar manner to that in healthy control participants.

2.1.5. Measurement of total intracranial volumes

Total intracranial volumes (TIV) were derived by applying the sequence of unified segmentation, as implemented in SPM12 (Malone et al., 2015), to the T1-weighted 7.0-Telsa PSIR images of each participant in order to normalise for inter-participant variation and premorbid head size (Jack et al., 1992; Lehericy et al., 1994). Volumes for grey matter, white matter, and cerebrospinal fluid (CSF) could also be obtained via this method. Adjustments for TIV also provide a basis to increase the power to detect between group differences in hippocampal volume (Nordenskjold et al., 2013).

Figure 2.1. Summary of the manual hippocampal subfield segmentation protocol at 7.0-Tesla in (a) health (left panel) and (b) in disease (right panel). Each of the white lines on the sagittal view of the hippocampus corresponds to the 8 coronal locations along the anterior–posterior axis.



2.1.6. Statistical Analyses

Repeat segmentation was performed after at least one month. Intra-class correlations (ICC) were used to calculate the agreement between the two segmentations and were conducted for every subfield (five: CA1, CA2, CA3, DG, and SUB) in each hippocampal region (three: head, body, and tail) for each side (two: left, and right) given 30 ICCs per participant. ICCs were calculated in three ways: (1) the patients as a single group, (2) the controls as a single group, and (3) the patients and controls combined into a single group. This was undertaken to ensure that the segmentation protocol was reliable in both healthy and diseased hippocampi, and to ensure that reliability was not being artificially inflated in patients. The ICC model used was a two-way mixed analysis of variance model to test the degree of absolute agreement. These were undertaken using SPSS Version 22.0 (Armonk, NY; IBM Corp). One patient could not be segmented twice for technical reasons. Therefore, the ICC values reported here are based on the results from 36 subjects, instead of the 37 scanned. Between group ICC analyses were not undertaken as ICCs are not normally distributed values (as one would always expect a negative skew with good reliability scores). ICCs are predominantly used to determine nominal scores of performance (e.g., good, excellent; Landis and Koch, 1977), and so these values are not then amenable to non-parametric analyses either. Therefore, between-group performance can only be assessed on a qualitative basis.

Uncorrected and corrected volumes were calculated for the subfields and regions according to the method demonstrated above, and reported below. These gave volumes for every subfield within each hippocampal region for both the right and left sides. These volumes were then used to create control and patient means and standard errors of the mean (SEM). Relative reduction between patients and controls for regional, total and averaged subfields were calculated by dividing the patient volume by the control volume, and are used for illustrative purposes. Each regional subfield volume was also divided by the total volume of the hippocampus from which it arose, in order to determine what percentage contribution it makes to the total hippocampal volume (Malykhin et al., 2010).

Comparisons between patients and controls were conducted by submitting the data to a standard mixed-model repeated measures omnibus analysis of variance (ANOVA) analysis for all 30 derived volumes (SPSS Version 22.0, Armonk, NY; IBM

Corp). Group differences were assessed using planned comparisons with significance modified with the Bonferroni-Holm least significant difference tests.

2.2. Chapter 4: Extensive neuropsychological assessment of VGKC-complex LE

2.2.1. Participants

Neuropsychological data was obtained in nineteen VGKC-complex LE patients (4 female, average age: 62.3±3.02). All patients were at least six months from their illness, and were considered clinically stable by the consultant neurologist responsible for their clinical management. AMI data was also obtained in 19 age-matched controls (average age: 60.7±2.80), as normative group data is not available for this test, and so that between-groups analysis could be undertaken. The mean time from illness to testing was 4.32 years (range: six months to nine years), by which time longitudinal neuroimaging studies of VGKC-complex LE demonstrate that the anatomical changes become static (Wagner et al., 2015; Wagner et al., 2014). All procedures were approved by the Hammersmith and Queen Charlotte's & Chelsea Hospitals Research and Ethics Committee (REC No. 04/Q0406/147).

2.2.2. Assembling the neuropsychological test battery

A battery of tests was assembled to assess the VGKC-LE patients on the following areas of cognition. All tests were administered by a trained practitioner (TDM), according to the standard practices as detailed in the test manuals, and as a single test session. Where possible and practical, multiple versions of a particular neuropsychological domain was undertaken in order to prevent type I errors (although increasing the risk of type II errors), so that index scores could be derived across multiple neuropsychological domains. Many of the tests used have been highlighted in Section 4.1 as suitable for assessing the domains they are assigned to, and so other similar tests were identified, where possible and practical, in order to constitute the index score.

1. *General intelligence:* Wechsler Adult Intelligence Scale (WASI) – Similarities and Matrix Reasoning (Wechsler, 1997a).
2. *Immediate verbal recall:* logical memory 1, logical memory 1 themes from Wechsler Memory Scale-III (WMS-III (Wechsler, 1997b) and Doors and People – People Task (Baddeley et al., 1994).

3. *Immediate visual recall:* Rey complex figure immediate-recall (Osterreith and Rey, 1944) and Doors and People – Shapes Task (Baddeley et al., 1994).
4. *Immediate single-item recall:* words list 1 from Wechsler Memory Scale-III (WMS-III)(Wechsler, 1997b)
5. *Delayed verbal recall:* logical memory 2, logical memory 2 themes and word list 2 (WMS-III),(Wechsler, 1997b) Doors and People recall measure,(Baddeley et al., 1994)
6. *Delayed visual recall:* Rey complex figure recall (Osterreith and Rey, 1944) and Doors and People visual forgetting score (Baddeley et al., 1994).
7. *Delayed single-item recall:* word list 2 (WMS-III; (Wechsler, 1997b)).
8. *Verbal recognition:* words list 2 recognition (WMS-III; Wechsler, 1997b), Recognition Memory Test for Words (Warrington, 1984.) and Doors and People – Names Task (Baddeley et al., 1994).
9. *Visual recognition:* Recognition Memory Test for Faces (Warrington, 1984.) and Doors and People – Doors Task (Baddeley et al., 1994).
10. *Retrograde memory:* Autobiographical Memory Interview (Kopelman et al., 1989).
11. *Language:* Graded Naming Test, Letter and Category Fluency (Delis-Kaplan Executive Function System, D-KEFS; Delis et al., 2001) and the Camel and Cactus Test (Bozeat et al., 2000).
12. *Executive function:* Category switching, letter-number sequencing and colour-word inhibition (Stroop test, D-KEFS; Delis et al., 2001), and digit span (WMS-III, Wechsler, 1997b).
13. *Visuomotor:* letter sequencing, number sequencing, motor speed and visual scanning (D-KEFS; Delis et al., 2001).
14. *Visuoconstruction:* Rey complex figure copy (Osterreith and Rey, 1944).
15. *Sustained attention:* Telephone Search with Count and Lottery subtests from the Test of Everyday Attention (TEA; Robertson et al., 1994).
16. *Auditory working memory:* Elevators with Distraction, Elevator with Reversal (TEA; Robertson et al., 1994).
17. *Attentional switching:* Visual Elevators (TEA; Robertson et al., 1994).
18. *Visual Selective Attention:* Map Search, Telephone Search (TEA; Robertson et al., 1994).

2.2.3. Analyses

2.2.3.1. Neuropsychological test battery

In order to conduct inferential statistics on the group level performance, the tests were converted into *Z*-scores in order to facilitate comparisons between VGKC-complex LE patient performance for each of the aforementioned neuropsychological domains listed above, and the normative population. Neuropsychology raw scores were converted into standard scores via their manuals (mean 10, standard deviation 3). These were then converted into *Z*-scores (mean 0, standard deviation 1) by subtracting the mean score of 10 from the standard score, and then divided by the SD score of three. A population mean was then calculated for each neuropsychological test, and for every domain tested. These population *Z*-scores were then converted to a *T*-score to allow a one-way Student's *T*-test to be conducted against the control population performance (Butler et al., 2014a). A one-tail test was chosen, as the hypotheses were directional.

Most neuropsychological tests determine significant deficits in performance as those scores that fall below the fifth centile of performance, when compared to a standardized control population (Benton and Hamsher, 1977). However, as detailed in Section 4.1.1, it is expected, *a priori*, that this VGKC-complex LE with their focal CA1 and CA3 lesions to have a group performance above this level. Indeed, this is suggested by the previous longitudinal studies in VGKC-complex LE (Bettcher et al., 2014; Butler et al., 2014a; Frisch et al., 2013). Therefore, given the patients are unlikely to reach this stringent criterion, or indeed the less stringent criteria used elsewhere (Helmstaedter et al., 1997), I elected to test whether there was a significant difference from the control population.

In order to assess for relationships between these neuropsychological domains, Pearson correlations were undertaken. In order to ensure that the degrees of freedom were fewer than the number of subjects undergoing neuropsychological assessment, the mnemonic components were collapsed into single scores. For this analysis the empirical question is whether the superordinate grouping of immediate- or delayed-recall memory performance correlated with other neuropsychological domains, and because the tests comprising these measures rely, in some degree, on the hippocampus for acquisition despite their notional independence at retrieval. Hence, the Immediate Verbal, Visual and Single-item indices were collapsed into Immediate Memory; Delayed Verbal, Visual and

Single-item indices were collapsed into Delayed Memory; and the Verbal and Visual Recognition indices were collapsed to form a Recognition Memory index.

2.2.3.2. Autobiographical Memory Interview

The scores from the individual components of the AMI were collated to form either episodic or semantic memory scores for three distinct epochs: Childhood, Adulthood, and Recent. Individual scores from patients and controls were then taken forward for analysis, after testing the assumption of sphericity with Mauchly's test, and correcting degrees of freedom where appropriate, with a mixed-model univariate ANOVA analysis,

The AMI scores are comprised of cumulative scores for semantic and episodic details across epochs (three: childhood, adulthood, and recent). The semantic component is scored out of 21 for each epoch giving a possible total semantic score of 63, whereas the episodic component is rated out of nine for each epoch giving a total of 27 possible marks for the test. One theory developed throughout this thesis has been that semantic memories should be intact in the current VGKC-complex LE group; hence it would be expected for them to score well for the semantic memory component but poorly for the episodic component. This could consequently mean that in the omnibus ANOVA that subtle loss in episodic memory performance might be diluted by the higher scoring semantic memory score. Therefore, AMI scores will also be converted to percentage scores for each detail type within each epoch so that total percentage scores could be submitted to an omnibus ANOVA.

Significance was set at $p = 0.05$. All statistics were conducted with SPSS Version 22.0 (Armonk, NY; IBM Corp).

2.3. Chapter 5: Standard and modified administrations of the Autobiographical Interview in health and disease

2.3.1. Participants

Seventeen patients (mean age: 62.3±2.23, age range: 24-80; years education: 11.1±1.90, range: 10-16) with a diagnosis of VGKC encephalopathy (with an antibody titre >200 pmols/l) participated in this study. All patients were at least 12 months from their illness and were considered clinical stable by the consultant neurologist responsible for their clinical management. 17 age-matched controls were recruited (mean age: 64.7±1.64; range: 46-76). Patients and controls were not matched for years of education, but were drawn from friend and family groups such that educational differences were minimzed. For the Five Years before illness measure, controls were constrained according to the time five years before their age-matched patients became unwell. All participants gave informed written consent, and all procedures were approved by the Hammersmith and Queen Charlotte's & Chelsea Hospitals Research and Ethics Committee (REC No. 04/Q0406/147).

2.3.2. Administration of the Autobiographical Interview

2.3.2.1. Standard and Modified Epochs

The Autobiographical Interview (AI; Levine et al., 2002) was modified in order to provide a more extensive assessment of retrograde episodic memory. Where possible, the original epochs were maintained in line with the standard administration of the AI; namely, five test periods, each of variable length, ranging from eight to 25 years (0-11, 11-18, 18-30, 30-55, Last Year). The AI was modified so as to acquire a single episodic memory from every decade of the participant's life beginning with the 0-11 period, moving sequentially through subsequent decades. The AI was also modified so as to obtain a memory from the period five years before the illness began, insodoing forming the reference memory internal point score for the planned comparisons. This memory is agreed to be hippocampally-dependent according to both the standard model of consolidation (SMC, Squire and Alvarez, 1995), and the multiple trace theory (MTT, Nadel and Moscovitch, 1997; see Section 5.1.3 for discussion). Due to the variation in the age of participants, the number of memories obtained for each participant ranged from five to seven.

2.3.2.2. Retrieval support

Two levels of retrieval support were given. Initially, participants were asked to recall a unique autobiographical episode that lasted for less than 12 hours, and was specific in time and place (Free Recall). This was followed by a nonspecific cueing phase (General Probe: "Anything else you can say about that event?"). Both the Free Recall and General Probe have five-minute cut-offs, 10 minutes combined, for those who produce lengthy memories. All participants were able to produce a memory during Free Recall, and undergo the General Probe in less than 10 minutes. If a memory could not be recalled for a particular epoch, the participant was shown a list of possible events as contained within the AI Administration Manual. If no memory was forthcoming, then the participant was deemed to have scored 0 for that epoch. Finally, a structured interview (Specific Probe) was administered after the Free Recall and General Probe of all the required events to help support retrieval for components conceptually central to episodic memory: event details, time, place, perceptual details and thoughts and emotions. Each AI was digitally recorded, and I then transcribed the digital recording for later scoring.

2.3.2.3. Scoring of the transcribed manuscripts

Memories were scored according to the standard method outlined in the Autobiographical Interview Scoring Manual (Levine et al., 2002). Scoring of the AI consists of segmenting the transcribed accounts into informational details, or those occurrences, observations or thoughts expressed as a grammatical clause.

Those details that are thought to relate directly to the event, that have a specific time and place or that have a sense of episodic re-experiencing (such as thoughts or emotions) were classified as "internal" or episodic details. Those details that could not be classified according to the aforementioned categories were deemed "external" details. External details were those details not directly related to the event and were then further subdivided into those listed above as well as semantic (factual information or extended events), repetitions (where previous details had been given with no new elaboration associated with it) and other (e.g. metacognitive statements, editorializing and inferences).

Additionally, qualitative ratings were given to each memory by the marker. The time, place, perceptual and emotion/thought sub-categories were rated on a scale from 0 (no information pertaining to that sub-category) to 3 (specific, rich detail relating to the sub-category). Episodic richness was scored on a scale from 0-6. A score from 0-3 was awarded to the ability of the participant to integrate that event into a wider time-context. A score pertaining to the AMI was also awarded for each memory and was assigned according to the standard AMI marking procedure (see Table 5.2). The ratings summed to 21.

2.3.2.4. Verification of narratives and confabulation

One problem raised in a previous study (Kirwan et al., 2008) is that it is difficult to ascertain whether a patient's account of an episodic event is veridical. Where possible, independent accounts of memories were checked with friends and families (themselves control participants) of the patient to determine whether the narrative of the account given was in keeping with their own recollection of the event (differences in personal reflections and thoughts notwithstanding).

As discussed earlier, confabulation, remains a significant problem in patients with significantly impoverished episodic recall (Dab et al., 2004; Nathaniel-James and Frith, 1996). This problem is discussed in greater detail earlier, but to summarise, all 17 patients within this study also completed the Haylings Sentence Completion Test (Burgess and Shallice), which itself requires the successful inhibition of prepotent responses; by contrast, confabulating patients do not successfully complete the Hayling Test (Fotopoulou et al., 2007). As a consequence of the vetting process, and the results from the Hayling Test, it would appear that there was no evidence to indicate that the memories that form the basis of the results from the AI involved significant confabulation.

2.3.2.5. Reliability of scoring

To prevent bias, two independent markers were used to double-mark every memory, and were given transcripts devoid of any personal details or anything that might pertain to group membership (other than allusions to their illness in the later memories; these details were not transcribed if they did not directly relate to the episodic event

being recalled. Intra-rater correlation coefficients were then calculated. This was done by combining the individual free recall and general probe internal and external scores, and the individual specific probe internal and external scores for patients and controls. A two-way mixed intra-rater correlation coefficient for absolute agreement was calculated using SPSS Version 22.0 (Armonk, NY; IBM Corp).

2.3.2.6. Assessing whether patients and controls have a differential reliance on the general and specific probes for successful retrograde episodic retrieval

One possible reason for any differences in patient and control performance in episodic recall could be a differential dependence on the semi-structured nature of the AI. In particular, it could be that, for instance, patients rely on the Specific Probe more than the Free Recall and General Probe to provide the majority of their scores, as it provides a retrieval strategy. In this case it might be expected to see impoverished performance on the General Probe, but normal or enhanced performance during the Specific Probe because the patients were unable to convey their response in the low retrieval support phase. If patients and controls were found to be recalling episodic memories differently across these phases, it might be more suggestive that any deficits might be due to a failure of retrieval strategy.

In order to overcome this potential problem, it was necessary to construct a measure of internal and external details recalled in the general probe and specific probe for both groups, and then assess the proportion of details that arose from each (i.e. is there a difference arising between the groups because they favour recall with a particular type of probe). Accordingly, the proportion of details recalled in the General and Specific Probes was devised by dividing the point score of these two probes by the total internal or total external detail score for that memory (i.e. General Probe internal detail score/total internal detail score). This proportion values were then used to construct a general:specific ratio score, by dividing the specific probe proportion by the general probe proportion. Scores greater than one signified that more details were recalled during the specific probe, whereas scores of less than one signified more details were recalled during the general probe. These scores were then subjected to a mixed-model ANOVA for further analyses.

2.3.2.7. Groupwise analyses of the patient and control performance for the Autobiographical Interview

The twelve objective scores arising from the response categories for each memory (five internal: event details, time place, perceptual details and emotions and thoughts; seven external: event details, time, place, perceptual details, emotions and thoughts, semantic details and repetitions) were then averaged across the two markers and taken forward for analysis. Firstly, total internal detail and total external detail scores were calculated. Within the external detail score repetitions, semantic facts and other details (such as editorializing) were not included in the overall score, as these were not felt to represent episodic or personal semantic memory. These total internal and total external detail scores were derived through the addition of all five-response categories associated with the respective internal and external detail scores (event detail, time, place, perceptual details, thoughts and emotions), and were analysed separately (= 10 + 2 global scores, for internal and external). All results underwent Mauchly's test to see whether the assumption of sphericity had been violated, and, if so, correction was applied to the degrees of freedom.

A mixed-model univariate ANOVA analysis was undertaken for all behavioural measures arising from the AI, and subsequent planned comparisons to test for differences between patient and control performance. For the modified administration of the AI, planned comparisons were undertaken for total internal point score between patients and controls for the 0-11 period (to assess whether the internal point scores at this time period were equivalent between the two groups), and two within-group comparisons for the internal point scores for the 11-18 and 50-60 epochs, and the 11-18 and Last Year epochs to assess for quantitative differences in internal point score generation between recent and remote retrograde episodic memories. The planned comparisons for the standard administration of the AI were exactly the same except for a within-group comparison made for the 11-18 and 30-55 epochs instead of the 11-18 and 50-60 epochs. Comparisons were made in reference to the 11-18 epoch because this time period would be predicted to not be affected by the transformation hypothesis, and so should be truly contextually-rich episodic memory. The AI is principally concerned with the accumulation of internal detail points in subjects, and does so with retrieval support specifically tailored for that detail type. As such the external point scores cannot be considered canonical measures of personal semantic memory function, because they are

not equally supported by the AI methodology. Undertaking detailed planned comparisons for the external details would not be appropriate, and so a between group planned comparison was undertaken for total external detail score, collapsed across all time epochs. To account for the effects of multiple comparisons, the level of significance was set at $p = 0.008$ according to the Bonferroni-Holm method. All data were analysed with SPSS Version 22.0 (Armonk, NY; IBM Corp), and Statistica version 6 (Tulsa, OK; StatSoft Inc.).

2.4. Chapter 6: Development of a standardized test of public event semantic memory, and results from patients with VGKC-complex LE

2.4.1. Participants

Healthy adult volunteers between the ages of 18-80 were invited to participate in this study via advertisements approved by the local research ethics committee, and posted at the John Radcliffe Hospital, and the Department of Experimental Psychology, University of Oxford. A total of 71 healthy participants, aged between 18-74 (mean age: 43.77±2.02; 27 male, 46 female) took part in the study. Participants were split according to the following birth decades: 1930s ($n = 3$; average age: 73.5±0.25), 1940s ($n = 8$; average age: 66.2±0.59), 1950s ($n = 9$; average age: 58.7±2.12), 1960s ($n = 17$; average age: 49.50±0.79), 1970s ($n = 7$; average age: 39.0±2.06), 1980s ($n = 15$; average age: 30.7±1.18), and 1990s ($n = 12$; average age: 19.0±0.40), and all were required to have English as a first language, and to have lived in the UK for most of their lives (maximum of fives years spent living abroad). All participants gave informed written consent, and all procedures were approved by the University of Oxford Central University Research Ethics Committee (REC ref MSD-IREC-C1-2013-110). Two undergraduate students collected this healthy adult data as part of their Final Honours School project, supervised by Dr Clive Rosenthal and Dr Thomas Miller.

Eight patients with VGKC-complex LE also took part in this study, but were limited to just the famous faces, and word meaning subtests due to methodological and time constraints. Four patients were born in the 1940s (average age: 67.8±1.43, one female), and four from the 1950s (average age: 54.8±2.58, one female). The mean time from illness to testing was 4.32 years (range: two to nine years), by which time

longitudinal neuroimaging studies of VGKC-complex LE demonstrate that the anatomical changes become static (Wagner et al., 2015; Wagner et al., 2014).

2.4.2. Design and testing materials

The questions were subdivided into three main categories: (1) general knowledge, (2) famous faces, and (3) word meanings. The general knowledge questions were designed to be wide-ranging and were therefore subdivided into five categories (to counter individual bias in area of interest), as a function of each decade. The number of questions within each category was matched within and between the decades. The category types and number of questions are shown in Table 6.2. Faces were also selected so that each of the five categories was represented at least once and the distribution of the faces within these categories was also controlled across the decades. In total, 800 forced-choice recognition questions were generate across the three main categories. The designated number assigned to the correct answer was counterbalanced within categories, and across decades. Three collaborators independently checked the temporal specificity for the questions comprising the SSM, and only those deemed to be specific were taken forward into the test battery.

2.4.2.1. Generation of temporally specific general knowledge and famous faces questions

The SSM was designed to assess knowledge from the 1930s to the present day, with the time unit of analysis specified at the level of decades. In keeping with a previous study (Cipolotti et al., 2001), candidate general knowledge and famous face questions were generated in conjunction with information available from online encyclopaedias, websites specialising in decade reminiscence, and news sources Events were selected on the basis of the reported prominence during the decade according to the number of news sources discussing the event or personality, followed by a fall in prominence in the subsequent five years according to popular opinion, and a reduction in news coverage since that time. This method is not infalliable, but it does reliably determine those events that appear to be relatively confined to a single decade, and unlikely to be known by those not present for the event itself, unless they have specialist knowledge of that subject. Further methods that could be used to corroborate the temporal specificity of these events, and words are discussed in Section 6.4.4.1. Once identified, corresponding

answers to each of the questions were presented in the form of a four-alternative forced choice recognition test (i.e. one correct answer, with three foils). Where possible, foils were derived from sources that would have maximal interference and plausibility for the target item, in order to limit the impact that other non-mnemonic processes, such as logical inference, could have on successful identification of the target item.

2.4.2.2. Generation of temporally specific questions concerning word meaning

New words and foils were devised in conjunction with collaborators from the Oxford University Press, Oxford English Dictionary. An initial list of list of over 24,000 words was provided by the OED; these words entered the dictionary (and hence the lexicon) in the years from 1920 to the present day. Many of these were immediately excluded because they were technical in nature, and related to the development of a particular field (e.g. antibiotic names). Other words were excluded on the basis that a definition was self-evident on reading the word (e.g. snowboarding). Of the remaining words, written word frequency and usage data from Google Ngram Viewer was used as the basis for objective selection of the candidate words. Google Ngram Viewer documents the frequency with which a particular appears within English written media, and extends to at least 1900. Words were chosen that had at least one discrete usage peak and decline within a 10-year period, and, as such, could be independently verified to have had written language usage confined to a temporally specific decade (see Figure 2.2). Once a candidate list of 20 words per decade had been identified using this methodology, the OED provided foils in the form of definitions informed potential shared etymology, phraseology, or implied meaning, so that the foil definitions appeared to be plausible candidates on the four-alternative forced-choice recognition test.

It was decided to not test the VGKC-complex LE patients on the general knowledge measures, as this was under development and so a final version of the test was not available. Given the SSM took approximately three hours to administer, this was deemed to be an excessive amount of time for these patients to undergo testing for.

Table 2.1. Question categories and numbers used per decade to construct the Survey of Semantic Memory

Subject area	Number of questions
General Knowledge	**64**
News events	32
Film	8
Music	8
Radio/television	8
Sport	8
Famous faces	**20**
Word Meanings	**16**
Total	**100**

Figure 2.2. Screenshot of the Google Ngram Viwer software for the example word 'quisling'. This demonstrates a narrow peak usage between 1940 and 1950, with a diminishing usage towards the present day (i.e., further along the *x*-axis). The *y*-axis measures the yearly count of any given word appearing in the written English language sources available to analysis to the Ngram Viewer software.

2.4.3. Stimuli presentation

Questions were presented to participants in one of three ways: (1) using E-prime Script based version, (2) a portable document file (PDF) format, and (3) a paper version based upon the PDF format.

2.4.3.1. E-prime Script version

The E-prime administration required the programming of questions into image files, and loaded into E-Prime Pro 2.0 (PST), according to whether they would be part of the general knowledge, famous faces, and word meaning blocks (i.e., one of each block per decade). Within each decade, the three main categories were always presented in the order of general knowledge, famous faces, and then word meanings, but the order of question presentation was randomized within these blocks. Responses were obtained by asking participants to choose the correct answer from the four presented to them using a numbered keypad (1-4). There was no time limit for question response, and natural breaks were built into the test both between decades, and between blocks within a decade. Participants were supervised, and were not allowed to access or Internet enabled devices. Participants were given an instruction slide, and given the opportunity to ask any questions they had prior to answering one practice question per category. If the participant did not know the answer to a questions, they were instructed to make an 'educated' guess.

The SSM was started in the decade that corresponded with the participants' decade of birth, and progressed in a remote-to-recent fashion thereafter. After the 2000s decade was completed participants would return to the 1930s epoch and progress through the decades up until the decade that immediately preceded their birth, such that all 800 questions comprising the SSM were completed by each participant. All VGKC-complex LE patients were tested on the E-prime version of the SSM, and just for the famous faces and word meaning questions. Once again they started with the decade of birth, and proceeded through to the present day, before returning to those decades prior to their birth. Performance was determined by assessing the participant response with the correct answer for the question. This way a metric for a proportion of questions answered correctly could be determined for each subtest on a decade-by-decade basis.

2.4.3.2. PDF and paper copies

The PDF and paper versions were administered under similar conditions to the E-prime version of the SSM. The PDF file was derived from images of the questions from the SSM, that were then modified with the inclusion of radio buttons, that allowed participants to select their chosen answer by clicking on the button corresponding to their answer. The SSM was sent to participants via DropBox, and they were told to work through the files in the order given to them. In this way the participant began with their decade of birth, and then proceeded in the same fashion as those undertaking the E-prime version.

The paper version was generated from the PDF format, with four questions appearing on a single A4 page. Participants were instructed to select their chosen answer by circling the numbered answer on the page.

The administration of both these forms of the SSM was not conducted under the supervision of an experimenter, and participants were told to not consult with books or online resources. The order of questions within each of the general knowledge, famous faces, and word meanings were fixed for both the PDF and paper versions of the SSM. The experimenter, according to a predesigned template for each question, determined scores once the participant had finished all questions.

2.4.4. Statistical analysis

Even though the data for control and patient performance for the three main categories of semantic memory were collected sequentially, the data will be treated as separate experiments, and thereby analysed independently. These analyses were designed to assess whether the Decade of Birth had a significant modulatory effect on participant performance, such that those alive during the question will have a significantly higher level of the performance when compared to those who were not yet born. The dependent measure was proportion of questions answered correctly for each modality (i.e., general knowledge, famous faces, or word meanings) for each decade (i.e., eight in total). This gave 24 measures of performance for each participant for the SSM. The VGKC-complex LE patients only underwent famous faces and word meanings for each decade giving a total of 16 measures of proportion of questions answered correctly.

2.4.4.1. Assessing the temporal specificity of the SSM

Prior to specifically testing the hypothesis of temporal specificity, the group mean proportion correct performance was compared against chance performance (i.e., 0.25), using a series of one-way *t*-tests, as it was predicted participants will be above chance should they have been alive during that decade. This was done to assess whether performance for each Decade of Birth was above chance for each modality for two time points: (1) the decade prior to their birth (denoted as -1), and (2) their third decade of life (denoted as +2). Ideally, the group level performance would not be above chance for questions arising before the year of birth; however, above chance performance by groups for those decades that arise *prior* to their decade of birth would not necessarily negate the temporal specificity of the SSM, as one cannot mitigate against specialist, or general knowledge for a particular subject or event (such as political or sporting events, or famous personalities).

To add between-group comparisons in performance to this analysis, the group mean proportion correct measures were taken forward as the dependent measure in a mixed-model univariate ANOVA. It was expected that there would be a main effect of group. In order to assess the hypothesis that the temporally specificity of the questions would result in higher scores for those with earlier decade of birth, a series of planned comparisons were undertaken to compare group mean proportion correct for each Decade of Birth group at two time points: (1) the decade prior to their birth, and (2) two decades after their birth (i.e., the third decade of life). This contrast would assess whether significant improvements in performance occurred as the participant acquired increasing public semantic memory.

Where the assumption of sphercity had been violated, the degrees of freedom were appropriately corrected using Huynh-Feldt correction.

2.4.4.2. Assessing the effects VGKC-complex LE has on retrieval of public semantic memory for faces, and word meanings

Comparisons between patient and control performance for the famous faces and word meanings were limited by the small number of participants in the VGKC-complex LE group. As the assumptions of parametric analysis were not met – specifically population variances were not equal, and that this was not a large enough sample from

the patient population – non-parametric Mann-Whitney U analyses were conducted to assess whether or not there were group differences in performance on the SSM. Significance values were corrected for multiple comparisons using the Bonferroni-Holm method. One-way *T*-test values were also obtained to assess patient performance against chance for the decade before (-1), and two decades after birth. All analyses for this chapter were undertaken with SPSS Version 22.0 (Armonk, NY; IBM Corp).

2.5. Chapter 7: Assessing the cognitive sequelae of VGKC-complex LE and its utility as a model of hippocampal amnesia

2.5.1. Participants

Eighteen participants with a diagnosis of VGKC-complex LE (mean age of onset: 58.1±3.26; median: 62; range: 18-78) underwent neuropsychological testing, the Autobiographical Interview, and 7.0-Tesla neuroimaging with subsequent subfield segmentation. Images from one patient could not be used for analysis due to movement artifact, and two patients did not undergo the whole neuropsychological battery. Of these 16/18 patients undertook the Autobiographical Interview. Therefore 16 patients met the inclusion criteria for regression-based analysis designed to assess the links between immediate verbal and visual recall, and delayed verbal recall-hippocampal subfield; 16 patients for the immediate verbal and visual recall, and delayed verbal recall-AI logistic regression; 15 patients and 15 controls (total = 30) for the regression analyzing the standard administration of the AI and CA3 volume; and, 10 patients and 10 controls met the inclusion criteria for the regression that assessed the modified administration of the AI against CA3 volume. Eighteen patients and 18 controls (total = 36) were included in the multiple regression-based analysess between personal semantic memory score from the Autobiographical Memory Interview and CA3 volume.

2.5.2. Neuropsychological and retrograde memory assessment and volumetric measurement of hippocampal subfield volumes at 7.0-Tesla

Neuropsychological and retrograde memory assessment and hippocampal subfield assessment were undertaken according the respective methods presented in Sections 2.1-4. All subfields volume estimates that were included in these analyses were corrected for intracranial volume (Section 2.1.5). The neuropsychology results were

grouped together into indices according to those described in Chapter 4, and those that were found to be exhibit impairment relative to standardized norms; namely, immediate verbal recall, immediate visual recall, and delayed verbal recall. The individual indices *Z*-scores were then used as dependent variables in the logistic regression analyses.

The Autobiographical Interview scores were formulated in several different ways (see Section 2.5.3 for more details).

Corrected hippocampal total subfield volumes were used as detailed in Section 2.1, and only the *total* hippocampal subfield volumes were used for the AI regressions, as there are no *a priori* reasons to predict an effect of hippocampal laterality, unlike for the neuropsychology regressions (see Section 7.1.2.1). Therefore, the neuropsychological-subfield robust linear regression was undertaken with left and right subfield volumes, providing 10 independent variables in total (two sides with five subfields each). The analysis undertaken in Section 3.3 found that there was an effect of region, with the body of the hippocampus being more atrophied following VGKC-complex LE than the head or tail. However, the planned comparisons demonstrated that this was predominantly due to significant CA3 loss, whereas the volume loss in CA1 was non-significant, suggesting that the observed total hippocampal regional volume loss was mediated by specific subfield loss (notably the tail was less affected than the body or tail, but this could be due to the smaller proportions of CA3 subfields within the tail).

2.5.3. Statistical analyses

2.5.3.1. Robust multiple linear regressions

The relationship between performance on the AI and hippocampal subfield volume estimates was undertaken using the following assumptions:

1. The ANOVA analyzing the performance of patients and controls on both the standard and extended administration revealed a significant main effect of time, but this was driven by patients and controls diverging in performance from the 0-11 period, and by the patients generating significantly fewer internal detail points for each subsequent time epoch (particularly when Group and Time were interaction terms). The planned

comparisons did not reveal significant differences in internal point scores for both patients and controls between the recent (30-55, 50-60, Last Year) and remote (11-18) epochs, suggesting these are equivalent memories as measured by the AI. Whilst internal detail point score was comparatively reduced in the controls for the 0-11, there is no reason to suspect that this memory is not episodic (although it may not be truly hippocampal-dependent; Section 5.4.2), and there are no priors in the literature that suggest this time period could be dropped. As such the total internal detail scores were collapsed across time to give a single score, and this was the dependent variable entered into the multiple linear regression model.

2. The only exception to this was that, conceptually, the Last Year score was obtained after the patients' illness and as such is a memory that was acquired after the hippocampal damage took place, whereas the retrograde memories were all acquired prior to hippocampal damage. This anterograde memory was therefore separated from the retrograde memories, and two separate simultaneous multiple linear regressions were run with these anterograde and total retrograde values.
3. One important question answerable with the current dataset is to what extent can anterograde episodic memory performance predict retrograde episodic memory performance (as operationalized by increasing internal detail point scores)? Chapter 5 suggests that there is an absence of a temporal gradient in retrograde episodic memory loss, and that therefore these could be considered equivalent memory types. Therefore, the anterograde memory internal point score was used as an independent variable to predict cumulative internal detail point scores from all epochs for both the standard and modified administrations of the AI, across patients and controls. This is the regression best supported by the data in Chapter 5; however, there is some theoretical interest in whether this anterograde internal detail score might predict retrograde internal detail point scores for each individual epoch of both forms of the AI. In this case, all scores for these epochs were entered into the regression model as dependent variables, with the independent variable being the anterograde internal detail point score. It could also be argued that the anterograde memory is not the same mnemonic construct as the retrograde memories,

as it was acquired in the postmorbid period. Therefore, a further exploratory regression was used to examine whether the internal detail point score of the early retrograde memory – acquired with a normal functioning hippocampus – could predict retrograde episodic point across the extended administration of the AI. These memories were all acquired with normal hippocampi, and so any predictive relationships seen with the early retrograde memory period would suggest they too are in some form reliant on the hippocampus for retrieval.

4. Patient lesion studies usually explore how particular regions of the brain contribute to cognitive function in health by measuring what a patient can and cannot do. As such the patients and controls were entered into the regression as a single group. This was done so that combining data from the patients and controls would increase the range of hippocampal subfields volumes, and specifically CA3, and performance on the AI. This means there is a wide range of values on two continuous variables where it could be predicted that increasing degrees of CA3 volume loss will predict poorer performance internal point scores for the AI. The second reason is to increase the number of cases entered into the regression model, and hence improve the predictive power of the model.
5. CA3 volume *alone* will be used as the independent variable for the regressions because it was the only subfield significantly atrophied following VGKC-complex LE. The only exception to this will be regressions involving the neuropsychology indices, as outlined in Section 7.1.2, there are several *a priori* reasons to include all subfield volumes in order to investigate the predictive relationship between subfields and neuropsychological performance.

For the personal semantic memory-subfield regression, the total accumulated personal semantic memory point score from the AMI will be used, because the ANOVA from Section 4.3.3 demonstrated no significant effect of time on this score for both patients and controls. As with hippocampal subfield volumes, cumulative point scores on the AMI are continuous variables, so are appropriate for use in linear modeling.

Robust linear regression with Huber's correction was used in all analyses that follow because given the relatively small sample sizes of patients and controls (n = 30 for the standard administration, n = 20 for the extended administration, n = 36 for the AMI, n = 17 for the neuropsychological indices). Robust regression is able to better handle outliers. These regressions were carried out NCSS version 9 (Kaysville, Utah; NCSS LLC).

2.5.3.2. Logistic regressions

A logistic regression is a multiple regression with outcomes that are categorical variables, and a predictor variable that is continuous or categorical. Many neuropsychological tests score subjects according to a binary system (i.e. did the participant get the answer or not), the scores of which are typically compared to an age-matched population, and a standard or *Z*-score derived (Smithson et al., 2011). This binary information allows another form of analysis, principally whether the heterogeneity in performance within a patient population across several neuropsychological domains (i.e., dispersion) can be predicted with continuous independent variable (Smithson et al., 2011). Using a binomial general linear model (GLM), it is possible to construct a logistic regression, in order to investigate the relationships between several numerical variables. This technique (Smithson et al., 2011) is structured to determine, firstly, whether a range of scores arising from a population demonstrate over-dispersion (that is whether there is heterogeneity within that population in terms of performance). Secondly, predictors can then be used to try and explain this variance within the population. To assess for independent predictors of patient performance heterogeneity for those neuropsychological indices found to be significantly reduced from Chapter 4 (immediate verbal and visual recall, and delayed verbal recall), the binomial GLM method reported in (Smithson et al., 2011) was used. An index score was transformed into a raw score for the tests in which raw scores were available (see Table 7.1), and the measure of heterogeneity and regression values are reported below.

Several measures from the AI were used as independent variables within the logistic regression to assess their relationship to neuropsychological performance. In order to demonstrate the specific relationship between patient AI and neuropsychological performance, the Anterograde Internal detail point scores from the patients' controls were used as independent variable, with the specific prediction of a non-significant relationship. These point score measures coded for: anterograde internal

details, anterograde external details, controls anterograde internal details, retrograde internal detail and retrograde external detail, and finally collapsing across all the internal details from each epoch (Total Internal). The logistic regression was performed on SPSS Version 22.0 (Armonk, NY; IBM Corp).

Table 2.2. Neuropsychological tests comprising the immediate verbal and visual recall, and delayed verbal recall indices, and maximum available subtest and total index scores used in the logistic regression.

Neuropsychological domain	Test	Max. score
Immediate verbal memory	WMS-III Logical Memory I	75
	WMS-III Logical Memory Themes I	23
	Doors and People: People	36
	Total	**134**
Immediate visual memory	Doors and People: Shapes	36
	ROCF Immediate Recall	36
	Total	**72**
Verbal delayed-recall memory	WMS-III Logical Memory II	50
	WMS-III Logical Memory Themes II	23
	Doors and People: People Delayed	12
	Total	**85**

ROCF, Rey-Osterreith Complex Figure; VOSP, Visual Object and Space Perceptual Battery; WASI, Wechsler Adult Scale of Intelligence; WMS-III, Wechsler Memory Scale-III

Chapter 3

In vivo quantification of hippocampal subfields in health and disease at 7.0-Tesla

3.1 Introduction

3.1.2. Magnetic resonance imagining findings in VGKC-complex LE

A brief survey of the literature relevant to the assessment of whole-brain pathology in VGKC-complex LE will be undertaken to demonstrate what questions remain in the neuroradiological description of VGKC-complex LE, and the general suitability of VGKC-complex LE as a model of hippocampal dysfunction.

3.1.2.1 Clinical neuroimaging studies in VGKC-complex LE

The majority of clinical MRI studies undertaken in acute VGKC-complex antibody LE demonstrate an active inflammatory process (as shown by high signal on T2 sequences and/or swelling) predominantly confined to the MTL structures (Bien et al., 2000; Bien et al., 2007; Thieben et al., 2004; Vincent et al., 2004). However, as a number of distinct clinical entities have been described, it is becoming increasingly clear that

there are some clinical syndromes (such as faciobrachial dystonic seizures, FBDS), and even cases of VGKC-complex LE as well, that present without hippocampal signal change at any stage during the disease process (Flanagan et al., 2010; Irani et al., 2013). Longitudinal scanning often demonstrates qualitative atrophy of the MTL structures in at least 48% of patients (Kotsenas et al., 2014). Rarely, signal change has been reported outside of the MTL, but this is in the context of small group series, and is believed to perhaps represent the pathophysiological process through which FBDS become manifest (Irani et al., 2008; Irani et al., 2013; Jacob et al., 2008). No mention is made of cognitive consequences of these changes, and so forms an empirical question framed in Chapters 4-6. Table 3.2 provides a summary of reported longitudinal imaging findings, with the acute features found before or at the time of diagnosis of treatment, with serial follow-up imaging following successful treatment (at least six months) where conducted.

3.1.2.2. Volumetric MRI analysis in VGKC-complex LE

Automated volumetric software programmes have been used to provide a quantitative assessment of cortical volume change during and after VGKC-complex LE. Irani *et al.* imaged eight patients with a predominantly FBDS phenotype – associated with less cognitive impairment clinically – and controls to acquire hippocampal, brain, and total intracranial volumes, to derive a series of ratios. Regression analysis found a significant negative association between brain/total intracranial volume and increasing age for both patients and controls, but no association between either hippocampal/total intracranial volume or brain/total intracranial volume, with either cognitive impairment or the dosage of corticosteroids received (Irani et al., 2013). One potential confound in this study is that more than 50% of the patients were older than the oldest control. These results are in keeping with an early volumetric study that undertook imaging during the acute phase of the illness and during the convalescence (Schott et al., 2003). In a single patient, there was 11.4% whole brain, 22.6% left hippocampal, and 39.6% right hippocampal, volume loss over a six-month period, The methods used to quantify derive these values were not made clear in the methods. Even though this was a single case report, the results have been used as a basis to critique the use of VGKC-complex LE as a model of hippocampal dysfunction (Squire et al., 2010).

Table 3.1. Clinical magnetic resonance features in acute and chronic VGKC-complex antibody encephalitis. Where clinical scanning is available for an individual patient, this is reported as a separate row. Those patients who undergo follow-up scanning after treatment of the illness, their findings are reported in the Chronic features column.

Reference	Patient *n*	Acute features	Chronic features
(Buckley et al., 2001)	2	1 x N MTL	-
		1 x L HPC abnormality	-
(Vincent et al., 2004)	10	1 x ↑ signal BL HPC	-
		1 x ↑ signal BL HPC	MTL atrophy, ↑ L HPC swelling, ↑ signal R insula
		1 x N	↑ signal esp. L HPC
		1 x atrophy with ↑ signal R insula	↑ signal normalized
		1 x N	N
		1 x N	BL HPC atrophy
		1 x ↑ signal HPC L>R	N
		1 x ↑ HPC and anterior TL signal	Minimal signal change in HPC
		1 x ↑ L MTL sclerosis and R TL abnormalities	HPC change
		1 x ↑ volume and signal in L HPC and AMYG	Atrophy and signal change L>R
(Bien et al., 2007)	4	1 x HPC swelling	N then atrophy with ↑ signal
(Urbach et al., 2006)	3	-	1 x BL MTL atrophy
		-	1 x L>R MTL atrophy
		-	1 x L HPC atrophy
(Chan et al., 2007)	3	1 x ↑ signal BL HPC	Mild BL MTL atrophy
		1 x ↑ in HPC and AMYG	R HPC atrophy
(Thieben et al., 2004)	7	6 x ↑ signal BL MTL	-
		1 x ↑ signal L MTL	-
(Jacob et al., 2008)	2	-	1 x BL HPC atrophy and ↑ signal R MTL
		1 x ↑ signal hypothalamus and MTL	-

(Sekiguchi et al., 2008)	1	↑ signal HPC	Hypothalamic ↑ signal
(Khan et al., 2009)	1	L HPC atrophy	-
(Chatzikonstantinou et al., 2009)	1	↑ signal and diffuse swelling of R HPC	R HPC atrophy
(Kaymakamzade et al., 2011)	1	↑ signal BL HPC and AMYG	-
(Kapina et al., 2010)	1	L HPC lesion	-
(Kartsounis and de Silva, 2011)	1	↑ BL HPC signal	-
(Wong et al., 2010)	7	7 x ↑ signal and oedema BL HPC	-
(Bataller et al., 2007)	2	2 x ↑ signal BL MTL	-
(Schott et al., 2003)	1	↑ signal BL HPC	22.6% L HPC atrophy, 39.6% R HPC atrophy; 11.4% whole brain volume loss
(Harrower et al., 2006)	2	1 x N	-
(Irani et al., 2008)	3	1 x ↑signal R caudate and putamen 1 x N 1 x ↑ signal in BL HPC	1 x mild R caudate atrophy 1 x N 1 x N
(Irani et al., 2013)	8	8 x N MTL 1 x ↑ putaminal signal	-

AMYG: amygdala; BL: bilateral; HPC: hippocampus; L: left; MTL: medial temporal lobe; N: normal; R: right; ↑: increased.

A more recent study in a larger group of patients (Wagner et al., 2014) quantified the longitudinal structural changes following autoimmune encephalitis using a fully automated software package (FreeSurfer), specifically to observe the longitudinal MTL changes seen during and after VGKC-complex LE. The results were based on data from 15 patients with VGKC-complex LE, and revealed larger amygdalae and hippocampal volumes on their first MRI. At the second MRI (six to 12 months from onset), the patients (n = 13) were found to exhibit a 14.0% mean reduction in amygdala volume and a 6.0% reduction in hippocampal volume. Between first and third MRIs (n = 8) there was

an 18.3% reduction in amygdala and a 10.7% reduction in hippocampal volumes 12-36 months after onset. These findings with corroborated by a subsequent study that used voxel-based morphometry (VBM) to assess grey matter subregional volumes longitudinally. Two groups were assessed: one group had a follow-up MRI within two years of VGKC-complex LE (n = 18), and another group had a follow-up MRI more than two years following their acute illness (n = 16). It is not clear how many patients contributed to both arms of the study. Critically, the authors did not report corresponding longitudinal results from the controls participants. These authors found increased amygdalae volumes in the early MRI group but not in the late group (Wagner et al., 2015). Within the late group though, there was evidence of *increased* left frontal opercular volumes. These two systematic studies in large groups of patients, suggest that, in part, the findings of (Schott et al., 2003) could reflect the natural history of VGKC-complex LE, with initial MTL inflammation followed by atrophy, and the attendant volume changes associated with each of those processes.

These clinical and volumetric studies demonstrate that VGKC-complex LE is neuroradiologically well-characterized, and is not known to be associated with atrophy in regions immediately outside of the hippocampus.

3.1.3. *In vivo* volumetric assessment of the hippocampal subfields in retrograde and anterograde amnesia

Section 1.2.3 describes how the hippocampus is comprised of five anatomically, if not functionally, distinct subfields. The use of ultra-high magnetic field imaging at 7.0-Tesla affords the opportunity to obtain two principal measures of theoretical importance to investigations of memory, for the first time in a large single aetiology group: (1) volumes of the regional hippocampal head, body and tail volumes along the longitudinal axis; and (2) the volumes of the five functional subfields of the hippocampus.

3.1.3.1. Rationale for regional analysis along the longitudinal axis of the hippocampus

Many of the studies cited in Table 3.1 refer to the hippocampus as a single functional region of the brain. In addition to the hippocampal subfields (see Section

3.1.3.2), it is important to quantify changes in hippocampal volume along the longitudinal axis of the hippocampus, in order to determine whether any observed hippocampal atrophy following VGKC-complex LE has a predilection for the head, body or tail. The hippocampus can be reliably identified and segmented into three regions, the head, body, and tail, in studies using field strengths ≥3.0-Tesla (Rajah et al., 2010). Each has been argued to provide discrete contributions to cognition, and is discussed below.

The quantification of subfield volumes as a function of longitudinal region also has the potential to have relevance for investigations into the regional hippocampal contributions to relational memory, and the behavioural consequences of this atrophy is discussed further in Chapters 4-6.

3.1.3.2. Regional hippocampal atrophy along the longitudinal axis in organic disease

One immediate question is whether anterior-posterior dissociations might be seen in organic disease of the hippocampus, and specifically VGKC-complex LE. Malykhin et al. (2008) found that there was a preponderance of posterior volume loss in healthy ageing (when compared to young adults); in contrast, a longitudinal study of patients with Alzheimer's disease found more generalized changes to shape of the hippocampal head, body and subiculum (Wang et al., 2003). In a study of healthy elderly participants who subsequently developed mild cognitive impairment, anterior hippocampal volume loss was more obvious in those who did not develop mild cognitive impairment (MCI; although this was not compared to young adults to assess for absolute changes in posterior hippocampal volumes associated with ageing, Martin et al., 2010).

Driscoll *et al.* also reported significant reductions in posterior but not anterior hippocampal volumes during ageing, but did not include all of the tail before the separation of the crus of the fornix (Driscoll et al., 2003). These data present mixed results concerning the atrophy patterns of healthy ageing or neurodegeneration, but suggest that consideration of the anterior-posterior volumes are important measurements for investigations of organic hippocampal pathology. Therefore, volumes of the head, body and tail will be obtained to both assess for differences between patients with VGKC-complex LE and controls, and to lay the foundations for the assessing the behavioural consequences of any discrepancy observed.

These studies (Driscoll et al., 2003; Martin et al., 2010) suggest that organic diseases of hippocampus are more likely to produce lesions to the anterior hippocampus, although it should be noted that MCI and Alzheimer's disease are neurodegenerative conditions, whereas VGKC-complex LE is an immune-mediated condition, therefore the same regional atrophy patterns might not be expected

The anterior hippocampus has been proposed to be critical to relational binding and/or associational processes (Giovanello et al., 2009; Giovanello et al., 2004), therefore any observed amnesia may be due to preferential atrophy of this region.

3.1.4. Rationale and empirical priors for subfield pathology following VGKC-complex LE

Anatomically, the hippocampus is composed a number of subregions: the cornu Ammonis (CA) regions 1-3, the dentate gyrus (DG) and the subiculum (SUB; Duvernoy, 2013). A central tenet of this chapter is that it is necessary to quantify these subfield volumes, because empirical and theoretical information might be lost when collapsing across the hippocampal subfields (e.g., Bayley et al., 2005; Cipolotti et al., 2001; Gold and Squire, 2005; Hassabis et al., 2007; Rosenbaum et al., 2005; Smith et al., 2013).

The assumption of this chapter thus far is that organic disease to the MTL structures will lead to differential pathology in hippocampal subfields. Several *a priori* reasons can be offered for why differential subfield pathology should be observed following VGKC-complex LE.

The two principal antigenic targets in VGKC-complex LE antibodies are targeted against two main antigenic targets – leucine-rich glioma inactivated-1 (Lgi1), or contactin-associated protein-like 2 (Caspr2) – component proteins of the voltage-gated potassium channel complex, and preferentially bind to mouse CA3 and CA1 hippocampal subfield loci (Irani et al., 2010). The anatomical localisation of gene transcripts of the Lgi family have restricted localisation to the intrahippocampal circuitry of the dentate gyrus and the CA3 field (Herranz-Perez et al., 2010). Conversely, Lgi2-4 transcripts were localized to the medial septal area, thalamic reticular nucleus,

hypothalamic nuclei, reticular formation and the pars compacta component of the substantia nigra (Herranz-Perez et al., 2010). In rodent transcript localization studies, Lgi1 was strongly expressed in the mossy fibre layer of the CA3-hippocampal subfield (Irani et al., 2010), with some expression in the radiatum and some in the pyramidal cells of the hippocampus (Irani et al., 2012). Caspr2 was expressed only in the stratum radiatum of CA3 (Irani et al., 2010; Irani et al., 2012).

Patch-clamp electrophysiological analyses in mice hippocampi show also that sera from VGKC-complex LE patients induces epileptiform activity in the CA3 pyramidal cells *in vitro* (Lalic et al., 2011), suggesting that specific CA3 volume loss might be expected secondary to an epileptic excitotoxic process.

Counter to this point – although still suggestive of focal pathology – pathological case reports in humans have found a loss of pyramidal cells from CA4, but sparing of CA1-3 alongside evidence of reactive astrocytosis (inflammation) extending to the SUB, stopping just prior to joining the parahippocampal gyrus (Khan et al., 2009). Importantly the rest of the temporal lobe demonstrated only mild reactive activation of microglial cells with no evidence of astrocytosis or neuronal death (Khan et al., 2009). Another post-mortem case report simply describes severe neuronal loss with reactive astrocytes, macrophages and scattered T-cells in the right amygdala and adjacent hippocampus (Dunstan and Winer, 2006).

These data suggest that following VGKC-complex LE, structures such as CA1 and CA3 will be atrophied to a greater degree than CA2, DG, and SUB, and therefore imaging at 7.0-Tesla MRI will be used to determine whether the chronic VGKC-complex LE phenotype leads to homologue pathology of human hippocampal subfields, according to natural biophysical boundaries.

3.1.5. *In vivo* hippocampal subfield visualization and quantification using ultra-high field MRI

Examining the hippocampal subfields *in vivo* have proved problematic because the majority of anatomical lesion and functional neuroimaging studies lack the spatial

resolution necessary to quantify these regions according to naturally occurring biophysical boundaries (Wisse et al., 2014b; Wisse et al., 2012).

Ultra-high field strengths (i.e., ≥7.0-Tesla) are associated with increases in both signal-to-noise and contrast-to-noise ratios, leading to improved visualization of microanatomy and *in vivo* pathology (Kraff et al., 2015; Yacoub et al., 2001). Several groups have attempted to segment the subfields at a variety of magnetic field strengths (from 1.5-Tesla to 7.0-Tesla). Table 3.3 demonstrates the range of both scanning and segmentation methodologies used to determine subfield volumes *in vivo*. Methodological differences pertaining to the parameters of scanning are beyond the scope of this thesis, but there are limitations with the segmentation protocols used in these quantitative studies of hippocampal subfields, the resolution of which necessitates the creation of the new segmentation protocol proposed in this chapter. These are elaborated below.

3.1.5.1. Failure to segment the whole hippocampus

It is critical that every subfield be accounted for along the entire longitudinal axis of the hippocampus. Many of the studies in Table 3.3 failed to segment and quantify the entire hippocampus (Ekstrom et al., 2009; Henry et al., 2011; Kerchner et al., 2010; Mueller et al., 2007; Shing et al., 2011; Van Leemput et al., 2008, 2009; Zeineh et al., 2003) or offered only morphological descriptions of the hippocampus as visualized at 7.0-Tesla in health (Theysohn et al., 2009; Thomas et al., 2008). Another study segmented CA1-3 in the body of the hippocampus, but not the head or tail, although it should be noted that this was semi-automated program, and the CA regions are more difficult to delineate in these regions (Yushkevich et al., 2010). Failure to segment along the entire longitudinal axis makes studies vulnerable to the potential confound of regional specific pathology (e.g. pathology arising in just the head, body or tail). Given that the head of the hippocampus is composed predominantly of CA1 and SUB, with the body containing relatively more CA3 (Malykhin et al., 2010), then should VGKC-complex LE result in specific CA1 and CA3 pathology, then it might be expected to be localized specifically to the head and body of the hippocampus.

3.1.5.2 Collapsing across subfields

It is notable that many of the studies listed in Table 3.3 collapse across the subfields either treating the CA regions as a single entity (e.g., (Henry et al., 2011; Van Leemput et al., 2008)), or fractionate the subfields in various grouping such as CA1, CA2/3 and CA4/DG, SUB (e.g., (Hanseeuw et al., 2011; Henry et al., 2011; Mueller et al., 2010; Mueller et al., 2007; Mueller and Weiner, 2009; Shing et al., 2011; Suthana et al., 2014; Van Leemput et al., 2009; Winterburn et al., 2013; Zeineh et al., 2000; Zeineh et al., 2003)). Whilst this often reflects the resolution of the imaging used to delineate these regions, there are reasons why it would be at least preferable to quantify these regions separately. First, these regions have functionally distinct roles within cognition (see Section 1.2). Second, collapsing across the regions makes direct comparisons to the comparative biology and computational literature difficult. Third, as shown in Section 3.1.5.2, the immunological and pathological targets of VGKC- complex LE appear to be CA fields (particularly CA1 and CA3). Collapsing across these regions negates the ability to identify any potential focal pathological signature of VGKC-complex LE, and will form a central part of the segmentation protocol developed in this chapter.

3.1.5.3. Extrapolation of the subfields

Another problem in the studies cited above is the extrapolation of the subfields on the basis of anatomical priors. For instance, Mueller and Weiner (2009) wanted to assess the CA1/2 transition zone, which could not be directly visualized, but demarcated it according to anatomical atlases of the hippocampus about where this region arose in the hippocampus. They defined the CA1/2 border with a line that divided the longest diameter of the hippocampus in two, and then a second perpendicular line was drawn along the widest diameter of the hippocampus. A square was then drawn in the superior most aspect of the outer CA layer of the hippocampus, as informed by the positions of these two lines. The anatomical priors for this segmentation were not described.

Table 3.2. *In vivo* hippocampal subfield segmentation conducted in healthy adult participants. All values are indicated, when reported in original publication. Hippocampal subfields separated by a solidus (i.e., /) were collapsed for delineation and measurement, whereas hippocampal subfields separated by a semi colon were individually delineated and measured (e.g., CA1/CA2/CA3 is shorthand for CA1 + CA2 + CA3).

Year of publication (ascending)	Magnetic Strength (Tesla)	Native Resolution Voxel size/Volume [mm × mm × mm = µl]	Number of slices (n)/Coverage	Labeled Subfields	Comments
Current Study	7.0	0.39 x 0.39 x 1.0 (0.152)	52	CA1; CA2; CA3; DG/CA4; SUB	Whole hippocampus
Zeineh et al. (2000)/(Zeineh et al., 2003)	3.0	0.39 mm × 0.39 mm × 3.0 mm	16/4.8	CA1, CA2/3/DG, SUB, ERC, PRC	
(Wang et al., 2003)	1.5	1.0 × 1.0 × 1.0	Whole brain	CA1; CA2; CA3; CA4; DG; SUB, alveus/fimbria	
(Mueller et al., 2007)	4.0, *in vivo*	(0.4 mm × 0.5 mm) × 2 mm	24	Whole (NA), CA1, CA2, CA3/CA4/DG, SUB, ERC	5 coronal slices segmented – did not segment head or tail
(Bakker et al., 2008; Kirwan et al., 2007)	3.0, *in vivo*	0.75 × 0.75 × 0.75	60/4.5	CA1; CA3/DG; SUB	
(Van Leemput et al., 2008)	3.0 in vivo,	(0.38 × 0.38) × 0.8	208/16.6 (whole brain)	Whole; CA1; CA2/CA3; CA4/DG; preSUB; SUB; hippocampal fissure, fimbria, hippocampal tail, inferior lateral ventricle, choroid plexus	Subfields in hippocampal tail not segmented; limited to right hippocampus; 5 acquisitions were averaged. N=5.

2008)				sublayers.	mm3
(Van Leemput et al., 2009)	3.0	0.38 × 0.38 × 0.8		Whole, CA1, CA2/CA3, CA4/DG, preSUB, SUB, hippocampal fissure, fimbria, hippocampal tail, inferior lateral ventricle, choroid plexus	Basis for parcelation scheme used for the FreeSurfer segmentation, which is based on the subfield distribution in one coronal section in the body of the hippocampus, and then used to segment subfields along the complete long axis of the hippocampus.
(Theysohn et al., 2009)	7.0-Tesla	0.50 × 0.50 × 3.0 (0.750)	32/96		*n* = 13; dentate gyrus/the granule layer measuring 100 lm in width were unsuccessful.
(Yushkevich et al., 2009)	9.4 *ex vivo*	0.2 mm × 0.2 mm × 0.2 mm		Whole (0.92), CA1 (0.88), CA2/CA3 (0.70), DG (hilus) (0.76), DG	Fixed; lacking detailed subfield segmentation in head, and did not segment the subiculum
(Cho et al., 2010)	7.0	0.35 × 0.35 × 0.35		Head; body; tail	*n* = 13 participants. End of the hippocampal tail as the area of disconnect between the hippocampus and the fasciolar gyrus
(Kerchner et al., 2010)	7.0				Borders between DG, CA4, CA3, stratum radiatum and stratum lacunosum-moleculare were not visible;
(Malykhin et al., 2010)	4.7-Tesla	0.52 × 0.68 × 1.0, Images interpolated in-plane to yield a final resolution of 0.26 × 0.34 x 1.0	90/9.0	CA1/2/3, DG, SUB	

(La Joie et al., 2010)	3.0	0.375 × 0.375 × 2.0	13/5.2	CA1; CA2/3/4/DG; SUB	Acquisition did not cover whole hippocampus (posterior slices excluded)
(Yushkevich et al., 2010)	4.0, in vivo	0.4 × 0.5 × 2.0	24/4.8	CA1; CA2; CA3; DG; SUB; ERC; PHG	
(Henry et al., 2011)	7.0	0.25 × 0.25 × 1.2	54	CA1-CA3; C4/DG	Hippocampal head not included.
(Hanseeuw et al., 2011)	3.0	0.81 × 0.95 × 1.0	150/15.0 (whole brain)		CA1, CA2/3, CA4/DG, SUB, pre-SUB, fimbria Automatic segmentation based on Van Leemput et al. (2009)
(Shing et al., 2011)	3.0	0.4 × 0.4 × 2.0	30/6.0	CA1/2; CA3/4/DG; SUB	Hippocampal head not included.
(Bonnici et al., 2012)	3.0	0.52 × 0.52 × 0.5	104/5.2	CA1, CA3, DG, SUB	
(Wisse et al., 2012)	7.0	0.7 mm isotropic voxels 0.35 mm × 0.35 mm × 0.7 m m		Whole (0.83), CA1 (0.85), CA2 (0.83), CA3 (0.69), CA4/DG 0.84), sub (0.84), ERC (0.83)	Posterior 7.4% of the hippocampus is not included in their protocol because they are unable to differentiate subfields in this region of the hippocampal tail
(Winterburn et al., 2013)	3.0	0.3 mm × 0.2 mm × 0.2 mm 0.3 mm × 0.3 mm × 0.3 mm		Whole (0.91), CA1 (0.78), CA2/CA3 (0.64), CA4/DG (0.83),	Entire hippocampus segmented; n = 5 (29 to 57 years (mean age of 37)
(Suthana et al., 2015)	7.0 in vivo,	0.35 x 0.35 x 2.0 mm	21	CA4/DG; CA2; CA3; CA1; SUB	

CA1, cornu Ammonis 1; CA2, cornu Ammonis 2; CA3, cornu Ammonis 3; ERC, entorhinal cortex; DG. Dentate gyrus; SUB, subiculum

Likewise, Wisse et al. (2012) used a similar method based on extrapolation across tissue boundaries to segment the CA2 region along the length of the hippocampus. CA2 was defined as a square arising from the superior flexure of the hippocampus, such that the medial side of the square contacted with the CA3 and the inferior side in touch with CA1. Once again this was performed along the length of the hippocampus, except for the posterior-most region of the hippocampus, where they felt their images were not of sufficient quality to reliably segment (Wisse et al., 2012). The methodology used to determine this protocol was based on a hippocampal atlas that aligns histology with *ex vivo* imaging of the human brain at 9.4-Tesla (Duvernoy, 2013), an atlas used to inform the protocol developed in this chapter. .

The problem with approaches such as these is that they may falsely attribute functional CA tissue to the CA2, when it actually represents either CA1 or CA3 (Wisse et al., 2014a). This may introduce a systematic confound into the assignment of hippocampal subfield. In the context of this thesis, there are good *a priori* assumptions that there will be focal CA3 or CA1 damage following VGKC-complex LE, pathology that could be distorted or missed by the systematic assignation of healthy tissue to either CA3 or CA1, two regions contiguous with CA2. Therefore, the methodology developed in this chapter attempts will use 7.0-Tesla imaging to directly visualize and quantify subfields according to *in vivo* biophysical boundaries, and to not extrapolate these subfields according to hypothetical priors.

3.1.5.4. Hippocampal subfield segmentation in disease at 7.0-Tesla

What remains to be demonstrated is whether using ultra-high field imaging techniques at 7.0-Tesla could have utility in provided more neuroradiological information concerning the long-term hippocampal subfield consequences of VGKC-complex LE. Wisse et al. (2014b) applied their segmentation protocol (Wisse et al., 2012) to patients with AD. They found that all regions of the hippocampus except CA2 were susceptible to atrophy when compared to controls (Wisse et al., 2014b). Segmentation was performed along entire length of the hippocampus, but CA2 was measured using extrapolation, thereby becoming limited by the problems of extrapolation discussed in Section 3.1.6.3. A further study has specifically assessed the white matter tracts within the hippocampus in AD, finding atrophy of the stratum radiatum, lacunosum, and

moleculare (Kerchner et al. (2010). These anatomical regions will not be described in this chapter. Overall, these studies do show that 7.0-Tesla imaging can have utility in delineating and quantifying the subfield volume differences associated with diseases of the MTL, and hence could be applied to VGKC-complex LE.

3.1.5.6. *In vivo* hippocampal subfield visualization and quantification using ultra-high field MRI: summary

In aiming to characterize VGKC-complex LE as a model of hippocampal pathology, as described at a subfield unit of analysis, Sections 3.1.5.1-5 demonstrate cogent reasons why 7.0-Tesla is preferable to lower strength MR fields to volumetrically quantify the five principal hippocampal subfields. The studies in the preceding discussions demonstrate the wide-variance in segmentation approaches to quantifying hippocampal subfields, suggesting that a several key areas warrant attention in order to improve how hippocampal subfields, are segmented along the full longitudinal axis of the hippocampus. Not only will this create a more complete neuroradiological description of the effect VGKC-complex LE on hippocampal subfield volumes, but it will also provide an anatomical foundation to test whether there are any relationships between focal volume loss and behavioural deficits that are observed in Chapters 4-6.

3.1.7. Summary: aims and hypotheses

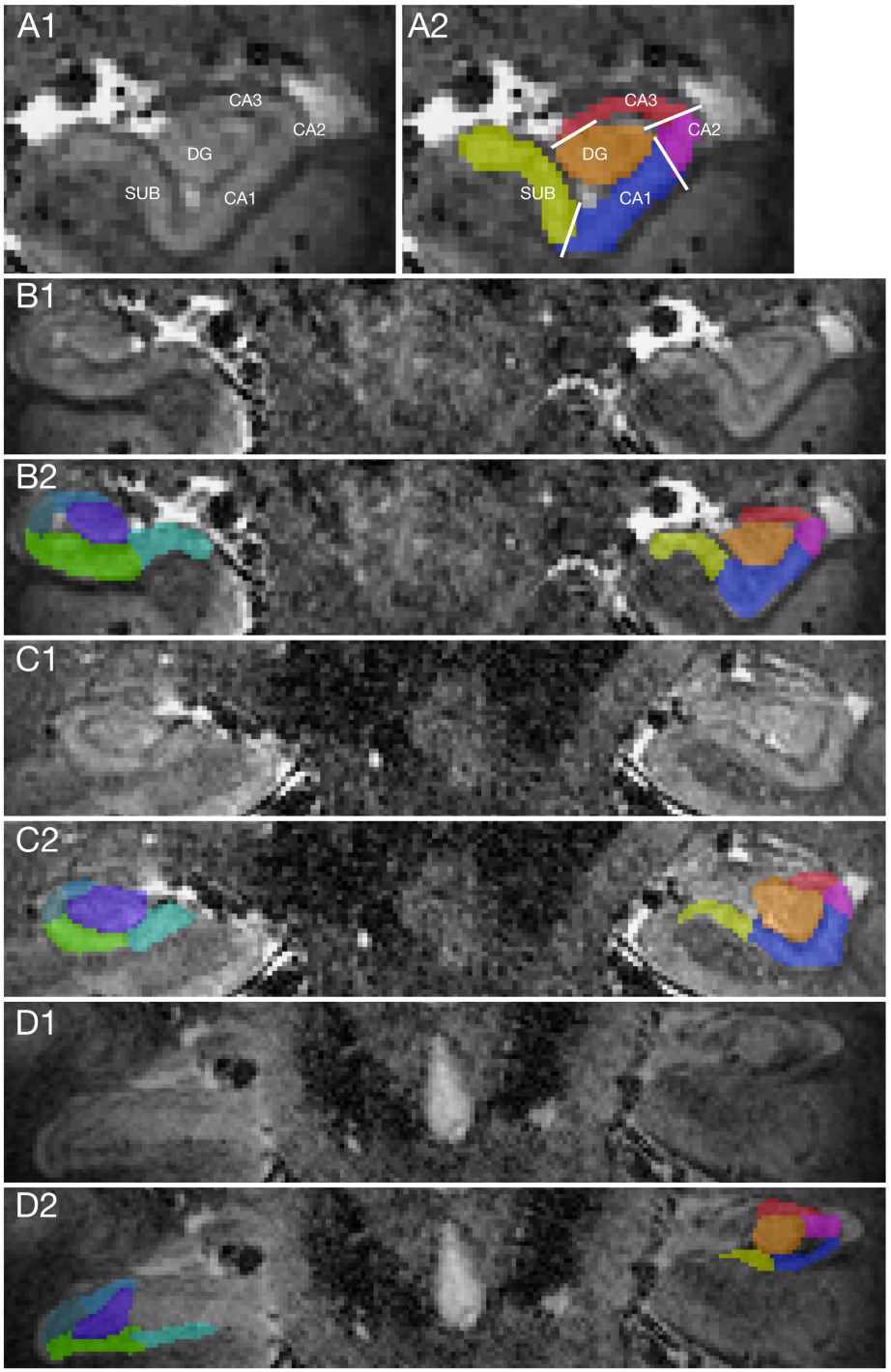
The aim of the current chapter was to conduct ultra-high field imaging at 7.0-Tesla in a group of 18 patients with a single aetiology, VGKC-complex LE, and to obtain volumetric data for each of the subfields constituting the hippocampus proper along the full longitudinal axis of the hippocampus. This approach will also yield regional volumes (head, body and tail), and as such describe the respective distributions of CA1-3, DG, and SUB subfields to these regional volumes. The segmentation protocol will attempt revise those presented in Table 3.2, principally by attempting to segment the subfields according to the anatomical boundaries arising from the differential subfield biophysical characteristics. This will be facilitated by the anatomical images acquired at 7.0-Tesla. The acquisition and segmentation techniques reported here are also directly relevant to establishing a robust and reliable measure of hippocampal subfield volumes in health and disease. The aims for this experiment are as follows:

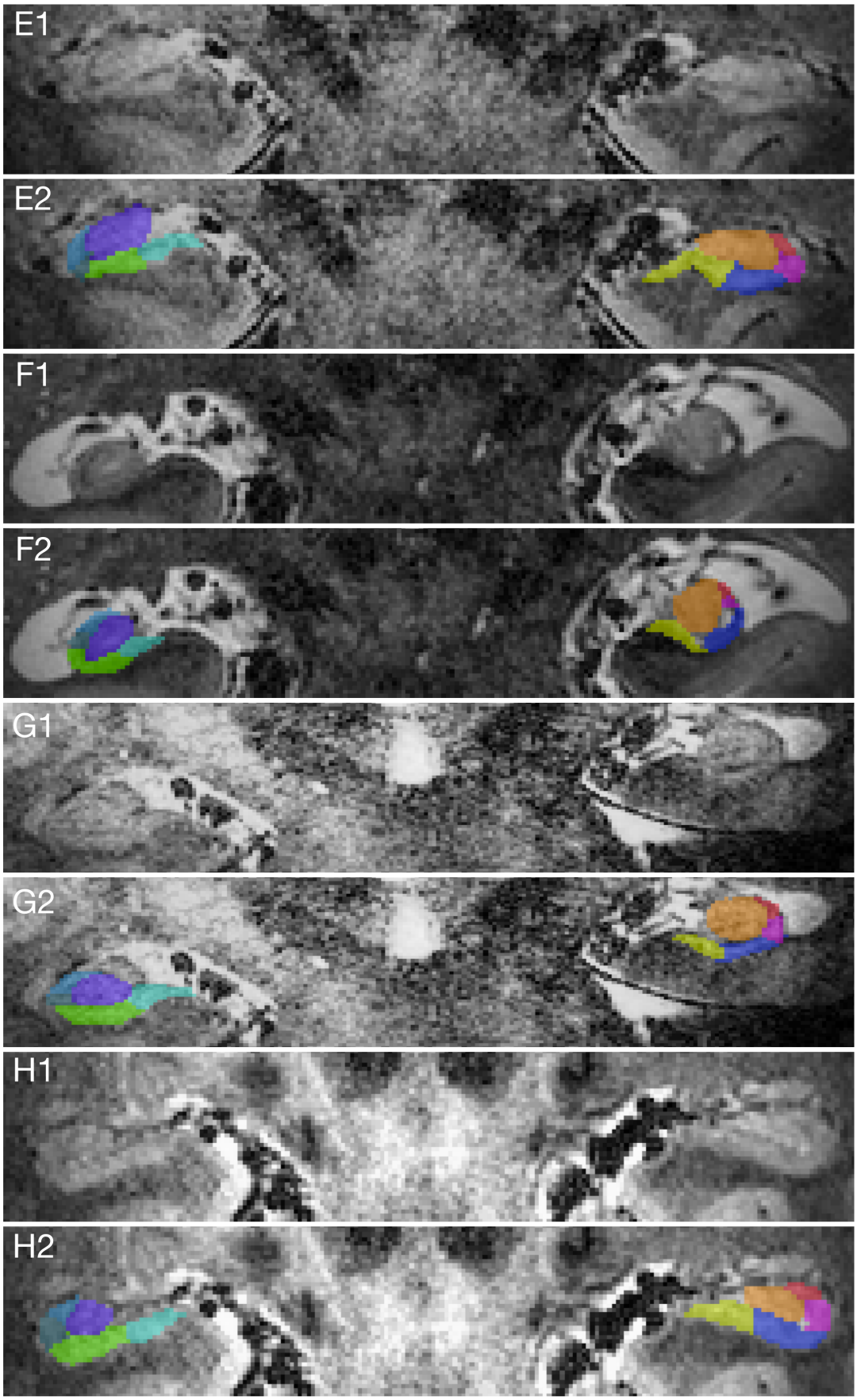
1. The hippocampal subfield segmentation protocol will be informed by naturally occurring, and directly visualized at 7.0-Tesla, biophysical boundaries between subfields. This will be informed, in part, by previous studies (Malykhin et al., 2010; Wisse et al., 2012) and a historadiological atlas (Duvernoy, 2013), but this new protocol will not extrapolate subfield boundaries across slices or regions.
2. The reliance on *in vivo* biophysical boundaries solely for segmentation will produce a protocol that is highly reliable across test and retest segmentations.
3. There will be a significant difference in total hippocampal volume between patients and controls, which is mediated by focal atrophy of the CA1 and CA3 subfields, as the human homologue of the mouse models demonstrated binding of both Lgi1 and Caspr2 to these subfields, and the probably excitotoxic damage caused by epileptic changes noted in patch-clamp analyses (Lalic et al., 2011).
4. The significant reduction in total hippocampal volume in the VGKC-complex LE group may arise in regions with a higher proportion of CA1 and CA3 subfields (e.g., the head or body), and because there is a greater volume of these subfields in the anterior portion of the hippocampus making regional differences more discernible (Malykhin et al., 2010).

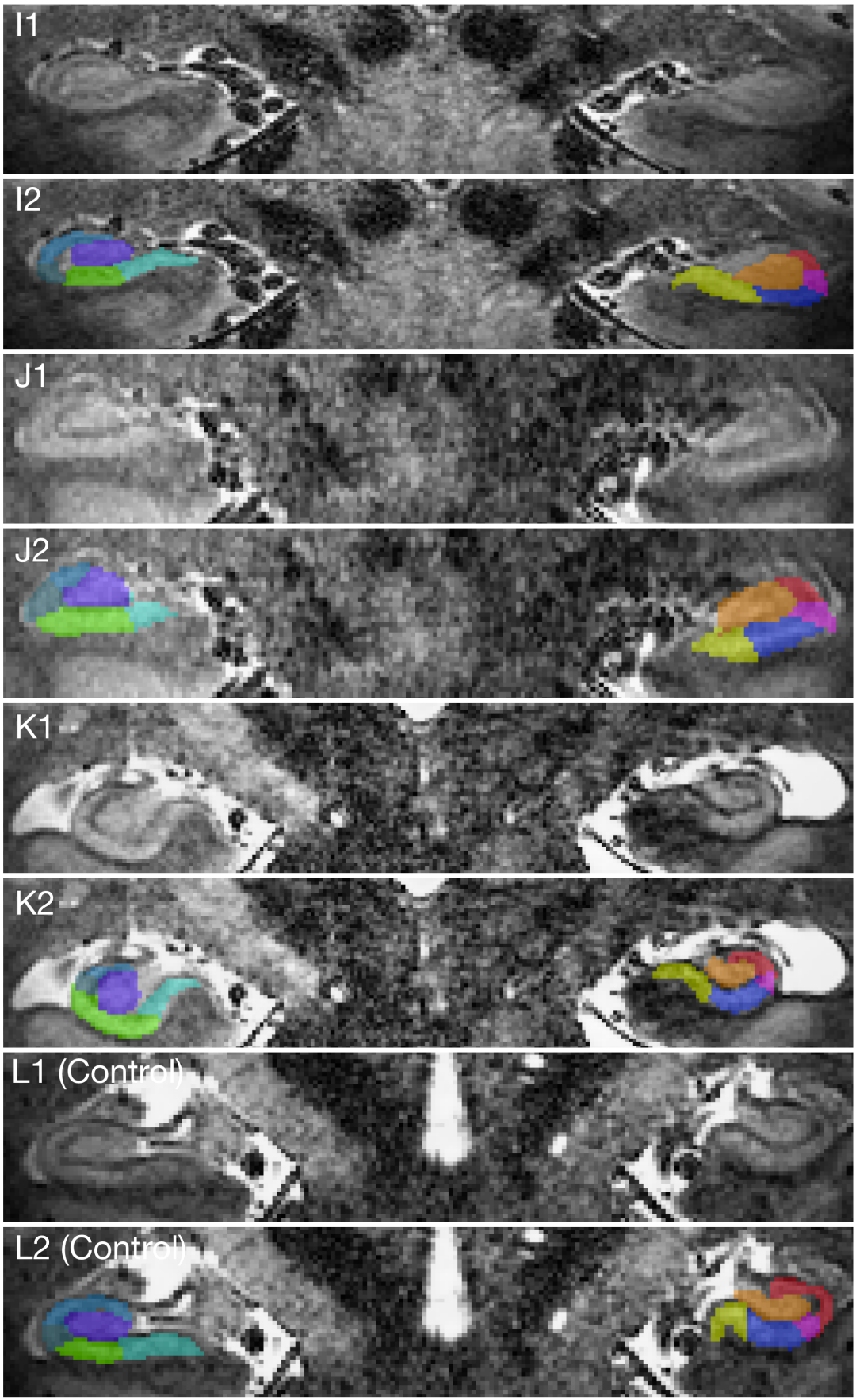
3.2. Methods and participants

See Section 2.1.

Figure 3.1. Coronal images demonstrating the hippocampal subfields at the body of the hippocampi as acquired at 7.0-Tesla. This figure demonstrates the subfields as visualized at 7.0-Tesla (A1) and then segmented according to naturally occurring boundaries (A2). The segmentation protocol developed for this thesis is then demonstrated *in vivo* before (1) and after (2) segmentation for patients (B-K) and a single control (L). The subfield key is shown at the bottom of each section.




E1
E2
F1
F2
G1
G2
H1
H2
Right hippocampus key: CA1 CA2 CA3 DG SUB
Left hippocampus key: CA1 CA2 CA3 DG SUB


I1
I2
J1
J2
K1
K2
L1 (Control)
L2 (Control)
Right hippocampus key: CA1 CA2 CA3 DG SUB
Left hippocampus key: CA1 CA2 CA3 DG SUB

3.3. Results

Figure 3.1 demonstrates the *in vivo* segmentation of 10 patients and a control for comparison.

3.3.1. Hippocampal segmentation at 7.0-Tesla yields highly reliable volumetric data in health and after VGKC-complex LE

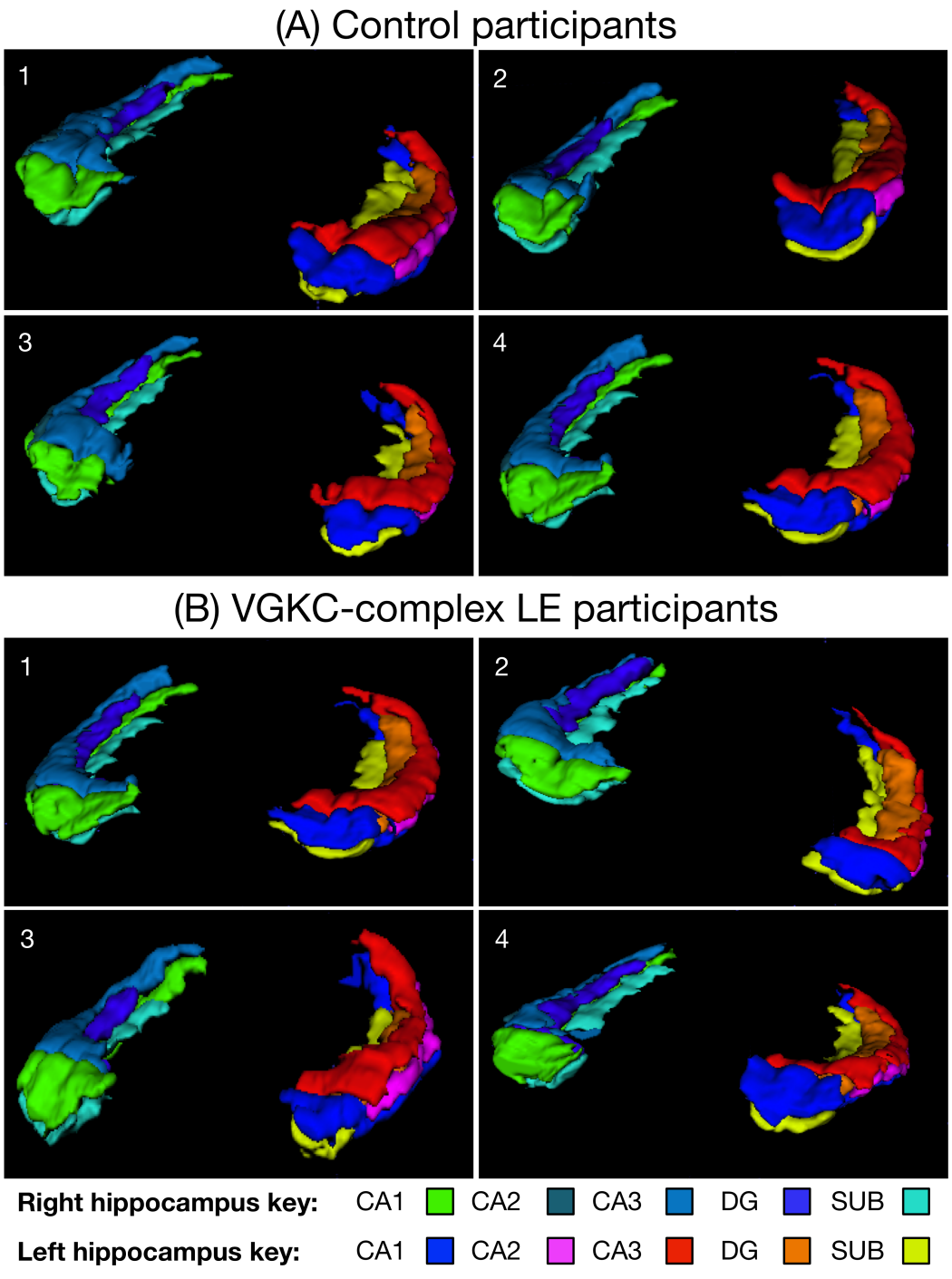
The ICCs for each subfield according to side and region within the hippocampus are shown individually for the 19 controls, and 17 patients and as a single group are shown in Table 3.4. As pathology is the principal variable in this chapter, it was important to demonstrate that its presence did not adversely affect the reliability of segmentation. These data indicate a high-to-excellent consistency for all subfields in all regions of the hippocampus (varying from 0.865 to 0.993).

Table 3.3. Intraclass correlation coefficients (ICC) for individual subfield segmentations according to hippocampal region for patients and controls and combined (total of 36 subjects)

		Patients (n = 17)		Controls (n = 19)		Combined (n=36)	
Region	**Subfield**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
Head	CA1	0.996	0.991	0.983	0.965	0.993	0.980
	CA2	0.883	0.906	0.983	0.971	0.964	0.941
	CA3	0.970	0.965	0.986	0.957	0.987	0.966
	DG	0.977	0.984	0.979	0.971	0.978	0.977
	SUB	0.983	0.935	0.945	0.967	0.965	0.957
Body	CA1	0.990	0.929	0.917	0.936	0.967	0.949
	CA2	0.908	0.883	0.886	0.906	0.896	0.896
	CA3	0.965	0.956	0.932	0.914	0.961	0.955
	DG	0.985	0.924	0.922	0.920	0.969	0.927
	SUB	0.984	0.918	0.964	0.964	0.978	0.949
Tail	CA1	0.976	0.972	0.981	0.970	0.978	0.970
	CA2	0.813	0.887	0.941	0.886	0.865	0.885
	CA3	0.993	0.969	0.986	0.935	0.989	0.947
	DG	0.945	0.969	0.982	0.985	0.959	0.975
	SUB	0.933	0.908	0.929	0.944	0.930	0.917

CA1: cornu Ammonis 1; CA2: cornu Ammonis 2; CA3: cornu Ammonis 3; DG: dentate gyrus; SUB: subiculum

Figure 3.2. Native 3-D renders of manual hippocampal subfield segmentations generated in ITK-SNAP 3.2. Top Panel (a) depicts four representative healthy adult participants, revealing topological relationship between the labeled CA1, CA2, CA3, DG, and SUB hippocampal subfields. Bottom Panel (b) depicts corresponding renders for four participants with chronic amnesia. Colour key corresponds to the respective left and right hippocampal CA1, CA2, CA3, DG, and SUB subfields.



3.3.2. VGKC-complex LE results in atrophy of the CA3 in the head and body but not tail of the hippocampus, and focal CA1 atrophy in the hippocampal body

Raw and normalized mean subfield volumes for patients and controls for the regional subfield are presented in Table 3.5 and Table 3.6 respectively. Three-dimensional representational renders of four patients and four controls is demonstrated in Figure 3.2 for illustrative purposes.

Table 3.4. Raw mean subfield volumes (and standard error of the mean), all conducted twice and averaged across repeated measurements. Upper panel: left and right hippocampi regional subfield volumes for VGKC-complex LE patients and healthy controls; Middle panel: mean total subfield volumes for left and right hippocampi; and Lower panel: averaged subfield volumes across the left and right hippocampi. The relative reduction between patients and controls is also shown for illustrative purposes. Results of interest are shown in bold.

			Mean volume (mm^3) and SEM		
Region	**Side**	**Subfield**	**Patients**	**Controls**	**Rel. Reduct.**
Mean regional subfield volumes for the left and right hippocampi					
Head	Left	CA1	339 (35)	383 (18)	0.88
		CA2	36 (2)	39 (4)	0.90
		CA3	**67 (7)**	**126 (17)**	**0.53**
		DG	166 (13)	178 (12)	0.93
		SUB	166 (11)	190 (10)	0.87
	Right	CA1	433 (30)	530 (28)	0.82
		CA2	47 (4)	45 (4)	1.04
		CA3	**78 (8)**	**127 (15)**	**0.61**
		DG	192 (16)	209 (15)	0.92
		SUB	198 (13)	237 (15)	0.84
Body	Left	**CA1**	**156 (12)**	**204 (10)**	**0.76**
		CA2	57 (4)	61 (3)	0.93
		CA3	**67 (5)**	**100 (6)**	**0.67**
		DG	199 (17)	214 (8)	0.93
		SUB	138 (10)	158 (7)	0.88
	Right	**CA1**	**164 (11)**	**216 (8)**	**0.76**
		CA2	61 (4)	68 (3)	0.90
		CA3	**72 (5)**	**108 (6)**	**0.67**
		DG	189 (12)	218 (7)	0.87
		SUB	135 (8)	164 (7)	0.82
Tail	Left	CA1	133 (10)	121 (10)	1.10
		CA2	17 (2)	14 (2)	1.20
		CA3	114 (10)	111 (8)	1.03
		DG	52 (7)	43 (5)	1.23
		SUB	39 (6)	36 (4)	1.11
	Right	CA1	133 (10)	139 (10)	0.96
		CA2	18 (3)	17 (2)	1.05
		CA3	125 (8)	138 (10)	0.91
		DG	48 (7)	43 (5)	1.11

	SUB	40 (6)	38 (4)	1.05
Mean total left and right subfield and hippocampal volumes				
Left	CA1	627 (54)	707 (24)	0.89
	CA2	109 (6)	115 (6)	0.95
	CA3	**247 (16)**	**337 (23)**	**0.73**
	DG	418 (26)	436 (16)	0.96
	SUB	344 (20)	385 (14)	0.89
	Total	1744 (105)	1980 (71)	0.88
Right	CA1	730 (44)	881 (34)	0.83
	CA2	126 (6)	131 (6)	0.96
	CA3	**275 (11)**	**369 (22)**	**0.74**
	DG	428 (24)	467 (19)	0.92
	SUB	372 (19)	438 (17)	0.85
	Total	1930 (87)	2285 (80)	0.84
Mean subfield and total hippocampal volumes averaged across left and right hippocampi				
	CA1	678 (49)	794 (29)	0.85
	CA2	117 (6)	123 (6)	0.95
	CA3	**261 (14)**	**353 (22)**	**0.74**
	DG	423 (25)	451 (17)	0.94
	SUB	358 (20)	411 (16)	0.87
	Total	1837 (96)	2133 (75)	0.86

CA1: cornu Ammonis 1; CA2: cornu Ammonis 2; CA3: cornu Ammonis 3; DG: dentate gyrus; Rel. Reduct.: relative reduction in subfield volume observed in patients compared to controls; SUB: subiculum

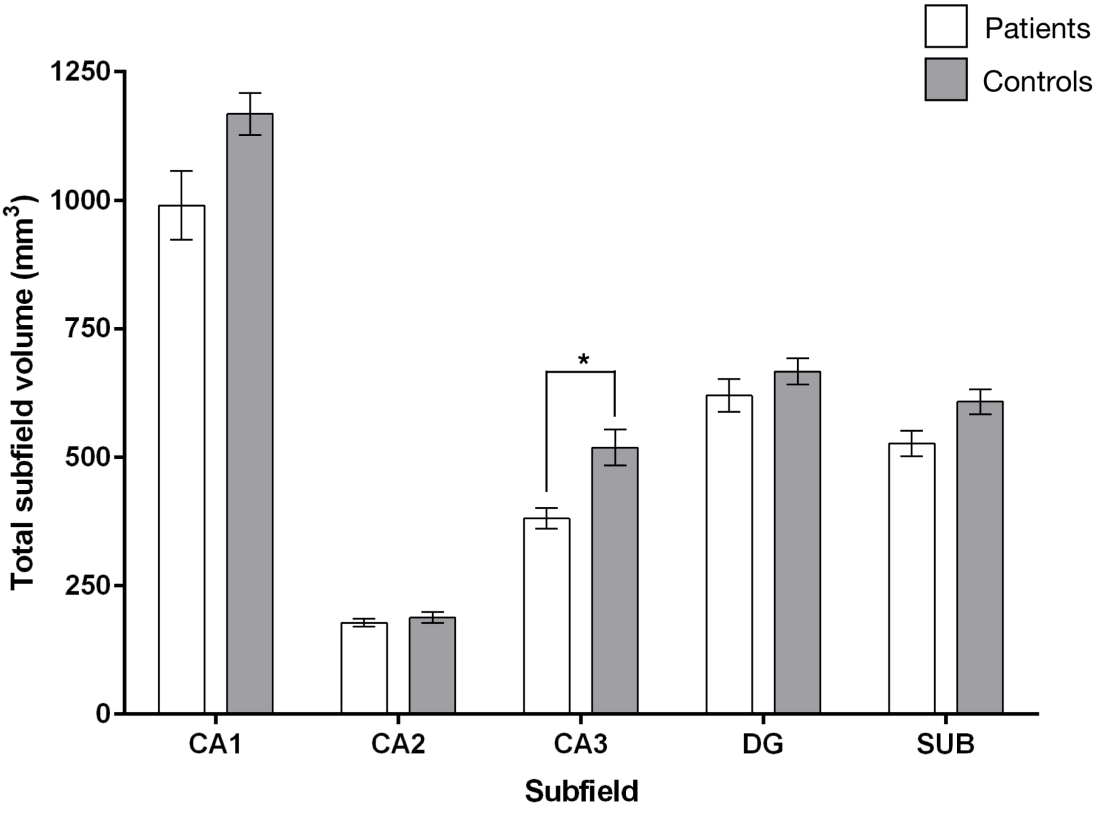
Table 3.5. Normalised mean subfield volumes (and standard error of the mean), all conducted twice and averaged across repeated measurements. Upper panel: left and right hippocampi regional subfield volumes for VGKC-complex LE patients and healthy controls; Middle panel: mean total subfield volumes for left and right hippocampi; and Lower panel: averaged subfield volumes across the left and right hippocampi. Percentage difference between patients and controls is also shown.

			Mean volume (mm^3) and SEM		
Region	**Side**	**Subfield**	**Patients**	**Controls**	**Rel. Reduct.**
Mean regional subfield volumes for the left and right hippocampi					
Head	Left	CA1	247 (24)	283 (14)	0.87
		CA2	26 (2)	29 (3)	0.90
		CA3	**49 (4)**	**93 (12)**	**0.52**
		DG	121 (9)	132 (10)	0.91
		SUB	121 (8)	141 (9)	0.86
	Right	CA1	317 (20)	391 (21)	0.81
		CA2	35 (3)	34 (3)	1.03
		CA3	**57 (6)**	**95 (12)**	**0.60**
		DG	141 (12)	154 (11)	0.91
		SUB	145 (9)	175 (11)	0.83
Body	Left	CA1	114 (9)	150 (8)	0.76
		CA2	42 (3)	45 (2)	0.94
		CA3	**49 (3)**	**74 (5)**	**0.66**
		DG	146 (12)	158 (6)	0.93
		SUB	102 (7)	116 (5)	0.88
	Right	CA1	120 (9)	159 (5)	0.76
		CA2	45 (3)	50 (3)	0.90
		CA3	**53 (4)**	**80 (4)**	**0.67**
		DG	139 (9)	161 (6)	0.87
		SUB	99 (7)	121 (5)	0.82
Tail	Left	CA1	98 (7)	89 (7)	1.10
		CA2	12 (2)	10 (1)	1.22
		CA3	84 (7)	82 (6)	1.03
		DG	39 (5)	31 (3)	1.26
		SUB	29 (4)	26 (2)	1.14
	Right	CA1	98 (8)	102 (7)	0.96
		CA2	13 (2)	13 (1)	1.04
		CA3	92 (6)	103 (8)	0.89
		DG	34 (5)	31 (3)	1.10
		SUB	29 (4)	28 (3)	1.03
Mean total left and right subfield and hippocampal volumes					
	Left	CA1	457 (39)	519 (18)	0.88
		CA2	83 (5)	88 (5)	0.95
		CA3	**180 (12)**	**246 (18)**	**0.73**
		DG	306 (18)	321 (12)	0.95
		SUB	254 (13)	286 (12)	0.89
		Total	1278 (74)	1406 (80)	0.91
	Right	CA1	533 (32)	649 (26)	0.82

CA2	95 (4)	101 (6)	0.95
CA3	**201 (10)**	**274 (20)**	**0.73**
DG	314 (16)	346 (14)	0.91
SUB	273 (14)	322 (13)	0.85
Total	1376 (92)	1620 (108)	0.85
Mean subfield and hippocampal volumes averaged across right and left hippocampi			
CA1	495 (33)	584 (21)	0.85
CA2	89 (4)	94 (5)	0.95
CA3	**190 (10)**	**260 (18)**	**0.73**
DG	310 (16)	333 (13)	0.93
SUB	263 (13)	304 (12)	0.87
Total	1327 (83)	1513 (97)	0.88

CA1: cornu Ammonis 1; CA2: cornu Ammonis 2; CA3: cornu Ammonis 3; DG: dentate gyrus; Rel. Reduct.: relative reduction in subfield volume observed in patients compared to controls; SUB: subiculum

Figure 3.3. Comparative total subfield volumes for patients and controls collapsed across side and subregion. The ANOVA in section 3.3.2 demonstrated that the highest interaction term was group x subfield. As side was not an independent factor for the group level differences, these data are collapsed across sides to give total hippocampal volume. The subsequent planned comparisons then demonstrated significant atrophy of the CA3 subfield. Further exploratory analyses demonstrated that CA3 was atrophied in the head and body of the hippocampus, but these results are not demonstrated here. * denotes $p < 0.0042$.



In order to test for significant differences in regional subfield volumes between patients and controls, a four-way mixed-model ANOVA was conducted for the subfield volumes. There were three within-subjects variables (subfield, region and side) and one between-subjects variable (group). Mauchly's test demonstrated that the assumption of homogeneity had been violated ($\chi^2_{(35)} = 265.65$, $p < 0.001$), therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.28$). A 2 (group: patients, controls) x 5 (subfields: CA1, CA2, CA3, DG and SUB) x 3 (region: head, body, tail) x 2 (side: left, right) four-way mixed-model factorial ANOVA revealed significant main effects of group ($F_{(1,35)} = 7.00$, $p = 0.012$), region ($F_{(1.72,66.31)} = 202.45$, $p < 0.001$), side ($F_{(1,35)} = 51.13$, $p < 0.001$) and subfield ($F_{(1.81,63.50)} = 410.04$, $p < 0.001$). There was a significant two-way interactions between group x subfield ($F_{(1.81,63.50)} = 4.61$, $p = 0.016$), group x region ($F_{(1.72,60.31)} = 5.81$, $p = 0.007$), region x side ($F_{(1.34,46.81)} = 21.79$, $p < 0.001$), region x subfield ($F_{(2.56,89.62)} = 213.02$, $p < 0.001$) and side x subfield ($F_{(1.98,69.11)} = 22.63$, $p < 0.001$) but not group x side ($F_{(1,35)} = 3.43$, $p = 0.072$). There was a significant three-way interactions for region, side and subfield ($F_{(2.20,77.11)} = 21.32$, $p < 0.001$) but not group, region and side ($F_{(1.34,46.81)} = 0.07$, $p = 0.86$), group, side and subfield ($F_{(1.99,69.11)} = 1.78$, $p = 0.18$), group, region and subfield ($F_{(2.56,89.62)} = 2.11$, $p = 0.115$). The four-way interaction for group, region, side, and subfield was not significant ($F_{(2.20,77.11)} = 1.62$, $p = 0.20$).

In order to determine which subfield and/or region was most atrophied following VGKC-complex LE, a series of between-group planned comparisons were undertaken. Significance was set at $p = 0.0042$. These comparisons revealed a significant reduction in CA3 volumes ($F_{(1,35)} = 13.49$, $p = 0.0008$), but not CA1 ($F_{(1,35)} = 5.69$, $p = 0.023$), CA2 ($F_{(1,35)} = 0.28$, $p = 0.60$), DG ($F_{(1,35)} = 1.32$, $p = 0.26$) or SUB ($F_{(1,35)} = 5.21$, $p = 0.028$). Regional analysis found no significant atrophy of the head of the hippocampus ($F_{(1,35)} = 6.67$, $p = 0.014$) or tail ($F_{(1,35)} = 0.11$, $p = 0.74$) but a trend towards significance for the body ($F_{(1,35)} = 8.90$, $p = 0.005$). Further exploratory analysis was then undertaken to see whether this trend towards atrophy in the body was due to more specific atrophy of either CA1 or CA3, the two regions most affected above. These analyses demonstrated that in the head there was only focal atrophy of CA3 ($F_{(1,35)} = 10.53$, $p = 0.0026$) but not CA1 ($F_{(1,35)} = 4.78$, $p = 0.036$). Analyses in the body demonstrated atrophy of both CA3 ($F_{(1,35)} = 22.02$, $p = 0.00003$) and CA1 ($F_{(1,35)} = 13.37$, $p = 0.0008$).

3.3.3. Relative contributions of regional subfields to hippocampal volume was equivalent in VGKC-complex LE and controls

Table 3.7 demonstrates the relative contributions to the hippocampal subfields to the three regions of the hippocampus (head, body and tail), as a percentage of total left or right hippocampal volume.

Table 3.6. Proportion of hippocampal volume as a function of side, subfield, and region (head, body, and tail) of total hippocampal volume. Upper panel: Mean proportion (and standard error of the mean) of each hippocampal region occupied by each subfield in VGKC-complex LE patients and healthy controls. Lower panel: Mean proportion (and standard error of the mean) of the total hippocampal volume occupied by each subfield in VGKC-complex LE patients and healthy controls.

		Patients		Controls	
Region	**Subfield**	**Left**	**Right**	**Left**	**Right**
Proportion of regional volumes occupied by hippocampal subfields					
Head	CA1	0.20 (0.02)	0.23 (0.02)	0.20 (0.01)	0.23 (0.01)
	CA2	0.02 (0.00)	0.02 (0.00)	0.02 (0.00)	0.02 (0.00)
	CA3	0.04 (0.01)	0.04 (0.00)	0.06 (0.01)	0.05 (0.01)
	DG	0.10 (0.01)	0.10 (0.01)	0.09 (0.00)	0.09 (0.01)
	SUB	0.10 (0.01)	0.10 (0.01)	0.10 (0.00)	0.10 (0.00)
Body	CA1	0.09 (0.01)	0.09 (0.01)	0.10 (0.00)	0.10 (0.00)
	CA2	0.03 (0.00)	0.03 (0.00)	0.03 (0.00)	0.03 (0.00)
	CA3	0.04 (0.00)	0.04 (0.00)	0.05 (0.00)	0.05 (0.00)
	DG	0.12 (0.01)	0.10 (0.01)	0.11 (0.00)	0.10 (0.00)
	SUB	0.08 (0.01)	0.07 (0.01)	0.08 (0.00)	0.07 (0.00)
Tail	CA1	0.08 (0.01)	0.07 (0.01)	0.06 (0.00)	0.06 (0.00)
	CA2	0.01 (0.00)	0.01 (0.00)	0.01 (0.00)	0.01 (0.00)
	CA3	0.07 (0.01)	0.07 (0.01)	0.06 (0.00)	0.06 (0.00)
	DG	0.03 (0.01)	0.03 (0.00)	0.02 (0.00)	0.02 (0.00)
	SUB	0.02 (0.00)	0.02 (0.00)	0.02 (0.00)	0.02 (0.00)
Proportion of hippocampal subfields comprising total hippocampal volume					
	CA1	0.37 (0.01)	0.39 (0.01)	0.36 (0.01)	0.39 (0.01)
	CA2	0.06 (0.00)	0.06 (0.00)	0.06 (0.00)	0.06 (0.00)
	CA3	0.15 (0.00)	0.15 (0.01)	0.17 (0.01)	0.16 (0.01)
	DG	0.25 (0.01)	0.23 (0.01)	0.22 (0.00)	0.21 (0.00)
	SUB	0.20 (0.00)	0.19 (0.00)	0.20 (0.00)	0.19 (0.00)

CA1: cornu Ammonis 1; CA2: cornu Ammonis 2; CA3: cornu Ammonis 3; DG: dentate gyrus; SUB: subiculum

In order to assess whether there were any significant difference between patients and control subfield contributions to each of these regions, a four-way omnibus ANOVA was conducted, with three within-subjects factors (subfield, side, and region) and one between-subjects (group). Mauchly's test of sphercity demonstrated that the assumption of sphericity had been violated ($\chi^2_{(35)} = 243.94$, $p < 0.001$), therefore, the

degrees of freedom were corrected using Grennhouse-Geisser estimates of sphericity (ε = 0.32). A 2 (group: patients, controls) x 5 (subfields percentage volume: CA1, CA2. CA3, DG and SUB) x 3 (region: head, body, tail) x 2 (side: left, right) four-way mixed-model factorial ANOVA revealed main effects of region ($F_{(1,35)}$ = 0.18, p < 0.001) and subfield ($F_{(2.00,70.04)}$ = 335.52, p < 0.001), but not of group ($F_{(1,35)}$ = 0.18, p = 0.68) or side ($F_{(1,35)}$ = 0.21, p = 0.65). There were significant two-way interactions between side and region ($F_{(1.39,48.66)}$ = 10.40, p = 0.01), region and subfield ($F_{(2.78,97.36)}$ = 180.52, p < 0.010) and side and subfield ($F_{(2.30,80.40)}$ = 8.15, p < 0.001), but not between group and region ($F_{(1.72,60.14)}$ = 1.71, p = 0.19), group and side ($F_{(1,35)}$ = 0.47, p = 0.50) or group and subfield ($F_{(2.00,70.04)}$ = 1.70, p = 0.19). There was a significant three-way interaction between side, region and subfield ($F_{(2.53,89.09)}$ = 9.52, p < 0.001), but not between group, side and region ($F_{(1.39,48.66)}$ = 0.20, p = 0.74), group, region and subfield ($F_{(2.78,97.36)}$ = 2.08, p = 0.11), or group, side and subfield ($F_{(2.30,80.40)}$ = 0.41, p = 0.70). The four-way interaction between group, side, subfield and region was not significant ($F_{(2.55,89.09)}$ = 0.54, p = 0.63). This suggested that the regional subfield contributions in VGKC-complex LE are equivalent to that of healthy controls.

3.3.4. VGKC-complex LE does not result in significant loss of whole brain grey matter, white matter, cerebrospinal fluid, or total intracranial volumes

Table 3.7. Mean grey matter, white matter, and cerebrospinal fluid volumes, and total intracranial volumes for VGKC-complex LE patients and controls

Tissue type	Patient mean litres (SEM)	Control mean litres (SEM)
Grey matter	0.58 (0.02)	0.63 (0.03)
White matter	0.50 (0.03)	0.50 (0.02)
CSF	0.29 (0.03)	0.23 (0.02)
Total ICV	1.37 (0.03)	1.37 (0.03

CSF, cerebrospinal fluid; ICV, intracranial volume

In order to assess for any significant whole brain differences in grey and white matter, and cerebrospinal fluid volumes following VGKC-complex LE, a two-way omnibus ANOVA was conducted, with one within-subjects factors (tissue type: grey matter, white matter, CSF), and one between-subjects (group). Mauchly's test of sphercity demonstrated that the assumption of sphericity had not been violated ($\chi^2_{(35)}$ = 2.57, p = 0.28). A 2 (group: patients, controls) x 3 (tissue type: grey matter, white matter,

CSF) two-way mixed-model factorial ANOVA revealed main effects of tissue type ($F_{(2,70)}$ = 69.55, $p < 0.001$) but not group $F_{(1,35)}$ = 0.00, p = 0.98. The two-way interaction was not significant ($F_{(2,30)}$ = 1.49, p = 0.23). No further analyses were conducted. A one-way ANOVA was also conducted between total intracranial volumes for the patients and controls, with no significant difference being observed ($F_{(1,35)}$ = 0.001, p = 0.98).

3.4. Discussion

This chapter examined whether it was possible to reliably segment CA1, CA2, CA3, DG and SUB hippocampal subfields along the longitudinal axis of the hippocampus in 18 patients with VGKC-complex LE, and 19 age-matched controls, specifically at a single convalescent time point (see Section 2.1) of at least six months from onset of VGKC-complex LE. There are five contributions this work provides.

First, the results demonstrate that high-resolution imaging at ultra-high field strengths (7.0-Tesla) provided excellent grey-white differentiation and hence could be used to reliably delineate and quantify these subfields in 18 patients with VGKC-complex LE and 19 age-matched controls. These results were also obtained over a wide range of age values, and yet reliable segmentation was possible in the elderly hippocampus, where white matter fibres become less pronounced with age and especially in those over 70 (Bennett et al., 2010).

Second, these results also show that the segmentation protocol devised in this thesis resulted in the full anterior-posterior segmentation of the hippocampus, in health and disease, without extrapolation of subfield tissue boundaries across slices. This resulted in ICC values were in the excellent range of values suggesting that the segmentation technique used here is able to reliably distinguish between subfields without extrapolation (Winterburn et al., 2013; Wisse et al., 2012).

Third, the results demonstrate that this combined imaging and segmentation technique yielded subfield volumes and relative subfield contributions to whole hippocampal volume in keeping with previous studies.

Fourth, these data show that VGKC-complex LE results in significant bilateral atrophy of the CA3 subfield in the head and body of the hippocampus, and CA1 in the hippocampal body, whereas the other subfields were not significantly different.

Fifth, that following VGKC-complex LE there is no significant difference between patients and controls for grey and white matter volumes, and CSF volumes.

3.4.1. Reliability of segmentation protocols at ultra-high MRI field strengths in health and disease

As Table 3.3 demonstrates, multiple segmentation protocols have been developed to volumetrically quantify hippocampal subfields, predominantly in health, but also in disease. As pathology is principal variable in this study, ICCs were obtained for the patients and controls as individual groups, in order to assess whether pathology affected the reliability of the segmentation. The ICC values for the patient group in the present study ranged from 0.815-0.996, and 0.886-0.986 for controls. All of these values are in the highly reliable-to-excellent range of values (Landis and Koch, 1977).

In a 7.0-Tesla study of healthy controls, Wisse et al. (2012) reported ICC values of between 0.74 to 0.98, but most of their values were in 0.80-0.83 range. Importantly, these ICC values arise by collapsing across the longitudinal regions of the hippocampus (i.e., head, body and tail), unlike the present study where ICC values were sought for each regional subfield volume. This study also did not segment the posterior-most 7.4% of the hippocampal tail. However, these ICC values did include ERC volumes (Wisse et al., 2012), a region not included in this study. In a follow-up study using 25 patients with AD or MCI using the same segmentation protocol, but the ICC values were not reported (Wisse et al., 2014b).

In an earlier study based on 4.7-Tesla anatomical neuroimaging, ICCs were 0.952-0.978 in a group of 11 younger adults (aged 23-56; Malykhin et al., 2010). Importantly, this study collapsed across CA1-3 subfields: CA1-3 ICC values were 0.952 on the left and 0.960 on the right. These values are comparable to all of the individual CA1-3 values for the regions obtained in the current study. Another study applying 4.0-Tesla field strength to a group of 42 healthy adults (21-85 years of age; mean: 48.7), used a segmentation protocol that yielded ICC values of 0.99 for CA1, CA2 and CA3/DG for one rater, and values of 066-0.98 for a second rater, with a generally high consistency of agreement between raters (ICC>0.75; Mueller et al., 2007). Once again, Mueller et al. collapsed across the hippocampal regions. It should also be noted that the values obtained in the present study arise from an older control population, suggesting the present segmentation protocol is robust even in older adults. Shing et al. (2011) obtained ICC values of 0.99 for CA1-2, 0.89 for CA3-DG and 0.89 for the SUB for 19 elderly

(mean: 75.4) and 10 younger (mean: 23) healthy adults, collapsing across both groups. As the effects of ageing was the principal variable in this study, then it would have been appropriate to report the ICCs for the two groups separately, as they may have had worse reliability for their elderly population, that was then masked with the younger participants. Moreover, the authors only segmented three contiguous coronal anatomical images from the body of the hippocampus to derive their volumes, limiting the generalizability of their results to either the head or tail of the hippocampus.

The principal difference between this study and those cited above in terms of the measures of reliability is that ICC values for each individual subfield in every region were sought. Reliability for all fifteen regional subfields was robust along the longitudinal length of the hippocampus for both VGKC-complex LE patients and controls. It is unclear from the other studies why they did not seek to obtain regional subfield volumes, as the transition zones for these regions should be visible at lower magnetic field strengths (e.g., 4.7-Tesla, Rajah et al., 2010). Therefore, the segmentation protocol developed, for use at 7.0-Tesla, in this chapter yields highly reliable *in vivo* assessment of hippocampal subfields in both health and disease.

3.4.2. Subfield contributions to regional and whole hippocampal volumetric anatomy in health and VGKC-complex LE

This study found that in both VGKC-complex LE and age-matched controls the largest subfield in terms of volume was CA1, followed, in descending order, by the DG, SUB, CA3 and CA2. It was also observed that the right hippocampus is larger than the left. This lateralized volume difference is in agreement with several previous studies (Malykhin et al., 2010; Winterburn et al., 2013; Wisse et al., 2012). However, the mean control subfield volumes obtained in this study are smaller for both patients and controls than for those cited above. For instance, Wisse et al. (2012) found a CA1 volume of 1.74±0.38 cm^3, CA2 volume of 0.078±0.027 cm^3, CA3 volume of 0.18±0.06 cm^3, DG volume of 0.95±0.25 cm^3 and a SUB volume of 0.80±0.22 cm^3 with an average age of 63.2±7.8 (compared to the control average in this chapter of 64.6±1.94 mm^3). These CA1 volumes are greater than those reported here (average volume: 583.97±20.59 mm^3), as are the DG volumes (average volume: 333.27±12.54 mm^3). CA2 (94.19±5.41 mm^3), CA3 (259.77±17.74 mm^3), and SUB (304.12±11.84 mm^3) volumes are similar to those

reported here for the control participants. Likewise, Winterburn et al. (2013) found (in a group of five adults, average age: 37, range: 29-57) an average CA1 volume of 857.46 mm^3, CA2/3 volume of 208.33 mm^3 (compared to 353.96 mm^3 in the current study), CA4/DG volume of 615.50 mm^3, SUB volume of 390.79 mm^3, and a total hippocampal volume of 2759.31 mm^3 (compared to 1513.26±96.94 mm^3 in the current study). (The authors also measured the SR/SL/SM volumes, a volume not obtained in this study). Malykhin et al. (2010) describe an average DG volume of 791.4 mm^3, CA1-3 1114.9 mm^3 (compared to 937.93 in the current study), SUB 547.7 mm^3, and a total hippocampal volume of 2481.1 mm^3, in 11 adults with an age range from 23-56. Shing et al. (2011) reported average CA1-2 volumes as ~350 mm^3, CA3/4/DG as ~250 mm^3 and SUB as ~200 mm^3, in a group of 19 elderly healthy subjects (mean age: 75.3). Therefore, there is wide variability in the values reported for individual and collapsed subfield volumes between previously published studies alongside the current results.

The various segmentation protocols applied above (Malykhin et al., 2010; Winterburn et al., 2013; Wisse et al., 2012), also probably included the alveus and/or the fimbria, white matter structures not usually considered part of the hippocampus proper. By comparison, the segmentation protocol here did not include white matter structures. The inclusion of white matter structures could also underlie the larger volumes of the CA1 field in these studies.

The segmentation protocol utilized in this study found the subfield contributions to regional volumes did not differ between amnesic patients and controls, with CA1 contributing the most to total hippocampal volume (0.36 for patients, 0.39 for controls), followed by DG (0.21 and 0.25), SUB (0.19 and 0.20), CA3 (0.15 and 0.17) and finally CA2 (0.06 for both patients and controls). These subfield ratios are similar to those in previous studies as shown in Table 3.3, which serves as an additional source of evidence to indicate that the five subfields accurately represent the *in vivo* anatomy for both patients and controls. Similar segmentation studies utilizing manual segmentation techniques at 7.0-Tesla did not report control or patient subfield volumes nor the relative contributions of the subfields to total hippocampal volume (Kerchner et al., 2014; Kerchner et al., 2012; Kerchner et al., 2010).

3.4.3. Hippocampal anatomical imaging in VGKC-complex LE

3.4.3.1. Subfield vulnerability following VGKC-complex LE

The principal finding of this study was that there was a generalized loss of CA3 volume along the longitudinal axis of the hippocampus. The planned comparisons found significantly reduced CA3 volume in the body of the hippocampus, but also for hippocampal body CA1 volumes. DG, SUB and CA2 volumes were otherwise preserved. The two-way interactions of Group and Region and Group and Subfield (and indeed the trend of Group, Region and Subfield) suggest that VGKC-complex LE is associated with significant hippocampal volume loss during the convalescence phase of the illness. This the first study to use ultra-high field MRI to volumetrically assess the subfields of the hippocampus following VGKC-complex LE.

These current data reveal that CA3 appears to be the subfield most affected following VGKC-complex LE, but that CA1 is also affected in the body of the hippocampus, but that all CA regions in the tail remain relatively preserved, and is line with the animal data (Irani et al., 2010). A pathological case report in VGKC-complex LE has found a loss of pyramidal cells from CA4 but sparing of CA1-3 alongside evidence of reactive astrocytosis extending to the SUB, stopping just prior to joining the parahippocampal gyrus (Khan et al., 2009). Another single case report simply describes severe neuronal loss with reactive astrocytes, macrophages and scattered T-cells in the right amygdala and adjacent hippocampus (Dunstan and Winer, 2006). The current data broadly agree with these post-mortem studies, although the resolution afforded by even ultra-high field strength MRI makes it difficult to assess CA4, not least in cases of hippocampal pathology. The relative perseveration of DG and SUB found in this study is corroborated by these post-mortem studies. CA4 region is adjacent to CA3, and projects efferents directly to the CA3 region. Therefore, it might be expected that the CA3 region would be most likely to be deafferentated, and therefore potentially atrophied, in instances of CA4 pathology.

One striking finding from this study was the disproportionate atrophy of CA3. A central clinical feature of VGKC-complex LE is the presence of temporal lobe epilepsy (TLE; Buckley et al., 2001; Schott et al., 2003; Vincent et al., 2004). It is possible that selective CA3 volume loss may arise from excitotoxic lesions associated with TLE, given that sera from VGKC-complex LE induces epileptiform discharges in CA3 pyramidal

neurons *in vitro* (Lalic et al., 2011) or from complement-mediated fixation of bound antibodies (Bien et al., 2012) suggesting the antibodies have direct pathogenicity in humans.

3.4.3.2. Regional vulnerability following VGKC-complex LE

This study has also shown that it is possible to segment the hippocampus along its longitudinal axis following VGKC-complex LE, and to derive regional volumes. Here the hippocampal head was atrophied to a greater degree than the body or tail, a finding not yet described in VGKC-complex LE, and that this atrophy was restricted to CA1 in the body and CA3 in the hippocampal head and body. None of the prior studies that were discussed above attempted to analyse regional subfield volumes in disease (Kerchner et al., 2014; Kerchner et al., 2012; Kerchner et al., 2010; Wisse et al., 2014b).

Investigations into TLE and AD again provide a useful basis of comparison. A manual volumetric study in patients with TLE found that the hippocampal head was most associated with atrophy (Bernasconi et al., 2003). A qualitative investigation of TLE at 7.0-Tesla found that there was a reduced degree and number of digitations in the hippocampal head, although no volumetric analysis was undertaken (Henry et al., 2011). Volumetric studies in AD and MCI have shown that the hippocampal head and body are more susceptible to atrophy than the tail in both AD and MCI (Greene et al., 2012; Martin et al., 2010). Malykhin et al. (2010) have shown that the hippocampal head is predominantly comprised by CA1 and to a lesser degree CA3; this finding is corroborated here. As shown above, CA1 and CA3 were associated with an increased degree of vulnerability to hippocampal pathology.

3.4.5. Implications for behavioural studies into human models of amnesia

VGKC-complex LE is neuroradiologically well-described both qualitatively (Table 3.2) and quantitatively (Wagner et al., 2015; Wagner et al., 2014). The data from this chapter extends this data to a spatial resolution and anatomical visualization that has been rarely described in diseases of the MTL (except AD, MCI, and TLE), and certainly for human models of hippocampal dysfunction. The present data demonstrate that reductions in hippocampal volume can arise from atrophy of CA3, and to a lesser degree

CA1. Therefore, it is not unreasonable to describe VGKC-complex LE as a disease of the hippocampus, and perhaps even of the hippocampal subfields.

Generally though, this study adds to the literature of human models of amnesia (e.g., Bayley et al., 2005; Bayley et al., 2003; Kirwan et al., 2008; Rosenbaum et al., 2008; Smith et al., 2013; Steinvorth et al., 2005) in several ways. Firstly, this study has attempted to use neuroimaging to quantify the subfields of the hippocampus, instead of previous studies that sought to place patients into MTL or MTL+ groups (Bayley et al., 2005; Bayley et al., 2003; Kirwan et al., 2008; Rosenbaum et al., 2008; Steinvorth et al., 2005). This quantification of subfield volumes then has two further implications for human models of amnesia: (1) that specific predictions can be made concerning the behavioural consequences of the focal volume loss observed (e.g., pattern separation and completion deficits, Chadwick et al., 2014; Ranganath, 2010; Rolls, 2013); and (2) that subfield volumes can be used as a continuous variable in order to use linear modeling to develop formal predictive relationships between anatomy and function (see Chapter 7). Moreover, for the purposes of this thesis, they could be used to specifically probe the relationship between subfield volumes and episodic memory retrieval (Chadwick et al., 2014)

3.4.6. Grey matter, white matter, and cerebrospinal fluid volumes are not significantly reduced following VGKC-complex LE

Previously, it has been shown that using automated cortical segmentation protocols that the MTL regions outwith the hippocampus are not atrophied following VGKC-complex LE (Wagner et al., 2015; Wagner et al., 2014). These were in contrast with an early single patient case report that reported whole brain volume loss following VGKC-complex LE (Schott et al., 2003), but that this study probably conflated the changes in cerebral volume observed during the acute and chronic stages of this neuroinflammatory disorder (Wagner et al., 2015; Wagner et al., 2014). The present findings corroborate those of Wagner et al. (2015) and Wagner et al. (2014), with the finding of a null difference between the patients (n = 18), and controls (n = 19), for grey matter, white matter, CSF, and total intracranial volumes. The data presented here suggest systematic reduction in whole brain volumes is not a feature of VGKC-complex LE.

This study is also the first to report these whole brain volumes for any amnesic patient group (Bayley et al., 2005; Bayley et al., 2003; Kirwan et al., 2008; Rosenbaum et al., 2008; Smith et al., 2013; Steinvorth et al., 2005), and helps mitigate against arguments of lesions outwith the hippocampus causing amnesia. These data could be extended, however, by using whole brain segmentation software (such as FreeSurfer) in order to assess regional cortical atrophy following VGKC-complex LE. This is discussed further in Section 8.1.1.2.

3.4.7. Limitations and future work

A central feature of this thesis is testing whether VGKC-complex LE is a valid model of focal hippocampal dysfunction, and, neuroanatomically at least, this would appear to be a reasonable assumption. The focality of the *in vivo* pathology observed accords well with the hypothesis that CA field atrophy was most likely to be observed, because of the localization of Lgi1 gene transcripts (the principal antigenic target in VGKC-complex LE) to the DG and the CA3 field (Herranz-Perez et al., 2010; Irani et al., 2010), and evidence from case reports that have found a loss of pyramidal cells from CA4 but sparing of CA1-3 (Khan et al., 2009). The CA3 atrophy may contradict pathological studies, but corroborates the antigenic target localization found in *in vivo* models (Irani et al., 2010).

One way of determining the difference between these reports would be to undertake formal *in vivo* quantification of the CA4 subfield. CA4 was not measured as a separate subfield in this study, and this does provide a future direction of experimental work. The existence of CA4 as a discrete functional subfield of the hippocampus remains under debate, as it has been variably argued to be part of the DG (Insausti and Amaral, 2004) or the CA3 (Insausti and Amaral, 2012). This region though has been shown to generate neuronal progenitor cells, and have been implicated in memory formation (Bruel-Jungerman et al., 2006). However, the DG metric presented here consisted collapsed across the DG and CA4 subfields, and the segmentation of CA4 has yet to be reliably undertaken in human studies. No between-group differences were observed for DG volumes, although it is possible that CA4 atrophy was lost when collapsing across DG and CA4 (and the opposite may be true, although without any *a priori* basis to

predict it). Further work, focusing on *in vivo* CA4 segmentation, will be needed to align the pathology seen in this chapter, and the CA4 findings found *ex vivo* (Khan et al., 2009).

3.4.9. Conclusion

Manual volumetry, undertaking on images obtained at the ultrahigh field strength of 7.0-Tesla, has demonstrated that it is possible to successfully and reliably segment the hippocampal subfields along the entire longitudinal axis of the hippocampus particularly in disease. Moreover, it is possible to segment these subfields according to natural occurring biophysical boundaries, instead of resorting to extrapolation. Importantly, this chapter has demonstrated that chronic VGKC-complex LE is associated with CA3 atrophy in the head and body of the hippocampus bilaterally, and bilateral CA1 volume loss in the hippocampal body. This is commensurate with the immunology of VGKC-complex LE and provides for the first time direct evidence that these antibodies mediate hippocampal pathology. More broadly, these results also provide the first evidence of subfield specific pathology in humans suggesting this aetiology can provide anatomical substrate for investigations into the roles of the hippocampal subfields in memory.

Chapter 4

Extensive neuropsychological assessment of VGKC-complex LE

4.1. Introduction

Neuropsychology has been central to our understanding of the neural basis of memory, and paved the way for more theoretical models of memory to be established. Early work on Henry Molaison (HM) helped formalise the different types of mnemonic processes that have been investigated in humans: free recall, forced choice recognition, semantic learning and recall, episodic learning and recall, priming, skilled behaviour, plus many others subsequently (Corkin, 2002). Neuropsychological characterization also attempts to dissociate impaired function of some particular domain, such as memory, from otherwise normal neuropsychological domains (i.e. language or executive function, Crawford and Garthwaite, 2006; Crawford et al., 2006), as typified by HM.

One abiding problem in neuropsychology, discussed at various junctures throughout this chapter, is how significant impairments are operationalized. Typically, significantly impaired performance is defined as a performance falling below the fifth centile of a standardized control population (Benton and Hamsher, 1977). This would correspond to any standardized performance falling being more than 1.67 standard deviations (SD) less than the control mean. As will be discussed in Section 4.1.3, there are multiple factors that could influence mnemonic performance in this study, not least

the effects of intelligence (see Section 4.1.3.1.1). In this way it is possible for a patient to be significantly impaired relative to his predicted performance, as measured by intelligence factors, yet not fall below the fifth centile of performance. Moreover, this method may miss subtle groupwise reductions in performance associated with disease processes – such as with this voltage-gated potassium channel-complex antibody-mediated limbic encephalitis, VGKC-complex LE, cohort – and as such, significance in this chapter will be defined by groupwise performance that is significantly different from the standardized group mean, even if that performance is not below the fifth centile ($Z < -1.67$). As will be discussed below, it is unlikely that this cohort, with their focal CA1 and CA3 lesions, have suffered enough damage to their medial temporal lobe (MTL) structures to cause this degree of impairment.

4.1.1. Neuropsychological profiles of amnesic patients who have undergone extensive retrograde memory testing

Table 4.1 provides a summary of the neuropsychological assessments undertaken on those patients in whom retrograde episodic experiments using measures allied to either the Autobiographical Memory Interview (AMI), or the Autobiographical Interview (AI) have taken place. This table demonstrates that there are varying opinions of what constitutes a thorough neuropsychometric evaluation of an amnesic patient. For instance, some groups have used a single measure for a given domain arising from just one test package (e.g. the Wechsler Memory Scale-Revised, WMS-R) to characterize their patients (Bayley et al., 2005; Bayley et al., 2003), whereas others rely on several neuropsychological tests spread across multiple domains such as language (Boston Naming Test, verbal fluency), executive function (Wisconsin Card Sorting Task, digit span), recognition memory (the Recognition Memory Test, California Verbal Learning Task (CVLT) recognition), visual memory (Rey-Osterreith Complex Figure, WMS-R visual reproduction), verbal memory (WMS-R logical memory, CVLT short- and long-delay), and retrograde memory (AMI; Rosenbaum et al., 2005; Rosenbaum et al., 2008).

Table 4.1 can also be used to help draw inferences about the similarities and differences in neuropsychological performance according the site, and size of lesions to the medial temporal lobe (MTL) structures. For the purposes of this chapter, four basic categories of lesion related pathology and neuropsychological performance will be

discussed according to a previously proposed scheme according to magnetic resonance imaging (MRI) or pathological findings (Spiers et al., 2001). These groupings are: (1) MTL+ lesions, those extending into the temporal lobe; (2) MTL lesions are those restricted to the hippocampus proper, the entorhinal cortex (ERC), the perirhinal cortex (PRC), and parahippocampal gyrus (PHG); (3) hippocampal lesions, defined as those limited to the hippocampal formation (CA fields; dentate gyrus, DG and subiculum, SUB); and (4) lesions limited to the cornu Ammonis (CA) 1 subfield, as proven by *ex vivo* studies (Rempel-Clower et al., 1996).

This approach provides a useful heurisitic for interpreting the neuropsychological profile that might be expected, *a priori*, from a cohort of patients with VGKC-complex LE who appear to have focal CA1 and CA3 atrophy, as evidenced by *in vivo* quantification of subfields using 7.0-Tesla MRI (see Chapter 3). What this classification cannot do is provide a full neuroanatomical account, including anatomical or functional connectivity, between the CA fields, hippocampus proper, the MTL structures, or wider cortical regions, for the patients described, primarily due to technical restraints at the time of investigations. Furthermore, the qualitative descriptions in Table 4.1 make no reference to the volume of atrophy observed, with some patients having the same type of damage (i.e., hippocampal), but with a wide range in the degree of volume loss observed (i.e., partial or total volume loss). In the context of this chapter, the purpose of this framework is to inform the pattern of neuropsychological deficits that *might* be expected in the context of focal CA1 and CA3 lesions observed in Chapter 3.

What this classification also demonstrates is that patients with focal CA field lesions are exceedingly rare (two cases, Rempel-Clower et al., 1996), whereas groups with larger MTL lesions are typically comprised of greater patient numbers (at least 11 patients). This suggests the 18 patients in Chapter 3 would comprise the largest patient group for any CA field, hippocampal, MTL or MTL+ lesion group.

4.1.1.1. Neuropsychological profile of patients with damage extending outwith the MTL (MTL+)

Eight patients have been observed to have damage extending beyond the MTL (MTL+; EP, GP, HC, PH, GT, KC, HM, WR). Patients EP, GP, HC, PH, and GT were

only tested on measures of memory arising from the WMS-R, and performed at, or below, the floor level for the measures of delayed memory. No other neuropsychological domains were tested. KC, HM, and WR all underwent more extensive neuropsychological testing. This testing demonstrated that these patients performed within two SDs of the population mean for intelligence (KC, HM, and WR), language (KC, HM, and WR), executive function (KC, HM, and WR), visuoconstruction (HM), and visuoperception (KC). Their performance demonstrated near floor performance for verbal memory (KC, HM, and WR), visual memory (KC), verbal and visual recognition memory (KC), and visuoconstruction (WR).

This suggests that MTL+ lesions will cause a universally poor anterograde memory performance (as defined as >1.67 SDs from the population norm, Benton and Hamsher, 1977), but that impairments in recognition memory might also be seen. Comparisons between KC, HM, and WR cannot be made to the remaining patients, as the neuropsychological evaluation in the remainder failed to systematically evaluate non-mnemonic modalities. Moreover, these authors failed to assess the different types of anterograde memory, enumerated in Section 4.1.3.2.1 below. What can be ascertained from this data is that more extensive MTL lesions produce the most severe impairment in anterograde memory.

KC also underwent testing with the AMI (Rosenbaum et al., 2008), and demonstrated a temporally extensive impairment of episodic memory performance (Childhood, 2/9; Adult, 3/9, Recent 1/9), but only the Recent epoch for personal semantic memories (Childhood, 16/21; Adult 13.5/21; Recent 8/21). These results would be predicted for MTL+ lesions, according to the standard model of consolidation (see Chapter 5), as the temporal lobe neocortex would be the site where the episodic memories are stored and recollected (Squire and Alvarez, 1995). This theory would also predict that personal semantic memories should be as affected as episodic memories, a pattern not seen in KC (although it is seen in VC).

4.1.1.2. Neuropsychological profile of patients with damage limited to the medial temporal lobe

Section 1.2.1, and the discussion below in Section 4.1.3, suggest that there are some aspects of memory performance that can be supported by regions within the MTL complex (such as object recognition memory in the PRC). The ERC is also the structure with the greatest amount of efferents into the hippocampus, and so it might be expected that lesions confined to the ERC might produce an extensive amnesia. Seven patients could be said to have had damage limited to their MTL structures (LD, WH, VC, SJ, RG, CB and DA). LD performed within one SD of controls on measures of verbal and visual memory, but was more than two SDs worse on delayed memory. WH performed within one standard deviation as controls on visual memory, but was within two for verbal memory and performed more than two standard deviations poorly on delayed memory. VC, SJ, RG, CB and DA had significant deficits (>2SDs) across all measures of memory. All of these patients had non-mnemonic neuropsychological testing and were found to perform within normal limits (see Table 4.1).

DG also underwent retrograde testing with the AMI (Rosenbaum et al., 2008), and demonstrated – as determined descriptively – a temporal gradient for episodic memory (Childhood, 9/9; Adult, 7/9, Recent 2/9), and personal semantic memories (Childhood, 18/21; Adult 20/21; Recent 1/21). A similar pattern was seen with DA (Rosenbaum et al., 2008), for both episodic (Childhood, 7/9; Adult, 6/9, Recent 3/9), and personal semantic memories (Childhood, 17.5/21; Adult 21/21; Recent 16/21). VC also underwent retrograde testing with the AMI (Cipolotti et al., 2001), scoring at near floor for every epoch for episodic memories (Childhood, 1/9; Adult, 2/9; Recent, 0/9), and also scored below average for the semantic measures as well (Childhood, 11/24; Adult 15/24; Recent 3/24).

The standard model of consolidation (see Section 5.1.2.1 for more extensive discussion), whereby the temporal lobe neocortical structures support temporally remote (i.e., 10 years or more) episodic and personal semantic memories (Squire and Alvarez, 1995), adequately explains the episodic and personal semantic memory performance for DG, and DA.

4.1.1.3. Neuropsychological profile of patients with damage limited to the hippocampus

Eight patients surveyed in Table 4.1 had damage limited to their hippocampal formation. (AB, LJ, MJ, RS, GW, JRW, JS, and KE). Across the various neuropsychological measures, the patients had reduced performance on measures of both verbal and visual anterograde memory. For verbal memory performance, two patients were within one SD and six were within two SDs of the standardized mean, although only JS was unimpaired for delayed memory (Gold and Squire, 2005). For visual memory, three patients performed within one SD of the mean and five within two. Information was not available for three patients. Unfortunately, the only other neuropsychological domain tested was intelligence, and it is impossible to comment on global neuropsychological performance for these patients. Overall these patients had qualitatively more dense amnesia than the CA1 lesion patients in terms of the verbal, visual, general, and delayed memory scores arising from the WMS-R.

Several of these patients have undergone tests of retrograde memory (discussed more in Chapter 5) with the predominant finding being that of a temporal gradient of retrograde memory performance (Bayley and Squire, 2003), conceptualized as improving point score performance the more remote the memory becomes. The methodology used to acquire the retrograde memory performance in these patients and the CA1 patients' differed, and so direct comparisons across tests, and forms of memories, cannot be made. However, the general pattern, as reported by the single centre conducting the research, was that patients with CA1 and hippocampally-limited lesions both have a temporal gradient of retrograde memory loss, alongside significant (i.e., performance ≥-1.67 SDs from the standardized group mean) deficits in anterograde verbal, visual, and delayed memory.

4.1.1.4. Neuropsychological profile following damage to CA1, as described *ex vivo*

Understandably, very few patients with focal CA region damage have been described, given that the spatial resolution needed to visualize these subfields *in vivo* with MR imaging requires ultra-high magnetic field strengths (>4.7T; Malykhin et al., 2010; Wisse et al., 2012). However, two patients (GD and RB, with lesions following transient hippocampal hypoxia (Rempel-Clower et al., 1996), with *ex vivo* pathology proven to be limited to just the CA1 regions bilaterally, and have subsequently been well-described neuropsychometrically. GD and RB both perform within one-to-two SDs of a control

population mean of 100 on anterograde memory tasks. However, they both perform at or below two SDs on measure of delayed-recall for both verbal and visual information, as well as on a measure of paired-associate memory, a process thought to be particularly hippocampal-dependent (Rempel-Clower et al., 1996). All other neuropsychological domains were normal. Both RB and GD were deemed amnesic for events temporally close to their injuring event, but their memory for events 10 years or more prior to their injuring event was normal (Rempel-Clower et al., 1996; Zola-Morgan et al., 1986). Retrograde memory was assessed via a modified Crovitz task that found RB and GD produced similar numbers of memories as controls that occurred during particular time epochs, yet no assessment of how re-experiential these memories are is made. Moreover, this method probably assesses semantic memory, a form of memory likely to be supported by the extra-hippocampal neocortical structures (Bernard et al., 2004; Graham and Hodges, 1997; Haist et al., 2001; Hodges and McCarthy, 1995; Kapur et al., 1995; Leveroni et al., 2000; Maguire, 2001; Maguire and Mummery, 1999; Maguire et al., 2000; Ryan et al., 2008). The relevance of these results to questions concerning the role of the hippocampus to mnemonic retrieval is therefore debatable.

Aside from these methodological and conceptual problems, RB and GD demonstrate that when damage is specifically limited to the CA1 region of the hippocampus, the nature of the pathology tends to be within two SDs across a range of anterograde, but not always retrograde, neuropsychological measures of memory. It is this pattern of pathology that would be most applicable to the current VGKC-complex LE cohort (see Chapter 3).

4.1.1.5. Neuropsychological assessment in medial temporal lobe patients: summary

The data summarized in Table 4.1 show that patients with relatively focal lesions to the CA regions of the hippocampus tend to perform within two SDs of the standardized control population for anterograde memory tasks. Patients tend to show increasing anterograde amnesia (i.e., >2 SDs away from the standardized control population), as the pathology extends from the hippocampus to include the MTL, and eventually MTL+ structures. These data also suggest that the neuropsychological consequences for the CA1 and CA3 lesions observed in Chapter 3 will demonstrate mild

impairment (i.e. <2 SDs difference from the standardized control population) for anterograde memory tasks.

It is also notable that many of the patients in Table 4.1 (AB, LJ, MJ, RS, GW, JRW, JS, KE, DA, EP, GP, HC, PH, and GT) have only undergone mnemonic neuropsychological testing. The data arising from the other patients suggests that neuropsychological performance for other domains is normal, even in MTL+ lesions. However, this cannot be assumed from inference, thereby requiring that any amnesic patient should undergo thorough neuropsychological investigation across multiple mnemonic (i.e., verbal, visual, recognition) and non-mnemonic (i.e., language, executive function, intelligence) faculties.

Table 4.1. Neuropsychological profile of patients used in retrograde memory experiments, grouped according to the extent of hippocampal damage observed. Neuropsycholometric performance has been divided into different theoretical domains as suggested by the authors in all cases. Where possible the specific test has been identified, and patient performance is reported in the format used by the authors. SS demotes standard scores where mean standardized group performance falls at 10, with a standard deviation of 3. *Z*-scores have a mean standardized group average of 0, with a standard deviation of 1.

Patient (reference)	Aetiology	Locus of damage	Domain	Neuropsychological test	Results
GD (Rempel-Clower et al., 1996)	Anoxia	CA1	Intelligence	WAIS-R (raw vocab. and inform. scores) (mean: 100, SD = 15)	Full-scale IQ: 92 Vocabulary: 39 Information processing: 16
			Verbal memory	WMS-R (mean: 100, SD = 15)	Attention: 109 Verbal memory: 86 Visual memory: 88 General memory: 85 Delayed memory: 60
			Visual memory	ROCF DR	7/36
			Paired-associate	(not specified)	Trial 1: 2/15 Trial 2: 1/15 Trial 3: 2/15
			Verbal memory	Word recall (not specified)	40%
			Recognition memory	Word recognition (not specified)	83%
				24-hour 50 words recognition	25%
				24-hour 50 faces recognition	28%
			Misc.	Dementia Rating Scale	116
RB (Rempel-Clower et al., 1996)	Ischaemia	CA1	Intelligence	WAIS-R (raw vocab. and inform. scores)	Full-scale: 103

				ROCF DR	3/36
				Paired-associate	Trial 1: 0/15
				(not specified)	Trial 2: 0/15
					Trial 3: 1/15
AB (Bayley et al., 2003)	Anoxia	HPC	Intelligence	WAIS-III (mean: 100, SD = 15)	IQ: 107
			Anterograde memory	WMS-R (mean: 100, SD = 15)	Attention: 87
					Verbal memory: 62
					Visual memory: 72
					General memory: 54
					Delayed memory: <50
LJ (Bayley et al., 2003)	UK	HPC	Intelligence	WAIS-III (mean: 100, SD = 15)	IQ: 101
			Anterograde memory	WMS-R (mean: 100, SD = 15)	Attention: 105
					Verbal memory: 83
					Visual memory: 60
					General memory: 69
					Delayed memory: <50
MJ (Bayley et al., 2003)	Ischaemia	HPC	Intelligence	WAIS-III (mean: 100, SD = 15)	IQ: 139
			Anterograde memory	WMS-R (mean: 100, SD = 15)	Attention: 125
					Verbal memory: 62
					Visual memory: 93
					General memory: 62
					Delayed memory: <50
RS (Bayley et al., 2003)	Anoxia	HPC	Intelligence	WAIS-III (mean: 100, SD = 15)	IQ: 99
			Anterograde memory	WMS-R (mean: 100, SD = 15)	Attention: 99
					Verbal memory: 85

					Visual memory: 81 General memory: 82 Delayed memory: <50
GW (Bayley et al., 2003)	Anoxia	HPC	Intelligence Anterograde memory	WAIS-III (mean: 100, SD = 15) WMS-R (mean: 100, SD = 15)	IQ: 108 Attention: 105 Verbal memory: 67 Visual memory: 86 General memory: 70 Delayed memory: <50
JRW (Bayley et al., 2003)	Anoxia	HPC	Intelligence Anterograde memory	WAIS-III (mean: 100, SD = 15) WMS-R (mean: 100, SD = 15)	IQ: 90 Attention: 87 Verbal memory: 65 Visual memory: 95 General memory: 70 Delayed memory: <50
JS (Gold and Squire, 2005)	CO poisoning	HPC	Intelligence Anterograde memory	WAIS-III (mean: 100, SD = 15) WMS-R (mean: 100, SD = 15)	IQ: 90 Attention: 92 Verbal memory: 85 Visual memory: 63 General memory: 81 Delayed memory: 75
KE (Smith et al., 2013)	Ischaemia	HPC	Intelligence Anterograde memory	WAIS-III (mean: 100, SD = 15) WMS-R (mean: 100, SD = 15)	IQ: 108 Attention: 114 Verbal memory: 64 Visual memory: 84

					General memory: 72 Delayed memory: 55
LD (Rempel-Clower et al., 1996)	Status epilepticus	HPC and ERC	Intelligence	WAIS-R (raw vocab. and inform. scores) (mean: 100, SD = 15)	Full-scale IQ: 109 Vocabulary: 55 Information processing: 25
			Verbal memory	WMS-R (mean of 100, SD of 15)	Attention: 124 Verbal memory: 94 Visual memory: 82 Delayed memory: 62
			Visual memory	ROCF DR Paired associate (not specified)	3/36 Trial 1: 1/15 Trial 2: 1/15 Trial 3: 3/15
			Recognition memory	Word recognition 24-hour 50 words recognition 24-hour 50 faces recognition	97% 32% 33%
			Misc.	Dementia Rating Scale	116
WH (Rempel-Clower et al., 1996)	Anoxia following arrhythmia	HPC and ERC	Intelligence	WAIS-R (raw vocab. and inform. scores) (mean: 100, SD = 15)	Full-scale IQ: 113 Vocabulary: 64 Information: 27
			Verbal memory	WMS-R (mean: 100, SD = 15)	Attention: 88 Verbal memory: 72 Visual: 82 General: 67 Delayed memory: <50

			Visual memory	ROCF DR	1/36
			Memory	Paired associate	Trial 1: 0/15
					Trial 2: 0/15
					Trial 3: 0/15
			Verbal memory	Word recall	40%
			Recognition memory	Word recognition	84%
				24-hour 50 words recognition	29%
				24-hour 50 faces recognition	24%
			Misc.	Dementia Rating Scale	116
VC (Cipolotti et al., 2001)	Anoxia following arrhythmia (best results shown)	BL HPC and L MTL	Intelligence	WAIS-R (mean: 100, SD = 15)	VIQ: 105
					PIQ: 141
			Language	Graded Naming Test objects	23/30 (75th centile)
				Graded Naming Test nouns	20/30 (75th centile)
			Perception	VOSP incomplete letters	20/20
				VOSP cube analysis	10/10
				VOSP object decision	17/20
			Executive function	WCST	Pass
				Hayling task	17 (average)
			Recognition memory	RMT-Words	36/50 (<10th centile)
				RMT-Faces	39/50 (<25th centile)
				Topographical memory	13/30 (5th centile)
				Famous Faces	3/12 (<5th centile)
				D+P verbal recognition A	5/12 (<1st centile)
				D+P verbal recognition B	2/12 (<1st centile)
				D+P visual recognition A	7/12 (<1st centile)
				D+P visual recognition B	1/12 (<!st centile)

			Anterograde memory	Story IR	7.5 (<5th centile)
				Story DR	0 (<5th centile)
				List learning	18/95 (5th centile)
				ROCF IR	35/36 (90th centile)
				ROCF DR	5/36 (<5th centile)
				D+P Names IR	3/36 (<1st centile)
				D+P Names DR	3/12
				D+P Shapes IR	13/36 (<1st centile)
				D+P Shapes DR	04/12
			Paired-associate	Trial 1	04/24 (5th centile)
			(test not specified)	Trial 2	8/24 (5th centile)
			Retrograde memory	AMI Semantic	Childhood: 11/21
					Adulthood: 15/21
					Recent: 3/21
				AMI Episodic	Childhood: 1/9
					Adulthood: 2/9
					Recent: 3/9
SJ (Rosenbaum et al., 2008)	Bacterial meningitis	MTL	Intelligence	WAIS-R (mean: 100, SD = 15)	FSIQ: 127
					VIQ: 123
					PIQ: 124
				NART	115
				WMS-R (mean: 100, SD = 15)	General: 56
					Auditory: 67.5
					Visual: 63.5
			Language	Boston Naming Test	14/15
				Category fluency (SS)	8
				Letter fluency (SS)	8

			Visuoconstruction	ROCF Copy	34/36
			Verbal memory	WMS-R Logical Memory IR	1st centile
				WMS-R Logical Memory DR	<1st centile
				CVLT Acquisition (T-score)	22
				CVLT IR (Z-score)	-5
				CVLT DR (Z-score)	-4
			Visual memory	ROCF DR	0/36
			Recognition memory	CVLT recognition (Z-score)	-4
				RMT-Faces	36/50
				RMT-Words	40/50
			Executive function	WMS Digit Span (score)	14
RG (Rosenbaum et al., 2008)	VE	MTL	Intelligence	WAIS-R (mean: 100, SD = 15)	VIQ: 92
				WMS-R	General: 45
					Auditory: 56
					Visual: 56
					WM: 85
			Language	Boston Naming Test	53/60
				Category fluency (SS)	7
				Letter fluency (SS)	10
			Visuoconstruction	ROCF Copy	30/36
			Verbal memory	WMS-R Logical Memory IR	<1st centile
				WMS-R Logical Memory DR	<1st centile
				CVLT Acquisition (T-score)	21
				CVLT short delay (Z-score)	-3.2
				CVLT long delay (Z-score)	-3.13
				WMS-R visual reproduction IR	3rd centile

				WMS-R visual reproduction DR	1st centile
			Visual memory	ROCF DR	0/36
			Recognition memory	CVLT recognition (Z-score)	-0.07
				RMT-F	24/50
				RMT-W	34/50
			Executive function	WMS Digit Span (SS)	10
				WCST categories	6
			Retrograde memory	AMI Semantic	Childhood: 18/21
					Adulthood: 20/21
					Recent: 1/21
				AMI Episodic	Childhood: 9/9
					Adulthood: 7/9
					Recent: 2/9
CB (Rosenbaum et al., 2008)	VE	MTL	Intelligence	WAIS-R (mean: 100, SD = 15)	VIQ: 98
				WMS-R (mean: 100, SD = 15)	General: 82
					Auditory: 92
					Visual: 78
					WM: 93
			Language	Boston Naming Test	53/60
				Category fluency (SS)	9
				Letter fluency (SS)	11
			Visuoconstruction	ROCF Copy	33/36
			Verbal memory	WMS-R Logical Memory IR	6th centile
				WMS-R Logical Memory DR	30th centile
				CVLT Acquisition (T-score)	38
				CVLT short delay (Z-score)	-1.5

				CVLT long delay (Z-score)	-1.84
				WMS-R visual reproduction IR	3rd centile
				WMS-R visual reproduction DR	7th centile
			Visual memory	ROCF DR	6.5/36
			Recognition memory	CVLT recognition (Z-score)	0
				RMT-F	45/50
				RMT-W	44/50
			Executive function	WMS Digit Span (SS)	9
				WCST categories	6
			Retrograde memory	AMI Semantic	Childhood: 17.5/21
					Adulthood: 21/21
					Recent: 16/21
				AMI Episodic	Childhood: 2/9
					Adulthood: 9/9
					Recent: 0.5/9
DA (Rosenbaum et al., 2008)	VE	MTL	Intelligence	WAIS-R (mean: 100, SD = 15)	FSIQ: 117
					VIQ: 121
					PIQ:106
				NART	117
				WMS-R (mean: 100, SD = 15)	General: 74
					Auditory: 74
					Visual: 81
			Language	Boston Naming Test	56/60
				Category fluency (SS)	12
				Letter fluency (SS)	8
			Visuoconstruction	ROCF Copy	35/36

			Verbal memory	WMS-R Logical Memory IR	15th centile
				WMS-R Logical Memory DR	<1st centile
				CVLT Acquisition (T-score)	9
				CVLT short delay (Z-score)	-4
				CVLT long delay (Z-score)	-4
				WMS-R visual reproduction IR	19th
				WMS-R visual reproduction DR	1st centile
			Visual memory	ROCF DR	0/36
			Recognition memory	CVLT recognition (Z-score)	-4
				RMT-F	21/50
				RMT-W	25/50
			Executive function	WMS Digit Span (SS)	13
				WCST categories	6
			Retrograde memory	AMI Semantic	Childhood: 17.5/21
					Adulthood: 21/21
					Recent: 16/21
				AMI Episodic	Childhood: 7/9
					Adulthood: 6/9
					Recent: 3/9
DA (Smith et al., 2014)	Anoxia	MTL	Intelligence	WAIS-III (mean: 100, SD = 15)	IQ: 95
			Anterograde memory	WMS-R (mean: 100, SD = 15)	Attention: 104
					Verbal memory: 90
					Visual memory: 91
					General memory: 90
					Delayed memory: 56
EP (Bayley et al., 2003)	VE	MTL+	Intelligence	WAIS-III (mean: 100, SD = 15)	IQ: 98

			Anterograde memory	WMS-R (mean: 100, SD = 15)	Attention: 94 Verbal memory: 57 Visual memory: 82 General memory: 61 Delayed memory: 56
GP (Bayley et al., 2003)	VE	MTL+	Intelligence Anterograde memory	WAIS-III (mean: 100, SD = 15) WMS-R (mean: 100, SD = 15)	IQ: 98 Attention: 102 Verbal memory: 79 Visual memory: 62 General memory: 66 Delayed memory: <50
HC (Bayley et al., 2005)	Ischaemia	MTL+	Intelligence Anterograde memory	WAIS-III (mean: 100, SD = 15) WMS-R (mean: 100, SD = 15)	IQ: 99 Attention: 96 Verbal memory: 83 Visual memory: 53 General memory: 68 Delayed memory: 51
PH (Bayley et al., 2005)	TLE	MTL+	Intelligence Anterograde memory	WAIS-III (mean: 100, SD = 15) WMS-R (mean: 100, SD = 15)	IQ:105 Attention: 117 Verbal memory: 57 Visual memory: 50 General memory: 50 Delayed memory: <50
GT (Bayley et al., 2005)	VE	MTL+	Intelligence Anterograde memory	WAIS-III (mean: 100, SD = 15) WMS-R (mean: 100, SD = 15)	IQ: 84 Attention: 120

					Verbal memory: 57 Visual memory: 50 General memory: 50 Delayed memory: <50
KC (Rosenbaum et al., 2005)	Trauma	MTL+	Intelligence	WAIS-R (mean: 100, SD = 15)	FSIQ: 99 VIQ: 99 PIQ: 99
				WASI Similarities (SS)	11
				WASI Matrix Reasoning (SS)	11
				American NART	102
			Anterograde memory	WMS-R (mean: 100, SD = 15)	General: 61 Verbal: 67 Visual: 69
			Verbal memory	WMS-R Logical Memory IR	5th centile
				WMS-R Logical Memory DR	<1st centile
				WMS-R visual reproduction IR	13th centile
				WMS-R visual reproduction DR	<1st centile
				CVLT Acquisition (T-score)	12
				CVLT short delay (Z-score)	-5
				CVLT long delay (Z-score)	-5
			Visual memory	ROCF IR	4/36
				ROCF DR	0/4
			Visuoperceptive	Line orientation judgement	23/30 (unimpaired)
				Benton Visual Discrimination	>95%
				Benton Face Recognition	2-16th centile
				ROCF Copy	36/36

			WAIS-R block design (SS)	9
		Language	Weston Aphasia Battery	98.2/100
			WAIS-R vocabulary (SS)	9
			Boston Naming Test	57/60
			Category fluency (SS)	10
			Letter fluency (SS)	6
		Executive function	WMS Digit Span (SS)	12
			WCST categories	6/6
			WCST perseveration response score (Z-score)	-0.9
			Trails A	138s
			Trails B	291s
			Concept Generation Test	4 (unimpaired)
		Recognition memory	RMT-F	25/50
			RMT-W	26/50
			CVLT recognition (Z-score)	-5
		Retrograde memory	AMI Semantic	Childhood: 16/21
				Adulthood: 13.5/21
				Recent: 8/21
			AMI Episodic	Childhood: 2/9
				Adulthood: 3/9
				Recent: 1/9
		Dementia Rating Scale	Attention	37/37
			Intention/preseveration	37/37
			Construction	6/16
			Conceptualisation	34/39
			Memory	14/25
HM	BL resection of MTL+	Intelligence	WASI (mean: 100, SD = 15)	FSIQ: 106

(Steinvorth et al., 2005)	MTL				
					VIQ: 104
					PIQ: 124
				WMS-R (mean: 100, SD = 15)	Attention: 87
					Verbal: 74
					Visual: 77
					General: 72
					Delayed: <65
			Verbal memory	RAVLT list learning	12/75
				RAVLT interference	10/15
				RAVLT list after interference	0/15
				RAVLT DR	0/15
				RAVLT 20min DR	4/15
			Visuoconstruction	ROCF Copy (Z-score)	-7.32
			Language	Boston Naming Test	64/85
			Executive function	WCST categories	5 (unimpaired)
				WCST perseveration response score (Z-score)	-0.39
				Porteus Mazes	TQ 110
WR (Steinvorth et al., 2005)	Infarct	MTL+	Intelligence	WASI	FSIQ: 112
					VIQ: 119
					PIQ: 102
				WMS-R	Attention: 79
					Verbal: 70
					Visual: 90
					General: 73

		Delayed: <65
Verbal memory	RAVLT list learning	20/75
	RAVLT interference	1/15
	RAVLT list after interference	1/15
	RAVLT DR	0/15
	RAVLT 20min DR	6/15
Visuoconstruction	ROCF Copy (Z-score)	-3.3
Language	Boston Naming Test	68/85
Executive function	WCST categories	5 (unimpaired)
	WCST perseveration response score (Z-score)	1.2
	Porteus Mazes	TQ 114

AMI, Autobiographical Memory Interview; CA1, cornu Ammonis 1; CVLT, California Verbal Learning Task; D+P, Doors and People Test; DR, delayed-recall; HPC, hippocampus; IQ, intelligence quotient; IR, immediate-recall; MTL, medial temporal lobe; MTL+, medial temporal lobe plus lesions; NART, National Adult Reading Test; RAVLT, Rey Auditory Verbal Learning Test; RMT, Recognition Memory Test; ROCF, Rey-Osterreith Complex Figure; SS, standard score; VOSP, Visual Object and Space Perception battery; WAIS-III, Wechsler Adult Intelligence Scale-III; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WASI, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sorting Test; WMS-R, Wechsler Memory Scale-Revised

4.1.2. Cognitive sequelae of VGKC-complex LE and limitations of previous assessments

Early case reports, or case series, of voltage-gated potassium channel-complex antibody-mediated limbic encephalitis (VGKC-complex LE) administered standardized neuropsychological-based assessment batteries to describe the cognitive deficits associated with the active inflammatory disease process within the MTL. These reports usual described a global impairment across several cognitive domains including memory, executive function and language (Buckley et al., 2001; Schott et al., 2003; Vincent et al., 2004). Studies that assessed neuropsychological performance following resolution of the illness usually found that the executive function and language dysfunction resolved (Buckley et al., 2001; Vincent et al., 2004). These early studies suffered from small patients numbers, ranging from one to seven, reflecting the emerging recognition of VGKC-complex LE as a distinct clinical syndrome (Irani et al., 2010). Table 4.2 summarizes the case series of patients where neuropsychological testing was undertaken.

Table 4.2 also reveals that a wide range of neuropsychological domains – including anterograde memory, recognition memory, language, visuoperception, and executive function – have been tested in individual patients, but not consistently across a large numbers of patients. The first case report of VGKC-complex LE described a below average verbal fluency, and retrograde episodic and semantic memory impairment which resolved after successfully treatment in a single patient (Buckley et al., 2001). Vincent et al., (2004) described the performance of a single patient, during the acute phase of their illness, with intelligence described as falling between 65-115 (measured by visual intelligence quotient, VIQ, and processing intelligence quotient, PIQ), and poor performance for the Adult Memory and Information Processing Battery (AMIPB) story immediate-recall (<1-28th centile), story delayed-recall (<1-12th centile), list learning immediate-recall (<1-38th centile), list learning delayed-recall (<1-4th centile), Recognition Memory Test (RMT) for faces (<5-25th centile), and words (<5-5th centile), impairment in the Rey Osterreith Complex Figure (ROCF) copy (11-16th centile), immediate-recall (<1-86th centile), and delayed recall (<1-76th), and naming on the Graded Naming Test (GNT; <5-37th centile).

Chan et al., (2007) found evidence of a chronic impairment for the AMIPB story task and list learning, but not RMT performance for both words and faces in three patients with VGKC-complex LE when followed up months after successful treatment of their illness. However, many of these early studies in VGKC-complex LE patients are either cross-sectional studies (Buckley et al., 2001; Vincent et al., 2004), or follow at most three cases longitudinally (Chan et al., 2007). They are also *ad hoc* in what tests are used across their patients, and demonstrate a bias towards only assessing mnemonic functions (Buckley et al., 2001; Chan et al., 2007; Vincent et al., 2004). These studies also limit analyses to descriptive statistics, which are difficult to generalize across a disease population.

The first longitudinal cohort study (Frisch et al., 2013) used standardized measures of anterograde memory (the Verbal Learning and Memory Test: free-recall and recognition of a word list) and executive function (the Epitrack battery: Trail-making tasks, response inhibition, digit span backwards, word fluency and a maze test), and found that in 15 patients there were significant deficits in executive functioning (~Z = -1.75), and verbal (~Z = 2.00) and visual memory (~Z = -1.70) at presentation. At follow-up (post-treatment; median delay: 25 months, range: 1-68 months), there was a resolution in the dysexecutive features (~Z = -0.2), but a significant deficit in verbal (~Z = -0.8) and verbal memory (~Z = -0.75) remained.

Using a larger battery of standardized neuropsychological tests in 19 patients (nine with Lgi1, one with Caspr2, and nine not specified), Butler et al., (2014b) demonstrated that acute VGKC-complex LE likewise impaired anterograde verbal (Z = -1.76), and visual memory (Z = -0.52), but was also associated with impaired processing speed (Z = -0.76), and executive function (Z = -0.90). At follow-up (range: 3-44 months), there was normalization in visual memory (Z = 0.23), processing speed (Z = -0.10), and executive function (Z = -0.02), but enduring deficits in verbal memory (Z = -1.07). These results stand in contrast to those of (Frisch et al., 2013), particularly concerning the normal performance of patients in visual memory. This may, in part, reflect the different tests used in the two studies.

A final study studied 12 patients with VGKC-complex LE (eight with either Lgi1 antibodies, four not further classified), with tests of anterograde verbal (California Verbal

Learning Test, CVLT) and visual (Benson Figure) memory, letter fluency (D-words), category fluency (animals) and visual fluency (Design Fluency), working memory (digits backwards), task switching (Modified Trails), inhibition (Stroop inhibition), visual localization and construction (Visual Object Space Perception) and naming (Boston Naming Test), single-word comprehension (Peabody Picture Vocabulary Test, PPVT) and sentence repetition (Bettcher et al., 2014). The cross-sectional results (time from illness not specified) revealed that patients had mild-to-moderate impairment on anterograde memory, as defined by a group average *Z* score of -1.9, which appeared to be driven by verbal memory performance (Z = -2.4). A mild impairment in executive functions (Z = -1.5), and language (Z = -1.1) were also found. Visuospatial function was normal (Z = -0.1). A further percentage break down of patients according to test showed that 83% were impaired on the CVLT, 64% on category fluency, 55% on letter fluency whereas very few performed badly on Stroop inhibition (11%), figure copy (8%) or repetition (18%) (Bettcher et al., 2014). These authors also had a qualitative assessment of longitudinal cognitive performance in five patients. Patient 1 had mild verbal memory impairment; Patient 2 had mild language impairment; Patient 3 had no objective impairment; Patient 4 performed normally on all neuropsychological measures, but this was below his expected performance with 20+ years of full-time education; and Patient 8 had subjective memory impairments.

In contrast to the two previous studies, this study describes category fluency deficits following VGKC-complex LE suggesting that the long-term sequelae might include dysexecutive problems. Category fluency requires a search through conceptual knowledge store for semantic extensions derived from a target word (Taler and Phillips, 2008), whereas letter fluency relies on word presentation strategies (Rohrer et al., 1999). Both these tasks require intact frontal lobe function (Lezak et al., 2004) to organize retrieval strategies, initiate verbal response, to monitoring of responses previously given and to inhibit those responses contrary to the selection criteria (Henry et al., 2004). This result stands in contrast to the remainder of the published data, and will therefore need to be specifically probed in this chapter.

4.1.2.1. When to test neuropsychological performance in chronic VGKC-complex LE

The conclusions of the data arising from the longitudinal studies of Butler et al., (2014a), Frisch et al., (2013), and Bettcher et al., (2014) are limited by the relatively small number of neuropsychological tests that were administered. Moreover, there was no attempt to explore hippocampal atrophy with mnemonic performance. Nonetheless, these studies demonstrate that in the acute phase of VGKC-complex LE there is evidence of impairment in executive function, language, processing speed and both verbal and visual memory. However, in the post-treatment phase (a combined range of 1-66 months) there is a resolution in those functions not dependent upon MTL function, with the most conspicuous deficits being those of anterograde, usually verbal, memory. Therefore this would suggest that testing a time period of not less than six months from treatment commencing, patients should have reached a chronic, and stable, level of performance, with deficits in at least verbal memory being found. This six-month time range coincides with when the hippocampal volume changes, associated with VGKC-complex LE, become static (Wagner et al., 2015; Wagner et al., 2014).

Table 4.2. Survey of neuropsychological studies undertaken in VGKC-complex LE cohorts. For longitudinal studies the time from illness onset to assessment is shown. Impaired scores are shown in bold. Solidus indicates neuropsychological tests combined together to create a composite domain score

Reference	Study *n*	Patient	Assessment 1 (months)	Test	Scores	Assessment 2 (months)	Scores	Assessment 3 (months)	Scores
Case reports/series									
(Buckley et al., 2001)	1		0.5	Verbal fluency	**Z = -0.71**	17.5	**Z = -0.63**	23	Z = 0.67
				AMI	Child.Sem. 21/21		Child.Sem. 21/21		AMI Child Sem 21/21
					Adult.Sem. 9.5/21		Adult.Sem. 18/21		**Adult Sem 5.5/21**
					Child.Epi. 2/9		Child.Epi. 7/9		Child Epi 9/9
					Adult.Epi. 6/9		Adult.Epi. 7/9		Adult Epi 8/9
(Vincent et al., 2004)	7	1	0	NART		Median: 89 (3-113)			
				VIQ	61-115				
				PIQ	65-112				
				AMIPB Story-IR	<1-28th centile				
				AMIPB Story-DR	<1-12th centile				
				AMIPB List-IR	<1-38th centile				
				AMIPB List-DR	**<1-4th centile**				
				RMT Faces	<5-25th centile				
				RMT Words	**<5-5th centile**				
				ROCF Copy	11-16th centile				
				ROCF IR	<1-86th centile				
				ROCF DR	**<1-76th centile**				

		PIQ	**65**		111		114
		RMT Words	**<1st centile**		>50th centile		25-50th centile
		RMT Faces	**<1st centile**		**<1 centile**		5-25th centile
		GNT	**1st centile**		5-25th centile		5-25th centile
KC2	0	VIQ	90	1	98	5	-
		PIQ	102		-		111
		RMT Words	25-50th centile		>50th centile		25-50th centile
		RMT Faces	5-25th centile		>50 centile		**5-25th centile**
		AMIPB Story-IR	25-50th centile		**5th centile**		>50th centile
		AMIPB Story-DR	**<5th centile**		**<5th centile**		25-50th centile
		Paired assoc. 1	**5-25th centile**		**<5th centile**		**5-25th centile**
		Paired assoc. 2	**<5th centile**		**<5th centile**		**<5th centile**
		GNT	5-25th centile		-		25-50th centile
KC3	0	VIQ	112	2	99		
		PIQ	92		-		
		RMT Words	>50		>50th centile		
		RMT Faces	>50		5-25th centile		
		AMIPB Story IR	25-50th centile		-		
		AMIPB Story DR	25-50th centile		-		
		Paired-assoc. 1	5-25th centile		**<5th centile**		
		Paired assoc. 2	**<5th centile**		**<5th centile**		
		GNT	25-50th centile		25-50th centile		

Cohort studies

(Frisch et al., 2013)	15	6 (range: 1-23)	Verb.Mem. (Word List-IR/DR/Recog,)	**Significantly impaired against normalized population**	Median: 25 (1-68)	**Significant improved but still below normal population**
			Vis.Mem. (Design learnin-IR/Recog.)	**Significantly impaired against normalized population**		**Significant improved but still below normal population**
			Exec.Func. (Trail making, response inhibition, digit span backwards, word fluency and maze).	**Significantly impaired against normalized population**		Improved to normal performance
(Butler et al., 2014a)	19	Median: 111 (16-377)	Verb.Mem. (WMS-III Story-IR/DR and AMIPB word list-IR/DR)	**Z = -1.76**	254 days (83-1395)	**Z = -1.07**
			Vis.Mem. (ROCF-IR/DR)	**Z = -0.52**		Z = 0.23
			Exec.Func.. (letter and category fluency, Trails B, digit span from WAIS-III)	**Z = -0.90**		Z = -0.02
			Proc.Speed (digit-symbol coding)	**Z = -0.76**		Z = -0.10
			Lang. (vocabulary and similarities WAIS-III)	Z = 0.20		Z = 0.43

			Percept. (ROCF or AMIPB copy, block and matric design WAIS-III)	Z = 0.28	Z = 0.47
(Bettcher et al., 2014)	12	394 (152-1205)	Memory (California Verbal Learning Test)	**Z = -2.4**	
			Visual memory (Benson figure)	**Z = -1.9**	
			Executive function (letter and category fluency, design fluency, digit span, modified Trails, Stroop inhibition)	**Z = -1.5**	
			Visuospatial (number location from VOSP, Benson figure construction)	Z = -0.1	
			Language (Boston Naming Test, single word comprehension (Peabody Picture Vocabulary Test, sentence repetition)	Z = -1.5	

AMI: Autobiographical Memory Interview; AMIPB: Adult Memory and Information Processing Battery; DR: delayed-recall; Exec.Func.: executive function; GNT: Graded Naming Test; Lang.: language; NART: National Adult Reading Test; Paired assoc.: paired associates; Percept.: perception; PIQ: performance intelligence quotient;

Proc.Speed: processing speed; Recog.: recognition; RMT: Recognition Memory Test; ROCF: Rey-Osterreith Complex Figure; Verb.Mem.: verbal memory; Vis.Mem.: visual memory; VIQ: visual intelligence quotient; VOSP: Visual Object and Space Perception battery; WAIS-III: Wechsler Adult Intelligence Scale Third Edition; WMS-III: Wechsler Memory Scale Third Edition.

4.1.3. Selection of the neuropsychology test battery

As discussed in Section 4.1.1, the evidence from VC (Cipolotti et al., 2001), SJ, RG, GB, DA (Rosenbaum et al., 2008), KC (Rosenbaum et al., 2005), HM, and WR (Steinvorth et al., 2005) suggests that even MTL+ lesions do not produce impairments in non-mnemonic neuropsychological domains. However, this cannot be assumed to be the case when assessing any patient with amnesia, and as such other non-mnemonic domains (for instance, intelligence, executive function, language) should be assessed. The evidence from HM (e.g., Steinvorth et al., 2005) suggests that MTL lesions should produce anterograde amnesia that is dissociable from other neuropsychological domains, and indeed this pattern is observed in Table 4.1. Therefore, any battery assessing the neuropsychological consequences of focal CA1 and CA3 lesions should have an emphasis on mnemonic-based tasks. As will be discussed in this section, there is would appear to be an interdependence of memory-based performance on other neuropsychological domains (e.g., language, executive function), and so the assessment of these domains is also critical in showing that any amnesia observed is due to isolated hippocampal dysfunction.

When considering what neuropsychological domains should be assayed when characterizing this VGKC-complex LE cohort, it is clear given the relationship between hippocampus and anterograde memory, that focus should fall on the different types of memory so far discussed (i.e., immediate-recall, delayed-recall, recognition, story learning, list learning). More recent longitudinal studies (Bettcher et al., 2014; Butler et al., 2014a; Frisch et al., 2013) have attempted to measure non-mnemonic functions such as executive function, and language. There are domains yet to be assessed that are crucial to memory performance, such as attention, and so this chapter will seek to further extend the neuropsychological characterization of VGKC-complex LE.

4.1.3.1. Non-mnemonic neuropsychological functions

4.1.3.1.1. Intelligence modulates memory performance

General intelligence is responsible for much of the predictive validity of cognitive tests (Deary et al., 2010). It is broadly taken that cognitive tests are able to discern individual differences between participants, and that these differences remain stable

throughout time (Deary et al., 2010). Intelligence is generally taken to be *"a very general capability that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience."* (Gottfredson, 1997), and a study of >7,000 patients shows that memory has an association factor of 0.66 with a general intelligence factor (*g*) across a wide range of memory tests (Salthouse, 2004).

Measures of intelligence seem to have most bearing on arguments of 'hidden pathology' (Aggleton and Brown, 1999). This argument states that in the case of a patient performing badly on tests of retrograde episodic memory, with evidence of focal hippocampal damage, there must also be cortical deficits due to hidden pathology, that may escape comprehensive cognitive testing and MRI analysis (Cipolotti et al., 2001).

Previous concern has been raised over the use of VGKC-complex LE patients as a model of hippocampal dysfunction (Squire et al., 2010). One amnesic participant (P04) was used in a measure of future imagining, a putatively hippocampal-based task (Hassabis et al., 2007b), but it was noted that this patient had a presumed decline in his intellectual function following premorbid estimations (Squire et al., 2010). Therefore, in order to address this concern directly, measures of intelligence should be tested to see whether there is any intellectual impairment for this VGKC-complex LE group, and whether any observed intellectual changes might be the sole explanation for mnemonic and non-mnemonic neuropsychological deficits potentially observed in this patient group.

4.1.3.1.2. Attention is needed for successful memory performance

Attention is a multifaceted cognitive ability, with multiple different forms including – but not limited to – sustained attention (Sarter et al., 2001), divided attention (Dannhauser et al., 2005), and auditory working memory (Baddeley, 2003). Table 4.1 demonstrates how attention is rarely tested in cases of organic amnesia.

Sustained attention has been suggested to represent a basic attentional function that underpins higher aspects of attention such as selective attention and divided attention, and it appears that the right prefrontal cortex (PFC) and parietal regions are central to this performance (reviewed in Sarter et al., 2001). Two complementary pathways mediate sustained attention: top-down, and bottom-up attention (Sarter et al.,

2001), both of which are critical to both anterograde and retrograde memory performance. Bottom-up processing may facilitate the ability to respond and reflect on new sensory information arising from mnemonic recall (i.e., introspection producing new elements of recall). For instance, in episodic memory retrieval, bottom-up attention could direct involuntary remembering according to some external cue, or whenever an interesting memory co-opts more attentional resources (Cabeza et al., 2008), whereas top-down attention would have a clear role in self-directed retrieval of mnemonic events or tasks.

Divided attention refers to attention split between two or more sources of information, and is associated with an increased demand on cognitive processing (Dannhauser et al., 2005), and has been shown to recruit the PFC bilaterally – as measured with functional MRI (fMRI) – during tasks requiring working memory and semantic processing (Iidaka et al., 2000; Koechlin et al., 1999). It has been suggested that impairment in divided attention results in the distortion of source monitoring (i.e., adherence to the current task), which might lead to memory impairment (Johnson, 1997). As impairments in mnemonic recall might be due to deficiencies in divided attention, and as such an assay for performance on this type of memory should be sought.

Auditory verbal working memory is important to many types of anterograde memory tasks, where it is used to transfer learned information into long-term storage (Wolk et al., 2011). Such regions involved in this encoding include the supramarginal and angular gyrus of the parietal lobe, structures associated with the auditory working memory (Baddeley, 1986; Buchsbaum and D'Esposito, 2008; Champod and Petrides, 2007; Markowitsch et al., 1999; Peters et al., 2009a; Peters et al., 2009b). With increasing repetition of list learning, the authors noted that the MTL structures activity began to correlate with neuropsychological performance (Wolk et al., 2011). In cases of organic amnesia, particularly where anterograde amnesia is seen, it is crucial that auditory working memory be assessed, as amnesia in these tasks could represent a failure of amnesic patients to learn or sustain either the task itself or the material learned.

Therefore a systematic and thorough assessment of attention – particularly sustained attention, divided attention, and auditory working memory – is crucial for any experiment investigating the effects of MTL lesions on memory recall. The Test of

Everyday Attention (TEA; (Robertson et al., 1994)) is a neuropsychological battery that is comprised of eight ecologically derived tasks of attention that can be combined to create indices for sustained attention, auditory working memory, attentional switching, and visual selective attention. Performance on all of these subtests would be predicted to be normal following VGKC-complex LE.

4.1.3.1.3. Executive function contributions to memory recall

Executive function is critical to successful mnemonic performance. Previous reports have shown that patients who are severely dysexecutive are unable to perform normally on a story learning paradigm arising from the WMS-R, and list learning from the CVLT (Tremont et al., 2000). This appeared as a graded function as the severity of the dysexecutive syndrome increased (Tremont et al., 2000). Similar results were found for the LM subtest of the WMS-R, but without any differentiation between a severely impaired patient group and a moderately impaired patient group (Tremont et al., 2000). These authors also found that the greater the impairment on tests of executive function, the greater the impairment on word list, but not LM, recall (Tremont et al., 2000). The authors interpreted these results as showing that as the story had an inherent structure and organization, the task involved less semantic processing and, therefore, may be a more direct measure of hippocampal function (Tremont et al., 2000). As the word list is disorganized, participants will tend to structure the learning and retrieval of these words themselves, something that requires strategy and planning (Tremont et al., 2000). Therefore, any evidence of word list impairment may be indicative of executive dysfunction, as opposed to the more hippocampal-dependent story learning (Tremont et al., 2000).

Aside from measuring both word list and story performance, there are also clear links between executive dysfunction and impaired memory performance. Many patients with frontal lobe lesions perform poorly on measures of episodic memory (Gershberg and Shimamura, 1995; Janowsky et al., 1989; Wheeler et al., 1995), with particular emphasis falling on functions supported by the PFC. The PFC appears to be the neural foundation for the controlled-strategic processing required during both encoding and retrieval essential to accurate memory retrieval (Alexander et al., 2009; Blumenfeld and Ranganath, 2007). It has long been considered that optimal episodic memory recall requires the active monitoring of the accuracy of a chosen retrieval search strategy (Burgess and Shallice, 1996; Norman and Bobrow, 1979), and that within episodic

memory retrieval, the PFC is involved in the strategic control of memory retrieval (Allan et al., 2000; Cabeza et al., 2003; Fletcher et al., 1996, 1998; Henson et al., 2000; Shallice, 1988; Stuss et al., 1994).

Whilst it is not possible to recreate each of these experimental measures of executive function, what this survey demonstrates that some assay of executive function needs to be made. Successful performance on the Stroop task (Stroop, 1935) requires dorsolateral PFC activity (as measured by fMRI), in order to counteract bias and irrelevant information (Banich et al., 2000). In the context of memory retrieval, it is important that participants are able to successfully identify, and select the appropriate stimuli for retrieval. Likewise, Trail making tasks, especially those that involving switching between letters and numbers, are believed to rely on multiple cognitive processes, including attention, the modification and execution of a plan, and the ability to maintain separate thought streams online for its normal performance (reviewed (Salthouse, 2011)). Therefore, within these tasks (i.e., the Stroop task, Trails B) several cognitive processes are assessed simultaneously. For the purposes of this chapter, these, and related tasks, can be used to screen for evidence of executive dysfunction. Poor performance on word list, but normal story performance, might suggest that amnesia is due to executive dysfunction rather than hippocampal dysfunction. In this scenario, executive function testing will be critical to determining the neuropsychological locus underlying the amnesia.

The evidence in Table 4.1 demonstrates that, by-and-large, that even patients with MTL+ lesions had normal measures of executive function. This cohort of VGKC-complex LE patients, with their CA1 and CA3 atrophy, should perform normally on measures of executive function, but this cannot be assumed. VGKC-complex LE is not known to be associated with lesions to any region of the PFC (Wagner et al., 2015; Wagner et al., 2014). Any neuropsychological test battery must be large enough to provide comprehensive assessment of executive function in relation the mnemonic encoding and retrieval, in order to partial out whether the amnesia is due to mnemonic or executive dysfunction.

4.1.3.1.4. The relationship between the temporal lobe and language performance

The neuropsychological assessment of memory has mostly relied on the verbal reports of patients to convey what they can and cannot remember, and, in so doing, assumes that patients comprehend and understand the task being asked of them (e.g., Bayley et al., 2003, 2006; Levine et al., 2002). Therefore it is critical that any neuropsychological deficit in declarative memory or otherwise is not due to a failure in task comprehension or verbal reporting.

Simple naming has been found to correlate with increased grey matter volume in the right anterior temporal lobe, and fMRI-based activity (Brambati et al., 2006). Therefore, it should be expected that these VGKC-complex LE patients should perform normally on simple naming (on a task such as the Graded Naming Test), and where simple semantic decisions need to be made about items.

One such task is the Camel and Cactus Test (Bozeat et al., 2000), during which participants have to make a make a semantic link between one object, and one of four other objects where only one has a semantic connection to the target object (for instance, a camel which could be matched to either a cactus, oak tree, a flower, or grass). Patients with VGKC-complex LE would be predicted to perform normally on both of these language tasks.

The comprehension of simple and complex sentences has been shown to be consistently associated with activity in the left posterior temporal pole, whereas complex sentences appear to also be associated with activity in the left inferior frontal lobe (Stowe et al., 2005). This centrality of temporal lobe to language performance has been highlighted by studies in semantic dementia, which have shown that patients with semantic dementia develop anterotemporal lobe atrophy, and generally experience a gradual loss of semantic memory, culminating in an inability to verbally identify stimuli (Hodges and McCarthy, 1995), and an inability to comprehend sentences (Grossman et al., 1998). These studies demonstrate that lateral temporal lobe integrity is critical to language performance. As Table 4.1 demonstrates, measures of language function are usually normal even in patients with MTL+ lesion, and so it would be expected that language performance in this VGKC-complex LE cohort would be likewise normal.

Typical neuropsychological-based measures of language ability, including category and letter fluency, tend to collapse across several cognitive domains, similar to the executive function tasks discussed above. For instance, successful category fluency performance requires a search through conceptual knowledge for further words semantically connected to a target word (Taler and Phillips, 2008). Letter fluency relies on participants deriving a retrieval strategy according to given letter (e.g., F, A, or S; (Rohrer et al., 1999)). Both these tasks require intact frontal lobe functioning (Lezak et al., 2004) to organize retrieval strategies, initiate verbal response, to monitor responses previously given and to inhibit those responses contrary to the selection criteria (Henry et al., 2004). fMRI studies have demonstrated that both measures are associated with increased BOLD signal activity within the temporal lobe, themselves implicated as semantic memory stores (Birn et al., 2010; Mummery et al., 1996); however, letter fluency is less reliant on these regions than category fluency (Lezak et al., 2004). This survey therefore suggests that neuropsychological measures of language may extend to include executive functions as well. Therefore, including measures of category and letter fluency would not only assess language production, but also frontally mediated language retrieval functions.

However, as discussed in Section 4.1.2, the hippocampus can also contribute to some aspects of language performance. Whether VGKC-complex LE results in category fluency deficits remains and empirical question, and has been found previously (Bettcher et al., 2014), and so should be tested in this neuropsychological test battery.

Neuropsychological assessments of language can be varied, ranging from simple item identification, through to semantic associations, and fluency tasks. Each of these assesses more than just simple language skills, but helps provide information concerning the integrity of the regions supposed to underlie their performance.

4.1.3.1.5. Visuospatial and construction contributes to episodic memory retrieval

Several lines of evidence indicate that episodic memory retrieval appears to rely, in part, on visuospatial constructive ability, and so consideration of what specific role the hippocampus has in visuoaptial construction needs to be undertaken, using neuropsychological screening of visuospatial and construction performance needs to be

undertaken. Evidence from health control participants (Hassabis et al., 2007a; Addis, 2007;Zeidman et al., 2015) implicates a network of coactivated regions including the hippocampus, PHC, retrosplenial cortex, and medial PFC. These data accord with models of episodic memory whereby the hippocampus is central to the reconstruction of retrograde and anterograde memories (Greenberg et al., 2005; Piolino et al., 2009; St-Laurent et al., 2014; St-Laurent et al., 2009), whereby the hippocampus is central to the associations required to recreate the richly re-experiential episodic retrieval (Maguire et al., 2010; Ranganath, 2010; Schacter and Addis, 2009; Yonelinas et al., 2010).

One further account of the MTL's contribution to episodic memories is that it integrates the visual details stored in higher order cortical areas (Greenberg et al., 2005), which would suggest that damage to the MTL should disrupt visual percept integration, a feature known to contribute to the self-rated vividness and imageability rating (Rubin et al., 2003). In healthy participants, hippocampal activity on fMRI has also been shown to correlate with ratings of vividness (Gilboa et al., 2004; Rabin et al., 2010), the use of imagery in those memories (Andrews-Hanna et al., 2010) and the intensity of re-experiencing (St Jacques et al., 2012); but see (Daselaar et al., 2008)) during the retrieval of episodic memories.

The data from Table 4.1 and 4.2 suggest that patients with varying degrees of hippocampal damage are not usually impaired (e.g., VC, (Cipolotti et al., 2001); SJ, RG, CB, DA, all (Rosenbaum et al., 2008); and KC (Rosenbaum et al., 2005), although both HM and WR were significantly impaired on Rey-Osterreith Complex Figure (ROCF, Osterreith and Rey, 1944) copy. (Steinvorth et al., 2005); this is critical as deficits in processing or creating scenes may be due to deficits in these neuropsychological domains, rather than a reflection of hippocampal dysfunction. Figure 1.1 demonstrates how the hippocampus receives both unimodal and multimodal visual information from several cortical regions, therefore should impairments be noted in visual aspects of episodic memory retrieval, it is critical to know whether this arises from hippocampal dysfunction, or from the early stages of visual processing pathway. This becomes more critical when experimental measures of episodic memories are undertaken in Chapter 5.

One difficulty with the neuropsychometric assessment of visuospatial or construction is that the tasks used do not accurately replicate any of the experimental

paradigms discussed above. As such, approximation with tasks such as the ROCF, and allied tasks, will at least demonstrate whether these domains are grossly impaired following VGKC-complex LE, and hence impair the quality of information reaching the hippocampus.

4.1.3.2. Mnemonic neuropsychological domains

4.1.3.2.1. Anterograde memory

The evidence from the patients listed in Table 4.1, and previous studies in VGKC-complex LE discussed in Section 4.1.2, suggest that this cohort of patients are expected to have a least some degree of anterograde amnesia. However, memory is usually not considered a unitary process (cf. Berry et al., 2008), and so critical evaluation of the different neuropsychological types of memory needs to be considered. This will inform the decisions made concerning what types of tasks should be included in the neuropsychological test battery in order to account for these memory types.

4.1.3.2.1.1. The relationship and interactions between immediate-recall memory and attention

Immediate-recall memory, also known as working memory, is generally understood as a limited capacity system that temporarily maintains and stores information, and is intimately related to attention (Baddeley, 2003). Immediate-recall memory has been argued to be a temporary activation of the neural representation of the long-term memory (Murre et al., 2013), and one of the key regions implicated for immediate-recall memory is the PFC. This is underscored by early work undertaken in HM where he performed normally in tasks of immediate-recall (Corkin, 1984, 2002; Eichenbaum, 2013). Evidence also suggests that the MTL may also be critically involved in immediate-recall memory, and so the contributions of both regions will be considered.

4.1.3.2.1.1.1. Medial temporal lobe and prefrontal cortex contributions to immediate-recall memory

The MTL demonstrates sustained mnemonic activity across short delays (Ranganath and D'Esposito, 2005), but this is not to say that the MTL is always recruited in every immediate-recall memory task, with evidence suggesting that the MTL structures

are selectively recruited depending on the stimuli presented. Immediate-recall deficits therefore might be only expected with stimuli known to uniquely processed by the MTL structures like complex novel objects (Lee et al., 2005; Murray and Bussey, 1999), and, indeed, deficits are noted in patients with these forms of stimuli (Aggleton et al., 1992; Buffalo et al., 1998; Holdstock et al., 2000; Holdstock et al., 1995; Owen et al., 1995), not attributable to lesions extending into the temporal neocortex (such as TE, Eacott et al., 1994; Zola-Morgan et al., 1989).

Most clinical tests of immediate-recall or working memory use stimuli that could be well represented outwith the MTL structures (such as words, WMS-III Word List Learning; Wolk et al., 2011), and so may not specifically recruit the MTL structures. Therefore, it might be expected that patients with focal MTL lesions would show minimal (if any) impairment across immediate-recall memory tasks involving simple word learning or digit span tasks, but deficits in more complex tasks such as story learning or paired-associate learning should be observed.

4.1.3.2.1.2. Delayed-recall memory

Delayed-recall memory is typically thought of memory that is recollected across a time delay from its encoding event (Squire et al., 2004). Typically, deficits in delayed-recall memory are more likely to be seen across delays of more than a few seconds, and where the subject is distracted from the learning event. HM could be observed to retain complex information across several minutes, but when he was distracted, or made to engage in another type of neuropsychological task, this accuracy and mnemonic information was then lost (Corkin, 1984, 2002; Eichenbaum, 2013; Ranganath and Blumenfeld, 2005). This pattern has been previously observed in patients with extensive MTL lesions (Insausti et al., 2013; Knutson et al., 2012), and circumscribed hippocampal lesions (Goodrich-Hunsaker and Hopkins, 2009), and is summarized in Table 4.1.

Previous research has demonstrated that the delayed-recall components of neuropsychological learning paradigms could be reliant upon full MTL functioning, but that only when the material being tested is in the form of a story, where multiple elements need to be combined together to form a single memory trace (Helmstaedter et al., 1997). In addition, other neuropsychological-hippocampal volume studies found that delayed verbal recall, as measured by story performance, appeared to more positively

associated with hippocampal volumes, with increasing volumes being associated with greater delayed verbal memory performance (Kohler et al., 1998; Travis et al., 2014).

Mueller et al., (2011) extended this finding into the subfields of the hippocampus, and described how CA1 volume was positively correlated with increased performance on a composite delayed memory score (consisting of the CVLT-II, a word list task), but other hippocampal subfield regions, such as the DG, were unrelated to this performance. It has also been observed that performance on Logical Memory 2 (LM2, a story learning task arising from the WMS) has previously been shown to correlate with CA1 volume (Mueller et al., 2012), suggesting that delayed story learning demonstrates some association with increasing hippocampal subfield volumes.

These studies do collapse across different material types (i.e., story learning, list learning), making direct inferences concerning the relationships between hippocampal anatomy and neuropsychological performance for specific mnemonic materials difficult. What they show, though, is that composite measures of delayed memory function can be observed to be associated with hippocampal volume.

Table 4.1 general shows that all patients, from those with CA-specific lesions through to MTL+ lesions, perform poorly on measures of delayed recall memory, and as such delayed memory tasks will be included in the neuropsychological battery in this chapter, and it would be expected that this cohort have impairment in delayed memory performance.

4.1.3.2.1.3. The medial temporal lobe structures and hippocampus demonstrate different specificities for visual and verbal materials

Section 4.1.3.1.2 mentions that collapsing across verbal and visual materials introduces a confound into neuropsychological studies of MTL dysfunction, so some exploration of how verbal and visual materials are processed by the MTL structures is required.

Functional MRI studies have shown that the hippocampus tends to show activity when associations between several different items and contexts need to be made across

multiple sensory modalities (Cansino et al., 2002; Davachi et al., 2003; Duarte et al., 2011; Staresina et al., 2011). Neuropsychological studies have shown that delayed verbal recall performance is correlated with total hippocampal volume (Kohler et al., 1998; Travis et al., 2014), but that the PHG was positively correlated with non-verbal delayed recall (Kohler et al., 1998). When considered together, these data suggest that in focal lesions of the hippocampus patients might have dissociation in verbal memory from visual memory, when source memory is not required for recall (such as with recalling the ROCF).

4.1.3.2.1.4. Single-item and story learning are supported by different anatomical structures

Single-item recall – typified by list learning – involves learning a list of non-connected items, usually over several repetitions (Wechsler, 1997b). As with other anterograde memory tasks, single-item learning requires initial activation of the auditory verbal working memory network (see Section 4.1.3.2.1.1.1; Wolk et al., 2011). However, with repeated exposure to the stimuli (as typified by the word list learning in WMS-III) recall performance becomes intimately associated with the temporal pole (Wolk et al., 2011), suggesting that the semantic processing of information is critical to the strength of memory trace for later retrieval (Craik and Lockhart, 1972; Goldblum et al., 1998). Story learning, whilst being more complex than list learning still, requires lateral temporal pole integrity for performance (Wolk et al., 2011). Delayed-recall of both list learning and story learning appears most reliant upon rostral MTL cortical structures (Wolk et al., 2011). This may appear counterintuitive given how Section 4.1.3.2.1.2 describes how story learning appears to demonstrate some hippocampal specificity; however, it is likely that these anterograde memories could be recalled without a contextual sense of prior exposure (a key feature of hippocampally-retrieved memories; Wolk et al., 2011), and, as such could be supported by the extrahippocampal MTL cortex regions such as the PRC and lateral ERC (Aggleton and Brown, 2006; Eichenbaum et al., 2007; Yonelinas et al., 2007).

Hippocampal activity therefore seen during learning could be more representative of associations made between the items during learning, but subsequently not required for retrieval (Wolk et al., 2011). This suggests that as no associations are needed for single-item learning, then retrieval should be hippocampal-independent.

However, whilst there is some suggestion that story learning could be retrieved by extra-hippocampal structures, the hippocampus will be central to creation of associations that constitute story learning. Therefore, in cases of focal CA1 and CA3 volume loss, it would be expected that patients perform normally on single-item memory but that verbal memory for more complex tasks such as story learning. As such both these materials should be tested for as independent mnemonic substrates.

4.1.3.2.1.5. Recognition memory

Recognition memory has its own large corpus of empirical work (reviewed in (Eichenbaum et al., 2007)), and so it is appropriate to outline the heuristic through which the data in this chapter will be interpreted. Two major models of recognition memory exist: (1) a one-process theory of memory, whereby recognition memory lies on a spectrum with recollection (i.e., episodic memories, story recall), with recognition memory being observed as a weak form of recall. Critically, both memory types are reliant upon the hippocampus and associated MTL structures for short period, the duration of which is not usually specified (Eichenbaum et al., 2007); and (2) dual-process theories where recognition memory and recollection are two separate mnemonic processes, with recognition memory relying on the MTL structures such as the ERC and PRC, whereas recall relies on hippocampus (reviewed in Eichenbaum et al., 2007).

In this VGKC-complex LE cohort, the one-process account would suggest that impairments in recognition memory will be observed, as recently acquired information will be hippocampally-dependent. Conversely, in the dual-process model, this cohort should perform normally – thereby dissociated from other tasks requiring hippocampal function, such as story recall – as their MTL structures are intact. Further discussion of the neuropsychological foundations of recognition memory will be undertaken, in order to determine what the specific hypotheses might be made for this VGKC-complex LE cohort.

4.1.3.2.1.5.1. Evidence for extra-hippocampal contributions to recognition memory

The hippocampus appears particularly vulnerable to hypoxic-ischaemic damage (Gadian et al., 2000; Hopkins et al., 1995; Rempel-Clower et al., 1996; Zola-Morgan et

al., 1986), and neuropsychological studies have shown that hypoxic patients exhibit deficits in recollective relational memory (such as story learning) compared to face or word recognition tests (Giovanello et al., 2004; Holdstock et al., 2005; Mayes et al., 2002; Turriziani et al., 2004). However, recognition memory for previously encountered faces and words (as measured by the RMT) can be impaired if the lesion extends to include the MTL structures, especially the PHG (Cipolotti et al., 2006; Eichenbaum et al., 2007). Conversely, lesion studies in human patients have shown that lesions restricted to the hippocampus have disproportionate deficits on recollection mediated episodic retrieval but not recognition memory (Aggleton et al., 2005; Holdstock et al., 2002; Mayes et al., 2004), although other groups have reported deficits in both in similar patients (Cipolotti et al., 2006; Jeneson et al., 2010; Manns et al., 2003; Wais et al., 2006).

These data suggest that in the case of hippocampal-restricted damage, patients should perform within normal limits for word and face recognition, as administered by standardized neuropsychological tests. Deficits are generally only seen with the more extensive lesions, and the behavioural data is more in keeping with the predictions of the dual-process model (although see Smith et al., 2014). These results are also consistent with fMRI evidence that indicates wider cortical areas are involved in recognition memory, but that these regions may interact with the other MTL structures (such as the PRC) for normal performance.

As a consequence, it is perhaps unsurprising that patients with MTL lesions can still perform above chance on many forms of recognition memory task. It has been previously observed – see Table 4.2 – that recognition memory has not been assessed as a separate mnemonic entity (Butler et al., 2014a; Frisch et al., 2013), but where it has deficits have been observed either in the acute part of the illness (Vincent et al., 2004), but also after successful treatment but without neuroradiological correlation or assessment (Chan et al., 2007).

4.1.3.2.1.6. Anterograde memory: summary and predictions

This section demonstrates that it is necessary, when performing neuropsychological characterization of patients with damage potentially limited to the MTL structures, that the battery should include tests that place different burdens on the hippocampus, and hence could provide evidence of dissociations based on theoretical priors. The specific predictions are that as a cohort, these VGKC-complex LE patients will:

1. Have impaired performance on immediate-recall measures that involve associations to be made between stimuli for both verbal and visual tasks.
2. Delayed-recall performance will be impaired for verbal memory, but may be observed to be normal for visual memory.
3. Both immediate- and delayed-recall single-item memory will not be significantly impaired compared to the standardized control population.
4. Recognition memory performance will not be significantly impaired compared to the standardized control population.

The above discussion makes it clear that neuropsychological mnemonic functions cannot be expected to map neatly onto a single neuroanatomical region; however, a thorough assessment of memory can provide insights into the integrity of the neural apparatus underlying different functional aspects of memory, and related cognitive operations.

4.1.3.3. The Autobiographical Memory Interview adequately measures personal semantic memory but not retrograde episodic memory

Neuropsychological examinations of retrograde memory have principally involved the applications of the AMI (Kopelman, 1994). The AMI is a semi-structured interview that constrains memory to three broad time-spans: 'Childhood', 'Adult' and 'Recent' epochs, and aims to distinguish episodic from semantic recall at the time of testing (Kopelman, 1994). Importantly, the marks available to each of these time periods are equally balanced across the time-spans, and the episodic memories are further constrained by subject type. Scoring of these episodic memories is performed according to the subjective richness of the event on a 0-3 scale. Semantic scores are derived from various factual questions arising from those three epochs, and are either correct (scoring between half to one mark), or incorrect (scoring no marks).

Although the AMI has proven a more reliable means of comparison to other earlier methods of assessing retrograde memories – such as word cues (Crovitz and Schiffman, 1974), or the quantity of self-reported memories from a particular epoch (Hyland and Ackerman, 1988; Rubin and Schulkind, 1997) – it places a constraint on the data available from these investigations. For instance, the marking guidelines suggest awarding three marks for those memories that have a specific time and place and which are episodically rich in nature. Thus ceiling performance is easily obtainable on the AMI, and so can lack sensitivity to detect individual differences in performance. The AMI also does not assess the presence of the central feature of episodic memories, which is a unique sense that the participant was part of the event itself, autonoesis (Tulving, 1983, 2002), and so one cannot be sure that the memory retrieved is truly episodic in nature. The semantic measures, though, do appear to be structured in an ecologically valid way (i.e., can the participant recall the memory or not), and are well distributed across the lifetime.

The use of the AMI has been superseded by other measures of retrograde episodic memory, such as the Autobiographical Interview (AI; see Section 5.1.4.2). However, as Table 4.1 and 4.2 make clear, it has been used in the neuropsychological characterization of organic amnesia, and VGKC-complex LE.

For patients with lesions limited to the MTL (CB, RG and DA; (Rosenbaum et al., 2008)), there is a general pattern of more recent episodic memory impairment, which improves the more temporally remote the memory becomes (i.e., in keeping with the standard model of consolidation). Patients with more extensive lesions (KC, Rosenbaum et al., 2005; VC, Cipolotti et al., 2001) tend to either have a global impairment in episodic recall across the lifetime (VC), or have a temporal gradient with both episodic and semantic memory loss (KC). This suggests that more MTL focal lesions will produce a temporal gradient of episodic memory loss, but more extensive lesions are associated with a more extensive loss of both episodic and semantic memory performance. The AMI has been previously used, serially, for a single patient with VGKC-complex LE (Buckley et al., 2001). This study found that during the acute stages of the illness that the patient had poor performance for both episodic and semantic components of the task, but this subsequently improved to normal performance (Buckley et al., 2001). Therefore,

it could be predicted that this cohort will perhaps show a temporal gradient of episodic memory loss, if amnesia is measured at all, and that semantic memory performance will be normal.

4.1.6. Summary: aims and hypotheses

The aim of this chapter was therefore to administer an extensive neuropsychological battery, across a number of neuropsychological domains in this single aetiology group (VGKC-complex LE). The literature cited above suggests that patients with circumscribed lesions to the hippocampus proper, generally perform to within one to two SDs of controls for anterograde memory tasks, with one exception being delayed memory (Rempel-Clower et al., 1996). As discussed above (Section 4.1), evidence of significant impairment on neuropsychological tasks has generally been defined as performance less than two SDs from a normative mean (Benton and Hamsher, 1977). Therefore, the performance of patients like RB and GD is within the normal range of performance. Statistical significance will be used to assess for significant differences between the group performance, and that of the normative population (see Section 2.2), and hence will be the operational definition used in this chapter. The predictions for this chapter are as follows:

1. This VGKC-complex LE cohort will have statistically significant impairment in both immediate-recall and delayed-recall of verbal and immediate-recall visual information, but that performance will fall within two SDs of the normative population.
2. That recognition memory and single item memory will be unimpaired.
3. There will be a temporal gradient of retrograde episodic memory loss, but not semantic memory as measured by the AMI.
4. That the non-mnemonic neuropsychological domains will not be significantly impaired, when compared to the normative control population.
5. That by undertaking a correlational analysis of neuropsychological domain performance in order to probe relationships between domains, intelligence will correlate with most measures of neuropsychological performance; that Immediate Verbal and Visual Recall, and Delayed Verbal and Visual Memory will correlate with one another, as these are ostensibly

hippocampal-dependent tasks; and that in keeping with the results of (Bettcher et al., 2014), there will be correlations between language performance, and the collapsed mnemonic domains (see Section 2.2 for full methods).

4.2. Methods

See Section 2.2.

4.3. Results

4.3.1. VGKC-complex LE results in significant differences of immediate verbal and visual recall, and delayed verbal recall from a normative control population

The cumulative neuropsychological data for this VGKC-complex LE patient cohort is presented in Table 4.3. These data suggest that, when considered as a group and compared to a normalized population, the VGKC-LE group were significantly above the normative data on the following subtests: WASI Similarities (mean = 0.8±0.17; t = 3.39, df = 17, p = 0.005), WASI Matrix Reasoning (mean = 0.8±0.22; t = 3.39, df = 17, p = 0.005), Doors and People Visual Forgetting (mean = 0.5±0.21; t = 2.12, df = 17, p = 0.01), Graded Naming Test (mean = 0.6±0.24; t = 2.62, df = 18, p = 0.01), Letter Fluency (mean = 0.4±0.3; t = 1.74, df = 18, p = 0.05), RMT words (mean = 0.4±0.3; t = 1.74, df = 18, p = 0.05), Category Fluency (mean = 0.4±0.3, t = 1.74, df = 18, p = 0.05), Category Switch (mean = 0.5±0.27; t = 2.18, df = 18, p = 0.025), Stroop test (mean = 1.0±0.14; t = 4.36, df = 16, p = 0.005), Digit Span (mean = 0.9±0.25; t = 3.92, df = 18, p = 0.05), Visual Elevator (mean = 0.9±0.18; t = 3.6, df = 16, p = 0.001) and Lottery subtest of the TEA (mean = 0.5±0.18; t = 2.00, df = 16, p = 0.025).

By contrast, the VGKC-complex LE group demonstrated significant negative differences in the following subtests: Logical Memory 1 (mean = -0.5±0.24; t = -2.18, df = 18, p 0.05), Rey Complex Figure Immediate Recall (mean = -1.1±0.28; t = -4.79, df = 18, p = 0.05), Logical Memory 2 (mean = -1.2±0.28; t = -5.23, df = 18, p = 0.005), Logical Memory 2 Themes (mean = -0.8±0.33; t = -3.49, df = 18, p = 0.0025), Doors and People Names (mean = -0.9±0.23; t = -3.82, df = 17, p = 0.025) and Elevators with Distraction (mean = -0.5±0.26; t = -2.00, df = 16, p = 0.025).

With so many neuropsychological measures there is an increased risk of Type I family-wise errors. To address for this issue, every patient had an index score derived by averaging the *Z*-scores of the tests constituting the given indices. This was then averaged across the group to give a group indices score. As a group, VGKC-complex LE patients were significantly better on general intelligence (mean = 0.8±0.19; t = 3.39, df = 17, p = 0.005), language (mean = 0.4±0.22, t = 1.74, df = 18, p = 0.05) and executive function (mean = 0.6±0.15; t = 2.62, df =18, p = 0.05) than the standardized norms. As a group,

VGKC-complex LE patients were significantly impaired on measures of immediate verbal recall (mean = -0.4±0.19, t = -1.74, df = 18, p = 0.05), immediate visual recall (mean = -0.7±0.26, t = -3.05, df = 18, p = 0.005), and delayed verbal recall (mean = -0.8±0.23, t = -3.39, df = 18, p = 0.005). There was no evidence of a group-wise impairment or enhancement in the other tests or indices.

Figure 4.1. Box-and-whisker plots showing group performance for the VGKC-complex LE patient cohort for (A) mnemonic and (B) non-mnemonic neuropsychological domains. The line indicates the median value with the whiskers representing the 5th-95th centiles. The circle denotes a significant outlier for the domain. The hatched line represents a *Z*-score of -1.67 corresponding to the 5th centile. * denotes significantly subnormal performance at $p < 0.05$. These data demonstrate that VGKC-complex LE is associated with a reduction in immediate verbal and visual memory, and delayed verbal memory.

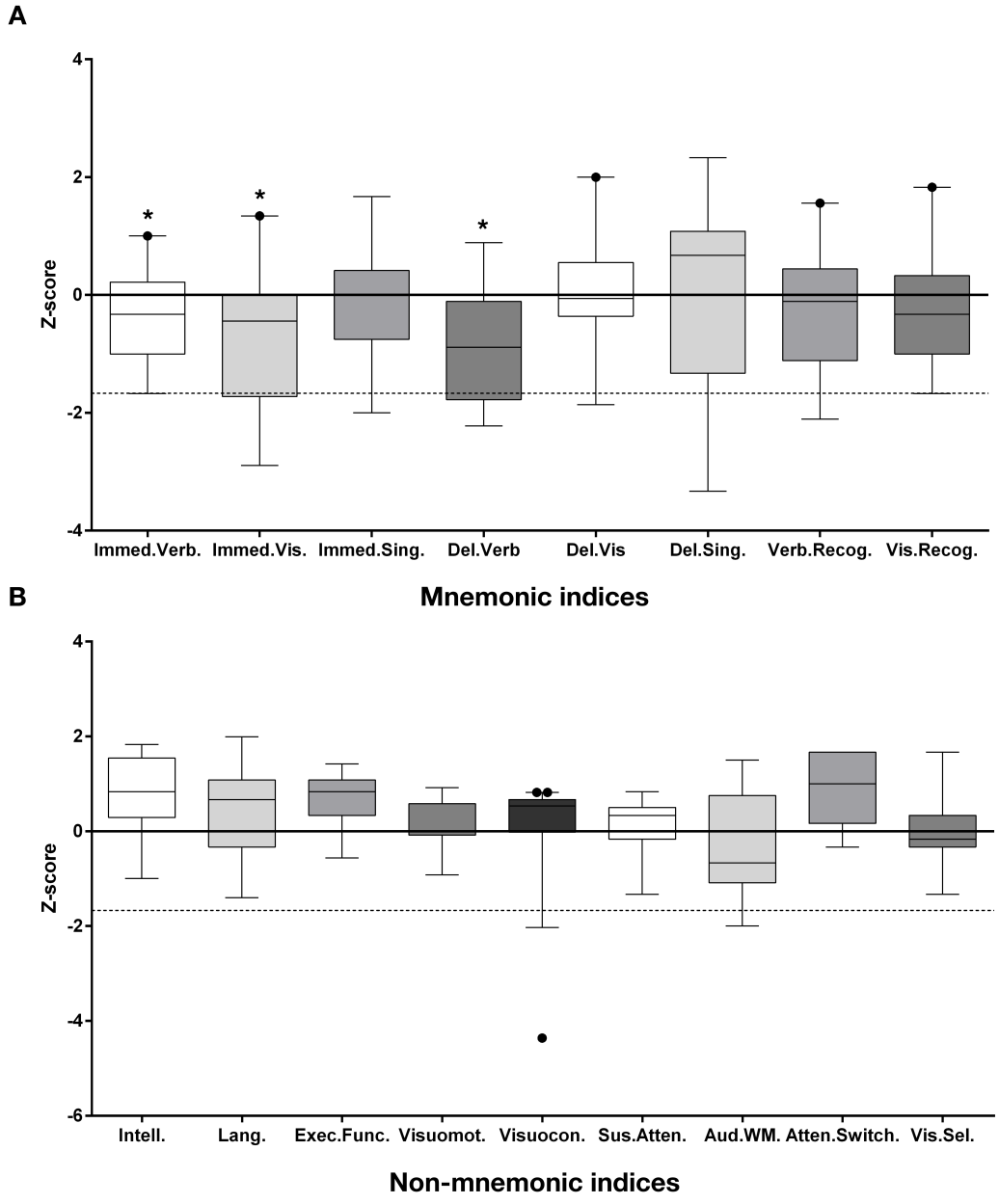


Table 4.3. Neuropsychological test and domain performance for 19 patients following VGKC-complex LE. Index scores are given shown in bold, with the neuropsychological subtests comprising the index listed above. *Z*-scores were converted to *T*-scores for analysis.

	n	*Z*-score	SEM	*T*-score	df	*p* (one tail)
General Intelligence						
WASI Similarities	18	0.8	0.17	3.39	17	0.005
WASI Matrix	18	0.8	0.22	3.39	17	0.005
Index Score	**18**	**0.8**	**0.19**	**3.39**	**17**	**0.005**
Immediate Verbal Recall						
Logical Memory I	19	-0.5	0.24	-2.18	18	0.05
Logical Memory I Themes	19	-0.1	0.24	-0.44	18	ns
Doors and People - People	19	-0.6	0.19	-2.62	18	0.01
Index Score	**19**	**-0.4**	**0.19**	**-1.74**	**18**	**0.05**
Immediate Visual Recall						
Doors and People - Shapes	18	-0.3	0.32	-1.31	17	ns
ROCF Immediate Recall	19	-1.1	0.28	-4.79	18	0.0005
Index Score	**19**	**-0.7**	**0.26**	**-3.05**	**18**	**0.005**
Immediate Single Item Recall						
Word List I	19	-0.1	0.24	-0.44	18	ns
Index Score	**19**	**-0.1**	**0.24**	**-0.44**	**18**	**ns**
Delay Verbal Recall						
Logical Memory II	19	-1.2	0.28	-5.23	18	0.0005
Logical Memory II Themes	19	-0.8	0.33	-3.49	18	0.0025
Doors and People - Verb.Forget.	18	-0.2	0.22	-0.85	17	ns
Index Score	**19**	**-0.8**	**0.23**	**-3.39**	**18**	**0.005**
Delay Visual Recall						
ROCF Delayed Recall	19	-0.5	0.22	-2.18	18	0.01
Doors and People - Vis.Forget.	18	0.5	0.21	2.12	17	**0.01**
Index Score	**19**	**0.0**	**0.19**	**0.00**	**18**	**ns**
Delayed Single Item Recall						
Word List II	19	0.3	0.33	1.31	18	ns
Index Score	**19**	**0.3**	**0.33**	**1.31**	**18**	**ns**
Verbal Recognition						
Word List II Recognition	19	0.1	0.32	0.44	18	ns
Doors and People - Names	18	-0.9	0.23	-3.82	17	0.0025
RMT Words	19	0.4	0.3	1.74	18	0.05
Index Score	**19**	**-0.2**	**0.23**	**-0.87**	**18**	**ns**
Visual Recognition						
RMT Faces	19	-0.3	0.17	-1.31	18	ns
Doors and People - Doors	18	0.1	0.23	0.42	17	**ns**
Index Score	**19**	**-0.2**	**0.22**	**-0.85**	**18**	**ns**
Language						
Camel and Cactus	18	0.2	0.25	0.87	17	ns
Graded Naming Test	19	0.6	0.24	2.62	18	0.01
Letter Fluency	19	0.4	0.3	1.74	18	0.05

Category Fluency	19	0.4	0.3	1.74	18	0.05
Index Score	**19**	**0.4**	**0.22**	1.74	18	**0.05**
Executive Function						
Category switching	19	0.5	0.27	2.18	18	0.025
Letter-number sequencing	19	0.2	0.15	0.87	18	ns
Stroop test (word inhibition)	17	1	0.14	4.36	16	0.0005
Digit span	18	0.9	0.25	3.92	17	0.005
Index Score	**19**	**0.6**	**0.15**	2.62	**18**	**0.005**
Visuomotor						
Visual scan	19	0.3	0.07	1.31	18	ns
Number sequencing	19	0.1	0.20	0.44	18	ns
Letter sequencing	19	0.1	0.05	0.44	18	ns
Motor speed	19	0.2	0.26	0.87	18	ns
Index Score	**19**	**0.1**	**0.10**	**0.44**	**18**	**ns**
Visuoconstruction						
ROCF Copy	19	0	0.29	0.00	18	ns
Index Score	**19**	**0**	**0.29**	**0.00**	**18**	**ns**
Sustained attention						
Telephone Search with Count	16	-0.3	0.17	-1.20	15	ns
Lottery	16	0.5	0.20	2.00	15	0.025
Index Score	**16**	**0.1**	**0.14**	**0.40**	**15**	**ns**
Auditory working memory						
Elevators with Distraction	16	-0.5	0.28	-2.00	15	0.025
Elevators with Reversal	16	-0.3	0.27	-1.20	15	ns
Index Score	**16**	**-0.4**	**0.27**	**-1.60**	**15**	**ns**
Attentional switching						
Visual Elevators	16	0.9	0.19	3.60	15	0.0025
Index Score	**16**	**0.9**	**0.19**	**3.60**	**15**	**0.0025**
Visual Selective Attention						
Map Search	16	0.0	0.25	0.00	15	ns
Telephone Search	16	0.1	0.22	0.40	15	ns
Index Score	**16**	**0.0**	**0.19**	**0.00**	**15**	**ns**

ns, not significant; RMT, Recognition Memory Test; ROCF, Rey Osterreith Complex Figure; Verb.Forget., verbal forgetting; Vis.Forget., visual forgetting; Verb.Recall, verbal recall; Vis.Recall, visual recall; WASI, Wechsler Adult Scale of Intelligence

4.3.2. Correlations between neuropsychological domains

A further analysis was undertaken to assess for relationships in performance between the cognitive domains using correlations. Table 4.4 demonstrates the Pearson correlation values between the neuropsychological domains. Significant correlations were found between intelligence and immediate recall memory (R = 0.61, p = 0.008), intelligence and executive function (R = 0.51, p = 0.03), immediate recall memory and delayed recall memory (R = 0.79, $p < 0.001$), immediate recall memory and language (R = 0.68, p = 0.01), and delayed recall memory and language (R = 0.53, p = 0.02).

Table 4.4. Correlations between neuropsychological domains (two-tailed). Significant results are shown in bold, and Pearson correlation coefficients are shown to two decimal places with significance values in parentheses.

	1	2	3	4	5	6	7
Intelligence (1)	-						
	0.61						
Immed.Mem. (2)	**(0.008)**	-					
	0.33	**0.79**					
Delay.Mem. (3)	(0.18)	**(<0.001)**	-				
	0.03	-0.15	-0.18				
Recog. (4)	(0.90)	(0.55)	(0.46)	-			
	0.75	**0.68**	**0.53**	0.43			
Language (5)	(0.18)	**(0.001)**	**(0.02)**	(0.73)	-		
	0.51	0.42	0.38	-0.93	0.39		
Exec.Func. (6)	**(0.03)**	(0.72)	(0.10)	(0.70)	(0.10)	-	
	0.13	0.28	0.26	-0.15	-0.08	-0.14	
Visuomot. (7)	(0.61)	(0.30)	(0.29)	(0.54)	(0.75)	(0.56)	-
	0.19	0.16	0.05	0.34	-0.46	0.21	0.03
Visuoconstr. (8)	(0.44)	(0.52)	(0.86)	(0.15)	(0.85)	(0.39)	(0.91)

Delay.Mem.: Delayed Memory; Exec.Func.: Executive Function; Immed.Mem.: Immediate Memory; Visucontr.: Visuoconstruction; Visuomot.: Visuomotor

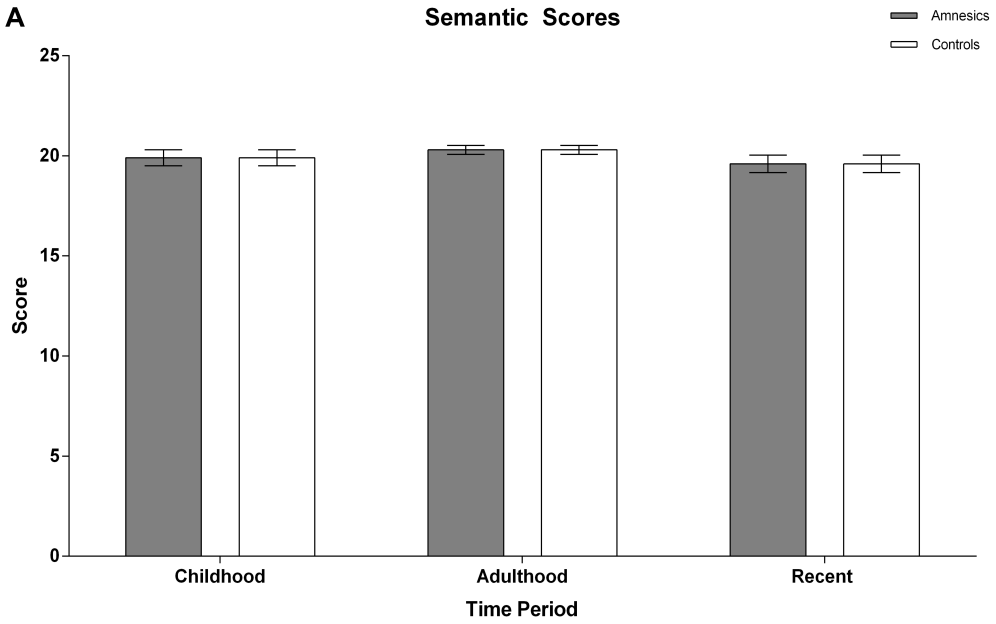
4.3.3. VGKC-complex LE does not result in temporal gradient of episodic memory loss as measured by the AMI

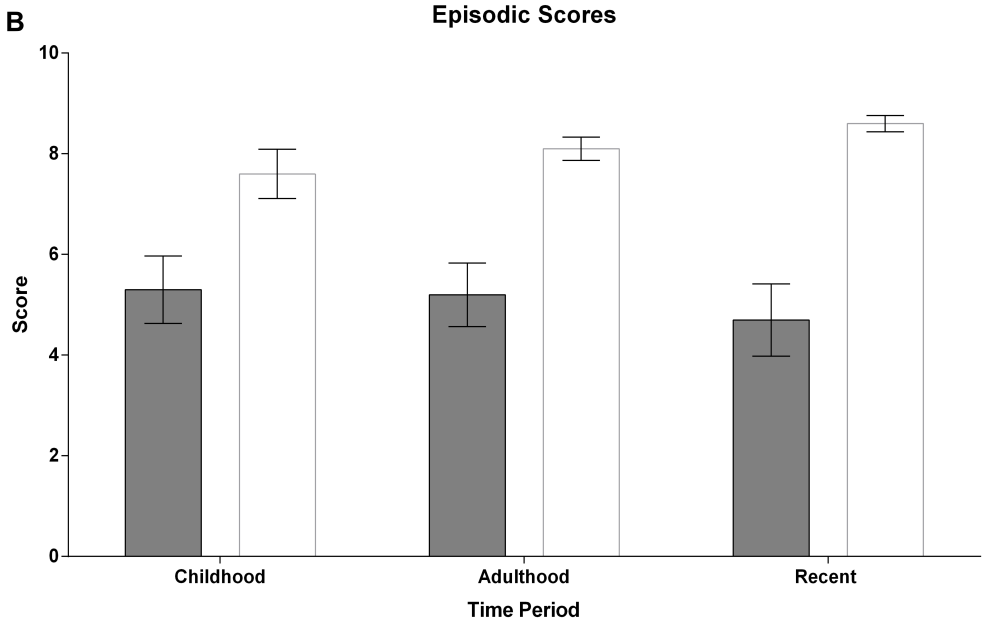
The Autobiographical Memory Interview was obtained in 19 patients and age-matched controls, who underwent neuroimaging. A 2 (Group: patients, controls) x 2 (Detail type: semantic, episodic) x 3 (Time: childhood, adulthood, recent) mixed-model ANOVA was performed on the points score, with Group as the between-subjects factor and Time and Detail Type as the repeated-measures factors. Mauchly's test demonstrated that assumption of sphericity had been violated ($\chi^2_{(2)}$ = 285.37, $p < 0.001$), and, so degrees of freedom were adjusted using the Greenhouse-Geisser method (ε = 0.50). There were no significant main effect of Group ($F_{(1,34)}$ = 0.80, p = 0.38), Detail Type ($F_{(1,34)}$ = 3.29, p = 0.079), or Time ($F_{(1,34)}$ = 1.00, p = 0.33). There were no significant two-

way interactions for Group by Detail Type ($F_{(1,34)}$ = 1.11, p = 0.30), Group by Time ($F_{(1,34.00)}$ = 0.96, p = 0.33), or Time by Detail Type ($F_{(1,34.00)}$ = 0.99, p = 0.33). The three-way interaction for Group, Detail Type and Time was not significant ($F_{(1,34.00)}$ = 1.01, p = 0.32). Given this absence of any interaction terms, planned comparisons were not undertaken. Results are shown in Figure 4.2.

Given the point differences that arise between the semantic and episodic components of the AMI, these episodic and semantic scores from each epoch were divided by the total point score available for that epoch (i.e., 27 for the semantic score, nine for the episodic) such that the larger total scores for the semantic memories did not mask significant differences in the groupwise episodic scores. A 2 (group: patients, controls) x 2 (detail type: semantic, episodic) x 3 (time: childhood, adulthood, recent) mixed-model ANOVA was performed on this percentage score, with group as the between-subjects factor and time and detail type as the repeated-measures factors. Mauchly's test demonstrated that assumption of sphericity had been violated ($\chi^2_{(2)}$ = 285.37, p < 0.001), and, so degrees of freedom were adjusted using the Greenhouse-Geisser method (ε = 0.50). There were no significant main effect of group ($F_{(1,34)}$ = 0.58, p = 0.45), detail type ($F_{(1,34)}$ = 1.39, p = 0.25), or time ($F_{(1.03,35.05)}$ = 1.00, p = 0.32). There were no significant two-way interactions for group by detail type ($F_{(1.03,35.05)}$ = 0.92, p = 0.34), group by time ($F_{(1.03,34.05)}$ = 0.96, p = 0.33), or time by detail type ($F_{(1.03,35.05)}$ = 0.99, p = 0.33). The three-way interaction for Group, Detail Type and Time was not significant ($F_{(1.03,35.05)}$ = 1.06, p = 0.34). Given this absence of any interaction terms, planned comparisons were not undertaken.

Figure 4.2. Mean scores for both the VGKC-complex LE patients (*n* = 19), and age-matched controls (*n* = 19) for both the (A) personal semantic, and (B) episodic schedules, according to the three time periods of Childhood, Adulthood, and Recent, from the Autobiographical Memory Interview.





4.4. Discussion

This chapter applied a comprehensive battery of standardized neuropsychological tests, with a particular emphasis on different forms of anterograde memory, to nineteen patients with VGKC-complex LE. There are three novel findings arising from this work.

First, the evidence indicated that there were significant subnormal performances for the immediate verbal recall, immediate visual recall, and delayed verbal recall indices. These were associated with significant deficits in the Logical Memory 1, Rey Complex Figure Immediate Recall, Logical Memory 2, Logical Memory 2 Themes, Doors and People Name Recognition, and Elevators with Distraction subtests. These deficits were within two SDs of the standardized control population, and so above the normal neuropsychological definition of impairment as performance falling below the fifth centile (Benton and Hamsher, 1977). Notably, this VGKE-complex LE cohort also exhibited supra-normal performance for the general intelligence, language and executive function indices, and also the WASI Similarities, WASI Matrix Reasoning, Doors and People Visual Forgetting, Graded Naming Test, Letter Fluency, RMT Words, Category Fluency, Category Switch, the Stroop test, Digit Span, Visual Elevator and Lottery subtest of the TEA.

Second, significant correlations in performance were found between general intelligence and Immediate Recall Memory, Intelligence and Executive Function, Immediate Recall Memory and Delayed Recall Memory, Immediate Recall Memory and Language, and Delayed Recall Memory and Language.

Third, there is no significant impairment for the VGKC-complex LE group for either the episodic or personal semantic components of the AMI.

4.4.1. Subnormal performance on immediate verbal and visual recall, and delayed verbal recall following VGKC-complex LE

The central finding was that this VGKC-complex LE cohort has a specific group-wise impairment for immediate visual and verbal recall and delayed verbal recall. Other types of anterograde memory such as immediate and delayed single item memory,

verbal and visual recognition memory and delayed visual memory were normal. No impairments were found in non-mnemonic domains.

It is important to restate how significant deficits have been operationalized in this chapter. Typically, significant deficits in neuropsychology are usually defined as performance falling below the fifth centile for a normalized control population, equivalent to a *Z*-score of ≤-1.67 (Benton and Hamsher, 1977). According to this definition both RB – a famously amnesic and well-studied patient (Rempel-Clower et al., 1996) – would not be considered amnesic, other than for delayed memory performance (Z = -2.67), nor would JS (Gold and Squire, 2005), or the VGKC-complex LE groups from the aforementioned longitudinal studies (Butler et al., 2014a; Frisch et al., 2013; cf. Bettcher et al., 2014) who found a *Z*-score of -2.4 for verbal memory, and -1.9 for visual memory, in the context of impaired executive function, Z = -1.5). This arbitrary designation of performance renders interpretation liable to Type II errors, particularly when you consider the supranormal intelligence of this cohort. Accordingly, significant deficits were defined as a group mean that was significantly different from that of the standardized group.

The distinction made in this study between immediate- and delayed-recall is without priors in the VGKC-complex LE literature, and will be discussed in more detail in Section 4.4.2.

These delayed-recall data largely accord with previous studies into the longitudinal cognitive sequelae of VGKC-complex LE. (Frisch et al., 2013) found in 15 patients with VGKC-complex LE, significant deficits in both delayed visual and verbal memory at a median time of 24 months (range: one-68 months) from the onset of the illness, a time range approximately half of the current data, yet still beyond the point where the anatomical changes associated with VGKC-complex LE become stable (Wagner et al., 2015; Wagner et al., 2014). The verbal memory index used by Frisch *et al.* collapsed across immediate-, and delayed-recall memory, and recognition memory, three measures kept distinct in this neuropsychological battery. This renders direct comparisons across the two studies difficult.

It should firstly be noted that verbal memory measure in (Frisch et al., 2013) consisted of a single-item word list task; in this study, performance on a comparable task was normal. However, whilst not explicitly reported in their study, the patients' mnemonic performance during the chronic phase of the study describes *Z*-scores of ~-1.0 for both visual and verbal memory, similar to the group-wise scores obtained in this study. This suggests that performance is reasonably consistent for verbal and visual measures across this current study and that of (Frisch et al., 2013), despite the observed differences in significance.

Therefore, the major difference between this study, and that of (Frisch et al., 2013) is the normal single-item word list performance found here, and the deficits noted by Frisch et al., and not the deficits arising from the delayed verbal recall index. Several reasons could underlie these observed differences. Firstly, the discrepancy could suggest the patients used by (Frisch et al., 2013) had pathology extending into the PHG, thereby removing the neuroanatomical substrate supporting list learning, although neither study acquired contemporaneous whole brain segmentation data. Secondly, given both this study and that of Frisch et al., (2013) only used one measure of single-item recall, this difference could also represent a Type I error in their study, or a Type II error in this one. Finally, Frisch et al., (2013) had no measure of auditory verbal working memory (a measure that was normal in this study), therefore this could also represent an acquisition error in their patient group, although there would be no *a priori* reason to suspect this would be the case. Finally, the word list used by Frisch et al., (2013) is not the same task used in this study, although the substrate should remain the same across both tasks.

The present delayed verbal recall index was comprised of story-recall (LMII) and the recall of verbal associations (Doors and People – Verbal Forgetting, performance for which was normal), and despite sharing many of related mnemonic neurocognitive mechanisms, the argument developed in Section 4.1.3.2.1 suggests that that single-item and story learning require different neuroanatomical structures for their expression. For example, both single-item and story learning require the initial activation of the auditory verbal working memory network (Wolk et al., 2011), but with repeated exposure to the stimuli (as typified by the word list learning), recall performance for both becomes more associated with the temporal pole (Wolk et al., 2011). This suggests that the semantic

processing of the types of information is critical to the strength of memory trace for later retrieval (Craik and Lockhart, 1972; Goldblum et al., 1998).

Story learning also involves creating associations between multiple items to create a coherent narrative, and it has been previously observed that greater hippocampal BOLD signal change during learning is able to predict delayed-recall performance for this task (Wolk et al., 2011). Hippocampal activity therefore observed during fMRI learning paradigms could represent the associations made between the items during learning, but are subsequently not required for retrieval (Wolk et al., 2011). Therefore, hippocampal damage may impair the acquisition of during story tasks, particularly as the surrounding MTL structures appear unable to support flexible memory representations (Eichenbaum et al., 2007). However, these findings have been contested where it has been demonstrated that the delayed-recall components of word lists appear to rely on intact MTL structures (Helmstaedter et al., 1997). Conversely, single item memory, because it does not rely on the creation of associations between the stimuli, could be supported entirely by the MTL structures such as the ERC and PRC (Eichenbaum et al., 2007 although cf. Stark et al., 2002; Stark and Squire, 2003 who counter this).

In greater accordance with the current data, another study based on the results acquired from 20 patients found deficits in delayed-recall verbal memory but not visual memory (Butler et al., 2014b). These results also demonstrated impaired performance in delayed recall of the WMS-III Story and Word List (Butler et al., 2014b). The average Z-score performance for verbal memory was -1.07, agreeing with both the present study and Frisch et al., (2013). Deficits in either immediate and delayed-recall of the word list recall were not found in this study. The differences between the delayed-recall of verbal and visual information is discussed below in Section 4.4.2.

Bettcher et al., (2014) found evidence of mild impairment in anterograde memory where the *Z*-score was -1.9, principally driven by verbal memory performance. However, in contrast to the studies by Butler et al and Frisch et al. and the present study, Bettcher et al. observed category fluency deficits, which suggest that the long-term sequelae might include dysexecutive problems. Category fluency is a task that requires a search through conceptual knowledge store for semantic extensions derived from a target word (Taler and Phillips, 2008), whereas letter fluency relies on word presentation strategies (Rohrer

et al., 1999). Both these tasks are dependent on intact frontal lobe functioning (Lezak et al., 2004) to organize retrieval strategies, initiate verbal responses, monitor past responses and inhibit those responses contrary to the selection criteria (Henry et al., 2004). Functional MRI studies have demonstrated that category and letter fluency are associated with temporal lobe regions implicated in semantic memory (Birn et al., 2010; Mummery et al., 1996), although letter fluency is less reliant upon this than category fluency (Lezak et al., 2004).

Finally, a fMRI study in nine patients with MTL lesions, due to several aetiologies including anoxia and viral encephalitis, found that there was a reduced activity of the temporal lobes during category fluency retrieval, a deficit thought be mediated by deficiencies in episodic recall (Greenberg et al., 2009). This discussion therefore suggests that the findings of (Bettcher et al., 2014) can to be interpreted, not as executive or frontal lobe dysfunction *per se,* but rather MTL dysfunction within the cortical network supporting category fluency. It should also be noted that the current VGKC-complex LE cohort performed at a supranormal level for both category fluency, and category switching, with normal performance for letter fluency.

4.4.2. Differences between verbal and visual recall during immediate- and delayed-recall

One difference between the current study and the three cited above is that immediate- and delayed-recall phases were separately analysed on the grounds that these temporal delays have distinct neuropsychological processes. It was found that both immediate visual and verbal recall and delayed verbal recall were impaired. By contrast, delayed visual recall was normal, (cf. Frisch et al., 2013).

Immediate-recall memory previously has been argued to involve the temporary activation of the neural representation of the long-term memory (Murre et al., 2013). However, the MTL demonstrates sustained mnemonic activity across short delays (Ranganath and D'Esposito, 2005), and patients with damage to the perisylvian fissure, a region central to the phonological loop (critical to most models of working memory (Baddeley, 1986), have impairments in both immediate- and delayed-recall verbal memory (Ranganath and Blumenfeld, 2005). However, most clinical neuropsychological

tests of immediate-recall use stimuli that could be well-represented outwith the MTL structures (such as words, WMS-III Word List Learning), and so may not selectively recruit the MTL (Ranganath and Blumenfeld, 2005). Immediate-recall deficits therefore might be only expected with stimuli known to uniquely processed by the MTL structures, such as complex novel objects, like the ROCF (Lee et al., 2005; Murray and Bussey, 1999). It has also been observed previously that the PRC is able to support visual recall when source memory is not required (Park et al., 2014), and neuropsychological studies have shown that delayed visual recall performance is correlated with PHG volume (Kohler et al., 1998). Therefore, these data corroborate the present findings of unimpaired delayed visual recall performance, as ostensibly this form of memory could be supported by the MTL structures, thereby dissociating from its immediate-recall counterpart which may be more MTL-dependent.

Interestingly, the apparent specificity from a behavioural perspective may – indirectly – indicate that VGKC-complex LE-associated neuropathology is relatively well confined to the hippocampus. For instance, many of the studies cited above in Section 4.1.3 described how a number of the neuropsychological domains measured by this current neuropsychology battery could, in theory at least, be supported by many MTL structures (e.g., the ERC, PRC, PHC, temporal pole) without involvement of the hippocampus partially explaining the preservation of single-item memory, and recognition memory. It is also possible that the stimuli constituting these tests were not specific enough to preferentially recruit the hippocampus, such as paired associated tasks (Rempel-Clower et al., 1996). The data summarized in Table 4.1 also suggest that more profound anterograde amnesia would be associated with damage to the surrounding MTL structures (e.g., Bayley et al., 2003; Bayley and Squire, 2003; Rempel-Clower et al., 1996; Rosenbaum et al., 2008). Therefore, the neuropsychological characterization of chronic (i.e., at least six months from successful treatment) VGKC-complex LE suggests that it is not only associated with focal amnesia, but does so in a pattern most in keeping with hippocampal subfield pathology. Critically, this amnesia also occurs in the presence of normal, or supranormal, performance for non-mnemonic neuropsychological domains.

4.4.3. Correlations between neuropsychological domains

This is the first study to assess for relationships between the neuropsychological domains in both VGKC-complex LE, and human models of hippocampal pathology, and as such it is difficult to draw comparisons to other studies of a similar nature. The correlations were used to assess for similarities in cognitive performance between various domains, in an attempt to assess for neuropsychological dissociations arising between domains. Where no correlation was found, that was taken as evidence of no association between domains.

The principal finding was that immediate recall memory was positively correlated with several cognitive domains including intelligence, executive function, language and delayed-recall memory. In a study by Tremont *et al.*, the extent of executive dysfunction was found to be associated with performance on a story-learning paradigm. Two groups of patients with executive dysfunction were tested, one with severe problems another with minor problems, on a story learning task from the CVLT, and demonstrated a negative correlation of immediate-recall performance with increasing severity of their dysexecutive syndrome (Tremont et al., 2000). Similar results were also found for the LM subtest of the WMS-R, but without any differentiation between a severely impaired patient group and a moderately impaired patient group (Tremont et al., 2000). These authors also found that the greater impairment on the tests executive function was correlated with impairment on CVLT recall, but not LM recall. By contrast, poor performance on Trails B, WCST and WASI Similarities were found to be negatively correlated with LM performance across both short- and long-delay periods (Tremont et al., 2000).

The current data follow a similar pattern where performance on immediate-recall tasks is positively correlated with executive function performance. Critically, the VGKC-complex LE group had supra-normal performance not only for the executive function index, but also the subtests constituting the index score. This suggests that the immediate-recall deficits are not caused by executive dysfunction, but that perhaps executive function helps to modulate immediate memory performance, or that they simply reflect shared neuroanatomical substrate such as the PFC (Alexander et al., 2009; Blumenfeld and Ranganath, 2007; Burgess and Shallice, 1996; Gershberg and

Shimamura, 1995; Janowsky et al., 1989; Norman and Bobrow, 1979; Shallice, 1988; Wheeler et al., 1995).

The relationship between immediate-memory and intelligence is perhaps to be expected given that general intelligence is responsible for much of the predictive validity of cognitive tests (Deary et al., 2010), and that memory shares an association factor of 0.66 with a general intelligence factor (*g*) across a wide range of memory tests (Salthouse, 2004). Moreover, given the experimental evidence that suggests an interdependence between immediate-recall memory and executive functions, it is likely that intelligence measures will play a larger role in the explanation of the differences within the group. The correlation between immediate-memory and executive function could also, in part, be explained by their correlations with intelligence, itself a superordinate neuropsychological domain (Salthouse, 2004).

A large study with over 200 subjects and multiple measures of IQ, executive function and memory (including both immediate- and delayed-recall) found that memory and executive function shared more than 50% variance within the neuropsychological performance (Duff et al., 2005). These authors also found that individuals who performed well on executive function tasks also performed well on memory measures and had higher IQs, accounting for 57% of the variance for that analysis (Duff et al., 2005). This accords well with other studies describing the overlap between verbal memory and executive functioning (Bryson et al., 2001; Proctor et al., 2000; Tremont et al., 2000). In contrast to Duff et al., (2005), we did not find any relationship between executive function and delayed-recall memory, which may reflect either the small numbers of participants, or the previous use of bivariate instead of canonical correlations. It has also been suggested that the overlap of multiple cognitive domains may not reflect their interdependence *per se*, but actually their reliability on a separate superordinate cognitive domain, such as intelligence (Larrabee, 2000).

Correlations were also found between immediate- and delayed-recall performance and language in the current study. Previously, Bettcher et al., (2014) found reductions in both semantic and phonemic fluency in a population of VGKC-complex LE patients, with the average group performance being Z = -1.5. It should be noted that the patients presented in this study had an average language performance of Z = 0.4 with

no impairments in phonemic or semantic fluency. The role of the hippocampus in fluency retrieval tasks has been outlined previously (see Section 4.4.1), and therefore it perhaps unsurprising to find a relationship between both immediate- and delayed-recall memory given the, albeit, small reliance of all these functions on the hippocampus.

Similar findings for category fluency have been found in patients with TLE with known hippocampal damage. Patients with restricted hippocampal lesions (as defined by clinical MRI evidence of CA field sclerosis) were worse on measures of semantic fluency than patients with damage to the surrounding temporal lobe cortex (Gleissner and Elger, 2001). Letter fluency was unaffected. The authors interpreted these findings as demonstrating dysfunction of the semantic retrieval network – which includes the hippocampus – rather than due to a loss of semantic knowledge (Gleissner and Elger, 2001). These patients were felt to have hippocampal-specific lesions (as defined by qualitative clinical scans), and so accord well with those of (Bettcher et al., 2014), and further demonstrate that the category fluency is not necessarily a good measure of executive function.

A parsimonious way to reconcile the results from the correlation-based analyses with the data presented by Bettcher et al., (2014) is that measures of language performance used in these studies may reflect the relative contribution of the hippocampus to language fluency tasks, and that the correlations reflect the degree of hippocampal dysfunction across several conceptually distinct tasks, each requiring normal hippocampal function. This could be specifically tested by undertaking both letter and category fluency tasks under fMRI conditions, where either total hippocampal or subfield volumes from Chapter 3 could be used as covariates, or by using the neuropsychological scores as the principal variable mediating fMRI signal strength in both the hippocampus and the temporal lobe structures.

Finally, correlations were also found between immediate- and delayed-recall memory. Both of these forms of memory are dependent on intact MTL structures for their expression, and it therefore follows that these two aspects of memory are interdependent. In a large series of 88 patients with TLE (Bell et al., 2004), there were no discrepancies between immediate- and delayed-recall memory performance on the Logical Memory story-learning task. It has been previously observed that within another

standardized test of memory (The Repeatable Battery for the Assessment of Neuropsychological Status, RBANS), immediate- and delayed-recall measures were strongly associated (0.63). The WMS-II technical manual reports a correlation of 0.88 between auditory immediate and delayed-recall and 0.84 for visual immediate- and delayed-recall. The correlation of 0.79 (collapsed across verbal and visual memory) reported here therefore is in keeping with these previous findings, and suggests that the well-established relationship between these two neuropsychological domains is maintained following VGKC-complex LE, but in the context of the deficits observed there is an overall baseline shift down in hippocampal-dependent mnemonic performance.

The lack of correlation of delayed-memory with many of these other neuropsychological domains is unclear, but it could be that delayed-recall performance is less dependent upon extra-MTL structures for retrieval, with the ERC and PRC are able to independently support many of the tasks constituting delayed-recall memory in this neuropsychological battery (Aggleton and Brown, 2006; Eichenbaum et al., 2007; Yonelinas et al., 2007). Accordingly, this would suggest that delayed-recall memory could operate in isolation from the other neuropsychological domains tested.

The observed data have also shown that there is a correlation between those neuropsychological functions that, in some way, rely on the hippocampus for normal expression. Despite their neuropsychological differences, these tasks all operate within a network, and are associated with hippocampal function for normal expression. It is important to note, though, that correlations do not define the direction of the relationship, nor do they imply causation. The conclusions that can be drawn from these data are that those tasks that are conceptually dependent upon the hippocampus show performance-related correlations, but that only immediate- and delayed-recall memory are specifically impaired

4.4.4. Comparisons to other human models of hippocampal dysfunction

The principal findings of this chapter are that VGKC-complex LE leads to selective but mild deficits for the anterograde memory indices of immediate verbal (Z = -0.4), and visual recall (Z = -0.7) and delayed verbal recall (Z = -0.8). Table 4.1 shows that lesion studies of retrograde memory show, by-and-large, a graded decrease in

anterograde memory performance as the pathology to the hippocampus and MTL structures increase. For instance, for those patients with damage limited to the hippocampus, they typically perform within two SDs of the control population, but that this is usually closer to -2 than -1. For those with damage to the extra-hippocampal MTL structures their amnesia is usually more than two SDs below the control population, with those with MTL+ lesions worse still (Bayley et al., 2003; Bayley and Squire, 2003; Rempel-Clower et al., 1996; Rosenbaum et al., 2008).

The modest deficits reported here are most in keeping with two patients, GD and RB, who were found to have focal CA1 lesions and performed within one-to-two SDs below the control population (Rempel-Clower et al., 1996). At most, these results could be extended to those with hippocampal damage. This gives reasonable indirect behavioural evidence to infer, at the very least, that on the basis of these neuropsychological data, VGKC-complex LE results in neuropsychological profile similar to those found in CA1, or at most hippocampal, lesion groups, and could be considered as focal as the other aetiologies characterized in these patient groups (e.g., viral encephalitis and hypoxia).

4.4.5. Autobiographical Memory Interview performance following VGKC-complex LE

Retrograde memory testing has not been conducted using the AMI previously in VGKC-complex LE; critically there were no interaction terms as a function of group, for both analyses, suggesting a null difference for this task. Three patients (KC, P03 and VC) in Table 4.1 demonstrate a flat gradient of episodic retrieval, whereas DA and RG had evidence of a temporal gradient of episodic memory loss. These data suggest that more extensive the damage to the MTL and surrounding structures is associated with poorer performance on the AMI. Indeed these findings have been found in other patients with focal lesions of the MTL structures, when tested with a similar three point marking scheme (Bright et al., 2006; Eslinger, 1998).

However, the data presented here, and other studies, are potentially limited by the three-point marking schemes central to the AMI. These schemes introduce a non-scalar method of measurement, and limits the potential differences both within a patient group and between patients and controls. Moreover, there is also a potential ceiling

effect that might introduce a degree of insensitivity to discriminate between patients and controls, or those memories that have a richly descriptive narrative and which still meet the full requirement for three points, but are quantitatively more impoverished (Levine et al., 2002). This is particularly the case for the episodic memories. This ceiling effect may then reduce the statistical power and variance needed by the ANOVA to detect significant group differences, particularly for the interactions terms. This may be exacerbated by the equivalent performance of patients on the semantic component of the task. Methodologically, it should also be noted that scores from the AMI or other studies using three-point scales of rating memory are inherently subjective, and thereby liable to bias as well. The discrepancy between the interaction terms and the planned comparisons help demonstrate the insensitivity of the AMI is in determining group-wise reductions in episodic memory performance, especially between normal and pathological performance.

Even with these considerations, these data are in broad agreement with those reports of a temporally limited amnesia for episodic memory in context of focal MTL lesions (Bright et al., 2006; Eslinger, 1998), thereby suggesting, by extension, that VGKC-complex LE could be associated with focal lesions to the MTL. The AMI results from this chapter would also suggest that, on more experimental measures of retrograde memory, a temporal gradient of retrograde episodic memory loss will be observed. This is explored further in Chapter 5.

4.4.6. Supranormal intelligence suggests that hidden pathology does not occur following VGKC-complex LE

As demonstrated in Section 1.5.1.2, concern has been raised concerning the use of VGKC-LE in cognitive neuroscience experiments (Squire et al., 2010). The clinical concerns have been addressed in Section 1.5.1. but another more pertinent concern will need to be addressed, that of hidden pathology. Specifically, the concern that *"…patient P04 was described as having verbal and performance intelligence quotient (IQ) in the normal range but was considered to have some intellectual deficiency in view of his estimated high premorbid IQ."* (Squire et al., 2010).

This is a valid concern; critically, these patients – as discussed in (Cipolotti et al., 2001) – usually have evidence of a global IQ drop, and evidence of widespread cortical

and subcortical atrophy, and neuropsychological impairment. However, the supranormal intelligence of the patients used in this study suggests that no global loss of intellectual function has occurred. It should be noted though that premorbid IQ estimates were not obtained for all patients (i.e., National Adult Reading Test), which would have provided a useful comparator pre- and post-disease. The likelihood of these unselected patients having a significant decline in their IQ post-disease to a supranormal level, particularly when previous reports do not report such losses in intellectual performance (Butler et al., 2014; Bettcher et al., 2014; Frisch et al. 2013), seems unlikely. Contemporaneous measures for pre-morbid IQ estimates could be obtained in the future to demonstrate that no decline in pre-morbid intellect has occurred. Moreover, the normal performance across a wide-range of other neuropsychological domains suggests that the hidden pathology argument is not valid for this patient group, at least from a neuropsychological perspective.

4.4.5. The limitations of neuropsychological assessment

This chapter has provided several cogent reasons for the extensive neuropsychological characterization of this VGKC-complex LE, and the types of neuropsychological domains that should be examined. The purpose of this neuropsychological assessment will be to provide neuropsychological evidence that any amnesia observed in this, or any other chapter, is not due to a failure of other neuropsychological functions (such as executive function, or attention). Should this be the case, it is then likely that VGKC-complex LE can be considered behavioural focal alongside the CA1 and CA3 data from Chapter 3, and from the whole brain segmentation data (Wagner et al., 2015; Wagner et al., 2014).

What the preceding discussion also demonstrates is that there is a not a 1:1 mapping of a neuropsychological test to either a particular cognitive domain, or indeed anatomical region. For instance, performance on the Stroop test requires attention, task switching and modification, as well as planning (Salthouse, 2011); intelligence does not localize to any particular brain region (Salthouse, 2004); and even word list performance requires some degree of executive function performance, in order that participants create a schema for remembering the items (Tremont et al., 2000). Precise measurements of single cognitive domains is probably best served by experimental paradigms; however, what neuropsychological can do is provide a detailed screening of multiple cognitive

functions, and anatomical regions subserving those functions, in order that more nuanced experimental questions might be later posed. Indeed, much discussion about the ecological validity of neuropsychology has taken place, especially concerning veridicality and verisimilitude of the tasks in truly engaging the functions, or region, they purportedly target (Chaytor and Schmitter-Edgecombe, 2003). Despite these limitations they still offer those working with such patients an opportunity to understand much about the general cognitive function and hence the patient's cognitive experience.

4.4.7. Limitations and future work

There are limitations to the work presented in this chapter. The most obvious is the lack of a paired associate task, a task that appears to preferentially recruit the hippocampus during learning and critically cannot be supported neurally by the surrounding cortical structures (Chalfonte et al., 1996; Dudchenko et al., 2000; Squire, 1992). This would provide a critical measure of hippocampal function when attempting to characterize this disease group.

Another limitation is the cross-sectional nature of this study. Given the relative recent characterization of VGKC-complex LE as a distinct disease entity it could be, despite the relative focality of the behavioral pathology shown in this chapter and in other serial clinical studies (Bettcher et al., 2014; Butler et al., 2014a; Frisch et al., 2013), that these patients suffer from accelerated focal or global cognitive decline. However, it is notable that save for HM that very few patients listed in Table 4.1 have undergone serial neuropsychological testing. However, this serial work could be undertaken at the time of disease (much like (Bettcher et al., 2014; Butler et al., 2014a; Frisch et al., 2013), six-months following acute treatment, and at 18 and 36 months. This would provide more temporal granularity, and would provide additional evidence to determine whether the deficit is stable for this cohort across several time points. This could be strengthened if contemporaneous whole brain, and hippocampal imaging were also undertaken.

The main focus of this chapter was to characterize the mnemonic deficits associated with VGKC-complex LE. To this end, several measures of memory were used including immediate- and delayed-recall, single item learning, visual and verbal memory and recognition memory. The results gained from this study have revealed that those subtests preferentially dependent on the hippocampus are specifically affected. However, these results did occasionally arise from single subtests (i.e., word list learning) rendering

them liable to Type I and II errors. Where possible multiple tests were used. Future neuropsychological work could aim to use multiple measures of these tests across both verbal and visual modalities. Likewise, theories have been offered concerning the role of the hippocampus in scene perception (for review, see Graham et al., 2010), therefore using tasks such as the RMT Scenes may yield further insight into the theoretical function of the hippocampus across multiple neuropsychological processes. Likewise, the battery used here limits, for practical purposes, the number of non-mnemonic tests used. The principal limitation arises from collapsing several different components of cognition together (e.g., naming, semantic and letter fluency, semantic associations). In mitigation though, there are innumerable tests one might like to construct a battery from, and as such increases the time of testing and burden on the patients. Yet it should finally be noted that the current battery still remains the most systematic and comprehensive of those studies summarized in Table 4.1.

4.4.8. Conclusion

The neuropsychological test battery administered in this chapter demonstrated that VGKC-complex LE is associated with subnormal performance for immediate verbal and visual recall and delayed verbal recall. Care was taken to ensure that these domains had the most hippocampal-specificity, within the constraints of the tests themselves. Moreover, this patient cohort demonstrated supranormal performance in non-mnemonic neuropsychological domains. These results broadly agree with previous reports that VGKC-complex LE results in mnemonic pathology, but has shown that the deficits are more hippocampal-specific than previously thought. A parsimonious interpretation of these data is that VGKC-complex LE is not associated with global neuropsychological deficits and can be considered, neuropsychologically speaking, a hippocampal specific disease. These data also demonstrate that the AMI is not necessarily a sensitive tool for assessing for retrograde episodic amnesia, as is shown in Chapter 5.

Chapter 5

Standard and modified administrations of the Autobiographical Interview in health and disease

5.1. Introduction

5.1.1. Episodic memory

Declarative memories are those memories that require the conscious recollection of facts and events for their expression, whereas non-declarative memory are those that predominantly rely upon performance of a skill, and, critically, have no associated re-experiential quality (e.g. motor skills, conditioning, priming; Squire et al., 2004). Critically, declarative and non-declarative memory are argued to rely on their own neuroanatomical apparatus, with the medial temporal lobe (MTL) being a key region for declarative memory, providing an anatomical foundation for the observed dissociations in Henry Molaison (HM, Corkin, 2002; Eichenbaum, 2013; Tulving, 1972a, 1983, 2002). Tulving then conceptualized a further subdivision within declarative memory: (1) an event memory associated a degree of re-experiential quality ('episodic' memories); and (2) those that represent a more fact-based memory system, and hence devoid of re-experiential quality ('semantic' memory), although there may be a degree of interaction between the two (Tulving, 1972a, 1983, 2002).

5.1.2. Models of retrograde memory consolidation

5.1.2.1. The temporal gradient and the standard model of consolidation

Particular controversy has always surrounded to the role of the MTL, and its temporal support of retrograde episodic memories, especially in the context of hippocampal lesions (Moscovitch et al., 2006; Squire, 1992b; Squire and Alvarez, 1995; Winocur and Moscovitch, 2011). Whilst there is much to say about the role of the hippocampus across multiple cognitive domains, this chapter will focus on one very specific account of the temporal role of the hippocampus in retrograde episodic memory retrieval.

In 1881, Ribot described how damage following closed head injuries could produce a temporally limited retrograde amnesia in which memories remote from the injuring event were recalled with greater fidelity than those closer to the event (Ribot, 1881). This was to be termed Ribot's Law, and has become a foundational component of memory consolidation theory (Squire, 1992b; Squire et al., 2001; Squire et al., 2004). HM demonstrated a temporal gradient related to this declarative memory loss because it extended at least 11 years from the age at which his surgery took place (he was 23 at the time of surgery; Corkin, 1984a). Steinvorth et al., (2005), however, later revised these results, through the use of a novel measure of retrograde episodic memory (the Autobiographical Interview, AI; see Section 5.1.4.2 below for more information). This measure demonstrated that HM's early retrograde memories were as quantitatively impoverished (in terms of episodic points scored, again discussed below) as those acquired after his surgery, thereby suggesting that the methodology used is critical to investigations of remote episodic memory. It should be noted though that these data are contested on methodological and neuroimaging grounds (Kirwan et al., 2008) and is discussed further in Section 5.1.4.

Neuropsychological investigations into episodic memories – as measured by tasks using subjective rating scales of episodic details such as the Autobiographical Memory Interview, see Section 5.1.4.1. – have typically found that those patients with damage limited to the hippocampal region as demonstrated on post-mortem studies (e.g. RB,

bilateral CA1 damage; GD, bilateral CA1 damage; LM, bilateral loss of all subfields and layers II and II of the midpoint of the entorhinal cortex; WH, bilateral lesions to the hippocampus proper; Rempel-Clower et al., 1996; Zola-Morgan et al., 1986) have a temporally limited retrograde episodic amnesia extending to five-10 years premorbidly. Conversely, investigations involving patients who had more extensive damage to the surrounding parahippocampal neocortex (e.g. HM, EP; Corkin et al., 1997; Stefanacci et al., 2000) reported a more temporally extensive retrograde amnesia extending for approximately 10-20 years (depending on when the patient was tested or retested; Kirwan et al., 2008). Importantly, temporally-graded retrograde amnesia has been described across a number of different experimental paradigms including those that probe semantic memory (Holdstock et al., 2002; Kapur and Brooks, 1999; Manns et al., 2003), spatial navigation (Teng and Squire, 1999), and episodic memory (Bayley et al., 2005; Bayley et al., 2003, 2006; Kapur and Brooks, 1999; Kirwan et al., 2008). The reconciliation of these disparate cognitive tasks arises from their relative dependence on the hippocampus for their acquisition, and early temporal expression (as suggested by the authors above). But as the learning event becomes more remote then their expression becomes decoupled from hippocampal integrity and hence establishing a temporal gradient.

To account for this pattern of amnesia, models of memory consolidation were devised where the MTL – and particularly the hippocampus – were central to the acquisition of the memory, and the initial neurobiological representation of the episode (Squire, 1992b; Squire et al., 2001; Squire et al., 2004). In this class of model, it is argued that the episode becomes consolidated into the overlying cortex, entrained by the hippocampus, thereby eventually becoming independent of the MTL structures for its expression (McGaugh, 2000). This consolidation process is often referred to as, the standard model of memory consolidation (SMC; Squire et al., 2004). Such has been the overwhelming evidence thought to corroborate this model that it has become the most accepted and well-established model of hippocampal function, particularly for retrograde episodic memory.

Another category of theoretical models of consolidation, based on computational neural network based accounts of information processing, have detailed how the hippocampus initially stores and then directs memory consolidation across a wide-range

of neocortical sites (Marr, 1971; Treves and Rolls, 1992, 1994). For instance, mnemonic recall, such as using a partial cue, of recent memories activates the hippocampus to reconstruct the memory using these neocortical sites; however, with time and repeated activation, these neocortical representations of the event are argued to become independent of the hippocampus (Marr, 1971; Treves and Rolls, 1992, 1994). Although the exact timeframe over which this consolidation occurs has yet been formalized, it is assumed to be a period of at least five years (Smith et al., 2013), but could perhaps run to even decades, although the empirical evidence underlying this is not always made clear (Squire et al., 2004; Squire and Zola, 1998; Squire and Zola-Morgan, 1983). The inclusion of these computational models demonstrates the alignment of several independent models of hippocampal function couched in terms of the temporal role of the hippocampus for episodic memory recall, and demonstrates the accepted convention into which the experimental work of this chapter, ultimately, must be interpreted.

However, as Section 5.1.4 below make clear, this model is becoming increasingly challenged across a number of different experimental paradigms. Therefore, it is important to characterize the presence, or absence, of a temporal gradient of episodic amnesia in any new model of hippocampal dysfunction, particularly that of VGKC-complex LE proposed in this thesis.

5.1.3.2. Multiple Trace Theory

5.1.3.2.1. The neuropsychological evidence and conceptualization of the MTT

Numerous case reports exist in the literature that are at variance with the SMC, whereby patients with apparently focal MTL/hippocampal damage experience dense retrograde amnesia extending to up 50-60 years (Cipolotti et al., 2001; Nadel and Moscovitch, 1997; Rosenbaum et al., 2009; Spiers et al., 2001). For example, patient NT, first reported in 1964 (Dimsdale et al., 1964), presented with a severe amnesia following a right temporal lobectomy, and was shown to have a severe and ungraded retrograde amnesia (Sanders and Warrington, 1971). Subsequent pathology demonstrated hippocampal sclerosis in her remaining hippocampus, which accordingly suggested that NT could reasonably be classified as a good example of a bilateral hippocampal lesion patient (albeit with only one functioning temporal lobe). A further patient has been

described (Kartsounis et al., 1995) with focal damage to the CA1 and CA2 subfields of the hippocampus, which was associated with an amnestic syndrome that was described as severe, although the temporal extent was not reported.

One further patient (VC; Cipolotti et al., 2001) was found to have lesions localized to the MTL proper (see Table 3.1), and presented with an ungraded retrograde amnesia for both episodic recall (as measured by the Autobiographical Memory Interview, see below for discussion) and the recognition of famous faces across all decades of his life. Proponents of the standard model of consolidation attribute these data to 'hidden damage' elsewhere in the cortex (where the SMC predicts these episodic memories should be stored) or inadequate behavioural or imaging data, running as these results to counter to the prevailing experimental evidence-base that is consistent with the SMC (Reed and Squire, 1998; Squire et al., 2004).

Far from being considered as problematic or insufficiently described, these patient neuropsychological data demonstrating a more extensive retrograde amnesia have encouraged a separate account of the temporal and consolidatory role of the hippocampus in episodic recall. In particular, multiple trace theory (MTT; (Nadel and Moscovitch, 1997; Rosenbaum et al., 2001)) states that the MTL system is needed to represent episodic memories, no matter how remote they are from the encoded episode. MTT is predicated on the notion that re-experiencing or recollecting the past in vivid detail is a hallmark of hippocampal function (Eldridge et al., 2000; Moscovitch and McAndrews, 2002; Moscovitch et al., 2005; Yonelinas, 2002). In this account, the neocortex provides the domain-specific and semantic representations arising from repeated events, but the MTL, in keeping with its position as the recipient centre for several multimodal inputs, is needed to bind these separate components of the memory together into a coherent and contextually rich ex-experiential memory. Every time a memory is remembered, a new trace is established or re-encoded within the hippocampus, such that, with time, older memories are represented by 'multiple traces', whereas more recent memories have fewer traces. These multiple traces are spatially separated along the longitudinal axis of the hippocampus, therefore partial hippocampal lesions are more likely to impair the more sparse-represented recent memories, but not the more densely-represented and spatially distributed older memories (Nadel and Moscovitch, 1997). Accordingly, partial hippocampal lesions should result in amnesia

with a temporal gradient whereas lesions damaging the entire hippocampal axis will result in a temporally ungraded retrograde episodic amnesia (Moscovitch et al., 2006).

5.1.3.2.2. Evidence supporting the MTT from functional neuroimaging

More recently, fMRI and PET studies have allowed formal investigations into the activity of the hippocampus across several remote time points in order to test the MTT account outside of the focal lesion neuropsychological framework. It is important to extend these patient neuropsychological studies into a more generalized account of hippocampal function during retrograde memory retrieval. In line with what might be hypothesised from a MTT-based perspective, several studies have shown that hippocampal activity is similar in tasks of episodic recall, even when recent and remote memories are separated by a period of days (Rekkas and Constable, 2005; Stark and Squire, 2000), weeks (Levine et al., 2004) or decades (Ryan et al., 2001). These data suggest that active engagement of the hippocampus is required for the successful retrieval of both remote and more recent episodic memories, although, critically, these data do not show the hippocampus is necessary for episodic retrieval. Contrary to these studies supporting the MTT, some fMRI studies have shown that hippocampal BOLD signal changes during episodic memory retrieval can be can be temporally graded (Fink et al., 1996; Piefke et al., 2003), suggesting that the hippocampus could have a temporally-limited role in episodic retrieval. Critically though, these studies failed to control for the effect time has on vividness, narrative detail or personal significance, factors that have been associated with episodic recall, and which are known to vary inversely with the age of memories (Moscovitch et al., 2006), an interpretation that has, as yet, remained unchallenged. Therefore, less visually rich memories would be expected to be associated with less BOLD signal activation within the hippocampi. Contrastingly, hippocampal activity has also been shown not be increased when the tasks shift to non-episodic memory paradigms such as sentence recognition (Maguire, 2001; Maguire and Frith, 2003; Maguire et al., 2001; Rekkas and Constable, 2005), cued words (Addis et al., 2004; Conway et al., 1999; Graham et al., 2003; Ryan et al., 2001) or family photos (Gilboa et al., 2004), suggesting that the hippocampal activity during the episodic data cited above is not due to some generic hippocampal activity during any mnemonic task. fMRI does not form a critical part of this chapter, however, these data inform the mnemonic milieu into which this chapter will be interpreted.

5.1.3.3. Models of episodic memory retrieval: interim summary

The SMC and MTT have contrasting predictions about the quality of episodic recall across the lifetime of a subject with hippocampal damage, with both being associated with compelling neuropsychological and fMRI data. The apparent reconciliation of these opposing views has not been forthcoming. For instance, Table 5.1 demonstrates the empirical studies in which retrograde episodic memory testing has been undertaken according to a variety of methods, and has led to results that are consistent with either the SMC or MTT. The point of disagreement between these two models usually appears to be remote memories or those furthest from their encoding event. Groups either describe entirely normal episodic function for this period when compared to a group of age-matched controls (Bayley et al., 2005; Bayley et al., 2003, 2006; Kirwan et al., 2008) or impaired episodic recall (Rosenbaum et al., 2011; Rosenbaum et al., 2005; Rosenbaum et al., 2008; Steinvorth et al., 2005). Therefore, particular experimental focus should fall on these most remote episodic memories.

5.1.3.4. Similar predictions across the SMC and MTT for retrograde episodic memory retrieval

The SMC and MTT differ from one another concerning the temporal role of the hippocampus in retrieving remote episodic memories across the lifespan. Both agree, however, that the hippocampus is required for the retrieval of recent memories (usually within five years), and, as such, predict that focal hippocampal damage will produce a retrograde amnesia for this vulnerable period (Bayley et al., 2003; Kirwan et al., 2008; Klein and Gangi, 2010; Nadel and Moscovitch, 1997; Rosenbaum et al., 2008; Squire and Alvarez, 1995; Squire et al., 2004). Probing this time point with a measure of retrograde episodic memory should provide an assessment of the most vulnerable episodic memory, and hence would yield an important metric against which other retrograde memories could be compared.

Table 5.1. Neuropsychological evidence for and against the temporal gradient of episodic memory loss following focal hippocampal damage

Temporal gradient (in keeping with SMC)			**No temporal gradient (in keeping with MTT)**		
Reference	Subject *n*	Pathology cited	Reference	Subject *n*	Pathology cited
(Kirwan et al., 2008)	5	3 hippocampal damage, 2 medial temporal lobe damage	(Noulhiane et al., 2007)	22	All temporal lobectomy
(Wais et al., 2006)	6	All hippocampal damage – aetiology unclear	(Chan et al., 2007)	3	All VGKC-LE
(Bayley et al., 2003)	6	All anoxia	(Squire et al., 2010)	2	Temporal lobectomy and hippocampal infarct
(Bayley et al., 2006)	5	Aetiology unclear	(Cipolotti et al., 2001)	1	Hippocampal anoxia
(Kopelman et al., 1999)	12	3 Korsakoff's syndrome, 9 herpes simplex encephalitis	(Viskontas et al., 2000)	25	Temporal lobe epilepsy
(Kapur and Brooks, 1999)	2	Both viral encephalitis	(Kopelman et al., 1999)	12	3 Korsakoff's syndrome, 9 herpes simplex encephalitis
(Reed and Squire, 1998)	4	All anoxia	(Kartsounis et al., 1995)	1	CA1 and 2 field ischaemia
(Rempel-Clower et al., 1996)	5	3 hippocampal ischaemia, 2 Korsakoff's syndrome	(Victor and Agamanolis, 1990)	1	Korsakoff's syndrome
(Barr et al., 1990)	12	All temporal lobectomy	(Barr et al., 1990)	12	All temporal lobectomy
(Corkin, 1984b)	1	Medial temporal lobectomy	(Warrington and McCarthy, 1988)	1	Viral encephalitis
(Cermak and O'Connor, 1983)	1	Viral encephalitis	(Corkin, 1984b)	1	Trauma
(Scoville and Milner, 1957)	1	Medial temporal lobectomy	(Damasio et al., 1985)	1	Herpes simplex encephalitis
			(Cermak and O'Connor, 1983)	1	Viral encephalitis

In particular, the SMC would predict that there should be significant improvements in quantitative measures of episodic memories for those memories acquired several decades prior to hippocampal damage, but more recent memories will have lower scores associated with them (Squire et al., 2004). The MTT would predict that, with increasing hippocampal volume loss associated with disease or injury, quantitative measures of remote memories should become diminished, eventually producing insignificant differences between recent and remote memories (Nadel and Moscovitch, 1997). With lesions that differentially affect the longitudinal axis of the hippocampus, then a linear gradient in episodic memory performance might be expected to emerge. Recent memories will have fewer associated traces rendering them susceptible

to just minor damage to the hippocampus; more extensive lesions will begin to disrupt the multiple traces associated with older memories, stored in multiple regions along the longitudinal axis of the hippocampus (Nadel and Moscovitch, 1997).

5.1.3.5. The transformation hypothesis, and its relevance to the retrograde episodic memory

An alternative account that may reconcile the SMC and MTT, suggests that memories supported by the hippocampus are fundamentally different from those supported by the neocortex (Winocur et al., 2010). In this account, memories undergo a 'transformation' with time, whereby the initial context-dependent memory is represented by the hippocampus, and is then transformed to a context-independent memory supported entirely by the neocortex. The transformation process occurs such that a general schema of the memory is ultimately less rigidly associated with the context in which it was learnt (Winocur et al., 2010). Hippocampal dysfunction prior to decontextualization is hypothesised to impair this process, thereby leading to a loss of both the general schema and the specific context.

Accordingly, patients with lesions isolated to the hippocampus should have deficits in both acquiring new episodic memories, and in retrieving temporally recent episodic memories (in agreement with both the SMC and MTT), two time periods that will be probed in this chapter. However, should a degree of this transformation have already occurred (such as with very remote memories), then the context-specific memory will be lost, but the schematic memory can be used to retrieve the memory (Winocur et al., 2010). Hence this schema-derived memory may give the appearance of episodic-recall, but when probed further, it is likely that relational and constructional aspects of the memory are lost (Winocur et al., 2010). Indeed, one investigation into the episodic recall of elder healthy controls found that their most remote memories were episodically impoverished when the memory arose from a time period beyond the age of younger participants (Levine et al., 2002). This so-called semanticisation of episodic memory into a schema-driven phenomenon has also been described elsewhere using a broadly similar technique (Eustache et al., 2004). Therefore, according to this hypothesis, we might putatively expect to observe no difference between patients with focal hippocampal

lesions and controls for the most remote memory, with both groups recalling intact hippocampal-independent memories.

The detection of these differences is heavily dependent on the neuropsychological tool used to probe episodic memories. As will be described in greater detail in Section 5.1.4 below, neuropsychological paradigms using subjective assessment rating methods (such as the Autobiographical Memory Interview) try to separate participant data into four ordinal groups, thereby diminishing the potential differences observable between patients and controls. However, quantitative methods of assessment (such as the Autobiographical Interview) rely on the accrual of episodic memory points assigned according to strict criteria, thereby allowing numerical point differences to arise between participants and hence patients and controls. With this method, it is more likely that significant group-level performances will be detected with a much wider range of values being available. Indeed, it is notable that those experiments reporting no differences between hippocampal-lesion patients and controls for remote episodic memories tend to use subjective assessments of episodic memory (e.g., Bright et al., 2006; Eslinger, 1998), although see (Kirwan et al., 2008), whereas those reporting differences between patients and controls for those most remote periods tend to use more quantitative methods (e.g., Rosenbaum et al., 2008; Steinvorth et al., 2005). The differences between these two methodologies itself is an empirical question and both a subjective rating method and a quantitative method will be used in order to probe these hypothetical differences.

5.1.4. Methodological considerations for retrograde episodic memory testing: the Autobiographical Memory Interview and the Autobiographical Interview

5.1.4.1. The Autobiographical Memory Interview and other early episodic memory tasks

The Autobiographical Memory Interview (AMI) was developed to both distinguish episodic from semantic recall, and to constrain retrieval to three specific epochs (Kopelman, 1994). The AMI is a semi-structured interview that constrains memory to three broad time-spans: 'childhood', 'early adult life' and 'recent' events. Importantly, the marks available to each of these time periods were equally balanced

across the time-spans, and the episodic retrieval is further constrained by subject type. Scoring of the events was performed according to richness of the event described, up to a maximum of three points, although is subjectively assigned (see Table 5.2).

Table 5.2. Scoring criteria for the Autobiographical Memory Interview (Kopelman, 1994)

Score	Criteria
3	An event which is well-described and specific in time and place
2	An event which is specific but time and place are not recalled
1	A vague personal memory
0	Absence of a response or a response based on general knowledge

Although the AMI has proven a reliable means of comparison between patients with varying degrees of MTL damage and healthy age-matched controls (Kopelman, 1994), it places a quantitative constraint on the data emerging from studies using this tool. The marking guidelines suggest awarding three marks for those memories that have a specific time and place, and which are episodically rich in nature, and thereby introduces a ceiling effect into AMI performance. Many memories will be well-described *and* have a specific time and place but this does not mean they are all equal in those descriptions or specificities. Therefore, this rigid marking scheme will group memories of different re-experiential descriptions – and hence quantities – together, and renders the measure potentially insensitive to more modest quantitative differences between patients and controls. Moreover, these 0-3 mark groupings essentially turn a scalar variable (that is how many quantitative re-experiential features there are for a retrograde episodic memory) into an ordinal variable (i.e., which of four groupings does this memory belong). This will necessarily limit the quantitative group means between patients and controls, thereby minimizing potential differences seen on inferential analyses. Therefore, whilst the AMI constrains memory recall by time, its marking scheme places limits on the data when comparing between groups. The AMI also constrains episodic retrieval to specific events (e.g., a wedding or a recent holiday). Whilst this is a form a retrieval support, designed to negate the effects that frontal lobe pathology may have on retrieval strategy and hence episodic memory (Wheeler et al., 1995), it may not represent particularly memorable events that participants would choose themselves and so may not represent their *best* possible memory.

5.1.4.2. The Autobiographical Interview

In 2002, Levine et al., (2002) developed a new method of assessing episodic memories that sought to address the ceiling effect associated with administrations of the AMI, as well as providing an opportunity for participants to retrieve events that were particularly memorable to them. The Autobiographical Interview (AI) is a semi-structured interview that was originally applied to provide retrieval support in order to investigate age-related changes in episodic memory retrieval, despite age-related changes along dimensions such as re-experiencing (Java, 1996; Norman and Schacter, 1997), and episodic recall (McIntyre and Craik, 1987; Spencer and Raz, 1995). Previous work has also shown that there is an age-related decline in the ability to retrieve explicit, effortful and unstructured memories (Zacks et al., 2000), and, as a consequence, the structured nature of the AI ensures that deficits seen in episodic memory can better separate performance from competence related issues. In line with the AMI, the AI was also designed to constrain participants by time, rather than by content, but provided additional retrieval support and strategies for memory retrieval even in cases of severe amnesia (Bayley et al., 2003; Steinvorth et al., 2005).

The AI is also designed to encourage responses that provide the most vivid memory available across several time periods. Administration of the AI by a trained interviewer is taped and transcribed for subsequent scoring, which is conducted in accordance with various phenomenological categories that are adapted from the Memory Characteristics Questionnaire as seen in Table 5.3 (Johnson et al., 1988). Accordingly, marks are awarded according to whether the content is considered to be central to the recalled event (internal details) or extraneous to the event (external details). Internal details are conceptually held to be those that are hallmarks of episodic memories (i.e., specific in space and time). These internal or external details are then further subdivided into five categories: event detail, time, place, perception and emotional/thought components. There is no specific measure for personal semantic memory on the AI, but the external details at best approximates this particular type of memory as these scores demonstrate the factual milieu present at the time of the episodic memory, but they rely on subjects producing them which of course they may not. One advantage of the AMI is that is has a structured questions specifically aimed at quantifying personal semantic memory.

Table 5.3. Description of Autobiographical Interview (AI) scoring categories

Category	
Internal	
Event	Happenings, individuals present, weather, physical/emotional actions or reactions in others
Time	Year, season, month, day, time of day
Place	Localisation including city, street, building, room, part of room
Perceptual	Auditory, olfactory, tactile, visual (including details), body position, duration
Thought/emotion	Emotional state, thoughts, implications
External	
Event	Details of an event external to the main event recalled
Semantic	General knowledge or facts
Repetition	Unsolicited repetition of details
Other	Metacognitive statements, editorializing
Ratings	
Episodic richness	Qualitative estimate of re-experiencing
Time	See above description
Place	See above description
Perceptual	See above description
Thought/emotion	See above description
Time integration	Integration into a larger time scale by inclusion of temporal contextual information or relation to other life periods

The benefit of assigning the content of each memory in this way is that there is no ceiling on the marks that can be awarded – it is a linear scale of performance and allows the comparison between composite scores in the episodic (internal) and semantic (external) features of the memory. A series of ratings much aligned to Tulving's (Tulving, 1972b) initial formulation of episodic memory are also described (see Table 5.2), and these are scored along similar lines to those indicated for the AMI.

5.1.4.2.1. The methodology of the Autobiographical Interview: general and specific probes

The retrieval support offered in the AI comes in two forms: a self-initiated free-recall phase, referred to as the general probe, and, a second semi-structured question-based, known as, the specific probe. The standardized prompting method, beyond that of general probing, is needed because autobiographical memory tends to be processed at a more general level that does not always place an emphasis on re-experiential details (Conway, 2001). As both subject and interviewer process autobiographical memoires at this level, an incomplete picture of the subject's abilities may emerge if no further and specific guidance is given (Steinvorth et al., 2005). The key role of retrieval support was revealed in an application to study the densely amnestic, KC (Rosenbaum et al., 2005). The authors found that he was able to produce a normal amount of semantic details, but

was found to be unable to produce a single episodic event on free-recall; however, the structured nature of the specific probe helped KC to provide some specific event details, but this was still well-below that of age-matched controls (Rosenbaum et al., 2005).

5.1.4.2.2. Episodic retrieval utilizes semantic support in the context of the Autobiographical Interview

Episodic and semantic recall are used simultaneously everyday, but MTL damage (or the hippocampus at least) tends to produce deficits in episodic recall, leaving MTL-based amnestic patients with a relatively intact recognition (Aggleton et al., 2000; Mayes et al., 2004; Yonelinas et al., 2002; Yonelinas and Levy, 2002), and semantic memory (the immediate premorbid period excepted; Manns et al., 2003). Conversely, patients with the semantic dementia, a form of frontotemporal dementia, demonstrate a loss of verbal identification skills (Hodges et al., 1995) alongside atrophy of their anterolateral temporal lobes. Episodic recall is affected, but not to the same extent as their semantic memory (Chan et al., 2001; Graham et al., 2000).

A more recent model of the interaction between episodic and semantic memories (Reder et al., 2009) posits that episodic memories depend on the binding of semantic concepts to either the general or specific context in which they appeared during encoding. This suggests that by separating episodic and semantic components during experimental probing could limit the amount of information available for either episodic or semantic memory or both. The AMI separates episodic and semantic memory at retrieval, thereby introducing a potential methodological confound for experiments using the AMI. Therefore, a probe should allow these distinctions to be made *post hoc* in order to provide maximal retrieval support.

The AI attempts to overcome problems of retrieval support by turning this first-person narrative into a phenomenological third-person account, and so becomes available to third-person scrutiny (Levine, 2004). An interview, once transcribed, can be dissected into information components that can then be assigned into these memory classifications. The AMI sought to separate semantic and episodic components of memory at the outset, whereas the AI seeks to separate them after collection of the responses, and as such allows episodic and semantic components of memory to support

one another during the generation of the guided first-person narrative responses (again another feature of retrieval support; (Levine, 2004)).

5.1.4.2.3. Autobiographical Interview performance in hippocampal lesion patients

The first reported application of the AI being in patients with MTL damage was with patients HM and WR (Steinvorth et al., 2005). These patients were required to recall a single episodic memory from the time periods <11, 12-17, 18-35, 36-55 and Last Year. This study found that WR was impaired for episodic recall for the <11 and 36-55 periods, with borderline normal performance, compared to controls, for the 12-17 period. HM could only provide one retrograde memory in the 12-17 period (which scored over 100 internal detail points), but was otherwise unable to recall a specific episodic memory. Recollection of external details was the same between patients and controls across all epochs (Steinvorth et al., 2005). These data were interpreted as evidence to indicate that the AI was more sensitive than other methods in elucidating episodic impairment in hippocampal lesions patients, and hence may be more sensitive in determining episodic retrieval deficits than previous studies (e.g. Bayley et al., 2003; Steinvorth et al., 2005). It is important to note, however, that no statistical analysis was conducted on these data. Rather the paper was descriptive in nature, possibly due to case study nature of the experimental work.

Kirwan et al., (2008) used the AI methodology in an attempt to extend the findings of Bayley et al., (2003) that had found no difference between patient and controls for remote memories using a modified Crovtiz method. Previous critiques of this work had suggested that fewer marks had been awarded for episodic retrieval to both patients and controls, thereby limiting the differences between these groups (Rosenbaum et al., 2008). Kirwan et al., (2008) administered the AI to three patients with damage limited to the hippocampus (the hippocampal group), and two patients with larger MTL lesions (MTL group). Memory was assessed by probing five retrograde time periods (<11, 12-17, 18-35, 36-55 and Last Year). The hippocampal group (KE, LJ, and GW) had a hippocampal volume loss of 49%, 46% and 48%, respectively, whereas volume loss of the PHG was measured at 17%, -8% and 12%. In the MTL group – comprised of EP and GP – the mean bilateral hippocampal volume reductions were 97% (EP) and 96% (GP), respectively, and the PHG were likewise substantially atrophied by

94% (EP) and 93% (GP), with further complete loss of the PRC and ERC, and significant damage to PHC (73% for EP and 71% for GP).

Kirwan et al., (2008) found a significant effect of time but not group, with a significant interaction between group and time, which the authors interpreted as evidence that both patient group were unable to recall memories for both the immediately premorbid and postmorbid periods (Kirwan et al., 2008). *Post hoc T*-tests showed that the control group recalled significantly more internal details than both patient groups for the most recent – anterograde - time period. The hippocampal group was better able to recall internal details from the 36-55 year period than controls and the MTL group. The SMC predicts that large MTL lesions will lead to an extensive retrograde episodic amnesia (Bayley et al., 2006), but that very remote memory is intact after both kinds of lesions (Bayley et al., 2005; Bayley et al., 2006; Bayley and Squire, 2003). When combined with the results from an earlier study (Bayley and Squire, 2003) – which again found evidence of unimpaired retrieval of episodic memories from very remote periods – these authors felt that no matter the type of test used, MTL damage produces behaviourally measurable retrograde episodic amnesia in a pattern consistent with the SMC (Bayley et al., 2005; Bayley et al., 2006; Bayley and Squire, 2003).

However, Rosenbaum et al., (2008) undertook neuropsychological, volumetric MRI and retrograde memory testing with the AI in four patients with differing degrees of MTL damage. The patients also had a range of retrograde pathology from extensive, ungraded retrograde amnesia (SJ, CB) to retrograde amnesia extending to decades, but with a temporal gradient (DA), and to moderate retrograde amnesia for the immediate premorbid period (RG). The authors analysed free recall (low retrieval support) separately from specific probes (high retrieval support). Although not made explicit, presumably this was to assess whether deficits in episodic recall could be due to search and retrieval strategy deficits (DA had evidence of a dysexecutive syndrome). These authors then compared individual patient performance against a group of eight controls, a method that only informs about an individual patient's performance but does not offer group level data. They found a significant difference in episodic (internal) detail recall between controls and patients SJ and CB, but not DA or RG. Further analysis demonstrated that patient CB had significant impairments in internal detail generation for the childhood period only, but was also impaired on the rating scales across her

childhood, adolescence, early adulthood and mid-adulthood periods. RG demonstrated significant impairment on ratings, but not internal or external detail generation. DA had significant impairment on ratings for the most recent time point. Once again, these ratings were derived in a manner similar to the AMI, and therefore differences between patient and controls should be interpreted in that light; however, what they suggest is that the retrograde episodic memory deficits are subtle and further demonstrate the strength of the AI over the AMI. Finally, SJ was significantly impaired for internal detail for the childhood, early adulthood and mid-adulthood periods, something repeated in the rating measures for those periods. Importantly, there were no significant differences for any patient on external detail recall. SJ had the greatest volume of hippocampal loss and the authors interpreted this as suggesting that the depth of his retrograde amnesia, and the relative preservation of the other patients, was a function of the degree of hippocampal damage observed. These data were therefore interpreted as being consistent with the MTT.

Certainly the combination of both anatomy and behavioural data is compelling, but the authors were unable to draw these conclusions from either correlative or regression based inferential statistics, thereby limiting the inferences that can be drawn from these observations. Kirwan et al., (2008) drew similar conclusions arguing that the more extensive the damage to the MTL then the more extensive the observed amnesia for internal detail point generation between patients and controls. Critically, Kirwan et al., (2008) interpreted their results as showing that the degree of MTL damage extends the temporal distance across which retrograde amnesia is seen but that at most this is up to 10 years, something more in keeping with the SMC.

What is immediately striking upon reviewing the available studies in the experimental literature is that only one has been able to use inferential statistics on populations of patients (Kirwan et al., 2008); the others have been limited to case-control studies. Likewise, Kirwan et al., (2008) are the only group that have been able to use either planned comparisons or *post hoc* testing in order to probe the nature of a temporal gradient, even this though was limited to just the immediate premorbid and postmorbid epochs (Last Year and 30-55). It would seem reasonable to test internal detail performance for both remote and more recent episodic memories. These studies utilize

small numbers of patients, and, as such, were limited in their power to detect significant interaction terms between their main variable; namely time and group.

The AI has clear application to MTL and hippocampal amnesic patients, and therefore has good utility for experimental work by: (1) offering semi-structured retrieval support (thus ensuring deficits are not due to competence); (2) retrieving internal and external details together (further aiding retrieval support); (3) constraining participant recall according to time; (4) adhering to many of the key features of episodic memory; and (5) not introducing a ceiling effect on scores through the provision of a continuous measure according to the number of details provided. These key features of the AI allow individual and group differences in episodic and personal semantic memory to be tested. The AI also provides a method for scoring episodic memories in a way that provides far more granularity and adherence to the original accounts of episodic memory, and so doing provides a large number of observations on which to base inferences that meet the criteria for parametric inferential statistics.

Applications of the AI to MTL, hippocampal and other patient groups (Addis et al., 2007; St-Laurent et al., 2009; St-Laurent et al., 2011) indicate that it is robust enough to be used across several disparate pathologies, and can be modified to suit experimental requirements. However, what is notable is that studies tend to report internal details collapsed across the five response categories supported by the AI (e.g. event details, time, place, perceptual details and emotions and thoughts) almost universally, something surprising given the theoretical foundations upon which the AI was developed (Levine et al., 2002). Theoretically, the AI allows experimenters not only to quantify episodic recall, but also to identify the components central to episodic memory that might be driving discrepancies between patient and control populations.

In a more recent study, eight hippocampal patients were assessed in an experiment that assessed both recent and remote memories and future imagining, but used the scoring method detailed within the AI (Race et al., 2011). This study also found that focal hippocampal lesions are associated with reduced internal detail recall across all of the detail dimension types contained within the AI (event details, place, time, perceptual details and emotions and thoughts); however, these data were collapsed across time, so inferences were not possible in how episodic memories varied with time. For the

purposes of this chapter, this is a severe limitation as the authors were unable to make comments about the temporal role of the hippocampus in retrograde episodic memory recall.

One final study – cited above – found that in patients with TLE, there was an overall reduction in internal detail recall, but that this was driven by a significant diminution in perceptual recall (St-Laurent et al., 2014). These studies suggest that when the AI is used in larger patient groups, it allow analyses to be conducted on the contents of retrieval as a function of the response categories (Levine et al., 2002). This is of critical importance given the different types and origins of information that constitute an episodic memory (e.g., event details, perceptual details, thoughts and emotions) may be variably affected following hippocampal or MTL damage and could have implications for the type of information that might be temporally supported by the hippocampus and/or MTL in episodic memory recall. Therefore, using the AI in a large group of patients (i.e., >10) with focal MTL/hippocampal lesions should yield enough power to detect potential behavioural deficits according to performance not only across the time periods tested but also across response categories.

5.1.4.4. The Autobiographical Interview and the Autobiographical Memory Interview as measures of personal semantic memory

The AI provides a measure of both public and personal semantic memory (via the semantic score and external details score respectively); however, these are not the primary aim of the tool and as such the conclusions inferred from the personal semantic measure on the AI are necessarily limited in scope given that participants are primarily tasked with episodic recall and not semantic recall. By contrast, the AMI specifically tests for personal semantic memory by having a series of structured questions for each time period it tests. The same is not true for the AI.

Given that personal semantic memory appears to represent our conceptual knowledge, it has been suggested that its neural substrate is similar to that as general semantic memory, the neocortical regions of the temporal lobe, but not the MTL (Greenberg and Verfaellie, 2010). This has been supported by neuropsychological studies that have shown the perseveration of personal semantic memory alongside the

impairment of episodic memories (Cernak and O'Connor, 1983; Damasio et al., 1985; Warrington and Duchen, 1992). However, following a large meta-analysis of fMRI data in the retrieval of personal knowledge, including autobiographical facts, it is suggested that the PHC may be necessary for the successful retrieval of these memories (Martinelli et al., 2013).

For instances of focal hippocampal damage, therefore, it would be predicted that patients should accrue the same number of external detail points as controls. The absence of a temporal gradient of personal semantic memory loss following focal MTL damage also suggests that these structures are not necessary for the retrieval of memories no matter their age (Grilli and Verfaellie, 2014; Klein and Gangi, 2010; Klein and Lax, 2010). These data would suggest that should patients perform significantly worse than controls on both internal *and* external measures of the AI, then one could reasonable assume that the damage observed extends beyond the MTL and into the anterior temporal pole (for instance). There are critics of this approach and view of personal semantic memory (Squire, 1992a) who posit a more unitary account of MTL, suggesting that it functions to support both episodic and semantic memory (presumably both types) for a similar amount of time whilst both undergo neocortical consolidation. Once this process has taken place, both forms of memory remain independent of the hippocampus. According to this view, focal hippocampal lesions should therefore not only produce a temporal gradient in episodic memory loss but also a temporal gradient for semantic memory as well (Squire, 1992a).

5.1.4.5. The Autobiographical Interview and confabulation

Confabulation, whereby amnesic patients report fictitious memories, remains a concern when working with patients with amnesia, particularly when retrograde memories are not always immediately verifiable (Kopelman, 1987). The approach adopted here was guided by previous work into confabulation, that found there is a relationship between confabulation and impairment on the Hayling Sentence Completion Test (Burgess and Shallice, 1997), a test in which subjects have to complete sentences in two stages: (1) by completing a sentence using an appropriate word (e.g., Our dog chased the cat up the… *tree/path/road*); and (2) by completing a sentence using an unconnected word (e.g., The captain wanted to stay with the sinking… *banana/table/rug*). Successful

completion of the second form of the test requires the inhibition of prepotent responses (Dab et al., 2004; Nathaniel-James and Frith, 1996), in order to deliver the desired unconnected word. However, these findings have not always been replicated when administering the Hayling Test (Lorente-Rovira et al., 2007), nor are such relationships seen between confabulation and other tests of executive function, such as the Wisonsin Card Sorting Test and verbal fluency (Nathaniel-James and Frith, 1996), or the Stroop test (Salazar-Fraile et al., 2004).

For the purposes of the current study, significant differences have been observed between confabulating and non-confabulating amnesic patients on the Hayling Test (Fotopoulou et al., 2007). Seven patients rendered amnesic after stroke were subdivided into confabulating and non-confabulating groups. Confabulation was assessed via the Della Barba Confabulation Battery (Dalla Barba, 1993), whereby higher scores are indicative of confabulation, and significant differences were found between the two groups. The authors also found that within a large neuropsychometric battery that other than explicit measures of confabulation, the two groups differed on their scores for the Hayling Test. Although, it was not the central focus of the paper, the authors showed that a group of four confabulating amnesic patients had an average score of 2.8 on the Hayling Test, whereas three non-confabulating amnesic patients had an average score of 5.7 (Fotopoulou et al., 2007). Similar findings have been found in a study of confabulation in patients with anterior communicating artery aneurysms (three patients, average performance 3.3; Turner et al., 2010), a region known to be associated with executive dysfunction following rupture (Al-Khindi et al., 2010).

The authors do not comment upon the diagnostic value or validity of Hayling Test in this regard. However, for the purposes of this study it can be operationalized that impairment in the Hayling Test of four or below may be indicative that the patient is liable to confabulation.

5.1.5. Summary: aims and hypotheses

The aim of current chapter was therefore to administer the AI to a large group of amnesic patients with a single aetiology – VGKC-complex LE – and to modify it to address the variable epoch length present in the standard administration of the AI. This

study will also attempt to apply measures of retrograde episodic memory to this single aetiology group in order to provide empirical support for either the SMC or MTT. Both models agree that memories acquired in the most recent time periods (i.e., the most recent five years) are the most susceptible to disruption following hippocampal pathology (Squire and Alvarez, 1995; Squire and Bayley, 2007; Squire et al., 2004). For the first time in a patient group, the effects of focal hippocampal lesions on response category scores will also be examined. The type and quantity of details constituting these 'Five Year' memories can then be used as direct comparisons for assessing the type and quantity of details arising from more remote memories. The predictions for this experiment are as follows:

1. Patients will have a significant impairment in internal detail point generation for both the Standard and Modified administration of the AI.
    a. This deficit will be across the lifetime of the patients in a temporally extensive fashion (i.e., in keeping with the MTT).
    b. This deficit will not be seen for the most remote memory arising from the 0-11 period. This memory will have fewer internal detail points associated with it, owing to its transformation into a contextless memory.
    c. This will be in contrast to the findings in Chapter 4 of a temporal gradient of episodic memory loss observed in this patient group with the AMI, as the AMI as it is unable to differentiate between a well-described personal semantic account, and a truly re-experiential episodic memory.
2. There will be no differences between patients and controls on measures of personal semantic memory as emerging formally from the AMI, and informally from the AI.

5.2. Methods

See Section 2.3.

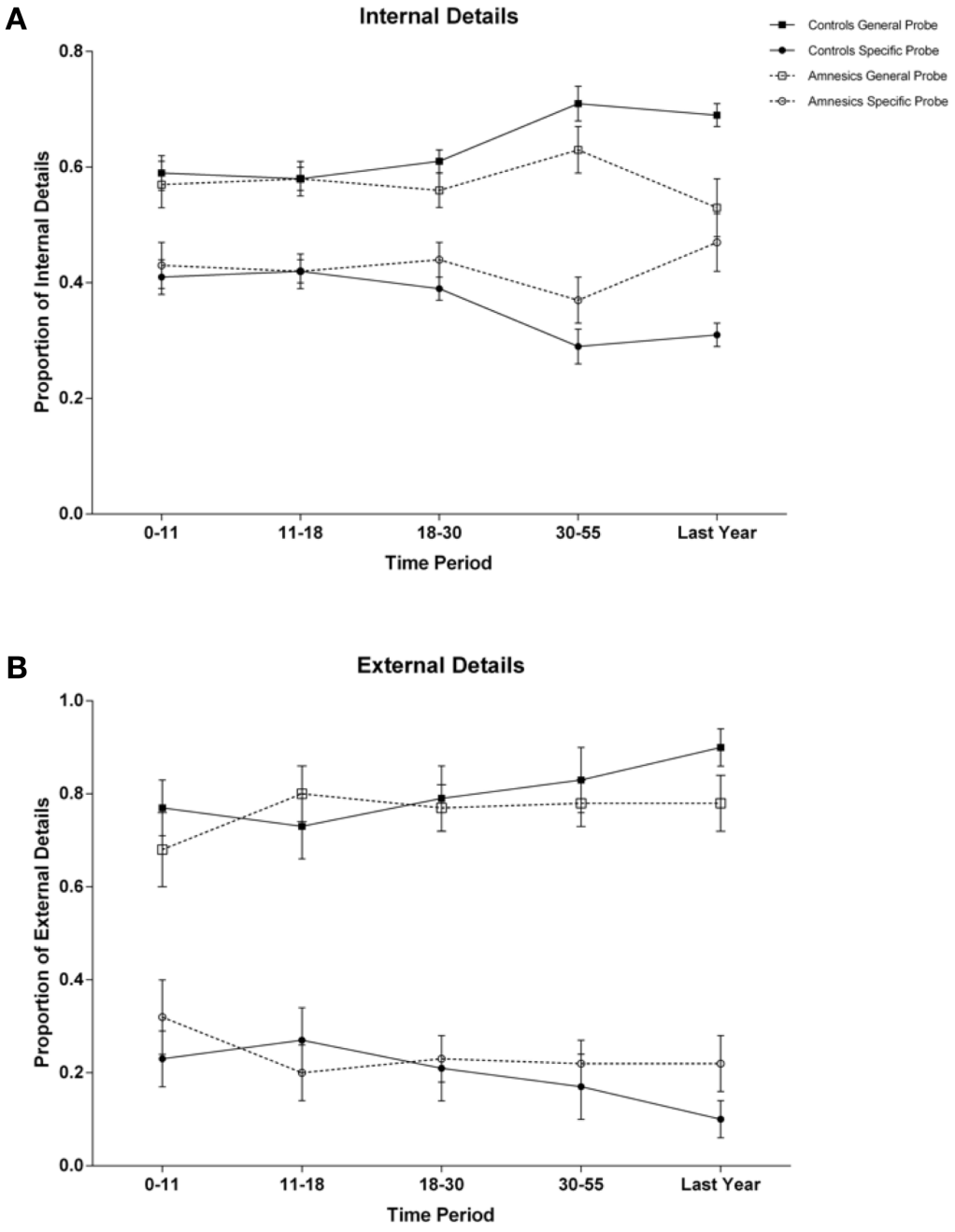
5.3. Results and Discussion

Seventeen patients were included in the standard administration, with 11 of those old enough to be taken forward into the extended administration. Memory verification found that 0.52 of the patient episodic memories could be independently checked and verified. A two-way mixed inter-rater correlation coefficient for absolute agreement was 0.82 across free recall and general probe internal and external scores and specific probe internal and external scores, suggesting excellent agreement between the two scorers (Levine et al., 2002).

5.3.1. VGKC-complex LE is associated with normal performance on the Hayling-Brixton sentence completion task

The mean standard score for the patient population was 5.8±0.21 (maximum score possible: 8; range: 4-8). The performance on the Hayling-Brixton sentence completion task, combined with memory validation procedure, suggests that the memories obtained were not confabulated.

Figure 5.1. Illustrative line plot demonstrating the mean proportion of internal and external details acquired by patients and controls during the general and specific probes of the AI. This is shown for both (A) internal and (B) external details. These values were derived by dividing the general and specific probe scores by the total point scores for individual memories, such that the proportions summed to 1. These plots demonstrate that patients and controls acquired most of their internal and external details during the general probe. The specific probe proportions were then divided by the general probe to derive the ratios analysed in Section 5.3.2.



5.3.2. Patients and controls do not differentially rely on the general and specific probes to accrue internal and external detail points

The General and Specific Probe recall proportion for patients across internal and external details is shown in Figure 5.1, and is done so for illustrative purposes. These proportions were then used to derive the specific probe/general probe ratios taken forward to a 2 (group: patients, controls) x 5 (time: 0-11, 11-18, 18-30, 30-55, Last Year) x 2 (ratio type: internal general probe, internal specific probe, external general probe, external specific probe) mixed-model factorial ANOVA was performed on the ratio scores with group as the between-subjects factor and time and ratio type as the repeated-measures factors. Mauchly's test indicated that the assumption of sphericity had been violated ($\chi^2_{(9)} = 36.59$, $p < 0.001$), and so degrees of freedom were corrected by the Greenhouse-Geisser method ($\varepsilon = 0.64$). There was only a main effect of Ratio Type ($F_{(1,32)} = 39.89$, $p < 0.001$), but no main effect of Group ($F_{(1,32)} = 2.59$, $p = 0.12$), or Time ($F_{(4,32)} = 1.15$, $p = 0.34$). There were no significant interactions between Time and Group ($F_{(4,32)} = 2.71$, $p = 0.12$), Ratio Type and Group ($F_{(1,32)} = 2.65$, $p = 0.12$), or Time and Ratio Type ($F_{(4,32)} = 0.76$, $p = 0.55$). The three-way interaction was not significant ($F_{(4,32)} = 0.25$, $p = 0.41$)

For the modified AI with seven time points ($n = 11$) Mauchly's test indicated that the assumption of sphericity had also been violated ($\chi^2_{(30)} = 64.82$, $p < 0.001$), and, so degrees of freedom were adjusted using the Greenhouse-Geisser method ($\varepsilon = 0.45$). Once again, there was only a main effect of Ratio Type ($F_{(1,20)} = 10.02$, $p = 0.005$), but not Group ($F_{(1,20)} = 3.66$, $p = 0.07$), or Time ($F_{(6,20)} = 1.44$, $p = 0.20$). There were no significant interactions between Time and Group ($F_{(4,20)} = 1.54$, $p = 0.17$), Ratio Type and Group ($F_{(1,20)} = 0.76$, $p = 0.39$), or Time and Ratio Type ($F_{(1,20)} = 0.64$, $p = 0.70$). The three-way interaction was not significant ($F_{(4,20)} = 0.36$, $p = 0.90$).

These data show that for both the standard and modified administrations of the AI, patients and controls derived the majority of their internal and external point scores during the general probe of the AI. This suggests that patients are able to recall and describe specific retrograde episodic events without relying on retrieval support afforded by the specific probe.

5.3.3. Autobiographical Interview results: modified administration (seven time points)

The extended AI included a further two time points that occurred in the 40-50 age range (the 30-55 period was shortened to 30-40) and a second memory five years prior to the illness (equating with 50-60 age range). This modified AI was administered to 11 patients (three female, average age: 70.1±1.37) and 11 age-matched controls (five female, average age: 67.1±1.62). Figure 5.2 shows the internal and external details for the patients, and Figure 5.3 shows the internal and external details for controls. Figure 5.4 demonstrates the collapsed internal detail score for patients and controls, and the results of planned comparisons.

5.3.3.1. VGKC-complex LE results in a temporally extensive significant reduction in internal detail score performance

Mauchly's test indicated the assumption of sphericity has not been violated ($\chi^2_{(20)} = 24.63$, $p = 0.22$), when collapsing across response categories. A three-way omnibus ANOVA was undertaken given there were two within-subjects factors potentially affecting point scores (time, information type) and one between-subjects (group). A 2 (group: patients, controls) x 7 (time: 0-11, 11-18, 18-30, 30-40, 40-50, 50-60, Last Year) x 2 (information type: internal, external) mixed-model factorial ANOVA was then conducted on point scores with group as the between-subjects factor and time and information type as the within-subjects factors. There was a significant main effect of group ($F_{(1,20)} = 245.13$, $p < 0.001$), information type ($F_{(1,20)} = 22.91$, $p < 0.001$), but not time ($F_{(6,120)} = 1.30$, $p = 0.26$). Importantly, significant interactions were found for group and time ($F_{(6,120)} = 2.88$, $p = 0.012$), group and information type ($F_{(1,20)} = 22.90$, $p < 0.001$), but not time and information type ($F_{(6,120)} = 174.56$, $p = 0.14$). The three-way interaction of group, time and information type was also significant ($F_{(6,120)} = 2.52$, $p = 0.043$).

To investigate the presence or absence of a temporal gradient in episodic recall across time for both groups, a series of planned comparisons were performed.

The first planned comparisons demonstrated that there was no significant difference between patients and controls for detail score for the 0-11 period ($F_{(1,20)}$ = 1.79, p = 0.20). This result suggests that there is a time-limited role for the hippocampus in re-experiential episodic memory retrieval, a finding previously reported elsewhere (Bayley et al., 2005; Bayley et al., 2006; Kirwan et al., 2008), although one that is contested (Cipolotti et al., 2001; Rosenbaum et al., 2008; Steinvorth et al., 2005). As alluded to earlier, the transformation hypothesis would predict that our most remote episodic memories are no longer supported by the hippocampus, and are therefore fundamentally different mnemonic phenomena (Winocur et al., 2010). The principal difference would be the transformation from a contextually-dependent (and hence hippocampally-dependent) to a contextually-independent memory supported by the neocortex. This semanticisation of episodic memory into a schema-driven phenomenon has been described elsewhere, and is particularly noticeable in the elderly (Eustache et al., 2004; Levine et al., 2002). Therefore according to this hypothesis, we might putatively expect to observe quantitatively similar memories between patients and controls in this epoch.

Given the conceptual difficulties surrounding the most remote memory, a series of planned comparisons were undertaken to investigate the presence of a temporal gradient against those memories that are largely agreed to be hippocampal dependent: the anterograde and immediate retrograde time periods (Nadel and Moscovitch, 1997; Squire et al., 2004). In patients, if distant retrograde internal detail generation, outwith the most remote memory, is equivalent to recent memory internal generation performance, then it would be highly suggestive that the hippocampus is involved in the generation of re-experiential memories no matter their temporal distance from acquisition. If the same pattern were observed in controls, again this would be suggestive that the hippocampus is required for re-experiencing typical of retrograde episodic memory retrieval.

In the amnesic patients, these planned comparisons revealed that there were no significant differences in episodic recall between the 11-18 and Last Year epochs ($F_{(1,20)}$ = 0.24, p = 0.63) or between the 11-18 and the Five Years prior to illness (50-60 on Figure 5.4; $F_{(1,20)}$ = 2.45, p = 0.13). The controls showed the same pattern for the 11-18 and Last Year ($F_{(1,20)}$ = 0.0001, p = 0.99) and the 11-18 and Five Years contrasts ($F_{(1,20)}$ = 0.08, p =

0.78). There was also no significant difference between patient total external detail recall and controls external detail score, when collapsed across decades (Patient mean: 32.2±6.11, Control mean: 55.3±6.00; $F_{(1,20)} = 6.33$, $p = 0.02$).

5.3.3.2. Temporally extensive deficits in internal detail performance following VGKC-complex LE is not attributable to a focal impairment for a specific response category

A four-way omnibus ANOVA was undertaken because there were three within-subjects factors that could explain the variance in point scores (time, information type and response category) and one between-subjects factor (group). A 2 (group: patients, controls) x 7 (time: 0-11,11-18, 19-30, 30-40, 40-50, 50-60, Last Year) x 2 (information type: internal, external) x 5 (response category: event details, place, time, perceptual details, and emotions and thoughts) four-way mixed-model factorial ANOVA was performed on the scores, with Group as the between-subjects factor and Time, Information Type and response category as repeated-measures factors. Mauchly's test indicated the assumption of sphericity has been violated ($\chi^2_{(299)}$ = figure not reported, $p < 0.001$). Therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.27$).

There was a main effect of group ($F_{(1,20)} = 22.8$, $p < 0.0001$), information type ($F_{(1,20)} = 210.6$, $p < 0.0001$) and response category ($F_{(1.45,29.043)} = 93.04$, $p < 0.0001$). Time did not have a significant main effect ($F_{(4.09,81.87)} = 1.15$, $p = 0.34$). Significant interactions were found between time and group ($F_{(4.09,81.87)} = 2.87$, $p = 0.012$), information type and group ($F_{(1,20)} = 22.7$, $p < 0.00001$), response category and group ($F_{(1.45,29.04)} = 9.5$, $p < 0.001$), time and response category ($F_{(6.19,123.80)} = 1.84$, $p = 0.00967$), and information type and response category ($F_{(1.71,34.19)} = 58.4$, $p < 0.001$). Significant three-way interactions were found for information type, response category and group ($F_{(1.71,34.19)} = 9.4$, $p < 0.001$), and time, information type and response category ($F_{(6.52,130.58)} = 1.9$, $p = 0.005$). The three-way interaction for group, information type and time was not significant ($F_{(4.30,86.00)} = 2.1$, $p = 0.062$). After correction, there was no evidence of a significant four-way interaction ($F_{(6.53,130.58)} = 0.69$, $p = 0.67$). No further analyses were undertaken.

5.3.3.3. Autobiographical Interview ratings: seven time points

A 2 (group: patients, controls) x 7 (time: 0-11, 11-18, 18-30, 30-40, 40-50, 50-60, Last Year) x 7 (response category: place, time, perception, emotions and thoughts, Autobiographical Memory Interview, time integration and episodic vividness) mixed-model factorial ANOVA was performed on the ratings, with Group as the between-subjects factor and time and response category the within-subjects factors. There were significant main effects of group ($F_{(1,20)} = 34.68, p < 0.0001$) and rating ($F_{(6,120)} = 85.10, p < 0.0001$), but the main effect of time was not significant ($F_{(6,120)} = 1.28, p = 0.27$).

Significant interactions were found between time and group ($F_{(6,120)} = 2.56, p = 0.023$), rating and group ($F_{(6,120)} = 22.06, p < 0.0001$) and rating and time ($F_{(36,720)} = 1.61, p = 0.014$). The three-way interaction was not significant ($F_{(36,720)} = 1.04, p = 0.40$).

Figure 5.2. Comparative internal detail score performance for patients and controls, collapsed across response categories for both the (A) modified and (B) standard administration of the Autobiographical Interview. Planned comparisons demonstrated no significant internal detail point score difference was found between patients and controls for the 0-11 epoch. Planned comparisons between the 11-18 and both the 50-60 and Last Year epochs for modified administration, and between the 11-18 and the 30-55 and Last Year epochs for the standard administration of Autobiographical Interview for patients and controls is likewise demonstrated. *n.s.* = not significant.

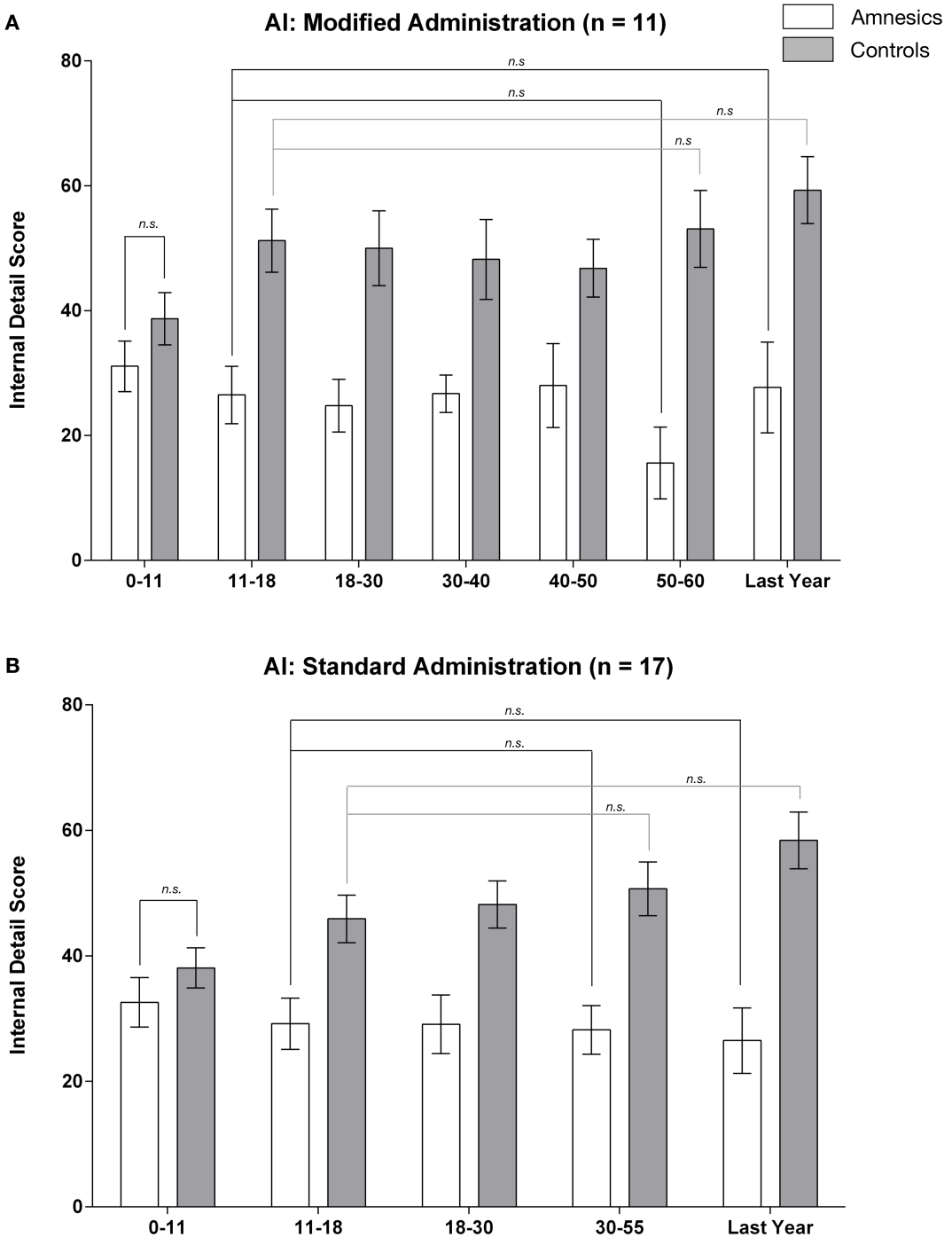
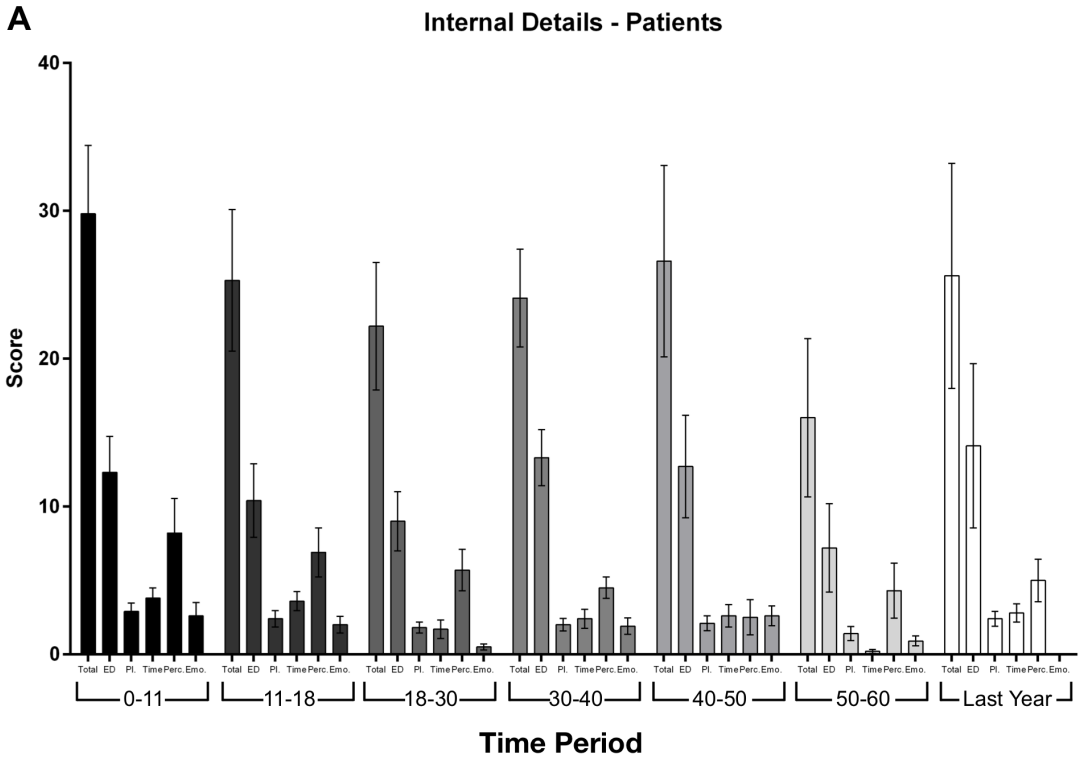


Figure 5.3. Patient group mean scores for the extended administration of the Autobiographical Interview, according to response categories (event details, time, place, perceptual details, and thoughts and emotions). This is for both (A) internal, and (B) external details.



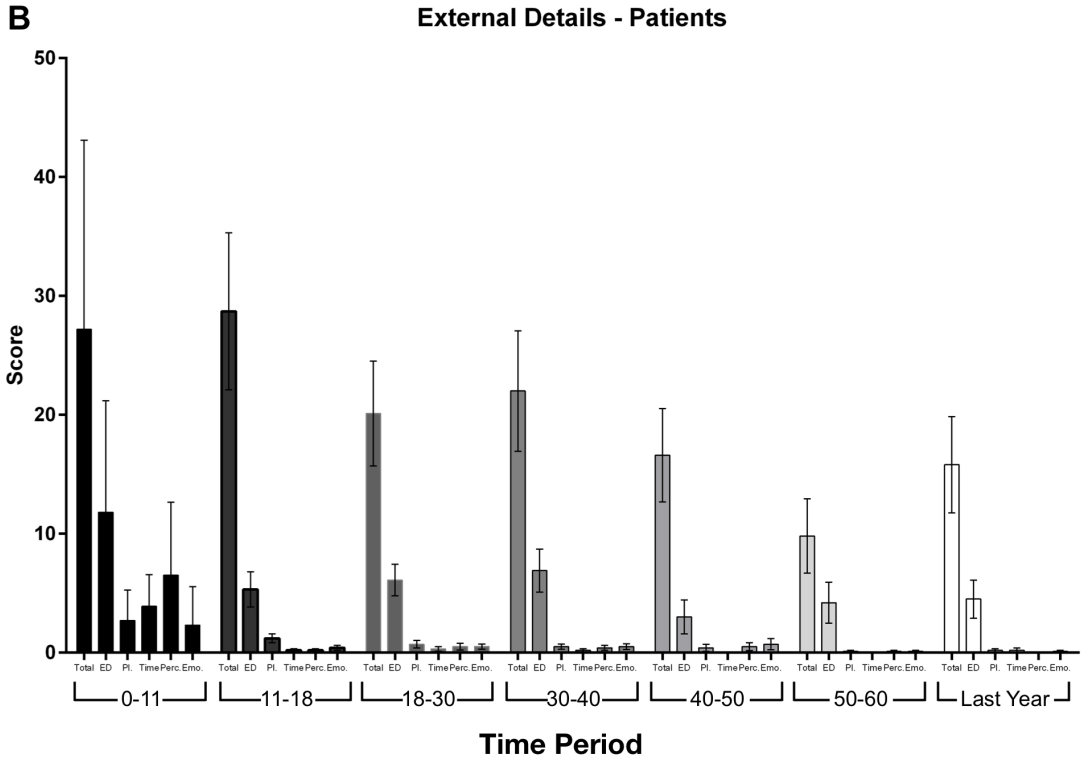
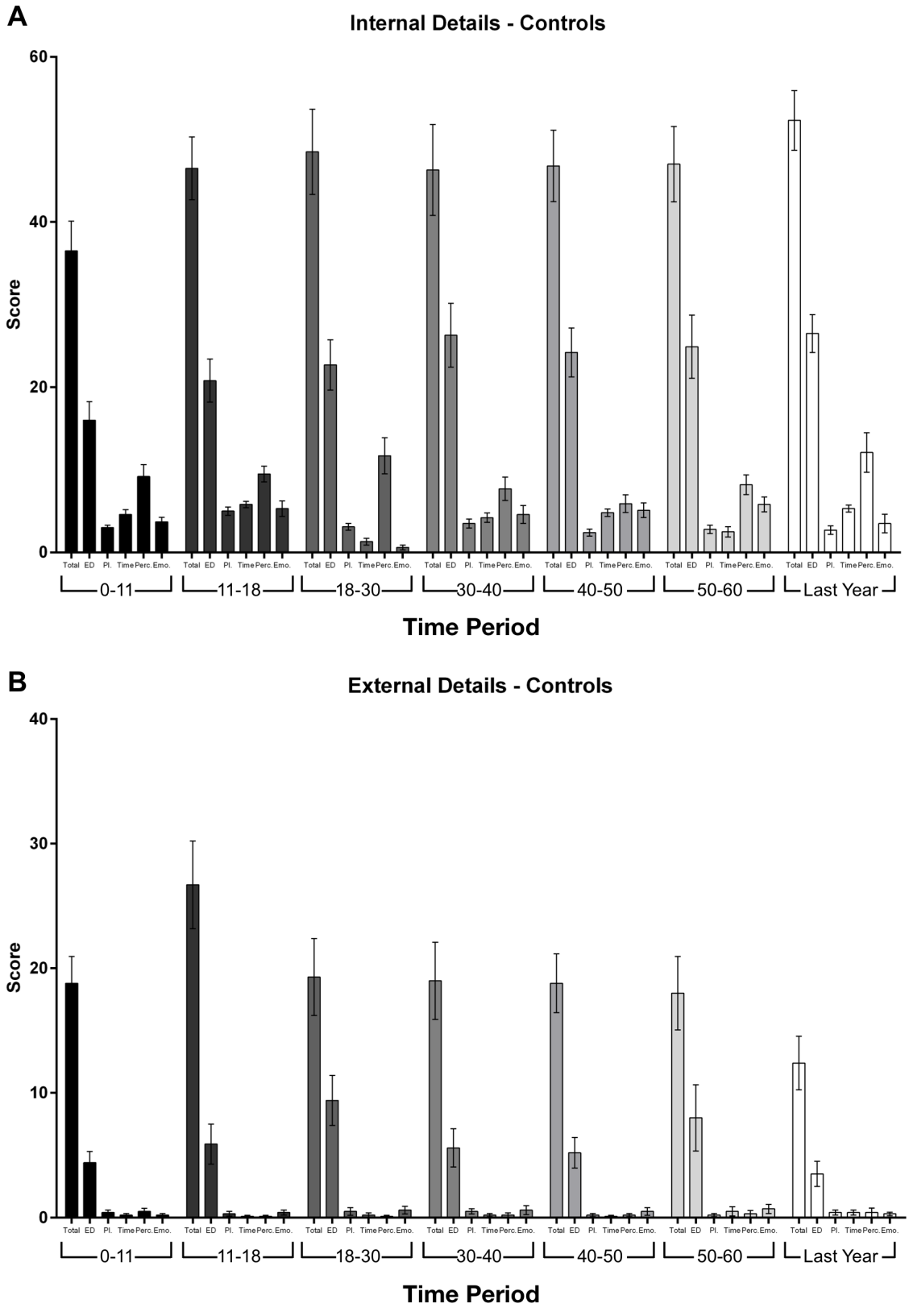


Figure 5.4. Control group mean scores for the extended administration of the Autobiographical Interview, according to response categories (event details, time, place, perceptual details, and thoughts and emotions). This is for both (A) internal, and (B) external details.



5.3.4. Autobiographical Interview results: standard administration (five time points)

The Autobiographical Interview in its standard format was administered to a total of 17 VGKC-complex LE patients (4 female, average age 64.6±2.45) and 17 age-matched controls (7 female, average age 63.9±1.65). Figure 5.5 shows the internal and external scores for each detail type (i.e. event details, place, time, perceptual details and emotions and thoughts), across the five time points measured (0-11, 11-18, 18-30, 30-55 and Last Year) for patients. Figure 5.6 shows the same data for controls. In all circumstances, the Last Year time point occurs after the illness, and so represents an anterograde memory.

5.3.4.1. VGKC-complex LE results in a temporally extensive loss of internal detail point score performance

Mauchly's test indicated that the assumption of sphericity had not been violated ($\chi^2_{(9)} = 15.76$, $p = 0.073$) when the data was collapsed across response categories (i.e. event detail, time, place, perceptual details, emotions and thoughts). A three-way omnibus ANOVA was undertaken because there were two within-subjects factors constituting point score (time and information type) with one between-subjects factor (group). A 2 (group: patient, control) x 5 (time: 0-11, 11-18, 18-30, 30-55 and Last Year) x 2 (information type: internal, external) mixed-model factorial ANOVA was performed on scores, with group as the between-subjects factor and time and Information type as the within-subjects factors.

There was a significant main effect of group ($F_{(1,32)} = 14.39$, $p = 0.01$), time ($F_{(4,128)} = 2.83$, $p = 0.027$), and information type ($F_{(1,32)} = 231.61$, $p < 0.001$). Significant interaction terms were found between group and time ($F_{(4,128)} = 6.29$, $p < 0.001$), group and information type ($F_{(1,32)} = 18.48$, $p < 0.001$), and time and information type ($F_{(4,128)} = 2.78$, $p = 0.029$). The three-way interaction term for group, time and information type was also significant ($F_{(4,128)} = 3.63$, $p = 0.008$).

The same planned comparisons were undertaken for the standard administration of the AI as with the modified administration. Significance was set at 0.008 using Holm-Bonferroni correction. There were no significant differences between patients and

controls at the 0-11 epoch ($F_{(1,32)}$ = 1.46, p = 0.24), between patient performance between the 11-18 and Last Year epochs ($F_{(1,32)}$ = 0.14, p = 0.71) or the 11-18 and 30-55 epochs ($F_{(1,32)}$ = 0.04, p = 0.85). There were no significant differences either in control performance between the 11-18 and Last Year ($F_{(1,32)}$ = 3.75, p = 0.06) or the 11-18 and 30-55 epoch ($F_{(1,32)}$ = 0.81, p = 0.37). Finally there were no significant differences in total external detail retrieval collapsed across time for patients and controls (Patient mean: 31.4±6.53, Control mean: 37.1±3.55; $F_{(1,32)}$ = 0.002, p = 0.96).

5.3.4.2. VGKC-complex LE results in significantly fewer perceptual internal detail points

In the case of the AI, the ability to meet the assumption of sphericity is dependent on the fact that each response category within the AI will have a normally distributed score amongst both populations. However, the construction of the AI includes some response categories that are very unlikely to feature regularly within a transcript of episodic recall (such as external time or perceptual details), and, as such, is likely to violate the assumption. Accordingly, Mauchly's test indicated the assumption of sphericity has been violated ($\chi^2_{(135)}$ = 444.84, p < 0.001). Therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε = 0.39), which resulted in no further analyses being supported by the main effects, and interaction terms. Despite this, an exploratory analysis was undertaken that include information from each of the five response categories, without correction of degrees of freedom.

A four-way omnibus ANOVA was conducted given there was three within-subject factors (time, information type, and response category) and one between-subjects factor (group). A 2 (group: patients, controls) x 5 (time: 0-11 years, 11-18 years, 18-30 years, 30-55 years and Last Year) x 2 (information type: internal or external) x 5 (response category: Event Details, Place, Time, Perceptual Details, Emotions and Thoughts) mixed-model factorial ANOVA was performed on point scores, with group as the between-subjects factor and time, information type, and response category the repeated measures factors.

There were significant main effects of group ($F_{(1,32)}$ = 13.80, p = 0.00078), time ($F_{(4,128)}$ = 2.58, p = 0.04), information type ($F(1,32)$ = 227.88, p < 0.00001), and response

category ($F_{(4,128)}$ = 4.97, p < 0.00001). Significant interactions were found between time and group ($F_{(4,128)}$ = 5.73, p = 0.00028), information type and group ($F_{(1,32)}$ = 17.85, p = 0.00019), response category and group ($F_{(4,128)}$ = 4.97, p = 0.00094), time and response category ($F_{(16,512)}$ = 3.89, p < 0.00001) and information type and response category ($F_{(4,128)}$ = 64.50, p < 0.0001). Significant three-way interactions were found for time, information type and group ($F_{(4,128)}$ = 2.7, p = 0.033), information type, response category and group ($F_{(4,128)}$ = 10.5, p < 0.0001) and time, information type, and response category ($F_{(16,512)}$ = 4.5, p < 0.0001). Finally, the four-way interaction between group, time, information type, and response category was also significant ($F_{(16,512)}$ = 1.9, p = 0.017). Importantly, however, after correction, the four-way interaction was not significant ($F_{(6.168,197.35)}$ = 1.92, p = 0.078).

Planned comparisons were used between the 0-11 and Last Year period to assess the nature of any temporal gradient in episodic recall for patients. Here, in addition, the scores from the individual response Categories were used to investigate quantitative differences of these measures between epochs. Significance was set at 0.005 using Bonferroni-Holm correction for multiple comparisons.

A significant difference was found for perceptual details ($F_{(1,32)}$ = 17.85, p = 0.0002) and but not event details ($F_{(1,32)}$ = 0.001, p = 0.98), time ($F_{(1,32)}$ = 2.85, p = 0.10), place ($F_{(1,32)}$ = 1.44, p = 0.24) or emotions and thoughts ($F_{(1,32)}$ = 0.018, p = 0.89). Further planned comparisons were undertaken to investigate any significant differences in recall of the components of the AI between the 0-11 and 30-55 period with no significant differences being found for event details ($F_{(1,32)}$ = 0.12, p = 0.91), place ($F_{(1,32)}$ = 4.25, p = 0.048), time ($F_{(1,32)}$ = 2.02, p = 0.17), perceptual details ($F_{(1,32)}$ = 4.91, p = 0.03) or emotions or thoughts ($F_{(1,32)}$ = 0.03, p = 0.86).

5.3.4.3. Autobiographical Interview ratings: seven time points

A 2 (group: patients, controls) x 5 (time: 0-11, 11-18, 18-30, 30-55, Last Year) x 8 (rating: place, time, perception, emotions and thoughts, Autobiographical Memory Interview, time integration and episodic vividness) mixed-model factorial ANOVA was performed, with group as the between-subjects factor and time and rating as the within-subjects repeated-measures factors.

There was a main effect of group ($F_{(1,32)}$ = 21, p < 0.001) and rating ($F_{(6,192)}$ = 162.8, p < 0.001), but not time ($F_{(4,128)}$ = 1, p = 0.396). Significant interactions terms were found for time and group ($F_{(4,128)}$ = 2.8, p = 0.029), rating and group ($F_{(6,192)}$ = 20.7, p < 0.001) and rating and time ($F_{(24,768)}$ = 2.42, p < 0.001). The three-way interaction of group, time and rating was significant ($F_{(24,768)}$ = 1.7, p = 0.021).

Once again, to assess for the presence of a temporal gradient contained in the ratings scores, planned comparisons were undertaken for the rating categories thought to be most episodic in nature: perceptual rating, emotional rating, AMI and episodic richness. The significance level was set at 0.0125 via Holm-Bonferroni correction. These analyses found no differences for perceptual rating ($F_{(1,32)}$ = 5.78, p = 0.02), thoughts and emotions ($F_{(1,32)}$ = 0.31, p = 0.58), AMI score ($F_{(1,32)}$ = 3.35, p = 0.077) or episodic richness ($F_{(1,32)}$ = 0.86, p = 0.36).

Figure 5.5. Patient group mean scores for the standard administration of the Autobiographical Interview, according to response categories (event details, time, place, perceptual details, and thoughts and emotions). This is for both (A) internal, and (B) external details.

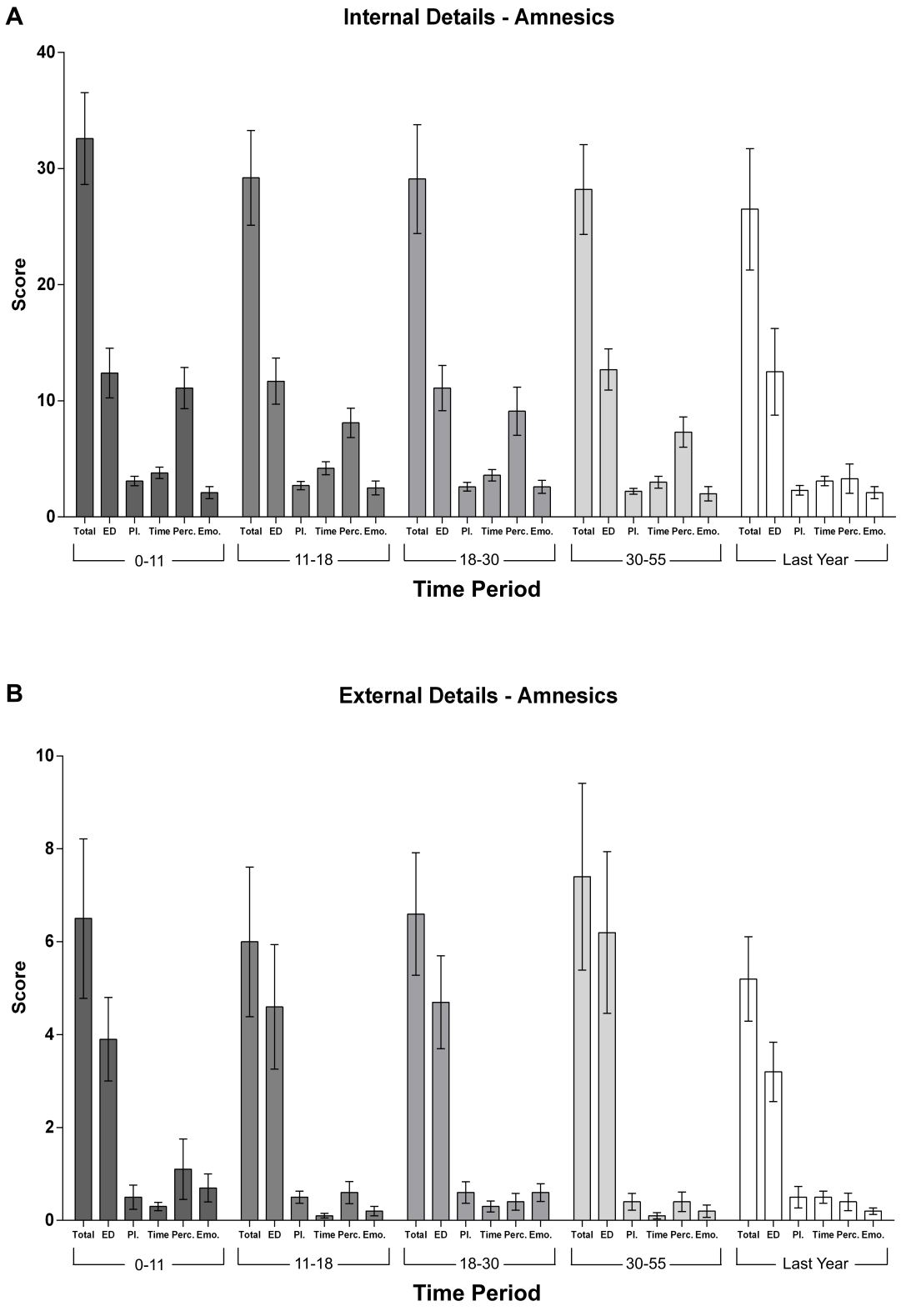
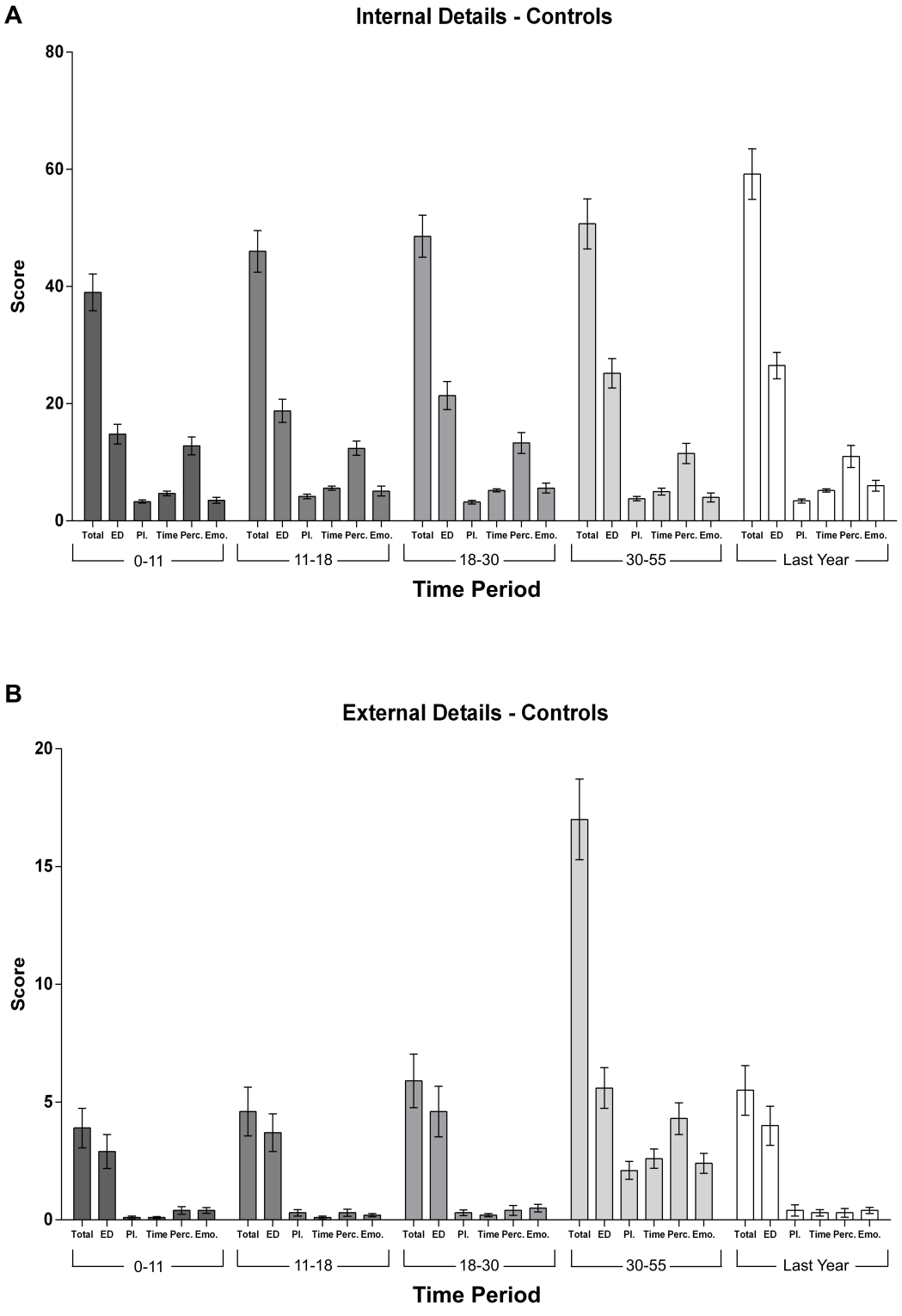


Figure 5.6. Control group mean scores for the standard administration of the Autobiographical Interview, according to response categories (event details, time, place, perceptual details, and thoughts and emotions). This is for both (A) internal, and (B) external details.



5.4. General discussion

This chapter examined whether it was possible to sample recent and remote episodic memories from five (n = 17), or seven (n = 11) time points in VGKC-complex LE patients using the Autobiographical Interview. There are several novel findings that emerge from this data.

First, patients also demonstrated an absence of a temporal gradient for internal detail recall between those memories conceptualized by the SMC to be more dependent upon the hippocampus (i.e. Last Year and Five Years before illness) and those memories that are not (i.e. 11-18 and 18-30).

Second, the results from the AI revealed that patients and age-matched controls have similar levels of internal detail performance for their most remote memories (i.e., 0-11), but there was significant impairment in the amnesic group on a near decade-by-decade basis thereafter for both the standard and modified administration of the AI.
Third, exploratory analysis of the response categories of the AI demonstrated that, for these VGKC-complex LE patients at least, the observed amnesia might be, in part, due to a reduction in internal perceptual detail score.

Third, external detail recall was similar in patients and controls across for both the standard and extended administration of the AI.

5.4.1. Hippocampal contributions to retrograde episodic memory

The principal finding, repeated across both the standard and extended administration of the AI, is that patients' show a significantly reduced quantity of internal detail score across every epoch tested except the 0-11 epoch. Moreover, no improvement in internal detail recall was found the more remote the memory became from the time of illness. These accord with two previous studies with patients with MTL lesions. In the first, Steinvorth et al., (2005) found that HM had internal and external detail deficits for the 0-11, 18-35, 36-55 and Last Year epochs of the standard AI, but normal internal and external performance for 11-18 epoch. The authors raised concern over the validity of this memory, given that it appeared to be an amalgamation of several events (Steinvorth

et al., 2005). HM's performance should also be tempered by the fact that his surgery was undertaken at the age of 27, and so the test epochs 36-55 and Last Year could be considered as a failure to acquire new anterograde episodic memories. WR had deficits confined to internal detail recall across all epochs tested.

The patients reported here, when considered as a group, were always able to retrieve internal details for each epoch (between 20 and 30 points), whereas both WR and HM scored fewer than 10 points for their memories. For WR and HM, the authors interpreted the differences in internal and external detail score as qualitative differences in temporal lobe damage pathology as found on MRI. The only MTL structures intact in HM were the ventral PRC and PHC bilaterally, whereas WR had the posterior right hippocampus, PHG, right ERC, left anterior hippocampus and left ERC intact (Steinvorth et al., 2005), suggesting that more extensive damage to the MTL is needed to impair external detail performance, but more focal lesions preferentially impairs internal detail retrieval - a finding that appears to be consistent across 147 cases of hippocampal amnesia (Spiers et al., 2001).

The second study Rosenbaum et al., (2008) found that two patients with extensive extra-MTL damage (DA, RG) were less impaired (although still only generating 20-30 points per epoch) at internal detail generation than two patients (SJ and CB, 10-20 points per epoch) who had more focal MTL damage. External detail points were only different in the immediately pre- and ongoing post-morbid period. Differences between these two groups were again interpreted on the basis of anatomical differences, whereby focal MTL lesions produce preferential deficits in internal detail generation. Control performance was largely comparable across all studies.

The divergence in the magnitude of internal detail generation between this study (20-30 per epoch) and others (10-20) suggests that, whilst still impaired, our patients are not as amnestic as these others. Several reasons may underlie this discrepancy. As seen in Rosenbaum et al., (2008), lesser degrees of MTL damage is associated with internal generation performance in the region of 20-30 points. Should the damage extend further into the neocortex (or perhaps even just the ERC or PRC) then greater deficits in internal detail generation should be seen (Rosenbaum et al., 2008).

However, the present data arise from a single aetiology, VGKC-complex LE, where it can be reasonably assumed that the same pathological process has occurred in all participants. Automated volumetric imaging (Finke et al., 2013; Wagner et al., 2014) (although see Irani et al., 2013; Schott et al., 2003), longitudinal neuropsychometric assessment (Butler et al., 2014; Frisch et al., 2013, although see (Bettcher et al., 2014) and pathological studies (Buckley et al., 2001; Khan et al., 2009; Park et al., 2007; Dunstan and Winer, 2006) suggest that VGKC-complex LE is confined to the hippocampus and amygdala (and not the other MTL structures). Therefore, one reasonable assumption would be that this magnitude of pathology seen in HM, WR, SJ and CB would not be seen our patients with putatively such focal hippocampal lesions. Indeed, given the nature of VGKC-complex LE it could be suggested that this is an entirely different model of MTL pathology represented by these other patients, especially at a group level.

By contrast, another research group administered the AI to three patients with MTL-restricted pathology, and two with more extensive MTL pathology (Kirwan et al., 2008). They found that the hippocampal group had internal detail retrieval deficits limited to the Last Year epoch (scoring <20 points, but critically 50+ points for the 0-11, 12-17, 18-35, 36-55 epochs), whereas the MTL group had deficits in the 30-55 and Last Year epochs (scoring <20 points, compared to >40 points for the 0-11, 12-17 and 18-35 epochs). Control performance was once again comparable to those reported here. However, the pattern of performance in their patients are at variance with those reported data, particularly as internal detail generation reaches control performance within one epoch for the hippocampal group and two for the MTL lesion group. *Post hoc* tests reported by Kirwan et al., (2008) found that a group x time interaction reflected poor performance by the patient groups in the Last Year epoch, and that hippocampal patients actually performed better in the 30-55 period than either the controls or MTL patients. By extending the standard administration of the AI we were able to increase the granularity of assessment across the lifetime of a patient, and the same deficits in internal details were observed. This suggests that the same pathological process to retrieval occurs equally across epochs and hence does not vary according to the age of the memory, the 0-11 epoch excepted.

Discrepancies of this nature have usually either been interpreted as methodological (see below), or, attributed to an incomplete anatomical description – the

latter is a more compelling potential issue here. However, as described throughout this thesis there are, as yet, no clinical reasons to suspect that VGKC-complex LE has differential pathological profiles given the substantial literature available describing the clinical course of this disease (Bataller et al., 2007; Bien et al., 2007; Buckley et al., 2001; Harrower et al., 2006; Irani et al., 2008; Jacob et al., 2008; Schott et al., 2003; Thieben et al., 2004; Vincent et al., 2004; Wong et al., 2010). Indeed, the present study sought to reduce the confounding factors of differing aetiologies of hippocampal pathology that normally comprise hippocampal lesion groups by only using patients with a single aetiology (Bayley et al., 2005; Bayley et al., 2003; Cipolotti et al., 2001; Rosenbaum et al., 2009; Rosenbaum et al., 2005; Rosenbaum et al., 2008).

Previous discrepancies in measures of remote episodic memory have also been described due to methodological differences (i.e., between those who used a modified Crovitz approach (Bayley et al., 2003) and those who utilize the AI (Rosenbaum et al., 2008; Steinvorth et al., 2005). Studies usually cited to corroborate the temporal gradient in episodic memory loss following MTL lesions have often utilized either the AMI or a similar three-point marking scheme (Bright et al., 2006; Eslinger, 1998). In these patients, the AMI revealed no evidence of an episodic amnesia, at clear variance with the present findings from the AI. Hence, a key concern with these cited data (Bright et al., 2006; Eslinger, 1998) is that they potentially suffer from scoring episodic recall on a 0-3 scale, and thereby introduce insensitivity to pathology, due to a potential ceiling effect in both patient and control performance (Levine et al., 2002). Had the AI been used, other results may potentially have emerged. However, the study by (Kirwan et al., 2008) used the AI, and, as a consequence, their findings are hard to reconcile with the present study.

At this stage, the most parsimonious interpretation of these data would be that in a group of patients with the same disease, with strong *a priori* assumptions for MTL specificity, VGKC-complex LE is associated with the absence of a temporal gradient of episodic memory performance across the lifetime of a participant, and stands in disagreement with the predictions underlying the SMC.

It is worthwhile noting from Chapter 4 that this patient cohort, as a group average, have supranormal intelligence as measured by standardized neuropsychometry. No such neuropsychological testing was undertaken for the controls. Formal links

between retrograde episodic memory performance, as measured by the AI, and intelligence has not been reported in the literature. It is though generally assumed that intelligence has a significant modifying effect on memory performance across several neuropsychological tests (Salthouse, 2004). One study found no correlations between IQ and autobiographical memory performance on a task that is similar to the Crovitz task outlined above (the Autobiographical Memory Test; Birch, 2007). These authors found that in a group of depressed adults that IQ did not correlate with the ability to recall specific autobiographical memories. It should be noted as well that the Autobiographical Memory Test simply categorises memories into four categories according to the quality of the memory recalled (i.e., specific, extended if >24 hours, semantic facts, no memory recalled). This task does not provide a quantitative measure of memory performance. One other study does describe a correlation between intelligence and episodic memory (Herlitz, 2002) but this study formalised a word list as the episodic memory task, and so is not directly comparable to the work presented in this chapter. What remains striking is that this supranormal population of patients still perform significantly below that of age- and background-matched controls, for whom it is assumed are not significantly more intelligent than the patients, suggesting that the patients' supranormal intelligence does not ameliorate their episodic memory deficits.

5.4.2. Hippocampal contributions to the most remote episodic memory

It is notable that in spite of the significant differences between patients and controls across all epochs from 11-18 up to Last Year, that there were no significant differences between patients and controls for the 0-11 period. This finding agrees with two studies, one using the AI (Kirwan et al., 2008), and one using the modified-Crovitz technique to further probe remote memories that scored three on their rating scale (Bayley et al., 2003). These studies all included hippocampal and MTL lesion groups to gauge the relative contributions of these regions to the recall of remote episodic memories.

The present study found that both patients and controls retrieved between 30-40 internal detail points for this epoch, comparable to the 40-60 found by Kirwan et al., (2008), whereas it exceeded the values - 15-25 reported by Bayley et al., (2003) (although a different marking technique was employed). The authors interpreted the equivalent

quantitative performances of patients with hippocampal and MTL lesions to healthy controls as sufficient evidence that a temporal gradient of episodic memory was present, and hence supportive for the SMC. It should be noted that Bayley et al., (2003) only probed remote memories limited to the first 20 years of life, and then only probed those memories deemed well-formed enough to score three on a subjective rating scale. It is conceivable that this method led to a bias in the quality of memory eventually scored in more detail. However, an abiding issues with the AI is that it is based only on the retrieval of one memory per epoch, and so conceivably patients may end up not retrieving their best memory in the AI (although care is taken to minimse this risk).

It is notable that after this 0-11 epoch that controls and patients diverge, where controls obtain more internal detail scores at every other epoch (including those universally agreed to be episodic such as Five years before illness and Last Year; Nadel and Moscovitch, 1997; Squire et al., 2001; Squire et al., 2004), whereas patients generated fewer internal detail scores. This suggests that there is something different about the quantity of internal details retrievable at this 0-11 epoch. The control data reported here accord with a study describing decreased internal detail scores on the AI for older adults (73.5±5.77, range: 66-89) recalling their most remote events, suggesting that these memories may not be retrieved with the same re-experiential detail as those that are more recent (Levine et al., 2002). Our controls (mean age: 64.7±1.64; range: 46-76) and patients (mean age: 62.3±2.23, age range 42-80) produced a similar number of internal details as the elderly subjects in the aforementioned study. In comparing control and patient response performance as a function of response category (Figure 5.2 and 5.3, but specifically Figures 5.5 and 5.6), it was possible to discern that the general pattern of internal response category is likewise similar. Therefore, it could be argued that the non-significance reflects poorer control performance at recalling internal detail points, and hence a less quantitatively re-experiential memory. This suggests that that perhaps what was been reported by Bayley et al., (2003), and found in the 0-11 in the current study, are those memories that may have undergone transformation, and as such may no longer be considered truly episodic memories (Winocur et al., 2010). This view is less likely to be the case with the data reported by (Kirwan et al., 2008), because it appears that control and patient performance only diverge at either the 36-55 or Last Year epochs.

These results for the 0-11 period also do not agree with other studies in MTL lesion patients. It is notable that WR and HM both have near floor performance for this epoch (Steinvorth et al., 2005), as were SJ and CB (Rosenbaum et al., 2008), although CB did perform better following the specific probe. However, the two patients with extra-MTL lesions (RG, DA) performed at a similar level to the patients reported here (30-40 internal details recalled), which suggests that the patients reported here are performing comparatively equally with those not known to have extensive MTL pathology. In summary, it appears reasonable when comparing across these studies, to suggest that from a behavioural perspective (i.e., the number of internal detail points accrued), that the current patients behave similarly to those patients previously known to have lesions to the hippocampus with intact surrounding MTL structures. It is the integrity of these extra-hippocampal regions are purported to support the impoverished but episodic-like memory associated with the 0-11 period (see Section 5.1.3.5).

5.4.3. Perceptual richness differences between remote and recent episodic memories

For the first time in any systematic temporal assessment of retrograde episodic memory recall in patients and controls, it has been possible to test whether or not there are numerical differences in the response categories within each memory generated on the AI (although this was only achievable for the standard, and not extended administration). The contrasts employed compared internal detail response category performance between those memories conceptually most dependent upon the hippocampus (i.e., those from the most recent five years, Nadel and Moscovitch, 1997; Squire et al., 2004), and those, which according to the SMC, would be the least hippocampal-dependent (i.e., more remote memories; Squire et al., 2004). These data showed that in patients there was evidence that the measure of perceptual details was significantly different between 0-11 and the Last Year, but the other categories appeared invariant across these epochs. This suggests that quantitative differences in perceptual details underlie the differences between those memories conceptually most dependent upon the hippocampus and those that are least.

Previously, patients with medial temporal lobe epilepsy (mTLE), a disease affecting the MTL, were asked to recall either autobiographical memories or memories

arising from watching a film clip with multiple perceptual features, in as much detail as possible (St-Laurent et al., 2014). The authors found that controls were able to recall a significantly greater number of perceptual details in both the autobiographical memory and story phases of the study than patients, but that narrative structure and recall was the same across the groups (St-Laurent et al., 2014). These results echo those previously obtained in a similar patient group that found in a modified version of the AI, mTLE patients delivered perceptually impoverished episodic accounts (St-Laurent et al., 2009).

Both of these studies collapsed across time to produce a single episodic memory score, thereby losing the temporal granularity reported in the present study. In a case of developmental amnesia (due to peripartum anoxia causing hippocampal hypoxic damage), patient Jon was unable to perceive previous episodic memories, although the narrative structure of these memories remained well-formed (Maguire et al., 2010b), in keeping with the present findings. One problem with the data in Maguire et al., (2010b) is that all these memories were obtained in the post-morbid period; however, taking the general response category information into account, and the results from the collapsed internal detail score, it appears that these anterograde memories are the same mnemonic construct as the retrograde memories.

It is also useful to interpret these data in light of fMRI experiments in healthy controls. As noted earlier, it has been theorized that internal detail recollection in the 0-11 epoch could be independent of the hippocampus and that memories from this period have numerically greater perceptual details than memories arising from the Last Year. One account of the MTL's contribution to episodic memories is that it integrates the visual details stored in higher order cortical areas (Greenberg et al., 2005), which would suggest that damage to the MTL should disrupt visual percept integration, a feature known to contribute to the self-rated vividness and imageability rating (Rubin et al., 2003). Therefore perceptual scores emerging from the AI should provide an objective measure of this pathology (St-Laurent et al., 2009). This pattern was observed within our patients; specifically, there was a diminution in internal perceptual details in those memories that are hippocampal-dependent, compared to those that are not (i.e., remote memories).

In healthy participants, hippocampal activity on fMRI has also been shown to correlate with ratings of vividness (Gilboa et al., 2004; Rabin et al., 2010), the use of imagery in those memories (Andrews-Hanna et al., 2010) and the intensity of re-experiencing (St Jacques et al., 2012; but see Daselaar et al., 2008) during the retrieval of episodic memories. Our results are not direct analogous with these fMRI data, but taking into account the behavioural similarity between the mTLE group and our patient group, and the integrative role of the hippocampus in perceptual recall during episodic recall, this suggests that the hippocampus is needed for the recall of perceptual details across the 11-18 to Last Year epochs, with the 0-11 period potentially becoming a hippocampal-independent memory.

Once again, it should also be noted that controls had significantly more internal details recollected after the 0-11 period, suggesting that this period is associated with less internal detail recall compared to the subsequent epochs. Given the observed dissociation in our patients between this 0-11 period and the Last Year, and the fact the Last Year is unequivocally hippocampally-dependent, it is difficult to reconcile why this period is more robust that the other epochs tested. It could be suggested that the damage in our patients extends beyond just the MTL; however, given the numerical similarity in internal detail performance across other studies with focal hippocampal lesions, and the fact that performance is not at floor elsewhere, suggests that this is unlikely. On these grounds, the results reported here suggest that the hippocampus is required for the perceptual recollection of memories, no matter how remote from the time of encoding and that the most remote memories are not associated with higher amounts of perceptual richness, and that the 0-11 period is not a truly episodic memory.

5.4.4. External detail recall across the lifetime is unimpaired following VGKC-complex LE

The AI is unique in that it supports episodic and semantic retrieval concurrently, and that it is designed to separate them after the data has been collected (Levine et al., 2002), unlike the AMI (Kopelman, 1994). This is done to heighten retrieval support, such that patients can use personal semantic knowledge to retrieve as many internal details as possible (Levine et al., 2002). The data here show that there is no numerical difference in external detail/personal semantic performance between patients and controls in either

the AI or AMI (see also Section 4.3.3). Therefore, the findings are in agreement with several studies that found the same results after administering the AI to patients with MTL lesions (Rosenbaum et al., 2008; Steinvorth et al., 2005). One exception to this was HM who had near floor external detail performance, a finding arguably related to his more extensive anatomical damage (Steinvorth et al., 2005).

Kirwan et al., (2008) found that external detail recall was reduced for the Last Year in hippocampal lesion patients and for the 36-55 and Last Year epoch in MTL lesion patients. This was not seen in either our study or those cited above – prior studies generally describe any external detail loss from premorbid memories as being conducive with extra-MTL pathology (Rosenbaum et al., 2008; Steinvorth et al., 2005). It has been previously suggested that MTL plays a more unitary role in supporting personal semantic memory, such that one would expect to see a temporal gradient with greater performance occurring for those memories remote from the time of hippocampal injury (Squire, 1992a). The results of Kirwan et al., (2008) would appear to agree with this. However, this predicted temporal gradient of personal semantic memory amnesia is not seen across other studies including this one. These findings accord well with theories concerning the neural representation of personal semantic memory and specifically the neocortical regions of the temporal lobe (Cernak and O'Connor, 1983; Damasio et al., 1985; Greenberg and Verfaellie, 2010; Warrington and Duchen, 1992), and especially the PHC (Martinelli et al., 2013). Should reduced retrieval be observed (as with HM), then this is probably reflects a more extensive lesion into the PHC.

The focus of the AI is episodic and not semantic retrieval, and therefore it is difficult to generalize across these results in terms of intact personal semantic retrieval. In this regard, the AMI is a more useful in assessing the differences between patients and controls, although it does limit this retrieval to three very broad test epochs (i.e., Childhood, Adulthood, Recent). With these caveats in place, the present AMI data appear to suggest that an intact hippocampus is not required to support the retrieval of personal semantic information across the lifespan.

5.4.5. Implications for the transformation hypothesis

The finding of a null difference in internal detail performance between patients and controls for the 0-11 epoch, for both the standard and extended version of the AI, is

striking. Immediately following this period, internal detail performance diverges and significant differences across patients and controls are sustained for every other epoch, denoting that this memory is quantitatively poorer than less remote memories. Moreover, patients retrieve significantly more internal details in this epoch than at any other stage, including those conceptually most reliant upon the hippocampus for retrieval (Last Year and Five Years). Analysis of the response categories suggest this is difference in internal score arises from reductions in perceptual details. This is not to ascribe episodic re-experiencing to perceptual richness, but it is certainly a key component of it (Conway, 2009; Moscovitch et al., 2005).

Previous fMRI experiments have shown found that the subjective sense of remembering and re-experiencing the original perceptual scene of the memory are associated with increased BOLD signal activity within the MTL, no matter the age of the memory (Piolino et al., 2009). Remote events, with a reduced subjective sense of re-experiencing and perceptual richness, were preferentially associated with activity in the right superior temporal pole and superior/middle temporal gyrus (Piolino et al., 2009). In fact, this pattern of increasing temporal lobe activity was associated with increasing age and reduced sense of re-experiencing of the memory (Piolino et al., 2009), suggesting that as the memories become semanticised they rely more on the surrounding temporal lobe cortex, with the re-experiential memories being reliant on the hippocampus (Piolino et al., 2009).

These data provide a notional anatomical and functional explanation of the results reported in the patients. The 0-11 memories could rely entirely upon the other temporal lobe structures, and so, whilst associated with a diminished quantity of internal details, are still quantitatively richer than patients' later memories. However, more recent memories are associated with diminished perceptual details and subjective sense of re-experiencing because they are still reliant upon the hippocampus for its full expression, a phenomenon clearly evident in the controls (Piolino et al., 2009). This view, that diminished internal perceptual detail recall could arise from hippocampal dysfunction, is tangentially corroborated by studies showing that the hippocampus is also central to scene construction and imagining the future; two tasks requiring the assemblage and retrieval of object and spatial details into complex scenes and events (Addis et al., 2011; Hassabis et al., 2007; Hassabis and Maguire, 2007, 2009; Schacter and Addis, 2009).

Therefore the hippocampus is not solely representing the memory *per se*, but rather assembling the key, in this case, perceptual details pertinent to episodic recall.

5.4.6. Implications of the current results for the standard model of consolidation and multiple-trace theory

According to both the SMC and MTT, the hippocampus is central to the acquisition and initial consolidation of episodic memories (Nadel and Moscovitch, 1997; Squire et al., 2001; Squire et al., 2004) for a period of at least five years (Smith et al., 2013). The monophasic nature of VGKC-complex LE made it is possible to date when the illness occurred, and thence to retrieve memories occurring within this critical five-year period. These most vulnerable memories were used as baselines for episodic dysfunction. The SMC and MTT also make opposing claims about the temporal role of the hippocampus in episodic retrieval. The AI allows self-generated episodic memories to be quantified, whereby higher point scores are associated with a greater fidelity of re-experiential content (Bayley et al., 2005; Bayley et al., 2003; Kirwan et al., 2008; Levine et al., 2002; Rosenbaum et al., 2008).

The principal finding arising from the current study was the absence of a temporal gradient of internal detail recall for patients across all epochs tested in both the standard and extended administrations of the AI, the 0-11 period aside. Therefore the general pattern of performance as a function of time is more in keeping with the MTT, rather than the SMC (Nadel and Moscovitch, 1997; Rosenbaum et al., 2008; Steinvorth et al., 2005). The SMC framework also usually assumes a more unitary perspective for the temporal role of the hippocampus in all forms of declarative memory, whereby all forms of declarative memory (e.g., episodic, personal semantic and public semantic memories) would be universally degraded after hippocampal damage, but should recover to normality the more distant they were acquired from the time of injury (Bayley et al., 2003; Kirwan et al., 2008; Squire and Alvarez, 1995; Squire et al., 2004). The current findings and other studies stand in direct opposition to this view. This study has found dissociation of personal semantic and episodic memory (see also the AMI, Section 4.3.3). By contrast, under the MTT, episodic memories should be more severely impaired than either type of semantic memory (Moscovitch and Nadel, 1998; Moscovitch et al., 2005; Nadel and Moscovitch, 1997).

Proponents of the SMC would argue that there is hidden pathology outwith the MTL region. However, it should be noted that our patients retrieved a similar number of internal details as patients in other studies with focal hippocampal pathology (Kirwan et al., 2008), and those with cortical lesions outside the MTL region (Rosenbaum et al., 2008). The case of HM is instructive in this instance: he had documented lesions extending beyond the MTL structures into the temporal neocortex, which were associated with extensive retrieval deficits in both internal and external details from the AI, a pattern that would be more in keeping with more extensive damage to the temporal lobe neocortex. Previously though, it had been argued that HM's performance. This pattern is arguably more in keeping with more extensive temporal cortical lesions. However, a further interpretation of these results suggested that HM's diminished performance on the AI was a consequence of ageing and its associated lesions to the temporal lobe neocortex (Kirwan et al., 2008). It should be noted, however, the site and nature of these lesions is never made entirely clear (other than being 'white matter lesions'), but rather are presumed to have been present (Kirwan et al., 2008).

But the current results are not entirely in agreement with the MTT either. The MTT would predict that the quantitative scores for the 0-11 internal scores should be numerical similar, not different, for memories arising from the other epochs because despite being well-consolidated due to multiple recollections within the hippocampus, the hippocampal pathology would prevent further generation of internal details. For instance, in those reporting results in keeping with the MTT, they find near floor performance in internal detail recall across all tested epochs, except where MTL involvement was minimal (Rosenbaum et al., 2008; Steinvorth et al., 2005). Again the current patients not only retrieved more details from the 0-11 period but the others as well, suggesting they still had access to the aspects of episodic retrieval mediated by distance cortical sites (Piolino et al., 2009; Poppenk et al., 2013; Poppenk and Moscovitch, 2011; St-Laurent et al., 2014; St-Laurent et al., 2009). Reconciliation of these data is difficult, other than proposing an anatomical explanation – many of the worst performing patients had damage to parts of the MTL such as the PRC and ERC, perhaps degrading the quality of information entering the hippocampus for recall.

5.4.7. Constructional accounts of episodic memory

Despite the significant differences in the temporal role of the hippocampus in episodic retrieval, both the SMC and the MTT ascribe some level of consolidation or storage of memories occurs in the hippocampus itself. However, retrograde memory recall is not a reduplicative process. During learning, the constituent features of a memory are widely distributed across a network (Schacter and Addis, 2007) and memory retrieval involves a pattern completion process, whereby the MTL structures bind together the distributed perceptual and conceptual features that comprise an event, so that it might be re-experienced (Marr, 1971; Norman and O'Reilly, 2003). Under this view, the central nexus region that binds these features at encoding subsequently becomes the site of pattern completion. Furthermore, bound episodes must be kept separate from one another within the neural representations of memory. If episodes overlap extensively with one another, individuals may recall the general similarities or gist shared by them (Brainerd and Reyna, 1998), but fail to remember distinctive item-specific information that distinguishes one episode from another (Schacter and Addis, 2007). This process has been referred to as pattern separation, and is another key process that must occur at encoding. The hippocampus has been identified in animal studies as a candidate region supporting pattern completion (Manns and Eichenbaum, 2006; Rolls, 2013).

5.4.7.1. The Binding of Items and Context Model

One recently proposed computational model of hippocampal function has sought to unite these reconstructive abilities of the hippocampal and MTL function in memory. The Binding of Items and Context (BIC; Diana et al., 2007) model posits that the perirhinal cortex (PRC) receives information concerning the qualities of the objects to be remembered (i.e. "who and what" information), and the PHC complex receives spatial information concerning the context and location of those objects (i.e. "where and when" information; (Eichenbaum et al., 2007)). The PRC and PHC then project to the ERC and thence the hippocampus proper, where these items and contexts are bound into a single representation (Diana et al., 2007). The basic prediction from the BIC and other related associational frameworks /formal models (Aggleton and Brown, 1999; Cohen and Eichenbaum, 1993) is that the hippocampus supports the recollection of the contextual information associated with the item, and that for simple item recognition the

PRC may suffice. Evidence from both human (Vann et al., 2009), and animal work (Fortin et al., 2004) appears to be consistent with this prediction. It should be noted, however, that these models only generally speak to the acquisition and recollection of anterograde memories, and not retrograde memories. Despite this, the similarity of hippocampal function across multiple cognitive processes is compelling and these models may also predict a similar function in retrograde episodic memory as well, particularly given the evidence cited concerning the role of the hippocampus in supporting perceptual aspects of episodic memories in disease (Maguire et al., 2010b; St-Laurent et al., 2014; St-Laurent et al., 2009) and fMRI paradigms (Andrews-Hanna et al., 2010; Gilboa et al., 2004; Greenberg et al., 2005; Rabin et al., 2010; St Jacques et al., 2012).

Constructional models such as the BIC or constructional model would predict that because the neural apparatus mediating the binding of items and contexts is damaged in hippocampal lesions, then there should be a flat gradient and hence no differences between recent and remote memories within the lesion group (Ranganath, 2010). In the case of comparisons to age-matched healthy controls, it would be expected that patients with focal hippocampal lesions would be impaired globally across all time epochs, representative of a general failure of functions supported by the hippocampus in cognition. Any recall associated is likely to be supported by the surrounding temporal neocortex (like the ERC and PRC), but would lack rich re-experiential content (Ranganath, 2010), a pattern observed in the current data.

The model best supported by the effect of the temporal variable on performance, and with more general interpretations of the hippocampal contributions to memory and cognition is the BIC (Diana et al., 2008; Ranganath, 2010). The data presented above are also in agreement with models of episodic memory that posit a reconstructive role for the hippocampus in retrograde and anterograde retrieval (Greenberg et al., 2005; Piolino et al., 2009; St-Laurent et al., 2014; St-Laurent et al., 2009), whereby the hippocampus is central to the associations required to recreate the richly re-experiential episodic retrieval (Maguire et al., 2010a; Ranganath, 2010; Schacter and Addis, 2009; Yonelinas et al., 2010).

5.4.8. Limitations

There are several limitations with this study. Firstly, is the question of whether these experiences, for both patients and controls, are truly autonoetic in nature. Previous work has shown that patients with AD not only had reduced perceptual details of their retrograde memories, but also reduced autonoesis when compared to controls and patients with semantic dementia (Piolino et al., 2003). Autonoesis was operationalized in this study according to a Remember/Know paradigm. Participants were asked whether they could indicate whether they could consciously recollect the content, place and date for the event in questions (i.e. remember it), or whether they just 'knew' the event happened. In order to assess the autonoetic component of this memory, the authors then asked participants to justify their responses according the number of phenomenological details obtained either during memory retrieval or during direct questioning, with a rater giving them a score out of 4 (therefore a maximum of 12 per memory). This derived a 'justified remember' response (Piolino et al., 2003). This approach is instructive, but again relies on subjective ratings derived by an external assessor, as well as leading to a potential ceiling effect in the measure.

By comparison, the AI gives a more objective sense of the autonoetic experience through the number of details given in those categories more first person reliant (e.g. thoughts, emotions, perceptual details). However, the AI is limited in its operationalization of time and place, diminishing the number of points realistically available for these measures. For example, to say that event happened at 10.30 in the morning of Monday 15th January 2015 would score five internal time marks, but this could be remembered semantically, and so serves no distinction between controls and patients. It might be the case that these time and place data are excluded from analysis because they potentially lack the ability to discriminate between truly episodic memories from those that are more semantically supported.

Secondly, the age range of the patients used in this study is broad. Whilst this is useful in the standard administration of the AI, it becomes more problematic when trying to gauge the re-experiential fidelity of more remote memories, because a memory from the 0-11 period would only be 40 years old in a 50 subject, but 50+ years in someone older than 60. Collapsing across age groups like this diminishes the granularity

available by our extended administration of the AI. One method of resolution is to try and only analyse those patients of a similar age (i.e., within one decade of another) as these memories will be roughly the same age. Another method would be to analyse the memories according to their age (i.e., Last Year, within the last 5 years, 10-20 years ago etc.). It has been previously shown that ageing is associated with diminished mnemonic re-experiencing (Java, 1996; Norman and Schacter, 1997), and episodic recall (McIntyre and Craik, 1987; Spencer and Raz, 1995). Previous work has also shown that there is an age-related decline in the ability to retrieve explicit, effortful and unstructured memories (Zacks et al., 2000). These data suggest therefore that comparing a 15-year-old memory from a 65-year-old participant to that of a 35-year-old is likely to introduce confounding factors into the analysis. Therefore, increasing the number of subjects of a similar age is probably the best way of improving this aspect of the study.

Thirdly, most studies administering the AI to hippocampal lesion groups try to obtain a control to patient ratio of 2:1; this has not been achieved in this chapter for practical reasons. This has usually been undertaken in order to increase the statistical power for detecting differences in means in such small patient sample sizes. However, the current study utilizes a patient size twice as large as those previously reported, all in a single aetiology (Kirwan et al., 2008; Rosenbaum et al., 2008; Steinvorth et al., 2005), and as such moves this study from a case-control methodology to a case series study. Indeed, similar studies using a patient group as large as this one tend to use a patient to control ratio of 1:1 (Barnabe et al., 2012; St-Laurent et al., 2009; St-Laurent et al., 2011; Tramoni et al., 2012) or less (Bastin et al., 2013). There is also no *a priori* reason to suspect that the magnitude difference reported between patients and controls here would disappear with an increased control size. So whilst a control to patient ratio of 2:1 is desirable, it does not appear to fundamentally negate the reported results.

Fourthly, the patient population was also heterogeneous in performance. This being the case it could be argued that the case series level information obtained in the current study is lost due to the range of patient performance. However, far from being a limitation, this could be overcome by trying to further subdivide the patients according to internal detail performance, and use anatomical volumes and/or AI response categories to characterize this difference. In a previous critique of HM's AI performance, (Kirwan et al., 2008) cited an anatomical study of HM that found evidence of global

cortical thinning and evidence of white matter disease in HM around the time of his AI testing (Salat et al., 2006). They suggest, without offering mechanistic explanations, that this would impair cognition and retrieval. It could be argued that cortical thinning in some patients or local hippocampal subfield losses might provide anatomical covariates for the heterogeneous behavioural performance of the patients in the current study. Longitudinal follow-up with both the AI and imaging would also help any behavioural changes alongside anatomical volume losses with time to assess whether ongoing behavioural impairment is due to hippocampal, MTL or extra-MTL volume loss.

Fifthly, the extended administration of the AI the higher-level interaction of group x time x detail type x response category was not significant. Higher-level interactions are associated with smaller effect sizes, and hence greater power is needed to assess these effect sizes. This can only be achieved either though increasing the number of patients given the number of observations is static within the AI, which can be far from ideal without formal effect size calculations. The degrees of freedom also become difficult to assess when the participant number is too small because the number of explainable variables approaches or exceeds the number of participants in a study and hence a breakdown in the assumptions of parametric analyses.

Sixthly, confabulation remains a problem even after the Haylings results and external corroboration. This could be partially ameliorated by revisiting the memories again with patients after a delay of at least six months, and either repeating the AI again for those same memories or by comparing the general narrative with the transcripts derived from the original experiment.

Finally, this study is a cross-sectional study and assumes that the pathology seen in patients remains static. The recruited patients were considered stable by their referring clinicians and reported a stabilization of the symptoms, and cognitive sequelae following treatment. However, in characterizing this disease group as suitable for experimental memory work, it would be important to perform longitudinal measurements of retrograde memory performance using the AI or a modified measure of it to ensure that the behavioural changes noted in this study are stable across time, or that they are diminished along those seen in normal ageing (Levine et al., 2002), although this would ideally necessitate the use of the same controls.

5.4.9. Future work

There are a number of future experiments that could be used to further the work presented in this chapter. The novelty of this patient group as a model of hippocampal dysfunction is that they all have the same aetiology and hence presumed pathology. This being the case it is possible to use these patients in numbers normally associated with large behavourial and/or fMRI studies (i.e., more than 10). Indeed, their ability to be used across modalities means that it will be possible to combine behavourial tasks within an fMRI setting to image the neural connectivity and activation patterns associated with successful or unsuccessful task completion.

The heterogeneity apparent within the group for internal detail scores could be used to test what measures of an episodic memory degrade with time, say at 1, 3 or 6 months, or what features of an episodic experience are most affected in cases of hippocampal lesions. Three episodic learning events could be devised, using a video paradigm similar to Chadwick et al., (2010), that would be equally weighted across the five features of the AI marking scheme (i.e., event details, time, place, perceptual details and thoughts and emotions). Independent assessors could externally validate these learning events. Patients could then be split into three groups according to the memories to be recalled at 1, 3 and 6 months (i.e., Group 1: 1, 2, 3; Group 2: 2, 3, 1; Group 3: 3, 1, 2). Patients' recollection of these events could be obtained and assessed in a manner similar to the AI, and the response categories assessed across these different memories and time. Given the hippocampus is critically involved in pattern separation and completion), then a further follow up experimental line of research could be to categorise the groups according to high and low pattern separation conditions for particular features (such as event details, events happening close together or further apart; perceptual details, varying the colour of an object central to the events according to different shades of the same colour, or making them entirely different colours). This would hopefully provide conditions under which the different components thought to be central to episodic memory could be investigated alongside more computational accounts of hippocampal function, specifically pattern separation and completion. This sort of experiment has yet to be undertaken in controls, let alone patients.

5.4.10. Conclusion

The Autobiographical Interview, analyzed in the context of the imaging and neuropsychological data from Chapters 3 and 4, demonstrated that patients with chronic VGKC-complex LE demonstrate a temporally extensive episodic amnesia for both the standard and modified administrations. Crucially, these data were obtained from a large cohort of single aetiology patients, more than has been previously examined in previous patient studies using the AI. The data demonstrate that patients accrue the equivalent numbers of internal detail points at each testing epoch, with their earliest memory generally scoring the greatest number of internal details. Overall, this data demonstrates a pattern of behavioural pathology that accords with neither the SMC nor MTT, but rather more holistic models of the hippocampus in mnemonic recall such as the BIC. These retrograde episodic deficits occurred in the context of normal external detail performance, which suggests that personal semantic memory is unaffected after VGKC-complex LE, providing indirect evidence, commensurate with the literature for personal semantic memory, that this is a hippocampal-specific disease. Combined these data suggests that the hippocampus is needed to support retrograde episodic re-experiencing of recent and remote events.

Chapter 6

Development of a standardized test of public event semantic memory, and results from patients with VGKC-complex LE

6.1. Introduction

6.1.1. Personal and public semantic memories are interdependent, yet distinct mnemonic entities

Semantic memory refers to the ability to acquire and recall facts and general knowledge about the world (Eichenbaum and Cohen, 2001; Squire, 1992a; Tulving, 1983). The distinction can also be made between public and personal semantic memory. Public semantic memory is conceptualized as those memories that refer to general knowledge of the world (e.g., that Paris is the capital of France). Public semantic memory can also include those events that have occurred during the extent of a lifetime and are shared by a community (e.g., the moon landing in 1969 or the fall of the Berlin Wall in 1989). Personal semantic memory refers to conceptual knowledge of oneself, and has been identified with a neural substrate that overlaps with general semantic memory (i.e., the neocortex of the temporal lobe; Greenberg and Verfaellie, 2010). The important conceptual distinction, however, between semantic memory and episodic memory is that semantic memories are devoid of the unique contextual and spatiotemporal details that

characterize an episodic event (i.e., re-experiential qualities such as emotions, thoughts, first-person perceptual details, or allocentric spatiotemporal information; Tulving, 1983).

Semantic memories (both personal and public) are thought to be acquired in an episodic fashion (Gabrieli et al., 1988), and, with time, both lose their specific spatiotemporal contextual information, and their re-experiential sense of autonoesis (see Section 5.1.1).

Two predominant views have emerged concerning the neural apparatus supporting both types of semantic memory. The first is a more unitary approach, whereby the medial temporal lobe (MTL) – including the hippocampus and its supporting cortical regions (e.g. the entorhinal, ERC, and perirhinal cortices, PRC) – are needed for both the acquisition and retrieval of recent episodic and semantic memories (Manns and Squire, 2002; Squire and Zola, 1998), but that recall of these both episodic and semantic memories, beyond five-ten year period of consolidation, eventually become independent of the MTL and are, therefore, not dissociable at any time point – that is recent episodic and semantic amnesia should always be observed in cases of MTL lesions. The other states that the hippocampal region is predominantly involved in supporting episodic memory recall, but the adjacent cortical structures are critical to semantic memory support and retrieval (Brown and Aggleton, 2001; Tulving and Markowitsch, 1998; Yonelinas, 2002). According to this view, both episodic and semantic memories are dissociable mnemonic functions.

Chapters 4 and 5 have shown that dissociations between remote and recent episodic and personal semantic memories are possible, at least in the case of VGKC-complex LE. Therefore it is also necessary to consider the neuropsychological, and functional magnetic resonance imaging (fMRI), to assess whether public semantic memory is dissociable from personal semantic and episodic memories following VGKC-complex LE.

6.1.1.1. Neuropsychological evidence for dissociations between episodic and semantic memory

Neuropsychological studies demonstrate that the relationship between episodic and semantic memories is complicated, showing both interdependence and

independence depending on the methods used to probe experimentally. For instance, in a diverse group of amnesic patients, personal semantic memory performance correlated with public semantic memory performance (Kopelman, 1989; Kopelman et al., 1989). In Alzheimer's disease (AD), episodic memory performance and public semantic memory performance have been found to be independent predictors of personal semantic memory performance (Kazui et al., 2003). However, episodic memories, and personal and public semantic memories can also be dissociated from one another: patients with left lateralized temporal lobe epilepsy (TLE) appear to have deficits in retrieving public semantic information, but not episodic or personal semantic memory (Barr et al., 1990; Bergin et al., 2000; Lah et al., 2004; Voltzenlogel et al., 2006), something seen in other aetiologies of amnesia (Cernak and O'Connor, 1983; Damasio et al., 1985; Warrington and Duchen, 1992).

Studies of semantic dementia, a condition known to disproportionately affect the temporal pole (Graham and Hodges, 1997; Hou et al., 2005), demonstrate that personal semantic memory is more affected than episodic memory (Ivanoiu et al., 2006; Maguire et al., 2010). The absence of a temporal gradient of personal semantic memory loss following focal MTL damage also suggests that these structures are not needed for the retrieval of temporally-recent or -distant personal semantic memories because of their representation outside the MTL (Grilli and Verfaellie, 2014; Klein and Gangi, 2010; Klein and Lax, 2010). Notably, criticisms of this approach have centred on unitary accounts, wherein the MTL contributes to the retrieval of both semantic and episodic memory (Squire, 1992a).

6.1.1.2. Functional MRI evidence for dissociations between episodic and semantic memory

Evidence from fMRI suggests that autobiographical memory retrieval is associated with increased activity in the ventrolateral and medial prefrontal cortices, retrosplenial and posterior cingulate cortices, temporo-parietal junction, middle lateral temporal cortex and medial temporal lobe, in a predominantly left-lateralised pattern (Svoboda et al., 2006). A recent meta-analysis found that personal semantic retrieval is associated with activity in the parahippocampal cortex (Martinelli et al., 2013). Conversely, public events retrieval is associated with activity of the left lateral inferior frontal and temporal lobes (Demonet et al., 1992; Graham et al., 2003), the left middle

temporal gyrus (Svoboda et al., 2006), posterior aspects of the left lateral temporal lobe (Graham et al., 2003), and is associated with increased connectivity between the left lateral temporal lobe and the temporal pole (Maguire et al., 2001).

However, fMRI has also shown that memory retrieval (episodic or semantic) does not rely on modular activity of cortical regions; rather, it relies on interconnected networks of brain regions. In keeping with the neuropsychological theories of the interactions between episodic, personal and public semantic memory (Gabrieli et al., 1988; Kazui et al., 2003), one study demonstrated that autobiographical events, public semantic memory, personal semantic memory and general knowledge were associated with activity in a similar network of temporal lobe structures (Maguire et al., 2000). Within this network though there were significant differences in the estimated connectivity between these regions depending on the type of memory being recollected. For instance, connectivity between the parahippocampal gyrus and hippocampus proper increased for episodic memories; the middle temporal gyrus and the temporal pole had increased activity for recollection of general knowledge and public events (Maguire et al., 2000). This suggests that the apparent neuropsychological dissociations noted above could be evidence of different weightings within a unitary network, as observed with the fMRI data (Gabrieli et al., 1988; Graham et al., 2003; Kazui et al., 2003; Maguire et al., 2000; Maguire et al., 2001; Svoboda et al., 2006).

It has been previously proposed that distinct memory systems only emerge when functional incompatibility between the properties of an existing system and the demands posed by new environmental problem (Sherry and Schacter, 1987). Accordingly, it would seem that formal dissociations can be maintained between declarative and non-declarative memory, and that dissociations, in these terms, between episodic and semantic memories are not entirely sustainable. What can be sustained is that there is a degree to which these different types of declarative memory can operate independently of the others, even in cases of amnesia.

These neuropsychological data suggest that episodic, personal semantic and public semantic memories can be, neuropsychologically at least, dissociated. This can be observed for this VGKC-complex LE patient cohort in Chapters 4 and 5, whereby personal semantic memory was normal – as measured formally by the Autobiographical

Memory Interview, see Chapter 4, and, informally, by the Autobiographical Interview – but that retrograde episodic memory performance – as measured by the Autobiographical Interview, see Chapter 5 – was impaired across the lifetime.

6.1.2. Public semantic memory

One primary aim of this chapter will, therefore, be the investigation of the status of public semantic memory in the current cohort of VGKC-complex LE patients, as part of the general characterization of these patients as a human model of hippocampal pathology. A further aim is the development of a large multimodal battery of public semantic memory, provisionally called the Survey Semantic Memory (SSM). Before the test is discussed in more detail, it is necessary to understand the neuropsychological and neuroimaging foundations of public semantic memory, so that the construction of the test might be informed from an experimental perspective. It is necessary to review the literature surrounding public semantic memory retrieval, in order to develop the aims and hypotheses for this chapter.

6.1.2.1. Neuropsychological studies of public event memory

As briefly discussed in Section 6.1.1, the acquisition and expression of anterograde semantic memory is thought to rely on an intact hippocampus, because lesion studies indicate that hippocampal pathology leads to moderate difficulties in acquiring new, predominantly public event, semantic memories (Manns et al., 2003; Reed and Squire, 1998; Verfaellie et al., 2000), compared to the more severe impairments associated with extensive temporal lobe cortical damage (such as the ERC; Kitchener et al., 1998; Verfaellie et al., 2000; Westmacott and Moscovitch, 2001). HM was observed to learn new semantic facts about people who became famous after his surgery (O'Kane et al., 2004). HM was also been observed to perform above chance on tests at distinguishing new English words from nonwords (Gabrieli et al., 1988). However, two patients (EP and GP) with a similar extent of temporal lobe damage were shown to be unable to acquire new semantic information under both recall and recognition paradigms (this distinction is discussed below in Section 6.1.3.1), when tested on twenty easy facts, news events, famous faces, living or nonliving famous persons and home floor plan (Bayley and Squire, 2005). The discrepancy between EP and GP and HM has been

suggested due to the relative preservation of HM's parahippocampal cortices and the ventrocaudal PRC (O'Kane et al., 2004), compared to the damage in EP and GP, which extended to include PRC, the parahippocampal cortex, the fusiform gyrus, and the insula (Bayley and Squire, 2005).

These lesion based studies therefore suggest that the temporal lobe neocortex supports semantic learning (Holdstock et al., 2002; Kitchener et al., 1998; McClelland et al., 1995; Tulving, 1991), and identify the hippocampus with only a time-limited role in semantic memory. In particular, this role involves the acute acquisition and initial retrieval of semantic memory, which diminishes as the neocortical representations of these memories become fully established in the neocortex (Squire, 1992b; Squire and Alvarez, 1995; Squire and Zola, 1998).

Experimental studies that have assessed retrograde public event memory retrieval mirror the proposal that the wider temporal lobe neocortex supports public semantic memory performance (Bayley and Squire, 2005; Corkin et al., 1997; Gabrieli et al., 1988; Holdstock et al., 2002; Kitchener et al., 1998; McClelland et al., 1995; O'Kane et al., 2004; Tulving, 1991; Vargha-Khadem et al., 1997). In particular, patients with lesions restricted to the MTL tend to show normal retrograde public semantic memory performance across their lifespan, or, if deficits are present, this does not usually extend beyond the most recent 10 years (for a review see Moscovitch et al., 2006; Winocur and Moscovitch, 2011). Case reports of more severe amnesia have been described, but these are usually in the context of greater degrees of temporal cortex loss (Cipolotti et al., 2001; Moscovitch et al., 2006; Reed and Squire, 1998; Squire and Bayley, 2007; Winocur and Moscovitch, 2011). In health, it has been proposed that most people will use episodic personal experience to aide public semantic retrieval, a strategy not available neuroanatomically in the amnesic patient group, thereby suggesting that deficits in retrieval could potentially arise due to a competence rather than substrate problem (Manns et al., 2003; Westmacott et al., 2004).

6.1.2.2. Neuroimaging the neural basis of public semantic memory.

Early neuropsychological studies of Alzheimer's and semantic dementia demonstrated that semantic memory tends to be more affected by damage to the lateral temporal lobe (Graham and Hodges, 1997; Hodges and McCarthy, 1995), providing a

neuroanatomical region of interest for studies using fMRI paradigms. Whilst fMRI is not a method of experimentation used within this chapter, the data arising from these studies will provide further evidence for the causal roles of the MTL structures in the retrieval of public event memory. Increased hippocampal BOLD signal activity has been observed during the retrieval of public events (Maguire, 2001), and famous faces (Bernard et al., 2004; Kapur et al., 1995; Leveroni et al., 2000), along with parahippocampal activity associated with famous faces (Haist et al., 2001). In another fMRI study that examined BOLD activity associated with a yes/no recognition task for autobiographical events and public events, the hippocampal activity was observed for both autobiographical and public semantic retrieval, although the level of activity was greater for autobiographical retrieval (Maguire and Mummery, 1999). These things considered, it is expected that public semantic memory should be intact in cases of focal MTL damage.

6.1.2.3. Face recognition

Famous face tasks have long been central to the neuropsychological characterizations of retrograde memory (Kopelman et al., 1999; Kopelman et al., 1989; McCarthy et al., 2005; Reed and Squire, 1998; Verfaellie et al., 2000; Warrington and Duchen, 1992; see also Table 6.1). Prosopagnosia arises when a patient is rendered incapable of recognizing familiar faces (Bodamer, 1947), and is normally associated with lesions to the ventral occipitotemporal cortex (Delvenne et al., 2002; Rossion et al., 2003). These findings have given rise to a rich but separate literature on facial processing and memory (for review, see Riddoch et al., (2008).

Tulving first posited that newly-learned faces and face-name associations is a capacity of episodic memory whereas recognition, identification and naming of famous faces is a function of semantic memory (Tulving, 1972). The encoding of name-face associations has been shown to lead to activity in a hippocampal-frontal network (Herholz et al., 2001; Sperling et al., 2001); the degree of which predicts subsequent recall (Sperling et al., 2003). Famous face recognition has been shown to be associated with activity in the right parahippocampus and bilateral anterior temporal poles (Sergent et al., 1992), the hippocampus, parahippocampal and the left superior temporal area (Kapur et al., 1995), and frontal, parietal and middle and superior temporal lobe (Gorno-Tempini et al., 1998; Leveroni et al., 2000). These data suggest that there are no specific areas that

subserve face memory (Werheid and Clare, 2007), although this an area of controversy outwith the scope of this thesis.

Generally though, it would appear from the data cited above that famous faces recognition tasks rely on a network of temporal lobe structures, and that they should be included in any measure of retrograde public semantic memory. These data also suggest that the recognition of famous faces should be normal in cases of focal MTL lesions.

6.1.2.4. Semantic memory for word meanings

As with famous faces, the retention of semantic meaning attached to new words is a common feature in tests of public semantic memory (Kopelman et al., 1999; Kopelman et al., 1989; McCarthy et al., 2005; Reed and Squire, 1998; Verfaellie et al., 2000; Warrington and Duchen, 1992).

Traditionally, investigations into vocabulary have relied on words that were acquired during childhood (McCarthy et al., 2005). This leads to a potential confound between the developmental stage at which the memory was acquired and the age of the memory. Previous work has shown that early word acquisition has a beneficial effect on vocabulary robustness in aphasia and semantic memory impairment (Hirsh and Ellis, 1994; Hodgson and Ellis, 1998), perhaps because they are likely to be used the most often, and, are therefore more well-established within the cortical circuits underlying language (Ellis and Lambon Ralph, 2000; Ellis and Morrison, 1998). As such, it could be that any measure preferentially probing semantic memory performance for knowledge of words acquired early in a participant's life may not be impaired due to its more robust representation within the cortical language circuits. Therefore, any measure of vocabulary must not only test those earliest words, but words acquired throughout the subject's lifetime (McCarthy et al., 2005) in order to prevent type I errors. Once again this forms an experimental question, one that can be empirically tested to assess the recall of the semantic meanings of words across the lifetime of a patient with MTL damage. As such, any test of semantic memory for word meanings should attempt to have a wide temporal range, such that semantic meanings of these words could be tested across the lifetime of a participant (Verfaellie et al., 1995).

6.1.3. Constructing the Survey of Semantic Memory (SSM)

The previous section has detailed the intimate relationship that exists between the various types of declarative memory, which can be dissociated on neuropsychological grounds, but perhaps not on a neuroimaging basis. Therefore, it is critical that before any conclusions can drawn about the role of the MTL in episodic memory retrieval, public semantic memory be appropriately assessed, given the overlap in the neuroanatomical regions required for both these forms of declarative memory. However, when constructing a large battery of public semantic memory, it is necessary to consider the evidence underlying the methodology upon which the test will be built. Several studies have attempted to measure the public semantic memory performance of patients with varying degrees of temporal lobe damage, which are summarized in Table 6.1. Further discussion concerning how the SSM should be constructed will be undertaken, in order that it is informed by appropriate neuropsychological criteria.

6.1.3.1. Different methods of retrieval support

What is immediately noticeable from the studies cited in Table 6.1 is that they vary across the methodologies used to probe public semantic memory, ranging from recall to recognition, or a mixture of the two. As detailed in Section 4.1.3.2, anterograde recognition and recall can be considered different mnemonic constructs (Jacoby et al., 1993), so discussion of the format public semantic memory is probed is required.

Evidence suggests that across the adult life span, age-related declines in memory performance is greater for tasks requiring recall than recognition (Jennings and Jacoby, 1993, 1997), and that the relative decline in recollection is greater than that of familiarity-based recognition memory (Craik and McDowd, 1987). These results imply that the processes of recollection are more effortful and resource demanding than task-based recognition memory, perhaps because older adults are less capable of strategizing and deploying processing resources such as self-initiation of retrieval strategies (Craik, 1983; Danckert and Craik, 2013). This problem can be circumvented with increased retrieval support, offered with recognition tests (Craik, 1983).

A recent study attempted to delineate these differences across a range of different experiment modalities (Danckert and Craik, 2013). The authors used a word list

paradigm in young and healthy controls with both a cued recall and recognition paradigm. They found that a significant interaction between age and test type, demonstrating that the age difference in recall was greater than the age difference in recognition, even when ceiling and floor performance was removed by subtracting the best young adults and the worst older adults from the analysis (Danckert and Craik, 2013). The authors then derived conditional probabilities for recall of a word given that it was recognized, and found a significant difference the performance of younger and older participants (0.59 versus 0.36; Danckert and Craik, 2013). These data suggest that recognition memory is relatively preserved in elderly adults and as such allows older adults to perform nearly was well as younger adults on recognition tests of item memory (Danckert and Craik, 2013; Jennings and Jacoby, 1993, 1997).

Retrieval support has been successfully used to facilitate performance on retrograde episodic memory tasks, having been shown to increase the number of details given by elderly participants, although it could not overcome age-related deficits in episodic re-experiencing (Levine et al., 2002), and so it is important that any potential effects of ageing on public semantic memory retrieval are addressed by experimental manipulations related to retrieval support.

This section demonstrates that recall and recognition do not always require the same neuroanatomical foundation for successful neuropsychological performance. They also demonstrate that there could be age-related changes in public semantic memory performance in more elderly participants, regardless of their disease state. Given the average age of this VGKC-complex LE cohort (mean age: 62.3±2.23, age range 24-80), the SSM would have to ensure that any observed deficits in public semantic memory were due to the disease process, and not just as a consequence of ageing. Likewise, if the SSM were rely entirely on recall for testing of public semantic memory performance, then it could not be determined whether observed deficits were due to a failure in public semantic network (see Section 6.1.2), or, rather, due to a failure of retrieval strategies and/or self-initiation (Craik and McDowd, 1987; Danckert and Craik, 2013). In the immediate context, the SSM should be constructed in a recognition, and not recall, format.

6.1.3.2. Selection of response format

Three principal methods have been used to test a participant's knowledge of an event: (1) a free-recall format, whereby a participant has to describe the event without or with minimal cues; (2) a yes/no (Y/N) or true/false assessment; and, (3) a forced-choice corresponding format (FC-C) whereby participants have to choose the correct answer from a selection of foils (Bayley et al., 2008b; Holdstock et al., 2002; Westerberg et al., 2006). The use of foils in FC-C formats appears to aid successful recognition, as the use of foils helps the participant make effective use of small, but consistent, differences between the familiarity signals caused by the previously encountered, and therefore familiar, target, and the unfamiliar foils (Norman and O'Reilly, 2003), although this view is contested (Jeneson et al., 2010). Y/N discriminations do not provide these slight differences in familiarity signals for the target item, as it no longer has the comparatively weaker familiarity signals of the foil items to be compared against, and are therefore less sensitive than FC-C formats (Jeneson et al., 2010).

Accordingly, patients with either a lesion restricted the hippocampus, or patients with mild cognitive impairment (MCI) have been shown to exhibit greater impairment on Y/N paradigms compared to FC-C based recognition memory. In one study, a single patient with presumed anoxic damage to the hippocampus, was presented a series of pictures, and then underwent two retrieval arms: (1) an FC-C paradigm where she was presented with a previously encountered object, and three similar yet unencountered foils, and (2) a Y/N phase where she had to say whether she had encountered the object previously. It was found that this patient was able to perform similarly to healthy age-matched controls for the FC-C portion of the task, but not the Y/N task (Holdstock et al., 2002). This study was followed by another (Westerberg et al., 2006), that sought to assess FC-C and Y/N performance in both Alzheimer's disease (AD; n = 8), and mild cognitive impairment (MCI; n = 8). This study used a similar format to that of (Holdstock et al., 2002), and found that the MCI patients, with damage putatively limited to the hippocampus, were only impaired for the Y/N task compared to age-matched controls, but that AD patients, with their larger regional damage to the MTL complex, performed poorly on both the FC-C and Y/N arms (Westerberg et al., 2006). This suggests that FC-C formats are associated with successful recognition performance, for objects at least, in cases of pathology limited to the hippocampus

The literature that has been reviewed thus far suggests that a FC-C format will help prevent the potential confound of disproportionately deleterious effects associated with recollection-based retrieval methods, as demonstrated in a Y/N paradigm, when testing the temporal integrity of semantic memory across the lifespan of a participant with focal hippocampal damage. However, it is also important to note that VGKC-complex LE patients – with lesions limited to the MTL (Wagner et al., 2015; Wagner et al., 2014), and in Chapter 3 – would be hypothetically more likely to perform poorly on both Y/N and/or free recall paradigms, compared to the FC-C format. Should they perform poorly on the Y/N or free recall format, the confound of retrieval support would remain; should they perform poorly on a FC-C task, then that would be suggestive of either more extensive damage into the MTL complex, or that there is a failure in the public semantic memory network.

6.1.3.3. Semantic batteries and their problems

Although methods exist for assessing public semantic memory, a United Kingdom-based standardized and comprehensive test is not available. Several groups have established their own assays, but either do not make the test publically available (for instance, (Bright et al., 2006; Cipolotti et al., 2001)), or only publish part of the battery used (e.g., Chan et al., 2007). Moreover, numerous methodological differences exist between tests used, making comparisons across studies impossible to make. Table 6.1 provides an overview of some of the public semantic memory batteries that have been used in patients with retrograde episodic amnesia, as part of their overall retrograde mnemonic characterization. What follows is a critique of these studies, so as to inform the decisions made concerning the construction of the SSM.

6.1.3.3.1. Structure of questions and responses

One of the most striking features of this survey is the different ways that semantic knowledge has been tested; tests have involved questions that require responses based on recall (Chan et al., 2007; Kopelman, 1989; Kopelman et al., 1999; McCarthy et al., 2005; Warrington and Duchen, 1992), recognition (Cipolotti et al., 2001; McCarthy et al., 2005; Steinvorth et al., 2005; Warrington and Duchen, 1992), a combination of both recall and recognition (recall is normally followed by recognition; Bright et al., 2006; Cipolotti et al., 2001; Manns et al., 2003; McCarthy et al., 2005; Reed and Squire, 1998;

Warrington and Duchen, 1992), or Y/N answers (i.e. dead or alive? Famous or non-famous?; Cipolotti et al., 2001; Manns et al., 2003; Reed and Squire, 1998).

As discussed above in Section 6.1.3.1-2 the format in which the questions are asked on these tests of public semantic knowledge have an influence on the neural apparatus that is engaged for retrieval, or the retrieval or monitoring strategies needed to successfully complete these tasks (Craik and McDowd, 1987; Danckert and Craik, 2013). Difference in the format of the question and answers presents an issue not only for comparing patients' data across studies, but also for interpreting the implications of results arising from mixed-design studies on a single patient (i.e., Bright et al., 2006; Cipolotti et al., 2001; Manns et al., 2003; McCarthy et al., 2005; Verfaellie et al., 2000; Warrington and Duchen, 1992). It is also imperative that the method used to assess public semantic knowledge should not confound performance with competence by overtly relying on recall, because this form of retrieval has been shown to be more reliant upon hippocampal integrity that other forms of retrieval (Danckert and Craik, 2013). Therefore, an FC-C task will be used in the development of the SSM.

6.1.3.3.2. The temporal-specificity of the questions

Test of public semantic memory are usually designed to experimentally probe the semantic memory of a participant, so that comparisons between the integrity of contemporaneous episodic memories and public semantic memories can be made. Episodic memories are characterized, in part, by a re-experiential and unique spatiotemporal context in which they occurred (see Section 5.1.1); public semantic memories, by virtue of their factual nature, do not have this aspect of re-experiencing, but they can have a specific temporal context. For example, Neil Armstrong landed on the moon on the 21st July 1969 is an example of a public semantic event with a specific temporal context. However, this is a semantic fact that has entered popular knowledge, and could therefore be answered by anyone with an interest in the Apollo space programme. Therefore, questions need to have as specific a temporal context as possible, in order that they can only be answered by those alive at the time of the event (Steinvorth et al., 2005) – although whether this is possible for every question is difficult to answer, as a participant might have specialist knowledge of a particular subject area. By ensuring that the public semantic questions have a high degree of temporal specificity, it then makes it possible to compare the integrity of both retrograde episodic and public

semantic memories when they are both constrained to the same time. This approach is similar to the Autobiographical Memory Interview (AMI, Kopelman, 1994).

The data obtained from these batteries of public semantic memory are often used as evidence for (Manns et al., 2003; Reed and Squire, 1998), or against (Chan et al., 2007; Cipolotti et al., 2001; Steinvorth et al., 2005) a temporal gradient in semantic memory recall. For those batteries that provide exemplar questions (e.g., Chan et al., 2007), it becomes apparent that many of them could be answered without necessarily relying on temporally specific semantic memory, and as such cannot be compared to retrograde episodic or personal semantic, as typified by the AMI. This problem is made more apparent with tests of new words; for instance, Verfaellie et al., (1995) sought to use new words entering the lexicon as a test of semantic memory. However, many of the words they used (e.g. hard-liner) do not need a temporally specific memory of the decade in which it was first coined, because they are so frequent in the current lexicon.

To demonstrate that at least some degree of temporal specificity can be accomplished, (Steinvorth et al., 2005) devised a FC-C task to apply to two patients with MTL+ damage (WR and HM, see Chapter 4). This public semantic test consisted for a question with the target item, and three foils for a series of events occurring in the decades between the 1940s and the 2000s. Whilst not explicitly demonstrating this with statistics, the authors comment that in a pilot study older controls were significantly better than younger adults (age ranges for either not explicitly stated) in answering questions from the more remote decades. This was taken as evidence that the questions were temporally specific, although, critically, group performance values for both older and younger adults was not reported. Ideally, younger controls should be at chance for periods occurring before their decade of birth, but this could not be predicted *a priori*.

Therefore, it is possible to create a FC-C public event questionnaire with questions that can be, at least, answered more consistently correctly by those who were alive when the event took place, and could be considered a valid measure of retrograde public semantic memory. As such, it will be possible to compare VGKC-complex LE patient performance for public semantic memory to those decades in which they have been shown to have retrograde episodic amnesia.

6.1.3.3.3. Methodological differences in determining how to test the semantic meaning of new words entering the lexicon

For those studies that have attempted to test public semantic memory through the meaning of new words that have entered the lexicon, there is usually insufficient information on the methodological basis through which selections were made (McCarthy et al., 2005; Reed and Squire, 1998; Verfaellie et al., 2000).

Some groups though have detailed their methodology used in determining which new words, and their semantic meaning, entering the lexicon should be tested. For instance, (Verfaellie et al., 1995) used several English language dictionaries in order to determine when words came into popular usage (as their entry was usually dated), in order to determine which specific decade/time period they could be reliably said to belong to (i.e., 1960s, or 1980s). Verfaellie et al. then used both a recall and recognition format (see Section 6.1.3.1-2 for difficulties with this) to assess the sematic knowledge of words (12 words across 12 five years time periods) for seven patients with mixed causes of amnesia (including anoxia, viral encephalitis, bilateral thalamic strokes, and anterior communicating artery rupture). They found that for both the recall and FC-C arms (one target item, three foils) of the study that the amnesic group performed within normal limits, compared to age-matched controls, for both recall and recognition. This was interpreted as showing that testing the meaning of these temporally specific words was a good measure of semantic memory performance. However, their exemplar word, hardliner, would no longer prove to be a temporally-specific word, as its usage has now entered popular use, and many born since the study was undertaken would be able to successfully complete the task.

Bayley et al., (2008a) also devised a novel measure of semantic meanings of words entering the lexicon, to test assess whether two patients with MTL+ lesions (both due to viral encephalitis) were able to acquire. This experiment used 25 words that had entered the lexicon since the time of their illness in a FC-C format, with eight foils that had semantic relevance to the target word (i.e. snowboarding, with foils of snowgliding, waterboarding). The patients were asked to firstly identify the target word from the foils, and then explain what action might be performed with the object identified. In this way the authors were testing not only recognition of the word, but also that the patients had specific knowledge of the word. The authors found that only one patient (GP) could

perform above chance for recognizing or defining new words. This method uses a mixed design of both recognition and recall, thereby providing full retrieval support. Therefore, the conclusions from this study – that patients with MTL+ lesions are impaired at learning new semantic information – cannot be fully supported, as the authors failed to provide more extensive methods of retrieval support, such as through a FC-C format with the definition of the word used as a target item, and three foils comprised of false definitions.

In order to assess competence of public semantic memory, it seems that the SSM should be comprised of words that can be precisely dated in terms of their entry into popular usage – as conceptualized by their entry into dictionaries – but that they fell out of popular usage within a decade of entering the lexicon. The testing of word meanings should be undertaken in a FC-C format, with the target and three foil definitions provided. This approach will provide retrieval support, and therefore be best placed to determine competence of this VGKC-complex LE cohort for temporally specific word meanings.

6.1.3.3.4. Foil selection for a two or more alternative forced-choice recognition test

Foil selection is a key consideration for those tasks utilizing FC-C paradigms. It is difficult to assess the foils of those batteries that have not been made publically available (Bright et al., 2006; Cipolotti et al., 2001); however, partial information can be gleaned from methods that have described the approach to foil selection. In several studies that have examined knowledge of public events, the aim has been to provide foils that specifically probe the ability of participants to discern between the target item, and, usually, three other options that share many overlapping features with the target item (Steinvorth et al., 2005; Verfaellie et al., 1995). For instance, any question pertaining to a particular member of the Beatles could use all four members for both target choice, and foil selection. On tests of the semantic meaning of new words entering the lexicon, foils have been provided on the basis of homophones, or plausible new words (e.g. snowboarding, snowgliding, waterboarding; Bayley et al., 2008b). The choice is foils is critical, as it is important that the question cannot be answered correctly simply by a process of elimination based on logical inference, as this would be assessing strategies that are unrelated to public event memory *per se*. Therefore, to remove this potential confound of logical inference from successful performance on the SSM, the foils should

be designed to share as many overlapping features as possible with the target item, such that only temporally specific knowledge of the event or word could be used to successfully answer the question.

Table 6.1. Summary of studies that have used measures of public semantic memory in patients with varying degrees of medial temporal lobe damage. The tests are detailed according to what specific modaility of public semantic memory was tested (i.e., news events, famous faces, or word meanings), how responses from patients and controls were assayed, how performance was scored, and the structure of the test used, in terms of question number and temporal groupings.

Reference	Test	Response method	Scoring	Test Structure
(Kopelman, 1989)	News events	Recall	1 point for full event	10 pictures precisely dated for each decade from 1930s to 1970s
			0.5 point for incomplete event	
	Famous faces	Recall		160 standardised pictures from pre-1930s to pre-1960s
(Kopelman et al., 1999)	News events	Recall	1 point for full event	30 famous events from 1960 to 1990 presented randomly
			0.5 point for incomplete event	
(McCarthy et al., 2005)	Public events	Recall	1 point for full event	Similar to (Kopelman et al., 1999); 38 questions over 22 years
	Word meaning	Recall	0-3 points depending on response	Premorbid testing: 1965-85, *n* = 50
				Postmorbid testing: 1986-2000, *n* = 16
	Word meaning	Recall and recognition		As per (Verfaellie et al., 1995); 10 questions for five year periods from 1955-90
	Famous names	Recall	UK	Historically famous people pre- (*n* = 24) and post-injury (*n* = 27)
	Famous faces	Recognition		15 stratified according to peal popularity
(Manns et al., 2003)	Public events	Recall and recognition	1 point for full event	251 questions from 1950-2002, half focused on the period 1995-2002
	Famous names	Forced choice		Is [name] famous or not? If famous, are they alive or not?
(Reed and Squire, 1998)	Word meaning	Forced choice	1 point if correct (4 options)	1955-59, *n* = 12; 1960-69, *n* = 24; 1970-79, *n* = 24; 1980-89, *n* = 22
	Public events	Recall and recognition	1 point for full event	1940s: *n* = 19; 1950s *n* = 17; 1960s *n* = 24; 1970s *n* = 27
			Best of 4 for recognition	1980s, *n* = 30; 1990s, *n* = 28
	Famous faces	Recall and recognition	1 point for full event	1940s, *n* = 24; 1950s, *n* = 27; 1960s, *n* = 27; 1970s, *n* = 27
			Best of 4 for recognition	1980s, *n* = 24; 1990s, *n* = 12
	Famous names	Completion	1 point for full name	1940s, *n* = 11; 1950s, *n* = 13, 1960s, *n* =11, 1970s, *n* = 13
				1980s, *n* = 11; 1990s, *n* = 6

(Warrington and Duchen, 1992)	Famous faces	Recognition	1 point if correct (famous or not?)	3 sets of 30 pictures: 15 famous, 15 not
	Famous names	Recall	1 point if correct (why were they famous?)	*n* = 24
	Famous names	Recognition	1 point if correct (3 options)	
	Name completion	Recall	1 point if name completed	
	Friends and family	Recall and recognition	1 point if correct	Faces and names presented to participant
(Verfaellie et al., 2000)	Word meaning	Recall	2 points if correct	1970-74, *n* = 12; 1975-79, *n* = 12; 1980-84, *n* = 12; 1985-89, *n* = 10
	Word meaning	Recognition	1 point if correct (4 options)	
(Chan et al., 2007)	Public events	Recall	2 points if correct, 1 point if partially correct	1981-85, *n* = 7; 1985-90, *n* = 7; 1991-95, *n* = 7; 1996-2000, *n* = 7
				2001-07, *n* = 10
	Famous faces	Recall	1 point if correct	5-10 years pre-morbidly, *n* = 10; contemporaneous, *n* = 10
			(description given if not recalled)	
(Cipolotti et al., 2001)	Famous names	Forced choice	1 point if correct (dead or alive?)	Covering 30 years
	Public events	Recall and recognition	1 point if correct	1960-64, *n* = 15; 1965-69, *n* = 15; 1970-74, *n* = 15; 1975-79, *n* = 15;
			1 point if correct (4 options)	1980-84, *n* = 15; 1985-89, *n* = 15; 1990-94, *n* = 15, 1995, *n* = 15
	Famous faces	Recall and recognition	1 point if correct	1960s, *n* = 31; 1970s, *n* = 32; 1980s, *n* = 43; 1990s, *n* = 39
	Famous faces familarity	Recognition	1 point if correct (4 options)	1960s, *n* = 15; 1970s, *n* = 15; 1980s, *n* = 15; 1990s, *n* = 15
				Foils were non-famous names
(Bright et al., 2006)	Famous faces	Familiarity, recall, then	UK	1950s, *n* = 10; 1960s, *n* = 10; 1970s, *n* = 10, 1980s, *n* = 10;
		recognition		1990s, *n* = 10
	News events pictures	Recall and recognition	UK	1950s, *n* = 10; 1960s, *n* = 10; 1970s, *n* = 10, 1980s, *n* = 10;
				1990s, *n* = 10
(Steinvorth et al., 2005)	Word meaning	Recognition	1 point if correct	1955-59, *n* = 7; 1960-64, *n* = 7; 1965-69, *n* = 7; 1970-74, *n* = 7;

				1975-79, *n* = 7; 1980-84, *n* = 7; 1985-90, *n* = 7
	Public events	Recognition	1 point if correct	1940s, *n* = 13; 1950s, *n* = 11; 1960s, *n* = 11; 1970s, *n* = 9; 1980s, *n* = 14
				1990s, *n* = 11; 2000 (single year), *n* = 8
(Verfaellie et al., 1995)	Word meaning	Recall and recognition	2 points if correct, 1 point if partially correct	1955-59, *n* = 12; 1960-64, *n* = 12; 1965-69, *n* = 12; 1970-74, *n* = 12;
			1 point if correct on recognition	1975-79, *n* = 12; 1980-84, *n* = 12; 1985-90, *n* = 10

UK, unknown

6.1.3.3.5. Determining the temporal length of question periods

Many of the studies shown in Table 6.1 try to assess retrograde public semantic memory according to five-year blocks in order to provide a high granularity of assessment (Bright et al., 2006; Chan et al., 2007; Cipolotti et al., 2001; Reed and Squire, 1998; Steinvorth et al., 2005; Verfaellie et al., 2000; Verfaellie et al., 1995), whereas others make no attempt to temporally constrain questions in this way (Kopelman, 1989; Kopelman et al., 1999; Manns et al., 2003; McCarthy et al., 2005).

The purpose of these measures of retrograde public semantic memory is determine the temporal extent of amnesia observed in case of MTL or MTL+ lesion patients, in order that comparisons to retrograde episodic memory performance can be made. This is done so that empirical evidence can be used to determine the differences between unitary accounts of declarative memory, that state both episodic and semantic amnesia should demonstrate a similar temporal extent (Bayley et al., 2005; Bayley et al., 2003, 2006; Reed and Squire, 1998), and those that consider them separate processes – that episodic and semantic memories are, at least in some neuropsychological sense, dissociable processes (Chan et al., 2007; Cipolotti et al., 2001; Steinvorth et al., 2005; Verfaellie et al., 2000).

Chapter 5 demonstrated that the Autobiographical Interview, and certainly in its modified state, attempts to assess retrograde episodic memory by temporally constraining recall according to the age of the participant, which equated, in the modified administration at least, to a decade-by-decade assessment of retrograde episodic memory. The SSM, therefore, sought to sample the temporal component associated with public semantic memory in analogous manner aligned to the Autobiographical Interview method (Levine et al., 2002), whereby knowledge of public semantic memories was sampled on a decade-by-decade basis.

6.1.3.3.6. The design rationale for constructing the Survey of Semantic Memory

A principal aim of this chapter was to develop and test a battery of public semantic memory, which could be amenable to a standardization process, and could then be used

across a range of experimental settings. In order to improve on existing measures, the SSM was designed to satisfy the following criteria:

1. General knowledge and face recognition to include five different categories of public memory (such as public events, sport, music, cinema). This was done so that as wide a range of public semantic events was represented.
2. Questions were deemed to have temporal specificity with limited permeation across decades.
3. The number of questions within each decade, and category type, were sufficient allow for parametric analysis.
4. Words should have a known year of entry into the lexicon (where possible), and, likewise be shown to have a usage restricted largely to a particular decade within written language use.
5. Foils should share as many features as possible with the target item, in order to prevent the target item being identified by processes other than semantic memory (i.e., logical inference).
6. All questions were formulated in a four-alternative FC-C paradigm, thereby circumventing potential confounds of recall in cases of focal MTL damage, or age (Craik and McDowd, 1987; Danckert and Craik, 2013; Levine et al., 2002). This paradigm will be best placed to assess the competence of participants for public semantic memory.

6.1.4. Retrograde semantic memory performance following VGKC-complex LE

One study, Chan et al., (2007), has assessed public semantic memory in three patients with VGKC-complex LE. The authors used two measures of retrograde semantic memory: public events test and famous faces. The response format was required the recall of the public events (i.e. "Who was Monica Lewinsky?"). The responses were scored on a two – point scale, with a partially correct response awarded one point (the criteria for these marks was not outline in sufficient detail to replicate the study). The time periods that were tested were as follows: 1981-85, 1985-90, 1991-95, 1996-2000, 2001-2007, with seven questions on famous events (except for the 2001-07 period where 10 questions were used). Famous face knowledge was also assessed in a

free recall format, with 10 faces in two groups, one contemporaneous (e.g. Bill Clinton) and the other from five-to-ten years earlier (e.g. Louise Woodward). If patients were unable to recall the identity of the well-known personality, then partial cues were given. Scoring was assigned in a dichotomous fashion as to whether the personality was identified or not. Patient performance was compared against that of two controls (Chan et al., 2007). The authors found that the patients demonstrated a temporally-extensive amnesia with no apparent improvement following resolution of the illness, all in the context of focal hippocampal lesions as seen on qualitative MRI imaging (Chan et al., 2007). The deficits found by Chan et al., (2007) suggest that, from a behavioural perspective, that the hippocampus, or MTL structures, is required to retrieve retrograde public semantic memory, more in keeping with a unitary account of declarative memory (Manns and Squire, 2002; Squire and Zola, 1998).

The data from Chan et al. illustrate why the format of responses is important when testing public semantic memory performance. The inclusion of question formats based on free-recall is likely to require the recruitment of the hippocampus over the parahippocampal cortices (Yonelinas et al., 2007), thereby making it more likely that deficits might be seen in cases of focal hippocampal damage. The discussion in Sections 6.1.3.1-2, suggest that maximal retrieval support needs to be offered before patients can be said to have reduced performance for public semantic memory. Such retrieval support includes a FC-C recognition format. Chan et al. used a free recall format, without a recognition format, and therefore probably was more biased to recruiting the hippocampus (Holdstock et al., 2002; Westerberg et al., 2006; Yonelinas et al., 2007). Given the PRC and ERC could support public semantic memory when questions are posed in a recognition format (Aggleton and Brown, 1999; Bowles et al., 2007; Norman and O'Reilly, 2003; Yonelinas et al., 2007), it becomes an empirical question to see whether a similar VGKC-complex LE cohort are able to perform as well as age-matched controls for public semantic memory when the questions are presented in a FC-C format.

6.1.5. Summary: aims and hypotheses

The aim of the current chapter was therefore to create a large battery of public semantic memory according to the criteria detailed in Section 6.1.3.3.6. Once constructed

it would then be used to test the public semantic memory performance for a group of amnesic patients with a single aetiology (VGKC-complex LE). The predictions for this experiment are as follows:

1. That it will be possible to construct a multimodal assay of public semantic memory for UK-based participants, and that it demonstrates temporal specificity such that performance across the entire test will be higher for those alive during the events when compared to those attempting to answer questions before they were born.
2. That using this FC-C format, there will be no differences observed between patients with VGKC-complex LE, and age-matched controls for measures of public semantic memory.

6.2. Methods

See Section 2.4.

6.3. Results

6.3.1. Assessing the temporal specificity of the SSM using healthy participants across a wide range of participant ages

Table 6.3 demonstrates the mean group performance, as a function of decade of birth, for the proportion of questions answered correctly across each decade assessed by the SSM. This is shown separately for the three subtests constituting the SSM.

6.3.1.1. Control group performance was above chance for all subtests, for both the decade prior to birth, and the third decade of life

Table 6.4 demonstrates the *T*-test results for the control population for each modality either the decade prior to birth (-1), or their third decade of life (+2). These data indicate that the only those born in the 1980s performed at chance for the decade prior to birth for all three modalities tested: word meaning ($t_{(11)} = 1.92$, $p = 0.08$), famous faces ($t_{(11)} = 1.18$, $p = 0.27$), and word meanings ($t_{(11)} = 0.39$, $p = 0.70$). All other groups performed above chance for both the -1 and +2 decades across all three tested modalities.

6.3.1.2. Comparative group performance improves as the decade of birth becomes earlier for word meaning, famous faces, and general knowledge

6.3.1.2.1. Word meaning performance

A 6 (decade of birth: 1940s, 1950s, 1960s, 1970s, 1980s, 1990s) x 8 (decade of question occurrence: 1930s, 1940s, 1950s, 1960s, 1970s, 1980s, 1990s, 2000s) mixed-model ANOVA was conducted on proportion of correct responses with decade of birth being the between-subjects variable and decade of question occurrence the within-subjects variable. Mauchly's test indicated that the assumption of sphericity had not been violated ($\chi^2_{(27)} = 20.65$, $p = 0.80$).

Significant effects were found for decade of birth ($F_{(5,62)} = 5.91$, $p < 0.001$) and decade of question occurrence ($F_{(7,34)} = 84.38$, $p < 0.001$). A significant interaction was found for decade of birth and decade of question occurrence ($F_{(35,434)} = 3.00$, $p < 0.001$).

A series of planned comparisons were undertaken to compare group performance between one decade prior to birth and two decades after birth in order to assess how temporally specific the questions were. Significance was set at $p = 0.01$. The planned comparisons demonstrated a significant improvement in proportion of correct answers for those born in 1960 ($F_{(1,62)} = 0.86$, $p = 0.004$), 1970 ($F_{(1,62)} = 38.52$, $p < 0.0001$), and 1980 ($F_{(1,62)} = 129.54$, $p < 0.0001$), but not in 1940 ($F_{(1,62)} = 0.86$, $p = 0.36$), or 1950 ($F_{(1,62)} = 0.33$, $p = 0.56$).

6.3.1.2.2. Famous face performance

A 6 (decade of birth: 1940s, 1950s, 1960s, 1970s, 1980s, 1990s) x 8 (decade of question occurrence: 1930s, 1940s, 1950s, 1960s, 1970s, 1980s, 1990s, 2000s) mixed-model ANOVA was conducted on proportion of correct responses, with decade of birth as the between-subjects variable and decade of question occurrence as the within-subjects variable. Mauchly's test indicated that the assumption of sphericity had been violated ($\chi^2_{(27)} = 65.90$, $p < 0.001$) so Huynh-Feldt correction was applied ($\varepsilon = 0.87$).

Significant main effects were found for decade of birth ($F_{(5,62)} = 14.48$, $p < 0.001$) and decade of question occurrence ($F_{(6.12,379.16)} = 101.66$, $p < 0.001$). A significant interaction was found between decade of birth and decade of question occurrence ($F_{(30.58,379.16)} = 5.61$, $p < 0.001$).

A series of planned comparisons were undertaken to compare group performance between one decade prior to birth and two decades after birth in order to assess how temporally specific the questions were. Significance was set at $p = 0.01$. The planned comparisons demonstrated a significant improvement in ratio of correct answers for those born in 1940 ($F_{(1,62)} = 16.37$, $p = 0.00015$), 1950 ($F_{(1,62)} = 69.85$, $p < 0.0001$), 1960 ($F_{(1,62)} = 21.04$, $p < 0.0001$), 1970 ($F_{(1,62)} = 36.83$, $p < 0.0001$), and 1980 ($F_{(1,62)} = 93.26$, $p < 0.0001$).

6.3.1.2.3. General knowledge performance

A 6 (decade of birth: 1940s, 1950s, 1960s, 1970s, 1980s, 1990s) x 8 (decade of question occurrence: 1930s, 1040s, 1950s, 1960s, 1970s, 1980s, 1990s, 2000s) mixed-model ANOVA was conducted on proportion of correct responses with decade of birth as the between-subjects variable and decade of question occurrence as the within-subjects variable. Mauchly's test indicated that the assumption of sphericity had been violated ($\chi^2_{(27)} = 81.00, p < 0.001$), so Huynh-Feldt correction was applied ($\varepsilon = 0.81$).

Significant main effects were found for decade of birth ($F_{(5,62)} = 12.67, p < 0.001$) and decade of question occurrence ($F_{(5.68,352.30)} = 25.36, p < 0.001$). A significant interaction was found between decade of birth and decade of question occurrence ($F_{(28.42,352.39)} = 8.07, p < 0.001$).

A series of planned comparisons were undertaken to compare group performance between one decade prior to birth and two decades after birth in order to assess how temporally specific the questions were. Significance was set at $p = 0.01$. The planned comparisons demonstrated a significant improvement in ratio of correct answers for those born in 1940 ($F_{(1,62)} = 15.20, p < 0.0001$), 1950 ($F_{(1,62)} = 22.66, p < 0.0001$), 1960 ($F_{(1,62)} = 19.68, p < 0.0001$), 1970 ($F_{(1,62)} = 30.52, p < 0.0001$), and 1980 ($F_{(1,62)} = 38.70, p < 0.0001$).

Table 6.2. Mean group proportion of correct answers (SEM) according to decade of birth across all the decades assessed by the SSM. This is shown according to the three individual subtests: word meanings (upper panel), famous faces (middle panel), and general knowledge (lower panel).

Word meanings

Dec.Birth	1930s	1940s	1950s	1960s	1970s	1980s	1990s	2000s
1930 (n = 3)	0.27 (0.07)	0.42 (0.05)	0.42 (0.02)	0.27 (0.05)	0.44 (0.03)	0.33 (0.06)	0.46 (0.02)	0.69 (0.03)
1940 (n = 8)	0.36 (0.07)	0.58 (0.06)	0.42 (0.06)	0.48 (0.05)	0.59 (0.06)	0.45 (0.05)	0.65 (0.04)	0.82 (0.02)
1950 (n = 9)	0.44 (0.02)	0.57 (0.06)	0.43 (0.04)	0.40 (0.04)	0.65 (0.04)	0.65 (0.04)	0.61 (0.04)	0.85 (0.03)
1960 (n = 17)	0.39 (0.02)	0.53 (0.04)	0.38 (0.04)	0.37 (0.03)	0.56 (0.03)	0.58 (0.04)	0.58 (0.03)	0.88 (0.02)
1970 (n = 7)	0.41 (0.05)	0.43 (0.05)	0.46 (0.05)	0.42 (0.06)	0.54 (0.04)	0.67 (0.05)	0.57 (0.05)	0.68 (0.06)
1980 (n = 15)	0.42 (0.04)	0.52 (0.04)	0.43 (0.03)	0.41 (0.03)	0.53 (0.04)	0.58 (0.04)	0.68 (0.04)	0.81 (0.04)
1990 (n = 12)	0.32 (0.03)	0.39 (0.05)	0.27 (0.03)	0.31 (0.03)	0.33 (0.04)	0.28 (0.05)	0.51 (0.05)	0.89 (0.02)

Famous faces

Dec.Birth	1930s	1940s	1950s	1960s	1970s	1980s	1990s	2000s
1930 (n = 3)	0.42 (0.04)	0.65 (0.06)	0.73 (0.01)	0.78 (0.03)	0.68 (0.07)	0.62 (0.01)	0.67 (0.07)	0.70 (0.05)
1940 (n = 8)	0.46 (0.04)	0.56 (0.07)	0.71 (0.07)	0.69 (0.06)	0.68 (0.06)	0.68 (0.05)	0.68 (0.04)	0.83 (0.03)
1950 (n = 9)	0.46 (0.03)	0.50 (0.05)	0.66 (0.05)	0.69 (0.06)	0.76 (0.04)	0.72 (0.04)	0.82 (0.05)	0.88 (0.03)
1960 (n = 17)	0.39 (0.02)	0.43 (0.03)	0.56 (0.04)	0.56 (0.04)	0.71 (0.03)	0.78 (0.02)	0.81 (0.04)	0.89 (0.02)
1970 (n = 7)	0.40 (0.04)	0.44 (0.07)	0.57 (0.05)	0.61 (0.05)	0.64 (0.06)	0.82 (0.08)	0.94 (0.03)	0.74 (0.06)
1980 (n = 15)	0.34 (0.03)	0.41 (0.04)	0.44 (0.04)	0.38 (0.05)	0.47 (0.04)	0.55 (0.05)	0.66 (0.07)	0.87 (0.03)
1990 (n = 12)	0.28 (0.02)	0.34 (0.04)	0.30 (0.03)	0.32 (0.04)	0.30 (0.04)	0.35 (0.03)	0.44 (0.05)	0.82 (0.04)

General knowledge

Dec.Birth	1930s	1940s	1950s	1960s	1970s	1980s	1990s	2000s
1930 (n = 3)	0.36 (0.01)	0.35 (0.02)	0.47 (0.03)	0.44 (0.03)	0.47 (0.03)	0.57 (0.03)	0.40 (0.04)	0.36 (0.06)
1940 (n = 8)	0.51 (0.04)	0.48 (0.06)	0.64 (0.06)	0.54 (0.04)	0.49 (0.05)	0.55 (0.04)	0.49 (0.05)	0.44 (0.02)
1950 (n = 9)	0.45 (0.03)	0.46 (0.02)	0.55 (0.04)	0.57 (0.04)	0.61 (0.04)	0.63 (0.04)	0.56 (0.05)	0.47 (0.03)
1960 (n = 17)	0.39 (0.02)	0.39 (0.02)	0.45 (0.02)	0.46 (0.02)	0.54 (0.03)	0.65 (0.03)	0.60 (0.02)	0.49 (0.02)
1970 (n = 7)	0.40 (0.02)	0.38 (0.03)	0.48 (0.05)	0.39 (0.03)	0.51 (0.04)	0.66 (0.05)	0.61 (0.04)	0.44 (0.03)
1980 (n = 15)	0.38 (0.02)	0.34 (0.02)	0.37 (0.03)	0.34 (0.02)	0.34 (0.04)	0.43 (0.03)	0.50 (0.04)	0.52 (0.02)
1990 (n = 12)	0.32 (0.03)	0.29 (0.01)	0.29 (0.02)	0.31 (0.02)	0.26 (0.02)	0.30 (0.03)	0.35 (0.03)	0.50 (0.03)

Dec.Birth.: decade of birth

Table 6.3. Upper panel: Control mean group performance against chance for proportion of questions answered correctly for the decade immediately prior to birth (1), or in the third decade of life (+2). Lower panel: The VGKC-complex LE mean group performance for questions arising from the famous faces, and word meanings in the -1 and +2 decades. Performance against chance was determined using a series of one-way *T*-tests.

Subject	Decade of birth	Test decade	Mean propor. correct	df	*T*-score	*p*
SSM test population performance against chance according to Decade of Birth						
Words	1940	-1	0.439	8	10.14	< 0.001
		2	0.397		3.66	0.006
	1950	-1	0.530	16	7.25	< 0.001
		2	0.559		9.67	< 0.001
	1960	-1	0.457	6	4.43	0.004
		2	0.670		8.96	< 0.001
	1970	-1	0.408	14	4.91	0.0002
		2	0.676		9.17	< 0.001
	1980	-1	0.325	11	1.92	0.08
		2	0.885		42.19	< 0.001
Faces	1940	-1	0.456	8	7.29	< 0.001
		2	0.689		7.70	< 0.001
	1950	-1	0.429	16	6.87	< 0.001
		2	0.709		13.10	< 0.001
	1960	-1	0.571	6	5.91	< 0.001
		2	0.821		7.20	< 0.001
	1970	-1	0.380	14	2.40	0.03
		2	0.670		5.71	< 0.001
	1980	-1	0.300	11	1.16	0.27
		2	0.821		15.36	< 0.001
GK	1940	-1	0.448	8	6.51	< 0.001
		2	0.568		9.00	< 0.001
	1950	-1	0.387	16	7.62	< 0.001
		2	0.543		9.15	< 0.001
	1960	-1	0.483	6	4.39	0.002
		2	0.659		8.36	< 0.001
	1970	-1	0.341	14	4.22	< 0.001
		2	0.503		5.82	< 0.001
	1980	-1	0.251	11	0.39	0.7
		2	0.498		7.31	< 0.001
VGKC-complex LE patient performance against chance for word meaning and famous faces						
Words	1940	-1	0.422	3	1.53	0.22
		2	0.475		1.85	0.16
	1950	-1	0.590	3	19.05	< 0.001
		2	0.563		4.08	0.03
Faces	1940	-1	0.388	3	2.67	0.08
		2	0.613		4.53	0.02
	1950	-1	0.488	3	3.45	0.04
		2	0.688		5.33	0.003

GK, general knowledge

6.3.2. Retrograde public semantic memory performance for word meanings and famous faces is normal following VGKC-complex LE

Patient performance on faces and words was then compared to this control population performance for word meaning, and famous faces. The patients were grouped into two groups according to birth decade (1940s, n = four, controls n = eight; or 1950s, n = four, controls n = nine). No formal matching for the controls to the patients was undertaken, as the controls arise from the SSM test population. General knowledge was not tested. The *T*-test results (Table 6.2) indicate that the 1940s group performed at chance for word meaning at the -1 ($t_{(3)} = 1.53$, $p = 0.22$), and the +2 ($t_{(3)} = 1.85$, $p = 0.16$) time points. They also performed at chance for the -1 ($t_{(3)} = 2.67$, $p = 0.08$) time point for famous faces, but performed above chance at the +2 ($t_{(3)} = 3.45$, $p = 0.04$) time point. The 1950s group performed significantly above chance at both time points for the word meanings, and famous faces.

6.3.2.1. Birth Decade: 1940

Multiple Mann-Whitney tests were conducted concurrently for the faces and words across each of the eight decades. Significance was set at $p = 0.003$ using the Holm-Bonferroni method. No significant group based differences were found (see Table 6.5).

6.3.2.2. Birth Decade: 1950

A Mann-Whitney test was conducted between patients and controls for the faces and words across each of the eight decades. Significance was set at $p = 0.003$ using the Holm-Bonferroni method. No significant differences were found between the two groups (see Table 6.5).

Figure 6.1. New word meanings and famous faces performance for VGKC-complex LE patients born during (A) the 1940s and (B) during the 1950s compared to age-matched controls. The symbol denotes the median group value to align to Table 6.5, with standard error of the mean also represented.

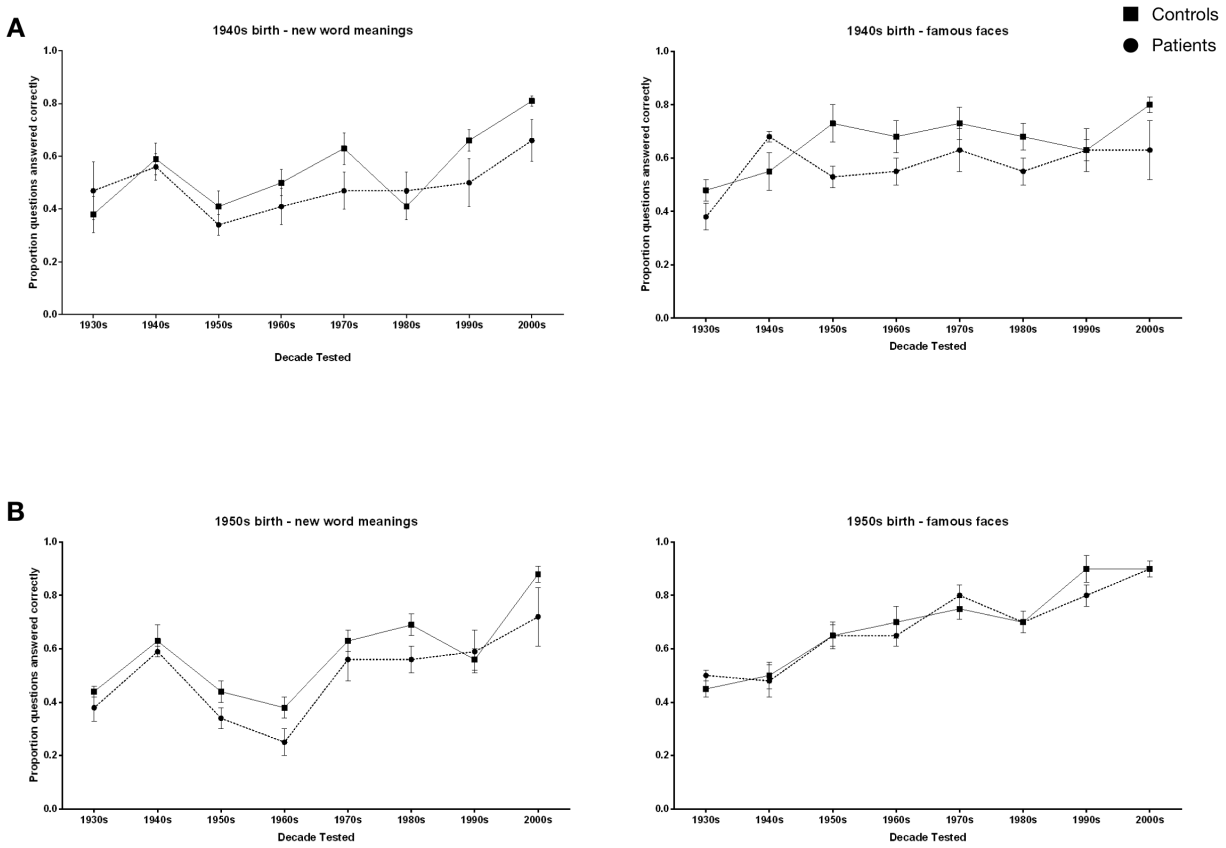


Table 6.4. Mann-Whitney *U* between groups tests comparing VGKC-complex LE patient performance against age-matched controls for word meaning and famous faces. Upper panel: Group patient performance for those born in the 1940s. Lower panel: Group patient performance for those born in the 1950s Significance was set at $p = 0.003$.

Modality	Decade tested	Patient median	Control median	*U*	*z*	*p*	*r*
Birth decade: 1940s (*n* = four patients, eight controls)							
Words	1930	0.47	0.38	12.5	-0.60	0.55	-0.17
	1940	0.56	0.59	14.0	-0.34	0.73	-0.10
	1950	0.34	0.41	12.0	-0.68	0.49	-0.20
	1960	0.41	0.50	8.0	-1.39	0.17	-0.40
	1970	0.47	0.63	9.0	-1.20	0.23	-0.35
	1980	0.47	0.41	15.0	-0.17	0.86	-0.05
	1990	0.50	0.66	8.5	-1.29	0.20	-0.37
	2000	0.66	0.81	6.0	-1.73	0.08	-0.50
Faces	1930	0.38	0.48	9.5	-1.12	0.26	-0.32
	1940	0.68	0.55	12.5	-0.60	0.55	-0.17
	1950	0.53	0.73	6.5	-1.63	0.10	-0.47
	1960	0.55	0.68	11.0	-0.87	0.38	-0.25
	1970	0.63	0.73	15.0	-0.17	0.86	-0.05
	1980	0.55	0.68	8.0	-1.38	0.17	-0.40
	1990	0.63	0.63	12.0	-0.69	0.49	-0.20
	2000	0.63	0.80	0.0	-2.82	0.005	-0.81
Birth decade: 1950s (*n* = four patients, nine controls)							
Words	1930	0.38	0.44	4.0	-2.20	0.03	-0.61
	1940	0.59	0.63	16.0	-0.31	0.76	-0.09
	1950	0.34	0.44	10.5	-1.17	0.24	-0.32
	1960	0.25	0.38	5.0	-2.02	0.04	-0.56
	1970	0.56	0.63	10.0	-1.25	0.21	-0.35
	1980	0.56	0.69	10.0	-1.24	0.22	-0.34
	1990	0.59	0.56	17.0	-0.16	0.88	-0.04
	2000	0.72	0.88	12.5	-0.86	0.39	-0.24
Faces	1930	0.50	0.45	15.5	-0.39	0.70	-0.11
	1940	0.48	0.50	17.0	-0.16	0.88	-0.04
	1950	0.65	0.65	13.5	-0.70	0.49	-0.19
	1960	0.65	0.70	13.0	-0.78	0.44	-0.22
	1970	0.80	0.75	17.5	-0.08	0.94	-0.02
	1980	0.70	0.70	15.0	-0.48	0.63	-0.13
	1990	0.80	0.90	8.5	-1.50	0.13	-0.42
	2000	0.90	0.90	13.5	-0.70	0.48	-0.19

6.4. Discussion

This chapter examined whether it was possible to construct, using FC-C for retrieval support, a novel measure of UK-based public semantic memory, for general knowledge, famous faces, and word meanings. This Survey of Semantic Memory (SSM) demonstrated a degree of temporal specificity. The famous faces and word meanings from this battery were then applied to eight patients during the convalescence phase following VGKC-complex LE – four born during the 1940s, and four born during the 1950s – in order to assess their public semantic memory for these modalities. There are three novel findings arising from this work.

First, the healthy participant data demonstrate that the methods used to construct the SSM produced an overall battery of 800 public semantic memory questions – across a wide range of subject areas – that demonstrated temporally specificity. The group level analysis from Section 6.3.1 show that decade of birth specifically modulates performance on the SSM, such that earlier birth decades are associated with greater proportion of correct responses. Moreover, the planned comparisons demonstrated that there was a significant improvement in performance when comparing the -1 decade to the +2 decade. This suggests that performance improves when the events occurred during the participants' lifetime, thereby further corroborating that the questions demonstrate temporal specificity. The planned comparisons for the word meaning analysis demonstrated that there was no significant increase in performance between the -1 and +2 decades for the 1940s and 1950s cohorts. However, it should be noted that the control group data is based on unequal group sizes, and is comprised of low number and, arguably, would not be eligible for parametric analyses.

Second, the *T*-test results from Table 6.3 suggest that those born between 1940 and 1970 performed significantly better than chance for questions arising in the decade prior to their birth. This tempers the results from the ANOVA and planned comparisons. These data suggest that the questions were not completely specific to the decade from they arose, but the planned comparisons demonstrate that performance still improves as the participant ages.

Third, four patients with VGKC-complex LE born during the 1940s, and four born during the 1950s were tested on this novel measure of public semantic memory, but for famous faces, and word meanings. Their performance for these modalities did not differ from that of age-matched controls. These data represent only a case-control series because of the low number of participants, for both patients and controls, and consequently have undergone non-parametric analyses. Despite this, the data are consistent with the prediction that there would be no difference between patients following VGKC-complex LE and controls on this measure of retrograde public semantic memory for famous faces and word meanings.

6.4.1. Pilot data for the Survey of Semantic Memory shows that the questions have temporal specificity

A key aim of this study to was devise a novel test of public semantic memory across a multiple modalities – specifically general knowledge, famous faces, and word meaning – that demonstrated that the questions were, to a large degree, temporally specific in nature, and that improvement in performance was observed when the questions arose from events that had occurred during the lifetime of a participant. However, the above chance performance of almost all the control groups for the -1 decade (except the 1980s for all three subtests), suggests that the questions were not as specific as hoped. One potential reason for this might be that participants acquire some semantic knowledge of temporally specific events that happened prior to their birth through personal interest, specialist knowledge, or education. Critically, this -1 performance is still significantly less than that of the performance during the +2 decade, suggesting that participants have a greater knowledge of events, personalities, and words entering the lexicon after they were born. This pilot data for the SSM arises from a small number of participants, and as such are reliable to distorting effects of extremes, either positive or negative, of participant performance. Even taking this into account, it is likely that the greater than chance performance will remain, and may be a feature of this type of public semantic memory task.

The only exception to this pattern of improving performance between the -1 and +2 decades was that no significant change in performance was found for the 1940s and 1950s cohorts for word meaning. This could be an effect of small participant numbers,

or that the words from the -1 decade for both groups did span across multiple time periods. Further testing will be needed to clarify these points.

6.4.4.1. Comparisons to previous examples of retrograde public semantic memory tasks

Steinvorth et al., (2005) devised a FC-C public semantic memory task to apply to two patients with MTL+ damage (WR and HM, see Chapter 4), for a series of events occurring in the decades between the 1940s and the 2000s. Whilst not explicitly demonstrating this with inferential statistics, the authors comment that their pilot study found that older controls were significantly better than younger adults (age ranges for either not explicitly stated) in answering questions from the more remote decades. This was taken as evidence that the questions were temporally specific, although, critically, group performance values for both older and younger adults was not reported. The current data extend this specificity to a decade-by-decade basis, and show that the SSM is at least comparable, for the three modalities tested, to previously published batteries.

6.4.2. Retrograde public semantic memory for famous faces, and word meanings is not impaired following VGKC-complex LE

The principal finding with regard to the VGKC-complex LE patients was that patients do not significantly differ from age-matched controls on this novel measure of retrograde public semantic memory. An important caveat was that patients and controls were not matched for educational attainment, or along other neuropsychological measures. As a general result though, this finding demonstrates that the VGKC-complex LE group appear to have intact semantic knowledge for at least word meanings and famous faces.

This intact performance for famous faces and word meanings is at variance with the evidence of an earlier study of retrograde public event memory in three patients with VGKC-complex LE (Chan et al., 2007). This study assessed public semantic memory using famous faces, and also public events, a modality not directly measured in the current study. As discussed earlier, responses required the recall of information that was scored on a two-point scale. These authors found that the patients had a temporally

extensive amnesia for both famous faces and public event memory – both during the acute illness and at 12 months – with no improvement in point score performance at either time point (Chan et al., 2007).

The major methodological difference between the two studies is that Chan *et al.* used a recall format to assess famous face performance, with partial cues being given if the face was not initially identified. Scoring was assigned in a dichotomous fashion as to whether the personality was identified or not (Chan et al., 2007). These data from Chan et al. perhaps illustrate why the format of response is important in semantic testing. FC-C paradigms (such as the one used in the current study) are more likely to test public semantic memory competence. Patients with hippocampally-restricted lesions tend to show a relative sparing of performance in FC-C paradigms (Holdstock et al., 2002; Westerberg et al., 2006). One candidate reason for the preserved FC-C memory performance could be that this form of memory is dependent upon anatomical structures such as the ERC and PRC for normal performance (Aggleton and Brown, 1999; Bowles et al., 2007; Norman and O'Reilly, 2003; Yonelinas et al., 2007), regions that have been previously been shown to remain intact following VGKC-complex LE (Wagner et al., 2015; Wagner et al., 2014). However, the relationship between ERC and/or PRC volume and performance was not assessed during this chapter, but shows, at best, a testable hypothesis for future experimentation.

Unfortunately, neither the current study or that of Chan et al., (2007) utilized a mixed design, where patients were tested contemporaneously for both retrograde public semantic memory recognition and recall performance, to determine whether the anterograde dissociations seen in Section 4.3.1 extend to retrograde public semantic memory. This is discussed in more detail below in Section 6.4.5.1.

The use of a FC-C recognition memory format was designed to provide as much retrieval support as possible, in order to assess for retrograde public event memory. Chan et al., (2007) have demonstrated that VGKC-complex LE is associated with impairment in retrograde public semantic memory, but without offering the retrieval support used in this current study, and so cannot be generalized to an impairment in public semantic memory. It has been shown above that when maximal retrieval support is offered to patients, normal performance for retrograde public semantic memory is observed.

However, this was tested on different patients, and so conclusions can only be made for the current patient cohort. Had there been a significant impairment in performance for the maximal retrieval support afforded by the FC-C format, then it could be reasonably concluded that a greater dysfunction to the semantic memory network could be observed in this cohort.

6.4.3. Public semantic memory performance following lesions to the medial temporal lobe

More broadly, the results presented here can be compared to other studies of public event memory in other patients with lesions restricted to the MTL or overlying cortex (MTL+). To summarise, the data presented in this chapter suggests that eight patients with VGKC-complex LE are unimpaired on a FC-C task for famous faces and word meanings, all of which have become prominent during the lifetime of a patient. The data from Chapter 3 suggest that VGKC-complex LE is associated with focal CA3 lesions, and that longitudinal whole brain imaging studies suggest that there is also just hippocampal atrophy in chronic VGKC-complex LE (Wagner et al., 2015; Wagner et al., 2014). However, the public semantic memory data emerging from other patients with presumed focal lesions to the MTL are mixed.

Some studies shown that those with MTL restricted lesions are normal for both recognition and recall of vocabulary, famous name familiarity and public events (Reed and Squire, 1998; Steinvorth et al., 2005; Verfaellie et al., 1995), when tested using a variety of modalities (i.e., FC-C or recall). Others have shown temporally limited deficits in both recognition and recall for vocabulary, famous faces or public events (Kopelman, 1989; Kopelman et al., 1999; Manns et al., 2003). Interestingly, more severe deficits were seen with more lateralized temporal lobe lesions (Bright et al., 2006), and in patients with AD (Kopelman, 1989), where the extra-hippocampal cortices (e.g., ERC) are implicated as being effected early in the disease (Dickerson et al., 2001; Du et al., 2007).

The behavioural data from this study seems to be in general agreement with a larger body of fMRI data and neuropsychological data suggesting that the lateral temporal cortices are more central to the storage of the different types of semantic memory – such as personal and public semantic memory – than more medial regions

(Graham and Hodges, 1997; Hodges and McCarthy, 1995; Maguire et al., 2000). fMRI studies have also shown hippocampal activity during the retrieval of public events (Maguire, 2001), and famous faces (Bernard et al., 2004; Kapur et al., 1995; Leveroni et al., 2000), as well as parahippocampal activation for famous faces (Haist et al., 2001).

In keeping with these data, the pattern of memory loss observed in those patients with MTL+ lesions show a more pervasive diminution of both recall and recognition across both personal (recall via the AMI), and public semantic (Y/N for dead or alive, recall and then FC-C for famous events and famous faces; Cipolotti et al., 2001; Reed and Squire, 1998; Steinvorth et al., 2005; Verfaellie et al., 2000). Interestingly, one study found dissociation between recall and recognition only for famous faces (McCarthy et al., 2005). This suggests that the separation between recognition and recall is either not easily amenable to experimental testing, that the relationship between these two mnemonic phenomena are more tightly linked than suggested by the data shown in Section 6.1.2, or that the damage in those patients not demonstrating dissociations extends beyond the hippocampi into the overlying cortical areas such as ERC and PRC.

The data obtained in this chapter suggest that patients with VGKC-complex LE had preserved, compared to control participants, retrograde public event memory when tested in a FC-C format. This pattern of retrieval is most in keeping with other neuropsychological studies of public semantic memory in patients with lesions to the MTL structures (Cipolotti et al., 2001; McCarthy et al., 2005; Reed and Squire, 1998; Steinvorth et al., 2005; Verfaellie et al., 2000), and that there is a relative preservation of public semantic memory following VGKC-complex LE.

6.4.4. Standardization of the Survey of Semantic Memory (SSM)

The present study sought to construct a measure of public semantic memory for United Kingdom-based memory experiments informed by experimental and theoretical treatments of semantic memory. Preliminary results from a small population of healthy participants (71 healthy participants: three participants born during the 1930s, eight from the 1940s, nine from the 1950s, 17 from the 1960s, seven from the 1970s, 15 from the 1980s, and 12 from the 1990s) show that these questions are tending towards temporal-specificity. In order to be able to use the SSM as a measure of retrograde semantic

memory across multiple experimental settings, it needs to be standardized such that performance of an individual participant can assessed by comparisons to a large normalized population, in order to derive a standardized metric such as a standard score, *Z*-score or centile performance.

6.4.4.1. Validating the individual questions

The initial analyses demonstrated that the questions, when comparing proportion of correct responses between the -1 and +2 decades, were associated with improved performance when the questions arose from time periods when the participant was alive. This suggested that there was a degree of temporal specificity for the questions used to construct the SSM, but the *T*-tests demonstrated that performance for these -1 decades was still above chance for every decade of birth from the 1940s through to the 1980s. Other independent methods can be used to determine whether this is the case. The temporal specificity of the questions could be assessed by asking at least 42 participants per decade (using a one-tailed tests, that assumes performance is better if the participant was alive during the decade in question, with an anticipated effect size of 0.8, a power level of 0.8, and with a probability of 0.05). These groups would rate how temporally specific they think each of the 800 questions are. This could be measured using a five-point Likert-type scale from 1 (not specific to this decade) through to 5 (very specific to this decade). Any questions found to have consistently low ratings across all participants could be excluded from the question battery, with those with consistently high scores (for instance, 3.5, although this is not based on any evidence in the literature) might suggest that the question is highly temporally specific. On a group level basis, the averaged Likert-type score for each individual question for each decade of birth could then be used as a covariate in an analysis of covariance (ANCOVA) in a method used below, such as principal component analysis.

6.4.4.2. Methodology for creating standard scores of performance for the SSM

The SSM is predicated on having multiple norms according to the decade of birth. One unavoidable problem with this approach is where the divisions are drawn between participants. A participant born in 1958 is likely to perform more in line with someone born in 1960 compared to a decade of birth peer born in 1951. Therefore we might expect age to have an influencing factor in performance (Capitani and Laiacona,

1997). It is also likely that the length of education influences performance on measure of retrograde public event memory (Capitani and Laiacona, 1997). This suggests that in any test population there are two potential modifying factors and that the standardization of the SSM might make use of multiple regressions to account for these modifying factors (Capitani and Laiacona, 1997). It was suggested above that 42 subjects would be required per decade of birth to standardize the SSM. When taking into account the modifying effects of age and length of education, a previous study has described how 90 or more participants are needed per decade group (Capitani and Laiacona, 1997). This number is required in order to be 95% confident that at least 95% of the test population are between the extreme observations of the modifying variables, in this case between those born at the beginning and end of a decade, and those with less time in formal education (e.g., 11 years in the UK), and those with longer periods of formal education (e.g., 21 years for those with postgraduate degrees).

A technique has been developed to standardize psychometric tests, whilst accounting for factors that can modify performance (Capitani and Laiacona, 1997; Della Rosa et al., 2014), including the recent development of a novel test of semantic memory (Della Rosa et al., 2014). This technique is based on applying simple linear regressions to identify significant predictors of test performance (usually age and years of education; (Della Rosa et al., 2014)) that are then be taken forward to a multiple regression. This multiple regression would then form the basis of an equation that converts the raw score into a corrected one using the regression values as constants. Once corrected, these scores can then be standardized, detailed below, to provide a measure of performance that can be compared across age groups or between a patient and a control population (as demonstrated in Chapter 4).

Most common standardization schemes aim to produce scores arising from a normal population, with the standard scores reflects the deviation from the mean expressed as the standard deviation. For example, most neuropsychological tests have a 19-point scale, where the mean score is assigned a value of 10, and where one standard deviation is equal to 3 (therefore a value ± 1 is equal to 0.3 of a standard deviation). This 1-19 range therefore covers three standard deviations and as such 99.73% of the population. Both the raw and corrected data should be tested for normality using the Shapiro-Wilk test, and if the assumption of normality is violated, then the data could be

transformed using a Box-Cox power transform, so that the data becomes normalized and therefore amenable to this parametrically-determined standardization process. The normal or transformed data form a series of ordered residuals that are then plotted against the corresponding quantile of the standard normal distribution to give values that equate to a standard score of ±1 (SD: 0.33), ±2 (SD: 0.67), ±3 (SD: 1.0), ±4 (SD: 1.33) etc. from the mean value assigned as a score of 10. The values between those that demarcate the boundary from one standard score to another would be used to provide a range of values assigned to any particular standard score. A similar methodology has been used in previous examples of standardized neuropsychological tests (e.g., the Test of Everyday Attention, (Robertson et al., 1994)).

6.4.4.3. Item-specific analysis

The discussion above concerning standardization assumes that all 100 questions from each decade will remain. For the famous faces and new words, it is reasonable to keep all of the questions, as the number of items within each decade is close to the lower limit of the number of items amenable to parametric analyses. The question forming these subtests should still undergo scrutiny to see whether they are too easy (i.e., answered by everyone), too hard (i.e., answered by no one), or that the temporal specificity analysis demonstrates that they are not specific to a particular decade.

The general knowledge subtest was constructed of 64 questions (Table 6.2) – 32 news event questions, and eight each of film, music, radio/television, and sport. The non-news event questions contain a small *n* so could not be reduced in number, although they should face the same scrutiny as the famous faces and word meanings. Therefore, only the news events could be reasonably pared down to a smaller number of questions (e.g., 20, as with famous faces).

Several techniques exist to determine which of these news event questions could be removed can reliably discriminate performance between subjects within any given decade. One recent method that could be applied is similar to that used during the recent validation of the Survey of Autobiographical Memory (SAM), designed to allow participants to self-report and assess their memory function across four autobiographical mnemonic categories: personal and episodic autobiographical memories (AM), future prospection (that is the ability to imagine future events from an allocentric perspective)

and spatial memory (Palombo et al., 2013). These authors used a multiple components analysis to determine which questions (from a bank of 42 episodic AM questions, 24 semantic AM items, 20 spatial items and 16 future prospection items) were able to best describe self-reported memory function, but these answers were obtained in an ordinal format (i.e., yes or no). However, with scalar data (as typified by the raw scores available here), a principal component analysis (PCA) should be used (Bartlett, 1950). PCA predicts that most variation in any dataset occurs in only a few dimensions, and that the remainder is dispersed randomly in the component space (that is to say variation within the data cannot be ascribed to components outwith the most predictive dimensions (Bartlett, 1950).

Analysis of the data using a PCA based approach would identify those questions that have discriminability between subjects within a particular decade of birth. Following the PCA, either an arbitrary number of questions that explain the group variability (perhaps 20 or 30) or all of the questions that account for 95% of the variability could be retained to construct the final battery. Performance across these questions could then be standardized according to the method outlined above. This will provide a standardized measure of a subject's performance for those questions known to have explanatory power within an age-matched population.

6.4.5. Limitations and future work

6.4.5.1. Hippocampal contributions to retrograde public semantic memory

The most pressing limitation of this work is that it was only administered to eight patients, and as such it is difficult to generalize this result to VGKC-complex LE, let alone patients with focal MTL lesions. Despite this low number of patients (though comparably more than Chan et al., 2007), these results suggest VGKC-complex LE patients were intact in their performance on retrograde public semantic memory for word meanings and famous faces, as tested with the FC-C format. There remains a discrepancy between the findings of this study and that of Chan et al., (2007), whereby the divergent results – methodological differences notwithstanding – could represent an undersampling of the patient population. Extending this study to include more patients would help distinguish between the two studies. It should also be noted that the patients were not tested on the general knowledge questions, due to time constraints and because

the news event questions might have been later reduced in number (see Section 6.4.4), and so the current results are only generalizable to famous faces and new words. VGKC-complex LE patient performance for the general knowledge questions could be easily assayed in a follow-up study, with the specific hypothesis being that they will have normal performance for this subtest as well, or at least when tested in the FC-C format.

Much of the discussion concerning the discrepancies found between the present study and that of Chan et al., (2007) focuses on the methodological differences between recognition and recall. This is an area that could be easily addressed with the battery presented here. The questions could be written in a free-recall fashion and patients could be presented in either a recall or recognition format (although this would need to be counterbalanced such that an equal number of recognition and recall questions were answered). The benefit of using the large number of questions used to construct the SSM would mean that even for the word meanings – the smallest subtest within each decade at 16 questions – there would be enough questions to meet the assumptions of parametric analysis (i.e., a minimum of eight) for every subtest in every domain.

6.4.5.2. Construction of a novel measure of retrograde public semantic memory

The chief limitation for this process of standardization in the current dataset is the small and unequal group numbers. As mentioned above, approximately 100 participants per decade would be required to yield enough statistical power to undertake appropriate inferential analyses. Moreover, the temporal-specificity of the questions would ideally have been independently assessed for temporal specificity, via the validation techniques outlined in Section 6.4.4.1. The interpretation of the current results that are reported here suggest that the at the level of the subtests, the SSM demonstrates some temporal specificity, given that there is a significant improvement in proportion of correct responses from the -1 to +2 decade. Without information independently rating how temporally specific the questions are, it is impossible to critique the suitability of each individual question. The validation method outlined above is one method that can be applied to address the extent to which each question can be considered temporally specific can be answered. Another would be use item-specific analyses to determine which questions appear to have sensitivity in distinguishing performance between subjects, and this could performed through the PCA analysis detailed in 6.4.4.3.

6.4.6. Conclusion

This chapter has two separate conclusions. Viewing the thesis as a whole, this chapter demonstrates that the SSM is an effective novel tool for assessing retrograde public semantic memory in VGKC-complex LE. This chapter also demonstrated that in eight VGKC-complex LE patients that public semantic memory for famous faces and new words is intact in the chronic phase of the disease. This data is at least equivalent to previous studies of public semantic memory performance following MTL damage, and accords well with the attendant literature suggesting that public semantic memory performance is independent of the hippocampus.

The second conclusion is that the SSM could provide a novel measure of public semantic memory that could be standardized and used in other UK-based studies of public semantic memory. Even at the early stage of research presented here, it seems that performance for the three separate domains of SSM improve for those decades during which the subject was alive. It is therefore reasonable to suggest that the SSM demonstrates a degree of temporal specificity. However, further work is needed to standardize and evaluate the SSM.

Chapter 7

Assessing the cognitive sequelae of VGKC-complex LE and its utility as a model of hippocampal amnesia

7.1. Introduction: VGKC-complex LE as a model of hippocampal dysfunction

The central tenant of this thesis has been to test whether VGKC-complex LE can be used as a human model of hippocampal dysfunction, and, if so, can causal relationships between behaviour and anatomy be described. The neuroradiological, neuropsychological, and mnemonic characterization undertaken in Chapters 3-6 can now be used to investigate not only the relationships between anterograde and retrograde memory performance after focal hippocampal damage, but also those between hippocampal subfield volumes and behavioural performance.

7.1.1. The theoretical relationship between hippocampal subfield volumes, and performance on mnemonic tasks

One mechanism by which inter-individual variability in behavioural experiments have been assumed to arise, is due to differences in volumes of the specific brain regions subserving any given cognitive process. In this model larger regional brain volume is linked with improved behavioural performance (Kanai and Rees, 2011). (Other

mechanisms may also include increased neuronal density (Sass et al., 1995), increased white matter connectivity (reviewed in Roberts et al., 2013), and neuronal coherence (reviewed in Fries, 2005). This introduction will firstly consider the evidence suggesting a relationship between standardized neuropsychological tests, and hippocampal subfield volume. Secondly, relationships between the anterograde memory, on both standardized neuropsychology tests and the episodic memory from the Autobiographical Interview (see Chapter 5), and retrograde memory will be considered. Thirdly, the relationship between both retrograde episodic and public semantic memory performance, and subfield volumes will be considered.

7.1.2. Hippocampal subfield volumes and anterograde mnemonic neuropsychological performance

Firstly, the neuropsychological hypotheses for this chapter need to be established, specifically by assessing material specificity of the left and right hippocampi, and then by the specific subfield contributions to neuropsychological performance, in both health and disease.

7.1.2.1. Material-specificity differences between the left and right hippocampi

A longstanding distinction exists between the type of materials that might differentially recruit the left and right hippocampus during normal behaviour (as briefly discussed in Section 4.1.3.2.1.3). Even though the left and right hippocampus are comprised of the same anatomical areas and connectivity – including cortical inputs, see Figure 1.1 – there appears to be material-specific differences in the type of information preferentially processed by the left and right hippocampi, with the left hippocampus being predominantly involved in verbal memory, and the right more concerned with non-verbal memory (Squire et al., 1992). It has been suggested that this material-specificity is dictated by asymmetry elsewhere in the brain: the left hemisphere makes greater contributions to tasks requiring language processing and increased BOLD signal is seen for the left hippocampus in verbal memory fMRI tasks (Hutsler and Galuske, 2003); the right hemisphere contributes more to visuospatial tasks, and the right hippocampus seems to show greater BOLD signal change in spatial memory tasks (Motley and Kirwan, 2012).

Therefore, the analyses in this chapter between hippocampal subfield volume, and neuropsychological performance will lateralize the subfield volumes, in order to assess for this well-described lateralized material-specificity.

7.1.2.2. The relationships between hippocampal subfield volumes and neuropsychological performance

One recent study evaluated the relationship between performance on standardized neuropsychological and hippocampal subfield volumes measured at 4.7-Tesla (Travis et al., 2014b). In 34 healthy controls, three hippocampal subfield volumes (CA1-3, DG and SUB) were quantified along the entire length of the hippocampus, and then correlated to a series of neuropsychological tests arising from the Wechsler Memory Scale-IV. These included: immediate visuospatial memory (Visual Reproduction 1, Designs 1 Content, Designs 1 Spatial), immediate auditory memory (Logical Memory 1, Verbal Paired Associates 1), delayed visuospatial memory (Visual Reproduction 2, Design 2 Content, Design 2 Spatial), and delayed auditory memory (Logical Memory 2, Verbal Paired Associates 2) (Travis et al., 2014b). CA1-3 and DG volumes in the left hippocampal head were positively correlated with performance on Logical Memory 1, a verbal memory task (as argued in this thesis), but no other associations were found.

Mueller et al., (2011) also measured subfield volumes at 4.0-Telsa from the body of the hippocampus, and found that the DG/CA3 and CA1 volumes positively correlated with performance on a word list from the California Verbal Learning Test-II (CVLT-II). As described above, Travis et al., (2014b) found that just subfield volumes from the hippocampal head were correlated verbal memory performance, a finding thought to be due to a difference in the neuropsychological task used, despite the general similarity in their underlying task structure. It is also hard to compare the conclusions of these studies on methodological grounds, given the significant differences between the segmentation protocols used to estimate hippocampal subfield volumes.

Mueller et al., (2011) also discovered that CA3/DG volume had a positive correlation with performance on a word list task for its immediate (i.e., seconds) retrieval, but for delayed retrieval CA1 volume was correlated with retrieval performance. It was found in Chapter 4 that word list performance is normal in the VGKC-complex LE

group, and, by extension, these data, and consonant data from fMRI, suggest that item-specific memories, such as word lists, can be supported elsewhere in the medial temporal lobe (MTL) complex (such as the temporal pole, Wolk et al., 2011).

Travis et al., (2014b) likewise found that visuospatial performance (as measured with forced choice visual recognition) was positively correlated with CA1-3 and DG volumes for both the left and right hippocampus. This is generally agrees with the discussion in Section 4.1.3.2, that suggests that the hippocampus is more likely to be involved with tasks where multiple stimuli have to be combined, in this case the binding of object and location. (Travis et al., 2014a) also found that in a group of 15 healthy controls that spatial memory – as measured in the WMS-IV Designs and Visual Reproduction tasks – was positively correlated with DG volume.

Neuropsychology-hippocampal subfield correlative experiments have been done in Alzheimer's disease (AD) at 7.0-Tesla, but these studies measured cell body layer widths and not subfield volumes (Kerchner et al., 2014; Kerchner et al., 2012). Therefore, direct comparisons between these studies and the current data cannot be undertaken.

These studies quantify hippocampal subfields differently from the present study; however, they show that such an approach in a disease population could be extended to include VGKC-complex LE. This chapter will also attempt to provide a more fine-grained approach to assessing relationships between neuropsychological function, analyzing both verbal and visual immediate recall separately, as well as delayed verbal recall.

7.1.2.4. Interpretative difficulties arising from correlation-based analyses

These studies cited in Section 7.1.2 generally show that using correlation-based analyses to assess for relationships between neuropsychological performance, laterality, and subfield volumes can produce variable results. Moreover, as the discussion in Section 4.1.3.2, and further discussion below indicate, it is difficult to reconcile the hippocampal specificity of neuropsychological tests with their reported subfield volume associations, given many of these tests are actually supported independently of the hippocampus or are mediated by large-scale networks. Moreover, correlation cannot imply causation, so

assessing for causal relationships between behavioural performance and anatomical volumes would necessarily require regression-based analyses.

Prior studies have also collapsed across subfields when examining the links between subfield volume and behaviour (e.g., Mueller et al., 2011; Travis et al., 2014a; Travis et al., 2014b). Such an approach limits the information can be gleaned from each individual subfield volume and neuropsychological performance, through such mechanisms as misattribution of function to specific subfield regions, or via the diluting effects of collapsing a functionally important one subfield with other, less functionally significant subfield. To tackle these limitations, this chapter will assess the relationship between individual hippocampal subfield volumes and neuropsychological test performance using a linear multiple regression-based analysis, using imaging data from Chapter 3 where the subfields were segmented according to directly visualized biophysical boundaries between subfields.

7.1.2.5. Neuropsychological performance and subfield findings from the current VGKC-complex LE population

The results from Chapter 3 demonstrate that the CA3 is the most atrophied subfield following VGKC-complex LE, and therefore may provide the best explanatory value for behavioural differences between VGKC-complex LE patients and controls. Intact volumes for the CA2, DG, and SUB subfields do not necessarily imply normal physiological functioning of the these subfields, nor of the remainder of the hippocampus, and, by extension, able to support normal behavioural performance. Given CA3 occurs early within the trisynpatic circuit (see Figure 1.1), it is plausible that the amnesia arises not from a specific reliance on CA3 for normal performance, but rather from a degradation in the quality of information reaching the critical subfield – such as CA1 or DG – resulting in amnesia. With this caveat in mind, the specific empirical question in this experiment is does the degree of CA3 atrophy observed, or any other volume, predict anterograde mnemonic performance? These data cannot specifically address the functional role of the CA3, or other subfields, in the successful performance of these tasks.

Moreover, the literature cited in Section 7.1.2.1 also support the ability to test whether or not left hippocampal subfield volumes predict verbal memory performance,

and right hippocampal volumes predict visual memory performance. The CA3 subfield damage was shown to be bilateral, but there is no reason, *a priori*, that CA3 volumes should specifically predict verbal or visual performance across the lateralized hippocampi, unless their volume loss impairs the physiological function of the entire trisynaptic hippocampal circuit. The current cohort of VGKC-complex LE patients were found to have significantly reduced neuropsychological performance for immediate verbal and visual recall and delayed verbal recall, as compared to a standardized control population. The preceding discussion suggests that the left hippocampal subfield volume might predict the immediate and delayed verbal recall performance, whereas right hippocampal subfield volumes might predict the immediate visual recall performance.

The literature cited in Section 7.1.2.1 also suggests that other subfield volumes (e.g., CA1, DG) are correlated with neuropsychological performance, and as such should be included in the analyses. Given the only neuropsychological indices impaired on testing were immediate verbal and visual, and delayed verbal recall, only these three domains should be tested, as impaired performance for these measures might be predicted by the pathological CA3 loss. The concerns regarding hippocampal dependence of the neuropsychological tests also suggest that undertaking regression-based analyses in the other hippocampal independent measures (e.g., recognition memory, single-item memory, see Section 4.1.3.2) may yield spurious results that are not easily reconcilable with the current literature.

7.1.3. The relationship between anterograde neuropsychological mnemonic performance, and retrograde declarative memory performance in disease

A notable absence in the amnesia literature is the exploration of the relationship between anterograde amnesia (AA), such as with the neuropsychological data from Chapter 4, and retrograde amnesia (RA), in this case the AI internal detail data from Chapter 5. The severity of AA is usually qualitatively correlated with the severity of RA (Kopelman, 1989; Squire and Alvarez, 1995; Wicklegren, 1979), although sometimes the RA can appear disproportionately severe in comparison to AA (Barr et al., 1990; Bright et al., 2006; Hornberger et al., 2010; Kapur et al., 1992; Milton et al., 2010; Reed and Squire, 1998; Sehm et al., 2011). Less frequently AA can occur despite the absence of RA, although these studies tend not to rely on quantitative methods of measuring

mnemonic performance (Russell and Nathan, 1946). Invariably, in these experiments, AA is assessed using standardized neuropsychological tests, and RA through personal and public semantic memory, such as with the AMI; both of these types of tests are rarely associated with hippocampal function (see Chapters 4-6). These studies have also generally relied on qualitative descriptions for the relationship between AA and RA, and do not apply any inferential statistics.

Previous work has demonstrated that the delayed-recall components of anterograde learning paradigms, such as story learning, are reliant upon the MTL structures (Helmstaedter et al., 1997), and so it would be expected that a causal relationship between delayed verbal recall, and the anterograde internal and retrograde internal detail point scores arising from the AI might be observed in the current patient group. As both the delayed verbal recall, and internal detail scores from the AI are scalar variables, they would be amenable to regression-based analyses aim to model the relationship between a dependent variable, and a series of predictive independent variables.

Commensurate with the preceding discussion, the operational definitions used to characterise AA and RA also vary across studies, as does how AA and RA are measured. For instance, a recent quantitative approach to this problem attempted to correlate cumulative measures of AA with measures of RA in a group of 11 patients with lesions ranging from purely hippocampal through to extensive medial temporal lobe (MTL+) lesions (Smith et al., 2013). AA was measured with the delayed-recall of the ROCF, paired associate learning (10 unrelated word pairs; Squire and Shimamura, 1986), RAVLT word list learning, WMS-R logical memory, and the memory subscale from the Dementia Rating Scale. *Z*-scores were determined for each of these measures and then averaged together to provide a composite *Z*-score for anterograde memory (Smith et al., 2013), at variance with the argument proposed in Section 4.1.3.2. Retrograde memory was assessed by a retrograde public events task – that is the hippocampal-independent pubic semantic memory, Chapter 6 – that covered notable news events from 1938 to 2004, with childhood memories left untested, as arguably recall from these periods is poor, even in healthy controls (Squire, 1974). The test was administered in a free recall paradigm (i.e. 'Who shot JFK?') offering no retrieval support, suggesting that public memory competence was not tested adequately, and thereby incompletely describing

patient competence for this type of memory (see Chapter 6 for further discussion). The authors found that the greater the severity of the AA was associated with increased severity of the RA but with no predictive relationship described. Moreover, the degree of damage to the MTL and surrounding structures was associated with the severity of the RA and AA. These results are broadly in keeping with other patient series (Blomert and Sisler, 1974; Russell and Nathan, 1946).

As the authors acknowledge, the conclusions regarding the relationship between retrograde episodic amnesia and anterograde memory are limited assessing RA only on memories for public events. Public semantic memory does not appear to be a hippocampal dependent task, so whilst this study explores relationships between those memories putatively subserved by the MTL complex (e.g., public or personal semantic memory), it cannot adequately describe the relationship between anterograde and retrograde mnemonic measures of hippocampal function.

This chapter will use the values for the Five Years prior to illness and Last Year internal detail point scores as the measure of retrograde and anterograde memory performance, alongside the neuropsychological measures already determined. As the results from Section 5.3.3-4 demonstrate, there appears to no temporal gradient to internal detail performance for this VGKC-complex LE cohort, so arguably these memories could be considered the same mnemonic entities. On these grounds, a global retrograde score from the AI derived from these collapsed epochs score will also be used later to evaluate its relationship to the neuropsychological measures.

7.1.4. The relationship between anterograde and early retrograde episodic memory performance

It is widely agreed that episodic memories from the most recent five years are hippocampal-dependent constructs (Nadel and Moscovitch, 1997; Squire and Alvarez, 1995), therefore should be sensitive markers of hippocampal function. Importantly, however, episodic memories from this period have not been evaluated within a regression-based model to assess whether the quality of episodic re-experiencing can be used to predict more remote episodic memory re-experiencing. The results from Chapter 5 found that there was no significant difference in episodic re-experiencing – as

operationalized by internal detail point score performance – across the lifetime when considering patients and controls as separate groups – that is no evidence of a temporal gradient of episodic memory loss. This result suggested that the hippocampus is central to episodic memory retrieval across the lifetime. To formalize and explore this relationship further, it should be possible use internal detail point scores for the anterograde and Five Years memories from the AI, in order to predict performance across the lifetime.

The extended administration of the AI from Chapter 5, by-and-large, provided a memory for each decade of life for the older participants (11 patients and 11 controls). If all internal detail point scores for each retrograde episodic memory (with perhaps the exception of the most remote memory, see Section 5.4.2) can be predicted by performance on the anterograde and/or Five Years memory, then this would suggest a causal relationship, and, by inference, indicate that greater degrees of hippocampal damage are associated with equivalent decrements in the retrieval of all retrograde episodic memories.

It could also be argued that the relationship between anterograde and retrograde episodic internal detail point score are not assessing the same mnemonic constructs, given the anterograde memory was acquired during the post-morbid period. Therefore, arguably, this memory was acquired with a damaged hippocampus. The early retrograde memory, acquired within five years of the illness, remains a hippocampal-dependent memory. As it was acquired with a normal hippocampus, any deficits in performance should reflect impaired hippocampal function. A further regression should be undertaken to assess whether early retrograde internal detail point score could predict internal detail point score for the more remote retrograde episodic memories for the extended administration of the AI.

7.1.5. Hippocampal subfields are critical to retrograde episodic memory performance

The relationship between hippocampal subfield pathology and episodic memory performance has been the subject of previous investigation. (Bartsch et al., 2011) sought to quantify retrograde memories that were both noetic (i.e., personal semantic) and autonoetic (i.e., episodic), and to relate behavioural performance to evidence of

hippocampal lesions in patients with transient global amnesia (TGA), a syndrome characterized by rapid onset antero- and retrograde memory for a period of six-ten hours (Bartsch et al., 2010). Highly focal, and transient, lesions occur in the CA1 field of the hippocampus, or at least to the Sommer region of the hippocampus (Bartsch et al., 2007; Bartsch et al., 2006; Bartsch et al., 2010), and are believed to induce a transient functional dissociation of the CA1, and hence the microcircuitry of the hippocampus (Bartsch et al., 2006; Bartsch et al., 2008; Bartsch et al., 2010).

Sixteen participants with TGA were assessed on a previously published questionnaire (Piolino et al., 2006) that involved describing four spatiotemporal events across five time periods (0-17, 18-30, ≥30 excluding the most recent five years, the most recent five years not including the most recent 12 months, and the most recent 12 months). All memories were scored according to a four point rating scale (similar to the Autobiographical Memory Interview, see Chapter 5). Memories that scored four *and* were self-rated by the participant as being consciously remembered were assigned as 'strictly episodic' memories. These were subjectively assigned notations, and differ from the conceptualization of autonoesis in the Autobiographical Interview (AI) whereby higher internal detail point scores are thought to represent increasingly re-experiential accounts. The behavioural data in Bartsch *et al.* resulted a series of non-linear performances (i.e., four ordinal groupings) in patients and controls, and as such a data set that would not be amenable to regression-based analyses on account of a lack of linear range in scores, and is relatively insensitive to objective differences in episodic memory performance afforded by the AI (see Section 5.1.4 for further discussion).

The principal finding was that patients were significantly impaired on all three measures of retrograde memory during their acute illness, but improved to the same level of performance as controls at follow-up. The authors interpreted this as demonstrating that the CA1 region is central to the experience of autonoetic memories. As discussed at length in Section 5.1.4, the tool used to assess autonoesis was a four-mark scale, which thereby limited the discrimination between detailed semantic, and true episodic memories difficult. Likewise, there was no relation of anatomy to function other than a description of the location of the lesion along the longitudinal axis of the hippocampus. The authors also report that the Sommer region is predominantly comprised of CA1; however, as the segmentation protocol from Chapter 3 and other studies show (Wisse et

al., 2014; Wisse et al., 2012), there can be on occasion CA2 and CA3 tissue that resides in the lateral-most aspect of the hippocampus, suggesting the approach of Bartsch *et al.* may misattribute CA fields.

The purpose of using the data from Chapters 3 and 5 will be two-fold: (1) to use anatomical accurate *in vivo* subfield estimations, according to the natural biophysical boundaries, to prevent the problem of misattribution, and (2) to use the linear nature of the both the segmentation and AI data as independent and dependent variables respectively in a linear regression, in order to assess for a specific predictive relationship between subfield volume and internal detail point score on the AI for both patients and controls.

7.1.6. Personal semantic memory performance should not be reliant upon hippocampal subfield volumes

As elaborated in Chapter 6, the important distinction between personal semantic memory and episodic memory is that personal semantic memory is devoid of the unique contextual details that characterize an episodic event (i.e. remembering the time, place and event details; (Tulving, 1983)).

The AI provides a measure of both public and personal semantic memory (via the semantic score and external details score respectively); however, these are not the primary aim of the tool and as such the conclusions inferred from the personal semantic measure on the AI are necessarily limited in scope. By contrast, the Autobiographical Memory Interview (AMI) specifically tests for personal semantic memory, and offers retrieval support by providing a series of structured questions for each time period it tests.

Given that personal semantic memory appears to represent conceptual knowledge, it has been suggested that its neural substrate is similar to that as general semantic memory, the neocortical regions of the temporal lobe, and not the medial temporal lobe (MTL; Greenberg and Verfaellie, 2010). This has been supported by neuropsychological studies that have shown the preservation of personal semantic memory despite the impairment of episodic memories (Cernak and O'Connor, 1983; Damasio et al., 1985; Warrington and Duchen, 1992), patterns demonstrated in Chapters

4 and 5. The absence of a temporal gradient of personal semantic memory loss following focal MTL damage also suggests that these structures are not necessary for the retrieval of memories no matter their age (Grilli and Verfaellie, 2014; Klein and Gangi, 2010; Klein and Lax, 2010). These data would suggest that should patients perform significantly worse than controls on both internal *and* external measures of the AI, then one could reasonable assume that the damage observed extends beyond the MTL and into the anterior temporal pole, for instance.

There are critics of this approach and view of personal semantic memory (Squire, 1992), who posit a more unitary account of MTL, suggesting that it functions to support both episodic and semantic memory (presumably both personal and public) for a similar amount of time whilst both undergo neocortical consolidation. Once this process has taken place, both forms of memory remain independent of the hippocampus. According to this view, focal hippocampal lesions should therefore not only produce a temporal gradient in episodic memory loss but also a temporal gradient for semantic memory as well.

The use of regressions between subfield volume and personal semantic memory performance would help distinguish between those who propound unitary accounts of hippocampal function, and those that suggest functional specialization exists with the MTL for different forms of declarative memory.

7.1.7. Summary: aims and hypotheses

The aim of this chapter was to conduct a series of robust multiple linear regressions using Huber's method to correct for outliers (detailed in Section 2.5.3.1), in order to investigate the relationships between neuropsychological pathology (immediate verbal and visual recall, delayed verbal recall), anterograde and retrograde episodic performance as conceptualized by internal detail point score from the AI, personal semantic memory performance as measured by the AMI, and the CA3 volume loss. The predictions for this chapter are:

1. Left hippocampal subfield volumes will predict immediate verbal and delayed verbal recall performance, and that right subfield volumes will

predict immediate visual recall performance. This will be specific to the CA fields, as detailed in Section 7.1.2.2.

2. Internal detail performance for the anterograde and retrograde memory will positively predict performance for the immediate verbal and visual recall, and the delayed verbal recall indices. Greater cumulative retrograde performance, as measured by internal detail performance from the AI, will also positively predict increased neuropsychological performance for the indices listed above.
3. Both anterograde and early retrograde memory internal detail point scores will predict internal point scores for the more remote episodic memories.
4. CA3 volume, in health and disease, will predict internal point score performance for both the standard and modified administration of the AI.
5. CA3 volume will not significantly predict performance for personal semantic memory, as measured on the AMI.

7.2. Methods

See Section 2.5.

7.3. Results

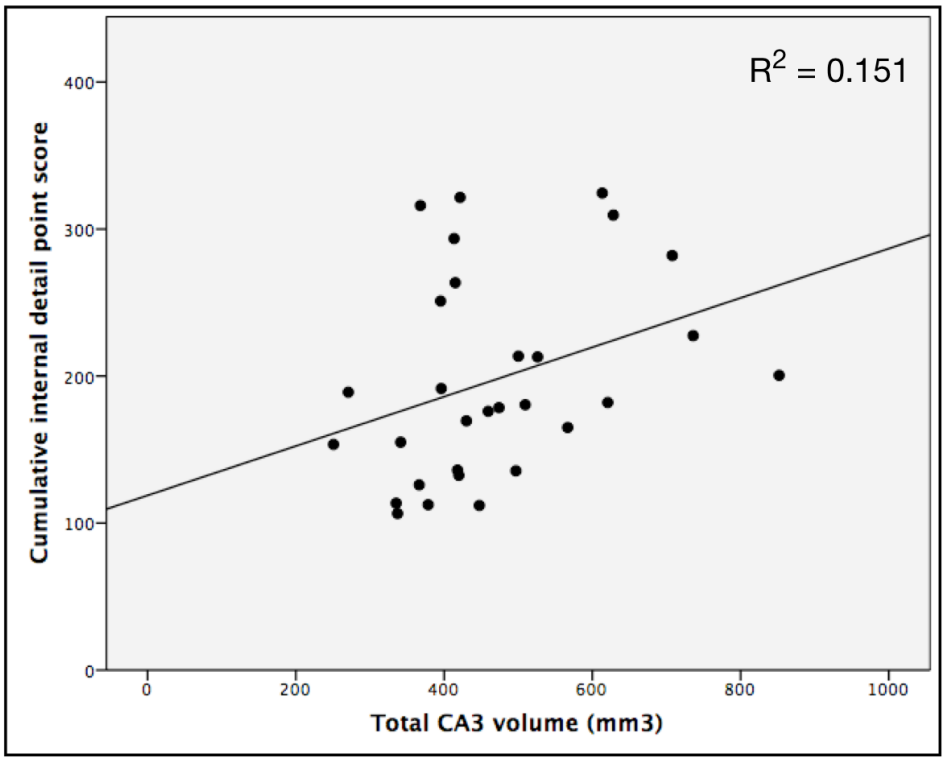
7.3.1. CA3 subfield volume predicts anterograde and retrograde internal point scores for both standard and modified administrations of the Autobiographical Interview

A robust multiple linear regression was conducted to test whether CA3 subfield volume estimates predicted internal detail scores on the standard administration of the AI (five time points, n = 30) for patients and controls. CA3 volume significantly predicted AI internal detail performance ($F_{(1,29)}$ = 4.99, p = 0.034, R^2 = 0.151, β_1 = 0.103). A further robust multiple linear regression was undertaken for the extended administration of the AI (seven time points, n = 20). This regression found that CA3 volume again significantly predicted AI internal detail performance ($F_{(1,19)}$ = 8.91, p = 0.008, R^2 = 0.331, β_1 = 0.51).

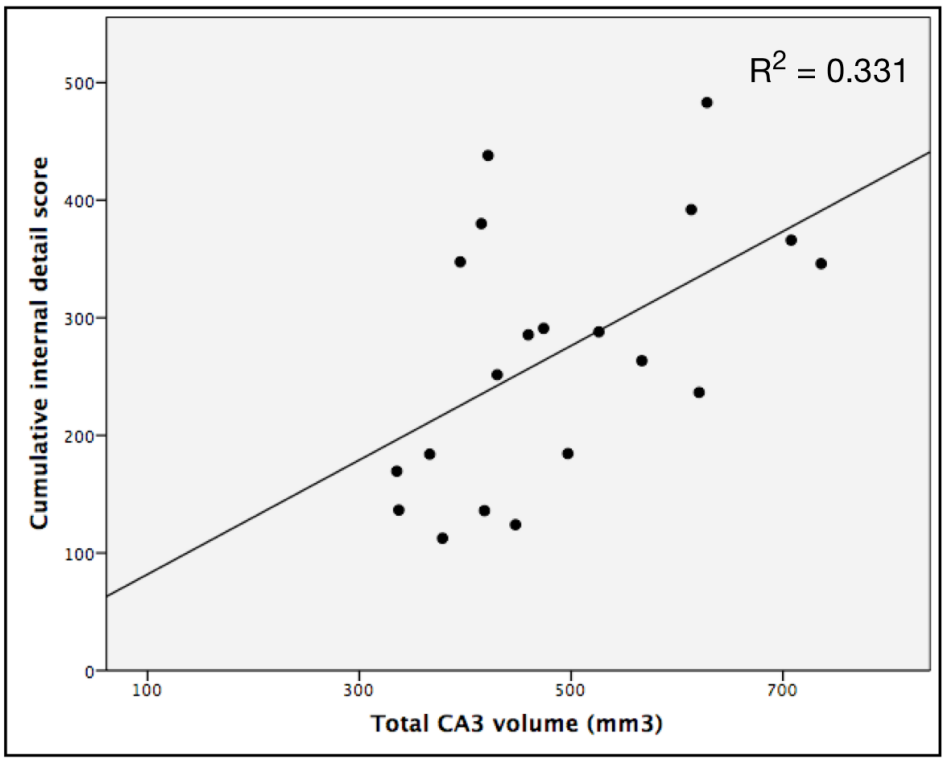
As this analysis collapses across both the retrograde memories acquired prior to illness (i.e., 0-11, 11-18, 18-30 and 30-55) and the anterograde post-morbid period (i.e., Last Year), a separate simultaneous robust multiple linear regression analysis was undertaken with anterograde performance (Last Year) separated from retrograde performance (0-11, 11-18, 18-30, 30-55). This analysis for the standard administration of the AI found that CA3 volume significantly predicted internal detail performance for the anterograde period ($F_{(1,29)}$ = 6.08, p = 0.02, R^2 = 0.179, β_1 = 0.065) but not retrograde performance ($F_{(1,29)}$ = 3.20, p = 0.085, R^2 = 0.103, β_1 = 0.11). Further regressions were undertaken for the extended administration of the AI, which found that CA3 volume significantly predicted both anterograde ($F_{(1,19)}$ = 4.99, p = 0.038, R^2 = 0.092, β_1 = 0.217) and retrograde ($F_{(1,19)}$ = 9.57, p = 0.006, R^2 = 0.347, β_1 = 0.40) internal detail performance.

Figure 7.1. Regression plots demonstrating the significant predictive relationships between total CA3 volume and cumulative internal detail performance for both the (A) standard and extended administrations of the Autobiographical Interview. These data are collapsed across patients and controls, and demonstrate that as total CA3 volume increases so does cumulative internal detail performance.

(A) Standard administration (five time points)



(B) Extended administration (seven time points)



7.3.2.1. Hippocampal subfield volume predicts immediate visual recall and delayed verbal recall, but not immediate verbal recall performance

A robust linear regression was used to test whether hippocampal subfield volume could predict performance on the three neuropsychological indices found to be impaired in Chapter 4 (immediate verbal recall, immediate visual recall, delayed verbal recall). The results are detailed according to neuropsychological indices.

7.3.2.1. Immediate verbal recall

The regression model was found to be non-significant ($F_{(10,16)} = 1.16$, $p = 0.45$, $R^2 = 0.658$) for the lateralized subfield volumes and performance on immediate verbal recall. None of the lateralized subfield volumes predicted immediate verbal recall performance: left CA1 ($F_{(1,16)} = 0.23$, $p = 0.65$, $R^2 = 0.0129$, $\beta_1 = 0.0027$), left CA2 ($F_{(1,16)} = 0.009$, $p = 0.93$, $R^2 = 0.0005$, $\beta_1 = 0.003$), left CA3 ($F_{(1,16)} = 0.018$, $p = 0.90$, $R^2 = 0.0010$, $\beta_1 = 0.0014$), left DG ($F_{(1,16)} = 0.053$, $p = 0.82$, $R^2 = 0.0030$, $\beta_1 = -0.0018$), left SUB ($F_{(1,16)} = 0.013$, $p = 0.91$, $R^2 = 0.0007$, $\beta_1 = 0.0017$), right CA1 ($F_{(1,16)} = 0.87$, $p = 0.39$, $R^2 = 0.0497$, $\beta_1 = 0.0041$), right CA2 ($F_{(1,16)} = 0.11$, $p = 0.75$, $R^2 = 0.0063$, $\beta_1 = 0.0041$), right CA3 ($F_{(1,16)} = 1.58$, $p = 0.26$, $R^2 = 0.0901$, $\beta_1 = -0.0263$), right DG ($F_{(1,16)} = 0.004$, $p = 0.95$, $R^2 = 0.0002$, $\beta_1 = -0.0005$), and right SUB ($F_{(1,16)} = 0.00$, $p = 0.99$, $R^2 = 0.000$, $\beta_1 = 0.0001$).

7.3.2.2. Immediate visual recall

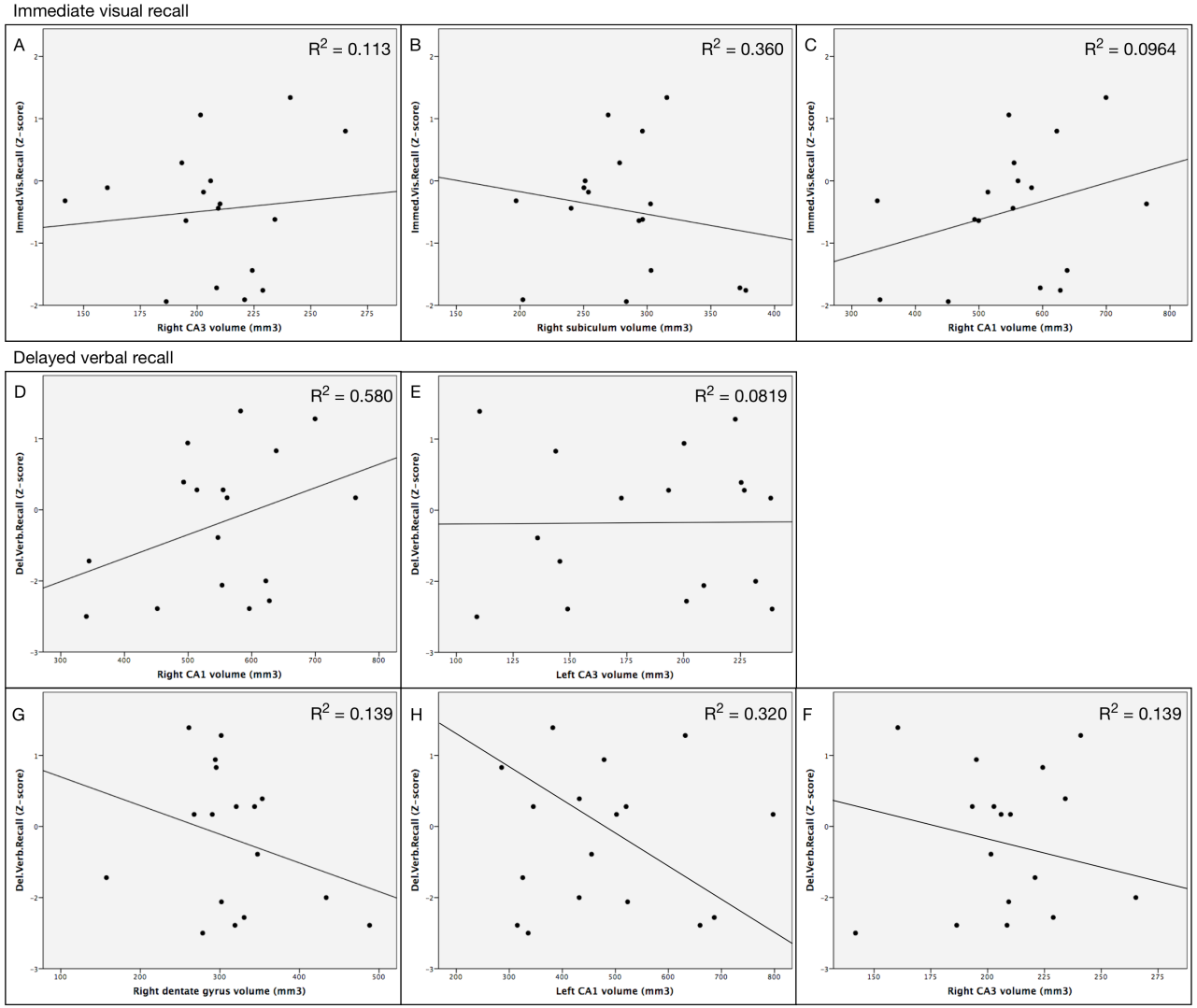
The regression model was found to be non-significant ($F_{(10,16)} = 7.48$, $p = 0.011$, $R^2 = 0.926$) for the lateralized subfield volumes and performance on immediate visual recall. Right CA1 volume significantly predicted immediate visual recall performance ($F_{(1,16)} = 7.79$, $p = 0.03$, $R^2 = 0.0964$, $\beta_1 = 0.0086$). Right CA3 ($F_{(1,16)} = 9.13$, $p = 0.023$, $R^2 = 0.113$, $\beta_1 = -0.0367$), and right SUB ($F_{(1,16)} = 29.11$, $p = 0.0017$, $R^2 = 0.360$, $\beta_1 = -0.027$) also significant predicted Immediate visual recall performance via a negative association. No other significant associations were found between subfield volumes and Immediate visual recall performance: left CA1 ($F_{(1,16)} = 3.31$, $p = 0.11$, $R^2 = 0.0434$, $\beta_1 = -0.0068$), left CA2 ($F_{(1,16)} = 3.74$, $p = 0.10$, $R^2 = 0.0463$, $\beta_1 = 0.0487$), left CA3 ($F_{(1,16)} = 2.25$, $p =$

0.18, R^2 = 0.0279, β_1 = 0.0095), left DG ($F_{(1,16)}$ = 0.56, p = 0.48, R^2 = 0.0069, β_1 = -0.0034), left SUB ($F_{(1,16)}$ = 0.38, p = 0.56, R^2 = 0.0047, β_1 = 0.0071), right CA2 ($F_{(1,16)}$ = 4.11, p = 0.089, R^2 = 0.0509, β_1 = 0.0272), and right DG ($F_{(1,16)}$ = 1.62, p = 0.25, R^2 = 0.0200, β_1 = 0.0065).

7.3.2.3. Delayed verbal recall

The regression model was found to be non-significant ($F_{(10,16)}$ = 7.63, p = 0.011, R^2 = 0.927) for the lateralized subfield volumes and delayed verbal recall performance. Left CA3 ($F_{(1,16)}$ = 6.74, p = 0.041, R^2 = 0.0819, β_1 = 0.0168), and right CA1 ($F_{(1,16)}$ = 47.73, p < 0.001, R^2 = 0.580, β_1 = 0.0173) volumes both significantly predicted delayed verbal recall performance. Significant negative predictive relationships were found for delayed verbal recall performance and left CA1 ($F_{(1,16)}$ = 26.32, p = 0.002, R^2 = 0.320, β_1 = -0.0165), right CA3 ($F_{(1,16)}$ = 14.21, p = 0.0093, R^2 = 0.173, β_1 = -0.451), and right DG ($F_{(1,16)}$ = 11.47, p = 0.015, R^2 = 0.139, β_1 = -0.0170). No other significant relationship were found: left CA2 ($F_{(1,16)}$ = 0.012, p = 0.92, R^2 = 0.0001, β_1 = 0.0024), left DG ($F_{(1,16)}$ = 1.44, p = 0.28, R^2 = 0.0174, β_1 = 0.0056), left SUB ($F_{(1,16)}$ = 4.56, p = 0.078, R^2 = 0.0547, β_1 = 0.0173), right CA2 ($F_{(1,16)}$ = 1.09, p = 0.34, R^2 = 0.0133, β_1 = 0.0138), and right SUB ($F_{(1,16)}$ = 6.58, p = 0.48, R^2 = 0.0070, β_1 = 0.0042).

Figure 7.2. Regression plots demonstrating the significant predictive relationships between lateralized hippocampal subfield volumes and neuropsychometry for (A-C) immediate visual recall and (D-F) delayed verbal recall. Both negative and positive predictive relationships are shown.



7.3.3. Anterograde and retrograde internal detail points predict performance on immediate verbal recall, and delayed verbal recall but not immediate visual recall

Table 7.2 shows the β_1 and p values for the logistic regressions between AI internal detail points score, and the neuropsychological indices.

7.3.3.1. Immediate verbal recall

Heterogeneity was found with the patient population for the measure immediate verbal recall (n = 134; $\chi^2_{(15)} = 164.59$, $p < 0.001$). Anterograde internal point significantly predicted immediate verbal recall performance ($\beta_1 = 0.02$, with a likelihood-ratio $\chi^2_{(1)} = 5.25$, $p = 0.022$), but not by retrograde internal point score ($\beta_1 = 0.01$, with a likelihood-ratio $\chi^2_{(1)} = 1.39$, $p = 0.24$), anterograde external point score ($\beta_1 = 0.026$, with a likelihood-ratio $\chi^2_{(1)} = 1.82$, $p = 0.18$), retrograde external point score ($\beta_1 = 0.035$, with a likelihood-ratio $\chi^2_{(1)} = 2.01$, $p = 0.16$), or control anterograde internal point score ($\beta_1 = -0.08$, with a likelihood-ratio $\chi^2_{(1)} = 0.48$, $p = 0.49$). There was no significant effect of the total internal point score ($\beta_1 = 0.003$, with a likelihood-ratio $\chi^2_{(1)} = 2.18$, $p = 0.14$) on immediate verbal recall performance.

7.3.3.2. Immediate visual recall

Heterogeneity was found with the patient population for the measure of immediate visual recall (n = 72; $\chi^2_{(11)} = 135.40$, $p < 0.001$). Performance for immediate visual recall was not predicted by either anterograde internal point score ($\beta_1 = 0.034$, with a likelihood-ratio $\chi^2_{(1)} = 3.82$, $p = 0.051$) or retrograde internal point score ($\beta_1 = 0.017$, with a likelihood-ratio $\chi^2_{(1)} = 1.95$, $p = 0.16$). No further analyses were undertaken.

7.3.3.3. Delayed verbal recall

Heterogeneity was found with the patient population for the measure delayed verbal recall (n = 112; $\chi^2_{(15)} = 181.98$, $p < 0.001$). Delayed verbal recall performance was significantly predicted by anterograde internal point score ($\beta_1 = 0.031$, with a likelihood-

ratio $\chi^2_{(1)} = 7.38$, $p = 0.007$) and retrograde internal point score ($\beta_1 = 0.021$, with a likelihood-ratio $\chi^2_{(1)} = 4.36$, $p = 0.037$), but not by anterograde external point score ($\beta_1 = -0.001$, with a likelihood-ratio $\chi^2_{(1)} = 0.13$, $p = 0.72$), retrograde external point score ($\beta_1 = 0.027$, with a likelihood-ratio $\chi^2_{(1)} = 0.70$, $p = 0.40$), control anterograde internal point score ($\beta_1 = -0.16$, with a likelihood-ratio $\chi^2_{(1)} = 0.28$, $p = 0.60$), or by total AI internal point score ($\beta_1 = 0.004$, with a likelihood-ratio $\chi^2_{(5)} = 1.56$, $p = 0.21$).

Table 7.1. Regression beta coefficients, and significance values for the logistic regressions undertaken on the immediate verbal recall, immediate visual recall, and delayed verbal recall neuropsychological indices. The independent variables arise from different measures arising from the Autobiographical Interview.

Domain	Antero.Int.	Retro.Int.	Antero.Ext.	Retro.Ext.	Cont.Int	All.Int.
Immed.Verb.Recall	**$\beta_1 = 0.02$**	$\beta_1 = 0.01$	$\beta_1 = 0.026$	$\beta_1 = 0.035$	$\beta_1 = -0.08$	$\beta_1 = 0.003$
	$p = 0.022$	$p = 0.24$	$p = 0.18$	$p = 0.16$	$p = 0.49$	$p = 0.14$
Immed.Vis.Recall	$\beta_1 = 0.034$	$\beta_1 = 0.017$	-	-	-	-
	$p = 0.051$	$p = 0.16$	-	-	-	-
Del.Verb.Recall	**$\beta_1 = 0.031$**	**$\beta_1 = 0.021$**	$\beta_1 = -0.01$	$\beta_1 = 0.027$	$\beta_1 = -0.16$	$\beta_1 = 0.004$
	$p = 0.007$	**$p = 0.0037$**	$p = 0.72$	$p = 0.40$	$p = 0.29$	$p = 0.21$

All.Int.: All internal scores summates; Antero.Ext.: Anterograde memory external point score; Antero.Int.: Anterograde memory internal details point score; Cont.Int.: Control Anterograde Internal details point score; Del.Verb.Recall: delayed verbal memory recall; Immed.Vis.Recall: immediate visual memory recall; Immed.Verb.Recall: immediate verbal memory recall; Retro.Int.: Retrograde memory internal point score; Retro.Ext.: Retrograde memory external point score. - = not tested.

7.3.4. Anterograde episodic memory performance predicts retrograde episodic memory performance

A robust multiple linear regression was conducted to assess whether internal detail performance obtained on the AI could be used to predict retrograde memory internal detail performance for the collapsed retrograde internal detail point score for patients and controls, on both the standard and modified administrations of the AI. Anterograde internal detail performance was found to significantly predict cumulative retrograde internal detail performance in both the standard ($F_{(1,29)} = 23.10$, $p < 0.001$, $R^2 = 0.452$, $\beta_1 = 1.24$), and modified ($F_{(1,19)} = 26.48$, $p < 0.001$, $R^2 = 0.595$, $\beta_1 = 2.44$) administrations of the AI.

A further exploratory set of regressions, overlooking the absence of a temporal gradient in episodic memory loss, were undertaken to see whether anterograde internal detail performance predicted internal detail performance for each epoch of the standard

(0-11, 11-18, 18-30, 30-55; n = 30) and modified (0-11, 11-18, 18-30, 30-40, 40-50, 50-60; n = 20) administrations of the AI.

For the standard administration of the AI, anterograde internal detail point score significantly predict internal detail performance for all epochs (0-11: $F_{(1,29)}$ = 5.45, p = 0.026, R^2 = 0.165, β_1 = 0.159; 11-18: $F_{(1,29)}$ = 8.48, p = 0.007, R^2 = 0.232, β_1 = 0.272; 18-30: $F_{(1,29)}$ = 14.86, p = 0.006, R^2 = 0.239, β_1 = 0.358; 30-55: $F_{(1,29)}$ = 14.86, p < 0.001, R^2 = 0.347, β_1 = 0.427).

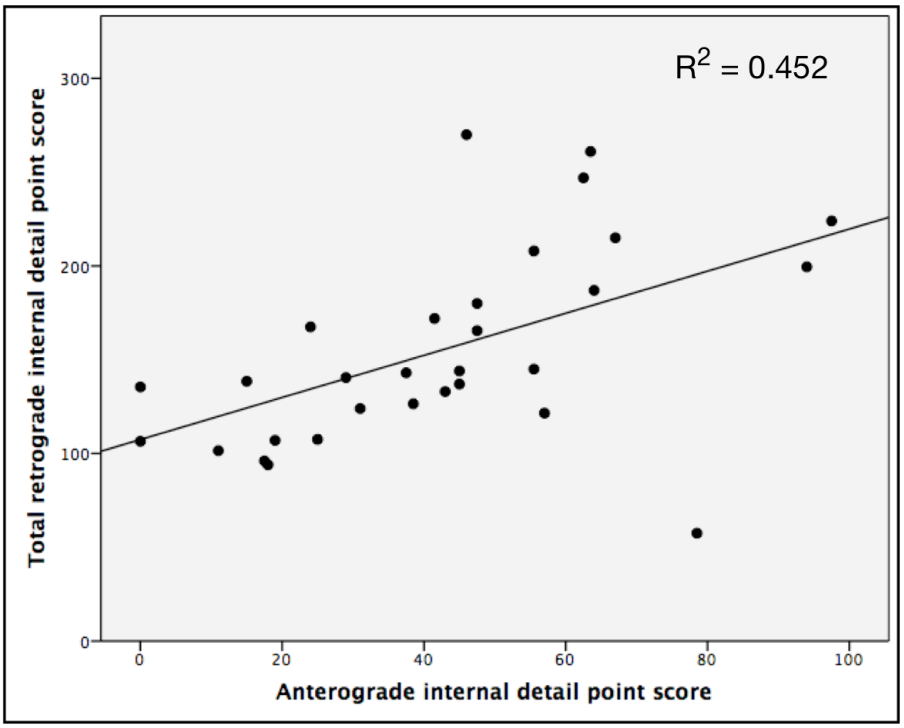
For the extended administration of the AI, anterograde internal detail point score significantly predict internal detail performance for the 11-18 ($F_{(1,19)}$ = 6.56, p = 0.02, R^2 = 0.267, β_1 = 0.294), 18-30 ($F_{(1,19)}$ = 17.76, p < 0.001, R^2 = 0.497, β_1 = 0.526), 30-40 ($F_{(1,19)}$ = 6.56, p = 0.02, R^2 = 0.267, β_1 = 0.294), and the Last Five Years ($F_{(1,19)}$ = 17.69, p < 0.001, R^2 = 0.504, β_1 = 0.647) epochs, but not the 0-11 ($F_{(1,19)}$ = 3.98, p = 0.06, R^2 = 0.181, β_1 = 0.173) or the 40-50 epochs ($F_{(1,19)}$ = 2.95, p = 0.10, R^2 = 0.504, β_1 = 0.647).

7.3.5. Early retrograde internal detail point score predicts remote episodic memory internal detail point score for the modified administration of the AI

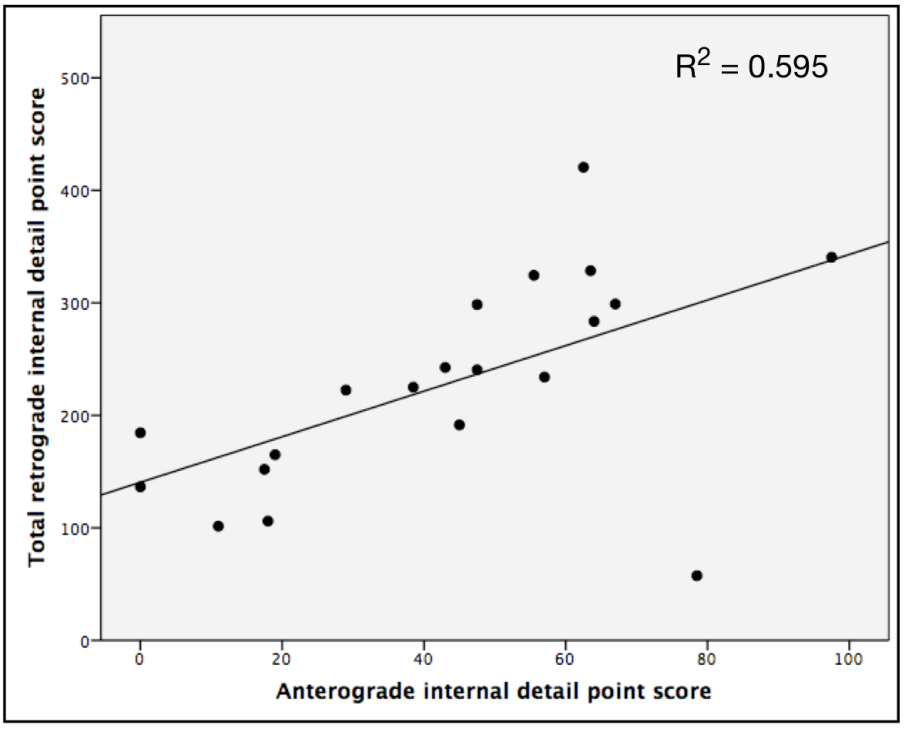
Early retrograde internal detail point score predicted performance for the 11-18 ($F_{(1,19)}$ = 7.69, p = 0.013, R^2 = 0.299, β_1 = 0.325), 18-30 ($F_{(1,19)}$ = 13.62, p = 0.002, R^2 = 0.431, β_1 = 0.506), 30-40 ($F_{(1,19)}$ = 14.01, p = 0.028, R^2 = 0.438, β_1 = 0.411), and 40-50 ($F_{(1,19)}$ = 29.21, p < 0.001, R^2 = 0.619, β_1 = 0.599) epochs, but not the 0-11 epoch ($F_{(1,19)}$ = 3.44, p = 0.08, R^2 = 0.160, β_1 = 0.156).

Figure 7.3. Regression plots demonstrating the significant predictive relationships between anterograde episodic memory performance, as denoted by internal detail point scores, and total retrograde internal detail performance for both the (A) standard and (B) extended administrations of the Autobiographical Interview. This demonstrates that as anterograde performance increases it significantly predicts total retrograde episodic memory performance. These data are collapsed across patients and controls.

(A) Standard administration (five time points)



(B) Extended administration (seven time points)



7.3.6. Hippocampal subfield volume does not predict personal semantic memory performance on the Autobiographical Memory Interview

A robust multiple linear regression was used to determine whether or not CA3 volume predicted the personal semantic memory point score on the Autobiographical Memory Interview (AMI, n = 30). CA3 volume did not predict the cumulative personal semantic score from the AMI ($F_{(1,29)}$ = 0.44, p = 0.51, R^2 = 0.015, β_1 = -0.292).

7.4. Discussion

This chapter examined whether it was possible, in amnesic patients and controls, to formalize relationships between hippocampal subfield volumes, neuropsychological performance, retrograde episodic memory performance (as operationalized by internal detail point score from the AI), and personal semantic memory (as operationalized by the semantic score from the AMI) by means of regression based analyses. There are five novel contributions arising from this work.

First, CA3 volume estimates, in both health and disease, were significant predictors for cumulative internal detail scores arising from the AI. This relationship was found for both standard (n = 30) and modified administrations (n = 20) of the AI. When the cumulative internal detail scores were divided into those memories occurring before (retrograde) and after (anterograde) the illness period, it was found that CA3 volume once again was a significant positive predictor of internal detail performance for the retrograde memories arising for the modified administration of the AI, whereas the results for the standard administration demonstrated only a trend towards significance. For the anterograde memory, CA3 volume significantly predicted the internal detail performance for both the standard and modified administration of the AI. This is the first instance of anterograde and retrograde episodic memory performance being predicted by a hippocampal subfield volume, a finding of great theoretical relevance.

Second, for the regressions between lateralized hippocampal subfield volumes and neuropsychological performance in 17 patients with VGKC-complex LE, immediate verbal recall performance was not predicted by the subfield volumes; immediate visual recall performance was predicted by right CA1 volume, and by right CA3 and right SUB volumes - the latter associations were negative; delayed verbal recall was significantly predicted by left CA3 and right CA1 volumes, but negatively predicted by right CA3 and right DG volumes. This demonstrates for the first time, in health or disease, a predictive association between hippocampal subfield volumes and performance on neuropsychological measures of anterograde memory.

Third, that in 16 patients with VGKC-complex LE, immediate verbal recall performance was predicted by anterograde internal detail point score; immediate visual

recall performance was not predicted by any measure from the AI; and delayed verbal recall performance was predicted by both anterograde and retrograde memory internal detail point scores. This demonstrates, for the first time in human models of hippocampal dysfunction, that there is a causal relationship between the anterograde amnesia, as measured with neuropsychological tasks, and both anterograde and retrograde episodic memory performance.

Fourth, anterograde internal detail performance from the AI predicted cumulative retrograde internal detail performance in health and in disease for both the standard and modified administrations of the AI. It was also found that anterograde internal detail point score predicted individual internal detail point scores for each epoch of the standard and modified administrations of the AI, except for the 0-11 and 40-50 epoch of the modified version. It was also seen that, for the extended administration of the AI, the early retrograde memory internal detail point score predicted internal detail performance for more remote episodic memories, except the 0-11 epoch. Once again, this is the first demonstration of a causal relationship between the severity of retrograde and anterograde episodic memory performance.

Fifth, none of the hippocampal subfield volumes predicted cumulative personal semantic memory performance, as measured formally by the AMI, in health and disease (n = 36). This agrees with the broad literature describing how extra-hippocampal regions are critical for the expression of this form of declarative memory.

7.4.1. The relationship between CA3 atrophy and internal detail performance from the Autobiographical Interview

Evidence presented here indicates that CA3 volume estimates in VGKC-complex LE and age-matched controls predict the number of internal detail points generated for both anterograde and retrograde memories. This suggests not only that CA3 integrity is central to episodic memory retrieval, but also that as CA3 volume increases, so does internal detail performance as measured by the AI. When the memories were dichotomized according to whether they were anterograde (i.e., post-morbid) or retrograde (i.e., premorbid) memories, the relationship remained intact – the exception was for premorbid memories acquired on the standard administration of the AI,

although a trend was clearly observed. Given that this is the first study to directly relate hippocampal subfield volume to retrograde and anterograde episodic memory performance, as measured by the AI, the results will need to be evaluated against more qualitative studies.

7.4.1.1. Hippocampal subfield pathology and episodic memory amnesia

Bartsch et al., (2011) undertook a study that quantified retrograde memories that were classifiable as autonoetic in nature, according to a four point rating scale, and then related behavioural performance to evidence of hippocampal lesions in 16 patients with TGA. Acute imaging during an attack has been found to induce a focal lesion confined to the CA1 field of the hippocampus, or at least to the Sommer region of the hippocampus (Bartsch et al., 2007; Bartsch et al., 2006; Bartsch et al., 2010). Acute CA1 lesions associated with TGA caused a temporal gradient of strictly episodic memory loss, which subsequently improved on follow-up. The results of Bartsch et al., (2011) diverge from the current results on two counts: (1) evidence of temporally-graded amnesia, and (2) CA1 lesions. The methodological limitations of using such a subjective rating, particularly where gradients emerge, are discussed in Section 5.1.4, and will not be discussed further here.

The critical observation in the study by Bartsch et al. is that CA1 lesions, and not CA3, lesions result in graded amnesia, compared to the non-graded amnesia demonstrate with the CA3 lesions observed in Chapter 3. One explanation for this difference arises from the fact that the imaging protocol used by Bartsch et al., (2011) assumes that the lesions they observe in the Sommer region are within the CA1 field. As discussed and shown in Chapter 3, there are occasions when this lateral-most component of the hippocampus is actually comprised of either CA2 or CA3, and so it is not necessarily appropriate to assume that all these patients have CA1 lesions. An additional consideration relates to the trisynaptic circuit of the hippocampus. Input to the hippocampus, by-and-large, terminate in the DG, following which the flow of information follows along CA3, CA2, CA1 with the SUB being the main outflow of the hippocampus proper. The subfields do not work in isolation, but in concert with the other subfields, in order to modify behaviour. This suggests that any lesion along this circuit could result in behavioural deficits.

Therefore, the current data appear to suggest that anterograde and retrograde episodic memory performance across the lifetime is reliant, at least in part, on the normal functioning of the CA3 subfield, and extends the literature beyond decriptions of retrograde episodic memory performance dichotomized according to MTL or MTL+ lesions (Bayley et al., 2005; Kirwan et al., 2008; Rosenbaum et al., 2008). Moreover, CA3 volume is predictive of episodic memory functioning in both health and disease.

7.4.1.2. The importance of CA3 for retrograde episodic memory retrieval

When considering the wider mnemonic literature, the current data are in agreement with recent evidence – arising from fMRI studies and specifically multivariate pattern analysis (MVPA)-based techniques – that reveal the centrality of the CA3 region to retrograde episodic memory retrieval. Furthermore, these data suggest that subjects with greater CA3 volume have better episodic re-experiencing, perhaps because of greater degrees of pattern separation/completion particularly for more remote memories.

MVPA involves comparing different distributed patterns of voxel activity across different behavioural conditions. This technique has been used in experiments of retrograde episodic memories, on the basis that each memory should have a different pattern of fMRI BOLD activity within the structures that support memory, and especially the hippocampus (Bonnici et al., 2012). For instance, Bonnici et al., (2013) found that the all subfield regions contained information concerning recent and remote episodic memories, but, for direct relevance to the current data, that the posterior CA3 and DG contained decodable information about remote memories. Previous work has also suggested that the posterior hippocampus may be central to the spatial framework needed for scene construction (Hassabis et al., 2007; Hassabis and Maguire, 2009), and patients with hippocampal damage lose the ability to construct spatially coherent scenes (Hassabis et al., 2007; Mullally et al., 2012; Race et al., 2011). Therefore, episodic retrieval would require the reconstruction of these scenes, with the posterior hippocampus supporting the spatial reconstruction. The greater BOLD signal change associated with more remote memories, is thought then to represent a greater amount of reconstruction being required (Bonnici et al., 2013).

7.4.1.2.1. Neurocomputational functions of the hippocampal subfields

Moreover, CA3 and DG have also been implicated in pattern separation, and CA3 implicated in pattern completion as well (Leutgeb et al., 2007; Leutgeb and Leutgeb, 2007; Marr, 1972; Treves and Rolls, 1994). Bonnici et al. hypothesized that as remote episodic memories require more hippocampal activation for their expression, then it is likely that the individual memories could potentially be associated with a greater number of potential mnemonic elements and spatial contexts, thereby triggering a CA3-mediated pattern completion and/or separation (Bonnici et al., 2012). In a further recent study, CA3 volume has been shown to be directly related to the ability of healthy controls to pattern separate (Chadwick et al., 2014). These data indicated that overlapping memory patterns are coactivated during episodic memory retrieval, but that CA3 size directly affects the efficiency with which those overlapping memories are differentiated. It should be noted though that this study used anterograde memories, whereas the data collected from Chapter 5 is derived from retrograde memories.

The current data demonstrate that CA3 volume predicted cumulative internal detail generation as measured by the AI, a task in which memories that generate more points are thought to be more re-experiential, and, by definition, need to be of a single event with a specific spatiotemporal context. Thereby, these results agree with those of (Chadwick et al., 2014), albeit for retrograde episodic memory, and suggest that the failure of internal detail performance may be due a failure in retrograde episodic memory pattern separation and/or completion. Yassa et al., (2011) have also described how DG/CA3 perforant pathway disruption reduces the ability of healthy controls to successful discrimination between highly similar objects. It is likely that VGKC-complex LE patients experience a disruption not just CA3 cell body volume but also the perforant pathway, and so a candidate pathological mechanism could be suggested for how these deficits emerge. This data relied on diffusion-tensor imaging (DTI) to assess white matter structure in the hippocampi, as an explanatory variable for performance on an object discrimination task. For instance, participants could be shown a series of objects, and then, either as a behavioural or fMRI experiment, try to decide whether objects were repeated (i.e., previously encountered), novel (i.e., never encountered), or a lure (i.e., never encountered but similar to previously encountered). The lures could be of a high-similarity or low-similarity, in order to place different burdens of activity on the subfield networks (Yassa et al., 2011). The analysis would assess whether either behavioral

performance (i.e., successful discrimination of repeated, novel, or lure objects), or hippocampal activity changes during fMRI – where BOLD signal change during the lure trials that was similar to the repeated objects was indicative of pattern completion, whereas lure activity in keeping with BOLD signal changes during novel objects was suggestive of pattern separation (Yassa et al., 2011) – could be analysed with white matter integrity (i.e., fractional anisotropy) used as a covariate.

These data can also be interpreted in light of more recent models of hippocampal function that are specified across multiple cognitive modalities. As discussed in Chapter 5, the model of hippocampal function best supported by the pattern of retrograde episodic memory loss seen following VGKC-complex LE is the binding of items and context (BIC) model (Diana et al., 2008; Ranganath, 2010). Under this model, every memory that required a degree of perceptual re-experiencing (for instance, this is not the only quality needed for episodic memory) requires hippocampal involvement to associate those perceptual features into their original contextual features, but that the CA3 region in particular will be central to the emergence of the visuoperceptual features of a specific episodic event.

7.4.2. Hippocampal subfield volumes and neuropsychological performance following VGKC-complex LE

7.4.2.1. Immediate verbal recall

The absence of a relationship between any of the hippocampal subfield volume estimates and immediate verbal recall performance is at odds with several other studies.

Generally, previous studies have found significant correlative relationships between hippocampal subfield volumes, and neuropsychological measures of anterograde memory, although these vary across task such as Logical Memory 1 and CA1-3, DG, and SUB volumes (Travis et al., 2014b), word list performance and DG/CA3 and CA1 volume (Mueller et al., 2011), and immediate recall memory correlating with CA1-SRLM volume (Kerchner et al., 2014). Strictly, the word list task used by Mueller et al. is a verbal single item memory task, and so direct comparisons are difficult across these memory indices constructed as they are from different neuropsychological tasks. One possible explanation for the variance between these

studies, including the present data, may be the different experimental design, either from a neuropsychological perspective, or that of *in vivo* hippocampal subfield quantification.

Several reasons account for why the current results may differ from previous studies. First, these data arise from a group of 17 subjects; - compared to 34 for Travis et al., 50 for Mueller et al., and 39 for Kerchner et al. – therefore the present study could be unpowered to detect subtle predictive effects for lateralized hippocampal volumes on performance. This would ideally at least require 42 VGKC-complex LE patients to be used to obtain an effect size of 0.8, with a power level of 0.8, and a probability value of 0.05 for a one-tailed test. Secondly, these data also arise from a patient population, whereas the results of Mueller et al., (2011) and Travis et al., (2014b) arise from healthy controls. It is difficult to predict whether, in the presence of focal CA3 damage, whether the remainder of the hippocampal trisynaptic circuit retains normal physiological function. Therefore, it is conceivable that the CA3 damage prevents other subfields from providing their normal physiological input to behavioural performance, potentially producing spurious predictive relationships. Thirdly, the results cited above arise from correlation based analyses, whereas the current study applied a robust regression-based approach to model neuropsychological performance according to subfield volume (Mueller et al., 2011; Sass et al., 1995; Travis et al., 2014b). Correlations assess whether two variables have a linear association, but, critically, is unable to describe how the dependent variable – in this case neuropsychological performance – will vary with different values for the dependent variable – that is with subfield volumes. Hence, it is possible that the findings presented could be replicated in the studies cited above, should they be reanalyzed with robust linear regressions. Fourth, the indices used here collapse across individual measures of immediate verbal recall, whereas the aforementioned studies utilized a measure arising from a single neuropsychological test. Indices were used in the current study, because averaging across several different tasks reduces the risk of type I errors (Butler et al., 2014), and the tasks are grouped together according to *a priori* predictions that they would preferentially recruit the hippocampus (see Section 4.1.3.2 for the rationale behind the construction of this index score). Finally, two studies (Mueller et al., 2011; Travis et al., 2014b) also collapse across the CA subfields, which diminish the ability to examine functional differentiation that is known to exist within the hippocampal subfields (see Section 1.2.3 for full discussion).

A further possibility for the absence of relationships between subfield volumes and immediate verbal recall performance could be the lack of hippocampal-specificity of the tasks used here, but also in the other studies cited above. This is not to negate the results, but the argument developed in Section 4.1.3 was that neuropsychological tests tend to require several cognitive processes, and hence neuroanatomical regions, for normal performance. Most clinical tests of immediate-recall or working memory use stimuli that are well represented outwith the MTL structures (such as word list learning), and so may not specifically recruit the hippocampus, but rather receive a modulatory input for behaviour in health (Ranganath and Blumenfeld, 2005). Immediate-recall deficits therefore might be only expected with stimuli known to be uniquely processed by the MTL structures like complex novel objects (Lee et al., 2005; Murray and Bussey, 1999), and, indeed, deficits are noted in patients with these forms of stimuli (Aggleton et al., 1992; Buffalo et al., 1998; Holdstock et al., 2000; Holdstock et al., 1995; Owen et al., 1995), and cannot be attributed to lesions extending into the temporal neocortex (such as TE (Eacott et al., 1994; Zola-Morgan et al., 1989)). Therefore, patients with focal MTL lesions might only show minimal (if any) impairment across immediate recall memory tasks involving simple word learning or digit span, and show more substantial deficits in more complex tasks such as story learning or paired-associate learning. Care was taken to construct the immediate verbal recall index score with tasks that would, on balance, be more hippocampal dependent than, say, single item learning.

In general, the results presented here are at variance with the literature in healthy adults describing associations between hippocampal subfields and immediate verbal memory performance. The reasons for this are manifold, but there are sufficient differences in methods and analysis to suggest that these outcomes are consistent with other source of experimental evidence, such that increasing hippocampal subfield volumes are related to increasing behavioural performance for measures of immediate verbal memory.

7.4.2.2. Immediate visual recall

The immediate visual recall index consisted of two tasks that required the reconstruction, from memory, of several complex figures, and so were more likely to recruit the hippocampus (for the rationale behind constructing this index score, see Section 4.1.3.2.1.3). Immediate visual recall performance was predicted by right CA1

volume, but negatively predicted by right CA3 and right SUB volumes. This pattern of results is in general agreement with other studies.

Right hippocampal volume loss, following TLE, has been shown to result in impairments in delayed recall of a complex geometric figure (Breier et al., 1996), object location tasks (Bohbot et al., 2000), to recognize famous faces (Glosser et al., 2003), and delayed facial recognition (Milner, 2003). Importantly, however, these studies do not describe these associations at the level of hippocampal subfields, thereby limiting any further comparisons with the present data. Within this patient cohort, it was also discovered that recognition memory was normal, and it was discussed in Section 4.1.3.2.1.5 that recognition memory is generally not a hippocampal-dependent task.

Extending the discussion to the right hippocampal subfields, Travis et al., (2014b) found that visuospatial performance was positively correlated with collapsed CA1-3 volumes for a visual recognition task. Travis et al., (2014a) also found that spatial memory – as measured in the WMS-IV Designs and Visual Reproduction tasks – was positively correlated with DG volume, and a study of 103 patients with multiple sclerosis (MS), and Longoni et al., (2015) found that CA1 and SUB volume was correlated with performance on the Rey-Osterreith Complex Figure (ROCF). One difficulty with the Travis et al., (2014b) study is that it is unlikely that the hippocampus is involved in simple item recognition tasks, suggesting that the present data are not directly comparable. For instance, visual recognition memory has been shown to be supported by other brain regions such as the parietal lobe (Konishi et al., 2000; Velanova et al., 2003; Wheeler and Buckner, 2004), and the parahippocampal gyrus (Daselaar et al., 2006; Davachi et al., 2003; Kensinger and Corkin, 2004; Ranganath et al., 2004).

As with the immediate verbal recall discussion, the subtests include in the current immediate visual recall index were associative in nature, and, therefore more likely to be vulnerable to hippocampal damage following VGKC-complex LE, particularly such things as novel objects like the ROCF (Lee et al., 2005; Murray and Bussey, 1999). It has been previously suggested that the parahippocampal cortex is recruited in visuospatial processing and the perirhinal cortext (PRC) is associated with object processing (Awipi and Davachi, 2008; Ekstrom and Bookheimer, 2007; Staresina et al., 2011; Wolbers and Buchel, 2005). The PRC also appears to have a specialized role in mediating source

memory for objects, especially if the context is processed as a feature of the object (Diana et al., 2007; Park et al., 2014; Ranganath, 2010) suggesting that the hippocampus is always needed in tasks of recollection (Park et al., 2014), such as with the ROCF.

7.4.2.3. Delayed verbal recall

7.4.2.3.1. The role of CA1 in delayed verbal recall

At the level of the hippocampus, previous fMRI results indicate that delayed-recall components of anterograde learning paradigms, especially story learning, are associated with increased BOLD signal activity of the hippocampus during retrieval (Helmstaedter et al., 1997). On this basis, performance on the tests used to construct the delayed verbal recall index should be sensitive to hippocampal pathology. Early studies also found that delayed verbal recall, as measured by story performance, appeared to more positively associated with hippocampal volumes, where increasing volumes were associated with greater delayed verbal memory performance (Kohler et al., 1998; Travis et al., 2014b). Importantly, however, the specific pattern of positive and negative associations, delayed verbal recall index was positively predicted by left CA3 and right CA1 volumes, and negatively predicted by right CA3 and right DG volumes - was not hypothesised *a priori*.

Evidence of right CA1 involvement in delayed verbal recall is in keeping with several previous studies. Mueller et al., (2011) described how CA1 volume was positively correlated with word list retrieval performance. CA1 volume has also been shown to positively predict performance on a composite delayed memory score (consisting of the CVLT-II, a word list task), but other hippocampal subfield regions, such as the DG, were unrelated to this performance. It is notable how different material types were collapsed in this study, making direct comparisons with the current data difficult, but the comparison at least indicates that composite measures of delayed memory function are associated with hippocampal volume. In addition, Logical Memory 2 (one of the key components of the current delayed verbal recall index) has been shown to correlate with collapsed CA1 volume (Mueller et al., 2012), which is in keeping with the current data.

The finding here that right CA1 volume positively predicted performance is well supported by those studies cited above. Arguing from a material-specificity perspective, it

is unexpected that the right CA1 volume was more associated with verbal performance, where it would normally be expected that the left hippocampus might be more associated with verbal stimuli (Baxendale et al., 1998; Sass et al., 1990; Witt et al., 2014; Zentner et al., 1999). However, the current data demonstrate that perhaps such dichotomy between the role of the left and right hippocampus in processing certain types of information is more nuanced than previously described, particularly with this being the first study to use linear regressions as opposed to correlational analyses.

7.4.2.3.2. The role of CA3 in delayed verbal recall

Studies finding relationships between CA3 volumes and performance on measures of delayed verbal recall have been less well described, partly because of the tendency to collapse across subfields during segmentation protocols (Mueller et al., 2011; Travis et al., 2014b). Computational accounts of the hippocampus suggest that both the CA1 and CA3 regions are involved in fundamentally the same computational process of pattern separation, but perhaps the CA3 is implicated to a greater degree in pattern completion (Bakker et al., 2008; Rolls, 2013). Several recent descriptions of the central role of the hippocampus in memory is to make associations between stimuli to create a richly re-experiential experience (Maguire et al., 2010a; Ranganath, 2010; Schacter and Addis, 2009; Yonelinas et al., 2010). Computational modeling suggests that the formation of these associations in the CA3 region (Rolls, 2013). Therefore, from a mechanistic perspective it is likely that both subfields can contribute to the successful performance of these tasks, and putatively by extension these neuropsychological measures. The predictive relationship for left CA3 volume on delayed verbal recall is more in keeping with the verbal material-specificity argument discussed above, but due to the novelty of the methods used in this chapter, direct comparisons to the literature are not possible.

7.4.2.4. Negative predictions between hippocampal subfield volumes and neuropsychological function

The presence of negative regression coefficients between immediate visual recall and right CA3 and SUB volumes, and between delayed verbal recall and right CA3 and DG is unexpected. Negative predicative relationships would appear to be at variance with the rationale used in this chapter: that larger volumes are associated with improved

performance on behavioural tasks. One consideration is that these data reflect a type I error, as a result of the low number of participants included in the regression. However, such a caveat would need to be applied to the positive predictive findings as well. A second consideration for these results is that this is the first use of regression-based analyses to investigate causal relationships between behavioural performance and individual subfield volumes, following a monophasic illness (in this case VGKC-complex LE), although, arguably, these results may have emerged from correlational analysis. As there are no priors in the literature to help inform these discussions, even in healthy controls, and had regression-based techniques been used in other studies (e.g., Kerchner et al., 2014; Kerchner et al., 2012), then similar results may have been found, although this is not certain to be the case.

These results could also be interpreted through material-specificity arguments, such that one might expect the right hippocampus is *less* likely to involved in verbal memory paradigms, and so the negative relationship with delayed verbal recall might be expected to emerge. However, such an argument would not be sustainable for the immediate visual recall results.

Another potential candidate explanation could be a reflection of premorbid subfield volumes, whereby increased hippocampal volumes are associated with poorer synaptic pruning during development, and hence poorer behavioural performance. For instance, fragile X syndrome is associated with aberrant synaptic pruning (Grossman et al., 2006), and that patients have larger hippocampi as quantified neuroradiologically (Reiss et al., 1994). A recent study has shown patients with fragile X syndrome have a negative predictive relationship between hippocampal volumes, but not subfield, and mnemonic performance collapsed across all measures of the WMS-Revised, a relationship not observed in healthy controls (Molnar and Keri, 2014). The authors suggest the worsening relationship noted here could be due to inefficient encoding processes (Molnar and Keri, 2014). However, this study arises from a germline disease population, and as such that pathophysiological mechanisms are probably not directly applicable to the current population, which ostensibly had normal hippocampi development and morphology prior to their illness. One line of future work could be administer a similar neuropsychological battery to healthy controls, and then apply similar techniques to see whether the negative predictive patterns emerge.

One further speculative reason could be compensatory hypertrophy of the surrounding hippocampal subfields in response to the CA3 damage. In cases of increasing CA3 damage, there could be an equally large, but compensatory, increase in neighbouring subfield volumes, perhaps a reflection of plasticity following disease or damage. In this case, the negative associations may not have a direct neurophysiological effect, but rather be a marker of severity of CA3 damage. There are, once again, no prior studies in the literature suggesting that this could be a likely causal mechanism.

7.4.2.5. Hippocampal subfield volumes and neuropsychological performance: summary

It could be argued that the hippocampal-specificity of many of these neuropsychological tests and indices is limited. However, care has been taken to construct the indices from tasks that are *most* likely to be hippocampal-specific, so these results are instructive for investigations into the relationships between hippocampal subfield volumes and neuropsychological performance. The subject numbers are low, and so the data are vulnerable to both type I and type II errors; however, the use of a robust regression with Huber's correction was used to help reduce the risk of either. The emergence of negative predictive relationships between increasing hippocampal subfield volume and decreasing neuropsychological performance is surprising, and again perhaps shows that this data remain vulnerable to type I due to being underpowered. This study was also the first to use such a large neuropsychological battery and acquire hippocampal subfields data at 7.0-Tesla, especially in a patient population, and so further work is needed in both health and disease to assess the reproducibility of these results.

7.4.3. The relationship between neuropsychological measures of anterograde memory and internal detail performance from the Autobiographical Interview

The logistic regression data demonstrate that internal detail performance arising from the anterograde (i.e., postmorbid) memory from the AI significantly predicts immediate verbal recall and delayed verbal recall performance, but not immediate visual recall, although a trend was observed. Internal detail point score for the retrograde memory had a significant predictive effect for only delayed verbal recall. The dichotomy

in the prediction generated by anterograde and retrograde internal detail score is interesting, and warrants further consideration.

7.4.3.1. Implications of anterograde internal detail point score associations

The relative specificity of the indices used in this chapter has been discussed above in Section 7.1.2.5, and in Section 4.1.3.2, but hippocampal-specificity in the neuropsychological measures used to construct the immediate verbal recall index would be reasonably predicted (Logical Memory 1 and a verbal-visual associational task, Doors and People – People). Immediate verbal recall was one of the three neuropsychological indices found to be significantly impaired following VGKC-complex LE (see Chapter 4), a finding that further suggests the relative dependence of these functions on hippocampal integrity. Both the Immediate verbal recall and anterograde memory were acquired with a damaged hippocampus, and therefore the predictive relationship between internal detail point score and Immediate verbal recall performance is to be expected, yet, still novel, in the context of amnesia research, where more qualitative descriptions are made to describe the relationship between severity of AA and RA (Barr et al., 1990; Bright et al., 2006; Hornberger et al., 2010; Kapur et al., 1992; Kopelman, 1989; Milton et al., 2010; Reed and Squire, 1998; Sehm et al., 2011; Squire and Alvarez, 1995; Wicklegren, 1979).

Data from Chapter 4 also demonstrated that patients were impaired on delayed verbal recall. Previous research has demonstrated that the delayed-recall components of anterograde learning paradigms (experimental or neuropsychological test based) are reliant upon the MTL structures (Helmstaedter et al., 1997). However, delayed-recall of story learning also appear reliant upon rostral MTL cortical structures (Wolk et al., 2011), suggesting that these anterograde memories could be recalled without a contextual sense of prior exposure (a key feature of hippocampally-retrieved memories; (Wolk et al., 2011), and, as such could be supported by the extrahippocampal MTL cortex regions such as the PRC and lateral ERC (Aggleton and Brown, 2006; Eichenbaum et al., 2007; Yonelinas et al., 2007). Hippocampal activity therefore seen during learning could be more representative of associations made between the items during learning but subsequently not required for retrieval (Wolk et al., 2011). As discussed above, the neuropsychological tasks that were used to construct these indices were chosen for their theoretical dependence on the hippocampus for normal expression. Therefore, the

modulating effect of the anterograde internal detail point score may demonstrate alterations in the ability of the hippocampus to make those associations, even if retrieval were subsequently independent of the hippocampus.

To summarise, the current data suggest that where the hippocampus supports a neuropsychological domain, then the anterograde internal detail point score will be impaired, with the internal detail score predicting performance on those tests. Given that both the anterograde memory *and* neuropsychological measures were acquired following VGKC-complex LE, it suggests these behavioural paradigms are converging around hippocampal intregrity.

7.4.3.2. Implications of retrograde internal point score associations

In the context of the experimental work presented here, the more remote retrograde memories were obtained prior to the illness period, and so were acquired with a normal functioning hippocampus. Given that performance on the early retrograde memory must theoretically arise from hippocampal-dependent retrieval processes, given they were acquired with normal hippocampi (Nadel and Moscovitch, 1997; Squire and Alvarez, 1995), then any causal relationships then discovered with neuropsychological measures suggest that these measures too are reliant upon the hippocampus for retrieval.

Retrograde memory internal point score was found to predict performance on delayed verbal recall (a measure significantly impaired for this patient group, Chapter 4). As discussed above, delayed-recall components of anterograde learning paradigms (experimental or neuropsychological test based) are reliant on MTL structures (Helmstaedter et al., 1997), particularly if they are recalled with a sense of context (Wolk et al., 2011). The association between retrograde internal detail score and delayed verbal recall performance likely suggests that these two separate behavioural measures are reliant upon the hippocampus. Therefore, this suggests that delayed verbal recall was the most sensitive neuropsychological measure of hippocampal function, at least following VGKC-complex LE, which in keeping with other longitudinal studies of VGKC-complex LE (Bettcher et al., 2014; Butler et al., 2014; Frisch et al., 2013). The result is also consistent with evidence that indicates the hippocampal-dependency of these neuropsychological tasks in terms of generating and retrieving associations between complex stimuli {Helmstaedter, 1997;Wolk, 2011).

This chapter has shown that the degree of impairment observed with memories that are generally agreed to be dependent on the hippocampus – specifically anterograde and early retrograde episodic memories – can predict performance for those neuropsychological tasks that are, at least, modulated by the hippocampus (e.g., immediate verbal recall, immediate visual recall, and delayed verbal recall) following VGKC-complex LE. This generally agrees with those qualitative studies that have found such an association (Kopelman, 1989; Squire, 1995; Wicklegren, 1979; Barr, 1990; Bright, 2006; Hornberger, 2010; Kapur, 1992; Milton, 2010; Reed, 1998; Sehm, 2011), although this is the first use of inferential statistics in such a study.

7.4.4. The relationships between anterograde and retrograde amnesia

The results above show that both anterograde and early retrograde episodic memory performance predicted anterograde mnemonic performance on a range of neuropsychological domains. These regressions were undertaken to re-evaluate and provide a conceptual re-assessment of the results reported by Smith et al., (2013).

7.4.4.1. The relationship between anterograde and retrograde episodic memory performance in health and disease

A series of regressions were undertaken to determine whether anterograde internal detail performance could predict retrograde internal performance across the lifetime of a subject. Chapter 5 has demonstrated that there is an absence of a temporal gradient, suggesting that the most appropriate data-driven approach was to regress anterograde performance against the cumulative retrograde internal detail point score collapsed across epochs.

Anterograde internal detail performance predicted retrograde internal detail performance in both health and disease. An additional exploratory analysis of the individual epochs found that, with the exception of the 0-11 and 40-50 of the extended administration of the AI; anterograde internal detail performance positively predicted retrograde memory performance for each epoch. For both the 0-11 and 40-50

regressions, this may have been a reflection of lower numbers used for these analyses (*n* = 20), especially given both were near significant.

One immediate implication of these predictive relationships is that the memories characterised by the internal detail score are similar constructs, even across the lifetime – a central finding of Chapter 5. Given that anterograde episodic memories and those acquired in the most recent five years are believed to particularly reliant upon the hippocampus (Nadel and Moscovitch, 1997; Squire et al., 2001; Squire et al., 2004), it is assumed that these are markers of hippocampal function. Therefore, the fact that anterograde internal detail performance predicted more remote episodic memory performance, suggests that these more distant memories too are reliant upon the hippocampus for their expression, or at least there is some causal role of the hippocampus in the retrieval of these memories.

It could be argued that the anterograde memory may not represent the same mnemonic entity as the retrograde memories, as it was acquired with a damaged hippocampus, and hence may be a qualitatively different memory from the retrograde memories. The early retrograde memory was acquired in the five years before VGKC-complex LE, and as such reduced re-experiential quality is solely due to impaired hippocampal-based retrieval, removing the potential confound associated with the anterograde memory. Therefore, using a further exploratory regression on the extended administration of the AI – which used five epochs as the dependent variables in the regression model, compared to just three for the standard administration – it was found that the early retrograde internal detail point score predicted internal detail point performance for every other epoch, except the 0-11 epoch (i.e., the most remote memory). This suggests that these memories rely the same fundamental processes for retrieval, whereas the lack of relationship with the most remote epoch may represent a memory not supported by the hippocampus. The parallels between these results and those of Chapter 5 are striking, where it was suggested that the most remote episodic memory might not be the same mnemonic construct.

These data extend the results of Chapter 5, and are consistent with models that posit that the hippocampus is needed to bind the many disparate features of an episodic memory such as perceptual and event details together into a single coherent experience

(Maguire et al., 2010b; St-Laurent et al., 2014; St-Laurent et al., 2009). Given the degree of impairment in anterograde episodic re-experiencing (as operationalized by increasing internal detail point score) predicted retrograde re-experiential quality, then this would suggest these processes are being retrieved, and possibly reconstructed, with the same apparatus.

The lack of causal relationship between the 0-11 and early retrograde memory (i.e., the five years memory) – a memory solely reliant on the hippocampus – suggests that the 0-11 memories could rely entirely upon the other temporal lobe structures. The view that diminished internal perceptual detail recall could arise from hippocampal dysfunction is corroborated by studies showing that the hippocampus is also central to scene construction and imagining the future; two tasks requiring the assembly and retrieval of object and spatial details into complex scenes and events (Addis et al., 2011; Hassabis et al., 2007; Hassabis and Maguire, 2007, 2009; Schacter and Addis, 2009). Therefore, the hippocampus is not solely representing the memory *per se* but rather assembling the key, in this case, perceptual details pertinent to episodic recall. The transformation hypothesis posits that remote memories change from a quantitatively rich account into a schema-based memory that retains its sense of narrative, but lacks many of the re-experiential components of memory (although quite what these are never specified; Eustache et al., 2004; Winocur et al., 2010).

The transformation hypothesis also predicts that the general schema of the memory becomes less rigidly associated with the context in which it was learnt, as it is consolidated and recalled in the surrounding temporal lobe cortex (Winocur et al., 2010). In this view, a schema-derived memory supported by the neocortex may give the appearance of episodic-like recall, but when probed further, it is likely that the autonoetic component of the memory will be lost (Winocur et al., 2010). These regression data help provide evidence that the transformation hypothesis may have a correlate process in humans, and that the hippocampus is required for the successful retrieval of retrograde episodic memories beyond the most recent five years.

7.4.4.2. Other studies assessing the relationship between retrograde and anterograde amnesia

Despite the mnemonic and methodological differences, the present data can be compared against other studies that have qualitatively assessed the extent to which AA correlates with RA. Results from these investigations indicate that the more extensive the AA, the more extensive the RA (Kopelman, 1989; Squire and Alvarez, 1995; Wicklegren, 1979), although sometimes the RA can appear disproportionately severe in comparison to AA (Barr et al., 1990; Bright et al., 2006; Hornberger et al., 2010; Kapur et al., 1992; Milton et al., 2010; Reed and Squire, 1998; Sehm et al., 2011). Russell and Nathan, (1946) assessed a large number of subjects, but did so through qualitative means, and so it is difficult to draw direct comparisons to the current study. However, the current data do broadly agree with previous studies.

Smith et al., (2013) correlated cumulative measures of AA based on neuropsychological subtest scores with measures of RA based on a public event questionnaire in a group of 11 patients with lesions ranging from purely hippocampal through to more extensive MTL involvement. The authors found that the more severe the AA so the more severe the RA became as well, which is in line with the results reported here. However, there was no temporal gradient in the current patient group. As the authors acknowledged, the RA described in their study was based on public semantic memory (i.e., memories for public events), which has minimal reliance on the hippocampus, and so the conclusions that can be reached concerning the relationship between retrograde episodic amnesia and anterograde memory are limited (Smith et al., 2013). Indeed, the current data have found a similar relationship between AA and RA for just episodic memory performance, thereby removing the confound of comparing neuropsychological data with public semantic memory performance (Smith et al., 2013).

7.4.5. Personal semantic memory retrieval and hippocampal subfield volumes

This chapter also found that hippocampal subfield volumes did not predict personal semantic memory performance, as measured by the accumulated semantic memory measure from the AMI. This is to be expected given the discussion in Section 6.1 concerning the role of the overlying temporal lobe cortex in supporting these memories. As such further discussion will not be undertaken here.

7.4.6. VGKC-complex LE as a model of hippocampal dysfunction

The results from Chapter 4 indicate that VGKC-complex LE leads to a significant groupwise reduction in immediate verbal and visual recall, and delayed verbal recall. The results from Chapter 5 demonstrate that there are significant impairments in anterograde and retrograde memory performance, as operationalized by internal detail point score on the AI. These current data suggest that the most sensitive behavioural marker of hippocampal function is internal detail performance from the AI. It has also been shown, for the first time in any amnesic cohort, that a direct predictive relationship can been established between a specific hippocampal subfield volume, CA3, and internal detail performance from the AI. The accumulation of these disparate areas of research around the central thesis of focal hippocampal damage, suggest that VGKC-complex LE is, at least, as good a model of hippocampal dysfunction as other pathologies that have studed, such as viral encephalitis (Bayley et al., 2005; Rosenbaum et al., 2008), trauma (Rosenbaum et al., 2009), or anoxia (Bayley et al., 2005; Cipolotti et al., 2001).

From a practical perspective, almost all cases of focal hippocampal pathology are rare, but the cohort used in this study arise from a single aetiology, and all appear to have fairly similar degrees of behavioural performance, the degree of which can be predicted according to hippocampal subfield volume loss after the disease has been treated.

7.4.7. Limitations and future work

Limitations of this chapter have been described at various junctures in this discussion. The over-riding limitation of this study is that with only 18 patients it could be potentially underpowered to find predictive relationships between 10 individual hippocampal subfield volumes and behavioural performance. This is particularly the case with the neuropsychology data where the number of *a priori* independent variables (10: five subfields on two sides) approaches the number of subjects being put forward into the model. Therefore, this study could be extended to include more subjects, in order to further probe the relationship between subfield volume and neuropsychological performance. The use of contemporaneous control data would help determine whether the negative predictive relationships between behaviour and subfield anatomy demonstrated in Section 7.3.1 exists in a non-pathological population.

Another limitation of the current study is the lack of DTI data between subfields, as shown by Yassa et al., (2011). Whilst immunological work has shown the CA3 region is the most targeted by the VGKC-complex antibodies (Lgi1 and Caspr2; Irani et al., 2010), it would seem unlikely that just the cell bodies would be affected after the illness. Therefore, it could be that the degree of white matter microstructural damage following VGKC-complex LE is a greater predictor of behavioral performance, as the trisynaptic circuit of the hippocampus is disrupted.

7.4.8. Conclusion

This chapter has shown, for the first time in investigations of retrograde episodic memory and hippocampal pathology, that a predictive association exists between CA3 volume and cumulative retrograde memory performance in chronic VGKC-complex LE. These data accord well with computational accounts of subfield function in episodic memory retrieval, and are consistent with neuropsychological models of episodic memory retrieval that suggest that the hippocampus is critical for memory retrieval across the lifetime. This provides the first human-based evidence that specific hippocampal subfield dysfunction can result in episodic memory impairment, and that VGKC-complex LE is a suitable as a model of hippocampal subfield dysfunction. These data also show that subfield volumes can predict neuropsychological performance but that some negative predictive relationships exist between subfield volume and neuropsychological performance. This is the first study of its kind, but there are suggestions from other fields of research that larger subfield volumes may have deleterious effects on neuropsychological performance. These complicated patterns of results provides interesting future avenues of research.

Chapter 8

General discussion

The premise on which this thesis has been undertaken was to determine whether voltage-gated potassium channel-complex antibody-mediated limbic encephalitis (VGKC-complex LE) is a suitable model of human hippocampal pathology, and to align the neuroradiological, neuropsychological, and mnemonic findings to other well-described human models of hippocampal dysfunction, such as viral encephalitis (Bayley et al., 2005; Rosenbaum et al., 2008), trauma (Rosenbaum et al., 2009), or anoxia (Bayley et al., 2005; Cipolotti et al., 2001). This hypothesis was tested using multimodal research methods including: (1) ultra-high field *in vivo* volumetric assessment of the hippocampal subfields (Chapter 3); (2) an extensive neuropsychological assessment, with an emphasis on tasks hypothesised to be hippocampal-dependent (Chapter 4); (3) an extensive test of retrograde autobiographical episodic memory performance for these patients using a semi-structured and quantitative assessment of these memories, the Autobiographical Interview (AI; Chapter 5); (5) the construction of a novel measure of public semantic memory to test competence of patients with VGKC-complex LE for this type of declarative memory (Chapter 6); and (6) the investigation into the causative relationships between hippocampal subfield volumes, neuropsychological performance, and anterograde and retrograde episodic amnesia (Chapter 7). The current chapter will discuss how these results contribute to the memory field, the limitations of the work, and proposes future research directions.

8.1. Chapter 3: *In vivo* quantification of hippocampal subfields in health and disease at 7.0-Tesla

The results demonstrated that the imaging protocol devised and applied in Chapter 3, alongside the specific imaging parameters used for the 7.0-Tesla imaging, delivers highly reliable intra-rater and robust hippocampal subfield volumes in both health and disease, comparable to field-leading protocols and without resorting to subfield extrapolation (Malykhin et al., 2010; Wisse et al., 2012). Significantly, Chapter 3 also demonstrated that VGKC-complex LE leads to significant bilateral atrophy of the CA3 subfield, with exploratory analyses demonstrating CA1 loss in the body of the hippocampus.

Chapter 3 also demonstrates there is a range of CA3 pathology seen after VGKC-complex LE, which when combined with the variation in the control group, enabled linear, and predictive, relationships between volumetric-based measures and individual variability in behavioural performance using tools such as regression-based techniques to be conducted. It was this approach that was utilized in Chapter 7. This is departure from the previous studies, where performance was just considered in terms of dichotomous group membership according to focal MTL or more extensive and MTL+ lesions.

8.1.1. Limitations of Chapter 3

8.1.1.1. Failure to quantify *in vivo* medial temporal lobe volumes

A critical limitation to the data presented in Chapter 3 is the lack of cortical volumes for other medial temporal lobe regions outwith the hippocampus (e.g., the entorhinal, perirhinal, and parahippocampal cortices, plus the amygdala). The entorhinal cortex (ERC) was successfully segmented at 7.0-Telsa in a previous study (Wisse et al., 2012), but whole brain sequences were acquired to enable segmentation of the MTL rather than the hippocampus specifically. The imaging parameters used in Chapter 3 were successful in producing partial volume three-dimensional fast spin echo (3D-FSE) hippocampal images, which did not require multiple scanning sessions or post-scanning reconstruction, to support reliable whole-hippocampal subfield segmentation, in comparison to previous studies (Wisse et al., 2012). However, optimized hippocampal visualization was achieved at the expense of signal dropout for regions immediately

outwith the hippocampus, making the segmentation of these cortical volumes unfeasible. Future studies should include the addition of contemporaneous whole brain T2-weighted scans, in order to permit, manual segmentation of other key MTL structures.

8.1.1.2. Failure to obtain whole brain volumetric analysis

The principal whole brain volumetric finding was that VGKC-complex LE patients did not significantly differ from controls for grey and white matter or cerebrospinal fluid (CSF) volumes. Previously, studies of retrograde episodic memory have not reported equivalent while brain segmentation data, focusing instead on MTL structures (Bayley et al., 2005; Cipolotti et al., 2001; Gold and Squire, 2005; Rosenbaum et al., 2008), perhaps the most critical brain region implicated for episodic memory retrieval. The current dataset suggests that the retrograde episodic amnesia observed occurred in the absence of generalized grey or white matter loss, although it cannot be specifically concluded that some focal cortical atrophy, beyond the hippocampus, did not occurred.

The data in Chapter 3 also failed to report cortical volumes from more distant cortical sites involved in episodic memory retrieval (e.g., parietal lobes, precuneus). Previously, two longitudinal automated whole brain segmentation studies in VGKC-complex LE have shown that during the acute illness there is swelling of both the hippocampus and amygdala bilaterally, but that at six months following successful treatment of the disease, focal hippocampal atrophy was observed, alongside a normalization of the amygdalae volume (Wagner et al., 2015; Wagner et al., 2014). This at least set the precedent of focal hippocampal atrophy VGKC-complex LE, the first aetiology associated with focal MTL involvement that has been subject to such whole brain segmentation studies (cf. Bayley et al., 2005; Cipolotti et al., 2006; Gold and Squire, 2005; Rempel-Clower et al., 1996; Rosenbaum et al., 2008; Smith et al., 2013).

Anatomical images in these VGKC-complex LE longitudinal studies cited above were acquired at 3.0-Tesla (Wagner et al., 2015; Wagner et al., 2014), the field strength on which the FreeSurfer algorithms have been trained. Fewer FreeSurfer studies at 7.0-Tesla exist due to the need to correct for the B0 inhomogeneity, particularly associated with the field changes seen surrounding air filled skull regions (such as the sinuses). This requires manual correction to be applied to the T1 images, and recently methods have been proposed of how to undertake such correction (Lusebrink et al., 2013). However,

given the FreeSurfer segmentation package has been trained on 3.0-Telsa MRI scans, a likely more valid approach to this automated FreeSurfer-based whole-brain segmentation in the current patient cohort would be acquire T1-weighted whole brain images at 3.0-Tesla (Wagner et al., 2015; Wagner et al., 2014).

8.1.2. Extending the VGKC-complex LE group data set with diffusion tensor imaging and resting state functional MRI

These current data elide two other critical measures of hippocampal function, specifically the functional and anatomical connectivity of the hippocampal subfields, but also the cortical areas that support memory recall.

The work in Chapter 3 does not provide any qualitative or quantitative measure of anatomical connectivity, either within the hippocampus, or between the hippocampus and the distant cortical regions implicated in episodic memory retrieval (e.g., the precuneus). The hippocampus is known to receive afferent and efferent connections with a diverse number of cortical regions, and sits atop a hierarchy in which it receives highly processed and associational information (e.g., Lavenex, 2012; Lavenex and Amaral, 2000; Ranganath, 2010; Rolls, 2013; Figure 1.1). Diffusion tensor imaging (DTI) has been used as measure the integrity of white matter tracts between interconnected cortical regions (Jbabdi et al., 2015). These techniques can also be used to measure the connectivity between two cortical regions that may be functionally connected – such as the hippocampus and the primary visual cortex – but also for those with intermediary cortical connections (Jbabdi et al., 2015). As will be discussed in more detail below, DTI is becoming more central in understanding the consequences in anatomical connectivity, particularly in disease states such as Alzheimer's disease (AD) where such connectivity, particularly within the MTL, is disrupted (Douaud et al., 2011). VGKC-complex LE warrants the assessment of white matter connectivity, as this may shed light on the impact of volumetric pathology on anatomical connectivity, such as disconnection from important afferent regions such as the ERC, leading to reduced neurocomputational capacity of the hippocampal subfields.

Other examples of organic brain pathology – such as epilepsy – have conceptualized their generation, spread, therapeutic response, and cognitive impairment as arising from a network-wide pathology (Centeno and Carmichael, 2014). A critical

study methodology used to define these networks includes resting state functional MRI (fMRI) that, as discussed below in Section 8.1.2.2, seeks to correlate brain regions that share similar levels of activity at rest. Insodoing, it becomes possible to create a 'connectome' of brain regions that are functionally connected with the region of interest, and then further assess the integrity of that network with methods detailed below. These methods could be applied in VGKC-complex LE to investigate whether there are reductions in the functional and anatomical connectivity both within the hippocampus, plus also between the hippocampus and the wider cortical regions involved in episodic memory recall.

8.1.2.1. Diffusion tensor imaging

DTI, therefore, can help assess the integrity of white matter tracts both within the hippocampus, and between the hippocampus and more distal cortical sites. In VGKC-complex LE, it might be predicted that greater degrees of white matter disruption may result in poorer behavioural performance on task believed to involve pattern separation and completion-based computations (Yassa et al., 2011), which are dependent upon the microstructural integrity of the CA1 and CA3 interconnections and auto-associational connections (Bakker et al., 2008; Rolls, 1995, 2013).

DTI studies have not been undertaken in VGKC-complex LE patients, but there is evidence to suggest *a priori* that disruption to the white matter structures within the hippocampus might be expected. For instance, the perforant pathway is the principal pathway by which information enters the hippocampal circuit (see Figure 1.1), and it has been shown to be sensitive to age-related changes in white matter integrity such that the anatomical connections supporting pattern separation and completion become disrupted (Yassa et al., 2011). DTI studies into mild cognitive impairment (MCI) have shown deterioration in white matter orientation of the perforant pathway – as measured by intervoxel coherence, a measure of similarity of orientation between adjacent voxels – with age (Kalus et al., 2006), or increased fractional anisotrophy – a measure of isotropic diffusion, itself a marker of tissue degradation – in older adults (Rogalski et al., 2009). Studies in AD have shown that the fractional anisotropy, that is how highly anisotropic the diffusion is, decreases in the parahippocampal white matter (Salat et al., 2010). These studies demonstrate that the white matter microcircuitry of the hippocampus might be at least partially disrupted following VGKC-complex LE, and as such could provide a

measure to use as either an independent variable in linear regressions, or as a covariate in an ANCOVA analysis of the AI data from Chapter 5. If retrograde episodic memory were dependent on successful pattern separation or completion (Bakker et al., 2008; Rolls, 1995, 2013), then some predictive or covariate relationship would be expected.

It is more difficult to predict what the consequences for more distal connections between the hippocampus and other canonical regions involved in episodic memory retrieval might be following VGKC-complex LE. However, DTI would help determine whether there is an anatomical disconnection of either the hippocampal subfields, or the hippocampus itself from the remaining cortical regions involved in episodic memory retrieval. Given VGKC-complex LE appears to be a disease specifically of the CA1 and CA3, as visualized on *in vivo* mouse models (Irani et al., 2010), then it is reasonable to suggest some disruption to the intrahippocampal microcircuitry, but not to the afferent and efferent connection as outlined in Figure 1.1.

8.1.2.2. Resting state functional magnetic resonance imaging

8.1.2.2.1. Default mode network

The default mode network (DMN; Greicius and Menon, 2004) is the principal network of cortical regions that support memory retrieval, and is comprised of the posterior cingulate cortex (PCC)/precuneus, bilateral parietal lobe cortex and the medial prefrontal cortex (Buckner et al., 2008; Raichle et al., 2001), regions all independently identified as crucial to episodic memory retrieval (Cabeza et al., 2004; Maguire, 2001a; Vincent et al., 2006). A substantial amount of cognitive processing that occurs during rest or low-level controls tasks seems to involve episodic memory retrieval (Andreasen et al., 1995; Mazoyer et al., 2001), and as a consequence significant overlap has also been observed in brain regions associated with episodic and autobiographical memory and the DMN has been identified (Daselaar et al., 2009; Spreng et al., 2009). These data suggest that VGKC-complex LE should be associated with disruption to the DMN, mediated via the hippocampal atrophy observed in Chapter 3.

A recent resting fMRI study (Kahn et al., 2008) has demonstrated that even within the hippocampus there are even distinct cortical connectivity differences between the head and body of the hippocampus:

1. **Hippocampal head:** anterior temporal lobe along the middle temporal gyrus immediately below the superior temporal sulcus and PRC and ERC.
2. **Hippocampal body:** inferior parietal lobule, retrosplenial cortex, the posterior cingulate, a portion of the ventral medial PFC and the posterior PHC.

The data from Chapter 3 suggest that the body of the hippocampus was most atrophied following VGKC-complex LE, argued to be as a consequence of a greater representation of CA3 within this region, in keeping with previous anatomical studies. Atrophy was also noted in the hippocampal head due to both CA3 and CA1 atrophy. According to the data of Kahn et al., (2008), DMN analysis in this patient group using this hippocampal head and body as distinct regions of the DMN, would predict a reduction in connectivity in both networks, each supported by the hippocampal head and body, but that within the patient population there may be a dissociation between the two, specifically that the network supported by the hippocampal body will be more greatly reduced than that of the hippocampal head.

Only one study has looked at the functional integrity of the DMN in three MTL amnesic patients (one due to herpes simplex encephalitis, one due to trauma, and one due to anoxia) using a fixed-effects model (Hayes et al., 2012). Using a seed-based correlation analysis approach the authors sought to assess the connectivity between the posterior cingulate cortex (PCC) and the canonical areas of the default mode network (DMN). Compared to controls MTL patients had a similar pattern of DMN connectivity with areas such as the precuneus, lateral parietal region and medial PFC regions, whereas the BOLD signal synchronicity in the PCC and MTL were less synchronized that controls. Decreased DMN connectivity was seen in some residual MTL tissue including left PHC, ventromedial PFC, posterior inferior parietal lobule, retrosplenial cortex and PCC/precuneus. Importantly, none of these differences were seen in another resting state network, the somatomotor network. However, these results were not related to any measure of mnemonic performance, much less retrograde memory. The basic approach applied in this study could be extended to the current cohort, where it would be expected that the synchronicity between the hippocampus and PCC would be reduced, perhaps in

a degree proportional to the degree of hippocampal atrophy observed, or indeed degree of CA3 volume loss.

However, another method of analyzing the DMN comes from high-resolution fMRI at 3.0-Tesla, whereby it is possible to assess the differential functional connectivity of the hippocampal subfield to different cortical regions. It has been observed that the CA1 and SUB showed preferential connectivity with the PRC, but not CA2/CA3/DG (Libby et al., 2012). This study also demonstrated that the anterior hippocampus has a preferential connectivity with the PRC, whereas the posterior hippocampus is more associated with PHC activity. Given the anatomical locations for the hippocampal subfields in both patients and controls is known, this experiment could be undertaken on the resting state fMRI data at 3.0-Tesla to assess the functional connectivity consequences of the CA1 and CA3 atrophy. The results of Libby et al., (2012) would suggest that reduced connectivity would be observed between CA1 and the PRC, but that no differences will be observed between CA3 and the PRC compared to controls. However, the Libby et al. study collapsed across three subfields, thereby potentially diminishing the effects observed for the CA3 atrophy. Given there is more CA3 within the body of the hippocampus compared to the head, it could be predicted that there will be a reduction in connectivity between the body of the hippocampus and the PHC. A study using this cohort would be aimed at specifically assessing what functional connectivity weightings are associated with the subfield pathology.

The hippocampus has also been previously shown to be central to the integration of perceptual details into a rich memory construct. The PHG receives spatial and scene representation from the posterior neocortex (Epstein and Kanwisher, 1998; Epstein, 2008) that, in turn, reaches the hippocampus by way of the ERC, converging in the CA fields, where it is combined with visual identification information from the ventral stream reaching the hippocampus by way of the PRC and ERC (Derdikman and Moser, 2010; Litman et al., 2009; Ranganath, 2010; Suzuki, 2010). A recent fMRI experiment has shown that there is increased BOLD signal change, and hence connectivity between the left anterior hippocampus and frontal lobes during scene construction and the bilateral posterior hippocampi with visual perceptual areas during elaboration (McCormick et al., 2014). Using a seed-based voxel analysis it would be possible to assess the functional connectivity between these hippocampal regions and other neocortical sites, specifically

looking at connectivity patterns in VGKC-complex LE patients, herein demonstrated to have impoverished episodic recall. Aside from the fact that there is only one report of resting state data in three patients with hippocampal amnesia has been undertaken (Hayes et al., 2012), hence this data would be in 18 patients with a single aetiology. Given this study found that there was reduced connectivity between the hippocampi and the posterior cingulate cortex, we might expect this pattern to observed but with normal connectivity between the remaining structures important to episodic memory recall such as medial prefrontal cortex, lateral parietal cortex and posterior medial cortex. This would help elaborate the functional connectivity between the regions known to contribute to retrograde episodic recall, but the scores from the AI could also be used as covariates in this analysis to assess for connectivity differences in perceptually rich and impoverished memories (i.e., Last Year and Five Years and the 0-11). Given the findings of McCormick et al., (2014) it would also be important to assess the functional connectivity between the hippocampi, frontal lobes and visual perceptual areas, using the perceptual internal detail scores as a covariate where it would be expected to find reduced connectivity between visual areas and the hippocampus.

8.1.2.3. Neuroimaging: summary

A full anatomical and functional connectivity-based account of the hippocampus would ideally include some information concerning the intra- and extrahippocampal white matter connectivity, alongside work on the functional connectivity of the regions known to be integral to retrograde episodic memory retrieval. These multimodal approaches have been used to understand the complex relationship between anatomical and functional networks underlying the emergence of schizophrenia (Sui et al., 2013). For instance, increased frontal DTI anisotropy is associated with a corresponding diminution in prefrontal cortical connectivity, relationships thought to be critical to emergence of positive symptomatology associated with schizophrenia (Sui et al., 2013). Moreover, this multimodal account of connectivity would finally address the question of hidden pathology in hippocampal lesion patients (Markowitsch et al., 1997), particularly findings that contradict the standard model of consolidation (Bayley et al., 2003, 2006; Kirwan et al., 2008), as it would be able to provide an account of global brain connectivity and function. Once this multimodal description of VGKC-complex LE was undertaken, the functional and anatomical connectivity of the hippocampus could be used as regressors for many of the behavioural measures in this thesis.

8.2. Chapter 4: Extensive neuropsychological assessment of VGKC-complex LE

Table 4.1 demonstrated that neuropsychological evaluation of patients with lesions limited to, or extending beyond, the MTL provides an important foundation for understanding the nature of pathology in more experimental measures of memory. The test battery administered in this thesis is at least as comprehensive, if not more so, than the majority of batteries used in earlier studies (see Table 4.1). Given previous studies have shown that VGKC-complex LE results in hippocampal atrophy (Wagner et al., 2015; Wagner et al., 2014), the neuropsychological battery had a particular detailed assessment of mnemonic function, with care taken to separate immediate- and delayed-recall, verbal and visual recall, single item memory, and recognitions memory, whereas, by contrast, many other studies in VGKC-complex LE have included these as single measures (Bettcher et al., 2014; Butler et al., 2014; Frisch et al., 2013). Other cognitive domains, such as language and executive functions, were not predicted to be affected following VGKC-complex LE given the previous neuropsychological studies undertaken in this disease group (Bettcher et al., 2014; Butler et al., 2014; Frisch et al., 2013), and so were not studied in such detail although pathology may have been overlooked. This is also the first time that attention has been extensively studied in cases of organic amnesia. The size of the battery did render it susceptible to type I and type II errors; however, care was taken to ensure that, where possible, more than one test was used to construct the indices. Type II errors were harder to mitigate for, but generally where one test constituting an index score demonstrated some level of impairment, the remaining scores were usually likewise impaired.

The one task that is not represented in this test battery is paired-associate learning, a sensitive measure of hippocampal function that is also amenable to neuropsychological testing (Chalfonte et al., 1996; Dudchenko et al., 2000; Squire, 1992). Examples of neuropsychological measures of paired-associates include the Verbal Paired Associates task from the Wechsler Memory Scale-III, or more recent iterations (Uttl et al., 2002). It would be expected that this cohort would demonstrate impairment for this type of task given it reported dependence on the hippocampus for successful performance.

What remains striking from Chapter 4 is relative preservation of even delayed verbal recall, certainly in terms of group performance falling below the fifth centile (Benton and Hamsher, 1977), yet the significant deficits observed in retrograde episodic memory retrieval (Chapter 5). This suggests that even with the detailed mnemonic assessment used here, that standardized neuropsychological tests do not fully describe the extent of amnesia seen following VGKC-complex LE, as demonstrated by the dissociation evidenced with the internal detail point scores arising from the AI.

It still remains that there is great utility in using the test battery described in this thesis, not just for the modest mnemonic results, but also from the evidence of relative preservation of the other cognitive domains. This battery also extends the degree to which patients thought to have MTL or hippocampal-specific lesions need to be characterized, particularly in light of arguments based on hidden pathology (e.g., (Bayley et al., 2003; Kirwan et al., 2008; Rempel-Clower et al., 1996)).

8.3. Chapter 5: Standard and modified administrations of the Autobiographical Interview in health and disease

The results of Chapter 5 demonstrate anterograde episodic amnesia (as conceptualized by increasing internal detail point score from the AI), alongside an extensive retrograde amnesia with no evidence of a temporal gradient, as evidenced by the planned comparisons. Personal semantic memory performance was unimpaired, as conceptualized by external detail point scores. These data were in stark contradiction with the predictions of the standard model of consolidation (SMC), but also the multiple trace theory (MTT), suggesting that perhaps the best way to conceptualize the role of the hippocampus in the retrieval of remote episodic memories is that of a reconstructive hub (Marr, 1971; Norman and O'Reilly, 2003), and was in keeping with more recent accounts such as the Binding of Items and Context model (BIC; Ranganath, 2010). Reconstructive models, such as the BIC, posit that the hippocampus does not act as the repository for retrograde episodic memories, unlike the SMC and MTT, but rather forms the neurocomputational hub that binds the multimodal precepts that constitute an episodic memory – such as perceptual details, event details, and emotions – into a single re-experiential event, and critically, for this data, is required across the lifespan.

Of additional note, it was possible for the first time to determine which response categories of the AI (event details, time, place, perceptual details, thoughts and emotions) are affected in this model of hippocampal dysfunction. Planned comparisons demonstrated that for patients the difference in internal detail point score between the 0-11 and 11-18 memories, that is between their best memory and the next most remote memory, was their accrued perceptual detail point score, with other response categories being comparable between these time points. These data were in agreement with similar studies in patients with medial temporal lobe epilepsy (St-Laurent et al., 2009), peripartum anoxia (Maguire et al., 2010), and fMRI experiments that have all shown the centrality of the hippocampus in mediating the perceptual richness associated with re-experiential episodic memory retrieval (Andrews-Hanna et al., 2010; Gilboa et al., 2004; Rabin et al., 2010; St Jacques et al., 2012), although the exact mechanisms underlying this are unclear. The data in Chapter 5 is the first to show this across the lifetime.

The standard administration of the AI had to be modified, as the traditional epochs probed were limited to five uneven time periods. Therefore, the AI was extended in all participants so that one memory per decade of life could be acquired. Memories from the five years prior injury were also obtained, as this time point alongside the anterograde memories, were deemed to be the most reliant upon hippocampal function, and as such provided sensitive contrasts for assessing retrograde against anterograde memory performance. This helped extend the conclusions concerning the integrity of retrograde episodic memories across the lifetime.

The results from the AI also revealed a wide dispersion of score associated with health and disease, which then amenable to robust linear modeling, in order to determine predictive relationships between anatomy and internal detail performance.

8.3.1. Retrograde episodic memory and fMRI

Beyond the phenomenological data obtained via the AI, a patient group of this size affords the opportunity to undertake task-dependent fMRI experiments, to specifically assess the temporal role of the hippocampus in retrograde episodic memory retrieval. This patient group generated a number of recent and remote memories that could be recalled, if modified, in a form that would be in line with experimental conditions used in a recent fMRI study (Soderlund et al., 2012). The patients could be

asked to recall memories of various ages – previously the last week, the last month, the last year, and the last 10 years, (Soderlund et al., 2012) – that all are re-experiential in nature. Previously, a network of regions were found to be involved in autobiographical memory retrieval including the thalamus, prefrontal areas, anterior and posterior cingulate, middle temporal gyrus, the hippocampus, the parahippocampal gyrus, precuneus and cerebellum (Soderlund et al., 2012), in keeping with previous studies (Maguire, 2001a; Svoboda et al., 2006). Soderlund et al. found that the anterior hippocampus had most BOLD signal activity with remote memories, alongside reduced activity of the posterior hippocampus. They also reported that remote episodic memory retrieval was associated with deactivation of the left inferior frontal gyrus, the left superior temporal gyrus, and the right cuneus relative to baseline. Currently, it is not possible to say what changes to the network activated by remote memory recall would be expected in the current VGKC-complex LE group, but it might be expected that greater degrees of hippocampal atrophy would be associated with reduced activity of this network. The discussion concerning the DMN above, Section 8.1.2.2, suggest that a reduction in functional connectivity between the PCC and PHC maybe associated with a reduced sense of re-experiencing.

A fMRI network-based analysis using whole brain and seed-voxel based approaches would be interesting in helping to determine whether the extent of hippocampal subfield volume loss might predict similar decrements in network activity. This could be extended further into a multimodal imaging analysis to assess whether any functional connectivity differences seen in such future experimental work overlap with DTI-based evidence of pathology in measures of anatomical connectivity.

8.4. Chapter 6: Development of a standardized test of public event semantic memory, and results from patients with VGKC-complex LE

Chapter 6 demonstrated that performance for famous faces and new words that in eight patients with VGKC-complex LE (four born in the 1940s, four born in the 1950s) did not significantly differ from age-matched controls. This finding is broadly in agreement with several other studies of public semantic memory in patients with focal hippocampal pathology (McCarthy et al., 2005; Steinvorth et al., 2005; Verfaellie et al., 2000; Verfaellie et al., 1995). These results do though appear to contradict previous

findings of Chan et al., (2007), that public semantic memory is significantly impaired following VGKC-complex LE. The reasons for this are discussed in Section 6.4.2.

In Chapter 6, the mechanism for the development and testing of this novel measure of public semantic memory was also described. Section 6.4.4 detailed the process through which the entire question base could be standardized to produce age-matched norms, but also how the number of questions could be refined according to those that show temporal specificity. The eventual standardized version of the SSM would represent a major departure from more commonly non-standardized tests of public semantic memory. The SSM, as currently devised in this thesis, is suitable only for those based in the United Kingdom; however, the rationale for the format and structure of the question and answer format could be applied to other geographical locations. The power calculations for the effect sizes hypothetically needed to standardize the SSM were also presented in Section 6.4.4.2.

8.5. Can retrograde episodic amnesia be considered a unitary phenomenon?

When considering the results of Chapter 4-7, what is clear from both the neuropsychological and episodic memory performance is that VGKC-complex LE patients are not as mnemonically impaired as index amnesic cases (e.g., HM or KC). Although there is clear evidence of amnesia occurring in the context of focal hippocampal subfield pathology, these patients do not perform at floor, compared to HM on the AI (Steinvorth et al., 2005). This suggests that there are differences between these patients groups in how their amnesia can be described, with these VGKC-complex LE patients at the group level having a milder degree of amnesia. However, within this cohort there were patients that performed at a near floor level for the AI, thereby performing at a level similar to index cases such as HM.

As suggested in Section 4.1.1.4, the VGKC-complex LE group were comparable in their neuropsychological performance to patients with postmortem proven CA1 lesions (e.g., GD and RB; Rempel-Clower et al., 1996; Zola-Morgan et al., 1986), and have internal detail scores from the AI equivalent to those who have lesions thought to be limited to the hippocampi (KE, LJ, GW; Kirwan et al., 2008). Previously it has been reported that in four amnesic patients that internal detail point score was positively associated with increasing hippocampal volume, even though two had more extensive

extra-hippocampal volume loss than the hippocampal-lesion patients (DA: posterior temporal lobe, left ventral frontal region, and left occipital cortex; RG: left temporal lobe, left ventral frontal lobe, right temporal lobe and right superior parietal lobe; Rosenbaum et al., 2008).

A cursory view of these data suggests that, in keeping with the SMC, that more extensive hippocampal and MTL volume loss is associated with increasing retrograde episodic amnesia. However, as suggested in in Chapter 4 and 5, there are several disparate cortical regions that all contribute to successful retrograde episodic retrieval including the PHC (Davachi et al., 2003; Duzel et al., 2003; Eacott and Gaffan, 2005; Hales et al., 2009; Henke et al., 1999; Kirwan and Stark, 2004; Tendolkar et al., 2008; Yang et al., 2008), the PRC (Bussey and Saksida, 2002; Murray and Bussey, 1999; Ungerleider and Mishkin, 1982), the ERC (Reagh and Yassa, 2014), the prefrontal cortex (Cansino et al., 2002; Eldridge et al., 2000), the parietal lobes (Berryhill et al., 2007), the precuneus (Kapur et al., 1995; Naghavi and Nyberg, 2005; Nyberg, 1999), and the posterior cingulate cortex (Maguire, 2001b; McDonald et al., 2001; Osawa et al., 2006; Valenstein et al., 1987). Therefore, a parsimonious account of the important and varied contributions that these extra-hippocampal cortices provide in episodic memory retrieval, suggest that the hippocampus has a modulating role, albeit a critical one, in episodic memory retrieval. It appears to be no longer appropriate to think of episodic amnesia in MTL or MTL+ terms, but rather in terms of whole brain cortical volumes, anatomical connectivity, functional connectivity, and, where appropriate, hippocampal subfield volumes.

The deficits seen in VGKC-complex LE might be mild in terms of neuropsychology, but they are significant for internal detail performance, although they can still retrieve more details than those with extensive MTL lesions. All this occurs in the presence of focal CA3 atrophy, at least as assessed in terms of hippocampal segmentation, in the presence of grey and white matter and cerebrospinal fluid volumes that did not differ from controls. This thesis has attempted to understand what this form of hippocampal pathology can tell us about the fundamental processes underlying memory performance, and has established novel methods of assessing the three main types of declarative memories.

This thesis has also specifically described how VGKC-complex LE causes focal lesions to CA3 region of the hippocampus, in the context of focal hippocampal atrophy observed in previous studies (Wagner et al., 2015; Wagner et al., 2014). (Although resting state and DTI would help produce a more thorough account of VGKC-complex LE). Therefore, this aetiological group can then be used to ask more specific questions concerning the computational role of the hippocampus in episodic retrieval, whether that be a binding role (Diana et al., 2008; Ranganath, 2010), a pattern separation and/or completion role (Chadwick et al., 2014; Yassa et al., 2011), or one of reconstruction (Greenberg et al., 2005; Piolino et al., 2009; St-Laurent et al., 2014; St-Laurent et al., 2009), but not what the roles of the other cortical regions for episodic memory retrieval may be (e.g., the ERC, precuneus, PCC). Therefore, it appears problematic to conceptualize amnesia as a unitary process; it is perhaps better characterized as a phenomenon emerging due to the disruption of a multiplicity of potential neuroanatomical – and hence neurocomputational – processes of which VGKC-complex LE is but one aetiological disruption to those mechanisms.

8.6. Future experiments in patients with focal hippocampal subfield pathology

8.6.1. Future imagining

It is important that any model of hippocampal function in memory must take account, and to a degree be harmonized with, non-mnemonic roles of the hippocampus in cognition. It has been previously observed that three patients with VGKC-complex LE perform poorly on a task of future imagining (Hassabis et al., 2007), a constructional process believed to be reliant upon the hippocampus (Schacter and Addis, 2007). In this task, subjects are asked to imagine a future event with as much visual information as possible, the event digitally transcribed, and marked with a schema similar to the AI (Hassabis et al., 2007). The analysis would be conducted as with the AI, and it could be predicted that this cohort will generate fewer points that are equivalent to internal details. It could be expected that this VGKC-complex LE group should perform significantly worse than age-matched controls, in keeping with a previous study (Hassabis et al., 2007). The future imagining data could then be subjected to a robust linear regression to assess what subfields volumes might predict behavioural performance. The neurocomputational roles of the hippocampal subfields has been extensively modeled (Rolls, 1995, 1996, 2013), with CA3 being most central to processes of pattern separation

and completion; it is not clear whether these subfields would have analogous roles for future imagining. However, given the predominant lesion in VGKC-complex LE is CA3 atrophy, and future imagining has been shown to be impaired in three patients with VGKC-complex LE, it might be expected that CA3 volume would predict performance for this task.

8.6.2. Functional MRI experiments

8.6.2.1. Pattern separation and completion

A recent study has demonstrated that CA3 volume is directly related to the ability of healthy participants to pattern separate (Chadwick et al., 2014). Participants were exposed to four movie clips in which either one of two events occurred in one of two spatial contexts (a 2 x 2 design), and hence four distinct, but overlapping, memories of an event with a specific spatiotemporal context. Subjects were then asked to recall each of these memories several times whilst undergoing fMRI scanning. Analysis aimed to discriminate between the individual patterns of BOLD signal activity underlying each of the four memories, analysed using algorithms that best predicted individual memory recall during each trial. It was suggested that success in doing so would suggest the presence of individual episodic memory traces within the episodic memory network, and that more distinct patterns of activity would be associated with better pattern separation and hence improved memory recall (Chadwick et al., 2014). This method demonstrated that the CA3 alone was associated with supporting distinct BOLD signal activity patterns for each memory, but that there was a high degree of overlap between the activity patterns within the CA3 region, a finding interpreted as a coactivation of the other memories due to their highly similar nature. The emergence of a specific memory, therefore, required an active competitive pattern completion process to occur within CA3 (Chadwick et al., 2014). The authors then used a correlation-based analysis to show that CA3 volume was negatively correlated the BOLD signal activation observed during the interference and overlap parts of the fMRI part of the experiment (Chadwick et al., 2014). These data were interpreted as evidence that overlapping memory patterns are coactivated during episodic memory retrieval, but that increasing CA3 size is associated with increasing efficiency of overlapping memory differentiation.

The extension of this experimental paradigm to VGKC-complex LE patients would help assess the effect of CA3 atrophy on successfully recalling these highly similar,

yet distinct, memories. Given the variability in CA3 volumes found in these VGKC-complex LE group, it would be hypothesied that larger CA3 volumes will be associated with more distinct BOLD signal activity during recall, as well as superior performance on the behavoural aspect of this experiment.

Multivariate pattern analysis (MVPA) is an fMRI analysis technique whereby it is possible to detect the spatiotemporal representation of stimuli within a region-of-interest during a fMRI experiment (Bonnici et al., 2012). MVPA is also able to distinguish between the distributed neuronal populations encoding multiple stimuli, and thereby can provide the spatiotemporal patterns for two separate stimuli within a given region-of-interest. For instance, (Bonnici et al., 2012) demonstrated that MVPA can be used to successfully decode individual BOLD signal differences associated with individual episodic memories arising from the last year or 10 years, and that this can be extended into the hippocampal subfields (Bonnici et al., 2013). MVPA analysis relies on four steps for analysis: (1) deciding which voxels or regions will be off interest, in this case the hippocampus; (2) pattern assembly through which voxels active for a given stimuli are identified within the region-of-interest – which is why multiple trials are needed during acquisition; (3) classifier training whereby a subset of these labeled patterns are put into a multivariate pattern classification algorithm such that the algorithm learns a function that maps the voxel activity patterns and the presented stimuli; and (4) generalization testing where new patterns of brain activity (i.e., the last one or two runs of the stimuli during data acquisition) are presented to the trained classifier, and it is assessed whether the trained classifier can correctly determine the experimental condition/stimuli associated with that pattern. Given the number of retrograde episodic memories obtained in Chapter 5, it would be possible to ask participants to recall these memories multiple times (i.e., >10) during fMRI data acquisition and then subjected to MVPA analysis. In this scenario, MVPA would be used to determine whether the BOLD signal changes could reliably decode individual memory events, but also to determine whether successful discrimination of the events relied on CA3. This could be assessed either through a univariate/MVPA analysis of CA3 activity before and during the task or by using CA3 volume as an independent variable in a regression model or as a covariate in the MVPA analysis.

One prediction is that reduced CA3 volumes could result in highly similar hippocampal, and perhaps CA3 activity, in patients with greater degrees of retrograde amnesia. This could then be extended by asking patients, and controls, to nominate say eight spatiotemporally unique events from their 20-30s – during the period often felt to be associated with the acquisition of the greatest number of episodic memories – and then use MVPA to determine whether recall of these memories, once again, produces distinct BOLD signal differences, and whether the distinctiveness of those patterns relies on CA3 volume. This would be more ecologically valid method of determining remote episodic memory pattern separation and completion; however, a subtractive univariate approach could also be used. The key benefit of MVPA in this scenario would be that it could provide an insight into how the damaged hippocampus may or may not spatially distribute the information for different stimuli, and may provide insight into how these processes become disrupted in amnesia.

To extend the results of these fMRI experiments, DTI sequences, in paradigms discussed above in Section 8.2, could also be obtained to see what effects anatomical connectivity may have on both behavioural performance and BOLD signal changes.

8.6.2.2. Dissociating functional contributions of the medial temporal lobe cortical regions *in vivo*

One of the key theoretical consequences of studying memory in HM was evidence that declarative memories can be dissociated from non-declarative memories, and most tasks of working memory. Given the evidence from whole brain segmentation was that VGKC-complex LE results in focal hippocampal atrophy, it would appear appropriate to assess what aspects of memory the VGKC-complex LE group can perform successfully. This would an attempt to investigate the role of the hippocampus outside of functions typically associated with other MTL structures. For instance, Reagh and Yassa, (2014) recently used high-resolution fMRI (1.5mm isotropic) to measure hippocampal subfield activity and those of the regions constituting the parahippocampal gyrus (lateral and medial entorhinal cortex, the perirhinal cortex and the parahippocampal cortex). Their protocol applied MVPA analysis of fMRI data acquired on a task designed to determine how interference between similar objects or similar spatial locations were hierarchically resolved in the PHC/medial ERC or PRC/lateral ERC. This task presented a series of objects constrained to one of 35 spatial locations

prior to entering the scanner, and then sought to assess whether participants could discriminate between two types of foils: an object lure where the object was similar, but distinct from a previously encountered object in its encoded location; and a locations lure where a previously encountered object was found to be in a different location from the learning phase. Reagh and Yassa, (2014) found that lateral ERC and PRC activity was greater during correction rejection of object lures (i.e., object interference), whereas the medial ERC and PHC demonstrated the most activity during spatial lures (i.e., spatial interference). Critically, it was also observed that DG/CA3 activity was increased during both phases of the study, thought to be due to its role in pattern separation (Reagh and Yassa, 2014).

A similar study design could be used in the current VGKC-complex LE group, to specifically observe whether they differ from healthy controls for BOLD signal activation for both the lateral ERC and PRC activity during object lures and medial ERC and PHC activity during spatial lures, as it would be predicted that patients should have equivalent BOLD activity for both these tasks. However, given the CA3 pathology found in this patient group, it might be predicted that patients would have less BOLD activity in the DG/CA3 relative to controls, and then that the magnitude difference in signal activity would either correlate or predict behavioural performance for the patients ability to successfully discriminate between the object and spatial lures. Moreover, it might also be predicted that the degree of CA3 volume loss would predict both DG/CA3 activity during scanning and the behavioural performance, perhaps in both patients and controls in keeping with the results in Chapter 7. Conversely, if the BOLD signal change in either the lateral ERC/PRC or medial ERC/PHC were reliant on computational processes mediated by the DG/CA3 complex, then it might be expected that patients will have reduced activity of these cortical regions compared to controls, commensurate with the expected reduced activity of the DG/CA3 complex.

8.6.2.3. Alterations in hippocampal efferent cortical layer responses during fMRI experiments following CA3 pathology

A more recent development in fMRI has been the advent of ultra-high field strength fMRI, at field strengths of ≥7.0-Tesla. Whilst most groups use partial volume acquisitions (i.e., limited to the MTL structures), the effective spatial resolution afforded

by these acquisitions is usually in the range of 0.35 x 0.35 x 1.0-2.0 mm – fMRI spatial resolution is usually less than this.

Figure 1.1 demonstrates that input into the hippocampus arises from the superficial layers II and III of the ERC, and outputs terminate in deeper layers such as V, VI, and VII. Maass et al., (2014) attempted to engage laminar activation of these input and output lamina of the ERC using an incidental encoding task comprised of 120 images of indoor or outdoor scenes ("is this scene indoors or outdoors"), alongside 60 'noise' scenes, and 60 repetitions of these previously encountered images. After the encoding phase subjects performed a recognition test where they had to rate how sure they were they had encountered the scene previously (from 1: sure new, to 5: sure old), the values for which were used as contrast weights for the multivariate Bayesian analysis (that is a model where the analysis technique attempts to best explain which structures within a region-of-interest are activated during a behavioural task). The data demonstrated that novel trials (i.e., noise scenes identified as new) were best predicted by activity in the input regions of the ERC (i.e., II and III), alongside similar activation of DG and CA2-3 (Maass et al., 2014). Recollection of previously encountered scenes, however, was best predicted by deeper layers of the ERC, and by activation of CA1 (Maass et al., 2014).

Extending this approach, either with a novel scenes or objects, to study VGKC-complex LE-mediated amnesia could demonstrate reduced deep layer ERC activity during memory retrieval in comparison to controls, potentially due to reduced neurocomputational functions secondary to the CA3 pathology in patients. A within-groups analysis may also show that for the patients there is a reduction in activity for the deep layers of the ERC, those layers that receive hippocampal efferents, when compared to the superficial layers which are more utilized during encoding and send efferents to the hippocampus. These superficial layers should, ostensibly, show equivalent levels of activation between patients and controls, as these upstream regions are argued to function normally throughout this thesis. The finding of reduced deep layer activity relative to controls may indirectly suggest that there is a reduction in hippocampal/CA3-mediated computations – computations normally required for performance of these types of task. This approach has limitations, not least of which it relies on partial volume scans, thereby diminishing the roles of other extra-hippocampal regions play in the

memory retrieval, and that from a practical perspective, it is not clear whether the increased CSF flow artifact around the hippocampus due to atrophy will disrupt the signal return during the EPI sequences. Despite these considerations it should be technically possible, and empirically interesting to see whether such laminar changes might be seen following VGKC-complex LE, particularly whether CA3 or CA1 volumes modulates the level of activity seen in the deep regions.

More generally, there are additional caveats to these task-dependent fMRI experiments. Firstly, they require large numbers of participants (typically >20 for MVPA studies), which should be feasible with this aetiology – with an equivalent number being required for DTI (usually >20 as well, depending on the number of orientations of diffusion acquired during scanning). Secondly, to gain data for both learning and retrieval would involve extended periods of time in the scanner, which from a practical perspective is often uncomfortable for participants.

8.7. Conclusions

This thesis has demonstrated that, at the very least, VGKC-complex LE is an equivalent model of hippocampal dysfunction as other aetiologies, specifically in terms of the neuroradiological findings, and the pattern of neuropsychological and retrograde declarative memory performance. The size of the cohort has also made it possible to leverage the observed variability in the anatomical and behavioural data into linear models, and thereby formally establish a relationship between these variables, for the first time in any patient study of retrograde memory. The characterization of this VGKC-complex LE cohort is not complete or without fault, and these have been discussed both the experimental chapters and in the current discussion chapter; the methods for overcoming these short comings have also been discussed and provide several lines of further research.

The over-riding conclusion that this thesis reaches is that, tentatively, VGKC-complex LE can be viewed as a model of CA3 hippocampal subfield-mediated amnesia, and that the behavioural data raise problems for both of the major theories of episodic memory consolidation (the SMC and MTT), but align to other models of the role of the hippocampus across multiple cognitive domains (such as the BIC). Human hippocampal

subfield pathology is not without precedent, with a previous report showing that transient CA1 lesion can produce a retrograde episodic amnesia during TGA (Bartsch et al., 2011). However, the current patient group extends this work, for the first time, (1) into a chronic and permanent behavioural state, compared to the transient amnesia associated with TGA, (2) have permanent lesions that can be quantified volumetrically, and (3) have been assessed with a more robust measure of episodic memory performance.

The presence of this chronic hippocampal subfield pathology could also allow often disparate research fields within memory research – animal, computational, neuropsychological – to potentially align with one another to help provide more unified accounts of the hippocampus across multiple research spheres. Surveying the literature cited in this thesis demonstrates that patient-based research into episodic memory has fallen out of favour in recent times. This thesis has shown that careful use of novel patient groups, such as VGKC-complex LE, are able to build on the rich legacy afforded to scientific enquiry by the generosity of people such as HM, so that their loss might, ultimately, become society's gain. .

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Appendix

Exemplar questions constituting the Survey of Semantic Memory

This appendix provides exemplar questions that have arisen from the Survey of Semantic Memory (SSM) developed in Chapter 6. The methods used to acquire these questions are detailed in Section 2.4. Briefly, I attempted to collate a series of questions that were, as much as possible, time-locked to a specific decade, such that performance should improve for the decades for which the subject was alive. Moreover, foils were selected such that they would have maximal interference and plausibility for the target item. This was done to limit the impact of other cognitive processes – such as logical inference – could have on successful identification of the target item. All questions are a forced-choice recognition with three foils to the target item, thereby reducing the chance of successfully guessing the answer as 25%. This appendix details 12 general knowledge questions, six famous faces, and six new words entering the lexicon. These questions have all arisen from the 1980s.

The first space shuttle was launched in 1981. What was its name?

1. Enterprise
2. Challenger
3. Columbia
4. Endeavour

In 1985 the Greenpeace ship 'Rainbow Warrior' was sunk in a harbour of which country?

1. New Zealand
2. French Polynesia
3. Marshall Islands
4. Australia

Which backbench Conservative MP directly challenged for Margaret Thatcher's leadership of the Conservative Party in 1989?

1. Ian Gilmour
2. Beata Brookes
3. Anthony Meyer
4. Nigel Birch

Where did Mathias Rust illegally land a small aircraft in 1987?

1. Near St. Basil's Cathedral, Moscow
2. East German Berlin
3. Chernobyl nuclear power plant in USSR
4. Stasi headquarters, Berlin-Lichtenburg

In 1984 who was charged with leaking documents concerning the sinking of the General Belgrano during the Falklands War?

1. Clive Ponting
2. Tam Dalyell
3. Patrick Haseldine
4. Sarah Tisdall

The Hillsborough disaster occurred during a FA Cup semi-final between Liverpool and which other team?

1. Everton
2. Norwich City
3. Nottingham Forest
4. Wimbledon

Which American series starred Bruce Willis and Cybill Shepherd as private detectives?

1. Cagney and Lacey
2. Cover Up
3. Masquerade
4. Moonlighting

What television game show starred Anneka Rice and Kenneth Kendall which had teams in a studio directing a someone in a helicopter to find treasure?

1. Challenge Anneka
2. Skyrunner
3. Treasure Hunt
4. The Crystal Maze

Which British teenage game show starred Bob Holness and was associated with the catch phrase “Can I have a P please Bob?”

1. Countdown
2. Blockbusters
3. Marathon
4. Challenge

Which American comedy show featured an alien from the planet of Melmac?

1. ALF
2. Mork and Mindy
3. Metal Mickey
4. Out of this World

In 1989 51 people drowned when the pleasure boat Marchioness was hit by which dredger?

1. Bowbelle
2. Bom Rei
3. Francesca
4. Geopotes

In 1988 which North Sea oil production platform suffered an explosion killing 167 men?

1. Alexander Kielland
2. Sea Quest
3. Piper Alpha
4. Ocean Ranger

Who is this person?

1. Corey Feldman
2. Corey Haim
3. Jerry O'Connell
4. River Phoenix

Who is this person?

1. Phoebe Cates
2. Jennifer Jason Leigh
3. Betsy Russell
4. Lea Thompson

Who is this person?

1. Peter Lilley
2. Chris Patten
3. Michael Heseltine
4. Geoffrey Howe

Who is this person?

1. Tony Benn
2. Edward Heath
3. Arthur Scargill
4. Ian MacGregor

Who is this person?

1. Dirk Benedict
2. George Peppard
3. Dwight Schultz
4. Tim Dunigan

Who is this person?

1. Paul Rutherford
2. Peter Gill
3. Mark O'Toole
4. Holly Johnson

1980s | Select the correct definition for this word

Aerobie

1. A thin plastic ring which is spun through the air, like a Frisbee, in a catching game
2. An organism, esp. a microorganism, that has the ability to live in the presence of oxygen
3. The branch of cybernetics that deals with the control and communication systems of living organisms
4. A person who performs aerobatics

1980s | Select the correct definition for this word

Laservision

1. A system for the reproduction of video signals recorded on a laser disc
2. An electrical method of viewing or recording images in darkness, fog, or poor light using infrared illumination
3. A particular way of viewing the world or of understanding the universe
4. The branch of economics that deals with large-scale economic factors

1980s | Select the correct definition for this word

Poindexter

1. An overly diligent student, an extremely intelligent person
2. A stitch; a layer of stitching
3. A diverse family plants indigenous to Mexico, of which Poinsettia is well known example
4. A ray or skate, specifically one belonging to the superfamily Rajoidea

1980s | Select the correct definition for this word

Sloane Ranger

1. Of, pertaining to, or characteristic of an upper class and fashionable but conventional young woman in London
2. Originally: a forester, a gamekeeper
3. An infantry soldier
4. A rover, a wanderer; a rake

1980s | Select the correct definition for this word

Valspeak

1. A form of slang dialect originating from San Fernando Valley in Los Angeles
2. A kind of trumpet that carries the voice a great distance or to be heard above loud noises
3. Information system in which a television displays alphanumeric information selected by the user
4. The action or practice of sending video messages

1980s | Select the correct definition for this word

Yomp

1. To march with heavy equipment over difficult terrain
2. In jazz, dance-music, etc.: to play an accompaniment, especially with rhythmic chords
3. A small drinking vessel
4. To produce quickly, with little preparation or planning