DECLARATIVE MEMORY FUNCTIONING

IN SCHOOL-AGE CHILDREN WITH A

HISTORY OF PERINATAL HYPOXIC-

ISCHAEMIC ENCEPHALOPATHY

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D. Clin. Psy. Thesis (Volume 1) 2006

University College London

UMI Number: U592049

UMI

Dissertation Publishing

UMI U592049

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ACKNOWLEDGMENTS

PART 1: REVIEW PAPER

What does the study of developmental amnesia tell us about the organisation of

declarative memory in humans?

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1 OVERVIEW

In this review paper, the implications of the recently discovered syndrome of Developmental Amnesia (DA) for two opposing theories of medial temporal lobe (MTL) amnesia are evaluated: Some researchers describe both episodic and semantic memory as subsystems of declarative memory, dependent on medial temporal lobe and midline diencephalic structures, with episodic memory additionally depending on the frontal lobes (Unitary Account). They explain MTL amnesia in terms of an overall impairment in declarative memory functioning. Others describe episodic memory as a memory system that is additional to declarative/semantic memory (Dual-Process Account). They explain MTL amnesia in terms of various patterns of dissociation between episodic and semantic memory functioning. These two opposing accounts are used to interpret studies of the recently discovered syndrome of Developmental Amnesia, a type of childhood-onset amnesia that is characterised by selective damage to the hippocampus and selective episodic memory impairment, and which therefore presents an interesting context for evaluating the two theoretical accounts of MTL amnesia. It is argued that the Hierarchical Account, an elaboration of the Dual-Process Account, presents the most parsimonious explanation of Developmental Amnesia.

1.1 Structure

In the Introduction (Section 2), an overview of the structure of human memory is presented, episodic and semantic memory are placed within the context of other memory systems, and the contribution of studies of amnesia to our understanding of memory is reviewed. In Section 3, the two theories of MTL amnesia are described and compared in terms of their positions on the organisation of declarative memory and the relationship between memory organisation and amnesia. Section 4 reviews studies of Developmental Amnesia and how these have been interpreted by different theorists. Finally, this material is summarised and evaluated in Section 5.

2 INTRODUCTION

The last half a century of memory research has been characterised by the notion of functionally and anatomically distinguishable memory systems (Squire, 2004). Certain distinctions are well established but others are a continuing source of controversy. The study of amnesia has formed the basis for much of our understanding of the structure of human memory.

In this section, declarative memory is placed within the context of other memory systems and the distinction between episodic and semantic memory is described. The syndrome of medial temporal lobe (MTL) amnesia is described and the way that studies of this syndrome have contributed to our understanding of the structure of human memory is outlined.

2.1 Declarative Memory in Context[1]

The collection of encoding, storage and retrieval processes that is encompassed by the term "memory" can be separated into different systems on the basis of various criteria. These include the time scale of the memory system (long-term versus short-term), the nature of the information being processed (auditory versus visual), the state of awareness associated with the memory system (conscious versus unconscious), and the neural circuitry that underlies memory processes. Table 1 summarises these distinctions.

The declarative memory system is part of the long-term memory system. In contrast to nondeclarative memory, which is unconscious, declarative memory involves the conscious retrieval of facts (semantic memory) and autobiographical events (episodic memory). Declarative memory is mainly concerned with associations between multiple

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[1] Unless otherwise specified, the account of memory presented here is taken from Kolb & Wishaw, 2003.

items and events; it allows remembered material to be accessed flexibly; and it is representational in nature. It is generally agreed that declarative memory depends on the integrity of structures in the medial temporal lobe, diencephalon and frontal lobes, forming the Papez circuit (Squire, 2004).

Table 1: Summary of Different Memory Systems

Memory System			Main Brain Structure
Short-Term Memory	Central Executive		Frontal and Temporal Lobe
	Auditory / Verbal		
	Visual / Nonverbal		
Long-Term Memory	Declarative verbal/nonverbal	Episodic (events)	Medial Temporal Lobe; Diencephalon
		Semantic (facts)	
	Nondeclarative verbal/nonverbal	Procedural (Skills and Habits)	Striatum
		Priming and Perceptual Learning	Neocortex
		Classical Conditioning: Emotional	Amygdala
		Classical Conditioning: Skeletal Responses	Cerebellum
		Nonassociative Learning	Reflex Pathways

Declarative memory can be divided into episodic memory and semantic memory, a distinction first proposed by Tulving in the 1970's (Tulving, 1972). Episodic memory involves an awareness of subjective time and memories personal to oneself (e.g. one's first day at school or what one had for breakfast this morning). Semantic memory involves remembering information about the world without having a specific memory of the acquisition of this knowledge (e.g. historical or literary knowledge or the ability to recognise other people). Although the distinction between episodic and semantic memory per se is not generally disputed (i.e. it is recognised that aspects of declarative memory can be described as being either episodic or semantic), there is disagreement about the degree to which episodic and semantic memory can function independently of one another, and over the neural substrates that distinguish the two.

2.2 Amnesia[2]

Much of our understanding of human memory is derived from the study of amnesia, an umbrella term for any disorder of memory. With the exception of functional amnesia (which is thought to have psychogenic causes), amnesia is caused by damage to particular brain structures involved in memory functioning, so there are at least as many different types of amnesia as there are memory systems in the brain (Markowitsch, 2000; Mayes, 2000). Of particular interest to our understanding of declarative memory is the type of amnesia brought about by damage to the medial temporal lobe.

Medial temporal lobe (MTL) amnesia is characterised by varying degrees of impairment in declarative memory in the context of normal intelligence, intact short-term memory storage (but see Olson, Page, Sledge Moore, Chatterjee, & Verfaellie, 2006), and intact nondeclarative memory. A distinction is made between retrograde amnesia (amnesia for information acquired before the onset of brain damage) and anterograde amnesia (amnesia for information acquired after the onset of brain damage). The focus of this paper is on anterograde amnesia. MTL amnesia has traditionally been described as involving severe impairments in all aspects of anterograde declarative memory (i.e. an inability to acquire new episodic and semantic information) and at least some degree of retrograde memory impairment (i.e. an inability to remember information acquired prior to injury).

The fact that MTL amnesia affects only declarative memory functioning and can seem to affect episodic and semantic memory in different ways has meant that studies of MTL amnesia have been used to develop what Baddeley refers to as the "conceptual fragmentation of human memory" (Baddeley, 2001, page 4). That is, evidence from amnesic patients has contributed to the distinction between long-term and short-term

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[2] Unless otherwise specified, the account of amnesia that is presented here is taken from Parkin, 1997.

memory functions and between declarative and procedural memory functions (Squire, 2004). This conceptual fragmentation has been both functional and neuroanatomical. One current area of controversy is the contribution that the study of amnesia is making to functional and neuroanatomical distinctions between episodic and semantic memory. In the next section, two accounts of these distinctions are examined.

3 TWO THEORIES OF MTL AMNESIA

In this section, two accounts of MTL amnesia are reviewed. They have been termed the Unitary Account and the Dual-Process Account for the purpose of this review. The Unitary Account, whose main proponents are Larry Squire, Stuart Zola and colleagues, has been so named because it conceptualises both episodic and semantic memory as subsystems of declarative memory (a unitary system) and explains MTL amnesia in terms of an overall impairment in declarative memory. The Dual-Process Account, whose main proponents are Endel Tulving and colleagues, conceptualises episodic memory as a memory system additional to declarative/semantic memory and explains MTL amnesia in terms of various possible dissociations between episodic and semantic memory functioning.

Whilst these two accounts agree on the conceptualisation of declarative memory as described in Section 2.1, they differ on two important issues: the organisation of human memory (i.e. the relationship between declarative, episodic and semantic memory) and the relationship between memory organisation and amnesia. These points of difference are described in detail below.

3.1 The Unitary Account

Squire sees declarative memory as being concerned with the detection and encoding of information that is unique to a particular event, at a particular time and place (Squire, 2004). Contrasting it with nondeclarative memory, he describes declarative memory as fast, not always reliable, and flexible because of its accessibility to multiple response systems (Squire, Knowlton, & Musen, 1993). Furthermore, it involves a deliberate retrieval process and conscious awareness of this process.

Adherents of the Unitary Account do make the distinction between episodic and semantic memory. Episodic memory is described as being uniquely concerned with "source memory" (memory for where and when information was acquired) and therefore is context-rich, whereas semantic memory concerns information without context (Squire & Kandel, 1999). Both episodic and semantic memory are seen as parallel subsystems of declarative memory, differing mainly in terms of the type of information they process (i.e. events versus facts).

In terms of the relationship between episodic and semantic memory, episodic memory is seen as the "gateway" to semantic memory (Squire & Zola, 1998): New information is always learned initially as being part of a specific event (episodic memory). Through rehearsal and repetition, this information can be abstracted from its original context (semantic memory).

3.1.1 Neuroanatomy of the Unitary Account

Squire et al. define declarative memory – including both episodic and semantic memory – as being dependent on the integrity of the hippocampus and related structures in the MTL and diencephalon (Squire et al., 1993). The distinction between episodic and semantic memory is based on the greater contribution that the frontal lobes make to episodic memory compared to semantic memory (Squire et al., 1993): Source memory is thought to be additionally supported by the frontal lobes (Squire & Kandel, 1999).

Within the MTL, the structures thought to be involved in declarative memory are the hippocampus (CA fields, dentate gyrus and subicular complex) and the perirhinal, entorhinal and parahippocampal cortices (Squire, Stark, & Clark, 2004). Information from the neocortex enters the MTL via the perirhinal cortex (predominantly visual information from ventral processing streams) and the parahippocampal cortex (predominantly spatial information from dorsal processing streams). The parahippocampal and perirhinal cortices project to, and receive projections from, the entorhinal cortex. The entorhinal cortex in turn projects to, and receives projections from, other structures in the hippocampal formation. The hippocampus is seen as a recipient of these different converging projections and is thought to be responsible for combining pieces of information from multiple sources and relating them to each other.

Proponents of the Unitary Account argue that there is evidence for a division of labour within the medial temporal lobe (Squire et al., 2004). For example, visual recognition memory appears to be more dependent on the perirhinal cortex than on the parahippocampal cortex, and spatial memory appears to be more dependent on the parahippocampal cortex than on the perirhinal cortex (Squire & Knowlton, 2000). However, they also assert that this division of labour is not reflected in simple dichotomies such as a division between the hippocampus and other MTL structures, between episodic and semantic memory, or between recollection and familiarity.

Although the MTL system is considered central to declarative memory functioning, its role in memory consolidation is seen as temporary (Squire & Kandel, 1999). It is supposed that, when new learning occurs, MTL structures (especially the hippocampus) support connections between the multiple cortical areas that together store a representation of an event (i.e. they are involved in both the storage and retrieval of this event). After a period of time that can range from days to years depending on what is

being remembered, the network of interconnected cortical areas becomes able to support storage and retrieval without the support of the MTL system (but see Nadel, Samsonovich, Ryan, & Moscovitch, 2000).

Figure 1: MTL Structures Important for Declarative Memory[3]

Hippocampal Region

- Subicular Complex
- CA1
- CA3
- Dentate Gyrus
- Other direct projections
- Entorhinal Cortex
- Perirhinal Cortex
- Parahippocampal Cortex
- Unimodal and Polymodal Association Areas (frontal, temporal and parietal lobes)
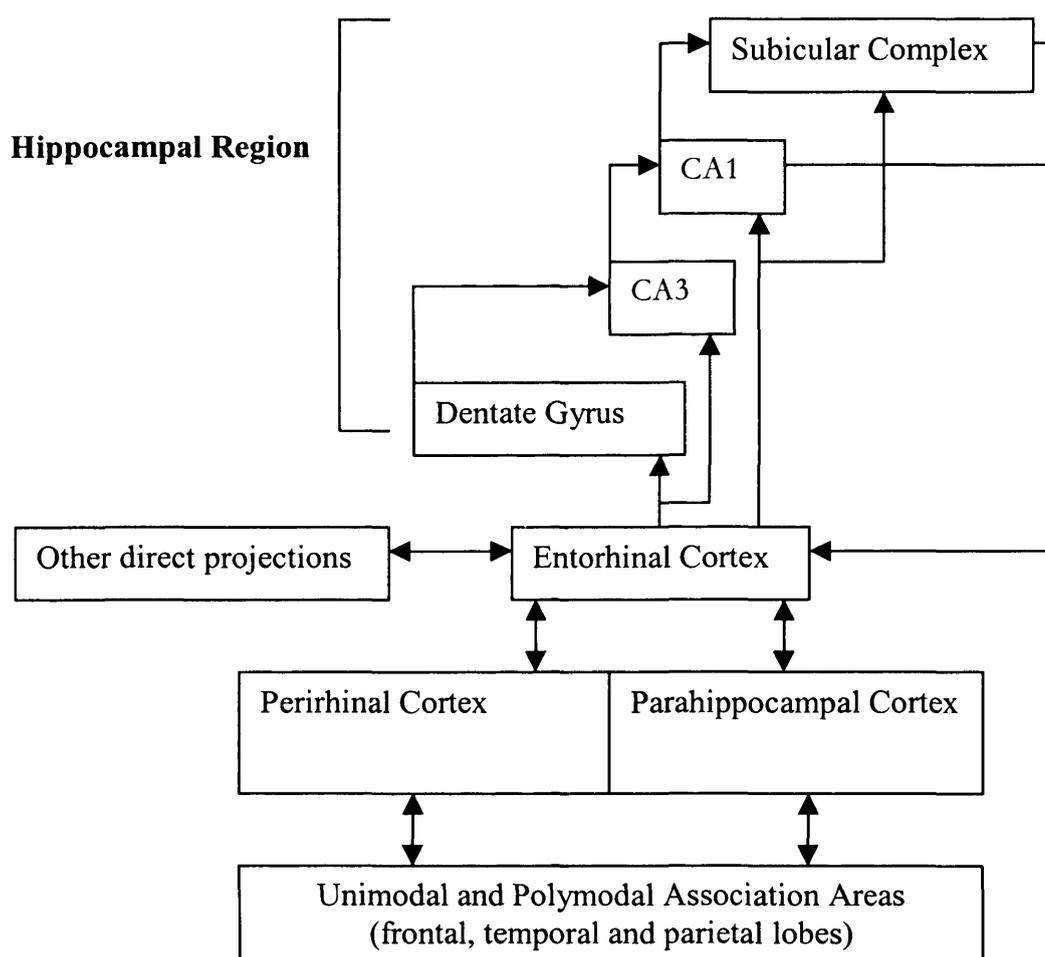
3.1.2 The Unitary Account and Amnesia

Proponents of the Unitary Account argue that MTL amnesia is best explained by a dissociation between (intact) procedural memory and (impaired) declarative memory. Episodic and semantic memory impairments are thought to vary together in a graded manner in MTL amnesia, depending on the extent of the damage to the MTL system as a whole (Squire et al., 1993). Damage to the MTL system is thought to be the reason for

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[3] From Squire et al., 2004, page 280.

impairments in anterograde memory and for impairments in retrograde memory for memories that have not yet been consolidated. Especially marked deficits in episodic memory are explained in terms of additional frontal lobe damage since the frontal lobes are considered crucial for source memory (Squire & Kandel, 1999; Squire & Zola, 1998).

Since declarative memory storage and retrieval become independent of the MTL system over time, some sparing of retrograde memory functioning can occur where damage is limited to the MTL system. This sparing generally has a temporal gradient (i.e. memories from the distant past are more likely to be spared than more recent memories) due to the amount of time that it takes for declarative memories to become independent of the MTL system (Squire et al., 1993).

3.2 The Dual-Process Account

In terms of a general description of declarative memory, the Dual-Process Account is similar to the Unitary Account, in that declarative memory is described by its adherents as involving conscious, deliberate retrieval of stored information. However, rather than seeing episodic memory as a gateway to semantic memory, the Dual-Process Account conceptualises episodic memory as a unique extension of semantic memory (e.g. Mayes & Roberts, 2002; Tulving, 1993; Tulving, 1995; Tulving, 2002). That is, declarative/semantic memory is defined in terms of features that are common to *both* episodic and semantic memory functioning, and episodic memory is defined as a set of capabilities related to personal experience of the world that are considered as additional to semantic memory. The main distinction concerns the re-experiencing of the event upon retrieval from episodic memory (mental "time travel") compared with the feeling of knowing that accompanies retrieval from declarative/semantic memory.

Tulving and colleagues provide a useful overview of the features of declarative/semantic memory (i.e. those shared by episodic and semantic memory) and the features unique to episodic memory (Tulving & Markowitsch, 1998). These features are summarised in Table 2:

Table 2: Features of Declarative/Semantic vs. Episodic Memory

Declarative/Semantic Memory (features common to episodic *and* semantic memory)	Episodic Memory (features additional to semantic memory)
• Large and complex • Multimodal • Characterised by similar, fast encoding operations • Stored information is representational • Stored information is propositionally describable • Stored information has truth value • Stored information is accessed and expressed flexibly • Stored information is used as a basis for inferences • Processing operations (encoding, storage and retrieval) are context sensitive • Processing operations are cognitive • Products of retrieval may or may not be expressed in overt behaviour • Interacts closely with other brain/behaviour systems	• System for remembering personal experiences rather than events • Oriented towards the past • Associated with autonoetic awareness • Includes but goes beyond knowledge of the world • Has process-specific relations with semantic memory (i.e. different encoding, storage and retrieval) • Develops later than semantic memory in young children • Impaired sooner than semantic memory in old age • Unique to humans • Associated with selective and unique cortical activity, especially in frontal lobes

The essential difference between the Unitary and Dual-Process Accounts in terms of their general description of episodic and semantic memory lies not so much in the features ascribed to each, but in the way that episodic memory is thought to be related to declarative memory. Within the Unitary Account, it is seen as a subsystem of declarative memory and a prerequisite to semantic memory. Within the Dual-Process Account, it is seen as a unique memory system, with additional capabilities.

Furthermore, the relationship between episodic and semantic memory is conceptualised differently within the two accounts: As described in the previous section, episodic memory is conceptualised as the gateway to semantic memory by proponents of the

Unitary Account. Proponents of the Dual-Process Account, on the other hand, see this relationship as being process-specific. That is, episodic and semantic memory are related in different ways for the processes of encoding and retrieval.

In his Serial Parallel Independent model (SPI), Tulving elaborates on this process-specific relationship (Tulving, 1995): In terms of memory *encoding*, information is thought to be encoded in a serial fashion, first by the semantic memory system and then by the episodic memory system, so that episodic memory depends on semantic encoding but not vice versa. In terms of memory *retrieval*, episodic and semantic memory are thought to be independent of each other, so that the retrieval of stored information can be supported by either the semantic memory system, or the episodic memory system, or both. In other words, a single dissociation exists between episodic and semantic memory for the process of encoding and a double dissociation exists for the process of retrieval.

Tulving also distinguishes between remembering and knowing as two different subjective states of awareness associated with memory retrieval. *Remembering* entails a type of mental time travel, in that past events are retrieved through a recreation of one's personal experience of these events, referred to by Tulving as *autonoetic* consciousness. *Knowing* refers to a general sense of familiarity, an awareness of past events as general, impersonal facts, which Tulving refers to as *noetic* consciousness. Autonoetic consciousness is thought to characterise episodic memory whereas noetic consciousness is thought to characterise semantic memory (Gardiner & Richardson-Klavehn, 2000; Tulving, 1985; Tulving, 2002). Adherents of Dual-Process theories of memory generally consider measures of free recall to reflect remembering and measures of recognition memory to reflect knowing (Gardiner & Java, 1993; Gardiner & Richardson-Klavehn, 2000; Kelley & Jacoby, 2000).

Proponents of the Dual-Process Account have not themselves proposed any specific neuroanatomical basis for episodic and semantic memory (e.g. Tulving & Markowitsch, 1998). However, as will be described in Section 4.2, other researchers (e.g. Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997) have extended this theory to include a neuroanatomical basis for the prediction of the SPI model (the Hierarchical Account).

3.2.1 The Dual-Process Account and Amnesia

Whereas adherents of the Unitary Account conceptualise MTL amnesia as a quantitative phenomenon, involving impairments in both semantic and episodic memory that vary together, adherents of the Dual-Process Account see the impairments found in MTL amnesia in terms of qualitative, process-specific distinctions between episodic and semantic memory (Mayes & Roberts, 2002; Tulving & Markowitsch, 1998):

- Since episodic encoding is thought to be dependent on semantic encoding, two different patterns of anterograde amnesia are possible: 1) equal impairment in episodic and semantic memory functioning; and 2) impaired episodic memory functioning with less impaired or spared semantic memory functioning. Because of the single dissociation between episodic and semantic memory for encoding processes, it is not thought possible that impairments in semantic anterograde memory functioning can occur in the absence of impairments in episodic anterograde memory functioning.

- Since semantic and episodic retrieval processes are thought to be independent of each other, three different patterns of retrograde amnesia are possible: 1) equal impairment in episodic and semantic memory functioning; 2) impaired episodic memory functioning with less impaired or spared semantic memory functioning; and 3) impaired semantic memory functioning with less impaired or spared episodic memory functioning.

3.3   Summary

The differences between the Unitary and Dual-Process Accounts of declarative memory, then, can be summarised as follows:

- *Conceptualisation of declarative, episodic and semantic memory and the relationship between them:* Adherents of the Unitary Account describe episodic and semantic memory as subsystems of declarative memory, with episodic memory functioning as a gateway to semantic memory. Proponents of the Dual-Process Account describe episodic memory as a system that is additional to declarative/semantic memory, with the relationship between episodic and semantic memory being process-specific.

- *Explanation of amnesia:* Adherents of the Unitary Account explain the impairments seen in MTL amnesia as deficits in declarative memory functioning (that is, both episodic and semantic memory are generally affected) due to damage to the MTL system as a whole. Proponents of the Dual-Process Account argue that episodic and semantic memory impairments *can* occur together but that various patterns of dissociation between episodic and semantic memory functioning are also possible.

3.4   Evaluating the Unitary and Dual-Process Accounts

One way of evaluating the relative merits of these two theoretical accounts of MTL amnesia is to apply them to empirical studies of patients with amnesia in order to see how well each account explains the pattern of deficits shown by these patients. Since both accounts allow for global impairment in declarative memory functioning, studies of patients showing such global impairments will be of limited use in differentiating between the two accounts. Instead, what is of interest are any cases of apparent dissociations between episodic and semantic memory functioning. A considerable body of empirical work on adulthood-onset amnesia now exists, and the theoretical implications of these studies are hotly debated (see Spiers, Maguire, & Burgess, 2001 for a recent review).

The study of childhood-onset amnesia has the potential to contribute further to this debate, especially since it has the potential to avoid some of the methodological shortcomings of studies of adulthood-onset amnesia.

3.4.1 Childhood-Onset Amnesia

Studying childhood-onset amnesia presents a particularly interesting arena for evaluating Unitary and Dual-Process Accounts of MTL amnesia because it provides an opportunity to avoid certain methodological shortcomings of adulthood-onset amnesia studies. One such shortcoming is the degree of memory consolidation, which confounds comparisons between episodic and semantic memory functioning in adult patients (Squire et al., 1993): People who develop amnesia in adult life have a consolidated store of semantic knowledge acquired long before the onset of amnesia whereas their episodic memories will not generally have been exposed to the same degree of rehearsal and consolidation (Ostergaard, 1987).

One way of reducing the confounding influence of memory consolidation is to study people who developed amnesia in childhood, at a time when both episodic and semantic memories are being formed and are both much less consolidated than in adulthood. The presentation and effects of childhood-onset MTL amnesia can be predicted on the basis of theoretical accounts of declarative memory. Adherents of the Unitary Account would expect global impairment in declarative memory functioning but spared procedural and short-term memory functioning. Adherents of the Dual-Process Account would predict a number of different possible patterns of impairment, including dissociations between episodic and semantic memory functioning.

4 DEVELOPMENTAL AMNESIA

In 1997, Vargha-Khadem published an account of three patients who had sustained damage to the hippocampus in childhood and who, at follow-up into adolescence and early adulthood, showed apparently spared semantic memory functioning in the context of severe episodic memory impairments. She termed this syndrome "Developmental Amnesia" (DA) to differentiate it from the presentation of MTL amnesia in cases of adulthood-onset. Subsequent research by Vargha-Khadem and her colleagues has consisted of detailed case studies of three further patients with DA as well as several group studies.

Although the number of cases of Developmental Amnesia reported so far is small, this disorder presents a particularly interesting context for evaluating the Unitary and Dual-Process Accounts of declarative memory and MTL amnesia for various reasons: Firstly, it is an example of childhood-onset amnesia, the relevance of which to evaluating the two theoretical accounts was described in Section 3.4.1, although it should be noted that the extent to which DA is representative of childhood-onset amnesia in general has been questioned (see Section 5.2). Secondly, it appears to be related to an aetiology of selective hippocampal damage. This is important because the Unitary Account explains MTL amnesia in terms of damage to the MTL structures as a unified system, whereas the Dual-Process Account can be extended to include a neuroanatomical basis for the specialisation of episodic memory (see Section 4.2.1). Finally, DA appears to be characterised by a dissociation between episodic and semantic memory that is at odds with a conceptualisation of declarative memory as a unified system (Unitary Account) and which may be better explained by considering episodic memory as being additional to semantic memory (Dual-Process Account).

4.1 Empirical Findings

In order to evaluate the two accounts of MTL amnesia presented earlier, a certain amount of empirical data needs to be described first. This is done in Sections 4.1.1 – 4.1.5, in which neuropsychological findings from research into DA conducted by Vargha-Khadem and colleagues are summarised. These studies have been chosen for this review because they represent the only empirical investigations into DA that have been conducted so far. The interpretation of these results is considered in Section 5.

The results summarised in this section are based on 6 individual case descriptions and 2 group studies (summarised in Figure 2)[4]. The descriptions of Beth, Jon and Kate come from Vargha-Khadem's original study (Vargha-Khadem et al., 1997). Cases 2, 3 and 5 are described in a study of the relationship between hippocampal atrophy and memory impairment by Gadian and colleagues (2000). Together with one additional case, Beth, Jon and Cases 2, 3 and 5 make up the "early-onset" group (children who sustained a hypoxic-ischaemic injury before the age of one year) in Vargha-Khadem's study of the relationship between age of injury and degree of memory impairment in DA (Vargha-Khadem et al., 2003). This study also includes a "late-onset" group (children who sustained a hypoxic-ischaemic injury between the ages of 6 and 14 years) which is made up of Kate and 4 other cases. Finally, additional data on recognition and recall come from a case-study of Jon (Baddeley, Vargha-Khadem & Mishkin, 2001).

Figure 2: Summary of DA Cases

Beth	→	
Jon	→	
Case 2	→	+1 = Early-Onset Group
Case 3	→	
Case 5	→	
Kate	→	+ 4 = Late-Onset Group

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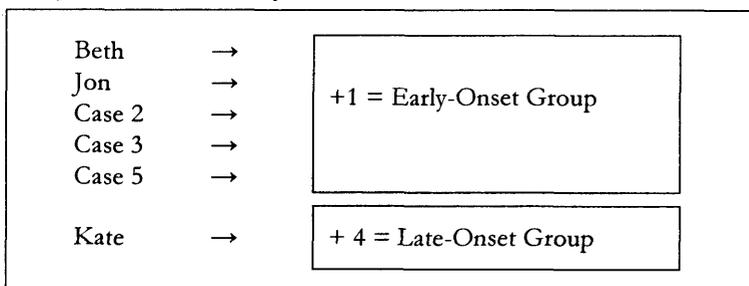
[4] This is clearly a small number of cases. The issue of whether the data from these cases is representative of childhood-onset amnesia in general is considered in Section 5.2.1.

Age at injury and follow-up: Of the cases described at an individual level, nearly all had sustained their injury perinatally or in infancy and were followed up in mid to late adolescence (see Appendix Table 1).

Aetiology and neuropathology: All of the DA cases have suffered from brain injuries that involved oxygen deprivation of some degree although there is some variation in individual aetiology. Neuropathological investigations have revealed damage confined to the hippocampal formation (See Appendix Table 2).

4.1.1   Intelligence

All of the DA cases have average to low average Verbal IQs. There is more variation in Performance IQs, which range from low to average (See Appendix Table 3). Beth is the only case who shows the verbal/nonverbal IQ discrepancy characteristic of adulthood-onset amnesia (Gadian et al., 2000).

4.1.2   Short-Term Memory

Short-term memory was tested using the Digit Span task (a test of auditory short-term memory that involves the immediate repetition of a string of numbers) and the Block Span task (a test of visual short-term memory that involves tapping a number of blocks in a certain sequence). Most of the DA cases show scores within the average range on these tasks compared to controls (See Appendix Table 4). The exception to this is the late-onset group, which was impaired on the forward Digit Span subtest relative to controls (Gadian et al., 2000; Vargha-Khadem et al., 2003; Vargha-Khadem et al., 1997).

4.1.3   Semantic Memory

Semantic memory was assessed using literacy tests (the basic Reading, Spelling and Reading Comprehension subtests from Wechsler's Objective Reading Dimensions test) and subtests from the Verbal IQ measures that tap into an individual's factual knowledge (Information, Vocabulary and Comprehension). The DA cases show scores

within the low average to average range on almost all of the literacy subtests, and these scores are generally within the range that would be predicted on the basis of their IQ. All DA cases show average scores on the Information, Vocabulary and Comprehension subtests (See Appendix Table 5).

4.1.4 Episodic Memory

Episodic memory was assessed using a range of tests to measure immediate and delayed recall of verbal and visual material: the Wechsler Memory Scale, for which the overall Memory Quotient (MQ) as well as scores on the Story Recall and Geometric Design subtests are reported; the Children's Auditory Verbal Learning Test, a test that involves learning a list of words; and the Rivermead Behavioural Memory Test, a test of everyday memory functioning (See Appendix Table 6).

WMS Memory Quotients: The DA cases nearly all show MQs that are similar to their VIQs, apparently indicating similar verbal and memory functioning. However, a study of 11 normal children with similar VIQs to those shown by the DA cases revealed that these children had MQs that were an average of 20 points higher than their VIQs. Therefore, it was argued, the DA cases show substantially lower MQs than would be expected on the basis of their VIQs, compared to controls (Gadian et al., 2000).

Immediate versus delayed recall: Most of the DA cases show some degree of impairment on some (but not all) of the immediate recall tasks, but patterns vary between individuals. There is some indication that the late-onset group shows more impairments in immediate recall tasks than the early-onset group (Vargha-Khadem et al., 2003). The DA cases show severe impairments on all of the delayed recall tasks relative to controls and relative to normative data, performing close to the lowest possible level on many of the tasks (Gadian et al., 2000; Vargha-Khadem et al., 2003; Vargha-Khadem et al., 1997).

Everyday memory functioning: All DA cases show scores on the Rivermead Behavioural Memory Test that are in the severely impaired range. Furthermore, parent and teacher reports indicate that these individuals have difficulties finding their way around in familiar surroundings, have trouble remembering the time and date, and do not remember everyday events even when these happened on the same day as they are being asked to recall them (e.g. what they ate for breakfast; what happened at school) (Vargha-Khadem et al., 1997).

4.1.5 Recall versus Recognition

Beth, Jon and Kate completed a series of recognition tasks modelled on tasks used with non-human primates. These included one-trial recognition tasks (recognising lists of words, familiar faces, non-words and unfamiliar faces) one-trial associative recognition tasks (recognising pairs of words, familiar faces, non-words and unfamiliar faces); and multi-trial associative recognition tasks (recognising pairs of non-words, pairs of faces, voice-face pairs and object-place pairs). All three participants showed normal performances on all of these tasks except for the voice-face and object-place pairs (Vargha-Khadem et al., 1997).

Vargha-Khadem and colleagues further studied the discrepancy between recognition memory and recall in Jon at age 20. They reported that he performed within the average range on various tests of recognition memory designed to include a range of different materials, speeds of presentation and recognition paradigms (See Appendix, Table 7) (Baddeley et al., 2001; Vargha-Khadem at al., 2001). This is in sharp contrast to his severe impairment on all measures of recall.

4.2   Interpretation: The Hierarchical Account (Dual-Process)

Vargha-Khadem and colleagues argue that the results summarised in the previous section indicate that patients with DA show a) severely impaired episodic memory functioning in the presence of spared semantic memory functioning; and b) better recognition memory than recall memory (Vargha-Khadem et al., 2001). They offer an explanation of their findings that is based on the conceptualisation of memory as a hierarchically organised system (referred to hereafter as the Hierarchical Account) within which two different types of dissociation can occur: a dissociation between episodic and semantic memory, and a dissociation between recall and recognition. The latter dissociation is an extension of the former, in that measures of recall and recognition are thought to reflect states of awareness (remembering and knowing) associated with episodic and semantic memory processes respectively.

The Hierarchical Account is an elaboration of Dual-Process theories of amnesia, in that the impairments seen in Developmental Amnesia are conceptualised as primarily episodic deficits (e.g. Eichenbaum, 2001; Tulving & Markowitsch, 1998), but it goes beyond these theories in proposing that the distinction between episodic and semantic memory is neuroanatomically based on a hierarchical relationship between MTL structures. According to the Hierarchical Account, semantic memory processing is lower down on hierarchy than episodic memory processing (Eichenbaum, 1997; Mishkin, Vargha-Khadem, & Gadian, 1998). Episodic memory involves an elaboration of semantic memory processing, adding the context-rich information of episodic memories to the factual information of semantic memories. Thus episodic memory depends on semantic memory but semantic memory can function without the involvement of episodic memory. In other words, the Hierarchical Account only allows for a single dissociation between episodic and semantic memory whereas traditional Dual-Process Accounts allowed for double dissociations in retrieval processes.

4.2.1 Neuroanatomy of the Hierarchical Account

The neuroanatomical basis of the Hierarchical Account is similar to the neuroanatomical basis of the Unitary Account, in that the same structures within the MTL (hippocampus, entorhinal cortex, perirhinal cortex and parahippocampal cortex) are considered central to declarative memory functioning, with additional involvement of the frontal lobes in episodic memory functioning (Eichenbaum, 1997; Tulving & Markowitsch, 1998). There is no dispute between the two accounts about the involvement of these structures or about the projections that run to and from and between them; a diagram of the neuroanatomical basis of the Hierarchical Account would look exactly the same as the diagram of the neuroanatomical basis of the Unitary Account depicted in Figure 1. However, whereas adherents of the Unitary Account argue that MTL structures function as a single entity in the service of both episodic and semantic memory functioning, proponents of the Hierarchical Account propose that different MTL structures contribute to episodic and semantic memory in different ways.

Proponents of the Hierarchical Account see the hierarchical relationship between different MTL structures as underlying the relationship between episodic and semantic and recall and recognition memory (Mishkin et al., 1997; Mishkin et al., 1998). Cortices subjacent to the hippocampus are considered necessary for both episodic and semantic memory, whereas episodic memory depends additionally on the hippocampus. At the bottom of the hierarchy, the perirhinal cortex is thought to be involved in recognition memory, perceptual processing, object identification and making associations between objects, and therefore to be central to semantic memory functioning (Bussey, Saksida, & Murray, 2005; Murray, Graham, & Gaffan, 2005; Murray & Richmond, 2001). At the top of the hierarchy, the hippocampus integrates information from many converging projections, binding together the contextually rich information that makes up episodic memories (Eichenbaum, 2001; Eichenbaum, Otto, & Cohen, 1992; Mishkin et al., 1997).

4.2.2 The Hierarchical Account and Amnesia

Adherents of the Hierarchical Account see the impairments found in Developmental Amnesia in terms of a qualitative distinction between (impaired) episodic and (spared) semantic memory (Mishkin et al., 1998). Impairments in episodic memory functioning are explained in terms of damage that is specific to the hippocampus; semantic memory impairments occur only where damage extends beyond the hippocampus into the surrounding cortices. As long as these surrounding cortices are intact, normal semantic memory functioning (including recognition memory) is possible. The Hierarchical Account differs from traditional Dual-Process theories in that the notion of a hierarchy implies the possibility of single (but not double) dissociations of deficits – it is possible to have deficits limited to episodic memory where only the apex of the hierarchy is damaged, but damage further down in the hierarchy is thought to result in both episodic and semantic memory deficits (Mishkin et al., 1998).

4.2.3 Limitations

It should be noted that the Hierarchical Account was developed specifically to explain the pattern of memory impairments observed in patients with Developmental Amnesia, and that the very term "Developmental Amnesia" was coined in order to distinguish it from adulthood-onset amnesia. The proponents of the Hierarchical Account acknowledge that it is important to exercise caution in making inferences both about other forms of amnesia and about "normal" memory functioning on the basis of these studies (Baddeley et al., 2001; Vargha-Khadem et al., 2001). Evidence relating to the degree of plasticity that the immature brain shows in recovering from different kinds of insults at different ages is still equivocal, so that the extent to which childhood-onset and adulthood-onset versions of the (apparently) same disorder are comparable is questionable (Anderson, Northam, Hendy, & Wrennall, 2001). It is possible that features of episodic and semantic memory functioning seen in childhood-onset amnesia

reflect some form of cerebral reorganisation that occurs during recovery (Vargha-Khadem et al., 2003), so that the structure of declarative memory in these patients is not the same as the structure of declarative memory in the general population. This issue of generalisability is taken up in more detail in Section 5.2.

4.3 Interpretation: The Unitary Account

Adherents of the Unitary Account have interpreted the findings reported by Vargha-Khadem and her colleagues in a way that is consonant with their conceptualisation of declarative memory. Squire and colleagues argue that Vargha-Khadem's cases do not show unequivocal evidence of spared semantic memory functioning, and that these cases also show some residual episodic memory functioning. They also argue that the evidence for spared recognition memory relative to impaired recall is equivocal. Therefore, they surmise, DA can be explained in terms of an impairment in declarative memory that affects both episodic and semantic memory functioning. Each of these points is examined in detail below.

In making these points, Squire and colleagues draw on the studies of the DA cases described above as well as two earlier studies of childhood-onset amnesia conducted by Wood and colleagues (Wood, Brown, & Felton, 1989) and Ostergaard and colleagues (Ostergaard, 1987). These cases (TC and CC) are summarised in Table 3. The pattern of impairments reported for TC is similar to that reported for the DA cases: Wood and colleagues argue that she shows severe episodic memory impairments but some sparing of semantic memory. CC's case is rather different: Ostergaard reports that he shows severe impairments in both episodic and semantic memory functioning.

4.3.1 Impaired Semantic Memory Functioning

In analysing the semantic memory functioning of the DA cases and TC, Squire and colleagues make two related points which are concerned with the way that the concept of spared or preserved functioning is defined (Ahern, Wood, & McBrien, 1998): Firstly, they apply rather stringent criteria to the definition of preserved functioning, arguing that this is unequivocally present only in cases where semantic memory functioning is entirely within the normal limits shown by the general population. Where semantic memory functioning is not within these normal limits, deciding whether it is preserved or impaired is a matter very much open to interpretation (Ostergaard & Squire, 1990). This view is in stark contrast to that held by Wood and colleagues, who define preserved functioning in one domain (e.g. semantic memory) in terms of a comparison with other domains (e.g. episodic memory), so that it is possible to talk about relative sparing even where an individual's performance on a memory task is not within normal limits (Wood et al., 1989).

The DA cases reported by Vargha-Khadem all show semantic memory functioning that is within normal limits and therefore meet Squire's first criterion for spared semantic memory functioning. This is in contrast to TC whose semantic memory functioning is impaired according to Squire's definition (in that her intellectual and academic development has not been entirely within the normal range) but preserved according to Wood's definition (who argues that TC's semantic memory functioning is preserved relative to her episodic memory functioning). It is also in contrast to CC, who shows severe impairments in both episodic and semantic memory functioning (Ostergaard, 1987).

Secondly, Squire and colleagues argue that it is difficult, if not impossible, to determine the level of semantic memory functioning that an individual might have attained had they not suffered from any brain damage. Therefore, it is difficult to tell whether the

cognitive development and educational attainments shown by the DA cases and by TC are at the level that would have been "normal" for them. Both IQ score and scores on measures of educational attainments tend to be at the bottom end of the average range or below for these patients, which is lower than would be expected in the general population. Therefore, these scores could be interpreted as indicating impaired semantic memory functioning and not, as Vargha-Khadem and colleagues argue, spared semantic memory functioning (Ostergaard & Squire, 1990; Squire & Zola, 1998).

4.3.2 Residual Episodic Memory Functioning

Squire and colleagues make the point that episodic memory functioning, whilst impaired, is not altogether absent in any of the cases that they review. That is, no individual obtained a raw score of 0 on every single test of episodic memory functioning administered. Squire and colleagues interpret the relatively intact performance shown by the DA cases on recognition memory tests as further evidence of some intact episodic memory functioning (Squire & Zola, 1998). Finally, for those cases where neuropathological investigations have been undertaken, results indicate that the hippocampal formation is damaged but not altogether absent or non-functioning.

Squire and colleagues acknowledge that there is no requirement that episodic memory be totally absent in order for the episodic/semantic distinction to be made; it is sufficient that it should be impaired relative to other memory functions (Ostergaard & Squire, 1990). However, they also argue that the residual episodic memory functioning present in the DA cases and in TC might account for the fact that these individuals are able to acquire some semantic knowledge, especially since normal individuals take advantage of their episodic memory functioning in order to acquire semantic knowledge (Eichenbaum, 1997). That is, what has been interpreted as spared semantic memory functioning might actually reflect semantic memory functioning that is in proportion to episodic memory functioning (Squire et al., 2004; Squire & Zola, 1998).

4.3.3 Recall versus Recognition

Squire and colleagues also argue that it is conceptually and methodologically difficult to separate recall and recognition processes, and question the idea that these processes represent different modes of consciousness associated with episodic and semantic memory functioning (remembering and knowing respectively). They point out that it is difficult to design measures of recognition memory that are sufficiently difficult to be considered equivalent to measures of recall and interpret the fact that patients with DA perform better on recognition tests than on tests of recall as a function of the fact that the former are easier than the latter (Squire, 1992; Squire & Knowlton, 2000; Squire, Schmolck, & Stark, 2001; Squire & Zola, 1998). Furthermore, they cite results from their studies of adulthood-onset amnesia that indicate no spared "knowing" responses relative to "remembering" responses (Squire & Zola, 1998).

5 EVALUATION

In trying to evaluate the implications of Developmental Amnesia for our understanding of human memory, it is important to make a distinction between two issues, one relating to the way that findings from DA studies are interpreted and the other relating to the conclusions made about normal memory functioning on the basis of these studies. The first issue concerns the interpretation of memory impairments in DA. It is striking that the same empirical data have been interpreted by proponents of the Hierarchical Account as indicating spared semantic memory functioning in the context of impaired episodic memory functioning and by the proponents of the Unitary Account as indicating a global impairment in declarative memory functioning. There are two issues that perpetuate the apparent stalemate between the two accounts, one relating to the assessment of neuropathology and the other to the definition of spared and impaired functioning. It will remain impossible to favour one theoretical account over another unless these issues are resolved.

The second issue – which is an issue only if the Hierarchical explanation of Developmental Amnesia is accepted – concerns the extent to which Developmental Amnesia is representative of other forms of MTL amnesia and what inferences can be drawn from it about "normal" memory functioning. Is it simply an anomaly that occurs when memory functioning is reorganised in response to the injury of a relatively plastic brain (and therefore of limited relevance to theories of adulthood-onset amnesia and theories of normal memory functioning), or is the pattern of preserved and impaired functioning in DA representative of the organisation of human memory in general?

These points are examined in greater detail below. Section 5.1 deals with the issue of differences in interpretation and Section 5.2 is concerned with the question of generalisability. The implications for future research are examined in Section 5.3.

5.1   Interpreting Findings from DA Studies

It has already been noted that the same empirical data have been interpreted very differently by adherents of the Unitary and Hierarchical Accounts. There are two issues which, until resolved, make it impossible to decide in favour of one account or the other. These issues are the assessment of neuropathology and the way that spared and impaired functioning are defined.

5.1.1   Assessing Neuropathology

Adherents of the Hierarchical Account predict impaired episodic memory and spared semantic memory only where brain damage is limited to the hippocampus. Where damage extends beyond the hippocampus into other MTL structures, proponents of both the Unitary and the Hierarchical Account would predict global declarative memory impairment. In order to evaluate the relative merits of the two accounts, it is therefore crucial to focus on cases where brain damage is limited to the hippocampus.

This is problematic because of limitations in neuroimaging technology. In most studies where investigations of neuropathology are conducted, magnetic resonance images (MRIs) are acquired, anatomical landmarks are identified, and the volume of each region of interest is measured (Gold & Squire, 2005). Some anatomical landmarks (such as the hippocampus) are straightforward to identify and measure on the basis of MRIs whereas others (such as the entorhinal, perirhinal and parahippocampal cortices, the integrity of which is thought to be central to spared semantic and recognition memory) do not have readily identifiable borders and are therefore identified and measured using landmarks derived from the histological study of healthy brains. These measurements can be normalised using different techniques; Squire and Gold recommend normalisation by intracranial volume as the technique that best reduces the variability in volume measurements of individuals with MTL damage (Gold & Squire, 2005).

However, Squire and colleagues point out that even high-resolution MRI cannot detect cell loss that is easily detected in histological examination (which is not usually possible with live human participants) (Squire & Zola, 1998). They point out that histological analyses reveal that a 40% loss of hippocampal volume as measured on the basis of MRI scans corresponds to an almost complete loss of hippocampal neurons (Gold & Squire, 2005). It appears, therefore, that MRI investigations underestimate the degree of brain damage compared to histological analysis.

Furthermore, a reduction in tissue volume does not necessarily indicate a loss of function. It is possible that the remaining tissue is still capable of supporting memory function. A recent functional MRI study investigating autobiographical memory in one of the DA patients, Jon, reported hippocampal activation during the retrieval of memories for which Jon claimed to experience recollection, in spite of a 50% bilateral hippocampal volume loss (Maguire, Varga-Khadem, & Mishkin, 2001).

The relative merits of the Unitary and Hierarchical Accounts cannot be evaluated accurately until neuroimaging techniques have advanced to a point where it is possible to identify isolated hippocampal damage with greater certainty and clarify whether atrophy equates to a loss of function. Until this point is reached, possible (undetected) damage to the cortices surrounding the hippocampus can always be cited by proponents of the Hierarchical Account as an explanation for any failure to find spared semantic and recognition memory functioning in patients with MTL amnesia. In contrast, proponents of the Unitary Account can cite remaining hippocampal function as an alternative explanation for residual episodic memory functioning and relative sparing of semantic memory.

5.1.2 Defining Impaired and Spared Functioning

One major point of difference between the Unitary and Hierarchical Accounts concerns the way that "spared" (or "preserved") and "impaired" functioning are defined. This difference in definition has allowed theorists from both sides to claim that the pattern of memory functioning shown by individuals with Developmental Amnesia supports their particular account of the structure of memory functioning.

Firstly, proponents of the Hierarchical Account argue that the DA patients show spared semantic memory functioning. Proponents of the Unitary Account argue that it is impossible to judge what these individuals' semantic memory capabilities might have been had they not sustained the brain damage responsible for their amnesia, and so it is impossible to label their actual capabilities as either impaired or spared. Furthermore, they argue, although individuals with DA have shown some capacity for acquiring new semantic knowledge, this capacity is impaired (the learning being slower and more limited) relative to the normal population.

One way of resolving these differences in defining spared and impaired functioning might be to focus on the baseline against which such definitions are made. This idea is best summed up by the grammatically clumsy but conceptually clear question: "Semantic memory is spared relative to what?" In examining possible dissociations between episodic and semantic memory, the point of interest is whether semantic memory has been speared *relative to episodic memory* rather than relative to population norms or to hypothesised levels of functioning that individuals might have attained. This type of sparing has been unequivocally demonstrated in case-control studies where individuals with DA showed severe episodic memory impairments but similar scores on tests of semantic memory compared to controls (e.g. Baddeley et al., 2001; Isaacs et al., 2003; Vargha-Khadem et al., 2003).

Secondly, proponents of the Unitary Account argue that individuals with DA are making use of residual episodic memory abilities in order to acquire semantic knowledge. In other words, what is interpreted as spared semantic memory functioning by proponents of the Hierarchical Account is interpreted as reflecting residual episodic memory functioning by proponents of the Unitary Account.

This particular aspect of the Unitary interpretation seems less plausible than the Hierarchical interpretation for two reasons: Given that it is reasonably well established that individuals with DA show impaired episodic memory functioning relative to their semantic memory functioning, it seems unlikely that the (spared) semantic functioning should rely on the (impaired) episodic functioning. Furthermore, there is evidence that the converse is the case: Individuals with DA use their spared semantic memory functioning to make inferences about specific episodes in their past. For example, when asked about his journey to the research lab on a specific day, Jon explained that he had come by train and had run up the last flight of stairs. When asked how he remembered

this, he answered that this was what he always did when coming to visit the researchers. He was unable to give any details to distinguish that particular day's journey from any other (Baddeley, Vargha Khadem, & Mishkin, 2001).

5.1.3 Conclusion

In spite of the limitations of neuroimaging techniques and in spite of the possibility of other interpretations, even proponents of the Unitary Account have recently conceded that there is such a syndrome as Developmental Amnesia and that it does seem to involve episodic memory functioning that is impaired relative to semantic memory functioning (e.g. Squire et al., 2004). Having established this point of consensus, the next step is to examine the implications of DA for theories of MTL amnesia and normal memory functioning.

5.2 Generalising from Developmental Amnesia

It has already been noted that Developmental Amnesia was so named in order to describe a particular form of childhood-onset amnesia and distinguish it from adulthood-onset amnesia. On the one hand, it is important to exercise caution in drawing conclusions about memory functioning in the general population on the basis of findings from DA cases; the very definition of this syndrome implies limited generalisability. On the other hand, the impact of DA on theoretical accounts of memory functioning is crucially dependent on the extent to which it is possible to generalise from DA to other forms of amnesia and to normal memory functioning. Examining how the findings from DA patients relate to other studies of childhood-onset amnesia as well as studies of adulthood-onset amnesia is one way of making a judgment about the generalisability of these findings.

5.2.1 Other Studies of Childhood-Onset Amnesia

Few detailed studies of childhood-onset amnesia have been carried out to date and the results of those that have been conducted are mixed (these studies are summarised in Table 3)[5] Some authors have reported impairments in both episodic and semantic memory functioning in childhood amnesia (Broman, Rose, Hotson, & Casey, 1997; Ostergaard, 1987). Others have reported spared semantic memory functioning as indicated by acquired factual knowledge and educational attainments (Benedict, Shapiro, Duffner, & Jaeger, 1998; Brizzolara, Casalini, Montanaro, & Posteraro, 2003; Vargha-Khadem, Isaacs, & Mishkin, 1994; Wood et al., 1989). Still others have reported spared semantic memory functioning in the context of episodic memory impairment, as indicated by the ability to learn new factual information in an experimental context (Ahern et al., 1998; Benedict et al., 1998; Guillery Girard, Martins, Parisot Carbuccia, & Eustache, 2004). The relationship between recall and recognition memory has not been widely studied in the context of childhood-onset amnesia.

It would seem, then, that spared semantic memory functioning in the context of episodic memory impairment has been found in studies of childhood-onset amnesia that do not explicitly identify their cases as suffering from Developmental Amnesia. Of course, just like the findings from DA cases, these studies could be interpreted as supporting either the Unitary or the Hierarchical Account.

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[5] The studies reviewed in this section were identified via a PsychInfo literature search in which "amnesia" was used as a major subject heading and the study population age was limited to childhood.

Table 3: Studies of Childhood-Onset Amnesia (chronological order)

Patient & Reference	Age of Onset	Aetiology	Structural Findings	IQ	Short-term Memory	Episodic Memory	Semantic Memory
CC (♂) (Ostergaard, 1987)	10	Seizure → respiratory arrest → anoxia	CT scan: left medial temporal lobe attenuation.	VIQ: 99 PIQ: 94 FSIQ: 96	Average (digit span)	Severe impairment: • Rey Complex Figure • Story recall • Word list recall	Severe impairment: • Reading age • Word fluency • Lexical decision-making Accurate but slow performance on semantic classification task
TC (♀) (Wood, Brown, & Felton, 1989)	9	Herpes simplex encephalitis	No abnormalities on CT scan, EEG or blood flow measures	VIQ: 78 PIQ: 91 FSIQ: 83	Not assessed	Severe impairment: • Rey Complex Figure • Taylor Complex Figure	Some acquisition of new declarative knowledge in domains of reading and arithmetic
Neil (Vargha-Khadem et al., 1994)	13	Pineal tumour; chemotherapy and radiotherapy	MRI: Atrophy of anterior corpus callosum, fornices, grey matter in medial diencephalon, left hippocampal formation, superior colliculi &right cerebellar hemisphere	VIQ: 109 PIQ: 55 FSIQ: Not reported	Impaired for verbal material (digit span); normal for nonverbal material (block span)	Intact retrograde memory functioning and severely impaired anterograde memory functioning for autobiographical events Impaired functioning on: • AMIPB (recall of verbal and visual material) • WMS • Rey Complex Figure • Rey Auditory Learning BUT able to recall some material in written form	Spared functioning indicated by scores on • Information, Vocabulary and Comprehension subtests on WISC-R • Word fluency task

Table 3 (continued): Studies of Childhood-Onset Amnesia (chronological order)

Patient & Reference	Age of Onset	Aetiology	Structural Findings	IQ	Short-term Memory	Episodic Memory	Semantic Memory
MS (♂) (Broman, Rose, Hotson, & Casey, 1997)	8	Seizure → respiratory arrest → anoxia	MRI: Lesion restricted to bilateral hippocampal formation	VIQ: 80 PIQ:91 FSIQ:83	Average (digit span)	Severe impairment: • Rey Complex Figure • Benton Visual Retention Test • WMS • CAVLT • RBMT • WRMT • Doors & People Test	Impairments indicated by: • Language development • Literacy skills • Information & Vocabulary subtests • Decline in IQ scores over time Preserved skills: • Mathematical skills
AC (♀) (Benedict et al., 1998)	10	Herpes simplex encephalitis	MRI: Extensive lesions over entire temporal lobes bilaterally	VIQ: 88 PIQ: 85 FSIQ: 85	Average (digit span)	Severe impairment: • WMS • HVLT-R • BVMT-R • WRMT (faces & words)	• Spared functioning on spelling, reading & arithmetic tests • Impaired Information & Vocabulary on WAIS • Impaired language (naming & vocabulary tests) • Able to acquire new semantic information at control level
TJ (♂) (Ahern, Wood, & McBrien, 1998)	0	Midline brain cyst; surgery; post-operative seizures	MRI: loss of right hemisphere mass, thalamic involvement, diminished frontal lobes	Not reported	Average (digit span)	Severe impairment: • Rey Auditory Verbal Learning Test • Story recall	Spared functioning: • Normal performance on vocabulary tests (WISC, Boston Naming Test) • Initial severe impairment on reading tests but functioning within the average range after one year of intense tuition

Table 3 (continued): Studies of Childhood-Onset Amnesia (chronological order)

Patient & Reference	Age of Onset	Aetiology	Structural Findings	IQ	Short-term Memory	Episodic Memory	Semantic Memory
AV (♀) (Brizzolara, Casalini, Montanaro, & Posteraro, 2003)	6	Viral encephalitis	MRI: Bilateral lesions in external capsule, ventral hippocampus, amygdala, hypothalamus, thalamus, lateral portions of pons & mesencephalon. Perirhinal & entorhinal cortices spared	VIQ: 102 PIQ: 78 FSIQ: 89	Average (digit span, word span, block span)	Severe impairment: • CAVLT (but normal immediate memory span & recognition) • Paired associate learning test • Word List Learning Test • Story recall • Biber Figure Learning Test • Rey Complex Figure Test • RBMT	Spared functioning: • Picture naming • Information & Vocabulary sub-tests on WISC • Pyramids & Palm Trees • Average school reports for literacy & numeracy
AB (♂) (Guillery Girard, Martins, Parisot Carbuccia, & Eustache, 2004)	3	Cranio-pharyngioma; surgery	Not reported	VIQ: 58 PIQ: 73	Impaired (digit span)	Severe Impairment:: • CMS • Autobiographical recall	Spared functioning: • Normal performance on questionnaire of semantic knowledge • Able to acquire new semantic information (slower than controls)

Table 3 (continued): Studies of Childhood-Onset Amnesia (chronological order)

Patient & Reference	Age of Onset	Aetiology	Structural Findings	IQ	Short-term Memory	Episodic Memory	Semantic Memory
FR (♀) (Guillery Girard, Martins, Parisot Carbuccia, & Eustache, 2004)	6	Optic nerve glioma, hippocampal tumour; chemotherapy & surgery	Not reported	FSIQ: 98	Average (digit span)	Severe impairment: • CMS • RBMT • Autobiographical recall	Spared functioning: • Normal performance on questionnaire of semantic knowledge • Able to acquire new semantic information (slower than controls)

Abbreviations:

AMIPB: Adult Information Processing Battery

BVMT-R: Brief Visuospatial Memory Test (Revised)

CAVLT: Children's Auditory Verbal Learning Test

CMS: Children's Memory Scale

HVLT-R: Hopkins Verbal Learning Test (Revised)

RBMT: Rivermead Behavioural Memory Test

WISC: Wechsler Intelligence Scales for Children

WMS: Wechsler Memory Scale

WRMT: Warrington Recognition Memory Test

5.2.2 Studies of Adulthood-Onset Amnesia

Adulthood-onset amnesia has been studied in much greater depth than childhood-onset amnesia. It is beyond the scope of this paper to review this large body of literature in detail, but it should be noted that the question of the relationship between episodic and semantic memory functioning in amnesia (both retrograde and anterograde) remains controversial: Some studies report spared functioning whereas others do not (Spiers et al., 2001). Similarly, there is some evidence that recall and recognition processes are separable in adulthood-onset amnesia, with some studies reporting that the former is more impaired than the latter (e.g. Aggleton & Shaw, 1996; Aggleton et al., 2005; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005), although this point also remains controversial (Gardiner & Java, 1993; Gardiner & Richardson-Klavehn, 2000; Kelley & Jacoby, 2000; Manns & Squire, 1999; Markowitsch, 2000; Mayes, 2000).

Studies of adulthood-onset amnesia are of course open to the same degree of interpretation as studies of childhood-onset amnesia, so that the findings briefly summarised above could be taken as evidence supporting either the Unitary or the Hierarchical Account.

5.2.3 Conclusion

It is difficult at this point to come to any definitive conclusion about the generalisability of DA studies. The issue of preserved semantic/recognition memory functioning in the context of episodic/recall memory deficits remains controversial in both childhood- and adulthood-onset amnesia, with some studies reporting this pattern of functioning whereas others report more global impairments. This variation in findings may be related to insufficient precision in neuroimaging techniques. The existence of even a few cases of Developmental Amnesia is sufficient grounds for further investigation of this phenomenon, since it is possible that these cases illustrate dissociations in memory that exist in everyone but are not apparent unless very specific brain damage has occurred.

5.3 Summary and Implications

The syndrome of Developmental Amnesia is explained more clearly by the Hierarchical Account, a variant of the Dual-Process Account of MTL amnesia, than by the Unitary Account. That is, DA is better explained as a selective episodic memory impairment in which semantic memory is relatively spared than as a global impairment in declarative memory functioning.

Whether this account of DA can be applied to other forms of MTL amnesia or normal memory functioning is currently unclear. It may be that the dissociation between episodic and semantic memory that is seen in DA cases is specific to this syndrome, or it may be that this dissociation also occurs in other forms of MTL amnesia. In order to determine the wider implications of the syndrome of Developmental Amnesia, further research into memory impairments in MTL amnesia needs to be carried out. In order to determine whether the pattern of impairment found in DA exists more widely, this research would ideally have the following characteristics:

1) It would be carried out on people who have sustained damage that is specific to the hippocampus, with surrounding cortices being intact. This would entail a level of neuropathological detail that might be beyond current neuroimaging techniques but should at least be strived for.

2) It would include people who had sustained such damage at *any* point in their lives, so that it could be determined whether the pattern of impairments found in DA is specific to childhood-onset forms of amnesia or not.

3) It would be carried out using a case-control paradigm, so that impaired and spared functioning could be defined relative to healthy control participants.

4) It would include measures of both established stores of memory and the capacity to acquire new learning in an experimental context, so that encoding, storage and retrieval processes would all be measured.

Until such research is carried out, it will be impossible to be certain about the implications of Developmental Amnesia for our understanding of adulthood-onset amnesia and of normal human memory functioning. However, there is no reason to suppose that the pattern of deficits seen in DA reflects a gross deviation from normal memory development. It seems more plausible that the dissociations seen in DA between episodic memory and semantic memory and between recall and recognition exist in everyone but are not apparent unless very specific damage to the hippocampus has occurred. The syndrome of Developmental Amnesia has alerted us to the possibility of important dissociations in declarative memory, continuing the tradition of studies of amnesia contributing to our understanding of normal memory functioning.

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APPENDIX

Table 1: DA Cases – Age of Onset & Age of Follow-Up

Age (yrs)	Beth	Jon	Kate	Case 2	Case 3	Case 5	Early	Late
Onset	0	0	9	0	0	0.25	0.04	10.2
Follow-up	12.8	16.3	19.2	11.7	11.6	12.3	12.9	16.1

Table 2: DA Cases – Aetiology & Neuropathology

Case	Aetiology	Neuropathology
Beth	Birth asphyxia; perinatal seizures	Bilateral reduction in volume of hippocampus. Remaining hippocampal tissue severely compromised.
Jon	Extreme prematurity; hypoxia	Bilateral reduction in volume of hippocampus. Remaining hippocampal tissue severely compromised. Further minimal damage to right temporal lobe.
Kate	Cardiac arrest; hypoxia	Bilateral reduction in volume of hippocampus. Remaining hippocampal tissue severely compromised. Further minimal damage to right temporal lobe.
Case 2	Birth asphyxia; seizures at 7 yrs	Aggregate data available only: see Early Group
Case 3	Hypoxia; perinatal seizures	Aggregate data available only: see Early Group
Case 5	Prematurity; respiratory arrest at 11 weeks	Aggregate data available only: see Early Group
Early Group	As above + one case of prematurity & hypoxia	Bilateral reduction of grey matter in hippocampus, thalamus and basal ganglia. Reduction of grey matter in right retrosplenial cortex. Average 40% bilateral reduction of hippocampal volume.
Late Group	Group included cardiac arrest, hypoxia, encephalitis, meningitis and seizures	Bilateral reduction of grey matter in hippocampus, thalamus and basal ganglia. Reduction of grey matter in right retrosplenial cortex. Average 40% bilateral reduction of hippocampal volume.

Table 3: DA Cases – Intelligence*

IQ**	Beth	Jon	Kate	Case 2	Case 3	Case 5	Early	Late
VIQ	82	109	86	84	87	89	93 (11.87)	86.4 (15.5)
PIQ	61	109	79	74	78	85	88.5 (23.16)	81 (18.45)

* Numbers in parentheses indicate standard deviations.

** Standard Scores on the Wechsler Intelligence Scale for Children – Third Edition or the Wechsler Adult Intelligence Scale - Revised

Abbreviations

IQ = Intelligence Quotient (Population Norms: mean = 100, SD = 15)

VIQ = Verbal Intelligence Quotient (Population Norms: mean = 100, SD = 15)

PIQ = Performance Intelligence Quotient (Population Norms: mean = 100, SD = 15)

Table 4: DA Cases – Short Term Memory*

Scaled Scores**	Beth	Jon	Kate	Case 2	Case 3	Case 5	Early	Late
Digit Span Forward	6	8	7	7	6	7	6.3 (0.52)	5.2 (1.79)
Digit Span backward	5	6	4	5	6	3	-	-
Block Span forward	4	7	5	7	6	7	-	-
Block Span backward	6	8	5	5	4	6	-	-

* Numbers in parentheses indicate standard deviations.

** Scaled Scores on the Digit Span subtest of the Wechsler Intelligence Scale for Children – Third Edition or the Wechsler Adult Intelligence Scale - Revised, and the Corsi Block Span Test (Population Norms: Mean = 10, SD = 15)

Table 5: DA Cases –Measures of Semantic Memory*

	Beth	Jon	Kate	Case 2	Case 3	Case 5	Early	Late
Basic Reading**	85 (83)	102 (106)	102 (89)	97 (86)	99 (89)	105 (92)	96.8 (6.31)	92.6 (18.5)
Spelling**	77 (85)	84 (105)	99 (89)	96 (88)	88 (90)	118 (93)	87.8 (7.96)	87.8 (17.8)
Reading Comprehension**	84 (81)	97 (107)	88 (87)	87 (85)	74 (87)	87 (91)	87.7 (11.76)	85 (11.2)
Information***	9	10	6	7	8	9	9 (1.74)	7 (3.10)
Vocabulary***	7	11	8	7	8	9		
Comprehension***	7	14	7	8	9	8		

* For individual cases, numbers in parentheses indicate scores predicted on the basis of IQ results. For group data, numbers in parentheses indicate standard deviations.

** Standard Scores on the Wechsler Objective Reading Dimension test (Population norms: Mean = 100, SD = 15)

***Scaled Scores on subtests of the Wechsler Intelligence Scale for Children – Third Edition or the Wechsler Adult Intelligence Scale - Revised (Population norms: Mean = 10, SD = 3)

Table 6: DA Cases – Measures of Episodic Memory*

Measure	Beth	Jon	Kate	Case 2	Case 3	Case 5	Early	Late	Controls†
MQ**	83	93	93	83	79	81	-	-	105.8 (13.9)
Story Recall immediate (percentage correct)**	25%	27.2%	-	38.9%	20.8%	11.3%	29.5% (9.56)	15% (4.64)	41.4% (14.9)
Story Recall delayed (percentage correct)**	2.2%	3.5%	-	2.8%	0%	3.4%	4.6% (3.46)	2.8% (4.04)	32.3% (15.4)
Geometric Design immediate (percentage correct)**	53.6%	64.2%	-	32.1%	57.1%	35.7%	-	-	82.2% (13.5)
Geometric Design delayed (percentage correct)**	14.3%	3.6%	-	14.3%	0%	10.7%	2.1% (1.32)	3.6% (4.74)	77.8% (16.9)
CAVLT immediate memory span***	105	109	-	82	89	74	-	-	100 (15)
CAVLT delayed***	69	63	-	60	61	60	3.3% (1.03)	4% (2.92)	100 (15)
RBMT (raw score)****	2/12	3/12	4/12	Mean 3.2/12 (1.3)	Mean 3.2/12 (1.3)	Mean 3.2/12 (1.3)	8/22 (2.53)	9.8/22 (4.09)	-

* Numbers in parentheses indicate standard deviations.

** From the Wechsler Memory Scale. MQ = Memory Quotient (Population mean = 100; SD = 15)

*** Standard Scored on the Children's Auditory Verbal Learning Test (Population mean = 100, SD =15)

**** Rivermead Behavioural Memory Test

† From (Gadian et al., 2000)

Table 7: Jon's Scores on Recognition Tests

Test	Score
CAVLT Recognition Accuracy (raw score and percentile)	29/32; <16th percentile
WRMT Words (raw score and percentile)	45/50; 25th percentile
WRMT Faces (raw score and percentile)	41/50; 25th percentile
D&P Verbal Recognition (scaled score and percentile)	11; 50th-75th percentile
D&P Visual Recognition (scaled score and percentile)	10; 50th-75th percentile
CRT (percent correct)	97.3%
DRT forced choice (percentage correct)	90%
DRT yes/no (accurate detection rate and false alarm rate)	81.3%; 20.1%

Abbreviations
CAVLT = Children's Auditory Verbal Learning Test
WRMT = Warrington's Recognition Memory Test
D&P = Doors and People Test
CRT = Continuous Recognition Test
DRT = Delayed Recognition Test

PART 2: EMPIRICAL PAPER

Declarative memory functioning in school-age children with a history of

perinatal hypoxic-ischaemic encephalopathy

TABLE OF CONTENTS

ABSTRACT

Memory functioning was tested in a sample of 23 children aged 9-12 years with a history of mild or moderate perinatal hypoxic-ischaemic encephalopathy (HIE). It was hypothesised that these children might show memory impairments similar to the pattern of impairments found in Developmental Amnesia (DA), since DA has been linked to selective hippocampal damage and the hippocampus is especially vulnerable to injury from hypoxic-ischaemia. This pattern of memory impairments consists of deficits in episodic memory functioning in the context of normal semantic memory functioning and intellectual ability. Participants were tested on measures of intellectual ability (Wechsler Intelligence Scale – Fourth Edition), semantic memory (Verbal Category Fluency Test and Information, Vocabulary and Comprehension subtests from the WISC-IV), episodic memory (Rey Complex Figure Test and Children's Auditory Verbal Learning Test) and everyday memory functioning (Rivermead Behavioural Memory Test and Everyday Memory Questionnaire). Results indicate normal intellectual ability, semantic memory functioning and verbal episodic memory in this sample, and deficits in visual episodic memory and everyday memory functioning. These results are interpreted as reflecting mild damage to the hippocampus that is insufficient to cause Developmental Amnesia but which may affect spatial episodic memory functioning in particular. Furthermore, it is suggested that perinatal HIE may be associated with subtle deficits in everyday functioning that are not necessarily apparent on laboratory measures of neuropsychological functioning.

1 INTRODUCTION

In this paper, the dissociations in declarative memory proposed by adherents of the Hierarchical Account are investigated in a sample of children with a history of perinatal hypoxic-ischemic encephalopathy (HIE). A brief overview of the theoretical basis of this study is given below; each of the points made here is then examined in greater detail in the following sections.

Proponents of the Hierarchical Account argue that the syndrome of Developmental Amnesia – a childhood-onset memory disorder that involves selective hippocampal damage and that is characterised by impaired episodic memory functioning, spared semantic memory functioning, and normal cognitive abilities – indicates that a hierarchical relationship exists between episodic and semantic memory (Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997; Vargha-Khadem, Gadian, & Mishkin, 2001). They argue that selective impairments in episodic memory can occur if damage is limited to the hippocampus, whereas additional damage to the surrounding cortices will lead to further impairments in semantic memory.

This conceptualisation of declarative memory remains controversial and is opposed by proponents of the Unitary Account, who see declarative memory as a unified system that depends on medial temporal lobe structures working together as a whole (e.g. (Squire & Knowlton, 2000). They argue that damage to any part of the medial temporal lobe system leads to impairments in both episodic and semantic memory functioning and interpret the deficits shown by individuals with Developmental Amnesia in terms of a general impairment in declarative memory (e.g. Squire, 1992; Squire & Knowlton, 2000; Squire & Zola, 1998; Zola Morgan & Squire, 1990).

Investigating memory functioning in individuals with selective hippocampal damage may contribute towards the debate between the Hierarchical and Unitary Accounts. It is therefore of interest to investigate episodic and semantic memory functioning in individuals who have a history of perinatal hypoxic-ischaemic encephalopathy (HIE), a condition that can be associated with selective hippocampal damage (Hill, 1991).

1.1 The Hierarchical Account and Developmental Amnesia

The Hierarchical Account is a variant of dual-process theories of declarative memory, developed in connection with the study of Developmental Amnesia. This syndrome and the theoretical account that was developed to explain it are reviewed below.

1.1.1 Developmental Amnesia

Developmental Amnesia is a memory disorder, first described by Vargha-Khadem and colleagues, in which episodic memory functioning (remembering specific details about one's own life) and recall memory are impaired whilst semantic memory functioning (remembering abstract facts about the world) and familiarity-based recognition memory are relatively spared (Vargha-Khadem et al., 1997).

The DA cases described by Vargha-Khadem and colleagues include four individuals who suffered from an anoxic episode in the perinatal period, described variously as hypoxia or birth asphyxia and including perinatal seizures, and who showed evidence of selective bilateral hippocampal atrophy (Gadian et al., 2000). These individuals are described, at age 11-19, as showing normal cognitive abilities and performing within the normal range on tests of educational attainments and tests of semantic knowledge acquisition (e.g. the Vocabulary, Comprehension and Information sub-tests of the Wechsler Intelligence Scales). At the same time, they have profound difficulties remembering specific episodes in their own life and perform poorly on such tests of episodic memory functioning as story recall and design recall (Gadian et al., 2000; Vargha-Khadem et al., 1997; Vargha-Khadem et al., 2001; Vargha-Khadem et al., 2003).

Furthermore, these individuals tend to perform better on familiarity-based recognition tests than recall tests, a dissociation that is thought to reflect the episodic/semantic dissociation (Baddeley, Vargha-Khadem, & Mishkin, 2001; Vargha-Khadem et al., 2001).

1.1.2 The Hierarchical Account

The Hierarchical Account is based on the idea of a hierarchical relationship between episodic and semantic memory functioning, with episodic memory depending on, and being additional to, semantic memory (Mishkin, Vargha-Khadem, & Gadian, 1998). The distinction between episodic and semantic memory is neuroanatomically based on a hierarchical relationship between structures in the medial temporal lobe (MTL) (See Figure 1). According to the Hierarchical Account, semantic memory processing is lower down on the hierarchy than episodic memory processing and depends on the integrity of the perirhinal, entorhinal and parahippocampal cortices. Episodic memory involves an elaboration of semantic memory processing, adding the context-rich information of episodic memories to the factual information of semantic memories, and depends additionally on the hippocampus (Mishkin et al., 1997; Vargha-Khadem et al., 2001).

Related to the dissociation between episodic and semantic memory functioning is the dissociation between remembering or recollection (a type of mental time travel, retrieving past events through the recreation of one's personal experience) and knowing or familiarity (a sense of familiarity and an awareness of past events as general, impersonal facts), two states of conscious awareness that are associated with episodic and semantic memory retrieval respectively (Tulving, 1972; Tulving, 1985; Tulving & Markowitsch, 1998). Proponents of the Hierarchical Account argue that performance on certain recognition memory tasks (e.g. simple item recognition) can be supported by familiarity-based recognition whereas free recall tasks are associated with the conscious state of remembering/recollection. It is suggested that familiarity-based recognition

memory depends on the perirhinal, entorhinal and parahippocampal cortices whereas free recall depends additionally on the hippocampus (Baddeley et al., 2001; Mishkin et al., 1997; Vargha-Khadem et al., 2001).

The memory deficits seen in Developmental Amnesia are explained by the Hierarchical Account in terms of selective hippocampal damage that compromises episodic memory functioning and free recall but leaves semantic memory functioning and familiarity-based recognition memory relatively intact (Vargha-Khadem et al., 1997; Vargha-Khadem et al., 2001).

Figure 1: Neuroanatomical Basis of the Hierarchical Account[1]

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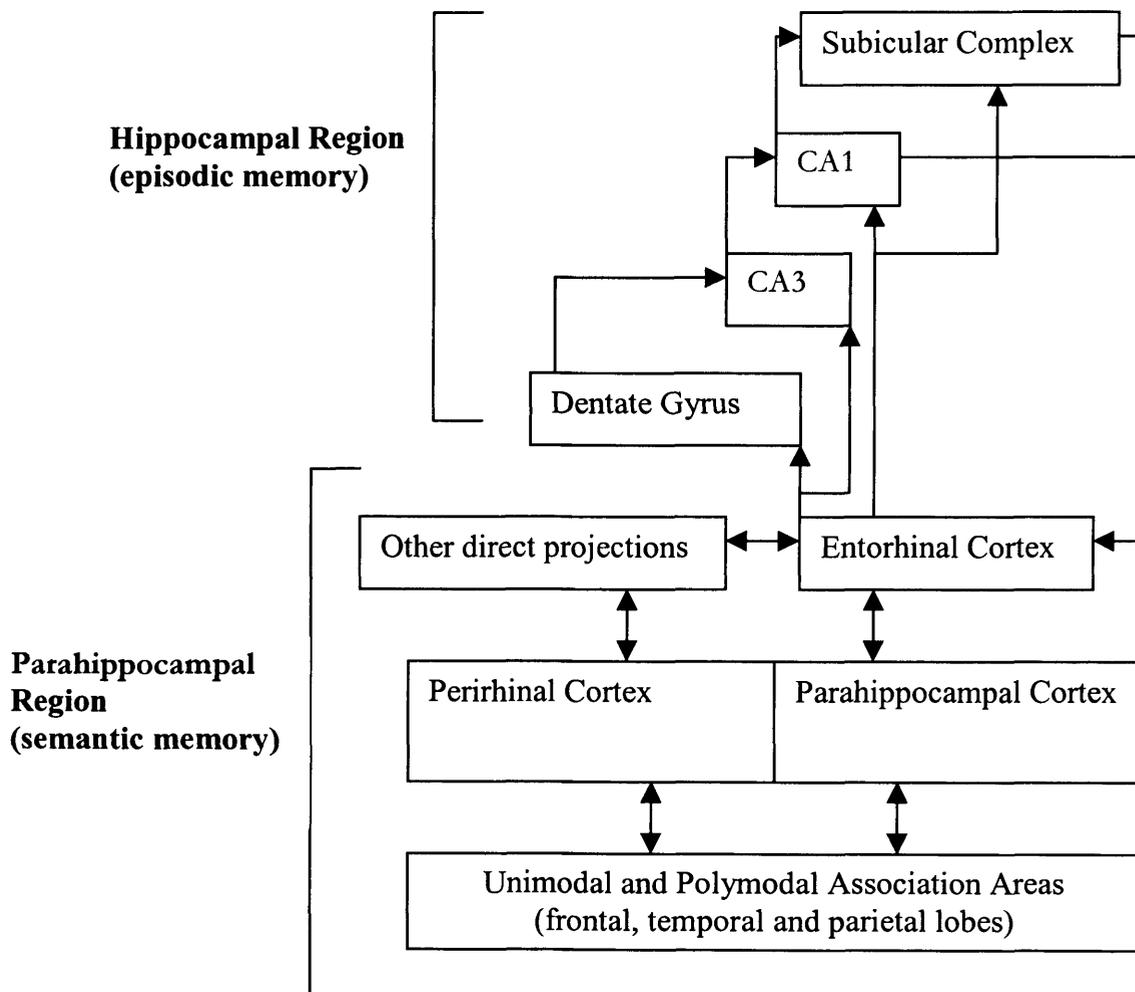
[1] Adapted from Mishkin et al., 1997

1.1.3 Other Explanations of Developmental Amnesia

It should be noted that the dissociations in declarative memory proposed by adherents of the Hierarchical Account remain controversial. Those researchers who subscribe to a Unitary Account of declarative memory (i.e. who see episodic and semantic memory as subsystems of declarative memory, dependent on medial temporal lobe structures working together as a unified system) have interpreted the deficits shown by the DA patients in terms of a general deficit in declarative memory, affecting both episodic and semantic memory functioning (e.g. Squire & Zola, 1998).

In order to resolve this controversy, detailed investigation of memory functioning in individuals with selective hippocampal damage is necessary, since it is only in the case of such selective damage that the two accounts differ in their prediction of impairments (Mishkin et al., 1997; Vargha-Khadem et al., 2001). Furthermore, studying childhood-onset rather than adulthood-onset amnesia is desirable because it avoids the issue of semantic memories being subject to a greater degree of rehearsal and consolidation than episodic memories in adulthood. This makes it difficult to compare episodic and semantic memory functioning in adults, whereas in children both types of memories are much less consolidated and therefore easier to compare (Ostergaard, 1987; Squire, Knowlton, & Musen, 1993). It is therefore of interest to investigate episodic and semantic memory functioning in individuals who have a history of perinatal hypoxic-ischaemic encephalopathy, a condition that fulfils these criteria for fruitful further research and which is described in the following section.

1.2   Perinatal Hypoxic-Ischemic Encephalopathy

Hypoxic-ischaemic encephalopathy (HIE) is a term used to describe the clinical features of brain injury that results from hypoxia, a reduction in the brain's oxygen supply, and/or ischaemia, a reduction in the blood supply to the brain (Johnston, 1998; Spreen, Risser, & Edgell, 1995; Vannucci, 2000; Volpe, 2001). HIE is a descriptive diagnosis

based on the infant's clinical presentation and is classified into mild/Stage 1, moderate/Stage 2 and severe/Stage 3. These categories are based on observations of the infant's reflexes, muscle tone and level of consciousness (see Table 1 for details), a classification first proposed by Sarnat and Sarnat (Sarnat & Sarnat, 1976) which is now widely used (Hahn, 2003; Hill, 1991; Johnston, 1998; Vannucci, 2000; Volpe, 2001).

Table 1: Clinical Staging of HIE*

Severity	Mild	Moderate	Severe
Consciousness	Alert	Lethargy	Coma
Tone	Normal or hypertonia	Hypotonia	Flaccidity
Tendon reflexes	Increased	Increased	Depressed or absent
Primitive reflexes	Uninhibited	Depressed	Absent
Autonomic function	Sympathetic overactivity		Autonomic dysfunction
Others	Irritability, jitteriness	Brainstem dysfunction	± Elevated intracranial pressure
Seizures	Absent		± Refractory to anticonvulsants
EEG	Normal	Low voltage, periodic or paroxysmal	Periodic or isolectric

* Based on Hahn, 2003

It is generally assumed that most hypoxic-ischaemic lesions are caused by perinatal asphyxia, an interruption in pulmonary or placental gas exchange that involves a depletion of oxygen (hypoxemia), the accumulation of carbon dioxide (hypercapnea), and metabolic acidosis (Berger & Garnier, 2000; Sunshine, 2003). A diagnosis of HIE is often used as the essential criterion for defining the occurrence of asphyxia (Dilenge, Majnemer, & Shevell, 2001; Hahn, 2003; Sunshine, 2003), to the extent that the terms "HIE" and "asphyxia" are generally used interchangeably. However, the assumption that most cases of HIE are due to asphyxia has been questioned by some authors, who have argued that it is more accurate to refer to "neonatal encephalopathy" in general unless a hypoxic-ischaemic aetiology has been explicitly established (e.g. Edwards & Azzopardi, 2000; Leviton & Nelson, 1992; Nelson & Emery III, 1993; Nelson & Leviton, 1991).

1.3   HIE, Hippocampal Damage and Memory Impairment

The hippocampus appears to be more vulnerable than other brain structures to hypoxic-ischaemic damage. This vulnerability has been well-documented in studies of perinatal HIE (Berger & Garnier, 2000; Hill, 1991; Mañeru et al., 2003; Vannucci, 2000; Volpe, 2001), as well as in studies of adulthood-onset episodes of hypoxia (Schmidt Kastner & Freund, 1991) and studies of experimentally-induced episodes of hypoxia-ischaemia in animals (Bachevalier & Vargha-Khadem, 2005; Squire, 1992; Zola Morgan & Squire, 1990). It is thought that the vulnerability of the hippocampus to hypoxic-ischaemic damage is due to the regional distribution of excitatory (glutamate) synapses: The hippocampus contains a particularly dense concentration of these synapses and this renders it more vulnerable to neuronal necrosis during an episode of hypoxic ischaemic-insult (Berger & Garnier, 2000; Hill, 1991; Mañeru et al., 2003; Volpe, 2001).

That the hippocampus plays an important role in memory functioning has been well established by studies of experimentally-induced hippocampal lesions in non-human primates and by studies of amnesia in humans (Bachevalier & Vargha-Khadem, 2005; Buckley, 2005; Eichenbaum, 1992; Eichenbaum, Otto, & Cohen, 1992; Manns, Hopkins, Reed, Kitchener, & Squire, 2003a; Manns, Hopkins, & Squire, 2003b; Markowitsch, 2000; Squire, 1992; Squire & Knowlton, 2000; Zola Morgan & Squire, 1990). Furthermore, the degree of memory deficits found in DA has been linked to the degree of hippocampal atrophy (Isaacs et al., 2003): It is estimated that DA only occurs when there is a bilateral reduction in the volume of the hippocampus of 20-30% or more. Therefore, the fact that the hippocampus is especially vulnerable to hypoxic-ischaemic insult makes it reasonable to suppose that memory impairment might follow perinatal HIE even in cases where no other type of impairment has been documented.

It can be hypothesised that individuals who suffer from a mild degree of HIE (i.e. who do not show evidence of general neurological disabilities, indicative of more widespread damage to the brain) are likely to show selective hippocampal damage. The Hierarchical Account would predict impaired episodic and spared semantic memory functioning in such individuals, whereas the Unitary Account would predict impaired episodic and semantic memory functioning.

1.3.1 HIE: Outcome Studies

There is now a well-established link between the stage of HIE, mortality rates, and neurological disability. That is, severe HIE has been linked to high mortality rates or neurological disability in all survivors; moderate HIE has been linked to low mortality rates and some neurological disability but mostly normal neurological outcome in survivors, and mild HIE has been linked to normal neurological outcome (Dilenge et al., 2001; Hahn, 2003; Hill, 1993; Mañeru, Junqué, Botet, Tallada, & Guardia, 2001; Robertson, 2003; Simon, 1999).

Studies investigating the relationship between HIE and neuropsychological functions are rare, as are studies that go beyond the pre-school period (Cowan, 2000; Dilenge et al., 2001; Gottfried, 1973; Mañeru et al., 2001; Marlow, Rose, Rands, & Draper, 2005; Robertson, 2003). This is an important point in the context of the current study, since the pattern of impairments found in DA with perinatal aetiology does not usually become apparent until middle childhood,[2] a finding which suggests that long-term follow-up studies (i.e. into middle childhood and beyond) are necessary for the detection of subtle memory deficits.

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[2] This may be related to the fact that episodic memory is thought to develop later in life than semantic memory (Bachevalier & Vargha-Khadem, 2005).

Where the long-term cognitive and neuropsychological outcome of HIE has been investigated, it has generally been concluded that, in the absence of gross neurological disability, mild HIE is associated with normal neuropsychological outcome whereas moderate HIE is associated with mild neuropsychological deficits (i.e. performance on neuropsychological tests that is within the normal range but lower than that of controls) (Handley-Derry et al., 1997; Marlow et al., 2005; Robertson, 1997; Robertson, 2003; Robertson & Finer, 1993; Robertson, Finer, & Grace, 1989; Viggedal, Lundälv, Carlsson, & Kjellmer, 2002).

To the author's knowledge, two studies have been conducted that have investigated the incidence of hippocampal pathology and memory deficits in individuals with a history of perinatal HIE. In 2001, Mañeru and colleagues (Mañeru et al., 2001) reported that adolescents aged 12 to 18 years with a history of moderate perinatal HIE (N = 20) showed impaired performance relative to controls on tests thought to reflect episodic learning (the Rey Auditory Verbal Learning Test and the Visual Reproduction Test from the Wechsler Memory Scale). These individuals did not differ from controls in terms of their performance on tests that are thought to reflect semantic knowledge (the Vocabulary and Similarities subtests of the Wechsler Intelligence Scale for Children and a word fluency task). There were no differences between individuals with a history of mild perinatal HIE or other signs of perinatal asphyxia (N = 8) and controls on any of the measures. Overall, the pattern of results shown by the individuals with a history of moderate HIE is similar to the pattern of impairment seen in Developmental Amnesia, although the deficits in episodic memory functioning were far less severe[3].

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[3] It should also be noted that individuals in the moderate HIE group showed some deficits in short term memory (performing at a lower level than controls on the forward but not the backward Digit Span subtest on the WISC-III) and executive functioning (performing at a lower level than controls on the Stroop Test but not on the Wisconsin Card Sorting Test), indicating that their impairments were not necessarily limited to episodic memory functioning.

Mañeru and colleagues studied those individuals with a history of moderate HIE further (N = 13, aged 13 to 19 years at testing) and reported selective bilateral hippocampal volume reduction and impaired performance on a test of auditory verbal learning relative to controls (Mañeru et al., 2003).

Although detailed investigations of memory functioning in survivors of perinatal HIE are rare, there is some evidence to suggest that a) subtle memory impairments can occur in the absence of gross neurological disability and b) in some individuals, these memory impairments resemble the pattern of deficits shown by individuals with Developmental Amnesia in that episodic memory is more affected than semantic memory. This study contributes to the body of literature on outcomes in HIE by focusing on memory functioning in greater detail than previous studies have done, and to the literature on Developmental Amnesia by using the Hierarchical Account to predict certain memory impairments in a specific clinical population.

1.4 Aims and Hypotheses

The aim of this study was to conduct a detailed investigations of the relationships between episodic and semantic memory functioning and between recall and familiarity-based recognition memory in individuals with a history of mild to moderate perinatal hypoxic-ischaemic encephalopathy. It was hypothesised that, due to the fact that the hippocampus is especially vulnerable to damage in perinatal HIE, these individuals would show a similar pattern of deficits to the one found in individuals with Developmental Amnesia – i.e. deficits in episodic but not semantic memory and deficits in recall but not familiarity-based recognition. If this were shown to be the case, such results would lend support to the Hierarchical Account of declarative memory rather than the Unitary Account of declarative memory.

2 METHOD

2.1 Participants

Participants were recruited from a cohort of children born at a London hospital. The

inclusion criteria were as follows:

a) A perinatal diagnosis of mild or moderate hypoxic-ischaemic encephalopathy (HIE)

(diagnosed by the Consultant Neonatal Neurologist)

b) Term births (gestational age of at least 37 weeks)

c) Date of birth between 1992 and 1996

Participants were invited to participate via a letter from the Consultant Paediatric

Neurologist who had been in charge of their care (See Appendix B for the invitation

letter and Appendix C for the information sheets). These invitations were followed up

with a telephone call. A total of 29 participants fulfilling the above criteria were

contacted; 23 (79%) agreed to participate. Of the 6 who did not agree to participate, one

family said they were too busy with their child's exams, one family had moved far away,

and four did not respond to the letter or the follow-up telephone call.

Following the initial contact from the consultant neonatal neurologist, those who agreed

to participate were invited to a testing session in central London. This testing session

was scheduled to last most of the day.

2.2 Ethical Issues

Permission to carry out this study was obtained from two Local Research Ethics

Committees[4] (see Appendix A). The main ethical issues identified in the context of this

study were participant fatigue, families feeling under pressure to participate because of

concerns about the child, and the possibility that testing could reveal neuropsychological

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[4] The details of these ethics committees have been omitted in order to protect the anonymity of the participants.

deficits in the child. These concerns were addressed by scheduling plenty of breaks into the testing session, discussing the aims of the study in detail with families, and providing an individual feedback report for each child (see Appendix E). Where there were concerns about a child's test results, families were offered a follow-up session with a neuropsychologist.

2.3   Design and Data Analysis

This is a descriptive study. The main aim was to describe memory functioning in a sample of children who might be expected to show dissociations between episodic and semantic memory and between recall and familiarity-based recognition similar to the dissociations that have been reported in patients with Developmental Amnesia. This description involved a) comparing the children's performance on different tests to normative data in order to ascertain any deficits in functioning at the level of the sample as a whole and b) constructing individual profiles of functioning to compare performance on tests of episodic memory with performance on tests of semantic memory.

2.4   Measures

The measures described in this section were selected in order to assess participants' intellectual ability, semantic memory, episodic memory, working memory, and visuo-motor functioning. Since this is a descriptive study without a control group, only tests with robust normative data were selected, so that test norms provide a baseline against which to compare participants' functioning. As far as possible the same tests were selected as have been used in studies of Developmental Amnesia in order to make it possible to compare the functioning of this sample with the functioning of DA patients. Information about the reliability and validity of each test is provided in Appendix F.

Table 2: Summary of Dependent Variables

Construct	Test	Variable(s)
Cognitive Functioning	Wechlser Intelligence Scale for Children – Fourth Edition (WISC-IV)	• Full Scale IQ • Verbal Comprehension Index Score • Perceptual Reasoning Index Score • Working Memory Index Score • Processing Speed Index Score
Semantic Memory	Vocabulary subtest (WISC-IV)	• Scaled Score
	Information subtest (WISC-IV)	• Scaled Score
	Comprehension subtest (WISC-IV)	• Scaled Score
	Category Fluency (animals)	• Z-score
Episodic Memory	Children's Auditory Verbal Learning Test (CAVLT)	• Immediate Memory Span (Standard Score) • Level of Learning (Standard Score) • Immediate Recall (Standard Score) • Delayed Recall (Standard Score) • Recognition Memory(normal/abnormal)
	Rey Complex Figure Test (RCFT)	• Copy accuracy (percentile range) • Copy speed Immediate Recall (T Score) • Delayed Recall (T Score) • Recognition Memory (T Score)
	Rivermead Behavioural Memory Test (RBMT)	• Profile scores on individual items • Overall screening score
	Everyday Memory Questionnaire	• Z-score
Working Memory	Digit Span subtest (WISC-IV)	• Scaled Score
Visuo-motor Functioning	Beery Test of Visuo-Motor Integration (VMI)	• Visual functioning (Standard Score) • Motor functioning (Standard Score) • Visuo-Motor integration (Standard Score)

2.4.1 Background Variables

Background variables are those variables which provide important general information about the participants in this study. They include descriptive variables as well as measures of areas of neuropsychological functioning that are indirectly, rather than directly, related to the main hypotheses about memory functioning.

Descriptive variables: For each participant, age and sex, were recorded. In addition, medical records were used to obtain information about the child's perinatal history (summarised in Appendix G).

Cognitive Functioning: The Wechsler Intelligence Scale for Children – Fourth UK Edition

(WISC-IV^{UK}) (Wechsler, 2004a) was administered in order to obtain a measure of

general cognitive functioning. This test gives a measure of a child's verbal reasoning

abilities (Verbal Comprehension Index) and nonverbal reasoning abilities (Perceptual

Organisation Index), as well as a measure of short-term memory functioning (Working

Memory Index) and the speed at which a child can process information (Processing

Speed Index). The test scores are given as a Full Scale Intelligence Quotient (IQ) score

that reflects overall intellectual functioning, as well as separate Index Scores for each of

the Indexes outlined above. The average IQ and Index score is 100 and the standard

deviation is 15.

Working Memory: Working memory was assessed using the Digit Span subtest from the

WISC-IV. The child is asked to repeat an increasing number of digits, first in the order

in which they are presented and then backwards. The child's performance on this test is

converted into a scaled score. The mean scaled score is 10 and the standard deviation is

3.

Visuo-motor Functioning: Visuo-motor functioning was assessed using the Visuo-Motor

Integration Test (VMI). This was done in order to exclude problems with visuo-motor

functioning as a possible reason for low scores on the Rey Complex Figure Test. The

VMI (Beery, 1997) is a test of visual and motor functioning, and of visuo-motor

integration. The child is asked to copy a series of increasingly complicated line drawings

(visuo-motor integration), to find a match for each of these line drawings from a list of

similar drawings (visual functioning), and to reproduce these drawings by joining dots

and tracing within an outline of each drawing (motor functioning). A standard score,

based on normative data, is calculated for each component of the test. The mean

standard score is 100 and the standard deviation is 15.

2.4.2 Semantic Memory

Information subtest of the WISC-IV: This is a test of general knowledge. The child has to answer factual questions such as "How many things make up one dozen?" and "What is the capital of Greece?" The child's performance on this test is converted into a scaled score. The mean scaled score is 10 and the standard deviation is 3.

Vocabulary subtest of the WISC-IV: This is a test of the child's knowledge of word definitions. The child has to provide definitions for a range of words. The child's performance on this test is converted into a scaled score. The mean scaled score is 10 and the standard deviation is 3.

Comprehension subtest of the WISC-IV: This is a test of the child's knowledge of normal social behaviour. The child has to answer "common sense" questions and questions about social norms such as "Why do we put stamps on letters?" and "Why should a promise be kept?". The child's performance on this test is converted into a scaled score. The mean scaled score is 10 and the standard deviation is 3.

Category Fluency: A version of Benton's Controlled Oral Word Association Test (COWAT) (Benton & Hamsher, 1989) was used to assess category fluency, which reflects access to semantic knowledge (Lezak, Howieson, & Loring, 2004). The child is asked to say as many animals as he can think of in one minute. Scores are given as Z-scores relative to published norms (from Strauss et al., 2006).

2.4.3 Episodic Memory

Children's Auditory Verbal Learning Test (CAVLT) (Talley, 1993): In this test of auditory verbal learning, a list of 16 words is read to the child five times and free recall is tested after each presentation. A second list is read once for immediate recall in order to determine the effects of interference, followed by a recall trial of the first list. After a period of 20 minutes, delayed recall of the first list is tested. This is followed by a

forced-choice recognition test in which a 32-item list is read out (containing the 16 items from the original list and 16 distractor items) and the child has to determine whether each item was on the original list or not. From this test, Standard Scores are obtained for Immediate Memory Span (derived from the first recall trial of each list), Level of Learning (a summary of the number of items recalled across the 5 recall trials of the first list), Immediate Recall and Delayed Recall. The mean standard score is 100 and the standard deviation is 15. Recognition Memory is scored as being either normal (above 16th percentile) or abnormal (below 16th percentile).

Rey Complex Figure Test and Recognition Trial (RCFT) (Meyers & Meyers, 1995): This is a test of visual learning. The child is asked to copy a geometric design and to reproduce it after a 3-minute and a 30-minute interval. A recognition test is also given in which components of the drawing have to be recognised amidst distractor shapes. The accuracy of the original copy is classified into percentile bands on the basis of normative data published in the test manual. T-scores are calculated on the basis of normative data published in the test manual for Immediate Recall, Delayed Recall, and Recognition Memory. The mean T-score is 50 and the standard deviation is 10.

Rivermead Behavioural Memory Test (RBMT) (Wilson, Baddeley, & Cockburn, 1991a): This is a test designed to measure recognition and recall in situations that resemble the demands of everyday life. The standard adult version was administered to children aged 12 years and over; a slightly modified version has been developed for younger children (Wilson, Ivani-Chalian, & Aldrich, 1991b). A Standardised Profile Score (scored as 0, 1 or 2, with lower scores indicating greater impairment) was calculated for each of 11 subtests[5]: immediate / delayed memory for a name, faces, pictures, a story and a route;

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[5] The 12th subtest, knowledge of the date, was omitted from the analysis as it is not given to younger participants.

prospective memory for an appointment and a belonging; and orientation to time and place. A total score was also calculated and classified as reflecting normal functioning, or mild, moderate or severe impairment.

Everyday Memory Questionnaire: A version of Sunderland's Everyday Memory Questionnaire (Sunderland, Harris, & Baddeley, 1983) adapted for use with children (Drysdale, Shores, & Levick, 2004) was given to parents to complete. This questionnaire covers a wide range of examples of episodic memory functioning in everyday life, such as remembering to take appropriate materials to school, remembering the names of new acquaintances, and being able to follow story lines in television programmes. The total score on this questionnaire was converted to a Z-score on the basis of published normative data (Drysdale et al., 2004).

3 RESULTS

In this section, data describing the general characteristics of the sample (age, sex, intellectual functioning, working memory and visuo-motor functioning) are presented (Section 3.1), followed by the results of memory tests across the sample as a whole (Section 3.2) and a description of the profile of functioning of individual participants (Section 3.3).

Where the psychometric properties of the test measure allow, the percentile range equivalents of the scores on each test are reported (calculated on the basis of the conversion tables reported in Strauss et al., 2006) to permit comparison across test measures. For the purposes of this study, Wechsler's system for classifying scores (Wechsler, 2004b) was adopted:

Table 3: Classification of Test Scores Using the Wechsler System

Classification	IQ/Standard Score	Z-score	T-Score	Percent Included	Lower Limit of Percentile Range
Very Superior	≥130	≥2	≥70	2.2	98
Superior	120-129	1.3 to 2	63-69	6.7	91
High Average	110-119	0.6 to 1.3	56-62	16.1	75
Average	90-109	±0.6	44-55	50	25
Low Average	80-89	-0.6 to -1.3	43-37	16.1	9
Borderline	70-79	-1.3 to −2	30-36	6.7	2
Extremely Low	≤69	≤-2	≤29	2.2	-

3.1 Description of the Sample

There were 10 girls and 13 boys in this sample (56.5% male). Age ranged from 9 years to 12 years 11 months; the mean age was 10 years and 8 months (SD = 12.5 months).

Cognitive Functioning

Most participants showed Full Scale IQ scores and Index Scores in the average range. One participant (4%) showed a Full Scale IQ in the borderline range, 4 (17%) scored in the low average range, 13 (56%) scored in the average range, and 5 (22%) scored in the high average range. The distributions of scores on the other Indices of the WISC-IV were similar to the distribution of Full Scale IQ scores.

Table 4: Mean IQ and Index Scores

	Mean Standard Score (SD)	Percentile	Range
Full Scale IQ	100.39 (10.42)	50th	78-119
Verbal Comprehension Index	98.61 (13.14)	45th	73-124
Perceptual Reasoning Index	99.61 (8.92)	47th	84-119
Working Memory Index	102.09 (11.57)	55th	80-123
Processing Speed Index	101.43 (10.96)	53rd	85-118

3.1.1 Visuo-Motor Functioning

Most participants scored in the average range or above on all components of the VMI. On the Visuo-Motor Integration component, 18 (78%) scored in the average range and above; the remaining 5 (22%) all scored in the low average range. On the Visual component, 17 (74%) scored in the average range or above, 4 (17%) scored in the low average range, and 1 (4%) scored in the borderline range. On the motor component 14 (61%) scored in the average range or above, 5 (22%) scored in the low average range, and 4 (17%) scored in the borderline range.

Table 5: Mean Standard Scores on the VMI

	Mean Standard Score (SD)	Percentile	Range
Motor Functioning	96.39 (17.20)	39th	72-137
Visual Functioning	98.35 (12.70)	45th	72-122
Visuo-Motor Integration	98.13 (8.08)	45th	86-112

3.1.2 Working Memory

Working memory was in the average range for most participants (8 (35%) scored in the low average range; the remainder scored in the average range or above), as indicated by their scaled scores on the Digit Span subtest (mean = 10.30; SD = 2.72; range = 7-16).

3.2 Memory Functioning: Summary of the Sample as a Whole

3.2.1 Episodic Versus Semantic Memory Functioning

Table 6 gives a summary of mean scores on various measures of episodic and semantic memory. Mean scores were in the average range for all tests except for the Rey Complex Figure Test, where mean scores were in the borderline range. Most participants scored below the average range on both the Immediate Recall component (N = 18; 78%) and the Delayed Recall component (N = 20; 87%) of this test.

Table 6: Mean Scores on Tests of Episodic and Semantic Memory

	Test	Mean (SD)	Percentile	Range
	Verbal:			
Episodic Memory	CAVLT Immediate Memory Span (standard score)	111.57 (16.00)	77th	71-140
	CAVLT Immediate Recall (standard score)	112.17 (15.56)	79th	76-136
	CAVLT Delayed Recall (standard score)	108.61 (15.16)	70th	73-135
	Visual:			
	RCFT Immediate Recall (T-score)	34.35 (11.45)	5th	20-66
	RCFT Delayed Recall (T-score)	33.22 (11.49)	5th	20-66
Semantic Memory	Vocabulary Subtest (scaled score)	9.48 (2.64)	32nd-42nd	5-16
	Information Subtest (scaled score)	9.22 (2.28)	32nd42nd	6-14
	Comprehension Subtest (scaled score)	9.78 (2.73)	32nd-42nd	3-14
	Category Fluency (Z-score)	0.29 (1.29)	61st	-2.87 – 2.63

Rey Complex Figure Test (RCFT): It should be noted that participants generally showed very low scores on the Copy Accuracy component of the RCFT as well as those components that measure memory functioning (see Table 7). The majority of

participants scored below the 16th percentile (i.e. below the normal range) on the Copy Accuracy component of the RCFT.

Table 7: Copy Accuracy Scores on the Rey Complex Figure Test

Percentile Range	Percentage of Sample
>1st percentile	30%
2nd – 5th percentile	22%
6th – 10th percentile	9%
11th – 16th percentile	9%
Above 16th percentile	30%

In order to remove the effects of the level of performance on the Copy Accuracy component from memory performance, a Percent Recall score was calculated for the Immediate and Delayed Recall components of the RCFT based on raw scores (= (Recall score/Copy score) x 100). The mean Percent Recall was 47% for the Immediate Recall component (SD = 24%) and 42% for the Delayed Recall component (SD = 24%). Although there are no normative data on Percent Recall scores using the Meyers & Meyers administration and scoring criteria, researchers using similar administration and scoring criteria have reported a mean Percent Recall score for the Delayed Recall component that ranges from 72% to 78% in children aged 9-12 years (Strauss et al., 2006). Only 2 children in the current sample obtained a Percent Recall score in this range or above for the Delayed Recall component.

Rivermead Behavioural Memory Test (RBMT): Ten of the 23 participants showed memory impairments on the RBMT (see Table 8). Participants most often lost marks on the "Name" test item (remembering a person's name) and on the "Appointment" test item (remembering to ask "Will I see you again?" when an alarm goes off). Five out of the 8 participants who scored in the mild impairment range, and both of the participants who scored in the moderate to severe memory impairment range, scored 0 on the "Name" item and lost at least one mark on one of the prospective memory items (remembering

an appointment, remembering to deliver a message, remembering to ask for a belonging). There were no consistent patterns of failure for other test items.

Table 8: Overall Performance on the Rivermead Behavioural Memory Test

Level of Memory Functioning	Percentage of Sample
normal memory function	57%
mild memory impairment	35%
moderate to severe memory impairment	9%

Table 9: Scores on Individual Items of the RBMT

Profile Score	Name	Belonging	Appointment	Pictures	Story Immediate	Story Delayed	Faces	Route Immediate	Route Delayed	Message	Orientation
0	8 (35%)	1 (4%)	1 (4%)	-	1 (4%)	2 (9%)	-	-	-	-	1 (4%)
1	5 (22%)	3 (13%)	7 (30%)	4 (17%)	4 (17%)	2 (9%)	1 (4%)	1 (4%)	2 (9%)	2 (9%)	4 (17%)
2	10 (44%)	19 (83%)	15 (65%)	19 (83%)	18 (78%)	19 (83%)	22 (96%)	22 (96%)	21 (91%)	21 (91%)	18 (78%)

Everyday Memory Questionnaire: The mean Z-score on the Everyday Memory Questionnaire was 1.19 (SD = 1.48; range = -0.425 – 5.416). In other words, this sample's mean score was over one standard deviation higher than published normative data, indicating a higher rate of memory problems in daily life.

3.2.2 Recall Versus Recognition Memory

The relationship between recall and recognition at a sample level was compared on the Children's Auditory Verbal Learning Test, the Rey Complex Figure Test, and the Rivermead Behavioural Memory Test.

Table 10: Mean Scores on Tests of Recall and Recognition Memory

	Test	Mean (SD)	Percentile	Range
Recall	**Verbal**			
	CAVLT Immediate Recall (standard score)	112.17 (15.56)	79th	76-136
	CAVLT Delayed Recall (standard score)	108.61 (15.16)	70th	73-135
	RBMT Story Immediate Recall (profile score)	1.74 (0.54)	n/a	0-2
	RBMT Story Delayed Recall (profile score)	1.74(0.62)	n/a	0-2
	Nonverbal			
	RCFT Immediate Recall (T-score)	34.35 (11.45)	5th	20-66
	RCFT Delayed Recall (T-score)	33.22 (11.49)	5th	20-66
	RBMT Route Immediate Recall (profile score)	1.96 (0.21)	n/a	1-2
	RBMT Route Delayed Recall (profile score)	1.91(0.29)	n/a	1-2
Recognition	**Verbal**			
	CAVLT Recognition (raw score)	30.65 (1.53)	n/a	26-32
	Nonverbal			
	RCFT Recognition (T-score)	41.41 (11.87)	19th	20-58
	RBMT Pictures Recognition (profile score)	1.83 (0.39)	n/a	1-2
	RBMT Faces Recognition (profile score)	1.96 (0.21)	n/a	1-2

Children's Auditory Verbal Learning Test: Unlike the other components of the CAVLT, the raw score on the Recognition component is not converted into a standard score but is classified as being above or below the 16th percentile. Furthermore, only 1 individual scored below the 16th percentile on the Recognition Memory component of the CAVLT, nobody scored below the 16th percentile on the Immediate Recall component, and only one individual scored below the 16th percentile on the Delayed Recall component. This makes statistical analysis of the relationship between recall and recognition memory on the CAVLT difficult.

Rey Complex Figure Test: A paired-samples t-test conducted to investigate the relationship between recall and recognition memory was statistically significant for the Delayed Recall component ($t_{(21)}$ = -2.22; p = 0.038; N = 23; two tailed test) but not for the Immediate Recall component ($t_{(21)}$ = -1.86; p = 0.078; N = 23; two tailed test), indicating

that participants' performance on the Recognition component was better than performance on the Delayed Recall component, and that performance on the Immediate Recall component was similar to performance on the Recognition component.

Rivermead Behavioural Memory Test: In order to limit the number of statistical comparisons being made for this test, the immediate and delayed scores on the Story Recall and on the Route Recall items were averaged to give a single Story Recall score and a single Route Recall score. A paired-samples t-test conducted to investigate the relationship between these recall measures and the recognition items on the RBMT revealed a statistically significant difference only for the comparison between Story Recall and Faces Recognition (see Table 11): For this comparison, participants scored higher on the recognition measure than on the recall measure.

Table 11: The Relationship between Recall and Recognition on the RBMT

		Recall Items	
		Story	**Route**
Recognition Items	**Pictures**	$t_{(22)} = 0.699$ $p = 0.492$ $N = 23$	$t_{(22)} = -1.226$ $p = 0.233$ $N = 23$
	Faces	$t_{(22)} = 2.206$ $p = 0.038$ $N = 23$	$t_{(22)} = 0.327$ $p = 0.747$ $N = 23$

3.3 Memory Functioning: Individual Profiles

3.3.1 Episodic Versus Semantic Memory

In order to test the hypothesis that the participants in this sample would show similar impairments to those seen in Developmental Amnesia, it was necessary to describe episodic and semantic memory functioning at an individual level. This is because mean scores for the sample as a whole might obscure differences between episodic and semantic memory functioning at an individual level.

In order to describe individual functioning, a profile of episodic and semantic memory functioning was constructed for each individual. It was decided to focus on those components of episodic memory tests that reflect immediate learning (i.e. the Immediate Memory Span score on the CAVLT and the Immediate Recall Score on the RCFT) rather than learning across a number of trials, since it has been suggested that semantic memory may be involved in learning paradigms that involve repeated trials (Baddeley et al., 2001). Furthermore, an average score for the semantic memory subtests from the WISC-IV (Vocabulary, Comprehension and Information) was computed (referred to as the WISC Semantic Composite score) in order to reduce the number of measures being compared.

Each individual's Full Scale IQ served as a baseline against which episodic and semantic memory functioning were compared. This was done in order to focus on *relative* strengths and weaknesses in memory functioning, allowing for the identification of memory deficits even where functioning was in the normal range. Using the descriptive categories outlined in Table 3, if an individual's score on a particular measure of memory functioning was two descriptive categories or more above or below the FSIQ (e.g. the difference between average functioning and superior functioning or between borderline functioning and high average functioning), then it was categorised as a strength or weakness respectively.

For each individual, a bar graph was constructed to summarise his or her Full Scale IQ and scores on the WISC Semantic Composite, the Category Fluency test, the Immediate Memory component of the CAVLT and the Immediate Recall component of the RCFT. These individual graphs are presented in Appendix H. Furthermore, in order to investigate whether the sample as a whole showed a tendency towards a particular profile of functioning, all of these individual profiles were plotted on a single graph

(Appendix I). This graph did not show any consistent patterns of functioning for the sample as a whole.

Each individual profile was categorised in terms of its pattern of strengths and weaknesses. The categories are summarised in Table 12.

**Table 12: Different Types of Individual Profiles of Functioning**

Strengths	Weaknesses	Number (%) who show this profile
None	None	7 (30%)
None	RCFT	5 (22%)
CAVLT	RCFT	5 (22%)
CAVLT & Category Fluency	RCFT	2 (9)
Miscellaneous	Miscellaneous	4 (17%)

This summary of individual profiles of functioning illustrates that the majority of the sample (74%) showed a weakness on the RCFT and that the most common area of strength was the CAVLT.

Miscellaneous profiles included one individual, Case 3, who showed weaknesses on the CAVLT and the RCFT but an otherwise even profile of functioning (pictured in Figure 3), a profile that is consistent with the pattern of functioning that has been reported in patients with Developmental Amnesia. This individual scored in the average range on the WISC-IV (FSIQ = 99) and on the WISC semantic composite (average of Information, Vocabulary and Comprehension subtests = 10.00), in the high average range on the Category Fluency test, (Z-score = 1.01) in the borderline range on the Immediate Memory Span component of the CAVLT (Standard Score = 71) and in the extremely low range on the Immediate Recall component of the RCFT (T-score = 23). This profile indicates impaired episodic memory functioning relative to intellectual ability and semantic memory functioning.

However, closer examination of this individual's scores revealed that he had scored in the average range on all other components of the CAVLT and that his score on the Digit Span subtest was 7. Furthermore, this individual did not show any memory problems on the Rivermead Behavioural Memory Test. Whilst the Immediate Memory Span component of the CAVLT may be a more accurate measure of episodic learning from single events than the other components (which rely on repeated learning trials), the importance of attentional factors must also be considered. That is, the low score on Immediate Memory Span and the relatively low score on the Digit Span subtest may be indications of fluctuating attention rather than memory problems.

Figure 2: Case 3's Profile of Functioning
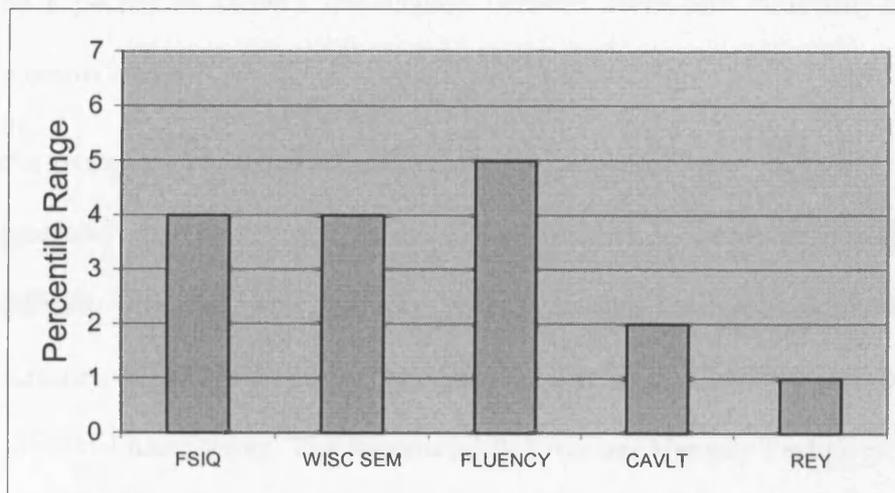
Legend

Percentile Ranges:	Tests:
1 = Extremely Low	FSIQ = Full-Scale IQ (WISC-IV)
2 = Borderline	WISC SEM = Information, Vocabulary & Comprehension Composite
3 = Low Average	FLUENCY = Category Fluency Test (animals)
4 = Average	CAVLT = Immediate Memory Span (CAVLT)
5 = High Average	REY = Immediate Recall (RCFT)
6 = Superior	
7 = Very Superior	

3.3.2 Recall versus Recognition

Individual profiles of functioning were not constructed for recall versus recognition measures. This was done for two reasons, one theoretical and one psychometric.

The Hierarchical Account explains the dissociation seen between recall and familiarity-based recognition memory in Developmental Amnesia as a function of the dissociation between episodic and semantic memory (Mishkin et al., 1997; Vargha-Khadem et al., 2001). That is, recall is relatively impaired because it relies on episodic memory functioning whereas familiarity-based recognition is relatively spared because it relies on semantic memory function. Since the children in this sample did not show the dissociation between episodic and semantic memory that exists in DA, they would not be expected to show a dissociation between recall and familiarity-based recognition memory either.

Furthermore, recognition and recall are measured very differently across the test measures that were used, making the comparison between recall and recognition difficult: The Children's Auditory Verbal Learning Test gives standard scores for recall memory but only allows the recognition score to be classified as reflecting normal or abnormal functioning. The Rivermead Behavioural Memory Test gives profile scores for individual test items so that those items that involve recall memory can be compared to those items that involve recognition memory, but these profile scores cannot easily be converted into percentile scores and therefore compared to other test measures. Only the Rey Complex Figure Test gives T-scores for both recall and recognition measures so that a comparison is possible between these components. Not only does this variation make it difficult to compare recognition and recall memory on any single test, it also makes it difficult to compare recognition and recall memory across different measures.

4 DISCUSSION

The aim of this study was to investigate memory functioning in a sample of children with a history of perinatal hypoxic-ischaemic encephalopathy (HIE). It was hypothesised that these children would be at risk of memory impairments similar to those seen in Developmental Amnesia (DA) since DA is thought to be a consequence of selective hippocampal damage and HIE has been shown to particularly affect the hippocampus. These memory impairments, it was hypothesised, would consist of deficits in episodic memory functioning and recall memory in the context of relatively spared semantic memory functioning, familiarity-based recognition memory and general intellectual ability. The presence of such memory impairments in this sample would support the Hierarchical Account of declarative memory, in which declarative memory is conceptualised as a hierarchy, with semantic memory at the bottom (dependent on the parahippocampal, perirhinal and entorhinal cortices) and episodic memory at the top (dependent additionally on the hippocampus).

Overall, there is no consistent pattern of impaired episodic memory functioning and spared semantic memory functioning, or impaired recall memory and spared familiarity-based recognition memory in this sample. However, the results of this study do indicate some deficits in memory functioning.

Nearly all of the children in the sample showed at least average levels of intellectual ability, average functioning on measures of semantic memory, and at least average functioning on the Children's Auditory Verbal Learning Test (CAVLT), a verbal measure of episodic memory. Most of the children scored in the impaired range on the Rey Complex Figure Test (RCFT), a visual measure of episodic memory. Almost half of the sample showed mild or moderate impairments in episodic memory functioning in an everyday context, as indicated by their scores on the Rivermead Behavioural Memory

Test (RBMT) and on the Everyday Memory Questionnaire. There was no consistent difference between performance on tests of recall and performance on recognition tests.

The very low scores on the Rey Complex Figure Test constitute the most marked impairment shown by this sample. The children showed moderate to severe impairments both in the accuracy of their copy of the figure and in the amount of information they retained, indicating possible problems with constructional abilities and executive functioning as well as visual memory functioning. In fact, it is difficult to separate out these components completely, as a poor copying strategy is in itself likely to lead to a poor rate of information retention (Strauss et al., 2006).

The RCFT is a complex test that requires various different types of processing, including visuo-motor functioning, visuo-spatial perception, executive functioning and episodic memory (Lezak et al., 2004; Strauss et al., 2006). It is therefore important to evaluate the children's performance on this test in the context of their performance on other tests in order to interpret an impaired performance. Thus it should be noted that

1) participants generally scored in the average range on all components of the VMI, indicating normal visual functioning, motor functioning and visuo-motor integration;

2) the children generally scored in the average range and above on those subtests of the Wechsler Intelligence Scale for Children which require visuo-spatial problem-solving;

3) children did not show any marked deficits in verbal episodic memory functioning, as measured by the CAVLT; and

4) observations of the children's behaviour during the testing session indicated no noticeable difficulties in executive functioning as shown by the children's ability to plan and monitor their problem-solving strategies across the different tests administered.

These observations indicate that the children's low scores on the RCFT may be due to the particular combination of cognitive processing skills that this test requires, namely the demands made on visuo-spatial as well as memory functioning.

The other measures on which this sample showed some deficits in functioning were the Rivermead Behavioural Memory Test (RBMT) and the Everyday Memory Questionnaire. Eight children (35% of the sample) scored in the "mild memory impairment" range on the RBMT and two children (9% of the sample) scored in the "moderate to severe memory impairment" range. Participants most frequently lost points on the test item that requires remembering a person's name and the test item that requires asking a particular question at the sound of an alarm. The mean score on the Everyday Memory Questionnaire was over one standard deviation higher than published norms, indicating a deficit in memory functioning. Overall, these data suugest a significant rate of problems with everyday memory functioning in this sample.

In addition to analysing neuropsychological functioning at a sample level, individual profiles of functioning were examined. This was done because summary statistics for the sample as a whole can obscure individual strengths and weaknesses. Furthermore, the focus of this study was on *relative* weaknesses in episodic memory functioning and/or recall memory – relative, that is, to an individual's semantic memory functioning and/or familiarity-based recognition memory – as much as on absolute deficits in comparison with normative data. Analysing individual profiles of functioning across measures of intellectual ability and episodic and semantic memory functioning revealed that almost three quarters of the sample showed a weakness on the Rey Complex Figure Test (visual episodic memory) and that the Children's Auditory Verbal Learning Test (verbal episodic memory) was the most common area of strength across the sample. There were no other consistent patterns of strengths and weaknesses.

4.1   Interpretation

Overall, the children in this sample do not show the pattern of impaired episodic/recall memory and intact semantic/familiarity-based recognition memory that characterises Developmental Amnesia. Although they show impaired spatial episodic memory functioning, their verbal episodic memory functioning tends to be a relative strength compared to their performance on other test measures. This is in contrast to patients with DA, who show severe impairments in both verbal and visual episodic memory (Vargha Khadem et al., 2001). It is a finding that also contrasts with Mañeru et al.'s observation of deficits in verbal episodic memory functioning in children with a history of moderate perinatal hypoxic-ischaemic encephalopathy and bilateral hippocampal damage[6] (Mañeru et al., 2003).

4.1.1   Memory Impairment and Degree of Hippocampal Damage

It seems probable that this apparent discrepancy between the findings of the current study and findings from studies of DA and studies of memory functioning in children with a history of moderate HIE can be explained in terms of the amount of damage sustained by the hippocampus. Thus Isaacs and colleagues, comparing a group of children born preterm (who are therefore vulnerable to hippocampal damage) to a group of DA patients and a group of controls on measures of memory functioning, report that the DA group was impaired on all measures of delayed episodic memory relative to controls whereas the preterm group showed impairment on only a few items of the Rivermead Behavioural Memory Test (Isaacs et al., 2000; Isaacs et al., 2003). They explain this finding as a reflection of the fact that the preterm group showed a mean bilateral reduction in hippocampal volume of 8-9% whereas the DA group showed a mean bilateral reduction in hippocampal volume of 40%. Isaacs and colleagues conclude

that early hippocampal pathology leads to the disabling memory impairments associated with Developmental Amnesia only when hippocampal volume is reduced by at least 20-30% bilaterally. Whilst they argue that this is a necessary condition for the development of DA, they also note that it may not be sufficient, and that additional brain pathology may also be involved.

Similarly, de Haan and colleagues report no significant memory impairments in a group of adolescents who suffered from severe perinatal asphyxia, and link this lack of impairments to the fact that these adolescents show hippocampal volumes that are similar to those of controls (de Haan et al., 2002).

It seems probable, therefore, that the participants in the current study, although vulnerable to hippocampal damage because of their history of perinatal hypoxic-ischaemic encephalopathy, did not sustain a sufficient degree of damage to result in the disabling memory impairments that characterise Developmental Amnesia.

4.1.2 The Hippocampus and Spatial Memory

Although these children do not show a profile of functioning that is consistent with Developmental Amnesia, they do show some significant memory deficits. They were particularly impaired on the Rey Complex Figure Test, a test that places demands on visuo-spatial, constructional, frontal executive and memory functioning. It is striking that this impairment in visual episodic memory occurred in the context of at least average performance on tests of verbal episodic memory. This deficit cannot easily be explained by the Hierarchical Account of declarative memory, since this account does not differentiate between verbal and nonverbal episodic memory.

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[6] In fact, Mañeru and colleagues used a very similar measure of verbal episodic memory functioning to the one used in this study: the Rey Auditory Verbal Learning Test, a list-learning test that is identical to the CAVLT in its administration.

O'Keefe and Nadel's theory of the hippocampus as a cognitive map may go some way towards explaining the deficit in spatial episodic memory shown by the children in this study, in that it presents an account of the role of the hippocampus in spatial functioning. In their original theory, O'Keefe and Nadel proposed that animals create a representational map of their environment which they use to guide their movements, and that this map is stored in the hippocampus (O'Keefe & Nadel, 1978). This theory was later extended to episodic memory in humans with the suggestion that the hippocampus stores the spatio-temporal context of personally experienced events (O'Keefe, 1993). It has been suggested that the role of the hippocampus in spatial processing is to create a "snapshot" type of memory in which a whole scene must be remembered (see Rolls, 2001 for a review of this idea).

It is possible, then, that the impaired performance on the Rey Complex Figure Test shown by the children in this study reflects a deficit in spatial memory functioning that may have its roots in hippocampal pathology. It seems to be the combination of spatial processing and memory that is particularly problematic, since the children performed in the average range or above on other tests of spatial functioning and on other tests of (non-spatial) memory functioning.

4.1.3 Everyday Memory

A significant proportion of children in this sample scored in the "mild memory impairment" or "moderate to severe memory impairment" range on the Rivermead Behavioural Memory Test. Furthermore, the mean score on the Everyday Memory Questionnaire, completed by the children's parents, was more than one standard deviation higher than published norms for the same age range, indicating deficits in memory functioning. It is possible, therefore, that these children are experiencing difficulties in coping with the demands that daily life makes on memory functioning which have not been picked up by other, more formal test measures.

This would certainly be consistent with findings from other studies that have investigated the long-term outcome of perinatal hypoxic-ischemic encephalopathy: A number of studies have reported that children with a history of mild to moderate perinatal HIE show average scores on various measures of neuropsychological functioning, but need extra support at school and lag behind their peers in terms of educational attainments (e.g. Marlow et al., 2005; Robertson, 1997; Robertson, 2003; Robertson & Finer, 1993; Robertson et al., 1989) Impaired memory functioning could be one possible explanation for these difficulties at school. It seems that laboratory test measures are not necessarily sensitive to functioning in an everyday context.

4.2   Limitations

This study has a number of limitations. In terms of methodology, two major shortcomings are the lack of neuroimaging data and the lack of a control group. Conceptually, the Hierarchical Account of episodic memory functioning is limited in terms of its power to explain the findings from the current study. These points are examined in detail below.

4.2.1   Methodological Limitations

Lack of neuroimaging data: Whilst it is reasonable to assume that the children in this sample suffered selective hippocampal damage as a consequence of perinatal hypoxia-ischaemia, this assumption has not been confirmed by neuroimaging data and therefore remains an assumption. Within the theoretical framework of the Hierarchical Account, the occurrence of specific episodic memory deficits is inextricably linked to the occurrence of selective hippocampal damage. Therefore, the interpretation of impaired test performance in this sample will remain somewhat incomplete until such impairments can be linked to neuroimaging data.

Descriptive design: Whilst a descriptive design is entirely appropriate for the purposes of this study (i.e. a description of a particular clinical population), having a control group

against which to compare results would have been a useful extension of the study. Studies of the long-term outcome of perinatal HIE indicate that mild to moderate HIE is often associated with neuropsychological test performance that is in the average range *but* significantly lower than the test performance of controls (Mañeru et al., 2001; Marlow et al., 2005; Robertson & Finer, 1993; Robertson et al., 1989; Viggedal et al., 2002). Such subtle deficits may be difficult to detect with a descriptive design that relies on normative data as a baseline for comparison.

4.2.2 Conceptual Limitations

In proposing that the hippocampus is crucial for episodic memory functioning, the Hierarchical Account does not differentiate between verbal and nonverbal memory. Furthermore, although it is postulated that the severe deficits seen in Developmental Amnesia will not occur unless a certain degree of damage to the hippocampus has occurred (as indicated by a volume reduction of at least 20-30%), it is not clear from the Hierarchical Account what the consequences of a milder degree of damage might be. The results of the present study suggest that a milder degree of hippocampal damage might result in impairments in episodic memory that are specific to nonverbal material. However, the neuroanatomical basis for such a phenomenon is not clear. The consideration of verbal versus nonverbal memory functioning and the consequences of mild hippocampal damage might provide an interesting extension to the Hierarchical Account of declarative memory.

4.3   Conclusion

The results of this study indicate that mild to moderate perinatal hypoxic-ischaemic encephalopathy may be associated with a) impairments in everyday memory functioning that are not readily apparent on laboratory tests of memory and b) a selective impairment in spatial/nonverbal episodic memory, in the context of average intellectual abilities and average performance on tests of semantic memory functioning and tests of

verbal episodic memory functioning. Whilst the Hierarchical Account of declarative memory does not fully account for these findings, the selective nature of the memory deficits is better explained by the idea that the hippocampus is specialised for episodic memory.

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APPENDIX A: ETHICAL APPROVAL

98

NHS

████████████████████████████████**Research Ethics Committee**

████████████
████████
London
████

09 March 2005

Prof ██████████████
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████████████████████████
████████████
█████████ London
████████

Dear Prof ████████████

Full title of study:	*Effects of perinatal hypoxic-ischaemia on the structure and memory functions of the medial temporal lobes*
REC reference number:	*05/Q0508/14*
Protocol number:	*Attached to application, but undated*

Thank you for your letter of 15 February 2005 (received on 3 March 2005), responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chairman at a meeting held on 08 March 2005.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type:	Version:	Dated:	Date Received:
Application		12/01/2005	12/01/2005
Investigator CV	CV for Professor ████████		12/01/2005

Peer Review	Peer review from Prof ▇▇▇▇▇		12/01/2005
Participant Information Sheet	Information Sheets for Parents of Patients, version 2	15/02/2005	03/03/2005
Participant Information Sheet	Information Sheet for Parents of Controls, version 2	15/02/2005	03/03/2005
Participant Information Sheet	Information Sheet for Children (Patients), version 2	15/02/2005	03/03/2005
Participant Information Sheet	Information Sheet for Children (Controls), version 2	02/02/2005	03/03/2005
Participant Information Sheet	Version 1, for patients of parents	12/01/2005	12/01/2005
Participant Information Sheet	version 1, Information Sheet for Parents of Controls	12/01/2005	12/01/2005
Participant Information Sheet	version 1, Information Sheet for Children (Patients)	12/01/2005	12/01/2005
Participant Information Sheet	version 1, Information Sheet for Children (Controls)	12/01/2005	12/01/2005
Participant Consent Form	version 1, Parental Consent Form	12/01/2005	12/01/2005
Participant Consent Form	Version 1, Child Assent Form	12/01/2005	12/01/2005
Response to Request for Further Information		15/02/2005	03/03/2005
Other	Memory Questionnaire (5 pages)		12/01/2005
Other	Version 1, Letter from Dr ▇▇▇▇▇▇	12/01/2005	12/01/2005
Other	Version 1, Letter to GP	12/01/2005	12/01/2005

Management approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final management approval from the R&D Department for the relevant NHS care organisation.

Notification of other bodies

The Committee Administrator will notify the research sponsor that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/Q0508/14	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project,

Yours sincerely,

███████████

████
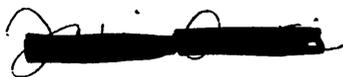
Research Ethics Coordinator

E-mail: ███████████████

Enclosures   *Standard approval conditions*

Site approval form (SF1)

APPENDIX B: INVITATION LETTER

NB: All references to specific institutions and researchers have been omitted in order to protect the anonymity of participants

Dear *Parent's Name*

We hope that you and your child, *Child's name* are well. We are contacting you as a follow up from the assessments that we performed when *Child's name* had just started school. We are always very grateful for your support and keen to know exactly how *Child's name* is doing. We would like to investigate further what *his/her* strengths and weaknesses are and whether anything has changed since we last saw you. We are now together with Institute X conducting a study on the effects of early lack of oxygen on later brain development, in particular the effects on memory functions.

We would be very grateful if you could read the information sheets enclosed (one for parents and one for children) and think about taking part. If you do decide to take part, please contact me, Dr X, to ask any further questions and give verbal consent. We will then give your first of two appointments at your convenience. When you attend for the first appointment we will go over the study details again and ask you to sign a written consent form.

Thank you for your time!

Yours sincerely,

Dr. X

Prof. Y

APPENDIX C: INFORMATION SHEETS

NB: All references to specific institutions and researchers have been omitted in order to protect the anonymity of participants

INFORMATION SHEET FOR PARENTS OF PATIENTS

Project Title: "Effects of perinatal hypoxic-ischaemia on the structure and memory functions of the medial temporal lobe"

INTRODUCTION

We are inviting you and your child to take part in a new research study that aims to investigate the later development of children who suffered some form of lack of oxygen when they were born. We are particularly interested in the association between subtle brain abnormalities and specific neuropsychological functions, especially memory. We have contacted you because your child is one of a group of children born at X Hospital who have participated in similar research in the past and was doing well on their last assessment. Being able to compare information from these past studies to information about current functioning is important for understanding how oxygen deprivation affects development.

The aim of the study

The main aim of the study is to perform a detailed investigation of your child's neuropsychological functioning now that they are older and able to perform more sophisticated tasks. This detailed investigation includes paper-and-pencil tests, measures of the electrical activity of the brain, and a brain scan (see next section).

How the study is being done.

There are different parts to this study:

1) You will be invited to Institute X for assessment by a neuropsychologist. This will include paper-and-pencil tasks and the measurement of electrical activity in the brain, described below. Participants will be tested from approximately 10 am till 4.30 pm, with a one and a half hour break for lunch. Further breaks will be given as needed. If the child becomes uncomfortable or distressed at any stage, the assessments will be stopped immediately.

The neuropsychological tasks will be used to assess memory, intelligence, visual perception, attention, reading abilities and arithmetic abilities. They include simple age-appropriate paper-and-pencil tests, involving putting together puzzles, answering simple questions, or trying to remember things. Clear instructions will be given so that your child understands what will happen during the tests.

We will also look at brain electrical activity from brain your child watches pictures on a computer screen (ERP tasks). This test is used to examine memory and visual processes in the brain. While the brain works, the cells of the brain communicate via electrical signals. These signals can be measured by sensors placed on the head. This procedure is painless – the sensors only

detect the natural electrical activity in the brain and do not themselves generate electrical activity (as an analogy, when you take your temperature, the thermometer measures your temperature but does not make you hotter or colder). The sensors themselves are wrapped in small sponges and sewn together with stretchy string, looking something like a hairnet.

2) For your second appointment you will be invited to the Hospital Y, for your child to have a magnetic resonance imaging scan, similar to those he/she has had in the past. Magnetic resonance imaging is a method of obtaining pictures of the inside of the body. The scanner is like a large cylinder with open ends (see the picture below). Your child will be checked before the scan to ensure that s/he has no metallic implants from previous operations or any metallic fastenings on his/her clothes. Any jewellery or hair clips will also be removed.
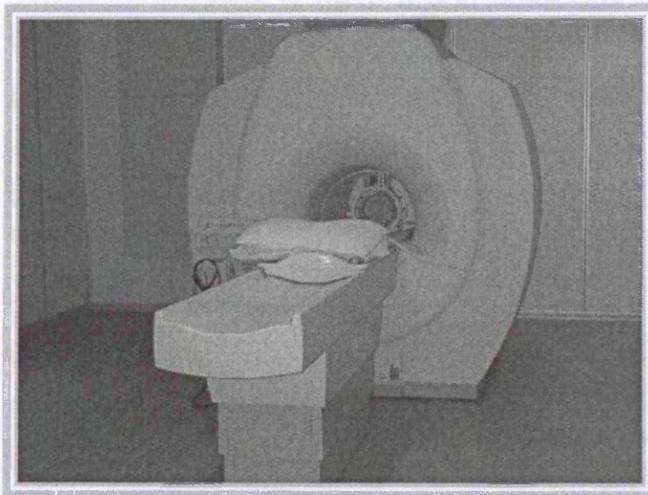
Your child will be asked to lie on his/her back on a bed inside the magnet with his/her head resting in a comfortable support. Provided you are free of metal attached either inside or outside of your body you may stay with your child during the examination. S/he will be given a buzzer to hold that can be pressed at any time and someone will come immediately to see what is wanted. Your child will be free to stop the examination at any time during the scan. There will be quite a loud knocking noise during the procedure, while the images are being taken. We will give him/her some earphones, which will cut down the noise from the scanner. There will be a light on in the scanner and we can play some music through the earphones. Your child can bring his/her own CD if they wish. S/he will need to lie as still as possible whilst we are scanning A paediatrician will be present throughout the examination. The scan will take around 30 minutes.

If you are not in the scanner room with your child you may be present just outside in the scanner control room during the scan if you wish.

What are the risks and discomforts?

There are no foreseeable risks from the tests themselves.

If you child should become uncomfortable or distressed, the examinations will be stopped immediately.

Who will have access to the case/research records?

Only the researchers, the doctor of your child and a representative of the Research Ethics Committee will have access to the data collected during this study.

The use of some types of personal data information is safeguarded by the Data Protection Act 1998 (DPA). The DPA places an obligation on those who record or use personal information, but also gives rights to people about whom information is held. If you have any questions about data protection, contact the Data Protection Officer via the switchboard on xxx.

What are the arrangements for compensation?

This project has been approved by an independent Research Ethics Committee who believes that it is of minimal risk to you. However, research can carry unforeseen risks and we want you to be informed of your rights in the unlikely event that any harm should occur as a result of taking part in this study.

This research is covered by a no-fault compensation scheme which may apply in the event of any significant harm resulting from involvement in this study. Under this scheme it would not be necessary for you to prove fault. You also have the right to claim damages in a court of law. This would require you to prove fault on the part of the Institute/Hospital and/or any manufacturer involved.

Who do I speak to if problems arise?

If you have any complaints about the way in which this research project has been, or is being conducted, please, in the first instance discuss them with the researcher. If the problems are not resolved, or wish to comment in any other way, please contact Ms X, Head of Research & Development by post via the Research and Development Office, Institute Y or if urgent by telephone on xxx.

Researchers who will have contact with the family

Researchers' details were provided here but have been omitted in the interest of participant anonymity.

INFORMATION SHEET FOR CHILDREN (Patients)

Who are we?

We are a group of scientists who investigate how people's brains work. We are especially interested in how children's brains grow and change. You may remember coming to see us a few years ago at Hospital X.

Why are we writing to you?

We are asking you to take part in a further study that we are doing. The aim of this study is to understand what kinds of thinking skills are easy for you and what kinds of thinking skills are a bit harder.

What happens if you take part in our study?

If you decide to take part, we will ask you to visit us with your parents twice, at two different places in London. On one visit we will ask you to come to Institute Y. There you will be given different problem-solving tasks to do, like doing puzzles or remembering lists of words. We will also measure your brain activity. This involves wearing a hairnet with sensors in it while you do some tasks on a computer. You can't feel the sensors working but they can measure what your brain is doing.

On another visit we will ask you to come back to Hospital X, where we will do a brain scan with you. You may remember having one before. This is like having an X-ray of your brain done. All you have to do is lie inside the machine, which is like a large tube, and keep very still. The scanner is a bit noisy but it doesn't move or hurt In anyway. You can listen to some music or a story whilst you are having a scan. Your Mum or Dad can come into the scanner room with you.

Other things you might like to know

You can change your mind about taking part at any point, without having to give a reason.

Thank you for reading this. We hope you decide to take part!

APPENDIX D: CONSENT FORMS

NB: All references to specific institutions and researchers have been omitted in order to protect the anonymity of participants

CONSENT FORM

Project Title: "Effects of perinatal hypoxic-ischaemia on the structure and memory functions of the medial temporal lobe"

Researchers' Names: *omitted*

Name of participant (child):_____

For parent(s) to fill in:

Please tick	
	I confirm that I have read and understand the information sheet for the above study (date , version) and have had the opportunity to ask questions.
	I understand that my child's participation is voluntary, and that we are free to withdraw at any time, without giving any reason, without our legal rights being affected.
	I give permission for my child to participate in the above study.

_____   _____   _____

Parent's Name   Parent's Signature   Date

For the child to fill in:

Please tick	
	I have read the information sheet about this study and I understand it. I have had the chance to ask questions about it.
	I understand that it's my choice whether I take part of not. I'm allowed to change my mind about taking part and I don't have to give a reason.
	I agree to take part in this study.

Child's Name	Child's Signature	Date

Investigator's Name	Investigator's Signature	Date

APPENDIX E: TEMPLATE FOR FEEDBACK REPORT

NB: Because this study was part of a larger project, the feedback report includes tests that are not reported in this paper. All references to specific institutions and researchers have been omitted in order to protect the anonymity of participants

Feedback on Neuropsychological Tests

Dear Mr. and Mrs. and X

Thank you for agreeing to participate in the above study. This document contains a description of the neuropsychological tests that we did, and some feedback about X's performance on these tests.

A note on scores: X's scores have been given in terms of a "performance range". That is, they give an idea of how X has performed compared to the general population of children his age. Below is an explanation of these descriptions:

Performance Range	Description
Extremely Low	0– 2nd percentile. This means that the bottom 2 % of the population would be expected to score in this range.
Borderline	2nd – 9th percentile. This means that 91% of the population would score higher than in this range.
Low Average	9th – 25th percentile This means that 75% of the population would score higher than in this range.
Average	25th – 75th percentile. This means that 50% of the population would be expected to score in this range.
High Average	75th – 91st percentile. This means that 75% of the population would score lower than in this range.
Superior	91st – 98th percentile. This means that 91% of the population would score lower than in this range.
Very Superior	98th – 100th percentile. This means that the top 2% of the population would be expected to score in this range.
Normal range of functioning	This description has been given where data are only available in terms of normal or abnormal performance. This is often the case where tests have been used for clinical purposes to diagnose impairment.

Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV)

This a test of intelligence consisting of 15 sub tests, each measuring a different facet of mental ability. Some tests are designed to assess the child's ability for verbal expression and grasp of verbal concepts and abstract reasoning, whereas others assess visual and spatial organisation and perceptual ability.

These sub-tests are used to obtain a Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index, Processing Speed Index, and Full Scale IQ. These scores and what they mean are given below.

X's scores on this test are summarised below:

Index	Description	Performance Range
Verbal Comprehension Index	The child's aptitude for verbal expression and verbal learning, understanding of verbal concepts, and ability to reason using words.	
Perceptual Reasoning Index	The child's ability to think and reason using pictures instead of words.	
Working Memory Index	The child's ability to store and process pieces of information over a short time span (i.e. a few seconds).	
Processing Speed Index	How quickly the child is able to perform different cognitive tasks.	
Full Scale IQ	Overall estimate of the child's intellectual ability.	

Childhood Behaviour Checklist

This is one of the questionnaires that we asked you to fill in about X's general behaviour at school and at home. It is designed to pick up any emotional or behavioural problems that a child might have. Responses are scored in terms of Total Problems, Externalising Symptoms (behavioural problems such as aggressiveness) and Internalising Symptoms (emotional problems such as anxiety or sadness). These scales can be further divided up into clusters of symptoms. Scores are given as being in the normal range, borderline clinical range, or clinical range.

X scored in the ?? range for the Total Problems scale, Externalising Symptoms scale and Internalising Symptoms scale, indicating that he experiences (no) more of these symptoms than other children his age.

Rivermead Behavioural Memory Test (RBMT)

This is a test of everyday memory functioning. It consists of a number of tasks that involve remembering things such as a story, pictures, faces, names, and remembering to do something in the future. Scores are given as being in the normal, borderline or impaired range / showing normal memory functioning, mild impairment, moderate impairment or severe impairment. X scored in the ?? range on this test.

Rey Complex Figure Test

This is a test of spatial memory and of visuo-motor integration. The child is required to copy a complex line drawing (Drawing Copy) and then reproduce it from memory after a delay of 3 minutes (3-minute Recall) and again after a further delay of 30 minutes (30-minute Recall). The child is also shown a number of patterns and asked which ones were part of the drawing (Pattern Recognition).

X's scores on this test are summarised below:

	Drawing Copy	3-minute Recall	30-minute Recall	Pattern Recognition
Performance Range				

Children's Auditory Verbal Learning Test (CAVLT)

This is a test of verbal memory and learning. A list of 16 words is read to the child, who is asked to repeat as many of the words as he/she can remember. This process is repeated 5 times and gives an indication of the child's verbal learning (Level of Learning). The child is then asked to recall this list after a distractor list has been read out (Immediate Recall), and again after 15 minutes have passed (Delayed Recall). Finally, the child listens to a list of words and is asked which ones were in the first list and which ones were not (Recognition).

X's scores on this test are summarised below:

	Level of Learning	Immediate Recall	Delayed Recall	Recognition
Performance Range				

Visuo-Motor Integration Test (VMI)

This is a test of visual perception (how accurately the child sees line drawings), motor functioning (the muscle co-ordination involved in reproducing these drawings), and how well visual and motor functioning are integrated. The child has three tasks: Copying a series of line drawings (Visual-motor Integration), choosing a drawing out a group of similar drawings that most resembles a particular target (Visual Functioning), and connecting dots to make up particular drawings (Motor Functioning).

X's scores on this test are summarised below:

	Visual-motor Integration	Visual Functioning	Motor Functioning
Performance Range			

FAS Fluency Test

This is a test of the child's ability to access stored verbal information. The child is asked to generate as many words as possible beginning with a particular letter (F, A and S were used) in one minute. X scored in the range on this test.

Memory & Information Processing Battery (AMIPB)

This is a test of general memory functioning and information processing speed. It consists of various sub-tests. For our study, we used only the Design Learning sub-test, which measures spatial memory. The child gets 10 seconds to look at a simple line drawing and is asked to reproduce this drawing from memory. This process is repeated 5 times and gives an indication of the child's spatial learning (Design Learning). The child is then asked to copy this drawing after he/she has seen and copied a distractor drawing (Immediate Recall), and again after 15 minutes have passed (Delayed Recall).

X's scores on this test are summarised below:

	Design Learning	Immediate Recall	Delayed Recall
Performance Range			

Pyramids & Palm Trees Test

This is a test of semantic memory (remembering facts about the world). The child is shown a picture (e.g. a pyramid) and asked which of two other pictures (e.g. a palm tree and an oak tree) best goes with the first picture. X scored within the normal range for adults but we do not have normative data on children.

Summary

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Please do not hesitate to contact me if you would like to discuss the results reported here.

Yours sincerely,

Kathrin Hicks

Trainee Clinical Psychologist

APPENDIX F: RELIABILITY AND VALIDITY

Background Variables

Cognitive Functioning: WISC-IV

A high degree of internal consistency and test-retest stability has been reported for the Full-Scale IQ score and all of the Index Scores (Wechsler, 2004b). The coefficients for these measures of reliability are reported below. Interrater reliability has also been reported to be high (r = 0.98-0.99 for all Indices).

Table 13: Reliability Coefficients of Index Scores on the WISC-IV*

Index	Internal Consistency (r)	Test-retest Reliability (r)
Verbal Comprehension	0.94	0.93
Perceptual Reasoning	0.92	0.89
Working Memory	0.92	0.89
Processing Speed	0.88	0.86
Full Scale IQ	0.97	0.93

*Taken from (Wechsler, 2004b)

Regarding the validity of the WISC-IV, it is important to note that a) expert reviews indicate that the content of the test adequately samples the domains of intellectual functioning that the test is intended to measure; b) qualitative studies of participants' response processes indicate that children engage in the expected cognitive processes when responding to subtest tasks; c) factor analysis has shown that scores on individual subtests are related to each other in the way that would be predicted on the basis of theoretical constructs of cognitive functioning; d) scores on the WISC-IV show a high degree of correlation with other measures of intellectual functioning and e) the WISC-IV has shown a high degree of sensitivity and specificity in discriminating between special groups of children such as those with learning disabilities (Wechsler, 2004b).

Working Memory: Digit Span Subtest (WISC-IV)

A high degree of internal consistency (r = 0.87), test-retest reliability (r = 0.83) and interrater reliability (r = 0.98-0.99) has been reported for this subtest (Wechsler, 2004b). Digit span tests are widely considered to be a valid measure of working memory and have been shown to have particularly high discriminant validity (Lezak et al., 2004).

Visuo-motor Functioning: Test of Visuo-Motor Integration (VMI)

A high degree of internal consistency, test-retest stability and interrater reliability has been reported for all components of the VMI (Beery, 1997):

Table 14: Reliability Coefficients of Scores on the VMI*

Component	Internal Consistency (r)	Test-retest Reliability (r)	Interrater reliability (r)
Visual Perception	0.85	0.85	0.98
Motor Coordination	0.87	0.86	0.93
Visuo-motor Integration	0.88	0.89	0.92

*Taken from (Beery, 1997)

That this test possesses a high degree of construct validity is indicated by studies demonstrating that the VMI is correlated more strongly with measures of nonverbal than verbal intelligence, that it is correlated with academic achievement, that the visuo-motor integration component is more demanding than the other two components alone, and that it discriminates accurately between children with conditions that affect visuospatial functioning (e.g. brain injury, learning disabilities or visual impairment) and controls (Beery, 1997).

Semantic Memory

Information Subtest (WISC-IV)

A high degree of internal consistency ($r = 0.86$), test-retest reliability ($r = 0.89$) and interrater reliability ($r = 0.96$) has been reported for this subtest (Wechsler, 2004b). In terms of validity, the main concern in the context of the current study was that this test should measure consolidated factual knowledge and not be strongly influenced by episodic memory functioning. Kaufman and Flanagan (2004), reviewing the different facets of intellectual functioning measured by different subtests of the WISC-IV, report that the Information subtest is a measure of factual knowledge. Furthermore, patients with dementia who suffer from severe episodic memory deficits can show preserved functioning on this subtest until their illness is fairly advanced, indicating that scores on the Information subtest are relatively independent of episodic memory functioning (Lezak et al., 2004; Strauss et al., 2006).

Vocabulary Subtest (WISC-IV)

A high degree of internal consistency ($r = 0.89$) test-retest reliability ($r = 0.92$) and interrater reliability ($r = 0.98$) has been reported for this subtest (Wechsler, 2004b). In terms of validity, the main concern in the context of the current study was that this test should measure consolidated factual knowledge and not be strongly influenced by episodic memory functioning. Kaufman and Flanagan, reviewing the different facets of intellectual functioning measured by different subtests of the WISC-IV, report that the Vocabulary subtest is a measure of factual knowledge (Kaufman & Flanagan, 2004). Furthermore, patients with dementia who suffer from severe episodic memory deficits can show preserved functioning on this subtest until their illness is fairly advanced, indicating that scores on the Vocabulary subtest are relatively independent of episodic memory functioning (Lezak et al., 2004; Strauss et al., 2006).

Comprehension Subtest (WISC-IV)

A high degree of internal consistency (r = 0.81) test-retest reliability (r = 0.82) and interrater reliability (r = 0.95) has been reported for this subtest (Wechsler, 2004b). In terms of validity, the main concern in the context of the current study was that this test should measure consolidated factual knowledge and not be strongly influenced by episodic memory functioning. Kaufman and Flanagan, reviewing the different facets of intellectual functioning measured by different subtests of the WISC-IV, report that the Comprehension subtest is a measure of general knowledge of shared social knowledge and rules governing social behaviour (Kaufman & Flanagan, 2004).

Category Fluency

Although the reliability of this test has not been researched in children, internal reliability coefficients in the region of 0.8, test-retest coefficients above 0.7, and interrater reliability coefficients above 0.98 have been reported in adults (Strauss et al., 2006).

In terms of validity, the main concern in the context of the current study was that these this test should measure consolidated factual knowledge and not be strongly influenced by episodic memory functioning. Lezak and colleagues, reviewing various studies of the validity of word fluency tests in adults, report that initial responses depend on rapid access of words from semantic memory with very little effort while later responses depend on effortful searching of semantic memory (Lezak et al., 2004). Convergent and discriminant validity analysis has shown that performance on word fluency tests is associated with attention, working memory and processing speed (Strauss et al., 2006). Furthermore, category fluency tests have been shown to be sensitive to deficits in semantic dementia whereas amnesic patients with severe episodic memory deficits can perform within the normal range on these tests (Strauss et al., 2006).

Episodic Memory

Children's Auditory Verbal Learning Test (CAVLT)

Because of the way that this test is administered (a free recall format and repeated learning trials), traditional internal and test-retest statistics are not considered appropriate measures of reliability for the CAVLT. Instead, the authors of the test assessed its reliability using generalisability theory[7]. The generalisability coefficients for different components of the CAVLT are reported below . Because of the skewed nature of the Recognition Memory score, a generalisability coefficient was not calculated for this test component.

Table 15: Generalisability Coefficients of Scores on the CAVLT*

Component	Generalisability Coefficient
Immediate Memory Span	0.62
Level of Learning	0.88
Immediate Recall	0.77
Delayed Recall	0.67

*Taken from(Talley, 1993)

In terms of validity, the main concern in the context of the current study was that this test should be a sensitive measure of episodic verbal learning. Factorial analysis of the CAVLT suggests the existence of a short-term memory factor which includes the Immediate Memory Span score and the interference trial, and a long-term memory factor made up of the remaining components. Convergent and discriminant validity analyses have shown that scores on the CAVLT show statistically significant but weak associations with measures of academic achievement, logical memory, and sustained

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[7] Generalisability theory uses Analysis of Variance methodology to analyse multiple sources of test score variance simultaneously. Generalisability coefficients, which are analogous to traditional reliability coefficients, are calculated by dividing the estimated variance attributable to subjects by the estimated variance attributable to subjects and error. A generalisability score of 0.60 or higher is regarded as demonstrating very good reliability (Talley, 1993).

attention, but are not strongly associated with verbal reasoning ability or measures of anxiety. Furthermore, the CAVLT has been shown to discriminate accurately between children with learning disabilities (who are likely to have problems with verbal learning) and control children (Talley, 1993).

Rey Complex Figure Test (RCFT)

A high degree of test-retest stability (coefficients are reported below) and interrater reliability (r = 0.93-0.99 for total raw scores). have been reported for all components of the RCFT (Meyers & Meyers, 1995).

Table 16: Reliability Coefficients of Scores on the RCFT*

Component	Test-retest Reliability (r)
Copy Accuracy	**
Immediate Recall	0.76
Delayed Recall	0.89
Recognition	0.87

*Taken from (Meyers & Meyers, 1995)

** Because the normative population tended to perform at ceiling levels for Copy Accuracy, a reliability coefficient was not calculated. Instead, mean Copy Accuracy scores were compared at time 1 and time 2 using a paired-samples t-test. There was no significant difference between the two Copy Accuracy scores(t = 1.11; p = 0.293), indicating stability over time.

In terms of validity, the main issue of concern in the context of the present study was that the RCFT should provide a measure of nonverbal episodic learning. Convergent and discriminant validity analyses have shown that performance on the RCFT is correlated more strongly with the Performance than with the Verbal subtests of the Wechsler Adult Intelligence Scale – Revised (WAIS-R). Similarly, scores on the RCFT are correlated with other measures of visual learning (e.g. the Benton Visual Retention Test) and with measures of visuo-spatial functioning (e.g. the Hooper Visual Organisation Test but not with language measures (e.g. sentence repetition or word fluency). Factor analysis of the different components of the RCFT reveals five factors:

Visuospatial Recall (Immediate and Delayed Recall measures), Visuospatial Recognition

(Total Recognition score and recognition false negatives), Response Bias (recognition

false positives), Processing Speed (time taken to copy the figure) and Visuospatial

Construction Ability (Copy Accuracy). Finally, the RCFT has been shown to

discriminate accurately between brain-injured patients with neuro-behavioural

impairment, patients with chronic psychiatric disorder, and healthy controls (Meyers &

Meyers, 1995).

4.3.1 Rivermead Behavioural Memory Test (RBMT)

Parallel-form reliability has been reported for both the adult version (correlations ranged

from 0.67 to 0.88 for different combinations of versions A, B, C and D, with all but one

being higher than 0.80) and the children's version (correlations ranged from 0.44 to 0.73

for different age groups) of the RBMT (Strauss et al., 2006). The lower correlations for

the children's version are thought to reflect ceiling effects in older age groups (Wilson et

al., 1991b).

In terms of validity, the main issue of concern in the current study was that this test

would give a measure of episodic memory functioning in an everyday context.

Summarising a large body of validity studies, Strauss and colleagues report the following

(Strauss et al., 2006): The RBMT has been found to be correlated with laboratory

measures of memory (e.g. Warrington Recognition Memory Test, Wechsler Memory

Scale), the Mini-Mental State Examination, and measures of attention, but not with the

Verbal Comprehension Index on the WAIS-R or with tests of executive functioning

(e.g. Stroop Test, Trail-making test), indicating that this test assesses specific memory

processes but is not dependent on remotely acquired, established memories.

Furthermore, poor performance on the RBMT has been noted in patients with a variety

of disorders known to affect episodic memory functioning, such as dementia,

diencephalic damage, exposure to neurotoxins, alcohol-related disorders, schizophrenia,

and traumatic brain injury. It also correlates well with therapist-observed rates of memory lapses and subjective ratings of memory problems by patients and relatives.

4.3.2 Everyday Memory Questionnaire

Drysdale and colleagues report a high level of internal consistency (Cronbach's alpha = 0.96) and test-retest reliability (r = 0.92). for this questionnaire. However, they note limited correlations with the Wide Range Assessment of Memory and learning (moderate correlations for children aged 10 but weak correlations for children aged 8 years) and a 40% rate of false positives in using it to discriminate between a sample of children with specific learning problems and healthy controls, indicating limited validity (Drysdale et al., 2004).

APPENDIX G: PERINATAL INFORMATION

Case #	Birth Weight (grams)	Gestational Age (weeks)	Apgar 1 minute	Apgar 5 minutes	Arterial pH	Seizures	Meconium in amniotic fluid	Resuscitation	HIE grade
1	3275	39.6	4	4	6.8	no	no	none	mild
2	2610	41.2	3	4	6.77	yes	yes	suction	moderate
3	3546	40.6	4	8	7.09	yes	yes	none	moderate
4	2855	40.4	2	3	6.9	yes	yes	suction	mild
5	2534	40.3	0	5	6.57	no	no	suction	mild
6	2880	40.1	2	3	7.07	yes	yes	none	mild
7	3740	40	0	2	7.34	yes	missing data	suction	mild
8	2690	38	8	9	n/a	no	no	none	mild
9	3020	38	3	6	7.21	yes	no	suction	mild
10	3360	40.3	3	7	6.87	yes	yes	none	mild
11	3120	40.2	1	5	7.09	yes	yes	suction	mild
12	2460	41	1	7	6.84	no	yes	none	mild
13	2400	38	2	8	6.9	no	no	suction	moderate

Perinatal Information continued

Case #	Birth Weight (grams)	Gestational Age (weeks)	Apgar 1 minute	Apgar 5 minutes	Arterial pH	Seizures	Meconium in amniotic fluid	Resuscitation	HIE grade
14	3735	41.2	5	8	7.25	yes	yes	none	moderate
15	2860	41.5	3	4	999	no	no	none	mild
16	2785	41.1	1	2	7.15	no	yes	suction	mild
17	3450	40+2	1	7	7.3	yes	no	none	moderate
18	2750	40.4	3	6	6.89	no	yes	suction	mild
19	4150	40	2	4	6.9	yes	no	suction	moderate
20	3415	37.1	2	3	6.78	yes	no	suction	mild
21	3440	41.5	1	4	7.19	yes	yes	suction	moderate
22	3490	40.4	6	8	n/a	yes	no	none	mild
23	3340	40.5	1	7	7.001	no	no	suction	mild

APPENDIX H: INDIVIDUAL PROFILES

Legend

Percentile Ranges:	Tests:
1 = Extremely Low	FSIQ = Full-Scale IQ (WISC-IV)
2 = Borderline	WISC SEM = Information, Vocabulary & Comprehension Composite
3 = Low Average	FLUENCY = Category Fluency Test (animals)
4 = Average	CAVLT = Immediate Memory Span (CAVLT)
5 = High Average	REY = Immediate Recall (RCFT)
6 = Superior	
7 = Very Superior	

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Case 2

Case 3

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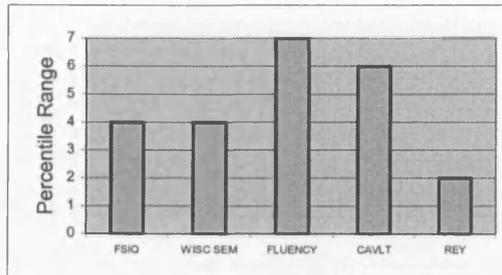
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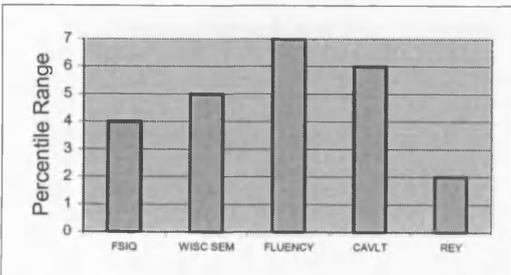
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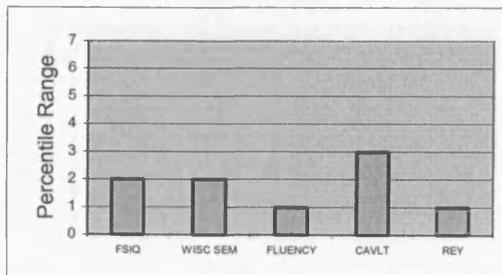
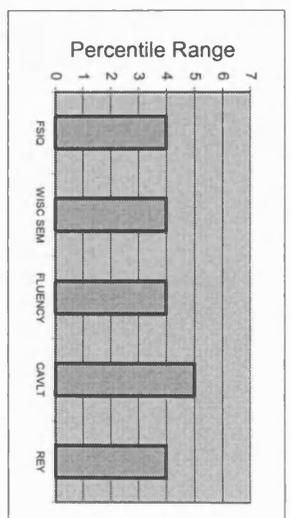

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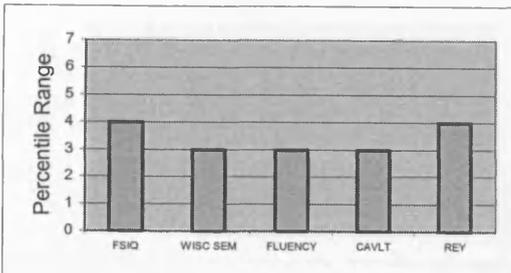
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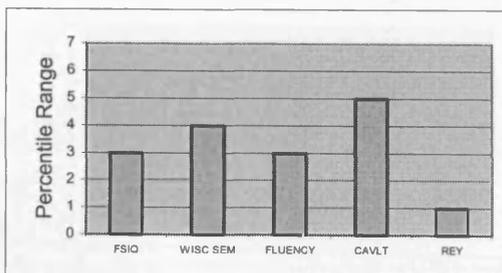
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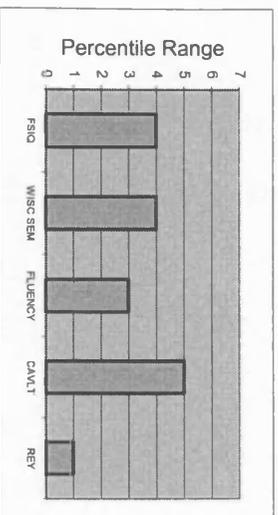
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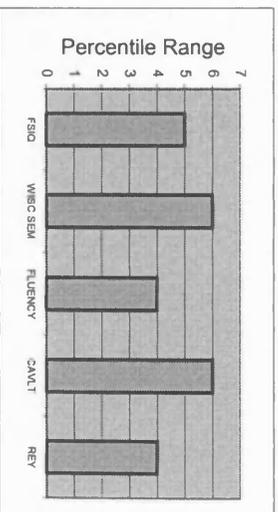
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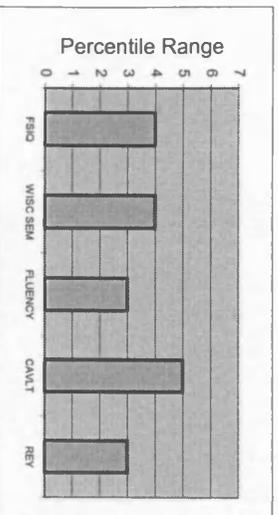
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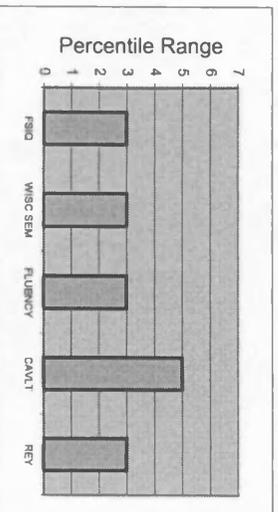
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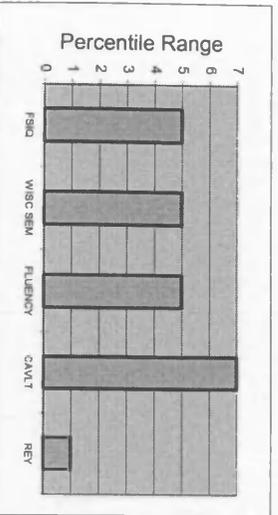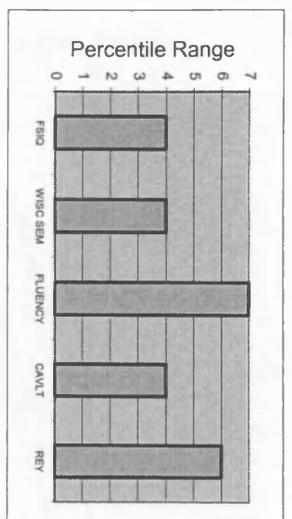
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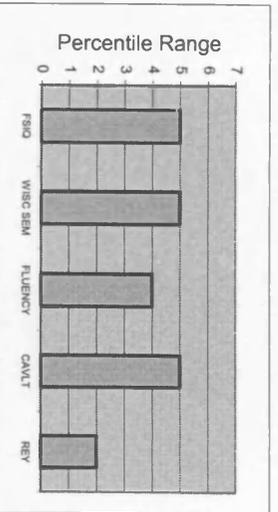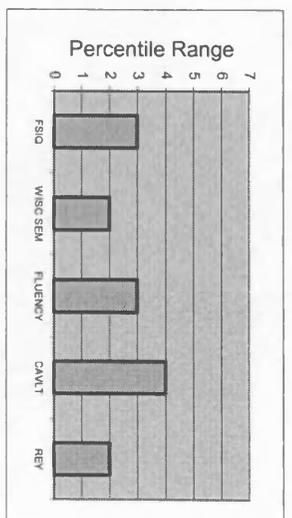
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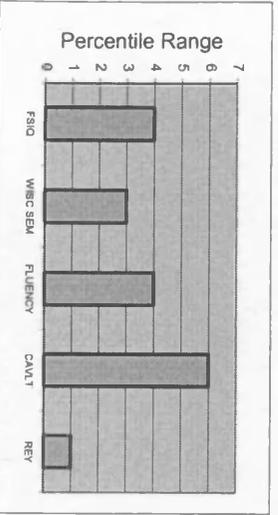
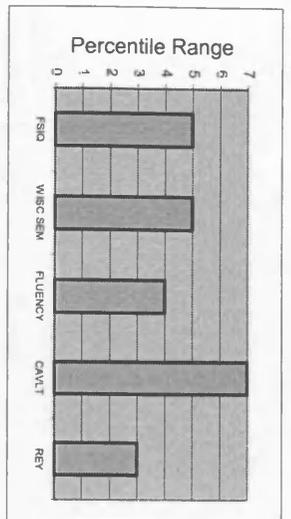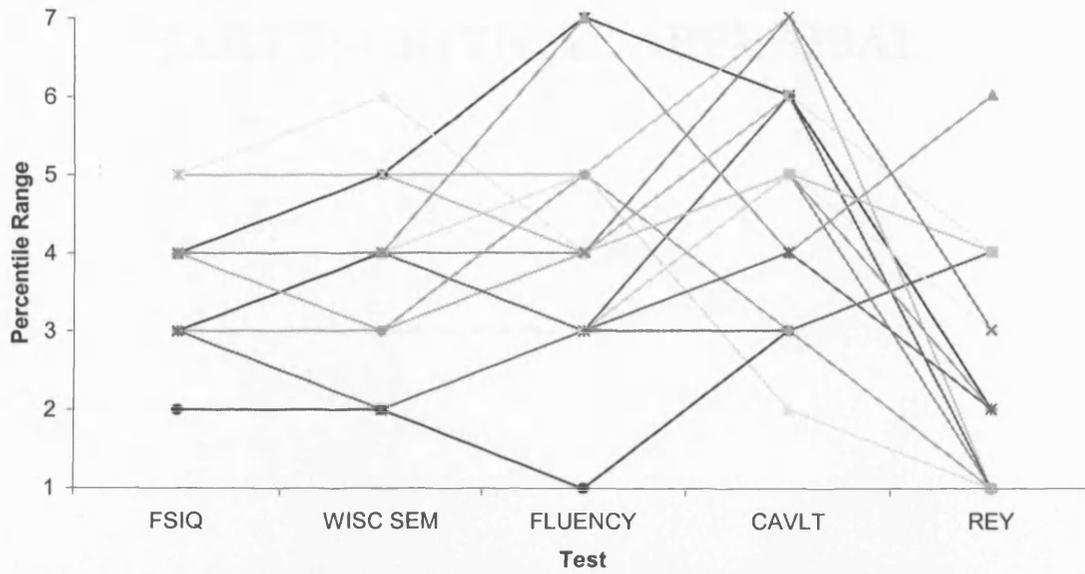Case 16
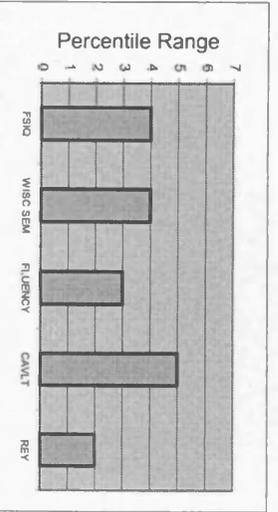
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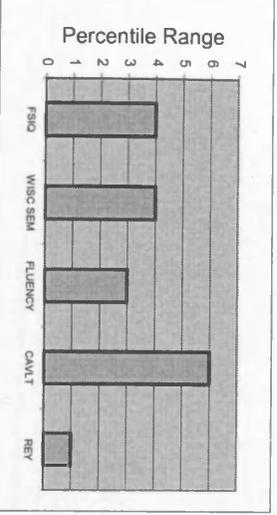
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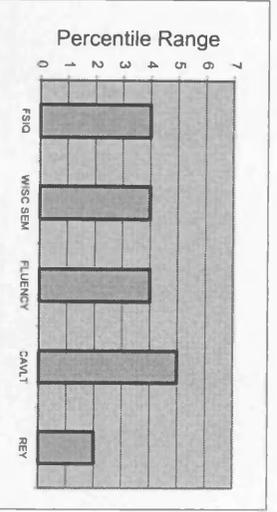
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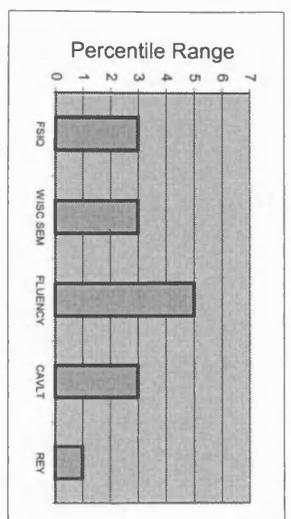
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Case 21

Case 22

Case 23

APPENDIX I: SUMMARY OF INDIVIDUAL PROFILES

Legend

Percentile Ranges:
1 = Extremely Low
2 = Borderline
3 = Low Average
4 = Average
5 = High Average
6 = Superior
7 = Very Superior

Tests:
FSIQ = Full-Scale IQ (WISC-IV)
WISC SEM = Information, Vocabulary & Comprehension Composite
FLUENCY = Category Fluency Test (animals)
CAVLT = Immediate Memory Span (CAVLT)
REY = Immediate Recall (RCFT)

PART 3: CRITICAL APPRAISAL

TABLE OF CONTENTS

OVERVIEW

In this part of the thesis, the empirical research project reported in Part 2 is reviewed. In Section 2 the research project is placed in its wider context and the influence of this context on its design, execution and interpretation is considered. In Section 3 some of the methodological an conceptual limitations of the project are evaluated and possible extensions to the research project that are suggested by these limitations are suggested. In Section 4 possible clinical and theoretical implications of this research project are explored. Finally, Section 5 contains some personal reflections on the process of conducting a research project.

1 SUMMARY OF THE EMPIRICAL STUDY

1.1 Theoretical Context

The debate between two different accounts of declarative memory, the Unitary Account and the Hierarchical Account, made up the theoretical background for this study. These two accounts offer different conceptualisations of the relationship between, and neuroanatomical basis of, episodic and declarative memory, and therefore explain the memory impairments seen in medial temporal lobe (MTL) amnesia in different ways. Proponents of the Unitary Account describe both episodic and semantic memory as subsystems of declarative memory, dependent on medial temporal lobe and midline diencephalic structures, with episodic memory additionally depending on the frontal lobes (e.g. Squire, Knowlton, & Musen, 1993; Squire & Knowlton, 2000; Zola Morgan & Squire, 1990). They explain MTL amnesia in terms of an overall impairment in declarative memory functioning. Proponents of the Hierarchical Account describe episodic memory as a memory system that is additional to declarative/semantic memory and uniquely dependent on the hippocampus (e.g. Mishkin, Suzuki, Gadian, & Vargha-

Khadem, 1997). They explain MTL amnesia in terms of dissociations between episodic/recall memory and semantic/recognition memory.

The Hierarchical Account is an extension of traditional Dual-Process models of episodic memory (e.g. Tulving, 1972; Tulving, 1993) and was developed specifically to explain the memory impairments found in Developmental Amnesia (DA). DA is a form of childhood-onset amnesia that is linked to selective hippocampal damage and that is characterised by severe deficits in episodic memory and recall memory in the context of average intellectual abilities and normal semantic memory and familiarity-based recognition memory functioning. Proponents of the Hierarchical Account explain DA in terms of the specialised role of the hippocampus in episodic memory functioning – since it is only the hippocampus that has been damaged, it is only episodic memory functioning that is impaired in DA (Mishkin et al., 1997; Vargha Khadem, Gadian, & Mishkin, 2001). Proponents of the Unitary Account have challenged this idea, arguing that the evidence for a specific episodic memory impairment in DA is limited and proposing instead that DA patients show impairments in both episodic and semantic memory functioning, due to the fact that damage to the hippocampus impairs the ability of medial temporal lobe structures to function together as a unified system (Squire & Zola, 1998).

Since there are relatively few patients with DA that have been studied so far, it is of interest to investigate memory functioning in populations who might be hypothesised to show similar memory impairments to those seen in DA. Such research would contribute to the debate between the Unitary and Hierarchical Accounts of declarative memory.

1.2 Aims and Hypotheses

Memory functioning was investigated in a sample of children aged 9-12 who had a history of perinatal hypoxic-ischaemic encephalopathy (HIE), a cluster of neurological symptoms that is indicative of the brain having suffered from oxygen deprivation (Volpe, 2001). It was hypothesised that these children would show memory impairments similar to those seen in Developmental Amnesia – that is, impaired episodic memory functioning and recall memory in the context of spared semantic memory functioning and recognition memory (Vargha Khadem et al., 2001) – because DA has been linked to selective hippocampal damage (Vargha-Khadem et al., 1997) and because the hippocampus has been shown to be especially vulnerable to damage during an episode of hypoxic-ischaemia (Berger & Garnier, 2000; Hill, 1991; Vannucci, 2000; Volpe, 2001).

1.3 Results

The results of this research project can be summarised as follows:

- The children generally showed intellectual abilities in the average range or above.

- They performed in the average range or above on all measures of semantic memory functioning and on the Children's Auditory Verbal Learning Test, a test of verbal episodic memory functioning.

- The children showed severe deficits on the Rey Complex Figure Test, a measure of nonverbal episodic memory functioning. Their performance was impaired both relative to normative data (participants typically scored around the 5th percentile) and relative to each individual's overall profile of functioning across the different measures administered.

- Almost half of the children scored in the "mild memory impairment" or "moderate to severe memory impairment" range on the Rivermead Behavioural Memory Test.

Furthermore, mean scores on the Everyday Memory Questionnaire were more than one standard deviation higher than normative data, indicating deficits in memory functioning. These results suggest that the children experience memory difficulties in daily life.

1.4   Interpretation

These results are not consistent with the pattern of memory deficits shown by DA patients. This is interpreted as reflecting the possibility that these children did not sustain a sufficient degree of hippocampal damage to cause such severe deficits. Such an interpretation is consistent with the finding that a hippocampal volume reduction of at least 20-30% is necessary to bring about the impairments seen in DA and that children who suffer milder damage than this (such as those who are born preterm) may not show any severe memory deficits (Isaacs et al., 2000; Isaacs et al., 2003).

Although these children do not show a pattern of memory impairments that is consistent with DA, they do show a severe deficit in nonverbal episodic memory. This is interpreted in terms of the dual role that the hippocampus plays in both spatial processing and memory (O'Keefe, 1993; O'Keefe & Nadel, 1978). It seems that the children sustained a sufficient amount of hippocampal damage to cause deficits in nonverbal/spatial episodic memory functioning but that their verbal episodic memory functioning remained unaffected. The exact neuroanatomical basis for this pattern of damage remains unclear.

The fact that these children show deficits on two measures of everyday memory functioning is consistent with previous studies that have investigated the outcome of perinatal HIE: Such studies have reported that these children score in the average range on tests of neuropsychological functioning but may show significant problems on such indicators of everyday functioning as educational attainments and parent and teacher

questionnaires (e.g. Marlow, Rose, Rands, & Draper, 2005; Robertson & Finer, 1993; Robertson, Finer, & Grace, 1989).

It was concluded that, overall, the memory deficits shown by these children are more consistent with the Hierarchical than the Unitary Account of declarative memory.

2 CONTEXT

Like all research, this project was conducted in a particular context which influenced its design and execution. There are two contextual aspects that are particularly salient: being part of a larger research project and undertaking a Doctorate in Clinical Psychology.

2.1   Context 1: Part of a Larger Project

This project was conducted as part of a larger project. The larger project involved relating memory functioning to structural neuroimaging and electroencephalography measurements in a sample of children with a history of perinatal hypoxic-ischaemic encephalopathy (reported here), a sample of children who suffered focal infarcts at birth, and a group of controls. I was involved in testing the first two groups of children. At the time of writing, the scanning of the clinical groups and the testing of the control participants were underway but not completed.

On the one hand, I could not have undertaken a research project of this scale on my own whilst completing clinical training, so being part of a larger project provided a great opportunity, particularly with regards to recruiting participants. On the other hand, being part of this larger project also constrained my own project in a number of ways, particularly its design as a descriptive study and the choice of test measures.

Design: The clinical groups had to be recruited and tested before the control group could be recruited, since controls would be matched to the cases on age, sex and intellectual

ability. This meant that I had to focus on a descriptive design for my research project. Whilst I believe that my project stands on its own without a control group, it would have been interesting to be able to compare the test performance of my sample to the test performance of healthy controls.

Measures: The results reported in Part 2 cover only two-thirds of the tests that were administered to participants as part of the bigger research project. The measures that were omitted from my project are those for which no robust normative data have been reported. These measures are appropriate in the context of a case-control study but not in the context of a descriptive study. Had I been conducting my research project on my own, I might have selected more measures of memory with robust normative data such as the Children's Memory Scale (Cohen, 1997), and left out the other measures.

2.2   Context 2: The Doctorate in Clinical Psychology

This research project was conducted in order to fulfil the requirements of the UCL Doctorate in Clinical Psychology. This influenced every stage of the research process by presenting a particular combination of constraints and demands. On the one hand, the time constraints of the course meant that I had to be realistic in choosing a project that I could undertake on a part-time basis over 2 years. On the other hand, the project had to be sufficiently sophisticated to demonstrate my competence as a researcher. This was part of the reason why I chose to be part of a larger research project, hoping that this would enable me to conduct more complex research than I might have been able to do on my own, without making the project unmanageable.

The context of my identity as a trainee clinical psychologist also influenced my research project. In particular, it affected my topic choice and my attitude to testing the participants and giving them feedback.

Topic choice: I was looking for a project that would enable me to pursue my interest in neuropsychology whilst also having the potential of being of some practical use to the participants I was seeing, both directly (providing neuropsychological testing that was of considerable interest to the families) and indirectly (developing our understanding of the outcome of perinatal hypoxia-ischemia).

Attitude to participants: My identity as a fledgling clinician certainly influenced my attitude towards my participants. I was conscious that my role as a researcher was very different from my role as a clinician. I was not providing the sort of detailed tailor-made assessment of each child's strengths and difficulties that I would have provided as part of a clinical service, since the research protocol had to be kept constant across participants. However, in my role as a trainee clinical psychologist, I also felt an obligation to make use of my clinical skills as far as possible. I spent more time than was perhaps necessary just to carry out the research protocol talking to the children and to their parents about any concerns they had, making follow-up telephone calls to discuss the feedback reports I had sent, liasing with schools and other professionals when parents were concerned about their children, etc. I found that it was possible to combine the role of clinician and researcher to some extent, but was somewhat uncomfortable with the fact that, since my primary relationship with the families was as a researcher, not a clinician, I could offer only very limited clinical input. Fortunately, being able to offer families a follow-up appointment with one of the clinical neuropsychologists on the research team went some way towards resolving this unease.

3 LIMITATIONS

In this section, some of the limitations of this research project are outlined and suggestions for extending the research to address these limitations are made.

3.1 Methodological Limitations

3.1.1 Measures: Psychometric Properties

There are a number of problems regarding the measures employed in this research project, two of which will be raised here. Firstly, there are no tests designed specifically to measure semantic memory functioning in children. This means that tests of educational attainments and intellectual abilities are generally used to gauge semantic memory functioning in children. Whilst it has been argued that intellectual ability and educational attainments *overlap* with semantic memory functioning by definition (Vargha Khadem et al., 2001; Vargha-Khadem et al., 1997), this paucity of specific measures of semantic memory means that there is a risk of *equating* semantic memory functioning with intellectual functioning. In other words, the constructs of intellectual ability and semantic memory risk being confounded.

Secondly, different memory tests are scored in different ways and do not all employ the same metric across different components of the same test, let alone across different tests. For example, the Children's Auditory Verbal Learning Test gives standard scores for all components except for the recognition component, which is simply classified as being within or below the normal range. This makes it difficult to compare recall memory and recognition memory on this test. The Rivermead Behavioural Memory Test used a system of profile scores and cut-off scores to describe impairment, which is more useful in a clinical context than in a research context where the focus is on differentiating between different levels of functioning that might all fall within the normal range.

In an ideal world, this research project would have employed a test battery that included a number of different tests of verbal and nonverbal episodic and semantic memory. All of these tests would have been scored using the same metric, preferably standard scores in order to make comparison with IQ measures easier, and all of these tests would have had robust norms. In the real world, a lack of suitable measures and difficulties in comparing functioning across different measures remain common limitations in developmental neuropsychology research.

3.1.2 Measures: Additional Information

Although it is probably not possible to obtain all of the information one might wish for in order to answer a particular research question, there are two specific areas in the context of this research project which warrant further data collection:

Neuroimaging: Memory functioning was investigated in children with a history of perinatal hypoxic-ischaemic encephalopathy because it was proposed that they would be particularly vulnerable to selective hippocampal damage and therefore to impairments in episodic and recall memory. The fact that there are no neuroimaging data available for this sample at this point means that the damage to the hippocampus is inferred from the fact that the hippocampus is particularly vulnerable to oxygen deprivation in HIE, rather than being confirmed by neuroimaging. It is possible that these children sustained some hippocampal damage but that this damage did not reach the crucial level of 20-30% atrophy that appears to be necessary to bring about the pattern of impairments seen in Developmental Amnesia (de Haan et al., 2002; Isaacs et al., 2003). It is also possible that these children *did* sustain such a level of damage but do not show the memory impairments characteristic of Developmental Amnesia for some other reason. Until neuroimaging data are available and can be related to functional impairments, the picture will remain incomplete.

Everyday memory functioning: The results of this study suggest that the children may experience difficulties with memory functioning in the context of daily life, even though these difficulties may not be readily apparent on laboratory measures. It is possible that the children are able to compensate for certain memory difficulties when they are in a testing environment since this environment is relatively free from distractions and they receive one-to-one attention, and that these difficulties only become apparent in the context of the demands of the real world. Whilst the Rivermead Behavioural Memory test and the Everyday Memory Questionnaire go some way towards giving an indication of memory functioning in daily life, it would be interesting to obtain more information about the children's memory functioning at home and at school, perhaps by means of parent and teacher interviews and observations of the children.

3.1.3 Design and Analysis

This study was descriptive in its design. Whilst this was partly due to the constraints of being part of a larger research project (see Section 3.1), this approach was justified by the fact that the impairments seen in Developmental Amnesia, and which were hypothesised to exist in this sample, are readily apparent relative to normative data. However, a number of studies investigating the long-term outcome of mild to moderate perinatal HIE have shown that these children perform in the average range on various neuropsychological test measures (including general intellectual ability and memory functioning) but that their scores are still significantly lower than those of control participants (Mañeru, Junqué, Botet, Tallada, & Guardia, 2001; Marlow et al., 2005; Robertson & Finer, 1993; Robertson et al., 1989; Viggedal, Lundälv, Carlsson, & Kjellmer, 2002). It is possible that a case-control paradigm would have enabled the detection of deficits in functioning in this sample that are not apparent when functioning is being compared to normative data.

The data analysis techniques used in this research project were limited to a description of average scores for the sample as a whole and a description of individual patterns of functioning. This meant trying to find consistent patterns in functioning across a whole range of different measures. It would have been interesting to construct a composite score for episodic memory and a composite score for semantic memory functioning in order to be able to compare these constructs more clearly. Such composite scores would consist of some sort of average of all measures of episodic memory (the Children's Auditory Verbal Learning Test and the Rey Complex Figure Test) and semantic memory respectively (the Similarities, Information and Comprehension subtests from the WISC and the Category Fluency Test). The composites would have to be constructed on the basis of the same metric – percentile scores or Z-scores, for example – so that one could compare children's scores on the episodic composite with their scores on the semantic composite.

This analysis was not undertaken for various reasons: Firstly, the different scoring systems and variations in the metric used by different tests meant that combining them into a single measure was not straightforward and risked compromising their psychometric properties. Secondly, combining the two measures of episodic memory functioning would have obscured important differences between verbal and nonverbal tests. Finally, even if the construction of these composites were achieved and it were shown that the children in this sample consistently scored higher on the semantic composite than on the episodic composite, it would be difficult to know how to interpret this result, since it would not be known whether or not such a pattern exists in controls.

3.2   Conceptual Limitations

For the purposes of this research project, the Hierarchical Account of declarative memory was used as a theoretical framework to guide both the design of the study and the interpretation of the results. However, the Hierarchical Account has certain limitations which mean that it cannot fully explain the results of this study. Firstly, it does not differentiate between verbal and nonverbal episodic memory, so that it cannot account for the fact that the children in this sample showed normal verbal episodic memory but impaired nonverbal episodic memory. An attempt has been made to use the Cognitive Map theory of the role of the hippocampus in spatial processing in order to account for this finding, but at the moment there is some tension between those accounts of hippocampal functioning that emphasise its role in memory functioning and those accounts that emphasise its role in spatial processing (Eichenbaum, Otto, & Cohen, 1992).

Secondly, it is not clear from the Hierarchical Account what the consequences of a milder degree of damage than the 20-30% hippocampal volume postulated to be necessary for causing the impairments seen in Developmental Amnesia might be. The results of the present study suggest that a milder degree of hippocampal damage might result in impairments in episodic memory that are specific to nonverbal material. However, the neuroanatomical basis for such a phenomenon is not clear.

A possible extension to the Hierarchical Account, based on the results of this study, might be made as follows: The hippocampus is uniquely involved in episodic memory functioning, *particularly nonverbal episodic memory*. Damage to the hippocampus that presents as a volume reduction of 23-30% or more results in severe impairments in episodic memory functioning *and milder forms of damage may affect nonverbal episodic memory functioning but leave verbal episodic memory functioning intact*. Such an extension to the

Hierarchical Account would, of course, need to be tested empirically, especially because the neuroanatomical basis for postulating that the hippocampus plays different roles in verbal versus nonverbal episodic memory functioning is unclear.

4 IMPLICATIONS

This research project has interesting theoretical and clinical implications. It implies that the Hierarchical Account of declarative memory provides a more parsimonious explanation of the memory deficits that may be associated with perinatal hypoxic-ischaemic encephalopathy than the Unitary Account does. It also suggests that the Hierarchical Account should perhaps be extended to take into account a possible relationship between mild hippocampal damage and dissociations between verbal and nonverbal episodic memory functioning.

Clinically, this research has implications for the follow-up care of children who experience perinatal HIE. If these children do not experience gross neurological disabilities, they are generally considered to be "normal" and there is little provision of routine neuropsychological assessment. The results of this study suggest that such follow-up care is extremely important, both in order to assess neuropsychological functioning and in order to provide appropriate support to help these children cope with any deficits they might have.

Furthermore, the fact that these children generally perform in the normal range on laboratory tests of memory but show difficulties in everyday functioning suggests that they have the resources to benefit from strategies aimed at improving their memory functioning at home and in the classroom. Such strategies might include educating parents and teachers about the child's difficulties so that memory problems are not interpreted as bad behaviour, making use of intact semantic memory abilities to help the child learn episodic information by rote, and providing external frameworks such as

timetables that help the child to mark his place in the environment and over time (Rankin & Hood, 2005).

Finally, having a baby who suffers from perinatal HIE is an extremely stressful experience for parents and they generally want to know what the likely outcome will be for their child. This project contributes to the body of literature on which we can base such predictions.

5 PERSONAL REFLECTION

In this section, I would like to consider my research project in terms of a personal learning process.

I was surprised to find that this research project taught me a lot about time management and motivation, which I had previously considered as personal strengths. The challenge of juggling clinical work, academic work and research work was far greater than I had anticipated. I have learned that estimating how long it is going to take to complete a piece of work is a real weakness of mine and that what feels like a gross over-estimation is likely to be accurate. I have learned that I do not work at a constant rate but that this is okay. I can spend hours or days apparently daydreaming and not achieving very much at all, which used to throw me into a state of panic. However, I have learned that I need this daydreaming time because it is a time of incubating ideas and reaching a state of clarity that then allows me to do a large amount of work in one big burst. Perhaps working at a more constant rate would have made my time management difficulties easier – it is very unsettling to be in a daydreaming phase when you know you only have one day a week to work on your research – but I don't think I want to alter my style. There is a buzz in the burst-of-work phase that I just do not want to give up.

Related to the issue of time management is the issue of being able to narrow down the focus of the research topic in order to delineate a project that can realistically be completed given the time constraints of the D Clin Psy qualification. I spent nearly as much time discarding certain avenues of research as I did writing about the ones I chose to focus on. For the review paper, there was the possibility of looking at memory development in infants and children and to consider whether episodic and semantic memory capacities develop at different rates; there was the vast body of literature on animal models of memory and a similarly vast body of literature on amnesia in human adults; there were almost countless other theories of amnesia that might at least have been mentioned... This list could go on for pages. Much of the actual "thinking" work (as opposed to the "doing" work of data collection) involved developing a coherent argument and then deciding what was relevant to that argument and what was not.

I have learned to accept a certain amount of uncertainty in research work. I am unsettled by uncertainty and had previously laboured under the illusion that all of the anxiety-provoking uncertainty of clinical work would be absent in the clear, neutral, objective world of scientific research. But I have come to realise that there is never a single, *right* way of asking a research question, choosing measures and data analysis techniques or developing an interpretation. All I can hope for is a way of approaching my research that I can justify, and even that will never necessarily be *the right* way. I still hope that this level of subjectivity is a feature of psychological research, and that somewhere in the pure, certain world of, say, mathematics or theoretical physics, it is possible to be certain that one is going about one's research in *the right* way. My mathematician and physicist friends point out that there is no such objectivity in their research but are content to leave me my comforting illusion.

I have learned how satisfying research can be. It was hugely satisfying to absorb a large amount of literature on new, challenging and somewhat unrelated topics, to digest this knowledge and to come up with a coherent way of relating it to an empirical question. Completing my data collection and seeing all of my variables entered into SPSS was also a very satisfying experience. Finding interesting trends in my results and relating these trends back to the theory that had gripped me in the first place was far more exciting than I had dared hope. There was a heady challenge in using my results to suggest extensions to this theory. And I am anticipating that seeing all of my work printed out and bound will be the most satisfying experience of all.

None of these things were new to me, exactly. I already knew before I undertook this project that time management is important and made easier by the clear delineation of a topic, that neutrality and objectivity in science have been dismissed as utter fiction by some more radical critics of empiricism, and that research can be a satisfying experience. But going through the process of doing a research project made these pieces of knowledge real. I suppose they became part of my store of episodic memories, linked to specific autobiographical events, rather than being abstract, acontextual pieces of factual knowledge.

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