Dissociations in Memory: A Study of Developmental Amnesia

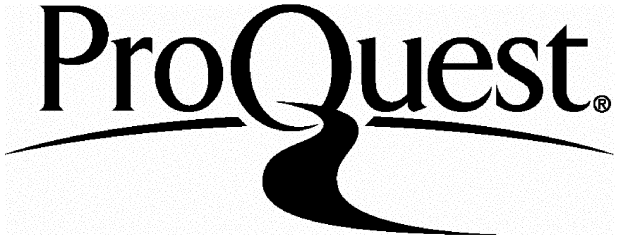
Anna-Lynne Ruth Adlam

Institute of Child Health

University College London

Thesis submitted for examination for the Ph.D. degree of the University of London

June, 2003



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ABSTRACT

Bilateral damage to the medial temporal lobes (MTL) is associated with declarative (explicit) memory deficits. However, there is some debate as to whether the MTL functions as a unified system supporting both episodic (event) and semantic (factual) memory (e.g. Squire and Zola, 1998), or as a dissociable system, such that different aspects of declarative memory are supported by distinct regions within the MTL (e.g. Mishkin et al., 1997; 1998; Aggleton and Brown, 1999).

Previous studies of patients with bilateral hippocampal pathology sustained in childhood have reported a selective impairment in episodic memory, and a relative sparing of semantic memory (e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000). This profile, termed developmental amnesia (DA), provides some support for the hypothesis of a dissociable MTL system.

This thesis investigates that hypothesis further. The performance of twelve patients with bilateral hippocampal pathology sustained in childhood is compared to that of a group of twelve age-, sex-, and IQ-matched controls using a combination of standardised tests and experimental measures to investigate dissociations between episodic and semantic memory, recall and recognition, and recollection and familiarity. In addition, functions presumed to be subserved by the frontal lobes and the basal ganglia are assessed using measures of executive function and motor skill learning, respectively.

Bilateral hippocampal pathology was confirmed using structural magnetic resonance imaging techniques, including hippocampal volumetrics, and voxel-based morphometry (VBM). Analyses of VBM data revealed morphological abnormalities in additional regions, including the thalamus and the white matter of the temporal lobes and near striatal areas. There was no evidence of basal ganglia structural abnormality, consistent with preserved motor skill learning.

The neuropsychological findings offer some support for the hypothesis that the MTL system is dissociable, in that episodic memory was more impaired than semantic memory, and recall was more impaired than recognition. However, recollection was not more impaired than familiarity-based recognition relative to controls. No impairments were found on measures of executive function, suggesting that the disproportionate episodic and recall deficits are not attributable to additional frontal lobe dysfunction.

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1 GENERAL BACKGROUND

The studies reported in this thesis set out to further characterise three dissociations in memory in a group of patients with developmental amnesia associated with bilateral hippocampal pathology sustained early in development. These dissociations are between episodic and semantic memory, recall and recognition memory, and recollection and familiarity.

This introductory chapter begins with a description of memory, differentiating between short-term and long-term memory, declarative and nondeclarative memory and episodic and semantic memory. The neuroanatomy thought to support long-term declarative memory is then described, as are theories of long-term declarative memory organisation. Next, evidence from human and animal experimental studies is presented in relation to theories of long-term declarative memory organisation, particularly with respect to dissociations between episodic and semantic memory, recall and recognition memory, and recollection and familiarity. In the last part of this chapter, the development of the neuroanatomical structures supporting memory and the developmental trajectory of memory function will be described. Finally, findings from animals and patients with hippocampal injury sustained early in development will be discussed in relation to theoretical models of long-term declarative memory organisation, and the general aims and predictions of the studies reported in this thesis will be outlined.

1.1 WHAT IS MEMORY?

Memory is the cabinet of imagination, the treasury of reason, the registry of conscience and the council chamber of thought. Saint Basil

Memory is the capacity to learn from experience. It is not the function of a unitary system but of many systems that vary in the type of information they store and the length of time they store it (e.g. for a discussion see Baddeley, 1997; but see Roediger *et al.*, 1990). Many theorists and clinicians differentiate between short-term and long-term memory (e.g. James, 1890; Atkinson and Shiffrin, 1968; for a discussion see Baddeley, 1997) as well as declarative (explicit) and nondeclarative (implicit) memory (e.g. Cohen and Squire, 1980; Schacter, 1987).

Short-term memory refers to memories that last for a few seconds and long-term memory refers to the ability to process, store and retrieve information for long periods of time e.g. hours, days or years (e.g. Baddeley, 1997). For the purpose of this thesis, short- and long-term memory are considered as separate memory systems; short-term memory is considered to have a limited storage capacity and is well described by the multi-component working memory model (Baddeley and Hitch, 1974). It is suggested that perceptual information passes into short-term memory before it can be encoded into long-term memory, and information from long-term memory can feed back to short-term memory; however, information can be retrieved from either system independently (e.g. Baddeley, 1997).

Information is encoded, stored and retrieved either with (declarative) or without (nondeclarative) conscious awareness (e.g. Schacter, 1987). Long-term nondeclarative memory includes skill learning (e.g. riding a bike) and priming (e.g. seeing the word 'memory' can influence the choice of word used to complete the word fragment 'Mem.....', that is the participant would be primed to choose 'memory' as opposed to 'Memphis'), and is supported by brain structures other than the medial temporal lobes (MTL) and diencephalon (see Figure 1:1; e.g. Squire and Zola-Morgan, 1991). Skill learning involves slow and gradual learning, and priming is modality-specific suggesting that it is inflexible (for a review see Schacter, 1995). Long-term declarative memory comprising episodic and semantic memory, is dependent on the medial temporal–diencephalic circuit (see Figure 1:1; e.g. Squire and Zola-Morgan, 1991). Declarative

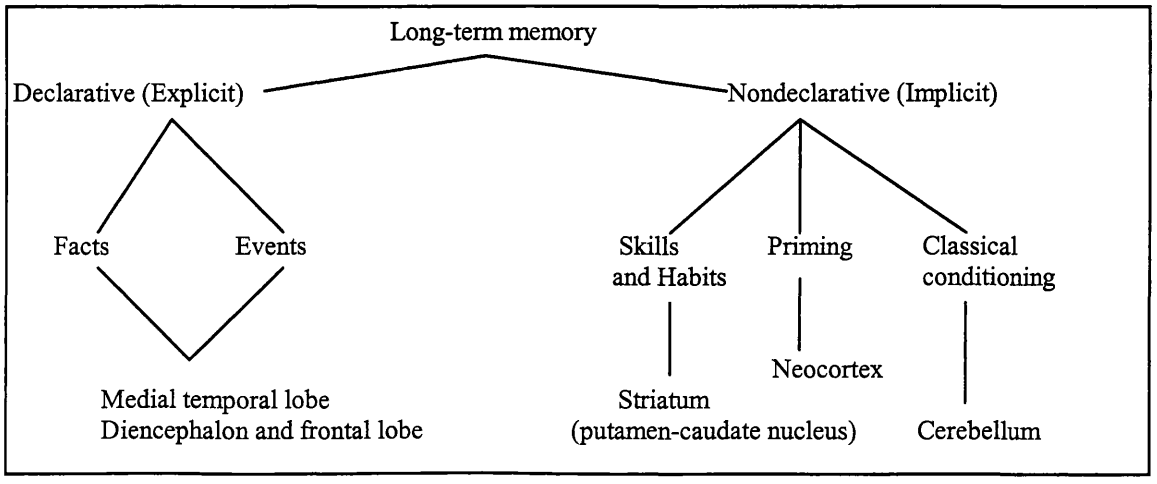
memory can be acquired after a single study episode, and is flexible in that retrieval is not dependent on specific features of the study episode being present.

Episodic memory is memory for contextually bound experiences that occur in a particular time and place (e.g. remembering climbing the Eiffel tower last spring), whereas semantic memory is memory for general knowledge (e.g. knowing that Paris is the capital of France), and as such is context-free, including information such as vocabulary and facts about the world and oneself (Tulving, 1972).

More recently, Wheeler *et al.* (1997) proposed a further distinction between episodic and semantic memory. Episodic memory is to do with one's 'autonoetic' (self-knowing) awareness of one's experiences, allowing both backward remembering (retrospective memory) and forward future-planning (prospective memory). This definition emphasises the role of self, autonoetic awareness, and a subjective sense of time, such that episodic retrieval is accompanied by recollection of the experienced event. Semantic memory, on the other hand, is to do with 'noetic' awareness of the existence of the world, including objects, events and other regularities that are independent of self, autonoetic awareness and a subjective sense of time, and retrieval is accompanied by a sense of knowing.

Autobiographical memory is part of the declarative memory system and can be either episodic or semantic depending on the contribution of self, autonoetic awareness and a subjective sense of time (e.g. Tulving, 2001).

Figure 1:1 A taxonomy of mammalian long-term memory systems (adapted from Squire and Zola-Morgan, 1991)



1.2 NEUROANATOMY OF THE MTL-CORTICAL MEMORY SYSTEM

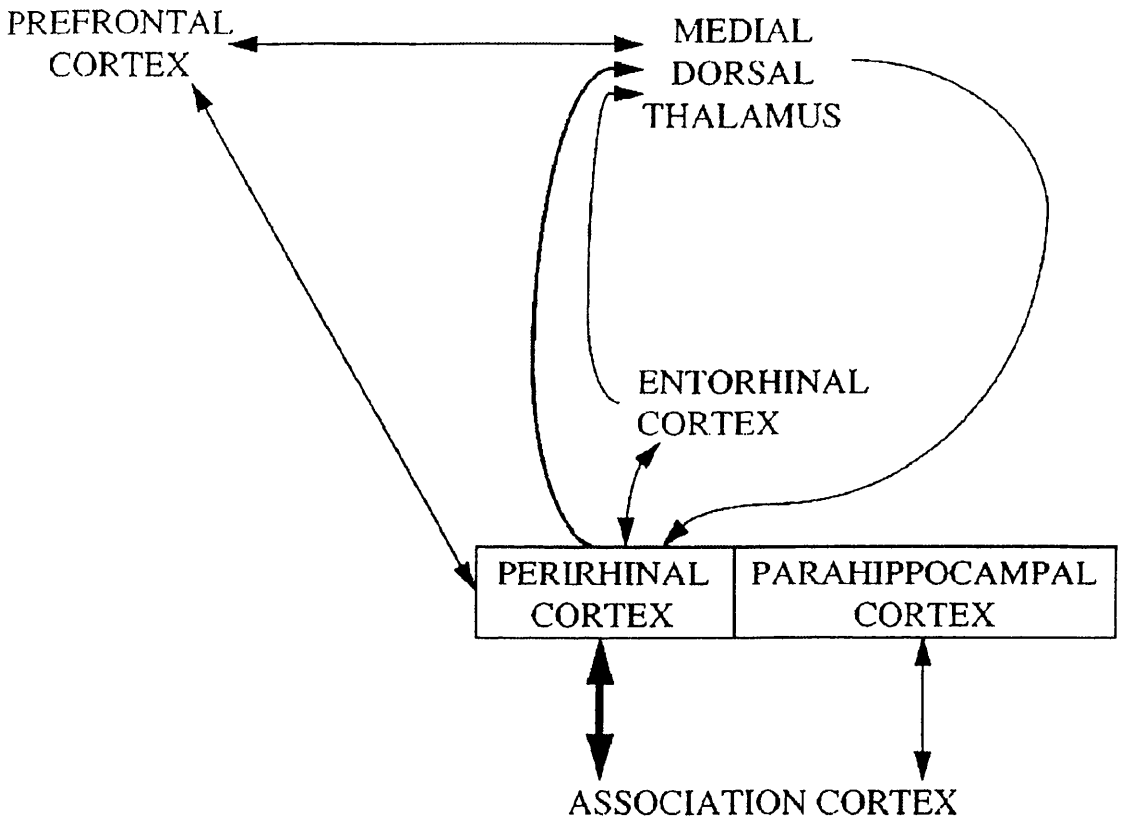
As shown in Figure 1:1, declarative memory is supported by the MTL-cortical memory circuit. Much of the characterisation of the MTL-cortical connectivity has been carried out in the rat and monkey. Rat hippocampal connectivity is largely homologous to that observed in the monkey and by, extension to that in humans. The main components of the MTL-cortical circuit are the hippocampus (cornu ammonis subfields CA1-4 (also known as the hippocampus proper), dentate gyrus, and subiculum), the parahippocampal region (entorhinal, perirhinal and parahippocampal cortices), the medial diencephalon (mamillary bodies and medial thalamus) and the prefrontal cortex. The three-layered cortex of the CA subfields and the dentate gyrus is continuous with the subiculum, which has four, five then six layers as it merges with the parahippocampal region.

Within the hippocampus there is a system of unidirectional connections; the 'trisynaptic' circuit (Swanson and Cowan, 1977; Amaral and Insausti, 1990; Amaral and Witter, 1995). The granular cells of the dentate gyrus send mossy fiber projections to CA3. Pyramidal cells in CA3 give rise to Schaffer collaterals, which provide a major input to CA1. Finally, pyramidal cells of CA1 project to the subiculum, which constitutes the major output structure of the hippocampal formation. Information enters the hippocampus via the parahippocampal region as described below.

The parahippocampal region consists of three distinct areas; the perirhinal cortex, the parahippocampal cortex and the entorhinal cortex. The perirhinal cortex is a polymodal information area and receives two-thirds of its reciprocal projections from the visual association areas TE and TEO (Van Hoesen, 1982; Suzuki and Amaral, 1994b). The perirhinal cortex also receives input from other association areas, including the auditory association areas on the superior temporal gyrus as well as powerful polymodal inputs from the parahippocampal cortex (Suzuki, 1996) and orbitofrontal cortex (Carmichael and Price, 1995; Suzuki 1996). The perirhinal cortex provides stimulus quality information indirectly to the hippocampus via the entorhinal cortex (reciprocal connections, Insausti *et al.*, 1987; Suzuki and Amaral, 1994a), directly to the hippocampus (Suzuki and Amaral, 1990; Witter and Amaral, 1991, but see Canning and Leung, 1997) and directly to the medial dorsal nucleus of the thalamus (Aggleton *et al.*, 1986; Russchen *et al.*, 1987), as it receives most of its connections from the ventral processing stream (Mishkin *et al.*, 1997). The medial dorsal nucleus of the thalamus has connections extending to the dorsolateral prefrontal cortex, the ventromedial prefrontal

cortex and the orbitofrontal cortex, and thus forms a perirhinal-thalamic-frontal circuit (Figure 1:2, Aggleton and Brown, 1999).

Figure 1:2 Schematic diagram of the main components of the perirhinal-cortical circuit (Aggleton and Brown, 1999)



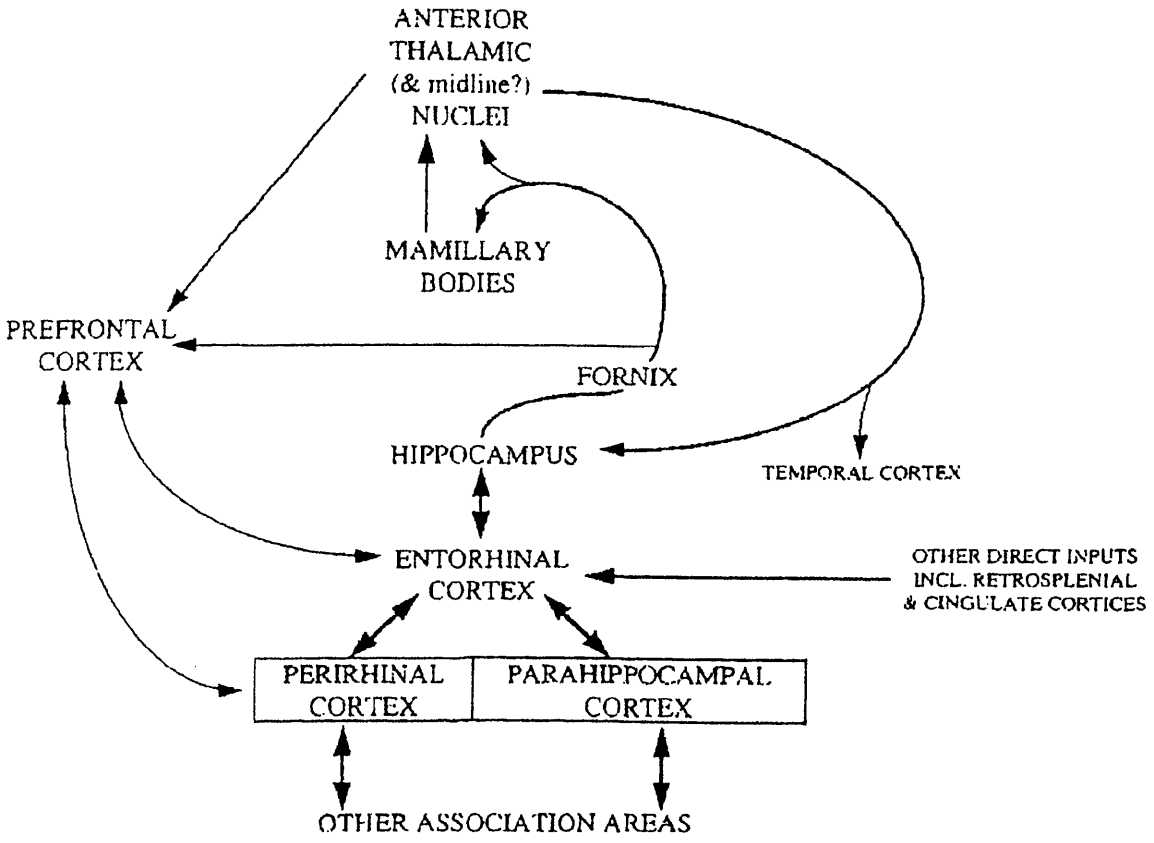
The parahippocampal cortex is also a polymodal information area and receives most of its reciprocal projections (Van Hoesen, 1982; Lavenex *et al.*, 1998) from posterior parietal cortex, retrosplenial cortex, dorsolateral prefrontal cortex and the dorsal bank of the superior temporal sulcus (Suzuki and Amaral, 1994b). As the parahippocampal cortex receives most of its inputs from the dorsal stream it is thought to provide stimulus location information directly to the perirhinal cortex and indirectly to the hippocampus via the entorhinal cortex (reciprocal connections, Suzuki and Amaral, 1994a).

The entorhinal cortex receives two-thirds of its reciprocal connections from perirhinal cortex and parahippocampal cortex (Insausti *et al.*, 1987) and thus provides a convergence of stimulus quality and location information to the hippocampus via the

perforant path (reciprocal connections, Amaral *et al.*, 1987; Witter and Amaral, 1991). There are also dense projections from the entorhinal cortex to the lateral dorsal nucleus of the thalamus and lighter projections to the anterior and medial dorsal nuclei of the thalamus (Aggleton *et al.*, 1986; Aggleton and Saunders, 1997). The entorhinal cortex also receives projections from superior temporal gyrus, insular cortex, orbitofrontal cortex, cingulate cortex and retrosplenial cortex (Insausti *et al.*, 1987).

As described above, the hippocampus receives inputs mainly from the entorhinal cortex (Amaral *et al.*, 1987; Witter and Amaral, 1991). Further inputs include direct innervation from the perirhinal (Suzuki and Amaral, 1990; Witter and Amaral, 1991) and retrosplenial (Wyss and Van Groen, 1992) cortices, and cholinergic innervation from the medial septum via the fornix (Aggleton and Brown, 1999). According to Papez (1937) the hippocampal formation projects to the mamillary bodies, which in turn project to the anterior thalamus, onto the cingulate cortex, back to the parahippocampal gyrus and the hippocampal formation, forming the 'Papez circuit'. Although the circuit has been refined based on subsequent anatomical findings (e.g. Shibata, 1992; Amaral and Witter, 1995; Van Groen and Wyss, 1995), the major links of the circuit remain the same. For example, the subiculum projects via the fornix to the mamillary bodies and anterior thalamus (e.g. Aggleton *et al.*, 1986). The mamillary bodies connect to the anterior thalamic nuclei, via the mamillothalamic tract, which in turn project to the anterior and posterior cingulate (Musil and Olsen, 1988), retrosplenial cortex (Morris *et al.*, 1999), and subicular areas (Aggleton *et al.*, 1986). The cingulate cortex, with its anterior thalamic inputs, projects to the prefrontal cortex (Musil and Olsen, 1988) and thus forms the hippocampal-thalamic-frontal circuit (see Figure 1:3, Aggleton and Brown, 1999). The hippocampus also projects directly to the orbitofrontal and medial prefrontal cortices (Barbas and Blatt, 1995; Insausti and Munoz, 2001), perirhinal cortex, posterior parahippocampal cortex, retrosplenial cortex (Insausti and Munoz, 2001) and amygdala (e.g. Witter *et al.*, 1989), and indirectly via the entorhinal cortex to the perirhinal and parahippocampal cortices (Suzuki and Amaral, 1994a).

Figure 1:3 Schematic diagram of the main components of the hippocampal-cortical circuit (Aggleton and Brown, 1999)



The thalamus connects to the frontal lobes via the cingulate but connections also arise from the medial dorsal nuclei (Fuster, 1997). These have topographically organised connections with the prefrontal cortex; for example, the medial (magnocellular) part of the medial dorsal nucleus connects with the orbital and rostral parts of the prefrontal cortex, whereas the lateral (parvocellular) part is connected to dorsal and dorsolateral prefrontal areas (Groenewegen, 1988).

The prefrontal cortex constitutes approximately one third of the entire mass of the human brain (Fuster, 1989; 1997) and is situated in front of the motor and premotor cortices (Brodmann areas 4 and 5) in the frontal lobe (Fuster, 1989; 1997). The prefrontal cortex includes (Petrides and Pandya, 1994; Fuster, 2001): (i) the ventromedial frontal cortex (including the orbitofrontal cortex (Brodmann areas 11, 13, 14, and ventromedial part of 10) and the anterior cingulate cortex (Brodmann areas 24, 25, and 32)), (ii) the dorsolateral frontal cortex (Brodmann areas 8, 9, 46, and dorsal part of 10), and (iii) the

inferior frontal cortex (or inferior frontal convexity: Brodmann areas 12, 45, and ventrolateral part of 10).

The prefrontal cortices are highly connected with each other and with posterior brain regions, and therefore are thought to play a supervisory role in cognitive functions, such as memory (Wheeler *et al.,* 1995; Desgranges *et al.,* 1998; Düzel *et al,* 1999) and attention (Stuss *et al.,* 1995; Shallice and Burgess, 1998). As already discussed, connections exist between the hippocampus and the prefrontal cortex, particularly the ventromedial and orbitofrontal cortices (Barbas and Blatt, 1995; Carmichael and Price, 1995; Cavada *et al.,* 2000). The parahippocampal region and thalamus also connect with the orbitofrontal and lateral prefrontal cortices (Carmichael and Price, 1995; Fuster, 1996; Cavada *et al.,* 2000) and the retrosplenial cortex connects with the mid-dorsolateral prefrontal cortex (Brodmann areas 9 and 46; Morris *et al.,* 1999). Most of these connections are reciprocal, except that there is evidence for only a weak direct connection between the orbitofrontal cortex and the hippocampus (Cavada *et al.,* 2000).

In addition to the main connections just described, the perirhinal, parahippocampal and entorhinal cortices (Van Hoesen *et al.,* 1981) along with the hippocampus (Witter and Groenewegen, 1992) project to the striatum (caudate and putamen) thus forming a medial temporal lobe-striatal pathway.

In summary, structures within the MTL are highly interconnected with each other and with extra-MTL structures, forming a network of connections. This MTL-cortical circuit is thought to support declarative memory and, as will be described in the following sections, damage to this circuit is associated with amnesia. Although the role of the MTL-cortical circuit in memory is well established, there exists a debate as to what role specific components of the circuit play in memory. It is this controversy that will be discussed in the following sections.

1.3 HOW ARE MEMORIES FORMED AND RETRIEVED?

Recent attempts to delineate the cellular mechanism of memory formation are based on the theory of cell communication proposed by Hebb in 1949. Hebb proposed that the synapses in a particular path become functionally connected to form a cell assembly. "When an axon of cell A is near enough to excite cell B and repeatedly or persistently

takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased" (Hebb, 1949, p. 62).

Recent connectionist models of memory function support the notion that cell assemblies form long-lasting memories. However, there remains a debate as to whether cell assemblies and therefore, memory traces can be activated independent of the hippocampus (Alvarez and Squire, 1994; McClelland *et al.*, 1995; Murre, 1997; Nadel *et al.*, 2000; Nadel and Bohbot, 2001; for a review see O'Reilly and Rudy, 2000). Connectionist models propose the existence of two learning systems that interact, the slow neocortical learning system and the rapid hippocampal learning system. Some models suggest that both semantic and episodic memories initially depend on the hippocampus for storage but gradually with consolidation become independent of the hippocampus relying on the neocortex for storage and retrieval (e.g. McClelland *et al.*, 1995). Others suggest that episodic memory is always dependent on the hippocampus for storage and retrieval (Nadel *et al.*, 2000; Rosenbaum *et al.*, 2001).

If the hippocampus plays a time-limited role in memory retrieval, such that with time memories become hippocampus-independent, the prediction would be that hippocampal injury would result in a temporally graded memory impairment where recent memories are more impaired than remote memories (the 'Ribot gradient', Ribot, 1882). In this case, a deficit in remote memory would occur if the damage extended to the neocortex.

Although retrograde amnesia (RA), an impairment in retrieving remote memories, has been observed following damage limited to the hippocampus, there is mixed evidence with respect to the temporal gradient observed. For example, some studies have shown that damage limited to the hippocampus results in temporally graded RA (e.g. Reed and Squire, 1998; Henke *et al.*, 1999a; Kapur and Brooks, 1999; Bayley *et al.*, 2003; Manns *et al.*, 2003a), and the extent of damage is related to the severity of memory impairment (Rempel-Clower *et al.*, 1996; Reed and Squire, 1998). In direct contrast to these findings, Hirano and Noguchi (1998) and Cipolotti *et al.* (2001) reported two patients (Case YK, Hirano and Noguchi, 1998; Case VC, Cipolotti *et al.*, 2001) who had extensive ungraded retrograde amnesia for episodic memory following reportedly selective bilateral hippocampal pathology. In a recent study, Bayley *et al.* (2003) reported preserved remote episodic memories in patients with either limited hippocampal pathology or extensive

MTL pathology and consequently suggested that regions beyond the MTL might support retrieval from remote episodic memory. In relation to this hypothesis they proposed that patients YK and VC with their extensive ungraded RA might have pathology outside the MTL (e.g. the lateral temporal cortex and/or frontal cortex) undetected on conventional magnetic resonance imaging (MRI).

In summary, the role of the hippocampus in memory retrieval remains controversial. Possible reasons for the conflicting findings in studies of RA other than extent of pathology may be differences in time since injury, age of the patient, level of intelligence, education, media exposure and executive function performance (e.g. Kapur *et al.*, 1999; Kopelman and Kapur, 2001). In the future, with further improvements in MRI techniques it should be possible to more clearly identify and quantify the underlying pathology associated with RA, and thereby the role of the hippocampus in memory formation and retrieval. Moreover, the 'episodic' and 'semantic' aspects of remote memory need to be more clearly defined in order to characterise and compare across studies the specific memory impairments experienced by these patients. For example, in the study of Bayley *et al.* (2003) the quality of memory (episodic vs. semantic) was determined after the assessment according to strict scoring criteria. Future studies should corroborate these objective scoring procedures with subjective reports from the patients. For example, a remember/know paradigm may help determine whether the participant recollects a memory (episodic retrieval) or whether the memory is known to the participant (semantic retrieval). This paradigm is discussed in relation to theories of episodic and semantic memory in Section 1.7.3.2.

1.4 AMNESIA ASSOCIATED WITH DAMAGE TO THE MTL: THE CASE OF HM

One of the most often cited examples of amnesia following bilateral damage to the MTL region is that of case HM (Scoville, 1954; Scoville and Milner, 1957; Scoville, 1968). HM had minor seizures from the age of 10 and major seizures from the age of 16. Despite many attempts to treat his epilepsy with anticonvulsant medication, HM's seizures increased in frequency and severity through the years, until at age 29 he underwent a bilateral medial temporal lobe resection. The resection included the hippocampus bilaterally, and a recent MRI study (Corkin *et al.*, 1997) revealed that the

amygdaloid complex and most of the entorhinal cortex had also been removed. The MRI study also revealed that the rostrocaudal extent of the lesion is 5 cm, not 8 cm as originally thought (Scoville and Milner, 1957), with 2 cm of posterior intraventricular hippocampal formation remaining.

Following surgery, HM underwent psychological evaluation. Two years after surgery, formal testing revealed good intelligence but poor immediate and delayed visual and verbal recall with some retrograde amnesia for the three years leading up to his operation (Scoville and Milner, 1957)[1]. Thirteen years following surgery, HM's motor skills were tested (Corkin, 1968). His performance improved from session to session and on one task (rotary pursuit) he showed complete retention several days after testing. Despite HM showing no recollection of the testing procedure from day to day, he nevertheless was capable of motor skill learning. A year later, HM was given a battery of neuropsychological tests to further characterise his cognitive profile (Milner *et al.*, 1968). Conversations with HM combined with formal testing revealed a marked impairment in the long-term retention for most ongoing events despite relatively intact general intelligence, short-term memory and perceptual functions. Combined, these studies suggest that bilateral removal of MTL structures result in impaired acquisition of everyday events and facts yet preserved acquisition of motor and perceptual skills. This dissociation between declarative and nondeclarative memory in HM has been supported more recently in studies showing intact performance on nondeclarative memory tasks such as odour detection, discrimination of intensity and adaptation (Eichenbaum *et al.*, 1983), eyeblink classical conditioning (Woodruff-Pak, 1993), and visuo-perceptual priming (Keane *et al.*, 1995), and impaired performance on tests of declarative memory, such as new semantic learning (Gabrieli *et al.*, 1988), and knowledge of post-morbid words (Postle and Corkin, 1998).

In summary, the study of HM suggested that MTL structures are necessary for forming and retaining declarative but not nondeclarative memories. Since the discovery of HM's profound amnesia for declarative memories, numerous studies have investigated the effect of MTL damage in adults (e.g. Warrington and Weiskrantz, 1970; Zola-Morgan *et al.*, 1986; Knowlton *et al.*, 1994; Reber and Squire, 1994). Like HM, these cases suggest that MTL damage is associated with an inability to maintain new information in

long-term declarative memory (*anterograde amnesia*) and sometimes a loss of previously formed long-term memories (*retrograde amnesia*), despite preserved short-term and nondeclarative memory.

1.5 COGNITIVE THEORIES OF AMNESIA

As outlined in Section 1.1, memory involves three processing stages, namely, encoding, storage and retrieval. Over the years, there has been extensive debate concerning the primary deficit in amnesia (e.g. for a review see Kopelman, 2002).

Encoding, or input, theories suggest that amnesia is associated with a deficit in spontaneously encoding information at a deep meaningful level (e.g. Cermak and Moreines, 1976; Cermak and Reale, 1978; Cermak and Butters, 1980). For example, studies have attempted to manipulate the level of encoding using the levels-of-processing (LOP) paradigm proposed by Craik and Lockhart (1972). In this paradigm, deep encoding is encouraged by asking the participant to make semantic judgements about the items at encoding. In healthy participants this deeper encoding results in better subsequent memory for the items compared to shallow encoding, such as making judgements about the physical characteristics of the items (for a discussion of this paradigm see Chapter 9). According to the semantic encoding hypothesis, patients with amnesia do not spontaneously engage in a deep processing strategy but should perform as well as controls when instructed to do so. Studies of LOP effects in patients with Korsakoff amnesia (KA, amnesia resulting from diencephalic damage) have found better memory for deep-encoded compared to shallow-encoded items when list-length was reduced (e.g. Cermak and Reale, 1978). Similarly, Meudell *et al.* (1980) found that patients with KA showed the standard LOP effect, but performance was substantially below that of controls. These findings argue against the 'semantic encoding deficit' hypothesis of Cermak and colleagues, as even when encouraged to encode deeply, the patients' level of learning was still lower than that of controls.

Storage theories focus on consolidation and maintenance of information. It is possible that amnesia reflects faster forgetting than normal due to inadequate

[1] A more recent study suggests that HM's retrograde amnesia extends back 11 years before his operation (Sagar *et al.*, 1985)

consolidation of a memory trace. Based on their studies of HM and patients with KA, Huppert and Piercy (1979) argued that patients with MTL lesions show accelerated forgetting, even when material has been adequately learned, but patients with diencephalic amnesia do not. However, Freed *et al.* (1987) failed to replicate the findings of Huppert and Piercy (1979) when they assessed HM, and other studies (e.g. Kopelman, 1985; Baddeley *et al.*, 1987) suggest that forgetting rates are broadly equivalent in healthy participants and patients with memory disorders (e.g. Alzheimer's dementia, patients with KA, and patients with head-injury).

Finally, an alternative possibility is that amnesia reflects a specific retrieval deficit. This may arise, as suggested by Warrington and Weiskranz (1970), due to amnesia being associated with an increased vulnerability to interference effects. They suggest that the apparent capacity for patients with amnesia to benefit from partial cuing may be due to the tendency of this procedure to rule out competing items from earlier learning. However, in a subsequent study, Warrington and Weiskrantz (1978) found that in a task requiring competing responses (e.g. participants first had to learn to respond to the letter cue *cyc* with "cyclone", then to respond "cycle" to the same cue), patients with amnesia (of mixed aetiology) did not demonstrate increased interference effects compared to controls.

In summary, it seems that the deficits associated with amnesia can not be explained by a specific encoding, storage or retrieval deficit. Instead, Weiskrantz and Warrington (1982) suggested that amnesia might be due to a disconnection between two sources of information in learning, one source comprising learning certain types of information (semantic) and the other comprising the ability to generate links between previously separate events (episodic). They propose that the primary deficit in amnesia is an inability to relate these two sources, and in particular to store the representation of the links between previously separate events.

1.6 THEORIES OF LONG-TERM DECLARATIVE MEMORY ORGANISATION

The discussions above have suggested that the MTL is essential for declarative memory (e.g. Scoville and Milner, 1957; for an alternative view see Gaffan, 2002). However its precise function is still unclear. This section will focus on a discussion of the

different theories of long-term declarative memory organisation in relation to the MTL-cortical circuit.

Squire and colleagues (e.g. Squire, 1987; 1992; 1994; Squire and Knowlton, 1995; Squire and Zola-Morgan 1991; 1996; 1998; Manns and Squire, 2002), have proposed a model in which semantic information is acquired though episodes, constituting a declarative memory system dependent on the MTL. The parahippocampal, perirhinal and entorhinal cortices, together with their interconnections with the hippocampus, form a unified memory system and are thought to support both recall and recognition, while the frontal lobes play an additional executive role in free recall. It is also postulated that the degree of impairment to declarative memory is dependent on the extent of pathology (e.g. Zola-Morgan *et al.*, 1994). Therefore differences in the severity of the amnesia caused by MTL damage are due to differences in the amount of bilateral damage to the MTL system irrespective of which components are affected (Squire and Zola, 1996). This model predicts that damage to the MTL would impair both episodic and semantic memory and recall and recognition to a similar degree unless there was additional frontal lobe dysfunction, in which case episodic memory and free recall would be more impaired than semantic memory and recognition.

A related model proposed by Eichenbaum *et al.* (1994; Eichenbaum, 2001) postulated that the parahippocampal region supports intermediate storage of individual items, and the hippocampus mediates an organisation of memories according to relevant relationships among items. Together, they form the 'hippocampal memory system', necessary for declarative memory.

Both of these neuroanatomical models suggest that declarative memory is dependent on the interaction between the hippocampus and subjacent cortices, and therefore damage to the hippocampus would impair both episodic and semantic memory.

The Serial Parallel Independent (SPI) model of declarative memory proposed by Tulving (1985; 1995; 2001; 2002) makes different predictions from that of Squire and colleagues. In the SPI model, semantic and episodic memory are organised in a serial fashion whereby perceptual and sensory information enters semantic memory before episodic memory. Information is stored in parallel and can be retrieved independently from any of the three systems (perceptual, semantic or episodic). Therefore at encoding, only single dissociations can occur, such that semantic memory can be preserved in the absence of episodic memory but not vice versa, while at retrieval double dissociations can

occur, such that episodic and semantic memory can be retrieved independently. According to this model, retrieval from episodic memory is associated with the conscious experience of remembering (autonoetic) and retrieval from semantic memory is associated with the conscious experience of knowing (noetic). Similarly, dual-process memory models (e.g. Mandler, 1980; Jacoby, 1991; Yonelinas, 1994) have proposed that remembering reflects recollection-based recognition, whereas knowing reflects familiarity-based recognition (these models are discussed in more detail in Chapter 9).

A neuroanatomical correlate of the SPI model has been suggested by Mishkin *et al.* (1997; 1998). This model postulates that the MTL system is hierarchically organised: perceptual information passes into the perirhinal and parahippocampal cortices, which reciprocally connect with the entorhinal cortex, which in turn reciprocally connects with the hippocampus; the hippocampus is necessary for episodic memory and therefore recollection, whereas the parahippocampal cortices can support semantic memory and therefore familiarity-based recognition.

Aggleton and Brown (1999) propose a similar model to that of Mishkin *et al.* (1997), but they extend the memory system of Mishkin *et al.* (1997) to include the anterior and medial dorsal thalamic nuclei. They propose that the hippocampal-anterior thalamic nuclei-frontal circuit supports recollection-based retrieval and independently, the perirhinal-medial dorsal thalamic nucleus-frontal circuit supports familiarity-based retrieval. With respect to encoding Aggleton and Brown (1999) propose that the perirhinal cortex encodes information independently of the hippocampus. Although they suggest, consistent with the hierarchical model of Mishkin *et al.* (1997), that the perirhinal cortex is a major afferent source to the entorhinal cortex and the hippocampus, they also suggest that, following brain injury to the perirhinal cortex (and postrhinal (parahippocampal) cortex in the rat, Aggleton *et al.*, 1997; Bussey *et al.*, 1999; Bussey *et al.*, 2000), the hippocampal-anterior thalamic nuclei-frontal circuit can support episodic memory encoding independently of the perirhinal cortex (and postrhinal (parahippocampal) cortex in the rat). This seems inconsistent with the hierarchical model proposed by Mishkin *et al.* (1997) and the serial encoding hypothesis proposed by Tulving (1995). However, these models can be reconciled if it is assumed that information can enter the hippocampal-anterior thalamic nuclei-frontal circuit via the entorhinal cortex independently of the perirhinal cortex (and postrhinal cortex in the rat).

In summary, there are two main theories of long-term declarative memory organisation, the unitary-system model (e.g. Squire, 1987; 1992; 1994, Squire and Knowlton, 1995; Squire and Zola-Morgan 1991; 1996; 1998; Manns and Squire, 2002), which refers to models that propose a unified function of the MTL; and the multi-system model (Tulving, 1985; 1995; 2001; 2002; Mishkin *et al.*, 1997; 1998; Aggleton and Brown, 1999; Brown and Aggleton, 2001), which refers to models that propose functional segregation within the MTL. These models make different predictions regarding memory function after injury to the MTL-cortical circuit outlined in Section 1.2. The multi-system model, but not the unitary-system model, predicts dissociations in declarative memory following selective damage to the hippocampus.

1.7 DISSOCIATIONS IN MEMORY

The theoretical models described above make different predictions with respect to dissociations in memory following bilateral damage to components of the MTL-cortical circuit. In this section, adult human and animal studies will be discussed in relation to dissociations in memory, including dissociations between declarative and nondeclarative memory, semantic and episodic memory, recall and recognition memory, and recollection and familiarity-based recognition. For the purpose of this introduction, only data from bilateral lesions will be considered in order to address the specific predictions of the theories described in Section 1.6. Furthermore, due to the developmental nature of the amnesia experienced by the patients reported in the studies of this thesis, only anterograde memory impairments will be described in this section.

1.7.1 Nondeclarative vs. declarative memory and the hippocampus

Both Squire and colleagues (e.g. Squire, 1987; 1992; 1994; Squire and Knowlton, 1995; Squire and Zola-Morgan 1991; 1996; 1998; Manns and Squire, 2002), and Tulving and colleagues (e.g. Tulving, 1985; 1995; 2001; 2002; Tulving and Markowitsch, 1997; 1998), agree that hippocampal pathology does not necessarily impair nondeclarative memory. For example, adult amnesia associated with MTL pathology has not been associated with deficits in motor skill learning (e.g. Corkin, 1968), probabilistic classification learning (Knowlton *et al.*, 1994), serial reaction times (Reber and Squire,

1994), artificial grammar learning (Knowlton and Squire, 1996), or priming (Shimamura and Squire, 1984; Musen and Squire, 1992; Delazer and Girelli, 2000).

It appears that in the main nondeclarative memory is not impaired following MTL lesions. However, impairments can be seen following hippocampal lesions if the tasks involve novel information (e.g. Gooding *et al.*, 2000), forming novel associations (e.g. Gooding *et al.*, 2000), an awareness of associations (e.g. Manns *et al.*, 2000), or memory for context (e.g. Chun and Phelps, 1999).

1.7.2 Semantic vs. episodic memory and the hippocampus

Neuroimaging studies in healthy humans have revealed activation in a number of structures during memory encoding and retrieval, including the frontal lobes (e.g. Tulving *et al.,* 1994), the MTL (e.g. Nyberg *et al.,* 1996; Stern *et al.,* 1996) and the parietal cortex (e.g. Kapur *et al.,* 1995; Cabeza *et al.,* 1997). More recently, neuroimaging studies have attempted to delineate the function of the hippocampus in memory. Some have suggested it is involved in novelty detection (e.g. Dolan and Fletcher, 1997; 1999), retrieval success (e.g. Nyberg *et al.,* 1996), recollection (e.g. Eldridge *et al.,* 2000), spatial memory (e.g. Maguire *et al.,* 1997) and relational memory (e.g. Henke *et al.,* 1997; Henke *et al.*, 1999b; Davachi and Wagner, 2002). In a review of the literature, Cohen *et al.* (1999) concluded that the relational memory explanation of hippocampal function could account for the majority of fMRI studies to date. This theory proposes that the hippocampus is involved in binding together converging inputs from various processors, permitting it to mediate representations of the relationships among various objects and events (e.g. Eichenbaum *et al.,* 1994), and thus it is considered the seat of episodic memory (e.g. Tulving and Markowitsch, 1997).

Although both the unitary-system (e.g. Squire and Zola, 1998) and multi-system models (e.g. Tulving and Markowitsch, 1998), as described in Section 1.6, agree that episodic memory is impaired following bilateral hippocampal pathology, they disagree in relation to anterograde semantic memory. The unitary-system model would predict an equivalent impairment in episodic and semantic memory following hippocampal pathology, while the multi-system model would predict impairments only in episodic memory due to semantic memory being supported by the parahippocampal region.

In order to investigate the ability to learn new semantic information in amnesia, a number of studies have attempted to teach such patients new information (e.g. Glisky *et*

al., 1986a; 1986b; Glisky and Schacter, 1988; 1989; Tulving *et al.*, 1991; Hayman *et al.*, 1993; Hamann and Squire, 1995; Bayley and Squire, 2002; Holdstock *et al.*, 2002). Tulving *et al.* (Case KC, 1991), Hayman *et al.* (Case KC, 1993), Hamann and Squire (1995) and Bayley and Squire (Case EP, 2002) attempted to teach three-word sentences to patients with severe amnesia of different aetiologies and varying extents of pathology. Although the patients demonstrated an ability to acquire the three-word sentences, the studies disagree with respect to what memory system is thought to support this new learning. Tulving *et al.* (1991) and Hayman *et al.* (1993) suggested that the new learning demonstrated by patient KC, although slow and gradual, was achieved through semantic memory, due to his ability to produce the targets in a different modality (flexible knowledge) and to produce many targets to conceptual (semantic) cues alone. Hamann and Squire (1995) suggested that the new learning demonstrated in a group of patients, including some with hippocampal injury and others with diencephalic-frontal damage, was at a level commensurate with their residual episodic memory, suggesting that episodic and semantic memory are spared/impaired to a similar degree. In a recent study of a single case, EP, a patient with extensive bilateral MTL pathology, Bayley and Squire (2002) suggested that his improved learning with repetition was supported by nondeclarative memory, as he was unable to produce the answer to a synonymous cue (inflexible knowledge) and he did not appear to experience conscious awareness of which answers were correct. Differences in performance between the patients reported in these studies may be accounted for by differences in aetiology, extent of lesion and task design.

To date anterograde semantic memory acquired in the laboratory has been assessed in only one patient with selective bilateral hippocampal pathology sustained in adulthood (Holdstock *et al.*, 2002). Although patient YR was able to recognise newly learned definitions, she was unable to recall the definitions despite repeated exposure. However, it is worth noting that only ten repetitions were given over a two-day period, and cued-recall was tested immediately after each presentation. This study-test procedure may have limited YR's recall ability due to intra-experimental interference effects (e.g. Hayman *et al.*, 1993). An alternative measure of post-morbid semantic acquisition is the amount of semantic knowledge gained after the onset of amnesia. Again, although YR demonstrated relatively preserved recognition of post-morbid famous events and names, she was unable to produce more detailed information about famous events, suggesting

limited anterograde semantic memory following adult-onset bilateral hippocampal damage (Holdstock *et al.*, 2002).

Other studies of post-morbid semantic knowledge in patients with amnesia have found evidence of limited anterograde learning. For example, Kitchener *et al.* (1998) found that RS, a patient with extensive bilateral damage to the hippocampus and parahippocampal region (more extensive on the left) had acquired limited information about people, public events and new vocabulary during the 13-year period since he became amnesic. Despite this, RS showed severely impaired anterograde episodic memory function or autobiographical memory. These findings suggest that some limited amount of semantic acquisition is possible in the absence of episodic memory. The authors proposed that in the absence of a functioning hippocampal system, the neocortex may be able to learn (albeit slowly) in isolation through repeated exposure. They emphasised the importance of spared temporal cortical areas, including the inferolateral temporal cortices and the entorhinal and perirhinal cortex on the right. However, it is worth noting that RS had damage that included the basal forebrain and frontal lobe, which may have contributed to his episodic memory impairments and also may have limited his semantic learning.

Additional evidence of relatively spared post-morbid vocabulary acquisition but impaired episodic memory can be found in patients without any evidence of frontal pathology, such as PS reported by Verfaellie *et al.* (2000) and AC reported by Van der Linden *et al.* (2001). PS (Verfaellie *et al.*, 2000) had selective hippocampal volume reduction with sparing of the parahippocampal region and frontal lobes. Like RS, PS demonstrated relatively preserved recognition of new vocabulary although her recall scores were impaired relative to the performance of controls. In addition, PS performed well above chance on a test of famous face knowledge.

AC (Van der Linden *et al.*, 2001), a patient with more extensive temporal and occipital lobe damage was found to have preserved knowledge of post-morbid words commensurate with the level of performance observed in controls but impaired episodic memory. However, due to the extensive temporal lobe damage in patient AC it is difficult to ascertain which regions of the MTL system support his relatively spared semantic knowledge.

Therefore, it seems that patients with MTL damage can acquire some new semantic information, although the level of performance ranges between patients. In a

recent review of a large number of studies investigating semantic learning in amnesia, Verfaellie (2000) concluded that the difference in the capacity for new semantic acquisition in patients with amnesia seems to be related to the sparing of the parahippocampal region (the perirhinal, entorhinal and parahippocampal cortices). Verfaellie (2000) proposed, consistent with the computational models outlined in Section 1.3, that the neocortex may be capable of slow learning with repetition in the absence of the rapid learning hippocampal system.

In contrast to this, Kartsounis, *et al.* (1995) and more recently Cipolotti *et al.* (2001) report the case VC, a patient with relatively selective bilateral hippocampal damage who performed poorly when tested for recall and recognition of knowledge for post-morbid vocabulary, famous events and people. These findings suggest that VC had not acquired any new knowledge since the onset of his amnesia. It is unclear as to why VC has not acquired any new semantic information since his injury. One possibility may relate to his additional, although mild, pathology in the left parahippocampal gyrus. However, a similar deficit in anterograde semantic memory has been noted in patients with hippocampal pathology and no known pathology to the parahippocampal region (Manns *et al.*, 2003a). Alternatively, time since injury may have an effect. VC was tested six years after amnesia onset, whereas patient RS was tested thirteen years post-onset, PS was tested twenty years post-onset and AC was tested fourteen years post-onset. It is possible, as suggested by Cipolotti *et al.* (2001), that VC's six year post-morbid period was not of sufficient length to establish slow neocortical learning; therefore longitudinal investigations of VC will be needed in order to test this hypothesis.

Although the findings of Cipolotti *et al.* (2001) and Manns *et al.* (2003a) argue against the hypothesis that anterograde semantic memory will be spared following selective hippocampal lesions, it is important to note that neither of these studies have conducted whole-brain morphology analysis (e.g. voxel-based morphometry, Chapter 3). Without such an analysis it is unknown whether any of these patients have relatively subtle pathology outside the MTL, which may additionally contribute to their deficits.

The SPI model proposed by Tulving (e.g. 1985; 1995; 2001; 2002) has recently received criticism from a slightly different line of evidence. The SPI model predicts that an impairment in semantic encoding would result in an impairment in episodic encoding. However, a series of studies conducted by Graham and colleagues (Graham and Hodges, 1997; Graham *et al.*, 1999; Graham *et al.*, 2000, Simons *et al.*, 2001) have found that

patients with a temporal variant of frontotemporal dementia affecting the semantic store, known as semantic dementia (SD, Hodges *et al.*, 1992), show a profile different from that predicted by the SPI model. Their neuroimaging studies (e.g. as reported in Graham *et al.*, 1999), have revealed focal atrophy of the inferolateral temporal neocortex on one or both sides with relative sparing of the 'hippocampal complex' (i.e. hippocampus proper, subiculum, and parahippocampal gyrus). These patients perform poorly on tests that require conceptual knowledge such as picture naming and category fluency, but seem to have preserved autobiographical and day-to-day, episodic memories (e.g. Graham and Hodges, 1997). In addition, new learning, such as recognition of test items perceptually identical to or in the same orientation as those presented at study is evident in some cases of semantic dementia despite the patients having degraded semantic information about the studied items (e.g. Graham *et al.*, 1997; Simons *et al.*, 2001). According to the authors, these findings suggest, inconsistent with Tulving's SPI model, that perceptual information can pass directly into episodic memory (Graham *et al.*, 2000; Simons *et al.*, 2001). However, as discussed in Section 1.7.3, processes other than episodic memory (such as familiarity) can support recognition. Recently, Simons *et al.* (2002) reported a study demonstrating that some patients with SD showed evidence of recollection-based memory (source memory task), suggesting that episodic memory does support recognition memory in these patients. Nevertheless, some patients showed good recognition of items despite poor memory for source suggesting that processes other than recollection-based memory may support recognition in these patients. A direct test of the subjective experience of the patients during recognition, such as the remember/know paradigm (see below), may help to further establish which processes support recognition in these patients. Tulving (2001) proposed a similar argument. He suggested that without corroborating evidence it is possible that recognition in patients with SD is supported by perceptual memory alone.

In summary, lesion studies have found evidence to suggest that some new learning is possible in spite of a severe episodic memory deficit, and in the case of semantic dementia, some form of access to episodic memory seems possible in spite of a severe semantic memory deficit. However, there is some debate as to whether this new learning is evidence of intact semantic memory, residual episodic memory, nondeclarative processes or, in the case of semantic dementia, intact perceptual memory.

1.7.3 Recognition and the hippocampus

A number of dual-process models of recognition have been proposed over the years (e.g. Atkinson and Juola, 1973; Mandler, 1980; Jacoby, 1983; Tulving, 1985; Yonelinas, 1994; Aggleton and Brown, 1999; but see Donaldson, 1996). Although these models differ in many ways and therefore make slightly different predictions (for a review see Yonelinas, 2002), they all share the common underlying assumption that recognition comprises two independent processes, recollection (remembering) and familiarity (knowing). For the purpose of this thesis, recollection is assumed to reflect retrieval of specific information about a study event and therefore episodic memory, whereas familiarity is described as reflecting a continuous index of memory strength without retrieval of information about the study context, and therefore semantic memory.

According to the unitary-system model (e.g. Squire and Zola, 1998), damage to the hippocampus would result in impaired recall and recognition (both recollection and familiarity), whereas according to the multi-system model (e.g. Mishkin *et al.*, 1997; 1998; Tulving and Markowitsch, 1998; Aggleton and Brown, 1999), damage limited to the hippocampus would impair episodic recall and therefore recollection but not familiarity-based recognition. Therefore the two models make different predictions with respect to recall and recognition, and recollection and familiarity following hippocampal damage.

In this section studies of human performance on tests of recall and recognition will be discussed in relation to these predictions, and then studies of human and animal performance on tests of recognition will be discussed in an attempt to address the prediction of a recollection-familiarity dissociation.

1.7.3.1 Recall vs. recognition and the hippocampus

In a study of HM, Huppert and Piercy (1979) concluded that bilateral MTL pathology can result in a dissociation between recall and recognition, in favour of recognition. Further support for this claim came from subsequent studies of patients with MTL pathology associated with hypoxic-ischaemic episodes (e.g. Volpe *et al.*, 1983; 1986). However, these studies were open to the criticism that tests of recognition are less demanding than tests of recall (Mandler, *et al.*, 1969; Loftus, 1978). In an attempt to account for this, investigators began to match the performance of patients and controls on one aspect of the task in order to determine group differences on another (e.g. Hirst *et al.*,

1988; Haist *et al.,* 1992; MacAndrew *et al.*, 1994; Kopelman and Stanhope, 1998). However, when control subjects were matched to patients with amnesia on recognition, recall performance was either disproportionate (Hirst *et al.,* 1988) or proportionate (Haist *et al.,* 1992; MacAndrew *et al.*, 1994; Kopelman and Stanhope, 1998). These conflicting results may be caused by differences in patients' pathology, such that more extensive lesions may result in impaired recognition (e.g. Aggleton and Brown, 1999).

In an attempt to address whether location and extent of pathology influences recognition performance, Aggleton and Shaw (1996) reviewed the performance of a sample of 112 amnesics, on a standard test of recognition, the Warrington Recognition Memory Test (RMT, Warrington, 1984), and categorised them into eleven different pathological groupings. It appeared that the performance of three groups of patients did not differ from age-matched norms and was slightly better than other amnesic groups. These three groups included those with restricted hippocampal damage (following hypoxia), patients with fornix damage, and those with selective diencephalic damage.

In contrast to these findings, Reed and Squire (1997) examined the performance of six amnesic patients with either confirmed (post-mortem) or suspected selective hippocampal pathology (three of whom were reported in Aggleton and Shaw, 1996) on 11-25 different tests of recognition memory (including RMT). They found that recognition performance was consistently impaired across tasks and patients. Reed and Squire (1997) suggested that a single administration of the RMT may not always demonstrate a recognition memory impairment (case LM demonstrated intact immediate face recognition on the RMT, but was impaired at the other 19 tests). However, as a majority of these patients became amnesic following an episode of anoxia, it is worth noting that this aetiology may be associated with additional pathology (e.g. Bachevalier and Meunier, 1996; Markowitsch, *et al.,* 1997; Reed *et al.,* 1999; Caine and Watson, 2000; Grubb *et al.*, 2000) which may contribute to the degree of recognition impairment.

In order to compare recall with recognition performance avoiding differences in task difficulty and scaling, Baddeley *et al.* (1994) devised a task of verbal and visual recall and recognition, the Doors and People task. This task is described in detail in Chapter 7, but briefly, it attempts to equate task difficulty by making recall easier (increased learning trials) and recognition harder (similarity of foils to the targets) and provides an adjusted scaling procedure.

Despite the improvement in task design, studies of patients with selective bilateral hippocampal pathology have found evidence to suggest contradictory results: impaired recall and recognition following hippocampal pathology (e.g. Manns and Squire, 1999; Cipolotti *et al.*, 2001; Manns *et al.*, 2003b), and evidence to suggest a selective deficit in recall (Holdstock *et al.*, 2000a). Details of these studies are presented in Chapter 7.

One possible reason for the difference between the performance of the patients reported by Manns and Squire (1999), VC (Cipolotti *et al.,* 2001), YR (Holdstock *et al.*, 2000a) and the patients reported by Manns *et al.* (2003b), could be extent and site of pathology. This is discussed in more detail in Chapter 7. Briefly, although all patients were reported to have relatively selective hippocampal pathology, the percentage of volume reduction ranged from as low as ~ 10% in the patients reported by Manns *et al.* (2003b) to as high as ~ 46% in patient YR (Holdstock *et al.,* 2000a). It is possible that the remaining hippocampal tissue in the patients reported by Manns *et al.* (2003b) adversely affected the activity of connected structures that support recognition performance (e.g. Murray and Mishkin, 1998; Baxter and Murray, 2001a; 2001b; but see Zola and Squire, 2001). Alternatively, the memory profile associated with hippocampal damage may vary depending on the location of damage within the hippocampus. For example, fMRI studies suggests functional segregation along the anterior-posterior axis of the hippocampus (e.g. Strange *et al.*, 1999), the anterior region showing increased activation during processing novel information, the posterior region showing increased activation during processing familiar information. Furthermore, the patients reported in these studies (i.e. Manns and Squire, 1999; Holdstock *et al.,* 2000a; Cipolotti *et al.,* 2001; Manns *et al.*, 2003b), had injury following a hypoxic-ischaemic episode, and as already mentioned, this may be associated with covert pathology in other regions in some patients (e.g. Markowitsch, *et al.,* 1997) that may affect recognition performance.

1.7.3.2 Recollection vs. familiarity and the hippocampus

A number of studies have attempted to dissociate recollection-based recognition from familiarity-based recognition using the remember/know paradigm (Tulving, 1985). In this paradigm, once subjects have indicated a test item to be "old" they are asked to indicate whether they remembered the test item (i.e. recollected episodic information about the study event) or whether they just knew the item (i.e. the item is familiar in the absence of recollection).

As with studies of recall/recognition performance, studies using the remember/know paradigm with patients with amnesia have produced conflicting results. For example, one study suggested that both recollection and familiarity are disrupted in amnesia (Knowlton and Squire, 1995), another suggested that familiarity was enhanced in amnesia (Schacter *et al.,* 1996) and a third suggested that familiarity was not consistently affected by amnesia (Schacter *et al.,* 1997). In a review of these studies Yonelinas *et al.* (1998) found that discrepancies between these experiments arose because large differences in false-alarm rates between patients and controls biased the estimates of memory processes, and because different models were used to interpret the data in these experiments. On re-analysis of the data, incorporating response bias, the results of the previous studies were in agreement, such that amnesia was associated with a deficit in both recollection and familiarity but that this deficit was greater for recollection than familiarity. However, the patients reported in these studies did not have selective hippocampal lesions, and therefore their familiarity deficit can be accounted for by extra-hippocampal damage (e.g. Mishkin *et al.*, 1997; 1998; Aggleton and Brown, 1999).

In an attempt to address whether selective hippocampal lesions result in selective deficits of recollection-based recognition, Lazzara *et al.* (2001) and Yonelinas *et al.* (2002) compared the performance of patients with extensive MTL pathology (e.g. left temporal lobectomy) to those with selective hippocampal pathology (suspected on the basis of their mild hypoxic-ischaemic aetiology). Lazzara *et al.* (2001) found that using the remember/know paradigm, patients with extensive MTL pathology were impaired at familiarity-based recognition compared to patients with suspected selective hippocampal pathology. Similarly, on the basis of separate measures of recollection and familiarity, i.e. remember/know responses and ROC curves, Yonelinas *et al.* (2002) suggested that recollection was more impaired than familiarity in the mild hypoxia group, whereas both recollection and familiarity were impaired in patients with more extensive MTL lesions.

The role of the hippocampus in recollection has also been demonstrated by Eldridge *et al.* (2000) using fMRI in healthy participants. Using the remember/know paradigm, fMRI revealed greater activation in the hippocampus for recollection-based ("remember" responses) than familiarity-based ("know" responses) recognised items, and correct rejections. Moreover, hippocampal activation did not differ significantly between items correctly judged to be familiar ("know" responses) and items correctly judged to be unfamiliar (correct rejections).

These findings suggest, as predicted by the neuroanatomical models of Aggleton and Brown (1999), that the hippocampus may be necessary for recollection-based recognition (but see Manns *et al.*, 2003b); however without confirmation of the location of injury in the patients reported by Lazzara *et al.* (2001) and Yonelinas *et al.* (2002) it is difficult to assume selectivity of pathology.

There is some debate as to whether animals demonstrate evidence of episodic memory and therefore recollection of past experience (e.g. Tulving, 1983; Clayton *et al.*, 2001, Morris *et al.*, 2001). However, animal studies have been informative in revealing functional segregation between the hippocampus and surrounding parahippocampal region on tasks of item and associative recognition (for a review see Eichenbaum *et al.*, 1994; Brown and Aggleton, 2001). According to Yonelinas (2002), single item recognition may be supported by familiarity-based recognition, whereas associative recognition may be supported by recollection.

There are a number of studies reporting intact item but impaired associative recognition in monkeys (item: Murray and Mishkin, 1996; 1998; Buckmaster *et al.*, 1999; associative: for a review see Gaffan, 1996), and rats (item: for a review see Mumby, 2001; associative: e.g. Bunsey and Eichenbaum, 1996) following selective hippocampal lesions. Moreover, there is a wealth of studies reporting impaired item recognition following lesions to the perirhinal cortex (rat: e.g. Ennaceur *et al.,* 1996; monkey: e.g. Murray *et al.,* 1989; Meunier *et al.*, 1993; Gaffan 1994). However, there is also evidence to suggest that the perirhinal cortex supports some types of associative recognition, including intramodal (e.g. object-object) associative recognition (e.g. Murray *et al.*, 1993). Therefore, as will be discussed in Chapter 8, it seems that the hippocampus supports some types of associative recognition, possibly involving cross-modal associations, whereas the parahippocampal region can support single item and intramodal associative recognition.

However, other studies have found evidence to suggest deficits in single item recognition following selective hippocampal damage (rat: for a review see Mumby, 2001; monkey: e.g. Zola *et al.*, 2000). Reasons for conflicting results between studies of recognition performance may be due to differences in methodology (e.g. Zola and Squire, 2000). For example, studies differ with respect to task difficulty, surgery technique (e.g. ibotenic lesions are more restrictive than ablations), surgery procedure (two-stage surgery may result in a reduced functional impairment compared to one-stage surgery), pre-

operative training (pre-operative training may enhance subsequent performance post-operatively, e.g. Ringo, 1988), and testing procedure (removal from the testing apparatus between study and test may interfere with rehearsal strategies, Nemanic *et al.*, 2001).

A further line of evidence for the role of the perirhinal cortex in recognition can be found in additional animal studies (for a review see Brown and Bashir, 2002), using techniques such as neuronal recordings (for a review see Brown and Xiang, 1998) and c-fos expression (e.g. Zhu *et al.*, 1995; 1996). For example, electrophysiological recordings from the medial temporal lobe of monkeys performing recognition tasks, such as delayed non-matching to sample (DNMS), have found that some neurons respond less to subsequent presentations of a visual stimulus (e.g. Brown, 1996; Rolls *et al.*, 1993; Xiang and Brown, 1998). These response reductions occur more commonly in the anterior inferior temporal cortex (~25% of recorded neurons), notably in the perirhinal cortex, and are much less frequent (~1%) in the hippocampus (Brown, 1996). Furthermore, these neuronal changes show single trial learning and long-term storage (up to 24-hours, Fahy *et al.*, 1993) suggesting that neurons in the perirhinal cortex have the properties required for contributing to familiarity-based recognition, recency discrimination and memory storage (e.g. Brown and Aggleton, 2001). Activation studies that image the activity of a population of neurons using immediate early genes, such as c-fos, have shown that the perirhinal cortex in the rat is more active to novel than to familiar stimuli (e.g. Zhu *et al.*, 1995) and that such changes are not expressed in the hippocampus (Zhu *et al.*, 1995; 1996). These findings suggest that the perirhinal cortex is necessary for novelty detection, another process necessary for performance on recognition tasks. Both electrophysiological recordings (e.g. Eichenbaum *et al.*, 1994; Wood *et al.*, 1999) and activation studies (e.g. Wan *et al.*, 1999) have suggested a special role for the hippocampus in spatial memory, and these studies will be discussed in more detail in Section 1.7.4.

In summary, there is evidence to suggest that bilateral hippocampal damage may be associated with a recall and recollection-based recognition deficit with relative sparing of familiarity-based recognition. These findings suggest that, as proposed by Mishkin *et al.* (1997) and Aggleton and Brown (1999), the perirhinal cortex can support some aspects of recognition independently of the hippocampus.

1.7.4 Spatial memory and the hippocampus

Although spatial memory is not equivalent to episodic memory, there are some aspects of spatial memory that are similar to aspects of episodic memory. For example remembering the location of items of furniture within a room before leaving the house on a given day would involve forming associations between the items of furniture and their location in relation to each other and to the viewer at the time of looking at the room. Some authors suggest that the hippocampus is necessary for spatial memory (e.g. O'Keefe, 1976; O'Keefe and Nadel, 1978), and that in humans the addition of temporal components provide the basis for episodic memory (spatiotemporal context of personally experienced events).

1.7.4.1 Item vs. associative memory and the hippocampus

Studies of monkeys with fornix lesions have suggested a role for the hippocampus in forming memory for objects in relation to their location and unique background (scene memory, Gaffan, 1994; for a review see Gaffan, 1996). Similarly, a neuronal activation (c-fos) study (Wan *et al.*, 1999) found that there was greater activation in the postrhinal cortex and subfield CA1 of the hippocampus when rats viewed novel arrangements of familiar items (scenes) compared to familiar arrangements. The perirhinal cortex and area TE of the temporal lobe were relatively more activated by pictures of novel than of familiar individual objects (Wan *et al.*, 1999). Furthermore, YR (Mayes *et al.*, 1999; Mayes *et al.*, 2001), a patient with selective bilateral hippocampal pathology, was impaired at object-place associative recognition but not single item recognition. Therefore, as will be discussed in Chapter 8 there is compelling evidence to suggest that the hippocampus is involved in forming memories for objects in relation to their location (but see Malkova and Mishkin, 2003).

1.7.4.2 Egocentric vs. allocentric memory and the hippocampus

Memory for locations, and therefore spatial memory, can be divided into allocentric, referring to memory for locations defined relative to the environment, egocentric, referring to memory for locations defined relative to the body, and sensory, referring to memory for locations defined by their sensory characteristics (e.g. King *et al.*, 2002).

Allocentric spatial memory as tested in rats using the radial arm maze and the Morris water maze was found to be impaired following lesions to the anterior thalamic nuclei (e.g. Aggleton *et al.,* 1996; Warburton *et al.,* 1997), mamillary bodies (e.g. Neave *et al.,* 1997), the cingulum bundle (e.g. Neave *et al.,* 1997), the fornix (Warburton and Aggleton 1999; Bussey *et al.,* 2000) and the hippocampus (e.g. Liu and Bilkey, 2001; Save and Poucet, 2000; Ainge *et al.,* 2002). However, lesions to these same sites did not disrupt egocentric memory (e.g. Aggleton *et al.,* 1996; Neave *et al.,* 1997). These findings suggest that the hippocampus with its anterior thalamic connections is necessary for allocentric spatial memory (for a review see Aggleton and Pearce, 2001).

Using a task that encouraged either allocentric or egocentric spatial memory, Holdstock *et al.* (2000a), tested patient YR. Their findings suggested that the hippocampus was needed for the consolidation of allocentric information into long-term memory as opposed to the initial encoding of allocentric spatial information, as reflected by YR's normal retention after a 5 second delay but impaired recall and recognition after 60 seconds delay. They further suggested that YR's impaired free recall and allocentric recognition reflected a problem in storing or retrieving certain kinds of associative information. The role of the hippocampus in allocentric spatial memory is also supported by the findings of a recent meta-analysis of twenty-seven studies on spatial-memory dysfunction in patients with hippocampal damage (Kessels *et al.*, 2001).

To summarise, it appears that human and animal studies of hippocampal function suggest a special role for the hippocampus in the storage and retrieval of long-term spatial memories that require the formation of associations between items and their location and the use of an allocentric frame of reference. However, it is important to consider that the hippocampus does not function in isolation of other structures (e.g. Aggleton and Brown, 1999). For example, a recent review of rat studies suggested an interaction with the associative parietal cortex as being necessary for allocentric representation (Save and Poucet, 2000), and previous lesion studies in the monkey have suggested a role for the anterior thalamic nuclei in object-in-place memory (e.g. Parker and Gaffan, 1997).

1.8 DEVELOPMENT OF MEMORY

Developmental amnesia (DA), the focus of the studies in this thesis, is a memory disorder that occurs as a result of selective hippocampal pathology sustained early in life. Nelson (2000) has suggested that hippocampal lesions sustained early in life may result in a different memory profile from that seen after hippocampal lesions sustained in adulthood due to the retention of connections that normally degenerate as a result of maturation or due to remaining structures compensating for the normally lost function. In relation to this, Pascalis and de Haan (2000) have suggested that the hippocampus plays an important role in the development of functional connectivity in other cortical areas during brain maturation. They suggest that damage to the hippocampus in the immature brain may not only affect its own function but may also affect the function of the developing cortex. Therefore connections that may normally degenerate during maturation may remain as functional viable pathways, and thus result in a more distributed functional circuit.

This section first describes the normal development of the memory systems and their neural substrates associated with DA. The first part describes the development of the neuroanatomical structures outlined in Section 1.2 and the developmental trajectory of memory function (for reviews see Nelson, 1995; 1997; Alvarado and Bachevalier, 2000; Seress, 2001). Findings from animals and humans with hippocampal injury sustained early in development will then be discussed in relation to the theoretical models outlined in Section 1.6.

1.8.1 Development of the MTL-cortical circuit neuroanatomy and function

The MTL-cortical circuit is described in Section 1.2, and includes the parahippocampal region (parahippocampal, perirhinal and entorhinal cortices), which receive information from high-order sensory processing areas in the temporal and parietal lobes, as well as from the hippocampus (cornu ammonis fields CA1-4, dentate gyrus, subiculum), the medial diencephalon and the prefrontal cortex.

The CA fields have three cell layers: the polymorphic layer, pyramidal cell layer and molecular layer, and the primary neurons of the hippocampus are pyramidal neurons. The dentate gyrus also has three cell layers: the polymorphic layer, the granule cell body layer and the molecular layer. The primary neurons of the dentate gyrus are granule neurons.

Using neuronal markers it has been shown, in rodents, monkeys and humans, that a majority of the neurons in the entorhinal cortex, subiculum, and CA fields of the hippocampus are formed before birth (Rakic and Nowakowski, 1981; Arnold and Trojanowski, 1996). Despite this early maturation, refinement of hippocampal circuitry continues well into postnatal life. In rats, dendritic growth and synaptic formation continues up to the 90th postnatal day (Seress and Pokorny, 1981), and dentate granule cells establish synaptic connections throughout gestation in the monkey and human (Seress, 1992, Seress, 2001), and this may continue in adult life (e.g. Gould *et al.*, 1999).

The first afferent fibers to the human hippocampus proper arise from the entorhinal cortex and establish synapses with neurons of the CA subfields early in foetal development (Kostovic *et al.,* 1989). However, the trisynaptic circuit (as described in Section 1.2) is not expected to reach full maturation before the 5th postnatal year (Seress, 2001). Therefore, it is reasonable to assume that children born at term have the synaptic connections necessary to establish memory traces. However, the later formation of neuronal connections between granule cells of the dentate gyrus and pyramidal neurons of CA fields may alter the functional circuits of the hippocampus proper.

It appears, therefore, that the hippocampus has reached a level of structural maturity shortly after birth. However, as described in Section 1.2, memory function depends on a circuit of structures, and therefore memory development also depends on the maturation of these other structures. For example, the inferior temporal cortical areas TE and TEO in monkeys, although they have established connections by the first week of life, have a different pattern of connectivity compared to that in the adult, and as such these areas do not reach full maturity before the end of the first year (Webster *et al.*, 1991a; 1991b; 1995). Neurogenesis in the perirhinal and parahippocampal cortices has not been directly examined; however based on the immaturity of their cortical inputs these areas appear to have protracted development compared to the hippocampus and entorhinal cortex (Alvarado and Bachevalier, 2000). The laminar subdivisions of the entorhinal cortex are identifiable by midgestation in the monkey, with the exception of the lateral entorhinal cortex which develops fully only in the last quarter of gestation (Berger *et al.*, 1993; 1999).

In line with the evidence described above, studies of memory function have shown that performance on different memory tasks develops at different rates. For example, novelty preference (and by implication recognition) after a short delay can be

demonstrated by the first postnatal month in the monkey (e.g. Bachevalier *et al.,* 1993) and within the first few days after birth in the human infant (e.g. Pascalis and de Schonen, 1994). However, recognition memory as measured by the DNMS task does not reach adult proficiency until two years of age in the monkey (Bachevalier, 1990) and ~19 months of age in the human (e.g. Overman and Bachevalier, 2001). Recognition memory as seen in the novelty preference (visual paired comparison, VPC) paradigm (passive viewing of stimuli) could be supported by the early developing allocortical structures, such as the perirhinal and entorhinal cortex (Resende *et al.*, 2002) and their connections with the hippocampus (Pascalis and Bachevalier, 1999). The later development of DNMS proficiency may be due to accurate performance requiring the association of the presence of a reward with the novelty of the object (Bachevalier, 1990; Bachevalier *et al.,* 1993). This rule abstraction may depend on structures that mature later than the hippocampus, e.g. the ventral portions of the prefrontal cortex (e.g. Goldman-Rakic, 1987; Meunier *et al.*, 1997).

In addition to recognition tasks, nonverbal recall has been assessed in young children using the deferred imitation paradigm (see Chapter 5). Recall measured in this way has been demonstrated by children as young as 9 months (e.g. Bauer, 1992), and by 14 months children can produce the target action sequence after a delay of a week (Meltzoff, 1988). This task is thought to reflect declarative memory (e.g. Bauer, 1997) in that it requires the child to recall sequences of events presented once for study, and recall can be demonstrated even when the first opportunity to produce the target sequence only occurs after a delay (i.e. without practice).

Although nonverbal declarative memory has been demonstrated in children as young as 9 months, according to Wheeler *et al.* (1997) the ability to consciously recollect a specific episode does not occur until a child is approximately four years of age. Indeed reliable verbal accounts of events do not occur until approximately three years of age (Nelson and Gruendel, 1986; Howe and Courage, 1993), whereas it is not until children are four years of age and older that they are able to recall details about the time and place of the event, and report a basis of their knowledge (Wimmer *et al.,* 1988; Perner and Ruffman, 1995).

In summary it appears that the MTL-cortical circuit and declarative memory continue to develop throughout childhood and adolescence and possibly into adulthood (e.g. Gould *et al.*, 1999). According to Nelson (1995; 1997), the memory function

demonstrated early in development (e.g. novelty preference) reflects 'pre-explicit memory' possibly dependent on the hippocampus. On the other hand, recognition as measured using DNMS (requiring the coordination of recognition and action schemes) and recall using deferred imitation paradigms require a more developed explicit memory circuit.

1.8.2 Developmental memory disorders in the monkey

A number of studies of monkeys with neonatal MTL lesions have reported deficits in recognition using the VPC paradigm (e.g. Bachevalier *et al.*, 1993), even when tested in adulthood (e.g. Saunders *et al.*, 1991), and when neonatal lesions are restricted to the hippocampus (e.g. Pascalis and Bachevalier, 1999). Similar deficits have been observed following lesions in adult monkeys (e.g. Nemanic *et al.*, 1998; Zola *et al.*, 2000), suggesting that the memory profiles associated with neonatal lesions or lesions in adult monkeys do not differ when measured using the novelty preference paradigm.

The DNMS paradigm yields different results. Recognition performance on the DNMS task is not impaired after hippocampal lesions in adult monkeys (e.g. Murray and Mishkin, 1998; but see Zola *et al.*, 2000) or after neonatal hippocampal lesions (Bachevalier *et al.*, 1999; Pascalis and Bachevalier, 1999), but is impaired after both late (e.g. Meunier *et al.*, 1993; Malkova *et al.*, 2001) and early (e.g. Nemanic *et al.*, 2001) lesions to the perirhinal cortex. However, unlike adult lesions to area TE or to the inferior prefrontal convexity (e.g. Mishkin and Phillips, 1990; Kowalska *et al.*, 1991) neonatal lesions to these areas do not impair performance on DNMS or do so only mildly (e.g. Bachevalier and Mishkin, 1994; Malkova *et al.*, 1995; Malkova *et al.*, 2000). These findings suggest that area TE and the inferior prefrontal convexity are not functionally mature at the age of test and therefore do not support rule learning, or that compensation has occurred. In support of compensation occurring after neonatal lesions to area TE, Webster *et al.* (1991a; 1991b) demonstrated the presence of direct cortical projections to the perirhinal cortex from area TEO (the visual area immediately posterior to area TE) after neonatal but not after adult-induced lesions of area TE. These findings suggest that normally transient pathways are retained following neonatal lesions to area TE (Webster *et al.*, 1991b). If it is the case that preserved rule learning following lesions to area TE or the inferior prefrontal convexity reflect compensation, the monkeys studied by Bachevalier and Mishkin (1994) and Malkova *et al.* (2000) should show a similar

preservation of rule learning with development. This was the case for the monkeys with neonatal lesions to area TE when tested at 4 years (Malkova *et al.*, 1995), but not for the monkeys who had neonatal inferior complexity lesions when tested at 2 years of age, as indicated by a mild impairment at this age (Malkova *et al.*, 2000). The findings of Malkova *et al.* (2000) suggest that before 2 years of age the inferior frontal convexity does not support rule learning in the monkey, but with further development the temporal-prefrontal circuit begins to provide a supplementary route for rule learning. However, the mild impairment at 2 years of age does suggest some degree of functional compensation as these monkeys were not as impaired as monkeys with lesions sustained in adulthood (Kowalska *et al.*, 1991). In order to determine whether this mild impairment is due to compensation or other factors, these monkeys will need to be re-tested in later years.

In summary, findings have suggested that neonatal lesions to area TE and to a certain degree the inferior prefrontal convexity can result in compensation of function possibly due to the retention of normally transient connections (e.g. Bachevalier and Mishkin, 1994; Malkova *et al.*, 1995; Malkova *et al.*, 2000). However, neonatal MTL lesions in monkeys, including those restricted to the hippocampus, result in memory impairments similar to those seen following lesions sustained in adulthood, suggesting no evidence for compensation of memory function.

1.8.3 Developmental memory disorders in humans

There have been relatively few reported cases of amnesia sustained in childhood (for a review see Temple, 2002). These studies have reported differing cognitive profiles following child-onset amnesia; some have reported semantic and episodic memory impairments with sparing of short-term and nondeclarative memory consistent with the unitary-system model of MTL function (e.g. Case CC, Ostergaard, 1987; Case MS, De Renzi and Lucchelli, 1990; Case MS, Broman *et al.*, 1997; Case Julia, Temple, 1997; Case AC, Benedict *et al.*, 1998; Case ON, Casalini *et al.*, 1999; 1 case, Meguro *et al.*, 1999; Case RD, Hughes *et al.*, 2002); while others have found an episodic memory impairment with relative sparing of semantic learning, short-term memory and nondeclarative memory consistent with the multi-system model of MTL function (e.g. Case TC, Wood *et al.*, 1989; Cases Jon, Kate and Beth, Vargha-Khadem *et al.*, 1997; 5 cases, Gadian *et al.*, 2000).

In some of these cases pathology was not detected on conventional imaging (e.g. De Renzi and Lucchelli, 1990; Casalini *et al.*, 1999; Hughes, *et al.*, 2002), other cases were reported to have an amnesia following pathology that included the MTL (e.g. Ostergaard, 1987; Wood *et al.*, 1989; Temple, 1997; Benedict *et al.*, 1998), while three studies reported amnesia following relatively selective hippocampal pathology (e.g. Broman *et al.*, 1997; Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000). For the purpose of comparing the predictions of the theoretical models outlined in Section 1.6, only cases with child-onset bilateral hippocampal lesions will be described in detail.

1.8.3.1 Semantic vs. episodic memory and the hippocampus

The case presented by Broman *et al.* (1997), MS, suffered a cardiac arrest at age 7 years 6 months, and at 8 years of age he suffered respiratory arrest. From the age of 8 years onwards he suffered from generalised tonic-clonic seizures, and these were treated with anti-epileptic medication. Conventional MRI investigations, at age 32 years, revealed selective bilateral hippocampal pathology. The reported cognitive profile of MS extended from ~9 to 27 years of age. His verbal and performance intelligence quotients were within the average range (but showed a decline in verbal IQ of 35 scaled scores between the ages of 8:09 and 27:00[2]), despite poor expressive language abilities, and impaired factual knowledge, vocabulary knowledge, and literacy and numeracy abilities, but he showed relatively preserved verbal reasoning and conceptual abilities. A range of memory tests indicated poor verbal and visual immediate and delayed recall and recognition but preserved short-term memory span. The authors suggested that MS's memory impairment was as severe as that of HM and more severe than other adult cases with hippocampal amnesia (e.g. Cummings *et al.*, 1984; Zola-Morgan *et al.*, 1986; Victor and Agamanolis, 1990; Kartsounis *et al.*, 1995). Furthermore, they suggested that amnesia resulting from relatively selective hippocampal pathology sustained in childhood is associated with impaired episodic and semantic memory, while the development of grammatical and logical comprehension may be spared. However, based on the reported medical history, MS may also have suffered extra-hippocampal pathology not detected by conventional MRI (e.g. Bachevalier and Meunier, 1996; Markowitsch *et al.*, 1997), which in turn may have contributed to his memory impairments. Importantly, patient MS does

[2] At age 8:09 MS was administered the WISC, and at age 27 years MS was administed the WAIS-R.

not suggest any evidence for compensation of function following injury sustained early in development.

Although the study of MS suggests that bilateral hippocampal pathology sustained in childhood can result in amnesia, it is possible that such an injury occurring even earlier in life may be associated with a different profile. There are two plausible reasons for this: one may be that damage to the memory system in infancy would compromise cognitive development resulting in global learning disabilities (e.g. DeLong and Heinz, 1997); the second may be that such damage would fail to produce a severe memory disorder due to the plasticity and functional reorganisational capacity of the immature brain (e.g. Nelson, 2000; Pascalis and de Haan, 2000).

Results obtained from a series of studies of five cases with amnesia associated with bilateral hippocampal injury sustained before the first year of life (Vargha-Khadem *et al.,* 1997; Gadian *et al.,* 2000) have disputed the first of these notions, namely that early injury would result in global learning disabilities. The cognitive profile associated with these five cases appeared to be different from that described in adult-onset cases (e.g. Cummings *et al.,* 1984; Zola-Morgan *et al.,* 1986; Victor and Agamanolis, 1990; Kartsounis, *et al.,* 1995; Rempel-Clower *et al.,* 1996) and in other cases of child-onset hippocampal damage (e.g. Broman *et al.,* 1997), in that semantic memory was relatively preserved despite a severe episodic memory impairment. This profile was labelled developmental amnesia (Gadian *et al.*, 2000). A study of recognition memory in two of these five cases (Jon and Beth, Vargha-Khadem *et al.,* 1997) revealed preserved single item and associative one-trial recognition relative to controls yet impaired multi-trial object-place and voice-face associative recognition. Further studies of Jon's ability to acquire new information are discussed in Chapter 6.

Magnetic resonance techniques confirmed bilateral hippocampal pathology in all five cases (Gadian *et al.,* 2000); moreover, in a group analysis, voxel-based morphometry (a statistical method allowing a comparison of whole brain grey matter density with that of a control group, Chapter 3) revealed additional bilateral putamen and ventral thalamic damage and abnormality in the brain stem, consistent with the known effects of perinatal hypoxic-ischaemic injury (e.g. Rutherford *et al.,* 1994, 1995).

The authors suggested that the memory profile of these children is consistent with intact parahippocampal regions, whereby the parahippocampal region supports semantic memory and some aspects of recognition (Mishkin *et al.,* 1998). However, as recognised

by the authors (see Vargha-Khadem *et al.,* 2001), alternative possibilities may account for this profile, such as partial sparing of the hippocampus or, as suggested by the second notion described above, a degree of functional reorganisation and compensation after very early injury that is not possible after damage acquired later in life.

1.8.3.1.1 Extent of pathology

According to the declarative memory model proposed by Squire (1987; 1992), the degree of episodic and semantic memory impairment is dependent on the extent of MTL pathology, and therefore partial sparing of the hippocampus may result in residual episodic and semantic memory.

In order to address this issue the performance of eleven cases with DA (six early-onset, five late-onset) were compared to eleven children born prematurely, on tests of semantic and episodic memory (Vargha-Khadem *et al.,* 2001). Relative to their age-matched controls the mean hippocampal volume reduction was 40% (range: 29% to 55%) in the DA group and 10% (range: -3% to 24%) in the preterm group. The episodic memory of the DA group was impaired relative to controls and the preterm group. However, none of the groups differed on semantic memory. These findings suggest that the degree of episodic but not semantic memory is dependent on the extent of hippocampal pathology. The authors suggested that bilateral hippocampal volume reduction must be at least 25-30% before DA will result. However, as the authors indicated, it is possible that the relationship between degree of memory impairment and amount of volume reduction could be continuously graded rather than all-or-none.

1.8.3.1.2 Age at injury

In a recent review, Vargha-Khadem *et al.* (2001) describe a study that investigated whether the cognitive profile and neuropathology associated with DA was a consequence of age at injury and therefore compensation mechanisms in the immature brain. Six cases who sustained hypoxic-injury early in infancy (up to 1 year of age) were compared to five cases who sustained bilateral hippocampal injury later in childhood (6–14 years). Quantitative voxel-based morphometry analysis of MR images (Salmond *et al.*, 2000a) revealed bilateral pathology in the hippocampus, putamen and thalamus, and the hippocampal volume was reduced in both groups. In addition there was abnormality in the right posterior cingulate cortex. Analysis of the cognitive data indicated a similar

memory profile in both groups whereby short-term memory span and semantic memory were in the average range despite impaired episodic memory.

In summary, the early- and late-onset groups demonstrated similar neuropathology and cognitive profiles. It appears, therefore, that this profile is somewhat independent of age at injury. However, with the different profile in adult-onset amnesia, it may still be argued that this results from some reorganisational capacity of the developing brain.

1.8.3.2 Recognition and the hippocampus

In addition to the group studies described above, more extensive investigations of the memory profile associated with bilateral hippocampal pathology sustained in childhood have been reported in a single case, Jon (Baddeley *et al.,* 2001; Düzel *et al.,* 2001; Maguire *et al.,* 2001; King *et al.,* 2002).

1.8.3.2.1 Recall vs. recognition

Baddeley *et al.* (2001) assessed Jon's recall and recognition abilities as measured on the Doors and People Test (Baddeley *et al.,* 1994). Unlike that of his controls, Jon's performance indicated a clear recall-recognition discrepancy in favour of the latter, thus confirming the previous findings of Vargha-Khadem *et al.* (1997) and his performance on a newsreel task (described in Chapter 6), which indicated that Jon has preserved recognition. Interestingly, Jon's performance is unlike that of the adult amnesic patients described in Section 1.7.3.1 who demonstrated impaired visual and verbal recall and recognition on this test (e.g. Manns and Squire, 1999; Cipolotti *et al.*, 2001; Manns *et al.*, 2003b). Baddeley *et al.* (2001) suggested that the relatively preserved learning and recognition observed in Jon and other cases of bilateral hippocampal injury might be a consequence of intact parahippocampal regions. This is supported by Schoppik *et al.* (2001), whose preliminary findings indicate that the volumes of the entorhinal, perirhinal and parahippocampal cortices of five (including Jon) individuals with DA are within the normal range.

1.8.3.2.2 Recollection vs. familiarity

As described in Section 1.7.3.2, cognitive models of recognition memory (e.g. Atkinson and Juola, 1973; Mandler, 1980; Jacoby, 1983; Tulving, 1985; Yonelinas, 1994; Aggleton and Brown, 1999) suggest that recognition has two qualitatively different bases,

recollection-based recognition and familiarity-based recognition. The role of the hippocampus in episodic memory suggests that it may have a specific role in recollection-based recognition (e.g. Tulving and Markowitsch, 1998). In support of this, Düzel *et al.* (2001) demonstrated the presence of the electrophysiological component thought to be associated with familiarity-based recognition in Jon, but not the one believed to reflect recollection. Düzel *et al.*'s (2001) event related potentials (ERP) study used the levels-of-processing paradigm (Craik and Lockhart, 1972; Craik and Tulving, 1975) to manipulate recollection-based recognition, as deep encoding is commonly associated with recollective experience in controls (e.g. Gardiner *et al.*, 1996; Yonelinas *et al.*, 1998). Previous studies have related different modulations in ERP waveforms to different recognition processes (Paller *et al.*, 1995; Rugg *et al.*, 1998a; 1998b; 1998c). For example, Rugg *et al.* (1998c) found that when comparing correctly recognised old words (deep and shallow) with new words, waveforms with a peak ~400 ms post-stimulus onset were more positive for old than new words. This component was thought to be associated with familiarity-based recognition (N400). A second component was identified when comparing correctly recognised 'deep' with 'shallow' old words. These waveforms with a peak ~600 ms post-stimulus onset were more positive for 'deep' than 'shallow' old words. This component was thought to be associated with recollective-based recognition (late positive component (LPC)). Düzel *et al.* (2001) found that unlike his controls, who demonstrated both the N400 and LPC components during the recognition test phase, Jon only demonstrated the ERP component associated with familiarity-based judgements (N400).

In summary, Jon's ERP waveforms indicated that his preserved recognition abilities are likely to be a consequence of familiarity-based recognition consistent with the hypothesis that intact parahippocampal regions support recognition (e.g. Mishkin *et al.*, 1997; 1998; Aggleton and Brown, 1999).

In relation to the functional reorganisation hypothesis, using a fMRI study, Maguire *et al.* (2001) found differences in Jon's hippocampal-cortical connectivity compared to controls. Jon was scanned whilst he attempted to retrieve memories to cues, including personal and public events (some of which he claimed to recollect) and personal and public facts. In addition to activating the same brain regions as control subjects, Jon activated homologous regions in the contralateral hemisphere. Furthermore, hippocampal activity, as with controls, was differential, being most responsive to retrieval

of autobiographical events compared with other memories. For the events that Jon claimed to recollect, the hippocampi and medial frontal cortex were significantly more active. Despite the similarities in the areas activated by Jon and controls, there were marked differences in the hippocampal-cortical connectivity. Unlike controls, Jon demonstrated greater interaction between the hippocampus and retrosplenial cortex, and retrosplenial and medial frontal cortex when retrieving autobiographical events. Together, these results suggest that early-onset bilateral hippocampal pathology might result in additional connectivity, possibly through cortical reorganisation.

1.8.3.3 Spatial memory and the hippocampus

1.8.3.3.1 Item vs. associative memory and the hippocampus

As already discussed, Vargha-Khadem *et al.* (1997) presented three cases who demonstrated impairments on object-place recognition, but not on tests of single item or intramodal associative recognition, suggesting a role for the hippocampus in forming memories for objects in relation to their location.

1.8.3.3.2 Egocentric vs. allocentric memory and the hippocampus

As discussed in Section 1.7.4.2 the hippocampus is also thought to play a role in allocentric spatial memory (e.g. for a review see Aggleton and Pearce, 2001). In a recent study, King *et al.* (2002) tested Jon on a task of allocentric spatial memory. Their task involved recognising objects in their locations either in the same or different (changed) viewpoint to that at study. Jon was impaired at recognising objects in the changed viewpoint (allocentric) condition, but his memory span was similar to that of controls in the same-viewpoint (egocentric) condition. Controls performed significantly better than Jon in the changed viewpoint condition even when the number of foils was increased for controls, indicating a specific impairment for allocentric representation in Jon.

1.8.3.4 Summary of developmental memory disorders in humans

In summary, the memory profile associated with bilateral hippocampal pathology sustained in childhood has offered support for both the unitary-system theory (e.g. Broman *et al.*, 1997) and the multi-system theory (for a review see Vargha-Khadem *et al.*, 2001) of long-term declarative memory organisation. The reason for the inconsistent

findings among different patients remains unclear. One possibility is that additional undetected pathology may contribute to the memory profile in the child-onset case, MS, reported by Broman *et al.* (1997). Another possibility may be that the single-case study, Jon, represents an atypical case of DA.

In order to rule out the possibility that MS has additional undetected abnormalities, additional quantitative MR techniques, such as voxel-based morphometry and volumetrics, would need to be applied. In order to rule out the possibility that Jon represents a special case of DA the tasks administered to Jon would need to be administered to more cases with bilateral hippocampal pathology sustained in childhood.

1.9 GENERAL SUMMARY

The aim of this chapter was to review evidence from lesion and imaging studies in an attempt to delineate the role of the MTL region in memory. Although all of the evidence discussed above suggests that the MTL regions are necessary for memory, there is some debate over the precise function of structures within the MTL-cortical circuit, particularly within the MTL. Neuroanatomical and functional evidence can be found to support both the unitary-system model (e.g. Squire and Zola-Morgan, 1991; Eichenbaum *et al.,* 1994) and the multi-system model (e.g. Mishkin *et al.,* 1997; 1998; Aggleton and Brown, 1999) of long-term declarative memory organisation. These models make different predictions about the memory profile associated with bilateral hippocampal pathology. The unitary-system model predicts that hippocampal pathology would be associated with general declarative memory impairments where both episodic and semantic memory, and recall and recognition are impaired. The multi-system model predicts that hippocampal pathology will result in specific episodic memory impairments leaving semantic recall and familiarity-based recognition intact. Previous reports of developmental amnesia provide evidence to suggest an episodic-semantic memory dissociation (e.g. Vargha-Khadem *et al.,* 1997; Gadian *et al.,* 2000), and in one case a dissociation between recall and recognition, and between recollection and familiarity (e.g. Baddeley *et al.*, 2001; Düzel *et al.,* 2001). Therefore, evidence so far supports the multi-system models of Mishkin *et al.* (1997; 1998) and Aggleton and Brown (1999). The aims of the studies reported in this thesis are to extend the previous reports of DA, and to test

whether these extended studies provide further support for the multi-system model of long-term declarative memory organisation.

1.10 GENERAL AIMS AND PREDICTIONS

For the purpose of the studies reported in this thesis, patients with developmental amnesia are defined as having intelligence within the average range and poor memory in the presence of bilateral hippocampal abnormality.

The next chapter (Chapter 2) describes the characteristics of the patients with DA and their controls. It includes baseline measures of IQ, and general memory. Chapter 2 also presents the findings from tests of executive function presumed to be subserved by the frontal lobes, in order to rule out any additional frontal lobe dysfunction. A test of motor skill learning, presumed to be subserved by the basal ganglia, was conducted in order to test whether the previously reported basal ganglia structural abnormality in patients with DA is associated with dysfunction in this region.

In Chapter 3, findings from quantitative MRI analyses are reported, including measures of hippocampal integrity (hippocampal volumes and T_2 values) and whole-brain integrity using voxel-based morphometry (VBM). Consistent with the previously reported VBM studies of DA (Gadian *et al.*, 2000; Salmond *et al.*, 2000a; 2000b), VBM is expected to identify areas of abnormality additional to the hippocampus including the basal ganglia, thalamus, and right posterior cingulate. Furthermore, VBM is predicted to identify white matter abnormalities within the MTL-cortical circuit that might be associated with the developmental nature of the disorder.

Chapter 4 presents the results from a variety of standardised episodic and semantic memory tests, in an attempt to quantify the expected dissociation between episodic and semantic memory. In order to relate the degree of spared and impaired function to previous studies of DA, the same tasks as those reported by Vargha-Khadem *et al.* (1997), Gadian *et al.* (2000) and Baddeley *et al.* (2001) were administered. Furthermore, the relationship between memory performance on these measures and hippocampal abnormality as revealed using the MR techniques described in Chapter 3 will be examined.

Chapter 5 describes a test of nonverbal recall adapted for use with children/adolescents designed to access episodic and semantic components of recall. It is expected that patients with DA will be impaired relative to controls on the episodic aspects of this task but not on the semantic aspects.

Chapter 6 presents findings from two learning tasks, the newsreel task described by Baddeley *et al.* (2001) and a word-list learning task designed to address the role of repetition and meaningfulness in acquisition of semantic knowledge. It is expected that patients with DA will show improved learning with repetition and that memory will be better for semantically related stimuli.

In Chapter 7 performance on the Doors and People task (Baddeley *et al.,* 1994) of recall and recognition is presented, with the prediction that patients with DA will be impaired at recall but not recognition.

Chapter 8 presents the performance on the item and associative recognition tasks previously described by Vargha-Khadem *et al.* (1997). Here it is expected that patients with DA will be impaired at object-place and voice-face associative recognition, but not at single item recognition or intramodal associative recognition.

Chapter 9 describes performance on a task designed to manipulate the contribution of recollection and familiarity-based recognition, a levels-of-processing task. It is predicted that patients with DA will show a reduced levels-of-processing effect attributable to decrease recognition of deeply encoded items due to impaired recollection.

Finally, in Chapter 10, the relationship between the findings presented in Chapters 2 to 9 are discussed in terms of the theories outlined in this chapter and directions for future research studies are suggested.

2 STUDY PARTICIPANTS AND BASELINE NEUROPSYCHOLOGY ASSESSMENT

This chapter describes the selection criteria and characteristics of the participants included in this study. This is followed by the results from a number of baseline neuropsychological tests evaluating preservation or impairment in several domains of function such as memory span, immediate and delayed visual and verbal memory, executive function, and attention. In addition, an aspect of basal ganglia function was investigated in view of previous reports of MR abnormality in this region (Gadian *et al.*, 2000; Salmond *et al.*, 2000a; 2000b).

2.1 SELECTION CRITERIA AND CHARACTERISTICS OF THE GROUPS

2.1.1 Patients with DA

The patients were referred to the clinical neuropsychology team, Great Ormond Street Hospital, for investigation of an emergent memory impairment in the course of childhood or adolescence. In some cases the memory difficulties became noticeable about the time of school entry without clear antecedent events, while in others the memory difficulties were obvious immediately after an acute medical episode (see medical histories, Appendix A). All patients were invited for initial screening. During this visit a clinical neuropsychologist conducted an interview in order to identify specific cognitive and memory problems and to obtain a developmental history. Parents were asked to complete the Sunderland questionnaire (Sunderland *et al.*, 1983) in order to identify the severity and frequency of everyday memory problems (see Section 2.3.1.2). Cognitive assessments included measures of intelligence (WISC-III (Bracken, 1992)/WAIS-III (Wechsler, 1997a)), and general memory function using the Wechsler Memory Scales adapted for children (Vargha-Khadem *et al.*, 1992). In addition, magnetic resonance scans were obtained for an initial clinical examination, and for subsequent quantitative analysis (see Chapter 3).

Twelve patients with reported memory problems were selected from a sample of seventeen on the basis of average intellectual ability (standard score of 80 and above, Wechsler, 1992) and evidence of hippocampal abnormality shown on clinical examination of conventional MRI scans (see Table 2:2). The patients were then invited to take part in a three-day assessment subsequently followed by a single day assessment. The five other patients did not meet the inclusion criteria for this thesis.

Six of the patients had previously been investigated at a younger age and were reported by Vargha-Khadem *et al.* (1997) and Gadian *et al.* (2000), with one of them (case DA1) also being investigated as a single case study (Jon in Baddeley *et al.*, 2001; Düzel *et al.*, 2001; Maguire *et al.*, 2001). The majority of the tasks reported in this thesis were re-administered in order to obtain up-to-date data on these six cases.

All patients attended mainstream school, except for patient DA4. A summary of their medical histories can be found in Appendix A

2.1.2 Normal controls (NC)

A control group matched to the twelve patients for age, sex and verbal intelligence was included. For the recruitment of school-aged controls, letters and questionnaires were sent to parents via local London schools. Older participants were recruited through local colleges that advertised the research project in student unions and/or job centres. Volunteers initially completed a questionnaire (see Appendix B) indicating their date of birth, contact details and medical history, and if suitable, they were subsequently screened for intellectual abilities. If they met the inclusion criteria as listed below they were invited to take part in the study.

IQ was used as a matching criterion because amnesia is defined as a selective memory impairment in the absence of an intellectual deficit (e.g. Mayes, 1988; Parkin, 1988). Verbal IQ was chosen because in some cases with DA there was a verbal-performance IQ discrepancy in favour of verbal IQ. The variables of sex and age were used as matching criteria because sex differences have been noted in some aspects of memory (e.g. Herlitz *et al.*, 1999) and some aspects of memory function are known to undergo changes with development (e.g. Perner and Ruffman, 1995).

Twelve normal controls (NC) were selected from a sample of fifty volunteers recruited as noted above from local London schools and colleges. The matching of a control to each of the cases with DA was done according to the following criteria: a) same sex; b) age at test within twenty-four months; c) verbal IQ within one standard deviation (±15 points). Furthermore, the inclusion criteria for the controls incorporated: d) no known memory or neurological impairment[1]; and e) no evidence of hippocampal abnormality shown on clinical examination of conventional MRI scans.

All participants and/or parents/legal guardians of those under the age of sixteen gave written informed consent (see Appendix C).

2.1.3 Age, Sex, and Intelligence of DA and NC groups

In order to match patients and controls on intellectual ability, the Wechsler Intelligence Scales for Children (WISC-III, Bracken, 1992) or, if over 17 years of age, the Wechsler Adult Intelligence Scales (WAIS-III, Wechsler, 1997a) was administered in full. Briefly, the IQ tests consist of twelve subtests (the adult scale has two additional

[1] NC5 had a provisional diagnosis of dyslexia and NC9 had query dyspraxia at the age of two.

subtests) each measuring a different facet of intellectual ability. The subtests are divided into verbal and performance scales that are combined to obtain full scale IQ. The IQs have a mean of 100 and a standard deviation of 15.

Despite the variability among the DA group with respect to aetiology and age at injury (as indicated by the medical summaries in Table 2:2 and Appendix A), all participants had bilateral hippocampal abnormality as revealed on conventional MRI (Table 2:2) and verbal IQ within the average range (Table 2:1). Table 2:1 shows the sex, mean (±range) age at test, mean (±range) verbal IQ, and mean (±range) performance IQ for the DA and control groups.

Table 2:1 Age and IQ scores of DA and NC groups.

	Sex	Age at IQ Test years:months	Full Scale IQ standard score	Verbal IQ standard score	Performance IQ standard score
DA	6 males, 6 females	16:09 (10:06–26:03)	90.0 (75-114)	91.7 (80-108)	90.3 (70-121)
NC	6 males, 6 females	16:09 (11:02-26:06)	97.5 (80-114)	95.3 (82-113)	101.4 (75-128)

Mean (±range)

There was no difference between the means of the groups on age at test or verbal IQ ($p > 0.1$). Although performance and full scale IQ were not used as matching variables, separate t-tests with a between-subjects factor of group (DA, NC) revealed no evidence of a group difference on either measure ($p > 0.1$). Furthermore, a mixed-model ANOVA with a between-subjects factor of group (DA, NC) and a within-subjects factor of IQ (verbal IQ, performance IQ) revealed no evidence of a verbal-performance IQ discrepancy in either group ($p > 0.1$).

Table 2:2 Description of cases with DA

Case	Sex	Age at injury year:month	Age at test year:month	Approx. time since injury year:month	Suspected aetiology	MRI scan report hippocampi
DA1	M	Perinatal	19:11	19:11	Birth asphyxia	very small
DA2	F	Perinatal	18:00	18:00	Birth asphyxia	small[2]
DA3	M	Perinatal	16:00	16:00	Birth asphyxia	slightly small
DA4	M	Perinatal	14:01	14:01	Birth asphyxia	small[2]
DA5	F	Perinatal	10:06	10:06	Birth asphyxia	very small
DA6	F	2 days	14:07	14:07	Hypoxia-ischaemia	very small
DA7	M	11 weeks	15:09	15:06	Hypoxia-ischaemia	small
DA8	F	0 to 2:06?	15:02	12:08-15:02?	Seizures?	small
DA9	M	0 to 4:06?	13:09	9:03-13:09?	Seizures?	slightly small
DA10	F	9:01	26:03	17:02	Hypoxia-ischaemia	very small
DA11	F	12:05	19:07	7:02	Hypoxia-ischaemia	very small
DA12	M	15:05	17:11	2:06	Hypoglycaemia	small

? = query

2.2 BASELINE NEUROPSYCHOLOGY TESTS

2.2.1 Introduction

Amnesia resulting from MTL or diencephalic pathology is typically associated with a selective long-term declarative memory impairment in the absence of major intellectual and cognitive dysfunction. Thus, short-term memory, and nondeclarative procedural memory remain largely intact (Mayes, 1988; Parkin, 1988). There is evidence to indicate, however, that the long-term memory function of patients with amnesia can be influenced markedly by the presence of frontal lobe dysfunction (e.g. Moscovitch, 1982; Squire, 1982; Squire and Zola, 1998).

[2] Previously reported scan (Gadian *et al.*, 2000).

2.2.2 Short-term memory span

Short-term memory has a limited storage capacity (7±2 chunks of information, Miller, 1956) and refers to the storage of information for a limited period of time. The working memory model proposed by Baddeley and Hitch (1974) describes short-term memory as comprising a controlling attentional system (central executive), which supervises and coordinates a number of subsidiary slave systems, including the phonological loop (phonological store, articulatory loop; possibly dependent on Brodmann areas 44, 40, and 6, according to Paulesu *et al.*, 1993) and the visuo-spatial sketchpad (thought to depend on the right hemisphere, Smith and Jonides, 1996). For the purpose of the discussions presented in this thesis, short-term memory span refers to the capacity of the phonological store/visuo-spatial system, whereas immediate memory (e.g. immediate recall of stories) refers to memory that exceeds the capacity of short-term memory span and is possibly supported by a temporary store that interfaces with short-term and long-term memory, such as the 'episodic memory buffer' (e.g. Baddeley, 2000; Baddeley and Wilson, 2002).

Patients with adult- and child-onset amnesia typically demonstrate intact performance on measures of short-term memory span. For example, a number of studies have reported normal performance on measures of verbal memory (digit) span (adult-onset: e.g. Scoville and Milner, 1957; Warrington and Weiskrantz, 1968; Tulving *et al.*, 1991; Henke *et al.*, 1999a; child-onset: e.g. Ostergaard, 1987; Broman *et al.*, 1997; Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000) and nonverbal memory (block) span (adult-onset: e.g. Milner *et al.*, 1968; Tulving *et al.*, 1991; De Renzi and Lucchelli, 1993; Schnider *et al.*, 1995; Henke *et al.*, 1999a; child-onset: e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000).

2.2.3 Long-term declarative memory

Adult-onset amnesia is associated with deficits in delayed visual and verbal declarative memory. For example, a number of studies of patients with adult-onset amnesia have reported delayed memory impairments as assessed using the Wechsler Memory Scales (WMS-R (Wechsler, 1987); Scoville and Milner, 1957; Zola-Morgan *et al.*, 1986; Victor and Agamanolis, 1990; Rempel-Clower *et al.*, 1996; Reed and Squire, 1997; Holdstock *et al.*, 2000a). A further measure of memory can be obtained from the

scale's memory quotient (MQ), a measure predominantly consisting of immediate memory measures on the WMS-R. General memory impairments have been noted in these same patients, as reflected by memory quotients substantially lower (e.g. 20+ points, Butters and Cermak, 1980) than full scale IQ (e.g. Scoville and Milner, 1957; Zola-Morgan *et al.*, 1986; Victor and Agamanolis, 1990; Rempel-Clower *et al.*, 1996; Reed and Squire, 1997; Holdstock *et al.*, 2000a). Until recently (CMS, Cohen, 1997; described in Chapter 4), no such test of general memory was available to test memory function in children. For this reason, Vargha-Khadem *et al.* (1992) adapted the adult Wechsler Memory Scales (WMS, Wechsler and Stone, 1945) for use with children (WMS-a), by using age-appropriate material and collecting age-appropriate norms. Using this test, Vargha-Khadem *et al.* (1997) and Gadian *et al.* (2000) characterised a delayed visual and verbal memory impairment in DA patients with bilateral hippocampal pathology sustained in childhood. These same patients were not significantly impaired on immediate memory measures, and this was reflected by the MQ[3] not being much lower than verbal IQ in most cases. However, as reported by Gadian *et al.* (2000) the MQ of healthy controls of a similar age and verbal IQ to that of the five patients reported in that study had MQ scores on average twelve points above their verbal IQ scores. These findings suggest that the patients with DA had lower MQ scores than expected from their verbal IQ performance.

2.2.4 Executive function

Amnesic patients with frontal lobe dysfunction exhibit deficits on tasks in which performance depends on memory for certain kinds of spatial and temporal information (for a review see Schacter, 1987). For example, patients with Korsakoff's amnesia were unable to identify whether an item was presented in a male or female voice (Schacter *et al.*, 1984) or on the first list or second lists (Huppert and Percy, 1976; Squire, 1982). These same patients (e.g. Squire, 1982; Schacter *et al.*, 1984) exhibited deficits on tasks assessing different aspects of executive function, such as the Wisconsin Card Sorting test (WCST, Grant and Berg, 1948; Heaton, 1981) and the test of verbal fluency (Thurstone, 1938). Based on these findings Squire and Zola (1998) suggested that episodic memory

[3] WMS-a MQ is obtained from predominantly verbal immediate memory measures.

and free recall might be more impaired than semantic memory and recognition in patients with amnesia following additional damage to the frontal lobes.

The WCST is one example of a test sensitive to executive function. Executive function is an umbrella term describing the ability to plan ahead and organise behaviour across time and space in order to fulfill goals and intentions (e.g. Luria, 1973; Shallice, 1982). The WCST assesses problem solving and the ability to change strategy in response to altered feedback about performance. Deficits on the WCST are often marked both by perseverations, in which the participant continues to produce a formerly appropriate response that is no longer appropriate, and by failure to maintain set, in which the participant switches from an appropriate to an inappropriate response. There are a variety of reasons for failure on the WCST but some consider it to reflect rigidity of processing and the incapacity to adapt an ongoing schema of action. Such perseverative and inflexible responding has been reported following prefrontal damage in adults (e.g. Milner, 1963) and children (e.g. Pennington *et al.*, 1985), whereas amnesic patients with MTL damage generally do not demonstrate deficits on WCST (Milner *et al.*, 1968; Tulving *et al.*, 1991; Rempel-Clower *et al.*, 1996; Kitchener *et al.*, 1998; Henke *et al.*, 1999a; Verfaellie *et al.*, 2000; Van der Linden *et al.*, 2001).

Data supporting an association between WCST performance and frontal lobes derive from the original investigation of Milner (1963) using epilepsy patients, and more recently functional (PET, fMRI and MEG) imaging studies (e.g. Weinberger *et al.*, 1986; Rezai *et al.*, 1993; Seidman *et al.*, 1994; Wang *et al.*, 2001). However, some studies of frontal lesioned patients have failed to find an associated WCST deficit (e.g. Heck and Bryer, 1986; Anderson *et al.*, 1991).

In an attempt to clarify the role of the frontal lobes in WCST performance, Stuss *et al.* (2000) tested 46 patients with ventromedial, dorsomedial or dorsolateral frontal injury. They found that patients with dorsomedial frontal lobe lesions (including anterior cingulate gyrus) were the most impaired on the standard WCST measures (i.e. total number of categories), patients with ventromedial frontal lobe lesions (including orbital frontal damage) were the most impaired at maintaining set, whereas patients with dorsolateral frontal lobe lesions generated the most perseverative errors. The findings of Stuss *et al.* (2000) suggest that different patterns of impairment are associated with different regions of frontal lobe injury. Ventromedial, including orbitofrontal abnormality may be associated with failure to suppress responses to irrelevant (but salient) stimuli and

thus result in a failure to maintain set (Levine *et al.*, 1998; Stuss *et al.*, 2000), whereas dorsolateral frontal lobe abnormality may be associated with rigidity of processing and an incapacity to adapt to an ongoing schema of action, resulting in more perseverative errors (Stuss *et al.*, 2000).

Other tests of executive functioning include verbal fluency (Thurstone, 1938) and self-ordered pointing (Petrides and Milner, 1982). Verbal fluency requires the individual to use a self-generated search strategy. This organised searching is thought to depend on executive skills, and indeed deficits; for example producing fewer words, rule breaks, and perseverations are seen following frontal lobe damage in adults (Milner, 1964). In addition, functional imaging studies have identified increased activation in the inferior frontal gyrus bilaterally during letter (e.g. Frith *et al.*, 1991) and category fluency (e.g. Pihlajamäki *et al.*, 2000). Activation was also found in the left hippocampus and parahippocampal region, the retrosplenial region and the parietal lobe during category fluency (e.g. Pihlajamäki *et al.*, 2000). Evidence for the involvement of the temporal lobes in category fluency can also be seen in studies of patients with semantic dementia (e.g. Hodges and Patterson, 1995).

The study of verbal fluency in patients with amnesia has generated mixed results. Some amnesic patients show a reduced number of correctly generated items on the letter fluency task (e.g. Tulving *et al.*, 1991; Kitchener *et al.*, 1998; Verfaellie *et al.*, 2000) and the category fluency task (e.g. Verfaellie *et al.*, 2000), while other studies have not reported such deficits (e.g. Milner *et al.*, 1968; Rempel-Clower *et al.*, 1996; Henke *et al.*, 1999a; Van der Linden *et al.*, 2001). It is difficult to know whether the reduced number of correct items generated reflect poor retrieval strategies or a reduced semantic/lexical store. In patients with semantic dementia, a reduction in the number of items generated is thought to reflect a reduction in the semantic store (e.g. Hodges and Patterson, 1995), whereas in patients with bilateral or left unilateral frontal lesions, a reduction in the number of items generated on letter and category fluency tasks is thought to be related to difficulties in searching and organising information within semantic memory (e.g. Janowsky *et al.*, 1989). Therefore, it is possible that patients with amnesia due to MTL damage who show impairments in generating items on fluency tasks have additional damage to the semantic store or frontal lobe dysfunction.

Self-ordered pointing (SOP) involves the use of both storage and executive systems within working memory. Patients with frontal lobe lesions are significantly

impaired in their ability to plan effectively within this task and to keep track of their progress (Petrides and Milner, 1982). In addition, patients with extensive unilateral temporal lobe lesions that includes the hippocampus are impaired at this task (Petrides and Milner, 1982). This deficit is material-specific dependent on the side of injury. In monkeys, lesions of the dorsal and ventral banks of the principal sulcus impair performance in SOP, but not mnemonic function (Petrides, 1991a; 1995). Functional imaging studies (e.g. Petrides *et al.*, 1993; Jahanshahi *et al.*, 1995) also demonstrate that the dorsolateral prefrontal cortex may be involved in successful SOP performance.

Finally, the frontal lobes play a supervisory role in attention (e.g. Shallice, 1988; Stuss *et al.*, 1995). The domain of attention can be divided into sustained attention, selective attention, switching attention and sharing attention. Sustained attention is required when relevant events occur at a relatively slow pace over prolonged periods of time, and is thought to involve the right dorsolateral prefrontal cortex (Cohen *et al.*, 1988; Petrides, 1991b; Wilkins *et al.*, 2000). Selective attention is required when relevant events are selected from an environment also containing irrelevant events, and this too is thought to involve the dorsolateral prefrontal cortex (e.g. Richer *et al.*, 1993). Switching attention involves shifting from one concept to another within one set of stimuli. Again, evidence suggests a role for the dorsolateral prefrontal cortex in switching attention (e.g. Owen *et al.*, 1993). Finally, sharing attention is required when two or more unrelated tasks have to be carried out at the same time. Fletcher *et al.* (1995), in a PET study, identified increased activation in the anterior cingulate during attention sharing. Therefore, subtests from the Test of Everyday Attention (TEA, Robertson *et al.*, 1996; and its child version, TEA-Ch, Manly *et al.*, 1999) were administered in order to assess these various aspects of attention.

2.2.5 Basal ganglia function

Previous studies of the neuropathology associated with DA, using voxel-based morphometry, have identified putamen grey matter abnormality, a finding consistent with the hypoxic-ischaemic episodes suffered by these patients (Gadian *et al.*, 2000; Salmond *et al.*, 2000a; 2000b).

Although the basal ganglia are thought to play a primary role in motor function (e.g. Mink, 1999), their precise function is unclear (e.g. Graybiel, 1995). According to Salmon and Butters (1995), the basal ganglia and cerebellum play important roles in

motor-skill learning. The basal ganglia are thought to sequence the component acts into a motor program and the cerebellum is thought to order events in time. The basal ganglia may also be important for perceptual skill learning (e.g. Knowlton *et al.*, 1996).

Basal ganglia function has been assessed using a number of different motor tasks, such as mirror drawing (e.g. Milner, 1962), serial reaction time (Vakil *et al.* 2000) and rotary pursuit (Heindel *et al.*, 1988; 1989). As discussed in Section 1.7.1, Chapter 1, adult amnesia associated with MTL pathology has typically not been related to deficits in motor skill learning. For example, HM demonstrated preserved motor skill learning on the rotary pursuit task (Corkin, 1968). In this task the participant is required to follow a light with a stylus for a set amount of time, and the amount of time on target (following the moving light) increases with learning trials. The rotary pursuit task is sensitive to putamen and caudate damage (Heindel *et al.*, 1988; 1989). For example, Heindel *et al.* (1989) compared the performance of patients with Huntington's disease (HD), Alzheimer's disease (DAT), and those with amnesia on the rotary pursuit task. In this study, they found that patients with HD (caudate damage), were impaired in the acquisition of this motor skill, whereas the time on target for the DAT and amnesia groups improved significantly with repetition. These findings suggest that deficits in motor skill learning are associated with basal ganglia damage.

2.2.6 Specific aims

The aims of the studies reported in this chapter are to quantify the long-term declarative memory impairments associated with DA and to establish a baseline of neuropsychological function. Short-term memory was assessed using measures of memory span (digit and block span). Long-term declarative memory was assessed using two baseline memory measures: the Sunderland parental questionnaire (Sunderland *et al.*, 1983) of everyday memory ability and the Wechsler Memory Scales adapted for children (WMS-a, Vargha-Khadem *et al.*, 1992). Tests of executive function, such as the WCST, verbal fluency and self-ordered pointing have been associated with frontal lobe pathology (e.g. Milner, 1964; Petrides and Milner, 1982; Stuss *et al.*, 2000) and therefore these tests were administered in order to rule out any possible contribution from frontal lobe dysfunction to the memory impairments associated with DA. The frontal lobes also play an important role in the control of attention. If a participant is not attending to a task, it is difficult to attribute any deficit in performance to the cognitive skill assessed by the task.

Therefore, assessment of attention (TEA/TEA-Ch) enabled this possible confounding factor to be taken into account when assessing other cognitive abilities.

As previous studies of DA have reported bilateral basal ganglia abnormality, a test of basal ganglia function, the rotary pursuit task, was administered in order to assess any basal ganglia dysfunction associated with DA.

2.3 METHOD

2.3.1 Procedure

The baseline neuropsychology assessment consisted of tests of memory span, long-term declarative memory, executive function and attention, and basal ganglia function.

2.3.1.1 Short-term memory span

The digit span subtest of the Wechsler Intelligence Scales (Bracken, 1992; Wechsler, 1997a) and the Corsi block span test (Corsi, 1972; Isaacs *et al.*, 1989) were used as measures of verbal and spatial memory span respectively. Both tests measure forward and backward span and these were calculated as the longest string of items correctly produced.

2.3.1.2 Long-term declarative memory

The Sunderland questionnaire (Sunderland *et al.*, 1983): This questionnaire requires parents/guardians to rate the frequency of different types of everyday memory problems encountered by the participant, for example, forgetting where s/he has left a belonging. Parents rated each of the 28 items from A (has not occurred in the past 3 months) to I (occurs once a day). Scores of 1 to 9 were assigned to ratings A to I, and these were summed for each participant. Parental ratings were not available for two of the adult control participants (NC10 and NC11) and therefore a self-rating was accepted.

The Wechsler Memory Scales adapted for children: The Wechsler Memory Scale – Form 1 (Wechsler and Stone, 1945) was administered in the standard way, but with age corrections and adaptations for children (Vargha-Khadem *et al.*, 1992). Measures of

immediate and unalerted delayed recall were obtained for a) story recall: two stories were read for immediate and delayed recall after a 90-minute filled delay; b) design recall: drawing three geometric designs immediately after presentation and after 40-minute filled delay; and c) paired-associate learning: 10 pairs of words, six semantically related (e.g. up-down) and four unrelated (e.g. cabbage-pen), were read three times for immediate cued recall after each presentation and delayed cued recall after a 90-minute filled delay.

The percentage correctly recalled was calculated from the raw scores of each subtest at each test phase. Furthermore, for paired associate learning, the number of correctly recalled semantically related and unrelated pairs was calculated across the three learning trials to provide a total learning score for each type of word-pair.

MQ was based on measures of immediate recall (stories, paired associates, and designs) plus the additional subtests of information (six questions on personal and current information, e.g. how old are you?), orientation (questions on general orientation, e.g. what year is this?), mental control (e.g. count backwards from 20 to 1), and digit span (taken from the Wechsler intelligence scales). This sum of scores was corrected for age; then, using the normative tables, a general memory quotient (MQ) was calculated (Vargha-Khadem *et al.*, 1992). The MQ consists of two verbal recall measures, one visual recall measure, and four additional verbal subtests, and therefore is considered to be a measure mainly of verbal immediate memory. In calculating an IQ-MQ discrepancy, verbal IQ was used.

2.3.1.3 Executive function

Wisconsin Card Sorting Test (WCST): The WCST (Heaton, 1981) consists of two sets of 64 response cards that the participants must match to 4 key cards placed in an array before them. The 4 key cards differ in colour, form and number. They comprise cards showing 1 red triangle, 2 green stars, 3 yellow crosses and 4 blue circles. The participant is required to match each of the 64 cards to one of the key cards. These cards bear shapes of different numbers and different colours. The examiner informs the participants whether the choice is correct or not, but this is the only feedback that is given. Colour is the first correct sorting dimension, followed by form and then number. A change in sorting principle is made after 10 correct placements have been made by the participant. Participants are not informed of the change and only become aware of it through the change in the examiner's response to each card placement. The participant is

therefore required to modify the response, taking into consideration the new feedback. The sorting proceeds until either 6 categories are completed (colour, form, and number, twice each) or until all 128 cards are used. Scores are derived by calculating the following: number of categories correctly sorted (max = 6), total correct responses (not including those in a run of 10 correct responses), total perseverations of the preceding category (PPC, Stuss *et al.*, 2000), total perseverations of the preceding error (PPR, Stuss *et al.*, 2000), failure to maintain set (FMS, the number of times an incorrect response occurred after 3 or more consecutively correct responses, Stuss *et al.*, 2000), unique errors (where the response card did not match the key card on either colour, form or number) and other nonperseverative errors. In addition to the score on failure to maintain set, a high number of correct responses is thought to reflect a failure to maintain set.

Self-ordered pointing (SOP): A new version of the SOP appropriate for children was designed (Vargha-Khadem *et al.*, unpublished test) based on the original task devised by Petrides and Milner (1982). This task consists of black-and-white abstract patterns designed to be verbally nondescriptive but easily discriminable. The task is divided into five blocks with three trials at each list length. The first section is a practice set consisting of three practice trials. Each trial consists of four pages, on which are printed an array of four different stimuli and a single blank page to indicate the end of the trial. The actual stimuli are the same on each page and on each trial within a set, but appear in different spatial positions. The participant is asked to point to one stimulus per sheet of paper and to point to each stimulus only once. Therefore, each time a page is turned, the participant is required to remember which stimuli have already been pointed to, and to point to a novel stimulus. The other sections of the task are the same except that they contain 6, 8, 10, and 12 stimuli, respectively, with the corresponding number of pages. Participants were administered all sections of the task. The score consisted of the summed errors made at each trial on each list-length. In addition, the time taken to complete each section was noted in order to calculate the total time taken.

Letter fluency (Thurstone, 1938): The participants are told they are required to say out loud as many words as they can think of beginning with the letter the experimenter is about to say. They are then told the three rules: no proper nouns, no numbers, and no same words with different endings. The experimenter then instructs 'Say as many words as you can think of starting with the letter F (A and S). Go!' The three rules are repeated before each letter is given. The participants were given a minute to produce the words.

The items produced were then scored for accuracy, perseveration (repetition of the items), and rule breaks (e.g. generating an item that did not begin with that letter or breaking any of the three rules).

Category fluency (Hodges and Patterson, 1995): The participants were asked to generate as many different items/words as possible within a given category. The categories included animals, birds, water creatures, breeds of dog, household items, vehicles, musical instruments, and types of boat. The participants were given a minute to produce the words. The items produced were then scored for accuracy, perseveration (repetition of the items) and rule breaks (e.g. generating an item not in that category or producing the same word with a different ending).

Sustained attention: Elevator counting (Test of Everyday Attention (TEA, Robertson *et al.*, 1996), ages 16+ years). In this subtest, participants are asked to pretend they are in an elevator whose floor-indicator is not functioning. They therefore have to establish which 'floor' they have arrived at by counting a series of tape-presented tones. Score! (Test of Everyday Attention for Children (TEA-Ch, Manly *et al.*, 1999), 6 to 16 years of age). In this subtest the children have to keep count of the number of 'scoring' sounds they hear on a tape, as if they were keeping the score on a computer game. These scores are standardised according to normative data for each age group to obtain scaled scores with a mean of 10 and standard deviation of 3.

Selective attention: Map search (TEA) and Map mission (TEA-Ch). In this subtest participants have to search for one type of symbol (e.g. a knife and fork sign representing eating facilities) among many different symbols on a colour map of the Philadelphia area. The score is the percentage number found in one minute in the child's version and two minutes in the adult's version. As some participants were administered the child's version of the test, and some were administered the adult's version, only the percentage number found in the first minute was analysed.

Switching attention: Visual elevator (TEA). Here, participants have to count up and down as they follow a series of visually presented 'floors' in the elevator. Arrows guide them when to change the direction in which they are counting. Creature counting (TEA-Ch). In this subtest participants are asked to count aliens in a burrow, with occasional arrows telling them when to change the direction in which they are counting. These are self-paced and have a time-per-switch measure as well as an accuracy measure.

These scores are standardised according to normative data for each age group to obtain scaled scores with a mean of 10 and standard deviation of 3.

2.3.1.4 Basal ganglia

Basal ganglia function was tested using the rotary pursuit task (Heindel *et al.*, 1988; 1989). The equipment consisted of a spot of light that moved around the shape of a circle at a set speed for a set time, and a light-sensitive stylus that was used to follow the light when it moved. The participants were told to maintain contact with the light using the stylus held in their preferred hand. The light could be adjusted to rotate at 15, 30, 45 or 60 rpm for a given 20-second trial. All participants were tested on 3 series of 8 trials each, with each series separated by 30 minutes. Within each series, the participants were given a 1-minute rest interval between the 4^{th} and 5^{th} trials, thereby creating a total of 6 blocks of 4 trials each. The total time on target was recorded for each 20-second trial. The first test series was preceded by a block of practice trials to determine the speed of rotation of the light. The participants were given four 20-second practice trials at each successive rpm. The light was then set for the remainder of the participant's testing to the speed which was associated with a score (i.e. time on target) closest to 5 seconds out of 20 seconds (i.e. 25% on target). In this manner, the initial level of performance of all the participants was equated. The learning score was calculated using the following formula: block 6 (trial 4) – block 1 (trial 1).

2.3.2 Analyses

The statistical analyses described in this section apply to the analyses used throughout the studies reported in this thesis.

Since large of numbers of statistical tests were performed in this thesis, the overall probability of a Type 1 error is expected to exceed 5%. Corrections for multiple comparisons were not made over the entire thesis, as these would reduce the power of detecting significant group differences. Instead, strong a priori predictions were made based on previous studies in the literature (high prior probability) predicting a specific pattern of results, including both impaired and intact performances across a range of tasks. Findings were interpreted using these guidelines: p-values of 0.05 to 0.1 were taken as weak evidence for a predicted effect; p-values of less than 0.05 were taken as evidence for a significant effect if predicted; and any significant results at this level that had not

previously been predicted were interpreted with caution, and were taken as indicators for future studies with a similar group of patients.

In order to examine the effects of possible confounding factors on group effects, i.e. age at test, and verbal and/or performance IQ, preliminary analyses were conducted on each measure reported in this thesis using an analysis of covariance (ANCOVA). The inclusion of the covariates was determined by the nature of the task. For example, age at test was included when raw scores were used, verbal IQ was included when a measure required verbal ability, and performance IQ was included when a measure required nonverbal ability. Details of the ANCOVA models are reported only if the main effect of group was affected by the covariate adjustment; otherwise the unadjusted analyses are reported for simplicity.

Tests of homogeneity of variance (Levene's test of homogeneity) and normality (Shapiro-Wilk) were conducted on the raw data or the residuals of the analyses of variance (ANOVA). If there was a significant difference in the variance of the groups, then nonparametric analyses, e.g. Mann-Whitney U tests, were carried out (in addition to the main analysis in the case of an ANOVA). If there was no significant difference in the variance of the group, then only parametric analyses were conducted. In the case of analysis of variance, this is very robust and violations of the normality assumption are unlikely to affect the validity of the analysis (Howell, 1992, pp 307). A two-sample t test was used to perform univariate tests where appropriate, and mixed-model analyses of variance (ANOVA) were used to examine within-subjects factors.

For mixed-model analyses (between-subjects and within-subjects factors) the F-ratios and p-values were obtained using a Greenhouse-Geisser degrees-of-freedom adjustment of the within-subjects effects for factors with more than two levels. This adjusts for correlation among the observations and is necessary since within-subject measures are not expected to satisfy the independent-errors assumption that underlies the conventional ANOVA calculation. The adjustment is negligible if the observations are effectively independent. In cases where within-subjects factors only had two levels Greenhouse-Geisser adjustments were not necessary since the correlation between the resulting pairs of observations does not affect the validity of the conventional F-test.

Significant main effects with more than two levels and significant interactions were analysed post-hoc using t-tests with a Bonferroni correction.

Only findings with a p-value of less than 0.05 are reported and predicted findings with a p-value less than 0.1 are described in the text.

2.4 RESULTS

2.4.1 Short-term memory span

Table 2:3 shows the mean memory span for the DA and control groups.

Table 2:3 Memory span

Raw scores	DA	NC
Digit span forward	6.4 (0.3)	6.0 (0.3)
Digit span backward	5.0 (0.3)	4.3 (0.4)
Block span forward	6.2 (0.3)	5.5 (0.3)
Block span backward	5.4 (0.4)	5.5 (0.3)

Mean (±SEM)

The analyses (t-tests) revealed no evidence for an effect of group on forward or backward digit or block span ($p > 0.1$).

2.4.2 Long-term declarative memory

2.4.2.1 Sunderland questionnaire

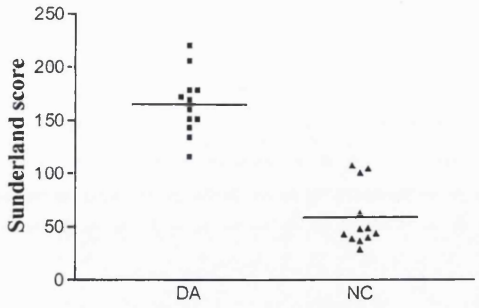
Table 2:4 shows the mean (±SEM) frequency rating for each group on the Sunderland memory questionnaire. Figure 2:1 shows the individual ratings on the Sunderland questionnaire and the mean rating (solid line) of each group.

Table 2:4 Sunderland memory questionnaire

	DA	NC
Total raw score	165.5 (8.4)	58.8 (8.3)

Mean (±SEM)

Figure 2:1 Sunderland memory questionnaire



The graph indicates that there was no overlap between the ratings of each group and the analysis (t-test), as expected, revealed that the DA group had a higher frequency (rating) of everyday memory difficulties than the control group ($t(22) = -9.0$; $p < 0.0001$).

2.4.2.2 Wechsler Memory Scales-adapted for children (WMS-a)

Table 2:5 shows the summary scores (mean±SEM) for each component of the WMS-a including the verbal IQ-MQ discrepancy in each group.

Table 2:5 WMS-a summary scores

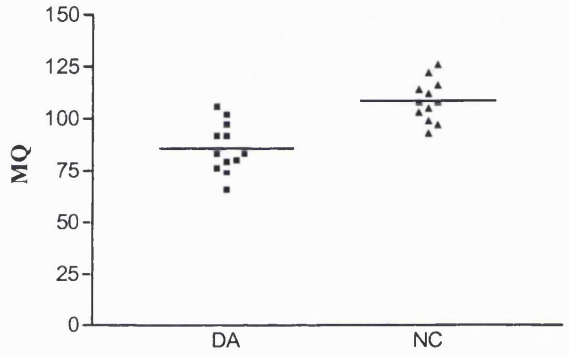
	DA	NC
MQ	85.8 (3.5)	108.6 (2.9)
VIQ-MQ discrepancy (VIQ minus MQ)	-6.0 (3.0)	13.0 (3.0)
Immediate story recall (%)	27.9 (2.7)	53.8 (3.7)
Delayed story recall (%)	3.0 (1.5)	44.8 (3.9)
Immediate design recall (%)	56.5 (7.6)	92.6 (2.5)
Delayed design recall (%)	15.2 (4.7)	78.0 (5.6)
Immediate (trial 3) paired-associate recall (%)	62.5 (4.5)	94.2 (2.6)
Delayed paired-associate recall (%)	50.0 (4.1)	86.7 (4.7)
Semantically related pairs (%)	71.5 (5.1)	89.4 (3.5)
Semantically unrelated pairs (%)	29.2 (8.6)	66.7 (5.9)

Mean (±SEM)

2.4.2.2.1 General memory quotient (WMS-a)

Figure 2:2 shows the individuals' MQ and the mean MQ (solid line) of each group. Note the MQ does not include the delayed recall scores. There was overlap between the groups, indicating that some patients with DA performed at a similar level to controls.

Figure 2:2 General memory quotient (WMS-a)



The analysis (t-test) revealed a significant general memory impairment in the DA group relative to controls ($t(22) = 5.04$; $p < 0.0001$).

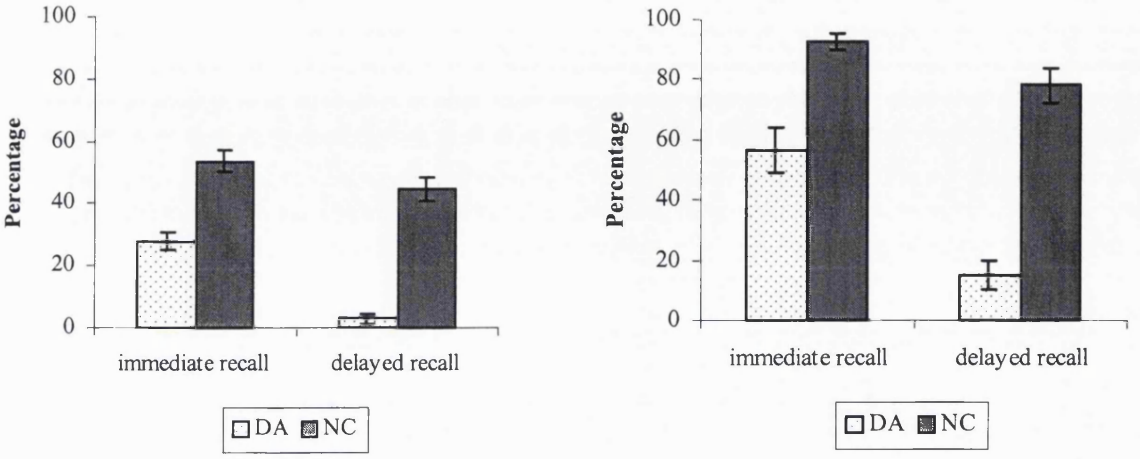
A verbal IQ-MQ discrepancy (see Table 2:5) was estimated from the MQ of the WMS-a. As expected from previous reports of DA (e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000) the analysis (t-test) revealed that the DA group had a mean MQ lower than predicted from verbal IQ relative to controls ($t(22) = 4.82$; $p < 0.0001$).

2.4.2.2.2 WMS-a subtests

Table 2:5 and Figure 2:3 (a), (b) and (c) show the mean (±SEM) percentage correct of the DA and control groups for immediate and delayed memory on story recall, design recall, and paired associate learning, respectively.

The analyses were conducted using separate mixed-model ANOVAs with a between-subjects factor of group (DA, NC) and a within-subjects factor of time (immediate, delay).

Figure 2:3 (a) WMS-a story recall *(b) WMS-a design recall*



The analysis (ANOVA) of recall of the stories revealed significant main effects of Group ($F(1,22) = 66.16$; $p < 0.0001$) suggesting that overall the control group performed better than the DA group, and Time ($F(1,22) = 189.91$; $p < 0.0001$) suggesting that overall immediate recall is better than delayed recall.

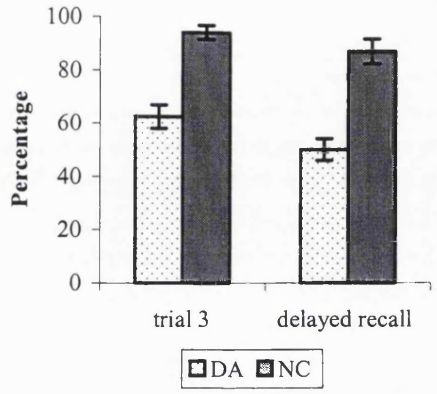
These main effects, as expected, were qualified by a significant Group by Time interaction ($F(1,22) = 41.69$; $p < 0.0001$). Follow-up analyses revealed that the control group performed better than the DA group at immediate ($t(22) = 5.72$; $p < 0.0001$) and delayed[4] ($t(22) = 10.10$; $p < 0.0001$) recall, but the mean group difference was larger on delayed recall (41.78) than on immediate recall (25.91).

The analysis (ANOVA) of recall of the designs revealed significant main effects of Group ($F(1,22) = 58.77$; $p < 0.0001$) suggesting that overall the control group performed better than the DA group, and Time ($F(1, 22) = 44.69$; $p < 0.0001$), suggesting that overall immediate recall was better than delayed recall.

These main effects, as expected, were qualified by a significant Group by Time interaction ($F(1,22) = 10.30$; $p = 0.004$). Follow-up analyses revealed that the control group performed better than the DA group at immediate[5] ($t(22) = 4.49$; $p < 0.0001$) and delayed ($t(22) = 8.58$; $p < 0.0001$) recall, but the mean group difference was larger on delayed recall (62.85) than on immediate recall (36.02).

[4] The variance on delayed story recall was heterogeneous; therefore the group difference was confirmed with a Mann-Whitney U test ($U = 0$; $p < 0.0001$).

Figure 2:3 (c) WMS-a paired associate learning



The analysis (ANOVA) of paired associate learning revealed significant main effects of Group ($F(1,22) = 46.29$; $p < 0.0001$) and Time ($F(1,22) = 13.71$; $p = 0.001$), but unexpectedly no Group by Time interaction. These findings suggest that overall the control group recalled more than the DA group and immediate recall was better than delayed recall, but there was no evidence of abnormal forgetting in the DA group relative to controls.

The paired-associate learning test involves learning both semantically related (e.g. knife-sharp) and semantically unrelated (e.g. in-although) pairs of words. The finding that fewer paired associates were recalled by the DA group both immediately and after a delay may be due to the DA group having learned fewer unrelated pairs than the control group over the three learning trials. Analysis of the total number of related and unrelated pairs correctly recalled over the three learning trials using a mixed-model ANOVA with a between-subjects factor of group (DA, NC) and a within-subjects factor of type (related, unrelated) revealed significant main effects for both factors. Overall, both groups recalled more semantically related than semantically unrelated pairs (Type: $F(1,22) = 31.47$; $p < 0.0001$), and the control group recalled more pairs than the DA group (Group: $F(1,22) = 19.38$; $p < 0.0001$). There was no evidence for a Group by Type interaction ($p > 0.1$). These findings suggest that both groups learned more semantically related than semantically unrelated pairs over the three learning trials.

[5] The variance on immediate design recall was heterogeneous; therefore the group difference was confirmed with a Mann-Whitney U test ($U = 11.5$; $p < 0.0001$).

2.4.3 Executive function

Table 2:6 shows the mean (±SEM) raw score for each index of the WCST for both groups.

Table 2:6 Wisconsin Card Sorting Test

	DA	NC
Categories	5.8 (0.2)	5.8 (0.2)
Total correct	14.1 (3.9)	13.0 (2.2)
Perseveration to previous category (PPC)	9.5 (2.7)	11.2 (2.9)
Perseveration to previous response (PPR)	2.4 (0.7)	4.2 (1.2)
Failure to maintain set (FMS)	1.4 (0.5)	1.3 (0.4)
Non-perseverative errors (Errors)	5.7 (1.0)	5.8 (1.0)
Unique errors	1.5 (0.6)	2.3 (0.9)

Mean (±SEM)

The analyses (t-tests) revealed no evidence for an effect of group on any of the WCST measures ($p > 0.1$).

Table 2:7 shows the mean (±SEM) total number of errors (raw scores) and the total time taken for both groups on the self-ordered pointing task.

Table 2:7 Self-ordered pointing task

	DA	NC
Total errors	19.4 (1.9)	14.9 (2.3)
Total time (seconds)	460.7 (41.2)	423.4 (26.3)

Mean (±SEM)

The analyses (t-tests) revealed no evidence for an effect of group on either the total number of errors produced or the total time taken ($p > 0.1$).

Table 2:8 shows the mean (±SEM) total correct and the mean (±SEM) number of errors (raw scores) for each group on the letter fluency task.

Table 2:8 Letter fluency (FAS)

	DA	NC
Correct	30.3 (3.2)	29.3 (2.8)
Perseverative errors	1.8 (0.9)	0.3 (0.2)
Rule break	2.7 (1.0)	1.1 (0.4)

Mean (±SEM)

The analyses (t-tests and Mann-Whitney U tests) revealed no evidence for an effect of group on any of the letter fluency measures ($p > 0.1$).

Table 2:9 and Figure 2:4 (a) and (b) show the mean (±SEM) total correct and the mean (±SEM) number of errors (raw scores) for each group on the category fluency task.

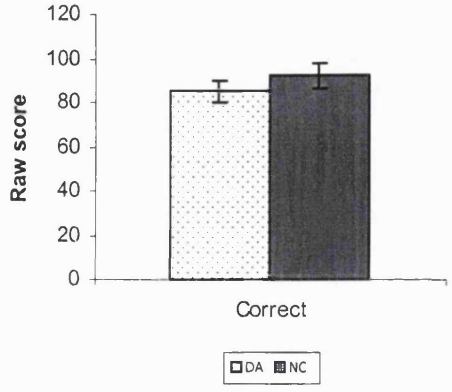
Table 2:9 Category fluency

	DA	NC
Correct	84.9 (4.9)	92.3 (5.7)
Perseverative errors	5.7 (2.2)	0.8 (0.3)
Rule break	4.5 (1.4)	1.8 (0.8)

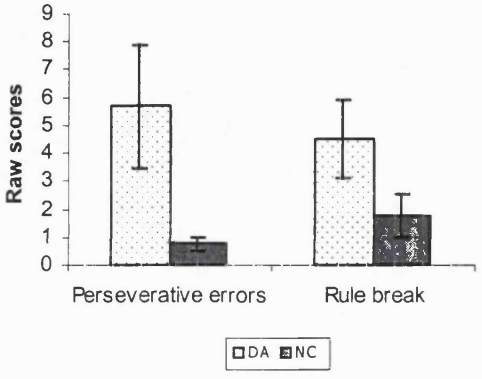
Mean (±SEM)

Figure 2:4 Category fluency

(a) *Total correct*



(b) *Errors: perseverative and rule breaks*



The analyses (t-tests and Mann-Whitney U tests) revealed no evidence for an effect of group on the total number correct or rule breaks ($p > 0.1$). However, there was evidence to suggest that the DA group generated more perseverative errors[6] ($U = 22.5$; $p = 0.003$), than the control group. In order to test whether the increase in perseverative errors in the DA group was a consequence of a deficient ability to monitor previously generated responses due to an immediate memory impairment as found in Section 2.4.2.2.2, an analysis of covariance (ANCOVA) was performed with the total percentage correct on immediate story recall (WMS-a) as a covariate. The ANCOVA analysis revealed no evidence of an effect of group when story recall percentage correct was included as a covariate ($p > 0.1$). These findings suggest that the increase in perseverative errors in the patients with DA may be related to their immediate memory impairment.

Table 2:10 show the mean (±SEM) standard scores for the visual subtests of the attention test and the mean (±SEM) percentage correct in the auditory counting attention subtest for each group.

Table 2:10 Test of Everyday Attention (TEA and TEA-Ch)

	DA	NC
Map search	7.9 (1.0)	10.2 (0.8)
Visual reversal counting	10.3 (1.2)	10.2 (0.7)
Visual reversal counting time	9.3 (1.3)	9.3 (0.9)
Auditory counting	95.1 (2.9)	92.6 (4.6)

Mean (±SEM)

The analyses (t-tests and Mann-Whitney U test) revealed no evidence for an effect of group on any of the measures of attention ($p > 0.1$).

2.4.4 Basal ganglia

Table 2:11 show the mean (±SEM) time on target on each test block, the initial speed, and total learning score for each group.

[6] The variance of the scores was not homogenous; therefore a non-parametric Mann-Whitney U test was used.

Table 2:11 Rotary pursuit performance

Block	DA	NC
1	23.6 (3.08)	22.4 (1.88)
2	29.7 (2.59)	26.1 (1.98)
3	31.7 (3.05)	32.3 (2.46)
4	32.8 (2.83)	33.3 (2.61)
5	33.8 (3.30)	35.5 (2.84)
6	35.8 (2.84)	39.0 (2.77)
Initial speed	57.0 (2.00)	55.0 (3.37)
Total learning score (block 6 – block 1)	12.2 (3.46)	16.6 (2.66)

Mean (±SEM)

The analysis (t-tests) revealed no evidence for an effect of group for the initial speed of rotation, or learning score ($p > 0.1$).

2.5 DISCUSSION OF BASELINE NEUROPSYCHOLOGY TESTS

Adult amnesia resulting from MTL or diencephalic pathology is typically associated with a selective long-term declarative memory impairment in the absence of any other intellectual and cognitive dysfunction. Typically, short-term memory and procedural skill learning (nondeclarative memory) remain largely intact (Mayes, 1988; Parkin, 1988). However, there is evidence to indicate that the memory function of patients with amnesia can be influenced markedly by frontal lobe dysfunction (e.g. Moscovitch, 1982; Squire, 1982).

Consistent with previous reports of adult-onset amnesia (e.g. Mayes, 1988; Parkin, 1988; Tulving *et al.*, 1991) and DA (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000), there was no evidence of a short-term memory span impairment in the DA group. However, patients with DA were impaired relative to age, sex and verbal IQ matched controls on tests of long-term declarative memory, as measured using the Sunderland parental questionnaire and the Wechsler Memory Scales adapted for children.

As expected, the patients with DA were impaired relative to the control group on MQ (WMS-a), even though there was considerable overlap. The control group had a mean MQ thirteen points above their verbal IQ, whereas the DA group had a mean MQ

six points below their verbal IQ. The overlap in scores between the groups may be a consequence of MQ being predominately a composite score of verbal immediate measures, as immediate memory is less impaired than delayed memory in patients with DA (see below). Previous studies have estimated the severity of amnesia from the IQ-MQ discrepancy, as amnesia is associated with a memory score lower than that expected from IQ (e.g. Scoville and Milner, 1957; Mayes, 1988; Parkin, 1988). Although a discrepancy of six points in the DA group may not seem that severe compared to some adult-onset cases[7] (e.g. Zola-Morgan *et al.*, 1986; Reed and Squire, 1997; Holdstock *et al.*, 2000a), it is in the opposite direction to that of the IQ-matched controls. It is also worth noting that the range of verbal (VIQ) and full scale (FS) IQ in patients with adult-onset amnesia is generally higher than that of the DA group: Zola-Morgan *et al.* (1986) RB = VIQ 111, FS 103; Reed and Squire (1997) adult range = FSIQ 92-120, VIQ not reported; Holdstock *et al.* (2000a) YR = VIQ 108, FS 102; DA range in this chapter = VIQ 80-108, FS 75-114. Yet the MQ, comprising predominantly immediate memory measures, is of a similar magnitude across studies: Zola-Morgan *et al.* (1986) RB = 91; Reed and Squire (1997) adult range = 67-89; Holdstock *et al.* (2000a) YR = 66; DA range in this chapter = 66-106. The difference in IQ range between adult-onset and child-onset cases may be due to the IQ measure in adult-onset amnesia reflecting intellectual abilities acquired prior to the onset of amnesia, whereas the IQ measure in patients with DA reflects intellectual abilities acquired post onset of amnesia. However, the finding that the MQs are of a similar magnitude between patients with adult- and child-onset amnesia suggests that their memory performance on this measure is at a similar level. This suggests that comparing IQ-MQ discrepancies across samples of patients with amnesia may not be the best comparison of severity of amnesia.

The patients with DA were impaired on measures of immediate recall memory relative to controls. Although previous studies of DA (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000) did not report a significant difference between patients with DA and controls on immediate memory measures, inspection of the data reported in these studies suggests a trend in this direction. This finding is consistent with some studies of adult-onset amnesia patients. For example, Scoville and Milner (1957) reported that HM showed impairments on story and design immediate recall (WMS), and low MQ's

[7] For purpose of comparison only studies of adult-onset amnesia reporting data from the WMS-R were included, as both the MQ of the WMS-R and WMS-a comprise immediate memory measures.

reported in more recent studies of patients with adult-onset amnesia are also indicative of poor immediate memory (e.g. Reed and Squire, 1997; Holdstock *et al.*, 2000a). Recently, Baddeley and Wilson (2002) found that although all twenty-seven patients included in their study were impaired on delayed prose recall there was varying performance on immediate prose recall. Some patients performed at normal levels, while others were impaired. This varying performance was associated with intelligence and executive capacity, such that high intelligence and executive capacity (WCST) was associated with better immediate memory recall (Baddeley and Wilson, 2002). Baddeley and Wilson (2002) concluded that immediate recall memory requires preserved long-term memory representations and schemata, executive processes, and maintenance in the episodic memory buffer. The finding of immediate recall impairments reported in this chapter may reflect impairments in the 'episodic memory buffer'. However, unlike the findings reported by Baddeley and Wilson (2002), no significant correlations were found between immediate prose recall and WCST performance or verbal IQ ($p > 0.1$). Nevertheless, the lack of relationship reported in this chapter may be a consequence of a lack of power in detecting such a relationship. This lack of power may be caused by the small sample size; Baddeley and Wilson (2002) included twenty-seven patients in their analysis, whereas the analysis reported in this chapter included only twelve patients.

Although the DA group was impaired relative to controls on measures of story and design immediate and delayed recall memory, delayed memory was more impaired than immediate memory. These findings suggest that, as expected, the DA group showed abnormal forgetting relative to the control group. This abnormal forgetting in patients with DA is consistent with previously reported studies of DA (e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000) and some studies of adult-onset amnesia (e.g. Isaac and Mayes, 1999a; 1999b). However, unexpectedly, there was no evidence of increased forgetting in the DA group relative to controls on paired-associate learning.

The performance on paired-associate learning (WMS-a) suggested that although the DA group was impaired relative to controls at recall after three learning trials and at delayed recall, they did not show evidence of abnormal forgetting. The finding that fewer paired associates were recalled by the DA group both immediately and after a delay was not due to the DA group having benefited less form the relatedness of the word-pairs compared to the control group, as might be expected from the 'semantic encoding deficit hypothesis' of Cermak and Moreines (1976). Together, these findings suggest that when

patients with DA were given repeated exposure to the study items (both semantically related and unrelated), their rate of forgetting was less than when they were given a single study exposure, such as story and design recall. One possible reason for this difference in performance may be the role of repetition. Repeated exposure to the study items may render the task less dependent on episodic memory as the information becomes less tied to a single study context and therefore more context-free (e.g. Baddeley *et al.*, 2001). The influence of repeated presentation on memory performance in patients with DA is investigated in more detail in Chapter 6. An alternative possibility may be due to the word-pair recall being a test of cued recall, whereas story and design recall are considered tests of free recall. Although free recall can in turn involve self-generated cued recall (i.e. remembering a piece of information may act as a prompt to remember other pieces of information; e.g. Spear, 1978) explicit cued recall may be relatively easier than free recall for patients with amnesia (e.g. Isaac and Mayes, 1999a; 1999b).

Consistent with previous reports of adults with amnesia, there was no evidence of impairments on measures of executive function e.g. WCST (Milner *et al.*, 1968; Tulving *et al.*, 1991; Rempel-Clower *et al.*, 1996; Kitchener *et al.*, 1998; Henke *et al.*, 1999a; Verfaellie *et al.*, 2000; Van der Linden *et al.*, 2001). These findings suggest that the DA group do not have difficulty in problem solving and the ability to change strategy in response to altered feedback about performance.

Unlike patients with semantic dementia (Hodges and Patterson, 1995), there was no evidence to suggest an impairment in the number of correct items generated by the DA group relative to controls on category fluency. According to Hodges and Patterson (1995) a reduction in the number of items generated reflects a reduced semantic long-term store in patients with semantic dementia. This suggests that the DA group has a lexical and therefore, semantic long-term store within a range expected for their age, sex, and verbal IQ, and that they are able to retrieve sufficient information from this store. The finding that the DA group generated more perseverative errors (repetitions) than the control group in category fluency suggests that the DA group have difficulty monitoring their previous responses in this task. In support of this, the group effect was removed when a measure of immediate memory recall was included as a covariate (immediate story recall), suggesting that their increased number of perseverations may be due to difficulty in remembering previously generated category related words. However, performance on letter fluency was not associated with a significant increase in perseverations, suggesting that patients with

DA only have difficulty remembering previous responses when items are from the same category. The effect of semantic relatedness on memory performance will be investigated in more detail in Chapter 6.

Although memory impairments may account for the increased perseverations in DA, this is not typically seen in adult-onset amnesia cases. Instead in adult-onset amnesia cases, deficits on fluency tasks seem to manifest as difficulties in generating items, but not in increased perseverations. For example, patient KC (Tulving *et al.*, 1991), with bilateral MTL and extra-MTL damage (extending to the superior frontal-parietal region) generated fewer words than expected for his level of education on the letter fluency task (perseverations were not reported). Patient PS (Verfaellie *et al.*, 2000), with selective bilateral hippocampal pathology generated fewer words on both the letter and category fluency tasks relative to controls, although both of these scores were within the normal range. Finally, patient RS (Kitchener *et al.*, 1998) with bilateral MTL and extra-MTL damage (including left medial frontal), was severely impaired at letter fluency in that he generated very few items. Therefore, the deficits in DA on fluency tasks seem to be different from the deficits experienced by patients with adult-onset amnesia. Moreover, although dorsolateral frontal lobe dysfunction is associated with increased perseverations (e.g. Stuss *et al.*, 2000), most patients with frontal lobe injury are impaired on more than this aspect of the task, including number of items generated and rule breaks (e.g. Milner, 1964). Therefore, patients with DA do not perform in the same way as frontal lobe patients either.

In relation to this, there was no evidence to suggest an impairment with respect to the number of errors committed or the time taken to complete the SOP task. Deficits on these aspects of the SOP task have previously been associated with frontal lobe impairments (e.g. Petrides and Milner, 1982), and therefore the performance of the DA group is not reflective of frontal dysfunction.

Finally, there was no evidence to suggest an attention deficit in the DA group on tests of sustained, selective, or switching attention. This suggests that the supervisory attention role of the frontal lobes is not affected in cases with DA, and therefore deficits in attention can not account for their severe memory impairments.

It thus seems that when presented with a variety of executive function tests, the DA patients show very little evidence of frontal lobe abnormality. It is interesting to note that the DA group did not show increased perseverative errors relative to their control

group on the WCST, either to the previous category or previous erroneous responses, suggesting that the DA group are impaired only when required to self-monitor their performance without external feedback when items are category related (i.e. category fluency task).

This increase in perseverative errors on a task that has a high memory load combined with the finding that this effect was removed when adjusted for immediate verbal recall memory, suggests some relationship between executive function and immediate verbal recall memory. It is possible that these two cognitive processes (i.e. monitoring previously generated responses of category related information and immediate recall) reflect the function of the 'episodic memory buffer' (e.g. Baddeley, 2000; Baddeley and Wilson, 2002), which possibly is impaired in patients with DA relative to controls. However, this impairment is much less severe than that seen in delayed recall memory, suggesting that immediate recall memory is relatively preserved compared to delayed recall memory.

Although frontal-lobe-type impairments were not detected on the tasks reported in this chapter, this does not entirely rule out the possibility of structural and functional abnormalities within the frontal lobes of these patients. For example, Maguire *et al.* (2001) found that unlike controls, Jon activated the frontal lobes bilaterally when retrieving autobiographical event memories, suggesting a difference in the connectivity of the MTL-frontal circuit in patients with DA. Indeed some studies have suggested that due to the protracted development of the frontal lobes (e.g. Chugani *et al.*, 1987; Chugani, 1994), early MTL pathology may additionally affect the connectivity to, and development of, frontal lobe structures (e.g. Bertolino *et al.*, 1997; Hanlon and Sutherland, 2000). Therefore, it is possible that impairments may be seen on frontal tests that tap into other executive functions such as the ability to plan ahead (e.g. Tower of Hanoi (Shallice, 1982)), which according to Tulving (2002) may require mental time travel, a component of episodic memory. Other deficits may be seen on tasks that require organisational skills (e.g. Behavioural Assessment Dysexecutive Syndrome (BADS, Wilson *et al.*, 1996)).

Finally, there was no evidence to suggest that the DA group was impaired relative to the control group on motor learning skills when tested on the rotary pursuit task. This task is thought to be sensitive to both putamen and caudate damage (Heindel *et al.*, 1988; 1989). Therefore, despite previous reports suggesting grey matter abnormality in the basal ganglia, this was not reflected in a functional impairment. The finding of intact basal

ganglia function is consistent with reports of intact nondeclarative memory abilities associated with amnesia in adults (Corkin, 1968; Squire and Knowlton, 1995; Heindel *et al.*, 1988) and may reflect either recovery of function in later development (e.g. Gadian *et al.*, 2000) or a lack of structural abnormality in this group of patients with DA (see Chapter 3).

2.6 GENERAL CONCLUSION

Twelve patients with selective hippocampal abnormality as revealed on conventional MR imaging, and twelve controls matched to the patients on age, sex, and verbal IQ were selected for participation in the studies reported in this thesis.

As expected, based on reasons for referral and parental reports, the patients were impaired relative to controls on measures of delayed visual and verbal recall memory. Although, there was also evidence to suggest an immediate memory impairment on visual and verbal memory measures, this was less severe than that seen after a delay, and memory span was not impaired. This possibly reflects impairments when the amount of information to be remembered is above memory span, thus requiring the 'episodic memory buffer' (Baddeley, 2000; Baddeley and Wilson, 2002). The finding that forgetting rate was not different between patients and controls following repeated exposure to word pairs suggests that repetition may prevent abnormal forgetting in this group of patients. This will be investigated in more detail in Chapter 6.

In general, the findings in this chapter suggest that DA is not associated with additional frontal lobe or basal ganglia dysfunction. It appears, therefore, that the memory deficits demonstrated by patients with DA can not be accounted for by additional frontal lobe abnormality as suggested by Squire and Zola (1998). However, it is possible that the memory deficit associated with DA can affect their ability to monitor previously generated responses as indicated, for example, by an increase in perseverations on category fluency.

3 MAGNETIC RESONANCE INVESTIGATIONS OF DEVELOPMENTAL AMNESIA

Previous studies of DA have revealed brain structure abnormalities using a variety of magnetic resonance image acquisition and analysis techniques (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000; Salmond *et al.*, 2000a; 2000b). This chapter describes investigations of the integrity of the hippocampus and other brain regions in a sample of patients with DA relative to age-, sex-, and IQ-matched healthy controls using neuroradiological visual inspection of conventional MRI scans (for the inclusion criteria), volumetric analysis, T_2 relaxometry, and voxel-based morphometry (VBM). Using VBM it was possible to assess brain morphology throughout the entire brain. The volumetric analysis, T_2 relaxometry, and VBM confirmed the presence of hippocampal abnormality in the DA group relative to controls. VBM analysis identified further morphological abnormalities in the grey matter of the thalamus, the middle frontal gyrus, and the white matter of the temporal lobes and near striatal areas.

3.1 INTRODUCTION

3.1.1 Neuropathology associated with DA

As discussed in Chapter 1, the main components of the MTL-cortical circuit include the hippocampus, the parahippocampal region, the thalamic nuclei (particularly the anterior and medial dorsal nuclei), mamillary bodies, and the prefrontal cortices. Furthermore, connections exist between the hippocampus and parahippocampal region and the basal ganglia (e.g. Van Hoesen *et al.*, 1981; Witter and Groenewegen, 1992).

There is a great deal of evidence to suggest that the hippocampus, thalamus and basal ganglia are particularly vulnerable to injury (Martin and Barkovich, 1995; Volpe, 2001; Singhal *et al.*, 2002), especially in the immature brain (e.g. Johnston, 1995; 1997; Takeoka *et al.*, 2002). The reasons for their vulnerability to injury are under continued investigation but a possible reason may be the abundance of N-methyl-D-aspartate (NMDA) type glutamate receptors/channels. Glutamate is often released in high doses during insult, such as hypoglycaemia or hypoxia-ischaemia (e.g. Auer *et al.*, 1984; Volpe, 2001), and appears to be toxic to neurons when present at elevated levels (excitotoxic injury). In addition, early over-expression of glutamate receptors has been demonstrated in the human hippocampus and deep nuclear structures in basal ganglia and thalamus, making the developing brain particularly vulnerable to excitotoxic injury (Johnston, 1997). It is important to emphasise that this is just one possible mechanism for injury; other factors include regional vascular factors (neuronal injury is more marked at vascular border zones), regional metabolic factors (high metabolic rate and energy utilisation of deep grey matter may render these neurons particularly vulnerable), and the severity and temporal characteristics of the insult (Volpe, 2001).

Previous studies of DA have identified structural abnormalities in regions of the MTL-cortical memory circuit, including the hippocampus (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000; Salmond *et al.*, 2000a; 2000b), thalamus (Gadian *et al.*, 2000; Salmond *et al.*, 2000a), and putamen (Gadian *et al.*, 2000; Salmond *et al.*, 2000a; 2000b). These structural abnormalities are consistent with the known pathology associated with hypoxic-ischaemic episodes (e.g. Volpe, 2001; Singhal *et al.*, 2002), the common aetiology of the previously reported DA cases, and were found to be independent of age at injury (Salmond *et al.*, 2000a).

This chapter describes the neuropathology associated with DA in a group of twelve patients, using newly acquired MR images. The suspected aetiology of each case is shown in Table 2.2 of Chapter 2. Briefly, nine of the patients have a history of hypoxia-ischaemia, two have epilepsy and one suffered from a hypoglycaemic episode. The neuropathology associated with hypoglycaemia is thought to have similarities with that associated with hypoxia-ischaemia (e.g. Auer *et al.*, 1984), whereas the neuropathology associated with epilepsy depends on seizure focus, duration, and type (e.g. Volpe, 2001)

Using a variety of MR techniques and a different three-dimensional MR sequence (fast low angle shot (3D FLASH)), this chapter aims to replicate the previous studies of DA, and to extend them, in particular by investigating the integrity of white matter associated with DA. White matter connections within the MTL-cortical circuit may be abnormal in patients with DA because the developmental nature of the disorder may affect the development of connections to and from the injured structures (e.g. Nelson, 2000; Pascalis and de Haan, 2000). This theory is supported in part by the findings of Maguire *et al.* (2001); patient Jon (DA1), unlike age-matched controls, demonstrated bilateral activation in a functional MRI study during the retrieval of long-term autobiographical event memories. These findings suggest differences in connectivity in Jon compared to controls. Therefore, due to the developmental nature of this amnesic disorder and due to the different developmental trajectories of the distributed memory circuit (e.g. Chugani *et al.*, 1987; Chugani, 1994; Nelson, 1995; 1997), DA may also be associated with white matter abnormalities.

The MR methods used to investigate the neuropathology associated with DA are described below.

3.1.2 MR Methods

Nuclear magnetic resonance (NMR) techniques provide a noninvasive means of defining the pathological basis of specific cognitive deficits and can help characterise the functional anatomy of the normal brain (Gadian, 1995). Two NMR approaches are magnetic resonance spectroscopy (MRS, used for the detection of metabolites) and magnetic resonance imaging (MRI, used for the spatial location and tissue integrity of brain structures). For the purpose of this chapter, only MRI will be described here.

3.1.2.1 MRI acquisition

NMR involves the measurement of signals emanating from nuclei in response to an oscillating magnetic field that has the same natural frequency (resonant frequency) as the nuclei themselves. Hydrogen has a nucleus containing a single proton and MRI involves the receiving and processing of signals from the proton in hydrogen nuclei, predominantly of water molecules. When protons are placed in a magnetic field (B_0), they take up one of two orientations (with or against the field), and as it requires less energy to align with the field the net magnetisation vector is along the direction of the field. The precession frequency of the protons is directly proportional to the strength of the main magnetic field. In order to observe a signal, the precession of the magnetisation vector needs to be disturbed by applying a radiofrequency pulse that has the same resonant frequency as the protons. For example, a 90° radiofrequency pulse causes the magnetisation vector to be tilted into the plane perpendicular to B_0. In order to detect the spatial location of the signal additional field gradient pulses are applied, which causes predictable variations in the magnetic field along predetermined axes.

Over time, processes take place whereby the magnetisation returns to its initial equilibrium value (which is in the longitudinal direction along B_0). These processes are characterised by two relaxation times, T_1 and T_2. T_1 is the time constant for the recovery of magnetisation along the direction of B_0, while T_2 is the time constant for the decay of magnetisation in the plane perpendicular to B_0. The relaxation times of the water protons depend, among other things, on whether the water molecules are free or bound.

The image contrast in MRI can be generated by a large number of properties of the water protons, including the proton density and the relaxation times T_1 and T_2. Variations exist in water T_1 and T_2 between different tissue types and between normal and diseased tissue. In MRI the degree of contrast generated by T_1- and T_2- dependent effects is influenced by the nature of the radiofrequency pulse sequences used. For example, a T_1-weighted sequence generates an image where the contrast is predominantly due to the difference in T_1 relaxation times. A T_2-weighted sequence generates an image where the contrast is predominately due to the difference in T_2 relaxation times. Variations in T_1 and T_2 generate greater soft-tissue contrast than variations in proton density; therefore T_1-weighted and T_2-weighted imaging are routinely used in diagnostic radiology (Gadian, 1995). Cerebrospinal fluid and atrophied tissue have long T_1 and T_2 relaxation times compared to grey and white matter due to the increased mobility of the water molecules.

Generally, T_1-weighted scans give better structural resolution, whereas T_2-weighted scans give a better view of pathology.

3.1.2.2 Data analysis

Visual inspection of MR images provide a qualitative assessment of tissue integrity, while quantitative measurements provide a stronger basis for the detection of pathology that might previously have gone undetected. Quantitative approaches include volumetric measurements of selected structures, T_2 relaxometry, and voxel-based morphometry. DA has previously been associated with bilateral hippocampal pathology, as revealed using each of these approaches (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000; Salmond *et al.*, 2000a; 2000b).

3.1.2.2.1 Volumetric measurements

Techniques for measuring hippocampal volumes include manually tracing the hippocampus using anatomical boundaries (e.g. Van Paesschen *et al.*, 1997; Gadian and Vargha-Khadem, 2000) and semi-automated computer packages (e.g. Colchester *et al.*, 2001). Although volume measurements have identified reductions of the hippocampus in a number of patient populations, they are limited by the following factors: reproducibility of identifying anatomical boundaries, slice thickness (potential partial volume effects), the gap between the sequential scan slices, and the number of slices used. Furthermore, the limitations caused by these factors may vary between studies, making comparisons of volumes across different studies difficult.

Despite these limitations, volume reduction of the hippocampus has been seen in Alzheimer's Disease (e.g. Laakso *et al.*, 1998; Krasuski *et al.*, 1998; Mizuno *et al.*, 2000), herpes encephalitis (e.g. Yoneda *et al.*, 1994), temporal lobe epilepsy (e.g. Van Paesschen *et al.*, 1995; Quigg *et al.*, 1997; Watson *et al.*, 1997; Salmenpera *et al.*, 2001), adult-onset amnesia (e.g. Holdstock *et al.*, 2000a; Verfaellie *et al.*, 2000; Cipolotti *et al.*, 2001; Kopelman *et al.*, 2001; Martin *et al.*, 2001) and DA (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000). Together these findings strongly support the use of volumetrics in determining the integrity of the hippocampus.

Hippocampal volume reduction has been associated with poor memory performance in adults (e.g. Kopelman *et al.*, 2001; Martin *et al.*, 2001) and children

(Isaacs *et al.*, 2000; Vargha-Khadem *et al.*, 2001). The relationship between hippocampal abnormality and memory performance will be examined in Chapters 4 and 7.

3.1.2.2.2 T_2 relaxometry

A further measure of brain tissue pathology can be obtained using T_2 relaxometry (e.g. Gadian *et al.*, 1999; Gadian *et al.*, 2000). For these measurements, a T_2 value is computed, pixel by pixel, using a series of images acquired at different echo times. As the echo time increases, the signal intensity in each pixel decreases as a result of T_2 relaxation, and T_2 describes the time constant of this decay in signal intensity. The resulting data are displayed in the form of a T_2 map of the selected slice, with the intensity of each pixel representing the calculated T_2 value for that particular pixel. T_2 values can then be compared between patients and healthy controls enabling abnormalities to be seen that may be too subtle to detect on conventional T_2-weighted scans. This technique does not rely on side-by-side comparisons and therefore provides a powerful approach to the detection of bilateral pathology.

Abnormal hippocampal T_2 values have been reported in patients with epilepsy (e.g. Connelly *et al.*, 1994; Scott *et al.*, 2001; 2002) and in three cases of DA (Gadian *et al.*, 2000). Although volumetric and T_2 measurements provide measures of hippocampal pathology, they do not necessarily reflect the same processes. For example, an atrophied hippocampus may well appear normal on T_2 relaxometry; and an abnormal T_2 value in an atrophied hippocampus suggests that even the remaining hippocampal tissue is compromised (Gadian *et al.*, 1999).

3.1.2.2.3 Voxel-based morphometry

Another technique that has proved especially useful in detecting structural abnormalities is voxel-based morphometry (VBM). VBM was developed to characterise cerebral grey and white matter differences in structural MRI scans (e.g. Wright *et al.*, 1995). It detects structural differences with uniform sensitivity throughout the brain and uses statistical parametric mapping (SPM99) to identify, and make inferences about, regionally-specific differences.

VBM has been used to look for grey and/or white matter structural abnormalities in a variety of patient populations, such as patients with schizophrenia (Wright *et al.*, 1995), an inherited speech and language disorder (the KE family, Vargha-Khadem *et al.*,

1998; Belton *et al.*, 2003), prenatal alcohol exposure (Sowell *et al.*, 2001), herpes encephalitis (Gitelman *et al.*, 2001) and DA (Gadian *et al.*, 2000; Salmond *et al.*, 2000a; 2000b). It has also been used to detect structural asymmetries in healthy young adults (Watkins *et al.*, 2001) and is now an established technique for detecting unilateral and bilateral grey and white matter structural brain differences in both abnormal and healthy brains (Ashburner and Friston, 2001).

In the study of DA, Gadian *et al.* (2000) revealed grey matter density abnormalities in the hippocampus, putamen, and ventral thalamus in both the left and right hemisphere, using the standard unilateral VBM method. The unilateral method, however, does not explicitly test for bilateral abnormalities. Salmond *et al.* (2000b) described a VBM method that searches explicitly for bilateral abnormalities. They conducted a bilateral conjunction analysis using the same five patients reported by Gadian *et al.* (2000) and confirmed the presence of bilateral hippocampal and putamen abnormality. A preliminary study by Salmond *et al.* (2000a; Vargha-Khadem *et al.*, 2001) investigated whether the neuropathology associated with DA differed with age at injury. A unilateral conjunction VBM analysis comparing six early-onset cases (age at injury, perinatal to 1 year; five previously reported by Gadian *et al.*, 2000) to four late-onset cases (age at injury 6 to 14 years) found bilateral hippocampal, putamen, and thalamic, as well as right posterior cingulate cortex abnormalities in both groups relative to their controls. These findings suggest that the neuropathology associated with DA is independent of age at injury.

3.1.3 Specific aims and predictions

This study aimed to replicate and extend previous MR findings in DA (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000; Salmond *et al.*, 2000a; 2000b). Aside from the inclusion criteria of hippocampal abnormality, it is predicted that bilateral abnormalities will also be present in the thalamus, putamen and white matter of the MTL-cortical circuit described above. Further abnormality is predicted to be present in the right posterior cingulate cortex.

3.2 METHODS

3.2.1 Participants

Ten of the twelve patients with DA were scanned. The previously reported scans of patients DA2 and DA4 were used in the analyses except for hippocampal volumes, as 3D FLASH scans were not available (Gadian *et al.*, 2000). The hippocampal volumes of one case, DA5, were not measured due to movement artifact; however, the patient's T_2-weighted axial and coronal images were available for visual inspection. Therefore, scans of all twelve patients were available for visual inspection and T_2 relaxometry, whereas the hippocampal volumes were measured in only nine patients.

Eleven of the controls were scanned (case NC7 had a fixed brace which would generate image artifact). The volumes of ten controls were measured as one case (NC2) did not have a 3D FLASH scan.

For voxel-based morphometry, ten patients with DA were compared to ten of the controls.

The groups did not differ significantly on age at scan, verbal IQ, or performance IQ.

3.2.2 MRI acquisition

All subjects were scanned unsedated for a total of 30 minutes using a 1.5 T Siemens Vision scanner (see Table 3:1).

Table 3:1 MR protocol details

Scan	TR (ms)	TE (ms)	Other
T_2 Axial	3548	96	19 slices, 5 mm thick
T_2 Coronal	3458	96	19 slices, 5 mm thick
3D FLASH	16.8	5.7	Flip angle = 21°, Voxel size 0.78 x 0.78 x 1 mm
MPRAGE	10.0	4	Flip angle = 12°, 128 slices, Voxel size 1 x 1 x 1.25 mm
Hippocampal T_2 Map	2400	22-262	1 slice, 5 mm thick

3.2.3 Data analysis

3.2.3.1 Visual inspection

The T_2-weighted axial and coronal images were reviewed by an experienced paediatric neuroradiologist, blind to the group membership of the participants, who recorded the presence or absence of abnormality on visual inspection of the images. Particular attention was paid to the medial temporal lobes, basal ganglia, thalamus, frontal lobes, white matter, and the ventricles.

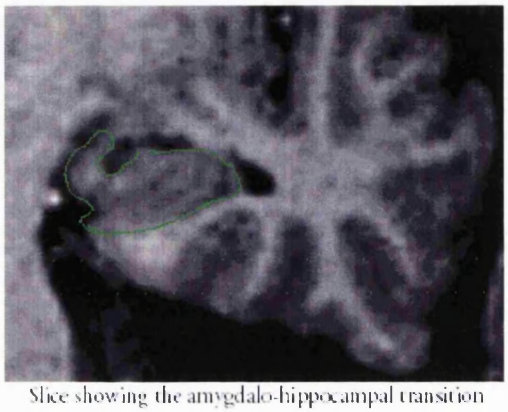
3.2.3.2 Volume measurements

Professor David Gadian measured the hippocampal volumes. The 3D FLASH data sets were reformatted into 0.78 mm thick contiguous slices in a tilted coronal plane that was perpendicular to the long axis of the hippocampal formation. Tracings were carried out in MEDx (Version 3.30, Sensor Systems). The volumes were calculated by summing the cross-sectional areas and multiplying by the distance between slices (Cavalieri's principle, Gundersen and Jensen, 1987; Cook *et al.*, 1992).

Structural boundaries were defined as described by Schoppik *et al.* (2001) where the hippocampus (H) was defined, for the purpose of reproducible tracings, as a composite of the following regions: Cornu ammons subfields CA1-CA4, dentate gyrus, subiculum, presubiculum, and the amygdalo-hippocampal transition area (Figure 3:1a). As seen in Figure 3:1b, the boundary rostrally, separating the hippocampus from the amygdala, was a combination of the alveus and the lateral ventricle. The lateral ventricle also served as the lateral boundary. Medially, the hippocampus was bordered by the entorhinal cortex; more caudally, posterior to the uncus, the boundary was the edge of the temporal lobe (Figure 3:1c). The caudal limit extended to include the last slice in which the hippocampus was distinct from the fornix (Figure 3:1d).

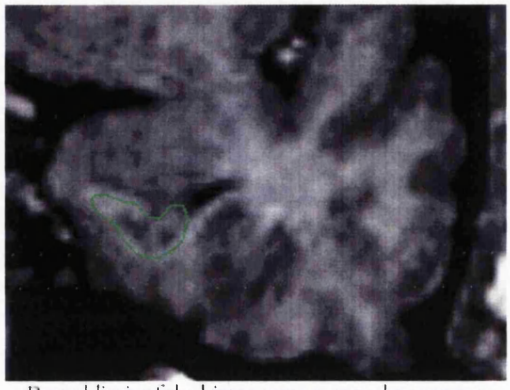
Figure 3:1 Courtesy of Schoppik et al. (2001). (a) Slice showing the amygdalo-hippocampal transition area; (b) Rostral limit of the hippocampus; (c) Slice immediately after the end of the uncus; (d) Caudal limit of the hippocampus.

(a)



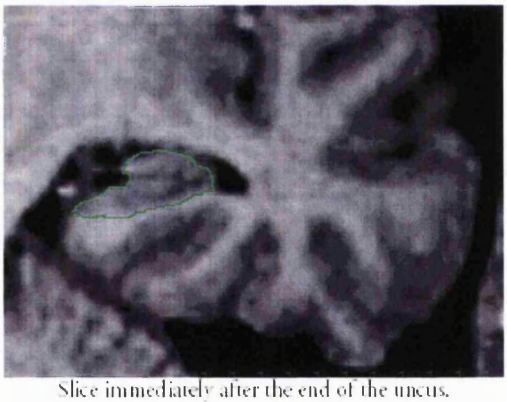
Slice showing the amygdalo-hippocampal transition area.

(b)



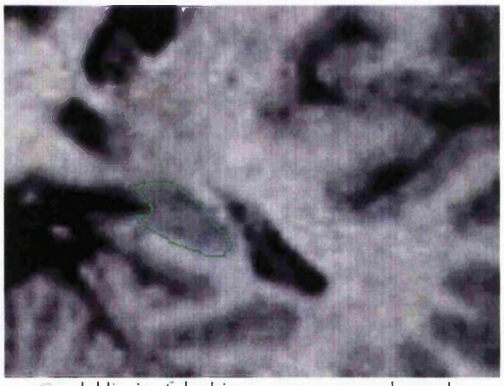
Rostral limit of the hippocampus: note the presence of the alveus dorsal to the medial extent.

(c)



Slice immediately after the end of the uncus.

(d)



Caudal limit of the hippocampus: note the angle.

Intracranial volume (ICV) was measured on the sagittal unreformatted FLASH dataset measuring every tenth slice, and hippocampal volumes were corrected as described by Van Paesschen *et al.* (1997).

3.2.3.3 T_2 relaxometry

Hippocampal T_2 maps were computed, pixel by pixel, within a single tilted coronal plane orientated along the anterior of the brainstem perpendicular to and at the level of the body of the hippocampus. The calculation was made from a series of 16 images acquired at different echo times (ranging from 22 to 262 ms, Jackson *et al.*, 1993). The resulting data were displayed in the form of a T_2 map of the selected slice. The

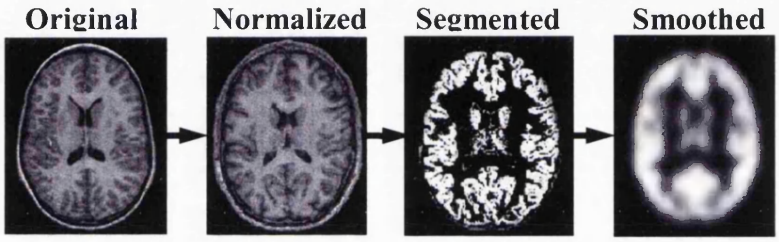
hippocampal T_2 value was measured by placing the largest possible circle as a region of interest (ROI) within the hippocampus, taking care to avoid boundaries where partial volume effects with cerebrospinal fluid (which has a long T_2) may occur. The T_2 values are expressed in milliseconds (ms). The left and right T_2 values of each patient were converted to a z-score in order to determine the number of standard deviations separating them from the control group mean (Van Paesschen *et al.*, 1997). The calculation of the z-scores was based on the mean value of the control group for each side (see Section 3.3.3.2). The raw data were also analysed using a between-subjects comparison.

3.2.3.4 Voxel-based morphometry

VBM analysis of the 3D FLASH data sets was carried out in SPM99 (Wellcome Department of Cognitive Neurology, London, UK) in two ways. The data were analysed firstly using the standard unilateral method described by Ashburner and Friston (2000), then secondly using the bilateral conjunction method described by Salmond *et al.* (2000b). Figure 3:2 illustrates the processing stages of VBM. Briefly, for the unilateral method each scan was normalised to a standard template transforming all the subjects' data to the same stereotactic space (Ashburner and Friston, 2000). This procedure does not attempt to match cortical features precisely, otherwise differences between brains would be rendered inestimable with the VBM procedure. Instead it accounts for any differences among subjects that are due to differences in brain size and it co-localises homologous regions. The images were then segmented into grey matter, white matter, CSF, and scalp images. This produced continuous probability maps where the values correspond to the probability that the voxel contained one of the aforementioned tissue classes (Evans *et al.*, 1992; 1993; 1994). The actual assignment of voxels to a particular tissue class is then determined iteratively depending on the mean and variance of the developing tissue clusters for the brain being analysed (Ashburner and Friston, 2000). The images were then smoothed with 4 mm, 8 mm, and 12 mm isotropic Gaussian kernels. Smoothing results, among other things, in the voxel values being more normally distributed, allowing the use of parametric statistics to make inferences about changes in grey/white matter density or concentration (Gitelman *et al.*, 2001). After smoothing, the voxel values provide an index of the amount of grey/white matter per unit volume, taking into account the surrounding voxels within the smoothing kernel. The term 'grey/white matter density' is generally used to refer to this probabilistic measure. A 4 mm smoothing

kernel was chosen as this corresponds roughly to the cross-sectional dimensions of the hippocampal formation. Smoothing kernels of 8 mm and 12 mm were also chosen in order to detect basal ganglia, thalamus, and cortex abnormalities.

Figure 3:2 Processing stages of VBM analysis



The second analysis used a method that searches specifically and selectively for bilateral abnormalities, which are predicted in the DA group. This method, termed a bilateral conjunction analysis, has the advantage that it offers greater sensitivity to the detection of such abnormalities (Salmond *et al.*, 2000b; Belton *et al.*, 2003). A conjunction analysis compares the results of two (or more) SPM's to find regions that are significant in both. To do this it creates a new statistical parametric map that contains the least significant T value from all the SPMs entered in the conjunction. After thresholding, this conjunction SPM can be regarded as the intersection of the component SPMs to assess the conjoint expression of grey matter density changes. P values for maxima in the conjunction SPM are then corrected for the volume analysed. The two component SPMs in the bilateral conjunction analysis are obtained by analysing flipped (right to left) and unflipped data.

For the bilateral analysis each scan was normalised to a symmetric template (Ashburner and Friston, 1999). The images were then segmented using a symmetric probability template using a modified Bayesian algorithm described in Ashburner *et al.* (1997). After smoothing with 4 mm, 8 mm and 12 mm isotropic Gaussian kernels, the grey matter and white matter images were duplicated, and one copy of each scan was flipped in the transverse plane along the anterior-posterior axis.

Abnormalities can manifest as an increase (e.g. Kassubek *et al.*, 2002; Merschhemke *et al.*, 2003) or a decrease (e.g. Gadian *et al.*, 2000; Sowell *et al.*, 2001) in grey or white matter density, and therefore both contrasts were conducted (see Tables 3:2 and 3:3).

The statistical analyses as indicated in Table 3:2 and Table 3:3 were then carried out for each method (unilateral and bilateral) using SPM99. The analyses involved the following groups.

Unilateral

1: Controls (n = 10)

2: DA Patients (n = 10)

Bilateral

1: Controls (n = 10)

2: DA Patients (n = 10)

3: Controls_flipped (n = 10)

4: DA Patients_flipped (n = 10)

Table 3:2 Unilateral analyses

Prediction	Matter	Smoothing	Contrast
Control group have an **increase** in grey matter relative to DA patients	Grey	4 mm, 8 mm, 12 mm	1 -1
Control group have a **decrease** in grey matter relative to DA patients	Grey	4 mm, 8 mm, 12 mm	-1 1
Control group have an **increase** in white matter relative to DA patients	White	4 mm, 8 mm, 12 mm	1 -1
Control group have a **decrease** in white matter relative to DA patients	White	4 mm, 8 mm, 12 mm	-1 1

Table 3:3 Bilateral analyses

Prediction	Matter	Smoothing	Conjunction
Control group have a symmetric **increase** in grey matter relative to DA patients	Grey	4, 8, 12 mm	1 -1 0 0, 0 0 1 -1
Control group have a symmetric **decrease** in grey matter relative to DA patients	Grey	4, 8, 12 mm	-1 1 0 0, 0 0 -1 1
Control group have a symmetric **increase** in white matter relative to DA patients	White	4, 8, 12 mm	1 -1 0 0, 0 0 1 -1
Control group have a symmetric **decrease** in white matter relative to DA patients	Grey	4, 8, 12 mm	-1 1 0 0, 0 0 -1 1

All differences of interest were assessed with contrasts of the group effects. For example, in the unilateral method the contrast (1 –1) would test the null hypothesis that the control group is not different from the patients with DA. Inferences about contrasts are made using the standard parametric statistics (t statistic, which is the contrast divided by its standard error). A bilateral conjunction analysis is simply a significant effect expressed jointly over two or more contrasts e.g. 1 -1 0 0 and 0 0 1 -1.

Initially, the data were examined for unilateral grey and white matter differences between the patients and their age-, sex-, and IQ-matched control group. The contrasts entered were as listed in Table 3:2. Next the data were examined for bilateral grey and white matter differences between the two groups as listed in Table 3:3. Finally, age at scan was entered into the unilateral and bilateral analyses as a covariate.

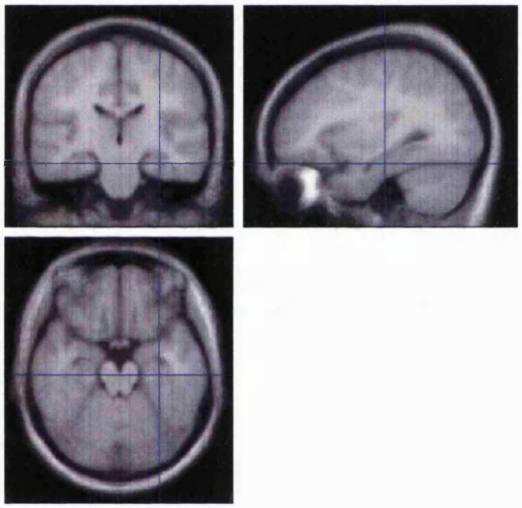
Inferences from statistical parametric maps were made at three different threshold levels. First, the significance values corrected for multiple comparisons across the entire brain were used to search for abnormalities throughout the entire brain (whole-brain correction, WBC). Second, incorporating the prior hypotheses of grey matter abnormality in the right posterior cingulate cortex, bilateral hippocampus, basal ganglia, and thalamus, threshold levels uncorrected for whole brain comparisons are reported (predicted uncorrected, PUC, i.e. p-value $p < 0.001$). Third, small volume corrections (SVC) were also used if the predicted regions did not survive correction for whole brain comparisons. The small volume corrections were each made using a box with dimensions that encompasses the regions of interest. The right posterior cingulate cortex was not present at the predicted uncorrected threshold at 4 mm smoothing, and therefore a SVC was not applied. The SVC for the hippocampus at 4 mm smoothing had dimensions of 17 x 36 x 16 mm, centred at ±32, -22, -20 (Figure 3:3a). In the case of the basal ganglia and thalamus, a box with dimensions large enough to encompass both structures was used due to their anatomical proximity to each other. The SVC at 8 mm and 12 mm smoothing had dimensions of 69 x 59 x 38 mm, centred at 0, -6, 3, (Figure 3:3b). In the case of symmetric analyses, peaks are reported provided the x co-ordinate of the peak was more than 2 times the resolution of the smoothing kernel (to avoid false positives near the midline, see Salmond *et al.*, 2000b).

The statistical parametric maps were superimposed on the mean normalised image of the group data in order to aid anatomical localisation. Identification of the anatomical location of the areas of abnormality was carried out with reference to Duvernoy's atlas

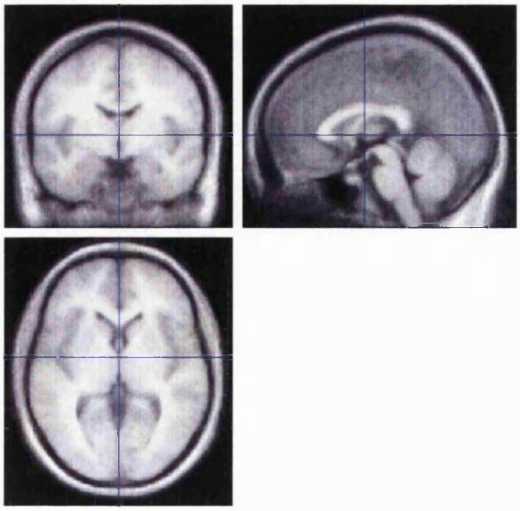
(Duvernoy, 1991). All figures show the statistical parametric maps superimposed on the mean normalised image of the group data, at a threshold of uncorrected $p < 0.001$ (Salmond *et al.*, 2000b; Belton *et al.*, 2003). The cross hairs on the figures indicate the location of the maximal peak (the colour scale indicates z-scores). Figures are displayed in neurological convention (left hemisphere is on the left).

Figure 3:3 Centre of small volume correction for (a) hippocampus (left and right separately); (b) bilateral thalamus and basal ganglia.

(a) SVC hippocampus (±32, -22, -20)



(b) SVC bilateral thalamus and basal ganglia (0, -6, 3)



3.3 RESULTS

3.3.1 Visual inspection

As shown in Table 3:4, all of the patients for whom scans were available for clinical examination (ten patients) showed bilateral hippocampal reduction on neuroradiological assessment. Previous clinical examination of the scans of the two missing patients (DA2 and DA4) confirmed the presence of bilateral hippocampal reduction (Gadian *et al.*, 2000). The present assessment identified one control as possibly having small hippocampi (control NC1). One control (NC6) and one patient (DA3) were reported to show mild atrophy of the cerebellum, and one patient (DA11) was reported to show gliotic changes in the mid-brain (brain stem). The white matter was bilaterally atrophic in the frontal lobes of one patient (DA12) and generally reduced in two patients (DA1 and DA12).

Table 3:4 Summary of results from clinical neuroradiological assessment

	Number of participants showing abnormality			Number of participants showing abnormality	
Grey matter	DA	NC	White matter	DA	NC
Hippocampus	12	1 possibly small (NC1)	Near hippocampus	*	*
Entorhinal cortex	*	*	Near parahippocampal gyrus	*	*
Perirhinal cortex	*	*	Internal capsule	*	*
Parahippocampal cortex	*	*	Peri-basal ganglia	*	*
Retrosplenial cortex	*	*	Peri-ventricular	*	*
Thalamus	*	*	Corpus callosum	*	*
Putamen	*	*	Frontal lobe	1 (DA12)	*
Caudate	*	*	Temporal lobe	*	*
Orbitofrontal cortex	*	*	Parietal lobe	*	*
Ventromedial PfC	*	*	Occipital lobe	*	*
Dorsolateral PfC	*	*	General white matter	2 (DA1 and DA12)	*
Cerebellum	1 mild (DA3)	1 mild (NC6)	Other	DA11 has a shunt	*
Brain stem	1 (DA11)	*		catheter through right frontal lobe	

* No abnormality detected.

3.3.2 Hippocampal volume measurements

3.3.2.1 Volume of the hippocampus (mm^3) corrected for intracranial volume

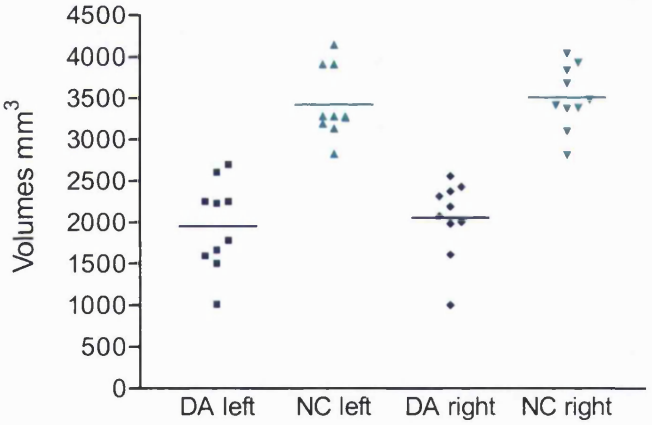
The hippocampal volumes for the DA and control groups are shown in Table 3:5 and Figure 3:4.

Table 3:5 Volume of the hippocampus (mm^3) corrected for intracranial volume

	DA	NC
Left hippocampus	2060 (149)	3418 (132)
Right hippocampus	2170 (96)	3503 (120)

Mean (±SEM)

Figure 3:4 Volume of the hippocampus (mean = solid line)



A mixed-design analysis of variance with a between-subjects factor of Group (DA, control) and a within-subjects factor of Side (left, right) revealed evidence for an effect of Group ($F(1,17) = 65.89$; $p < 0.0001$), where the control group volume was greater than DA group volume. There was no evidence for an effect of Side ($p > 0.1$) or a Group by Side interaction ($p > 0.1$), indicating that the group difference was bilateral. These findings were replicated when age at scan was included in the model as a covariate.

3.3.2.2 Percentage of volume reduction relative to controls

The percentage left and right volume reduction in the DA group was calculated from the left and right mean volumes of the ten controls (NC) reported in this study (left mean = 3418±418 mm^3; right mean = 3503±380 mm^3).

The volume reductions in the DA group relative to the NC data were also converted to z-scores. This was calculated using the left and right means of the control group (as above). The following formula was used: z-score = (DA volume – NC mean volume)/NC SD

The results are shown in Table 3:6. A z-score of 2 or above indicates a volume outside the normal range.

Table 3:6 Percentage volume reduction (%) and z-scores of the patients with DA relative to controls (n = 9)

Case number	Percentage reduction		z scores	
	Left	Right	Left	Right
DA1	56.6	40.7	-4.63	-3.76
DA3	34.2	32.3	-2.79	-2.98
DA6	48.1	43.4	-3.94	-4.01
DA7	34.8	33.9	-2.84	-3.13
DA8	23.8	27.1	-1.94	-2.50
DA9	21.2	30.7	-1.73	-2.83
DA10	34.2	37.5	-2.80	-3.46
DA11	51.3	54.1	-4.19	-4.99
DA12	53.5	42.7	-4.38	-3.94
Mean (±SD)	39.7 (13.1)	38.1 (8.2)	-4.15 (2.21)	-4.55 (2.41)

The percentage volume reduction ranges from 21.2% to 56.6% in the left hippocampus and 27.1% to 54.1% in the right hippocampus. The z-scores indicate that all of the patients with DA have right hippocampal volumes greater than 2 z-scores below the control mean. Seven of the nine patients with DA have left hippocampal volumes greater than 2 z-scores below the control mean and two patients with DA (DA8 and DA9) have left hippocampal volumes within 2 z-scores of the control group mean.

3.3.3 T_2 relaxometry

The T_2 values for the left and right hippocampi were calculated as described in Section 3.2.3.3.

3.3.3.1 Actual T_2 values of DA patients and their controls

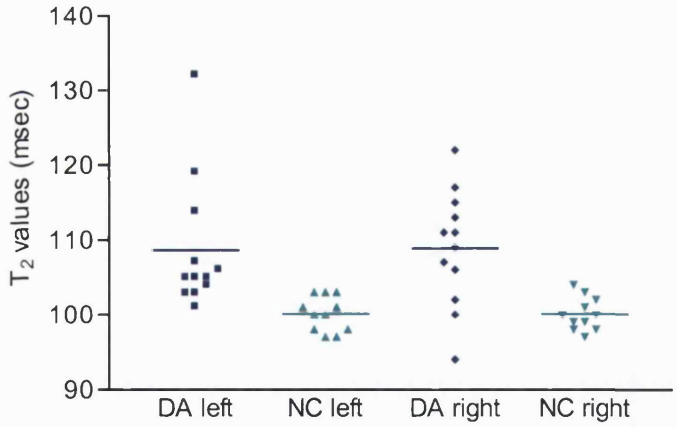
The T_2 values for the DA and control groups are shown in Table 3:7 and Figure 3:5.

*Table 3:7 Hippocampal T_2 values (*ms*)*

	DA	NC
Left hippocampus	108.7 (2.57)	100.1 (0.71)
Right hippocampus	108.9 (2.24)	100.1 (0.67)

Mean (±SEM)

Figure 3:5 Hippocampal T_2 values (mean = solid line)



As shown in Figure 3:5 there is considerable overlap between the T_2 values of the patients and the controls. An analysis of variance with a between-subjects factor of Group (DA, control) and a within-subjects factor of side (left, right) revealed a significant main effect of Group[1] ($F(1,21) = 13.21; p = 0.002$), where the hippocampal T_2 value of the DA

[1] The variance of the residuals was not homogeneous; therefore the data were also analysed using a Mann-Whitney U test. There was a main effect of group on left T_2 value ($U = 7.0$; $p < 0.0001$) and right T_2 value ($U = 18.5$; $p = 0.002$).

group was higher than that of the control group. There was no evidence for an effect of Side ($p > 0.1$) or Group by Side interaction ($p > 0.1$). These findings were replicated when age at scan was included as a covariate.

3.3.3.2 T_2 values of DA patients (z scores)

Table 3:8 shows the z-scores for each individual patient relative to the control group. The z-scores were calculated using the control group's left hippocampal mean±SD of 100.09±2.34 msec, and right hippocampal mean±SD of 100.09±2.21 msec. A z-score of 2 or above indicates a T_2 value outside the normal range.

Table 3:8 Hippocampal T_2 values of DA patients (z scores)

Case number	Left T_2	Right T_2
DA1	2.10	0.86
DA2[2]	8.08	7.65
DA3	2.95	5.84
DA4[2]	2.53	2.67
DA5	1.67	-2.76
DA6	0.39	-0.04
DA7	5.94	4.94
DA8	2.10	6.75
DA9	1.24	4.94
DA10	13.64	9.91
DA11	1.24	4.03
DA12	2.10	3.13

As can be seen from Table 3:8 seven of the twelve patients with DA have bilateral hippocampal T_2 values greater than 2 z-scores above the control mean. Two patients (DA 9 and DA11) have right (but not left) hippocampal T_2 values greater than 2 z-scores above the control mean. One patient (DA1) has a left (but not right) hippocampal T_2 value greater than 2 z-scores above the control mean. One patient (DA5) has a right hippocampal T_2 value greater than 2 z-scores below the control mean, and a left hippocampal T_2 value within 2 z-scores of the control mean. One patient (DA6) has

[2] T_2 values were previously reported in Gadian *et al* (2000).

bilateral hippocampal T_2 values within 2 z-scores of the control mean and, therefore, within the normal range.

3.3.4 Voxel-based morphometry

3.3.4.1 DA group versus controls: unilateral VBM comparisons

The unilateral VBM analysis revealed significant decreases in grey matter density in the DA group compared to the control group at the three smoothing levels (4 mm, 8 mm and 12 mm). These decreases were found in the left and right hippocampus and thalamus but not the basal ganglia or right posterior cingulate cortex (see Figure 3:6 and 3:7 and Table 3:9). There were no significant increases in grey matter density in the DA group compared to the control group.

Analyses of white matter density did not reveal any significant increases or decreases in the DA group compared to controls.

These findings were replicated when age at scan was included as a covariate. The whole brain corrected (WBC), small volume corrected (SVC) and predicted uncorrected (PUC) levels are reported.

Decreases in grey matter density in the DA group compared to controls

Figure 3:6 Right hippocampus 38, -27, -12 (4 mm, SVC p = 0.003)

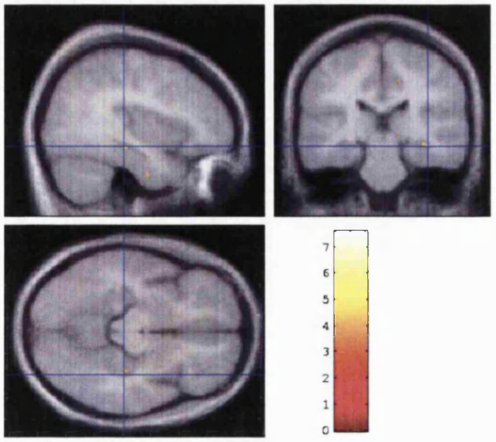
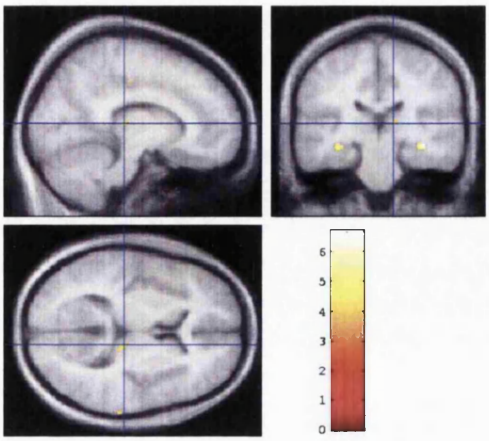


Figure 3:7 Right thalamus 12, -26, 8 (8 mm, PUC p < 0.0001)



Additional co-ordinates are shown in Table 3:9.

Table 3:9 Unilateral decreases in grey matter density in the DA group compared to controls (4 mm, 8 mm, and 12 mm)

Region	Smoothing	Coordinates			Corrected/ uncorrected	Z scores	p values
		x	y	z			
Right hippocampus	4 mm	38	-27	-12	SVC	5.01	0.003
Left hippocampus	4 mm	-30	-12	-20	SVC	4.64	0.012
Left hippocampus	4 mm	-33	-18	-14	PUC	3.6	<0.0001
Right thalamus (pulvinar)	8 mm	12	-26	8	PUC	3.74	<0.0001
Left thalamus	8 mm	-8	-3	10	PUC	3.37	<0.0001
Right thalamus (pulvinar)	12 mm	14	-26	8	PUC	3.62	<0.0001
Left thalamus	12 mm	-8	-3	9	PUC	3.76	<0.0001

SVC = small volume correction; PUC = predicted uncorrected

3.3.4.2 DA group versus controls: bilateral VBM comparisons

The bilateral VBM analysis revealed significant decreases in grey matter density in the DA group compared to the control group at the three smoothing levels (4 mm, 8 mm and 12 mm). These decreases were found in the hippocampus and thalamus but not the basal ganglia (see Figure 3:8, Figure 3:9 and Table 3:10 below). In addition, there was a significant increase in grey matter density in the middle frontal gyrus in the DA group compared to controls (see Figure 3:10).

Analyses of white matter density revealed significant increases in the DA group compared to the control group at all three smoothing levels (4 mm, 8 mm and 12 mm). These increases in white matter density were found near the temporal stem, temporal horn of the lateral ventricle, in the internal capsule, above the basal ganglia, near the superior frontal gyrus, collateral/central sulcus (8 mm), and the post-central gyrus (8 mm and 12 mm) (see Figure 3:11– Figure 3:18 and Table 3:11). These white matter differences were also present at an uncorrected level in the unilateral analyses.

All of these findings were replicated when age at scan was included as a covariate. The whole brain corrected (WBC), small volume corrected (SVC) and predicted uncorrected (PUC) levels are reported.

Decreases in grey matter density in the DA group compared to controls

Figure 3:8 Bilateral hippocampus ±34, -18, -15 (8 mm, WBC p = 0.0001)

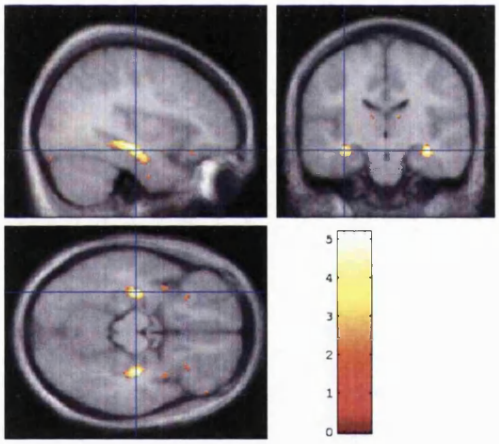
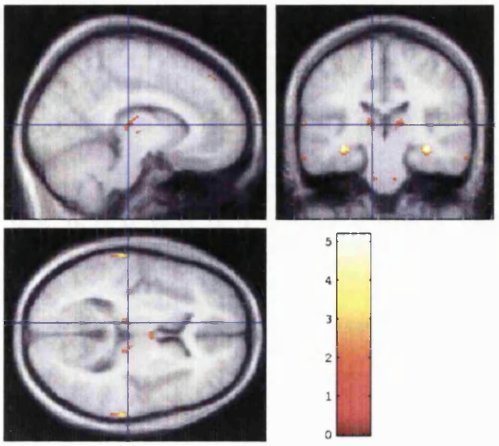


Figure 3:9 Bilateral thalamus ±10, -24, 8 (8 mm, PUC p < 0.0001)



Additional co-ordinates are shown in Table 3:10.

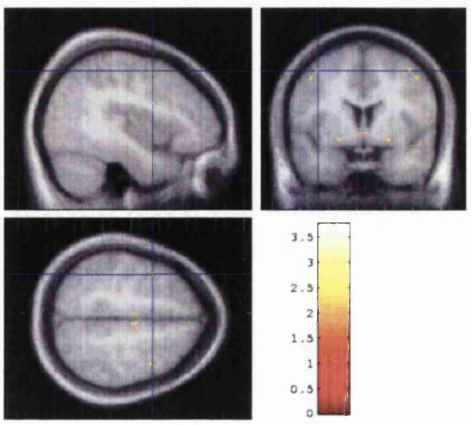
Table 3:10 Bilateral decreases in grey matter density in the DA group compared to controls (4 mm, 8 mm, and 12 mm)

Region	Smoothing	Coordinates			Corrected/ Uncorrected	Z scores	p values
		x	y	z			
Hippocampus	4 mm	±32	-14	-18	WBC	5.17	0.04
Hippocampus	4 mm	±33	-18	-14	SVC	5.15	0.001
Hippocampus	4 mm	±34	-24	-12	SVC	5.00	0.002
Hippocampus	8 mm	±34	-18	-15	WBC	6.59	<0.0001
Thalamus (pulvinar)	8 mm	±10	-24	8	PUC	3.84	<0.0001
Thalamus (ventral lateral)	8 mm	±10	-14	3	PUC	3.43	<0.0001
Hippocampus	12 mm	±32	-16	-18	WBC	5.53	0.001
Hippocampus	12 mm	±34	-30	-10	WBC	5.12	0.008
Thalamus (medial dorsal)	12 mm	±9	-16	10	SVC	3.78	0.019
Thalamus (pulvinar)	12 mm	±14	-26	8	PUC	3.71	<0.0001
Thalamus (medial dorsal)	12 mm	±10	-18	9	PUC	3.79	<0.0001

WBC = whole-brain corrected; SVC = small volume correction; PUC = predicted uncorrected

Increases in grey matter density in the DA group compared to controls

Figure 3:10 Bilateral middle frontal gyrus ±40, 3, 52 (4 mm, WBC z = 5.21; p = 0.033)



Increases in white matter density in the DA group compared to controls

Figure 3:11 Bilateral near temporal stem ±38, -20, -12 (4 mm, WBC p = 0.0001)

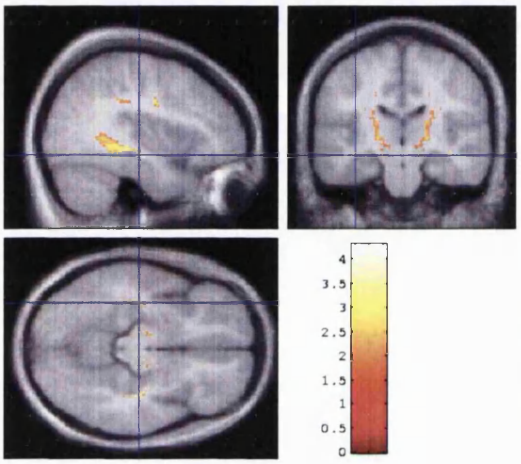


Figure 3:12 Bilateral near temporal horn of lateral ventricle ±36, -22, -12 (8 mm, WBC p = 0.001)

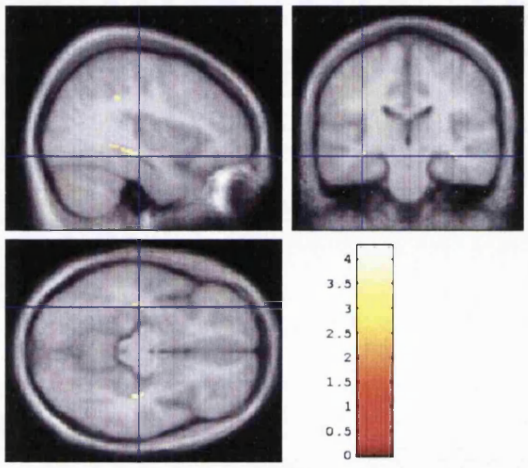


Figure 3:13 Bilateral internal capsule ±14, -12, 0 (8 mm, WBC p = 0.005)

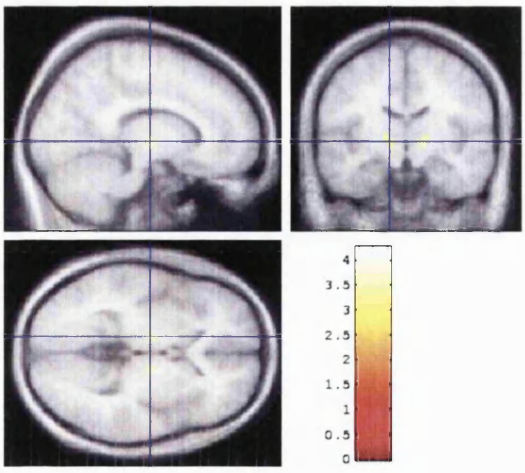


Figure 3:14 Bilateral above basal ganglia ±36, -4, 28 (4 mm, WBC p = 0.022)

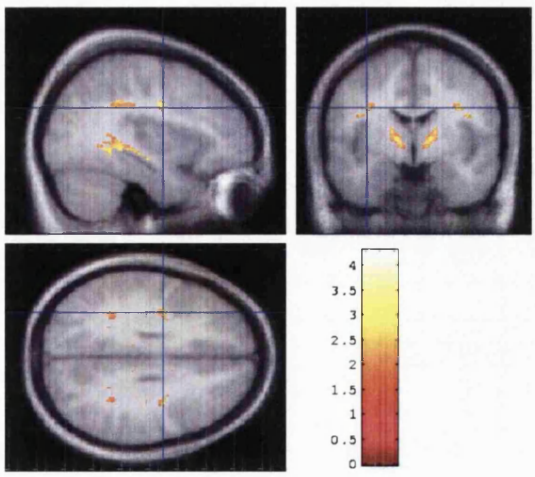


Figure 3:15 Bilateral near superior frontal gyrus ±16, -16, 50 (4 mm, WBC p = 0.038)

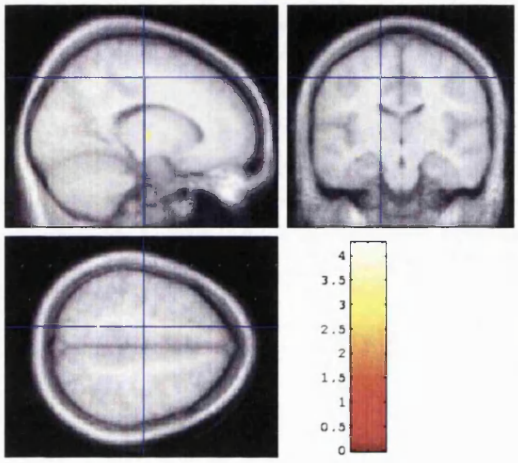


Figure 3:16 Bilateral near post central gyrus ±33, -39, 33 (8 mm, WBC p = 0.0001)

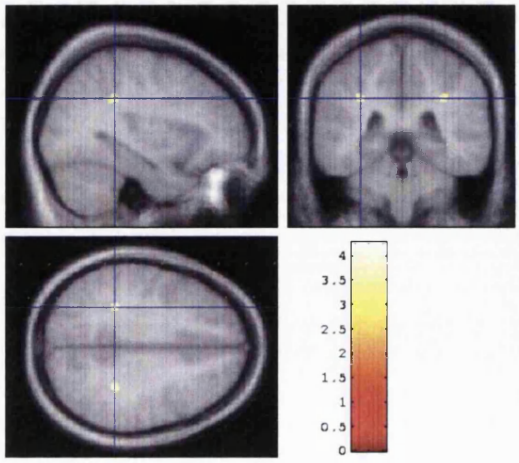


Figure 3:17 Bilateral near cingulate ±22, -27, 40 (8 mm, WBC p = 0.003)

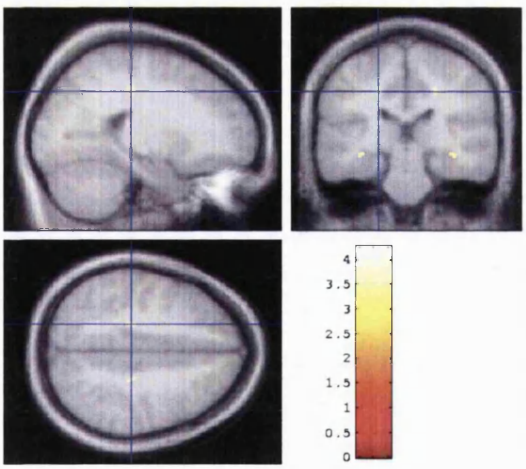
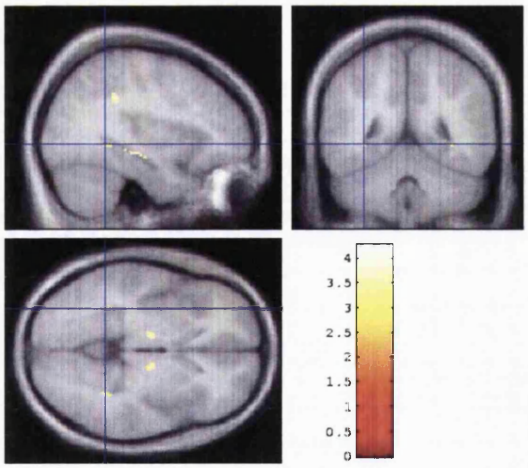


Figure 3:18 Bilateral near collateral sulcus ±34, -48, -3 (8 mm, WBC p = 0.018)



Additional co-ordinates are shown in Table 3:11.

Table 3:11 Bilateral increase in white matter density in the DA group compared to controls (4 mm, 8 mm,12 mm)

Region	Smoothing	Coordinates			Corrected/ Uncorrected	Z scores	p-value
		x	y	z			
Near temporal stem	4 mm	±38	-20	-12	WBC	5.76	0.0001
Near temporal horn of lateral ventricle	4 mm	±38	-33	-9	WBC	5.45	0.002
Internal capsule	4 mm	±12	-15	2	WBC	5.39	0.003
Above basal ganglia	4 mm	±36	-4	28	WBC	4.98	0.022
Near superior frontal gyrus	4 mm	±16	-16	50	WBC	4.86	0.038
Near post-central gyrus	8 mm	±33	-39	33	WBC	5.72	0.0001
Near temporal horn of lateral ventricle	8 mm	±36	-22	-12	WBC	5.51	0.001
Near temporal horn of lateral ventricle	8 mm	±36	-30	-9	WBC	5.17	0.007
Near superior frontal gyrus/cingulate	8 mm	±22	-27	40	WBC	5.34	0.003
Internal capsule	8 mm	±14	-12	0	WBC	5.23	0.005
Near collateral sulcus	8 mm	±34	-48	-3	WBC	4.97	0.018
Near post-central sulcus/intraparietal sulcus	12 mm	±33	-40	33	WBC	5.42	0.001
Near superior frontal gyrus/cingulate	12 mm	±22	-26	42	WBC	5.07	0.006
Internal capsule	12 mm	±15	-12	0	WBC	4.79	0.019

WBC = whole-brain corrected; SVC = small volume correction; PUC = predicted uncorrected

3.3.4.2.1 Homogeneity of the neuropathology

In order to determine the homogeneity of the neuropathology of the patients in the DA group, individual analyses were also carried out. The methods used were identical to the bilateral analysis described in Section 3.2.3.4, but involved comparing each child in

the DA group against the entire control group. Interpretation of such unbalanced designs is complex, as these analyses are prone to false positives and do not possess the statistical power of group comparisons to detect significant regions of abnormality (see Salmond *et al.*, 2003). According to Salmond *et al* (2003), the former point can be addressed by using a lenient statistical threshold of uncorrected $p < 0.001$, and the latter point can be addressed by acknowledging that absence of abnormality in a particular region does not indicate normality. In order to address the problem of false positives, the results from the statistical parametric maps were not interpreted as described in Section 3.2.3.4. Instead, presence or absence of abnormality was noted in each of the regions where corrected (WBC) bilateral grey or white abnormality was found in the between group analyses, namely, grey matter decrease in hippocampus (4 mm), grey matter increase in middle frontal gyrus (4 mm), white matter increase near the post-central gyrus, temporal horn of the lateral ventricle, cingulate/superior frontal gyrus, internal capsule and in the collateral sulcus (all at 8 mm smoothing).

The results from the individual voxel-based morphometric analyses are shown in *Table 3:12.*

Table 3:12 Results from individual bilateral VBM analyses where Y indicates presence of abnormality at threshold uncorrected $p < 0.001$, and N indicates no significant abnormality at threshold.

Name	4 mm grey Hippocampus	4 mm grey Middle frontal gyrus	8 mm white Post-central gyrus	Temporal horn of lateral ventricle	Cingulate/ superior frontal gyrus	Internal capsule	Collateral sulcus
DA1	Y	N	Y	N	Y	Y	Y
DA3	Y	Y	N	Y	Y	Y	Y
DA5	Y	N	Y	N	Y	Y	Y
DA6	Y	N	Y	Y	Y	N	Y
DA7	Y	N	N	Y	Y	Y	Y
DA8	Y	N	Y	N	N	N	Y
DA9	Y	N	N	Y	Y	Y	Y
DA10	Y	N	N	Y	Y	N	N
DA11	Y	N	Y	N	N	Y	N
DA12	Y	N	N	Y	Y	Y	Y
Total	10	1	5	6	8	7	2

3.3.4.2.2 Additional VBM analyses

In order to test possible reasons for differences between the results reported here and those reported by Gadian *et al* (2000), the analyses described in Section 3.2.3.4 were also conducted using MPRAGE 3D data-sets as in the study of Gadian *et al* (2000). In addition, as the group of DA patients studied in this thesis is of mixed aetiology (see Chapter 2), analyses were conducted on sub-groups of the 10 patients. The 10 patients were divided into those with hypoxia-ischaemia (n = 7), those with confirmed injury occurring under 1 year of age (n = 5), those with a history of epilepsy (n = 5), and finally, those without a history of epilepsy (n = 5). The data were analysed in the same way as described in Section 3.2.3.4, comparing each sub-group with their controls. The results of these additional analyses were largely the same as those described in Sections 3.3.4.1 and 3.3.4.2. However, caution must be taken when interpreting the results of small sample sizes as the analysis is prone to false positives (see Salmond *et al.*, 2003). Therefore, only the regions of grey matter originally predicted to be abnormal and only regions of white matter at 8 mm already identified in Section 3.3.4.2 are reported. A summary of the analyses as shown in Table 3:13 and Table 3:14.

↓ = decrease; ↑ = increase; - = not present; WBC = whole-brain corrected; SVC = small volume corrected; PUC = predicted uncorrected.

Table 3:13 Summary of grey matter sub-group analyses.

Regions of interest	MPRAGE (n = 8)	Hypoxia-only (n = 7)	< 1 year (n = 5)	Epilepsy (n = 5)	No Epilepsy (n = 5)
Right posterior cingulate cortex	↓ (PUC)	-	-	-	-
Bilateral hippocampus	↓ (WBC)	↓ (WBC)	↓ (SVC)	↓ (PUC)	↓ (WBC)
Bilateral putamen	-	-	-	-	-
Bilateral thalamus	↓ (WBC)	↓ (SVC)	↓ (PUC)	↓ (PUC)	↓ (PUC)
Bilateral middle frontal gyrus	↑ (WBC)	-	-	-	↑ (WBC)

WBC = whole-brain corrected; SVC = small volume correction; PUC = predicted uncorrected

Table 3:14 Summary of bilateral white matter sub-group analyses.

Regions of interest	MPRAGE (n = 8)	Hypoxia-only (n = 7)	< 1 year (n = 5)	Epilepsy (n = 5)	No Epilepsy (n = 5)
Near post-central gyrus	-	↑ (WBC)	↑ (WBC)	↑ (PUC)	↑ (PUC)
Near temporal horn of lateral ventricle	↑ (WBC)	↑ (WBC)	↑ (WBC)	↑ (PUC)	↑ (PUC)
Near cingulate/ superior frontal gyrus	↑ (WBC)	↑ (WBC)	↑ (WBC)	↑ (PUC)	↑ (PUC)
Internal capsule	↑ (WBC)	-	↑ (WBC)	↑ (PUC)	↑ (PUC)
Near collateral sulcus	↑ (WBC)	-	-	↑ (PUC)	↑ (PUC)

WBC = whole-brain corrected; SVC = small volume correction; PUC = predicted uncorrected

3.4 DISCUSSION

3.4.1 Confirmation of bilateral hippocampal abnormality

On visual inspection of clinical scans, all twelve patients with DA showed bilateral hippocampal abnormality as indicated by a reduction in size, whereas only one control case had questionably small hippocampal size (but this was not confirmed with volume measurements), thus satisfying the inclusion criteria.

Quantitative measurements of the hippocampal volumes confirmed visual inspection reports of the patient scans, in that the group of patients with DA for whom volumes were measured showed bilateral volume reduction relative to controls. Analysis of the hippocampal volumes for each individual patient revealed that seven of the nine patients with DA had bilateral hippocampal volumes below the normal range, while two of the patients, although had left hippocampal volumes within 2 z-scores of the control group mean, these were close to 2.

A quantitative group analysis of the hippocampal T_2 values confirmed that the patients with DA had mean hippocampal T_2 values bilaterally greater than the control group even when the data were adjusted for a possible confound of age. Analysis of each individual patient revealed that seven of the twelve patients with DA had hippocampal T_2

values above the normal range, and three others had unilateral hippocampal T_2 values above the normal range, suggesting abnormality in the remaining tissue of the hippocampi with these elevated T_2 values. These findings suggest that the remaining hippocampal tissue is commonly abnormal bilaterally in the DA group compared to controls.

Both unilateral and bilateral VBM analyses confirmed grey matter density decrease in the hippocampus consistent with visual inspection and volumetric measurements.

3.4.2 Whole brain morphology

On visual inspection, regions of grey matter abnormality were noted in the cerebellum of one patient with DA and one control participant, and in the brain stem of one patient with DA. Visual inspection also suggested a general reduction in white matter in two of the patients with DA.

VBM analysis in the DA group relative to the controls revealed bilateral grey matter density decrease in the thalamus; bilateral grey matter density increase in the middle frontal gyrus; and bilateral white matter increases near the temporal stem, near the temporal horn of the lateral ventricle, in the internal capsule, above the basal ganglia, and near the post-central gyrus, cingulate/superior frontal gyrus, collateral sulcus and the post-central sulcus/intraparietal sulcus. These findings are consistent with the prediction that DA is associated with abnormalities in grey matter structures associated with memory function and white matter connections between these structures (see discussion below).

A decrease in thalamic grey matter density as revealed in the VBM analysis is consistent with previous findings of DA (Gadian *et al.*, 2000) and with the known pathology associated with the aetiology of most of the patients (hypoxia-ischaemia: Volpe, 2001; Singhal *et al.*, 2002; hypoglycaemia: Auer *et al.*, 1984). There is a great deal of evidence from both lesion (human: for a review see Van der Werf *et al.*, 2000; animal: e.g. Aggleton and Mishkin, 1983; Warburton *et al.*, 2000; Van Groen *et al.*, 2002) and imaging studies (human: e.g. Shallice *et al.*, 1994; Rugg *et al.*, 1997; Konishi *et al.*, 2000; animal: e.g. Vann *et al.*, 2000) to suggest a role for the thalamus in memory function. As discussed in Section 1.2, Chapter 1, the thalamus has reciprocal connections with the hippocampus, surrounding parahippocampal region and the prefrontal cortex.

These anatomical connections suggest structural (e.g. Fuster, 1997; Aggleton and Saunders, 1997) and possibly functional (Aggleton and Brown, 1999) segregation within the thalamus. Unfortunately, due to the small volumes of some of the separate nuclei it was not possible to locate the precise area of thalamic damage; however, the medial dorsal thalamus nuclus, pulvinar and ventral lateral thalamic nuclei were suggested. The medial dorsal thalamic nucleus connect with the perirhinal cortex and is implicated in familiarity-based recognition (for a review see Aggleton and Brown, 1999). Therefore, it is important to consider the possibility that abnormality within the medial dorsal nucleus of the thalamus may contribute to the cognitive profile associated with DA. The pulvinar receives afferents from all areas of the occipital cortex and adjacent areas of the parietal and temporal lobes. It is thought to be involved in visual processing, particularly dorsal stream processing (Casanova *et al.*, 2001), and therefore may contribute perceptual information to the memory circuit. The ventral lateral thalamus has reciprocal connections with the primary motor cortex (e.g. Kultas-Ilinsky *et al.*, 2003) and basal ganglia (e.g. McFarland and Haber, 2002). As a result of these connections and its involvement in Parkinson's disease the ventral lateral nucleus of the thalamus is thought to play a role in motor function (e.g. Kassubek *et al.*, 2001).

Further grey matter abnormality was noted in the middle frontal gyrus. However, this appeared as an increase in grey matter in DA patients compared to controls. The middle frontal gyrus has been associated with recognition memory, for example, increased activation in this region has been reported in PET (e.g. Nyberg *et al.*, 1996a; 1996b; Tulving *et al.*, 1999) and fMRI studies (e.g. Eldridge *et al.*, 2000; Ranganath *et al.*, 2003) of recognition memory. It is possible therefore, that an increase in grey matter density in this area contributes to the memory profile associated with DA.

In contrast to earlier studies, the VBM analysis did not reveal any evidence for grey matter abnormalities in the basal ganglia or posterior cingulate cortex. Furthermore, these areas did not appear abnormal on visual inspection. Although lack of evidence for an abnormality does not equate to normality (see Salmond *et al.*, 2003), it is possible that unlike previous reports of DA (Gadian *et al.*, 2000; Salmond *et al.*, 2000a; 2000b) these areas are not affected. However, a decrease in right posterior cingulate cortex grey matter density was present at an uncorrected level (previously whole-brain corrected, Salmond *et al.*, 2000a) when the MPRAGE data-sets were analysed, suggesting that differences in the sequence type used might account for the lack of right posterior cingulate cortex

abnormality in this chapter. The lack of basal ganglia abnormality is not due to differences in the data-sets used, the aetiology of the patients, or age at injury, as the sub-group analyses did not reveal any basal ganglia abnormality. There are several other possible reasons for the lack of basal ganglia abnormality in this chapter: (i) differences in the control group used. This chapter compared the patients with DA to age-, sex-, and IQ-matched controls, whereas previous studies of DA (Gadian *et al.*, 2000; Salmond *et al.*, 2000a; 2000b) compared the patients with DA to controls matched for age and sex only. It is possible that removal of the potentially confounding factor of IQ (e.g. Salmond, 2001) may account for the differences in findings; (ii) this chapter included six new patients with DA, which may account for some of the differences in findings between the studies; (iii) although the analysis reported by Gadian *et al* (2000) is identical in design to the unilateral analysis reported here, the study by Salmond *et al* (2000a) reported a unilateral conjunction analysis. Statistically the conjunction analysis is different from the unilateral analysis reported in this thesis; (iv) VBM may have difficulty segmenting grey and white matter in the basal ganglia because this structure has a signal intensity that is intermediate between that of white and cortical grey matter.

The white matter abnormalities appeared as an increase in the DA group compared to controls. Previous VBM studies of DA did not report white matter density analysis so it is not possible to compare the present results with previous findings. Comparison with other studies indicates that this is a rather unusual finding as most studies have detected decreases in white matter in abnormal brains (e.g. Perlman, 1998; Sowell *et al.*, 2001; Hermann *et al.*, 2002; Nosarti *et al.*, 2002). Furthermore, visual inspection of the scans indicated a general reduction in white matter in two of the DA cases (DA1 and DA12). However, the increases in white matter can be interpreted with some confidence as they were also present at an uncorrected level in the unilateral analysis, in analysis of the MPRAGE data-sets (suggesting they were not a consequence of the MR sequence used) and when sub-groups were analysed (suggesting they are consistent among the different aetiologies of the group).

The increase in white matter might indicate an increase in myelinated fibers. Possible biological reasons for such aberrant fibers include, failure of regressive events (including cell death, axon pruning, and synaptic elimination) or abnormally large axons. It is possible that such aberrant fibers are a consequence of the aetiology associated with DA, the developmental nature of this disorder, or both. However, it is also worth

considering that the abnormal increase in white matter density in patients with DA may, at least in part, be simply an epiphenomenon of grey matter density reductions; if the proportion of grey matter within a particular region decreases then the proportion of white matter will increase, if these are the only tissue types within that region. The abnormal increase in white matter therefore needs to be confirmed using other MR techniques, such as diffusion tensor imaging (e.g. Basser *et al.*, 1994; Eriksson *et al.*, 2001).

3.4.3 Conclusion

In conclusion, bilateral hippocampal abnormality in the patients with DA as revealed on visual inspection was confirmed quantitatively by volumetric measurements, VBM, and T_2 values. The VBM analyses supported the prediction that DA is associated with bilateral thalamic damage. However, unexpectedly, there was no evidence of abnormality in the basal ganglia or the right posterior cingulate cortex. The failure to detect abnormality in these regions may be due to the MR sequence used (at least in the case of the right posterior cingulate cortex), the addition of new patients, the comparison with an IQ- matched control group, or difficulties with segmenting the basal ganglia into grey and white matter. In addition, the VBM results extend the previously reported findings of DA, suggesting that DA is associated with an increase in grey matter density in the medial frontal gyrus and an increase in white matter density in the temporal lobe and near striatal areas. However, the white matter findings require further imaging evaluation. It is possible that these abnormalities, in addition to the hippocampal abnormalities, contribute to the memory profile associated with DA. The cognitive profile of DA will be discussed in relation to these abnormalities in Chapter 10.

4 EPISODIC VERSUS SEMANTIC MEMORY

This chapter aims to characterise the dissociation between episodic and semantic memory associated with DA relative to a group of age-, sex- and IQ-matched controls. The results were largely concordant with previous studies of DA (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000) indicating severely impaired episodic memory and relatively preserved semantic memory. In addition, significant impairments were noted in immediate memory, and delayed recognition, and verbal memory, which was more affected than nonverbal memory. Furthermore, although in the main, performance was relatively preserved on measures of semantic memory, there was some evidence for impairments in two aspects of this domain: Information retrieval (WISC-III/WAIS-III) and reading comprehension. Unexpectedly, the degree of episodic memory impairment associated with DA did not significantly relate to the degree of hippocampal abnormality as indicated by hippocampal volumes, hippocampal T_2 values or VBM. However, semantic memory did correlate with grey matter density in the parahippocampal region suggesting that a decrease in grey matter was associated with a decrease in semantic memory. The findings in this chapter provide support for the multi-system model of long-term declarative memory organisation, suggesting that many aspects of semantic memory acquisition are preserved following hippocampal injury.

4.1 INTRODUCTION

As discussed in Section 1.6, Chapter 1, theories of long-term declarative memory organisation can be divided into multi-system and unitary-system models. Multi-system models, such as that of Tulving and colleagues (e.g. Tulving, 1985a; 1995; 2001; 2002; Tulving and Markowitsch, 1998) suggest that a dissociation can occur between episodic and semantic memory. According to this model it is possible to encode, store and retrieve semantic memories without a contribution from episodic memory, but only retrieval from episodic memory is independent of semantic memory. The neuroanatomical correlate of this model postulates that episodic memory is supported by the hippocampus, and semantic memory (including familiarity-based recognition) is supported by the surrounding parahippocampal region (e.g. Mishkin *et al.*, 1997; 1998; Aggleton and Brown, 1999). Unitary-system models, such as that proposed by Squire and colleagues (e.g. Squire, 1987; 1992; 1994; Squire and Knowlton, 1995; Squire and Zola-Morgan, 1991; 1996; 1998; Manns and Squire, 2002), on the other hand, do not suggest a dissociation between episodic and semantic memory. This model proposes that both episodic and semantic memory rely on the hippocampus and surrounding parahippocampal region and therefore are impaired to a similar degree following injury to any component of the MTL (Squire and Zola, 1996; 1998). These models make different predictions regarding the memory profile associated with selective hippocampal pathology: according to the multi-system model, selective hippocampal pathology will be associated with an episodic memory impairment with relative sparing of semantic memory (e.g. Mishkin *et al.*, 1997; 1998); according to the unitary-system model selective hippocampal pathology will be associated with an impairment in both episodic and semantic memory (e.g. Manns and Squire, 2002).

4.1.1 Dissociation between episodic and semantic memory

Episodic memory measures reported in this chapter include a test of everyday memory and tests of verbal and nonverbal recall. The test of everyday memory (Rivermead Behavioural Memory Test, Wilson *et al.*, 1991) includes measures of prospective memory, such as remembering an appointment. This is considered to place a high demand on episodic memory as it involves mental projection of anticipated events into one's subjective future (e.g. Wheeler *et al.*, 1997). Tests of verbal and nonverbal

recall are also believed to reflect episodic memory in that the participant is required to recollect information from a single study episode (e.g. Tulving, 1972). Measures of semantic memory, on the other hand, include knowledge of facts, such as vocabulary, and information about the world, and reflects memory that is acquired in a variety of contexts.

Studies of episodic and semantic memory in patients with selective hippocampal injury sustained in adulthood have provided evidence to support both the multi-system model (e.g. patient PS, Verfaellie *et al.*, 2000; patient YR, Holdstock *et al.*, 2002) and the unitary-system model (e.g. patient VC, Cipolotti *et al.*, 2001; Manns *et al.*, 2003b). The reason for these conflicting results is unclear. One possibility may be additional damage either to the parahippocampal cortex or memory-related structures outside of the MTL not seen on conventional MR images. For example, Chapter 3 of this thesis presented results from VBM analyses that detected additional subtle pathology, which was not detected by visual inspection of the MR scans. Although the implication of these findings for memory has not yet been investigated, these findings highlight that studies investigating the pathology associated with amnesia need to employ techniques other than conventional MRI.

The difficulty with investigating semantic memory in patients with adult-onset hippocampal injury is that without conducting a longitudinal study of new learning it is difficult to ascertain the level of anterograde semantic relative to episodic memory. Although some studies have attempted to teach patients with amnesia new information (e.g. Glisky *et al.*, 1986a; 1986b; Glisky and Schacter, 1988; 1989; Tulving *et al.*, 1991; Hayman *et al.*, 1993; Hamann and Squire, 1995; Bayley and Squire, 2002; Holdstock *et al.*, 2002), these have included patients with damage that extends beyond the hippocampus (see Chapter 6), or have presented information using a study-test procedure with only a few repetitions (e.g. Holdstock *et al.*, 2002), and therefore may have underestimated the amount of anterograde semantic learning possible in the presence of impaired episodic memory.

Patients with selective hippocampal injury sustained early in development provide a unique opportunity to study the acquisition of semantic memories post-injury. As discussed in Section 1.8.3, Chapter 1, there are only a few studies of patients with relatively selective hippocampal injury sustained in childhood (Broman *et al.*, 1997; Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000), and only two of these included patients whose injury was sustained perinatally and therefore before any pre-morbid semantic

knowledge could be acquired (2 cases, Vargha-Khadem *et al.*, 1997; 3 additional cases, Gadian *et al.*, 2000). Details of these studies were described in Section 1.8.3.1, Chapter 1, and therefore will not be repeated here. It is important to note that Broman *et al.* (1997) found that patient MS, who sustained hippocampal injury at ~8 years of age, had impaired episodic and semantic memory as measured using a variety of tasks. However, the studies of Vargha-Khadem and colleagues (e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000) found that all six patients with selective hippocampal pathology sustained in childhood (five of whom sustained their injury before the first year of life) demonstrated relatively preserved semantic memory as evidenced by average intelligence quotients, factual and vocabulary knowledge, and academic attainments, despite impairments on episodic memory measures, such as tests of everyday memory and delayed verbal and nonverbal recall (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000).

Nevertheless, despite having the advantage, over adult-onset studies, that assessment of semantic memory in child-onset cases is evidence of anterograde memory, there is still uncertainty as to whether relatively selective hippocampal injury is associated with preserved semantic memory in the presence of impaired episodic memory (e.g. Squire and Zola, 1998).

4.1.2 Memory function in relation to extent of MTL abnormality

Hippocampal abnormality as indicated by percentage volume reduction has been associated with poor episodic memory performance in adults (e.g. Kopelman *et al.*, 2001; Martin *et al.*, 2001) and children (Isaacs *et al.*, 2000; Vargha-Khadem *et al.*, 2001). Furthermore, in a recent review, Vargha-Khadem *et al.* (2001) describe a comparison of eleven patients with DA to eleven children born extremely pre-term. This study found that the DA patients, with the greater volume reduction (~40%), were more impaired than the pre-term group (with ~10% reduction) on episodic but not semantic memory, suggesting that hippocampal volume reduction is associated with episodic but not semantic memory performance.

4.1.3 Specific aims and predictions

As described in Chapter 2 the patients with DA who participated in the studies reported in this thesis were recruited on the basis of having average intellectual abilities (suggesting average semantic memory), poor long-term declarative memory (suggesting

poor episodic memory) and selective hippocampal pathology as revealed by conventional MR techniques. This chapter has two aims: first, to characterise the episodic-semantic memory dissociation in a sample of children and adolescents with DA relative to a group of age-, sex- and IQ-matched controls using the tasks described by Vargha-Khadem *et al.* (1997) and Gadian *et al.* (2000); second, to examine the relationship between memory performance and MTL abnormality, as measured by hippocampal T_2 values, hippocampal volumes, and grey matter density (Chapter 3).

Based on the discussion above, it was expected that:

(a) Patients with DA will be impaired relative to controls on tests of episodic memory including everyday memory, and delayed verbal and nonverbal memory will be more impaired than immediate memory.

(b) Patients with DA will not be impaired relative to controls of tests of semantic memory and academic attainments.

(c) Given that the hippocampal abnormality is bilateral (see Chapter 3), the patients with DA are not expected to show a material-specific memory disorder (e.g. Moscovitch, 1979; Kim *et al.*, 2003).

(d) According to the unitary-system model, damage to any component of the MTL system will be associated with both episodic and semantic memory performance, while according to the multi-system model, damage in the hippocampus will be associated with episodic memory but not semantic memory performance, and damage in the parahippocampal region will be associated with semantic memory performance.

4.2 METHODS

4.2.1 Participants

Twelve patients with DA and a group of twelve age-, sex- and IQ-matched controls took part in the neuropsychology studies reported in this chapter. As described in Chapter 3, hippocampal T_2 values were available for all twelve patients. However, only the hippocampal volumes of nine patients were measured, and datasets for only ten patients were available for VBM anaylsis. Details of the participants are presented in

Chapters 2 and 3. The groups did not differ with respect to age at test (or scan), verbal IQ or performance IQ.

4.2.2 Procedure

4.2.2.1 Everyday (episodic) memory

The Rivermead Behavioural Memory Test (RBMT, Wilson *et al.*, 1991): This test is made up of twelve different real-life tasks, for example, remembering a route around the room. There are two versions of this test, one for participants between the ages of 5 to 10 years, and one for participants over 10 years. The only difference between the two versions is that those aged 10 years and under are not asked the orientation question (i.e. "What is the date today?").

Performance was assigned a score of 0 (inaccurate), 1 (accurate with prompt) or 2 (accurate without prompt). The full profile score was calculated for each participant to determine level of performance (normal, moderate, poor, or impaired). In order to obtain an equivalent total profile score for each participant the profile score was calculated minus the date score (max = 22) because some of the participants were below eleven years of age at time of test. This 'equivalent' total score was used for statistical analysis. In addition, an estimate of prospective memory (e.g. Isaacs *et al.*, 2000) was calculated from a combination of three subtests (max = 6): belonging (remembering the item and location of a hidden object after ~20 minutes delay), appointment (remembering to ask a question after an alarm sounds, ~20 minutes delay) and message (remembering to take and leave a message in the correct location, both immediate and after ~20 minutes delay).

4.2.2.2 Verbal and nonverbal memory

4.2.2.2.1 Tests of general memory

In addition to the WMS-adapted (WMS-a) scale described in Section 2.3.1.2, Chapter 2, the more recently standardised Wechsler Memory Scale-III (WMS-III, Wechsler, 1997b) for adults and its child equivalent, Children's Memory Scale (CMS, Cohen, 1997), were administered. In these tests the participants are alerted that they will be required to remember the information immediately after presentation and after ~ 30 min delay. The verbal indices of the CMS consist of a) story recall: two stories were read for

immediate and delayed recall; b) paired-associate learning: fourteen pairs of words were read three times with immediate cued-recall after each presentation and delayed free recall. The visual indices consist of a) dot location recall: an array of dots was presented three times for immediate recall followed by a single presentation and recall of an interference array, then immediate and delayed recall of the first dot array; b) face recognition: a series of twenty-four faces were presented for immediate and delayed recognition with an additional twenty-four distractor faces.

The verbal indices of the WMS-III also consisted of story recall and paired-associate learning. However, the second story was read twice in story recall, and in paired associate learning eight pairs of words were read four times for immediate cued-recall after each presentation and delayed cued-recall. The visual indices consisted of face recognition and family pictures, where pictures of family members performing different activities were presented and the participant was asked to indicate who was in the picture, their location, and the activity they were performing, both for immediate and delayed recall.

The core memory indices of verbal immediate, visual immediate, verbal delay and visual delay have a mean of 100 and a standard deviation of 15.

The MQ obtained from the CMS is based on both immediate and delayed verbal and nonverbal indices, whereas the MQ obtained from the WMS-III is calculated on the basis of only the delayed verbal and nonverbal indices. The MQ from the CMS/WMS-III was not reported in this chapter because each participant was administered either the CMS or the WMS-III depending on age at test and therefore the composite indices of the MQ would be different depending on which test was administered.

4.2.2.2.2 Design copying and delayed recall

The Rey-Osterrieth Complex Figure (Rey, 1964): This figure was presented for copying and then recall was assessed after a 40-minute delay. The design is scored with respect to the accuracy of the 18 key features, where 2 points were given for a correctly placed feature, 1 point for a poorly placed feature or a distorted/incomplete but recognisable feature correctly placed, 0.5 points for a distorted/incomplete but recognisable feature poorly placed, and 0 points for an absent or not recognisable feature (max = 36). Three measures were obtained: percentage correct at copy; percentage correct at delay; and percentage forgetting.

4.2.2.2.3 Auditory verbal learning

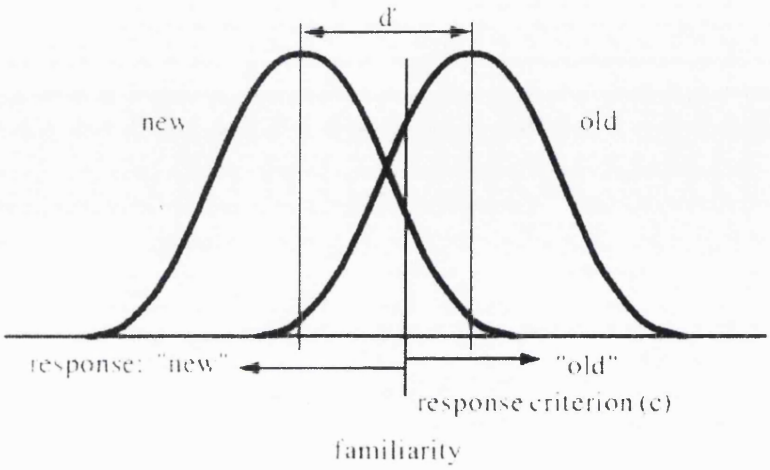
The Children's Auditory Verbal Learning Test – 2 (CAVLT-2, Talley, 1993): In this test a supra-span list of sixteen words was read to the participant five times with free recall after each presentation (List A). Next, a second list (List B) of sixteen words was read to the participant once for recall. The measures obtained included: *immediate span* (list A1+B1), *total learning score* (trial 1 to 5)[1], *interference recall* (B1), *immediate recall* (A6), *delayed recall* (after a 20-minute delay (A7)), *delayed recognition* (of list A) and *intrusion errors*. Although this test is standardised for children between the ages of six years six months to seventeen years eleven months, correct percentage raw scores are reported in this chapter in order to enable comparison with the Design Learning Test, which is not standardised for children (see below). A further memory estimate was calculated from the percentage forgetting over the 20-minute delay.

This task includes a measure of yes/no recognition. This type of task is assumed to be prone to differences in response bias and discrimination between groups (e.g. MacMillan and Creelman, 1991). Therefore, further analysis of the recognition data was conducted to assess group differences in discrimination (d') and response bias (c) between old ("yes") and new ("no") items, based on the signal detection theory (SDT).

The signal detection theory assumes that even before an experiment items differ in their levels of familiarity, and that presenting them for study increases the level of familiarity for each item presented. It is also assumed that as some items start with a low level of familiarity, their new level of familiarity after being presented is still lower than the initial level shown by some items which have not been presented (see Figure 4:1). In this model response criteria (c) can be placed along a single continuum of trace strength and items are accepted as being "old" if their trace strength is above the response criterion. One assumption of this model is that the more lenient the response criteria the more the increase in false-alarm rate, such that new items will be incorrectly accepted as old if they have sufficient familiarity (false alarm). According to Yonelinas (1994) familiar hits and false alarms will be a function of d' (the distance between the means of the old and new item distribution, see Figure 4:1), and c is an estimate of the participants response bias.

[1] This is an adaptation of the standardised score of 'level of learning' that includes trials 3, 4 and 5 only.

Figure 4:1 Familiarity distributions for old and new items for an equal-variance signal-detection model (Yonelinas, 2001).



Using the proportion of correct hits (old is classified as old) and false alarms (new is classified as old) d^1 is calculated. The proportion of correct hits and false alarms are converted to z-scores and then the false alarms z-score is subtracted from hits z-score (as described in Macmillan and Creelman, 1991). The response bias index (c) is also calculated using the z-scores for hits and false alarms, these are added together and multiplied by – 0.5 as described by Macmillan and Creelman (1991).

These (d^1 and c) were calculated separately for each participant in order to ascertain whether any potential differences between the groups on recognition memory were due to a truly decreased ability to discriminate old from new items in the DA group, or a difference in response criterion (bias) rather than discrimination sensitivity per se.

4.2.2.2.4 Design learning

The Design Learning subtest of the Adult Memory and Information Processing Battery (Coughlan and Hollows, 1985): This subtest was administered as a nonverbal analogue of the CAVLT-2. A pattern, formed by joining dots in a matrix (nine lines), was presented for five learning trials, then an interference pattern was presented for one recall trial, followed by immediate and delayed recall. Measures analogous to those of the CAVLT-2 were obtained, except for delayed recognition.

4.2.2.3 Semantic memory

Although verbal IQ was used to match the patient and control group, an estimate of semantic memory was obtained from the performance on three verbal IQ subtests: Information (knowledge of common events, objects, places, and people), Vocabulary (knowledge of word definitions), and Comprehension (requires the participant to solve everyday problems or to show understanding of social rules or concepts). This subtest analysis was performed in order to test whether the group of patients with DA showed a similar preserved performance on these subtests as reported in previous studies of DA (e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000).

In addition, the Pyramids and Palm Trees test (Howard and Patterson, 1992) was used to assess knowledge of semantic associations using drawings of objects. In this test, participants are presented with three pictures, one at the top of the booklet and two at the bottom, and are asked to point to the picture at the bottom that is associated with the one picture presented above. For example, a picture of a pyramid is presented with a picture of a palm tree and a fern tree and the participant is required to indicate which picture, the palm tree or the fern tree, is associated with the pyramid.

Finally, a test of verbal category fluency was administered (Hodges and Patterson, 1995). This task is described in detail in Section 2.3.1.3. Briefly, the participant was asked to generate words within a given category. The categories included animals, birds, water creatures, breeds of dog, household items, vehicles, musical instruments, and types of boat. The number of words produced in one minute was scored for accuracy. Only the total number correct is reported as a measure of semantic retrieval. The number of perseverations and rule breaks are discussed in more detail in Chapter 2.

4.2.2.4 Academic attainments

Tests of attainments in the areas of literacy and numeracy provided information about the participant's level of function in the academic environment. The Wechsler Objective Reading Dimensions (WORD, Rust *et al.*, 1993) was used to assess literacy skills in the form of basic reading, spelling and reading comprehension. The Wechsler Objective Numerical Dimensions (WOND, Rust, 1996) was used to assess numeracy skills in the form of numerical operations and mathematical reasoning. These tests have a mean of 100 and a standard deviation of 15.

4.2.2.5 Memory function in relation to extent of MTL abnormality

In order to examine the relationship between MTL abnormality and memory performance a regression analysis was conducted. First, the memory measures were grouped according to the domain of memory they tested (see Table 4:1). In most cases there was more than one dependent measure. Although these measures are related, they are not perfectly correlated and therefore a principal component analysis (PCA) was conducted (see Appendix I). The first PCA was of interest if it accounted for more than 50% of the total variance. The variance contribution for each component of interest is shown in Table 4:1 below.

Table 4:1 Total variance for each component of interest

Component 1	Variables included	% of total variance
Immediate verbal recall	WMS-a story recall, CAVLT-2 recall trial A1	73.05
Delayed verbal recall	WMS-a story recall, CAVLT-2 recall trial A7	79.33
Everyday memory	RBMT total score, Sunderland questionnaire total score	82.84
Semantic memory	Information, Vocabulary and Comprehension	71.23

Linear regressions were then conducted in order to examine the relationship between hippocampal abnormality and memory performance in the DA group. There was only one measure of visual recall that was tested both immediately after presentation and after a delay (WMS-a design recall); therefore a principal component analysis was not conducted and raw scores were entered into the regression.

The hippocampal abnormality was measured using volumetrics and T_2 values as described in Chapter 2. As left and right hippocampal volumes (Pearson correlation: 0.82; $p = 0.006$) and T_2 values (Pearson correlation: 0.71; $p = 0.01$) were highly correlated an average volume and T_2 value was calculated across hemispheres in order to obtain a bilateral measure of hippocampal abnormality. The relationship between bilateral hippocampal volume was then examined using separate linear regressions with each memory measure and with age at scan as a covariate, and the analysis was repeated with the bilateral hippocampal T_2 value.

The VBM analysis was conducted in accordance with the analysis procedure described in Section 3.2.3.4, Chapter 3, except that a correlation analysis was conducted

with the memory factors listed above in the DA group only. Instead of the inter-group comparisons, intra-group correlations were entered into the design with age at scan as a covariate. Significant results were determined in accordance with the method described in Section 3.2.3.4. For the purpose of small volume correction in the parahippocampal and hippocampal regions a sphere with a radius of 15 mm centred at ±27, -15, -15 (encompassing many regions in the MTL) was used in order to obtain a conservative correction.

4.3 RESULTS

The data were analysed in accordance with the procedure described in Section 2.3.3, Chapter 2. Details of ANOVA models are provided where appropriate.

4.3.1 Everyday (episodic) memory

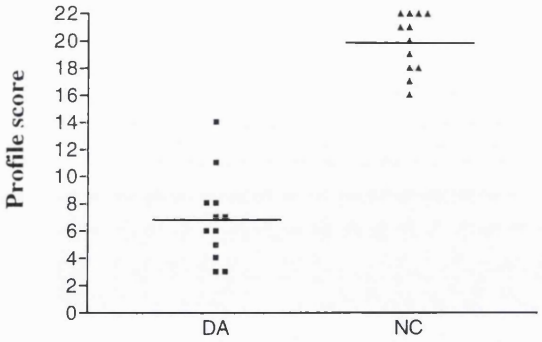
Table 4:2 shows the mean performance of the DA and control group on the RBMT. Figure 4:2 shows the individual total scores on the RBMT and the mean score (solid line) of each group. There was no overlap between the groups on total score; all of the patients with DA performed in the impaired range and all of the controls in the normal range.

Table 4:2 Everyday (episodic) memory

	DA	NC
RBMT total standard score (max 22)	6.92 (0.99)	19.80 (0.63)
RBMT Prospective (belonging, appointment, message, max = 6)	2.08 (0.40)	6.00 (0.00)

Mean (±SEM)

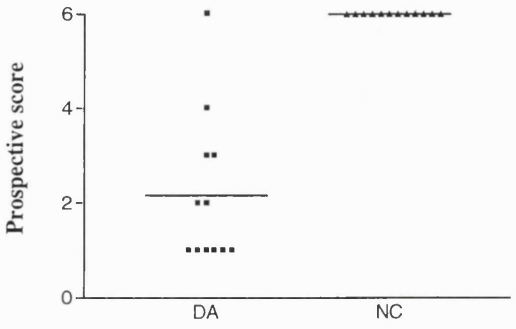
Figure 4:2 Rivermead behavioural memory test total score (minus date score)



The analysis (t-test) revealed that, as expected, the control group remembered more than the DA group ($t(22) = 11.03$; $p < 0.0001$). These findings are concordant with the parental ratings of everyday memory difficulties as measured by the Sunderland memory questionnaire (Section 2.4.2.1, Chapter 2).

Figure 4:3 shows the individual prospective memory scores on the RBMT and the mean score (solid line) of each group. The analysis (Mann-Whitney U test) revealed that the control group remembered more than the DA group ($U = 0$; $p < 0.0001$). On account of the lack of variance in the scores of the control group, caution should be taken when interpreting the statistical analysis. However, as shown in Figure 4:3, every member of the control group obtained the maximum score on the prospective memory subtest, whereas only one case with DA (DA8) obtained this score. The ceiling effects in the control group may underestimate the prospective memory impairment in the DA group.

Figure 4:3 Prospective memory composite score



4.3.2 Verbal and nonverbal memory

4.3.2.1 Tests of general memory

General memory was assessed using the standardised CMS and WMS-III scaled scores. These were analysed for immediate and delayed verbal and nonverbal memory. A three-way mixed-model ANOVA with a between-subjects factor of group (DA, NC) and within-subjects factors of time (immediate, delay) and task (verbal, visual) was conducted.

4.3.2.1.1 CMS/WMS-III indices

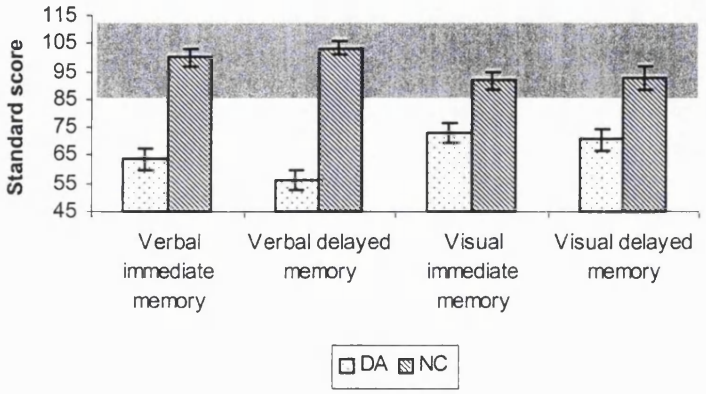
Table 4:3 and Figure 4:4 show the mean (±SEM) standard scores of the DA and control groups on the WMS-III and CMS.

Table 4:3 CMS/WMS-III indices

Standard scores	DA	NC
Verbal immediate	63.7 (3.8)	100.1 (3.1)
Verbal delayed	56.2 (3.3)	103.4 (2.4)
Visual immediate	73.1 (3.7)	91.7 (3.0)
Visual delayed	70.7 (4.0)	92.7 (4.4)

Mean (±SEM)

Figure 4:4 WMS-III/CMS



The shaded area represents normal range (100 ± 1 SD = 15 points), indicating that the mean performance of the control group falls within the normal range on all measures, while the mean performance of the patients with DA falls outside the normal range on all of the memory measures.

The analysis (ANOVA) revealed, as expected, a significant main effect of Group ($F(1,22) = 76.52$; $p < 0.0001$), suggesting that the control group remembered more than the DA group. There was no evidence for a main effect of Time ($p > 0.1$) or Task ($p > 0.1$). The main effect of Group was qualified, as expected, by a significant Group by Time interaction ($F(1,22) = 8.45$; $p = 0.008$), but unexpectedly there was also a significant Group by Task interaction ($F(1,22) = 13.48$; $p = 0.001$). Also as expected, there was no evidence for a Time by Task interaction ($p > 0.1$) or a Group by Time by Task interaction ($p > 0.1$).

Follow-up analyses of the expected Group by Time interaction, revealed that although the control group performed better than the DA group on measures of both immediate ($t(22) = 7.69$; $p < 0.0001$) and delayed ($t(22) = 8.81$; $p < 0.0001$) memory, the mean group difference was smaller at immediate (27.5) than delayed memory (34.6).

Follow-up analyses of the unexpected Group by Task interaction revealed that the control group performed better than the DA group on measures of verbal ($t(22) = 10.04$; $p < 0.0001$) and visual ($t(22) = 4.05$; $p = 0.001$) memory, but the mean group difference was smaller on visual (20.3) than verbal memory (41.8). As it was expected, based on their bilateral hippocampal pathology, that patients with DA would not show a discrepancy between visual and verbal memory, further follow-ups were conducted. This revealed that the control group did not show a significant discrepancy ($p > 0.0125$) but the patients with DA tended to remember more visual than verbal information ($t(11) = -2.76$; $p = 0.019$).

4.3.2.2 Design copying and delayed recall (Rey-Osterrieth complex figure)

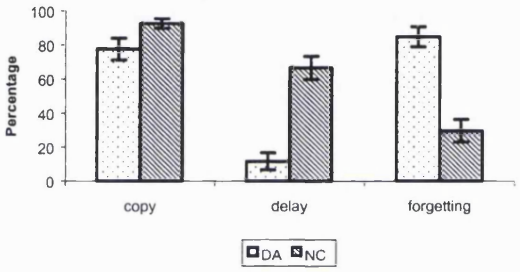
Table 4:4 and Figure 4:5 show the mean (±SEM) percentage correct at copy, delayed recall, and the percentage of forgetting in the DA and control groups on the Rey figure.

Table 4:4 Rey-Osterrieth figure

Percentage	DA	NC
Copy	77.7 (6.4)	92.7 (2.7)
Delayed recall	11.8 (5.0)	66.7 (6.7)
Forgetting	84.8 (5.9)	29.5 (6.7)

Mean (±SEM)

Figure 4:5 Rey-Osterrieth Figure



A test for homogeneity of variance revealed significant differences between the variance of the groups on the copy of Rey-Osterrieth figure. A nonparametric test (Mann Whitney U test) was therefore carried out. As expected, the groups did not differ with respect to percentage correct on the copy of the Rey-Osterrieth figure ($p > 0.05$). Also, as expected, the control group recalled more than the DA group after a delay ($t(22) = 6.58$; $p < 0.0001$) and the DA group showed more forgetting than the control group over the delay ($t(22) = -6.23$; $p < 0.0001$).

4.3.2.3 Auditory verbal learning

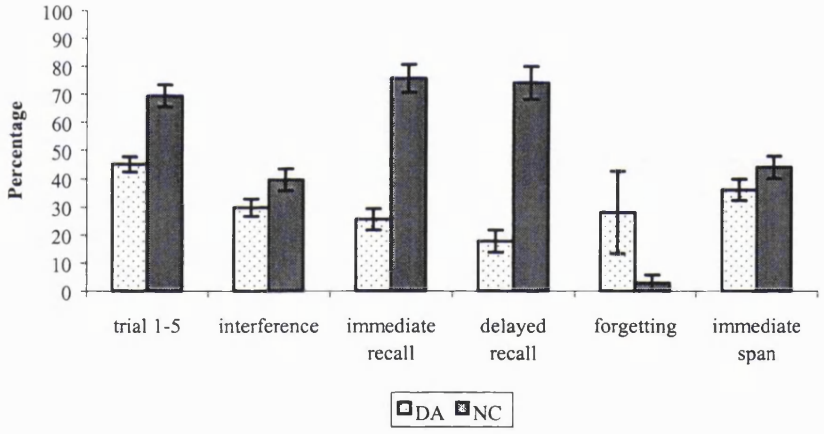
Table 4:5 shows the mean (±SEM) percentage correct/raw scores and percentage forgetting in the DA and control groups on the indices of the CAVLT-2. Figure 4:6 (a) shows the mean (±SEM) percentage correct and forgetting in the DA and control group. Figure 4:6 (b) and (c) show the mean (±SEM) raw scores on recognition and intrusion errors.

Table 4:5 Auditory verbal learning

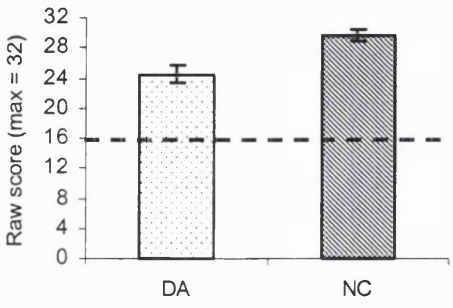
Percentage	DA	NC
Total learning score (Trial 1-5)	45.1 (2.7)	69.4 (3.9)
Immediate recall	25.5 (3.8)	75.5 (5.0)
Interference recall	29.7 (3.0)	39.6 (3.9)
Immediate span	35.9 (3.8)	44.0 (4.0)
Delayed recall	17.7 (4.0)	74.0 (5.9)
Forgetting	28.0 (14.6)	2.87 (2.9)
Delayed recognition (raw score)	24.5 (1.1)	29.6 (0.7)
Intrusion errors (raw score)	12.7 (2.9)	4.08 (2.4)

Mean (±SEM)

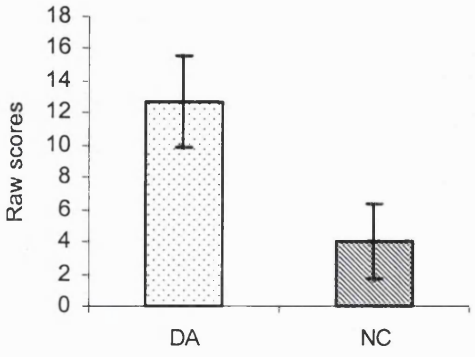
Figure 4:6 (a) CAVLT-2 Percentage correct/forgetting



(b) Delayed recognition



(c) Intrusion errors



The analyses (t-tests) of the indices revealed that the control group performed better than the DA group on total learning score ($t(22) = 5.13$; $p < 0.0001$), immediate recall ($t(22) = 7.95$; $p < 0.0001$), delayed recall ($t(22) = 7.95$; $p < 0.0001$) and recognition ($t(22) = 3.84$; $p = 0.001$). There was also evidence to suggest that the control group generated fewer intrusion errors than the DA group ($t(22) = -2.30$; $p = 0.032$). There was no evidence for an effect of group on the other indices ($p > 0.1$), including percentage forgetting ($p > 0.1$).

Analysis (one-samples t-test) revealed that the recognition performance of both groups was significantly above chance ($p < 0.0001$). Further analysis of the recognition performance was conducted to ascertain whether the deficit in recognition was associated with a difference between the groups in discrimination between old and new items (d^1) and/or response bias (c). This analysis is reported in detail in Chapter 6. Briefly, as most of the control group performed at ceiling either in their proportion of hits and/or false alarms, it was not possible to estimate d^1 or c for them, and therefore, a between-groups statistical analysis was not conducted. However, all of the patients with DA had d^1 scores above zero, indicating an ability to discriminate between old and new items. Both the patients with DA and the few controls for whom c estimates were available showed a slight negative bias, indicating that both the controls and the DA participants have an increased tendency to give a "yes" response; therefore, the false alarm rate exceeds the miss rate.

4.3.2.4 Design learning

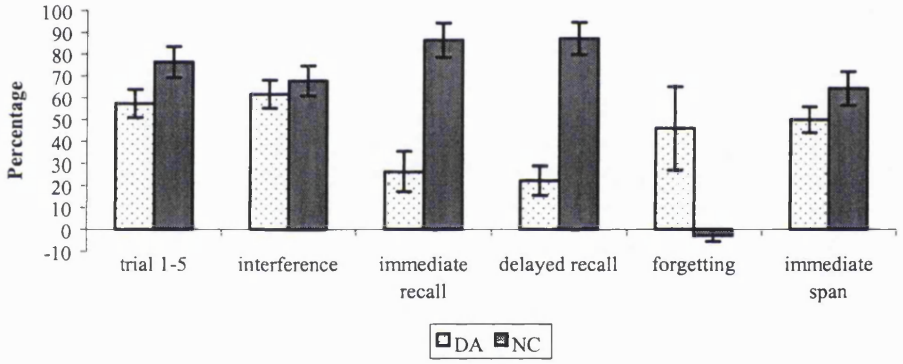
Table 4:6 and Figure 4:7 shows the mean (±SEM) percentage correct and percentage forgetting in the DA and control groups on the indices of the Design Learning task.

Table 4:6 Design learning indices

Percentage	DA	NC
Total learning score (trial 1-5)	57.4 (6.4)	76.3 (7.1)
Immediate recall	26.3 (9.0)	86.1 (8.0)
Interference recall	61.6 (6.4)	67.6 (6.9)
Immediate span	50.0 (5.9)	64.4 (7.7)
Delayed recall	22.2 (6.7)	87.0 (7.5)
Forgetting	46.0 (19.1)	-2.8 (2.8)
Intrusion errors (raw score)	18.1 (4.2)	7.8 (2.5)

Mean (±SEM)

Figure 4:7 Design Learning indices



The analyses (t-tests) of the indices revealed that the control group performed better than the DA group on immediate recall ($t(21) = 4.98$; $p < 0.0001$) and delayed recall ($t(21) = 6.42$; $p < 0.0001$) and that the DA group showed increased forgetting (Mann Whitney U: $U = 23$; $p = 0.03$). There was also evidence to suggest that the control group generated fewer intrusion errors than the DA group ($t(21) = -2.18$; $p = 0.04$). There was no evidence for an effect of group on the other indices ($p > 0.1$).

4.3.3 Semantic memory

Table 4:7 shows the mean (±SEM) standard score of the DA and control group on the verbal IQ subtests.

Figure 4:8 shows the individual scores and means (solid bar) of the DA and control groups on the Information subtest.

Table 4:7 Verbal IQ subtests

Standard score	DA	NC
Information	6.9 (0.4)	9.6 (0.7)
Vocabulary	7.9 (0.7)	9.2 (0.8)
Comprehension	9.4 (0.7)	9.8 (0.5)

Mean (±SEM)

A test for homogeneity of variance revealed significant differences between the variance of the groups on the Information standard score. A nonparametric test was therefore carried out (Mann-Whitney U test). Unexpectedly, the control group performed better than the DA group on the Information subtest ($U = 27$; $p = 0.008$). As expected, the groups did not differ on the Vocabulary ($p > 0.1$) or the Comprehension ($p > 0.1$) subtests of the intelligence scales.

Figure 4:8 Information subtest (WISC-III/WAIS-III)

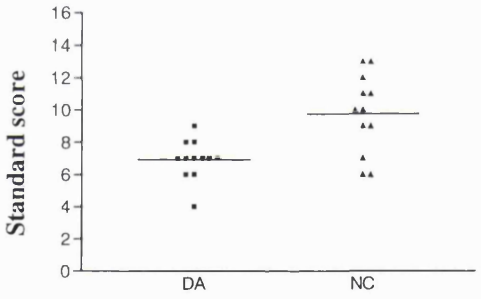


Figure 4:8 shows that the individual scores within the two groups overlap but the DA group mean (solid bar) is lower than that of the control group.

Table 4:8 shows the mean (±SEM) performance of both the DA and control groups on the Pyramids and Palm trees test and category fluency (the full analysis of category fluency is presented in Chapter 2).

Table 4:8 Semantic association and fluency

Raw score	DA	NC
Pyramids and Palm Trees	48.5 (0.7)	49.8 (0.5)
Category fluency (total)	84.9 (4.9)	92.3 (5.7)

Mean (±SEM)

The analysis (t-tests and Mann-Whitney U tests) revealed no evidence for group differences on the Pyramids and Palm Trees test of semantic association ($p > 0.1$) or category fluency ($p > 0.1$; see Chapter 2 for analysis of category fluency).

4.3.4 Academic attainments

Table 4:9 shows the mean (±SEM) standard scores of both the DA and control groups on the WORD and WOND. Both the actual score obtained and the score predicted from full scale IQ are shown.

Table 4:9 Academic attainments (WORD and WOND)

Standard Scores	DA actual	DA predicted	NC actual	NC predicted
Basic Reading	100.5 (2.1)	93.9 (2.2)	101.7 (2.8)	98.4 (1.8)
Spelling	101.1 (2.7)	94.9 (1.9)	98.3 (3.1)	98.8 (1.6)
Reading Comprehension	92.3 (2.5)	93.3 (2.5)	99.1 (3.6)	98.4 (2.0)
Mathematical Reasoning	92.8 (3.4)	92.6 (2.7)	100.5 (3.9)	98.3 (2.2)
Numerical Operations	93.9 (4.5)	94.2 (2.1)	100.1 (3.4)	98.6 (1.7)

Mean (±SEM)

Separate mixed-model ANOVAs with a between-subjects factor of group (DA, NC) and a within-subjects factor of score (actual, predicted) were conducted for each of the indices.

The analysis of basic reading revealed that overall the actual score was greater than the score predicted from full scale IQ (main effect of Score: $F(1,22) = 5.10$; $p = 0.034$). As expected, there was no evidence of a main effect of Group ($p > 0.1$) or a Group by Score interaction ($p > 0.1$).

There was no evidence for a main effect of Group ($p > 0.1$), score ($p > 0.1$) or a Group by Score interaction ($p > 0.1$) on spelling.

The analysis of reading comprehension scores revealed, unexpectedly, that the control group performed better than the DA group (Group: ($F(1,22) = 4.39$; $p = 0.048$). There was no evidence for a main effect of Score ($p > 0.1$) or a Group by Score interaction ($p > 0.1$) on reading comprehension.

There was no evidence for a main effect of Group ($p > 0.1$), Score ($p > 0.1$) or a Group by Score interaction ($p > 0.1$) on mathematical reasoning or numerical operations.

4.3.5 Memory function in relation to extent of MTL abnormality

Separate regression analyses were conducted in order to examine the relationship between hippocampal abnormality (both hippocampal volumes and T_2 values) and memory performance on each of these measures in the DA group. VBM correlation analyses were also conducted in order to examine the relationship between hippocampal and parahippocampal region grey matter densities and memory performance in the DA group. Age at test was included as a covariate in all analyses except for the analysis of semantic memory, as semantic memory was obtained from age-scaled scores.

4.3.5.1 Hippocampal volumes and memory performance in the DA group

The results of the linear regression analysis are shown in Table 4:10.

Table 4:10 Hippocampal volumes and memory performance

Measure	R Square	β (confidence interval)	t	df	p-value
Everyday memory	0.28	0.0010 (-0.002,0.004)	0.86	2, 6	0.43
Semantic memory	0.32	-0.0018 (-0.004,0.001)	-1.80	1, 7	0.11
Immediate verbal recall	0.07	0.00033 (-0.003,0.003)	0.26	2, 6	0.81
Delayed verbal recall	0.07	0.00063 (-0.003,0.004)	0.48	2, 6	0.65
Immediate visual recall	0.16	-0.027 (-0.097,0.043)	-0.94	2, 6	0.39
Delayed visual recall	0.31	0.014 (-0.03,0.06)	0.76	2, 6	0.48

As can be seen from Table 4:10 none of the analyses reached significance. This was expected for semantic memory but unexpected for measures of recall and everyday memory.

4.3.5.2 Hippocampal T_2 values and memory performance in the DA group

The results of the linear regression analysis are shown in Table 4:11.

Table 4:11 Hippocampal T_2 values and memory performance

Measure	R Square	β (confidence interval)	t	df	p-value
Everyday memory	0.34	-0.040 (-0.13,0.05)	-1.00	2, 9	0.34
Semantic memory	0.26	-0.066 (-0.15,0.013)	-1.86	1,10	0.09
Immediate verbal recall	0.06	-0.036 (-0.14,0.072)	-0.76	2, 9	0.47
Delayed verbal recall	0.04	-0.028 (-0.14,0.08)	-0.57	2, 9	0.58
Immediate visual recall	0.07	-1.02 (-3.86,1.82)	-0.81	2, 9	0.44
Delayed visual recall	0.03	-0.31 (-2.09,1.47)	-0.39	2, 9	0.70

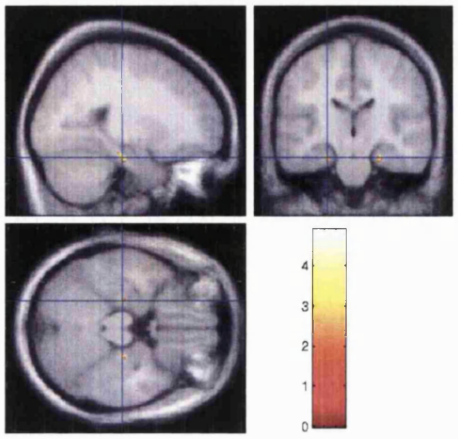
As can be seen from Table 4:11 there was no evidence for a significant relationship between episodic memory and hippocampal T_2 values.

4.3.5.3 VBM correlation with memory performance in the DA group

None of the episodic memory measures (everyday memory, immediate verbal recall, delayed verbal recall, immediate visual recall, and delayed visual recall) correlated with grey matter density in the hippocampus or parahippocampal region at 4 mm smoothing in the DA group.

However, semantic memory performance correlated with bilateral grey matter density in the parahippocampal region (see Figure 4:9), suggesting that a decrease in grey matter density in this region is associated with a decrease in semantic memory in the DA group.

Figure 4:9 Parahippocampal gyrus ±24, -21, -22 (4 mm; SVC p = 0.007)



4.4 DISCUSSION

The aims of this chapter were two-fold: first, to characterise the episodic-semantic memory dissociation in a sample of children and adolescents with DA relative to a group of age-, sex- and IQ-matched controls using the tasks described by Vargha-Khadem *et al.* (1997) and Gadian *et al.* (2000); second, to examine the relationship between memory performance and MTL abnormality, using hippocampal volumes, T_2 values, and grey matter density (VBM). The results generally supported the first prediction, in that episodic memory was impaired but semantic memory was generally preserved. The second prediction was somewhat supported in that semantic memory was related to parahippocampal grey matter density, but hippocampal abnormality was not related to episodic memory.

4.4.1 Episodic versus semantic memory

In relation to the first aim, a measure of everyday memory confirmed the severity of the episodic memory disorder in this group of patients. As expected, all patients performed in the impaired range on the RBMT consistent with the parental ratings of their memory difficulties reported in Section 2.4.2.1, Chapter 2. Furthermore, a measure of 'prospective' memory consisting of three RBMT subtests indicated that eleven of the twelve patients with DA scored below their controls. It is possible that the ceiling effects in the control group underestimated this prospective memory impairment. This episodic memory impairment was expected on the basis of previous reports of DA (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000) and confirm that bilateral hippocampal abnormality is associated with a severe episodic memory deficit (Mishkin *et al.*, 1998; Tulving and Markowitsch, 1998; Squire and Zola, 1998).

Tests of general memory included the recently standardised CMS/WMS-III. Although the WMS-a (reported in Chapter 2) and CMS/WMS-III are similar, they differ in a number of ways; for example, unlike the WMS-a, the CMS/WMS-III is an alerted memory task, in that the participant is informed there will be a test of delayed recall. Furthermore, the CMS/WMS-III has a delay of ~30 minutes for both verbal and visual information, whereas the WMS-a has a delay of 40 minutes for design recall and 90 minutes for story and paired-associate recall. In addition, the material to be remembered differs between the tests (see Sections 2.3.1.2 and 4.2.2.2.1). Despite these task

differences, the findings were largely consistent across the tests, such that, although both immediate and delayed memory in the DA group was impaired relative to controls on the measures of the CMS/WMS-III, as expected, delayed memory was more impaired than immediate memory. As discussed in Chapter 2, the impairment on immediate recall might reflect impairments in the 'episodic memory buffer' (Baddeley and Wilson, 2002, for further discussion see Chapter 10). However, the finding that on all measures apart from the word-list learning task, patients with DA were more impaired relative to controls at delayed than at immediate memory, suggests that DA is also associated with accelerated forgetting of verbal and nonverbal information, consistent with the storage/consolidation theories of amnesia (e.g. Huppert and Piercy, 1979; Isaac and Mayes, 1999b). This is also consistent with previous reports of DA (e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000) and with the findings reported in Chapter 2.

The CMS/WMS-III enabled a direct comparison between visual and verbal memory as the scores were standardised and therefore account for differences in task difficulty. This analysis unexpectedly revealed that verbal memory was more impaired than visual memory in the DA group compared to controls and therefore the DA group showed a visual-verbal discrepancy relative to controls in favour of visual memory. This verbal-visual discrepancy was not associated with a discrepancy in left and right hippocampal abnormality as might have been expected (e.g. Moscovitch, 1979; see Chapter 3).

A further test of nonverbal recall was the Rey-Osterrieth figure, and the results were consistent with other tests of nonverbal recall in previous reports of DA (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000), and adult-onset amnesia (e.g. Zola-Morgan *et al.*, 1986; Verfaellie *et al.*, 2000); the DA group was impaired relative to controls at delayed recall and showed abnormal forgetting. This task also measured the participants' ability to copy the design, where the lack of group difference indicated that the group difference on delayed recall was not due to differences in their drawing abilities. These findings thus confirm the presence of abnormal forgetting in the DA group following a single study exposure.

Although the findings of the WMS-a (Chapter 2), the CMS/WMS-III, and the Rey-Osterrieth figure suggest that DA is associated with abnormal forgetting, this was not the case on the word-list learning task of the CAVLT-2. However, the patients with DA did show abnormal forgetting relative to controls on the Design Learning task (DLT).

Although the DLT is considered a nonverbal analogue of the CAVLT-2, these tasks differ in many respects. For example, the word-lists of the CAVLT-2 are semantically related (although not organised by category), whereas the designs of the DLT are abstract lines joining dots and therefore do not conform to any semantic organisation. This addition of semantic relatedness in the word-list task may have rendered the information easier to remember over the delay. This could be further investigated using designs based on common objects. The influence of semantic organisation on memory performance will be examined in more detail in Chapter 6.

Despite these differences between the tasks, the DA group was impaired relative to controls at immediate and delayed recall of a word-list and design, and the learning of a word-list (but not design) with five sequential presentations. Each of these findings will be discussed below.

Factors affecting the measure of immediate recall are discussed in more detail in Chapter 6, and therefore will only be discussed briefly here. The immediate recall index is a measure of recall of the first list/design (list/design A) after five study-test presentations and a single study-test presentation of the interference list (list B/design B). Therefore, like adults with amnesia, the DA group may be impaired relative to controls due to interference from the second list/design (B) or previously erroneous responses generated over the five learning trials (e.g. Warrington and Weiskrantz, 1970; Hayman *et al.*, 1993; Hamann and Squire, 1995).

This possible increased tendency to the effects of interference may have prevented normal learning of the word-list with repeated study-test trials as indicated by the impairment on total learning score of the CAVLT-2 in the DA group (e.g. Hayman *et al.*, 1993; Hamann and Squire, 1995). However, there was no evidence for a learning impairment on the DLT. Although these tasks are similar in their design, there were only nine features to recall from the design, whereas the word-list consisted of sixteen words. Therefore, the better learning of the design may be due to differences in memory load.

Immediate memory was also estimated from the single-trial recall of list/design B and the immediate span score (trial 1 of list/design A + list/design B). These measures give an estimate of a participant's immediate memory without the influence of learning trials or interference from a second list, and in the case of the word-list task, measure short-term memory of a supra-span list (i.e. sixteen items). There was no evidence for impairment on the immediate memory span score on either the CAVLT-2 or the DLT,

suggesting short-term memory span was not impaired in the DA group. This is supported by the absence of group difference on the recall of the interference list/design (i.e. one-trial recall) and on digit and block span as reported in Chapter 2.

The patients with DA were, as expected, impaired relative to controls at delayed recall after ~ 20 minutes delay on both the CAVLT-2 and the DLT. This impairment on the CAVLT-2 was not greater than that expected from immediate recall performance (trial 6), as there was no evidence of increased forgetting in the DA group relative to controls. This finding does not support the 'storage/consolidation' hypothesis of amnesia (e.g. Huppert and Piercy, 1979; Isaac and Mayes, 1999a; 1999b). However, the DA group showed increased forgetting on the DLT. As already discussed above, this may be due to the design information being difficult to store due to its lack of inherent semantic organisation despite the reduced memory load compared to the CAVLT-2.

Although both groups performed significantly above chance on the delayed recognition subtest of the CAVLT-2, unlike previous reports of DA (Vargha-Khadem *et al.*, 1997), the DA group was impaired relative to controls. This is consistent with some studies of adult-onset hippocampal pathology (e.g. Manns and Squire, 1999; Cipolotti *et al.*, 2001; Manns *et al.*, 2003b), and may reflect general recognition impairments in patients with DA. This is tested in more detail in the studies reported throughout this thesis. However, it is worth noting that the recognition task of the CAVLT-2 is one of yes/no recognition, a procedure known to be influenced by differences in response criterion and therefore response bias. Unfortunately, due to ceiling effects in the control group it was not possible to compare the response bias or discrimination sensitivity between the groups. However, as reported in Chapter 6 (List RC), the DA group did score above zero on d', a measure of discrimination sensitivity, indicating an ability to discriminate between old and new items. Furthermore, both controls (for whom scores were available) and patients showed a slight bias (as indicated by a positive *c* score) towards responding "yes" during recognition, and therefore generating more false alarms. Possibly a better comparison of the recognition performance between patients with DA and their controls would be to use forced-choice recognition tasks, as this paradigm is thought to be less prone to differences in response bias (e.g. MacMillan and Creelman, 1991). This will be investigated in more detail in Chapters 6, 7 and 8.

The patients with DA also generated more intrusion errors than the controls on the word-list and design learning tasks. This increase in intrusion errors may reflect a

retrieval strategy in the patients, i.e. generate as many items as possible with the hope of generating the target. For example, the experimenter observed that the patients generally generated intrusion errors that were consistent with the categories presented on the word lists. This suggests that the patients with DA remembered the gist of the to-be-remembered word lists but not the specific details. Alternatively this may reflect frontal dysfunction, as frontal dysfunction is often associated with increased confabulation (e.g. for a review see Schnider, 2001). Although frontal dysfunction was not indicated on the tests presented in Chapter 2, these tests did not directly test confabulation.

Despite impairments on tests of verbal and nonverbal immediate and delayed memory, the DA group was relatively unimpaired on tests of semantic memory. Although detailed analyses revealed that unexpectedly the DA group had a lower score than the control group on the Information subtest of verbal IQ, they did not differ from their controls on the Vocabulary and Comprehension subtests. A number of other studies of patients with MTL (e.g. Ostergaard, 1987) or relatively selective hippocampal (e.g. Broman *et al.*, 1997) pathology sustained in childhood have reported impairments on the Information subtest of the Wechsler intelligence scales. However, both of these studies have reported additional impairments on measures of Vocabulary, and in the case of CC (Ostergaard, 1987), verbal fluency. The deficit on the Information subtest in the patients with DA reported in this chapter is quite marked (~7) in that the mean group score is one standard deviation below the population mean (10), and therefore is in the low-average range, and the group range is between 4 and 8 points (control range: 6 – 13).

Previous studies of DA (e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000) did not report significant deficits on this subtest of verbal IQ. However, inspection of the raw data reported in these studies suggests a trend in some patients to show a low performance on this scale.

This may reflect a semantic memory impairment in the DA group reported in this chapter. However, as this impairment appears to be specific to the Information subtest it is worth considering what this scale is testing. The Information subtest requires retrieval of factual information such as, 'Name three oceans' (WISC-III) and 'At what temperature does water boil?' (WAIS-III), and therefore places a high demand on semantic memory. However, although this may require knowledge that is acquired over time it possibly reflects knowledge that is acquired with only a few presentations. For example, the names of oceans and the boiling temperature of water may be information that is only presented

once or twice during school lessons or on television programs. Learning what a bicycle is (vocabulary, WISC-III) or what the word breakfast means (vocabulary, WAIS-III) is knowledge that is acquired with frequent, and in some cases daily, exposure in a variety of contexts. In addition knowing what to do if you cut your finger (comprehension, WISC-III) and why we pay taxes (comprehension, WAIS-III), may reflect knowledge that is acquired with more frequent presentation. If patients with DA learn with repeated exposure (e.g. Baddeley *et al.*, 2001), they may be more impaired on tasks that test knowledge that is acquired with only a few repetitions, such as Information, compared to tasks that test memory for knowledge that is acquired with many repetitions, such as Comprehension and Vocabulary. The effects of repetition on learning in patients with DA are examined in more detail in Chapter 6.

There was no evidence for an impairment in the DA group on nonverbal semantic association (Pyramids and Palm Trees, Howard and Patterson, 1992) or semantic fluency (Hodges and Patterson, 1995), suggesting that semantic retrieval was intact.

There was no evidence for an effect of group on numeracy, spelling, and basic reading. Furthermore, there was evidence to indicate a main effect of score on basic reading which indicated that both groups performed above the level predicted from their full scale IQ. There was, however, evidence for an effect of group on reading comprehension. On this task, although the control group performed better than the DA group, there was no evidence for a Group by Score interaction, suggesting that both groups performed at a level predicted from their full scale IQ.

Although the motor routines and behavioural skills needed to first learn to read and write must depend largely on nondeclarative procedural learning, the ability to comprehend and express ideas through reading and writing can only come from the semantic component of cognitive memory. Therefore the impairment in reading comprehension was unexpected. This task involves the participant reading a short story, and, after they have indicated that they have finished reading, the examiner asks a comprehension question. The stories increase in difficulty and quantity. However, the participant is always permitted to re-read the story before answering the question. Two possible explanations for an impairment in the DA group are that either: (i) they did not take advantage of the fact that they were permitted to re-read the story before answering the question; or (ii) the memory load required to hold the question in mind and simultaneously read the story in order to find the answer may be greater than that of

working memory. If relying on memory of the story or if memory of the question and the story exceeds working memory, an impairment might be expected due to their episodic memory impairments. Indeed it was observed during testing that unlike the controls, the patients with DA were quick to respond and did not seem to spend time re-reading the story despite these instructions. Therefore an impairment in Reading Comprehension may be caused by the episodic component in the task. Their intact performance on the verbal IQ Comprehension subtest, although testing a slightly different facet of semantic comprehension (i.e. long-term knowledge and social understanding established prior to assessment), suggests that they do not have general deficits in comprehension per se.

Like reading, spelling, and comprehension, numeracy may also require long-term retrieval of facts, in this case arithmetic facts (e.g. Jordan and Montani, 1997; Geary, *et al.*, 2000) and thus semantic memory. Therefore, the findings of intact reading, spelling and numeracy (numerical operations and mathematical reasoning) are consistent with evidence for preserved semantic memory.

Although different measures have been used across studies, this relative preservation of anterograde semantic memory is unlike that seen following adult-onset hippocampal pathology. Indeed even though some studies of patients with relatively selective hippocampal pathology demonstrate evidence of anterograde semantic memory (e.g. Verfaellie *et al.*, 2000; Van der Linden *et al.*, 2001), these patients seem to show a limited capacity to acquire new semantic memories relative patients with DA. This is best illustrated by the performance of patient YR on a range of anterograde semantic memory tasks (Holdstock *et al.*, 2002). Although YR was able to discriminate old from new definitions (forced choice recognition), and post-morbid famous events and names from non-famous events and names, she was impaired at recalling definitions of newly learned words, and details of post-morbid famous events (Holdstock *et al.*, 2002).

The reason why patients with DA have a greater capacity to acquire anterograde semantic memory compared to adult-onset cases with reportedly similar selective hippocampal pathology, despite severe episodic memory impairments is unclear. One possibility is that the dissociation is due to the selectivity of the pathology (i.e. relatively more intact parahippocampal cortices in patients with DA compared to adult onset cases). Alternatively, the dissociation may be due to the plasticity of the developing brain, such that early onset pathology may result in reorganisation of function through alternative connections (e.g. Pascalis and de Haan, 2000; Maguire *et al.*, 2001). A further possibility

is that patients with DA develop better learning strategies compared to adult-onset cases due to them having to cope with their disorder from such a young age. A final possibility is that the dissociation may be due to an interaction of these.

4.4.2 Memory function in relation to extent of MTL abnormality

In relation to the second aim of this chapter, it was predicted that the degree of episodic memory impairment would be related to the extent of hippocampal abnormality (hippocampal T_2 values, volumes, grey matter density reduction) in the patient group. On the other hand the multi-system model predicts that tests of semantic memory would be related to parahippocampal but not hippocampal abnormality (grey matter density reduction).

Unexpectedly the regression and VBM analyses did not indicate any evidence of a relationship between hippocampal abnormality and episodic memory impairment. These results must be interpreted with caution, as it is possible that the lack of relationship between hippocampal abnormality and episodic memory measures reflects a lack of power in the analysis due to the small sample size, and lack of dynamic range in scores in the DA group. Furthermore, hippocampal volume measurements have the potential for errors due to the manual tracings and T_2 values are from just one coronal slice through the hippocampus (see Chapter 3). As predicted by the multi-system model there was also no evidence of a relationship between hippocampal volume, T_2 values or grey matter density and semantic memory. The VBM analysis, however, indicated that performance on measures of semantic memory correlated with parahippocampal grey matter density. This association suggests that low performance on the semantic memory composite score (principal component) was associated with a decrease in parahippocampal grey matter density. The inference that there is variability in the integrity of the parahippocampal gyrus in the DA group needs to be confirmed using parahippocampal volume measurements. Meanwhile, however, this finding offers support for the multi-system model of MTL function, in that semantic memory correlated only with the grey matter density of the parahippocampal region, suggesting that this region, but not the hippocampus, may indeed support semantic memory in patients with DA (e.g. Mishkin *et al.*, 1998).

4.4.3 Conclusion

In summary, these findings both replicate and extend the previous studies of DA (e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000). For example, as before, the patients with DA were impaired relative to normative standards on the RBMT, and delayed verbal and visual recall. Despite these impairments in episodic memory the patients were unimpaired on two of the three 'semantic' subtests of verbal IQ, measures of numeracy, spelling, and basic reading, and tests of semantic association and retrieval. In addition, in this chapter it is reported that the patients with DA were impaired relative to controls at immediate memory (although less so than delayed memory), delayed recognition, and two of the semantic memory measures, the Information subtest of verbal IQ, and reading comprehension. There was also some indication of a verbal-visual memory discrepancy in favour of visual memory (CMS/WMS-III).

The unexpected finding that recall and everyday memory performance was not associated with extent of hippocampal abnormality may reflect a lack of power in the analyses. However, there was a positive correlation between semantic memory and parahippocampal grey matter density, suggesting that a decrease in semantic memory was associated with a decrease in grey matter in the parahippocampal region.

In relation to models of long-term declarative memory organisation, the results reported in this chapter support the multi-system model, such that semantic memories are acquired in the presence of impaired episodic memory, and this preservation of semantic memory appears to be related to the integrity of the parahippocampal gyrus. This dissociation between episodic and semantic memory will be examined in more detail in the following Chapters (5 and 6).

5 NONVERBAL IMITATION IN DEVELOPMENTAL AMNESIA

Previous studies of DA have associated bilateral hippocampal volume reduction with impaired episodic declarative memory (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000; Vargha-Khadem *et al.*, 2001). So far, tests of episodic memory have included alerted and unalerted recall of verbal information (stories and word-lists) and geometric designs. Both of these measures have proved useful in establishing levels of episodic memory abilities; however, potentially they are limited by a patient's verbal comprehension and drawing abilities. The aim of the experiments described in this chapter was to investigate whether severe memory impairments would be observed in an unalerted memory task without verbal or drawing requirements. To this end, a nonverbal task frequently used to study infant memory, deferred imitation, was modified for use with children and young adults. In this task, props are used to demonstrate actions that the participant is permitted to imitate either immediately or after some delay. Versions of this task were designed to allow investigation of the key variables: (a) delay: immediate memory was compared to memory after a 24-hour delay; (b) memory type: action sequences included both 'semantic' components (causally ordered steps, script-typical steps) and 'episodic' components (arbitrarily ordered steps, script-atypical steps); (c) practice: delayed memory after an immediate memory test was compared to delayed memory without an immediate memory test. The results show that: although the DA group generally showed evidence of memory following demonstration, memory was impaired at both immediate and delayed recall relative to controls; although memory for the arbitrary sequences was not more impaired than the causal sequences in the DA group, patients with DA were severely impaired at recall of the most 'episodic' components of the scripted sequences; and the immediate recall trial appeared to interfere rather than facilitate memory in patients with DA.

5.1 INTRODUCTION

In nonverbal imitation, props are used to produce an action or a sequence of actions (target steps) that the participant is then permitted to imitate, either immediately or after a delay (deferred). The nonverbal reproduction of the event, rather than a verbal description of it, serves as a measure of recall. For each sequence the participant is initially given a set of props to manipulate. This provides a baseline measure of the spontaneous occurrence of the target steps and their order. Differences between an initial baseline measure of the spontaneous production of the target actions and their order and performance after exposure to the model are taken as evidence of memory for the event sequence. Recall of temporal order is measured by counting the number of pairs of actions that are recalled in sequence. The aim of the experiments reported in this chapter was to investigate whether patients with DA show impairments on this nonverbal memory task, and whether their memory is influenced in the same way as controls by factors such as delay, event structure, familiarity and practice.

5.1.1 Factors influencing nonverbal imitation

Memory for event sequences is influenced by a number of factors, including the structure of the event. The events to be remembered are made up of sequences of steps that are ordered according to their temporal and causal connections. When one action in an event must be carried out temporally prior to another in order to achieve the desired end-state or goal, the pair of actions is said to be causally ordered. For example, if the desired end-state was to transfer water from one cup to another with a straw, logically the straw must be placed in the cup containing water, a finger must be placed over the top of the straw, and the straw must then be released in the empty cup. In order to achieve the desired end-state, in this case transferring water, alternative temporal orders of causal actions are logically impossible; therefore, they must occur in an invariant temporal order to achieve the outcome. In contrast, actions in an event that are not inherently constrained to a temporal position are by definition, arbitrarily ordered. For example, to balance coins on a ruler resting on a block, the coins can be placed on each side of the ruler before or after the ruler is balanced on a block. In this example, the actions can be performed in either order without preventing the achievement of the final end-state, in this case, balancing coins on a ruler.

Several studies have found that children and adults have superior ordered recall of events that are characterised by causal actions, compared with events that lack such relations (e.g. Bauer and Mandler, 1992; McDonough *et al.*, 1995; Barr and Hayne, 1996) and that this effect is maintained over a delay (e.g. Bauer and Hertsgaard, 1993; Mandler and McDonough, 1995; McDonough *et al.*, 1995). This effect is obtained even when equivalent numbers of individual target actions are produced in events with and without causally ordered actions (Bauer, 1996), indicating that the differences in ordered recall are not necessarily an artefact of differential opportunities for production of pairs of target actions. Moreover, the performance at baseline (i.e. without exposure to the target actions) did not differ between these action types, suggesting that the superior ordered recall of causal sequences is not because these sequences are easier to "figure out" (e.g. Bauer, 1992; Bauer *et al.*, 1995; Bauer, 1996).

It seems, therefore, that the more causal the structure in a sequence, the better the recall of temporal order of its steps. This is similar to the superior recall of category-ordered word-lists compared to unordered word-lists found in healthy adults (e.g. Channon *et al.*, 1989; Channon *et al.*, 1993; Daum *et al.*, 1995; Channon *et al.*, 2000; see Chapter 6). Like category-ordered word-lists, the superior recall of causally ordered sequences may be due to their increased meaningfulness compared to arbitrarily ordered sequences. In this way, recall of the order of causally ordered sequences may be considered more 'semantic' compared to arbitrarily ordered sequences.

Another factor that can influence memory for event sequences is prior familiarity. It is well established that children and adults develop accurate, generalised representations (i.e. scripts) of typical experiences of their day-to-day lives (e.g. Shank and Abelson, 1977; Fivush, 1984; Nelson, 1986). Scripts are spatially-temporally organized sequences of actions, actors, and props that are most likely to be present during any given instantiation of an event (Fivush, 1997). For example, when we go to a restaurant to eat, we know that a member of staff will greet us, show us to our table, give us a menu, and take our order and so on. Scripts are a basic form of representation that develop as part of our knowledge about the world (e.g. Mandler, 1983). Familiar event sequences are sometimes used in tests of nonverbal imitation with children e.g. putting teddy to bed (Bauer and Mandler, 1992). The child may have a pre-existing representation (script) for putting teddy to bed, such as putting teddy in a bed, covering teddy with a blanket and switching out the light. Memory for sequences, tested both

immediately after presentation and after an imposed delay, has been shown to be facilitated by prior familiarity, such that memory is better for familiar compared to novel sequences (e.g. Bauer and Shore, 1987; Bauer and Hertsgaard, 1993). Although these findings suggest that recall is aided by already acquired schematic knowledge of the events, to reproduce the modeled sequence from memory, the child must still recall the specific actions presented in the task and their order (Bauer and Mandler, 1989).

Memory models propose that memory for a specific episode of a repeated event is represented hierarchically within a script, with details of the unique episode tagged separately (e.g. Bartlett, 1932; Graesser *et al.*, 1979; Schank, 1982). Essentially, we recall the script and then the script representation 'points' to the distinctive episode in memory. Retrieval of these script representations may be considered as retrieval from semantic memory, in that their retrieval is context-free, whereas retrieval of details specific to the event may be considered as retrieval from episodic memory, in that the memory is context-dependent.

These models suggest a close association between a script representation of an event and memory for a specific event episode. Such associations can be seen in tasks that require the participant to recall script-based and script-atypical actions. For example, when asked to recall script-based stories in which atypical actions are embedded, adults and children tend to recall atypical actions quite well at immediate recall. However, in delayed recall, both adults and children intrude script information not included in the originally presented story and have difficulty recalling the atypical actions (Graesser *et al.*, 1979; Adams and Worden, 1986). Such associations between script-based sequences and atypical actions have not been investigated using nonverbal imitation.

5.1.2 Nonverbal imitation as a test of declarative recall?

There is some debate as to what type of memory underlies performance on nonverbal imitation tasks. Some suggest that accurate performance on nonverbal imitation may not necessarily reflect declarative recall. For example, participants might learn a sensori-motor association between an object and an action by observation alone, thus, presentation of the object might prime the production of the target actions (Werker, 1990). However, according to Mandler (1990) nonverbal imitation tasks require recall (i.e. declarative memory) when the events are entirely novel at the time of the learning session, the participants are not allowed to practice the actions, and the actions are not

modelled again after the initial 'learning' session (for a detailed discussion see Bauer, 1997).

Consistent with this argument is the finding that adult human amnesics are unable to perform an age-appropriate version of the task in either an instructed (asked to reproduce the previously demonstrated sequences from memory) or uninstructed (presented with props without instruction to reproduce the sequences from memory) memory condition (McDonough *et al.*, 1995). McDonough *et al.* (1995) tested four groups of participants (frontal lobe patients, amnesic patients, 'experienced' (with demonstration) healthy controls, 'inexperienced' (without demonstration) healthy controls) using two different memory conditions (uninstructed and instructed) on nonverbal imitation (recall after a 24-hour delay). The task was presented as incidental events, using word-list recall as the supposed main task, making its presentation similar to that described in the child literature. Participants were given the props to manipulate (baseline); then, for all the participants except the 'inexperienced' controls the experimenter demonstrated the target actions and sequences; after a 24-hour delay participants were required to recall the target actions and sequences. In the uninstructed recall condition, the props were placed in front of the participant for 1-minute; in the instructed condition, the participants were asked to produce the actions in the same order as demonstrated by the experimenter. The frontal lobe patients and the 'experienced' controls produced significantly more target actions and target pairs in both memory conditions than in the baseline condition and compared to the patients with amnesia and 'inexperienced' controls. In addition, significantly more target actions and target pairs were produced in the causal sequences than in the arbitrary sequences.

In summary, the patients with amnesia were not able to perform the sequences they had seen in either the instructed or uninstructed condition. This suggests that the uninstructed condition did not automatically or nonconsciously prime them to perform the sequences. Furthermore, the finding that the frontal lobe injured patients were able to recall the actions and their order suggests that nonverbal imitation is not a task of problem-solving, a function thought to be impaired after frontal lobe injury (e.g. Goel and Grafman, 1995; Colvin *et al.*, 2001). This study is the only study to date to test deferred imitation in patients with amnesia and therefore needs replication.

It is also important to dissociate nonverbal imitation from other tests of declarative memory, such as recognition, where the presence of the stimulus (the target) may cue the

correct response. Although, similar to recognition, the re-presentation of the props for recall does provide perceptual support or cues, they do not necessarily cue accurate recall of the steps or their order. For example, critical information about the order of the actions is not perceptually cued: once the demonstration is completed, so are the cues to temporal order. Therefore, in nonverbal imitation, to reproduce the target actions in their target pairs, order must be encoded during demonstration and later retrieved from a representation of the event in the absence of ongoing perceptual support.

The circumstances of nonverbal imitation thus closely resembles those of verbal recall (e.g. Mandler, 1990), and the behaviours derived from it meet the definition of declarative recall.

5.1.3 Immediate versus delayed recall and effects of practice

Nonverbal imitation can be tested either immediately after presentation or after an imposed delay (deferred). Accurate deferred imitation after varying delays (from 10 minutes to 8 months) has been shown in non-human primates (e.g. Bering *et al.*, 2000), infants as young as 9-months-old (e.g. Meltzoff, 1988), children (e.g. Bauer *et al.*, 1994) and healthy adults (e.g. McDonough *et al.*, 1995). Indeed some studies have shown that by 20 months of age, on short event sequences, children show little or no decrement in performance over delays of two to six weeks: delayed recall performance is equivalent to that at immediate testing (Bauer and Shore, 1987; Bauer and Mandler, 1989).

In six patients with DA reported by Vargha-Khadem *et al.* (3 patients, 1997) and Gadian *et al.* (3 additional patients, 2000) delayed recall of stories, designs and word-lists was more impaired than immediate recall of these same stimuli relative to normative data.

To date, only one study has tested deferred nonverbal imitation in patients with amnesia (McDonough *et al.*, 1995). In this study, patients who sustained amnesia as adults were impaired at delayed (24-hours) recall of target actions and action pairs relative to controls. However, there was no immediate recall condition; therefore, it is difficult to know whether this impairment reflects solely a long-term memory deficit or a general memory deficit.

Although the addition of an immediate recall trial enables the comparison of immediate with delayed memory, the immediate recall trial itself may itself act as an additional practice or learning trial. For example, in a study comparing the performance of infants (~19 months of age) on deferred imitation with and without an immediate recall

phase, infants who were given the opportunity to produce the target actions immediately after demonstration performed better after a one week delay than infants who were not given the opportunity to practice (Barr and Hayne, 1996). Therefore, in order to control for the possible effect of practice given by an immediate recall trial, in the study reported in this chapter, both immediate and delayed memory will be tested in one condition and delayed-only memory will be tested in another condition.

5.1.4 Summary of nonverbal imitation

In summary, nonverbal imitation is considered a test of declarative memory and recall of the target actions and sequences, tested immediately after presentation and/or after an imposed delay, is influenced by the structure of the event (causal order, arbitrary order), and prior familiarity (script-typical sequences, novel sequences). This task has been used to study memory in children, monkeys, and healthy adults, and one study has tested deferred nonverbal imitation in patients with amnesia (McDonough *et al.*, 1995). That study did not include an immediate memory test, and therefore it is not known whether the impairments on causal and arbitrary novel sequences, shown by the patients after a 24-hour delay, was associated with a specific long-term memory deficit or a deficit in both relatively short-term memory and long-term memory of the sequences. Moreover, that study included patients with adult-onset amnesia, and as such it is not known whether patients with DA will show similar deficits at delayed recall of causal and arbitrary sequences. Finally, the study did not include scripted sequences to determine the effects of prior familiarity.

5.1.5 Specific aims and predictions

The aims of this study were fourfold. First, to replicate the study of McDonough *et al.* (1995) using the same novel 3-step sequences reported in their study. Second, to extend the study of McDonough *et al.* (1995), delayed memory performance was compared to immediate memory in order to measure relatively short-term memory and the amount of forgetting. Third, to investigate further the dissociation between episodic and semantic memory in DA, recall of causally ordered sequences was compared to arbitrarily ordered sequences and recall of script-typical steps was compared to script-atypical steps. Fourth, the effect of immediate memory on delayed recall was tested to investigate the effect of practice on subsequent recall. To this end, immediate and 24-hour

delayed memory for novel arbitrarily ordered, novel causally ordered sequences and for scripted sequences with novel events inserted were tested.

The specific predictions are:

(a) Consistent with the findings reported by McDonough *et al.* (1995), it is predicted that the DA group will be impaired relative to controls at delayed recall but not at baseline performance.

(b) Previous reports of DA (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000) have suggested that delayed recall may be more impaired than immediate recall. Therefore, it is predicted that relative to controls, the patients with DA will be more impaired at delayed recall compared to immediate recall of the 3-step action sequences.

(c) Based on the discussion in Section 5.1.1, it was expected that memory for novel arbitrary events and for script-atypical steps would make the most demands on episodic memory due to their lack of 'meaningfulness' and thus be most impaired in DA.

(d) Finally, it was predicted that if immediate recall can act as an additional practice or learning trial then delayed recall would be better after a test of immediate recall compared to delayed recall without a test of immediate recall.

5.2 METHOD

The method used was based on that previously described by McDonough *et al.* (1995) with two exceptions, a) only the instructed condition was included and b) an immediate recall condition was included.

5.2.1 Participants

Twelve patients with DA and twelve controls participated in the tasks reported in this chapter except for the immediate and delayed recall condition, where only eleven[1] patients with DA participated. The participants are described in full in Chapter 2. The groups did not differ with respect to age at test, verbal or performance IQ.

[1] DA4 did not participate in this phase of the study.

5.2.2 Event sequences

There were sixteen novel 3-step action sequences (eight described by McDonough *et al.*, 1995 plus eight additional sequences): eight with causal relations, and eight with arbitrary relations. In addition, there were six script-based sequences that ranged in length from 7 to 10 steps. Each of these contained script-typical steps and two novel script-atypical steps and included both causally and arbitrarily ordered steps. For a list of objects and action sequences see Appendix D.

5.2.3 Procedure

For each sequence, the objects were given to the participants for an initial baseline period of 1 minute. Once all of the sequences had been presented for baseline, the experimenter modelled each sequence once without narration. Half of the novel sequences (four causal, four arbitrary) and half of the script-based sequences were tested for 24-hour delayed recall only. The other half were tested for both immediate and 24-hour delayed recall. Thus, in the morning of day 1 eleven sequences (eight 3-step and three script-based sequences) were modelled, and in the afternoon eleven of the sequences were modelled and tested for immediate recall. Recall for all twenty-two sequences was tested 24-hours after modelling. The presentation of the tasks was counter-balanced across participants applying the following restriction: the morning session always contained the original 3-step sequences described in McDonough *et al.* (1995). This was done to allow a direct replication of that experiment.

To make the task an incidental memory test, as it is typically given to nonverbal infants and as done in McDonough *et al.* (1995), the sequences were embedded as filler tasks in tests of learning and recalling words. Two lists (A and B, Appendix E) of sixteen simple English words were presented as a word-list task using the same procedure as the CAVLT-2 (for method and results, see Chapter 6).

5.2.4 Phases of the experiment

The study was conducted in three phases, which were video-taped for later scoring. Phases 1 and 2 were administered on day 1 (morning for delay-only recall and afternoon for delay-with-immediate recall), Phase 3 was administered 24-hours after Phases 1 and 2. A summary of sessions is shown in Table 5:1.

In Phase 1, the experimenter (E) administered one of the two word-lists. Then during the imposed word-list delay E told the participant: "Now I am going to have you do some things to keep you from thinking of those words. I will give you different sets of objects, which I want you to handle, manipulate, or do whatever you like with them. It is important that you pay close attention to the objects, so please do not talk while you are handling them." Then E brought out, one at a time, each of the object sets. The participants were given 1 minute to manipulate each object set (baseline condition).

Phase 2 followed immediately. E said, "Now I want you to observe some objects while I manipulate them. Please pay close attention, do not talk, and try not to think of the words that I read to you earlier." E then modelled the target actions for each of the twelve sets of objects. In the afternoon session, immediate memory for the actions associated with each set of objects was tested explicitly. After modelling had been completed, the object sets were placed in front of the participant, one at a time, in the same order as previously presented and E said, "I want you to show me as accurately as you can remember the actions I performed and the order in which I performed them." After a participant was clearly finished with an object set, it was removed and the next set was presented until the participant had an opportunity to manipulate all twelve sets.

After the twelfth set of objects was removed, the participant was asked to recall as many of the words on the list as could be remembered (approximately a 20-minute delay). E then read the recognition word-list to the participants instructing them to say "yes" if the word was on the first word-list and "no" if it wasn't. After the recognition test, E read the word-list one more time telling the participant that recall of the words would be tested again the next day.

On the next day, Phase 3 began when the participants were asked to repeat the words that they had been read the day before. E then read the words again, instructing the participants to remember them. Then, each object set was presented in the same manner as in the immediate recall condition of the afternoon session.

On the morning of the second day, after Phase 3, participants were questioned to assess their understanding of the purpose of the study. E asked, "What do you think is the purpose of this experiment? At any point in the experiment did you expect to be asked to demonstrate the actions I performed for you yesterday?" Participants who expressed any understanding of the purpose of the experiment were asked when it occurred to them. These questions were asked in order to determine whether the participant was aware of

the purpose of the task (i.e. delayed recall) during the first day of testing, as this awareness may influence subsequent recall on the second day. These questions were asked on the morning of day 2, after Phase 3, in order to optimise the chance of detecting the participants' awareness of the purpose of the experiment occurring during the first day of testing. For example, if asked "At any point in the experiment did you expect to be asked to demonstrate the actions I performed for you yesterday?" in the afternoon of day 2, their reply could be "yes" based on their experiences in the morning.

Table 5:1 Example of Phases 1, 2 and 3

Day 1 am	
Phase 1	Presentation of word-list A
	Baseline Set A (eight 3-step novel sequences and three scripted sequences)
Phase 2	Model Set A
	Delayed recall and recognition of word-list A; presentation of word-list A
Day 1 pm	
Phase 1	Presentation of word-list B
	Baseline Set B (eight 3-step novel sequences and three scripted sequences)
Phase 2	Model Set B
	Immediate recall of Set B
	Delayed recall and recognition of word-list B; presentation of word-list B
Day 2 am	
Phase 3	24-hour delayed recall of word-list A; presentation of word-list A
	Delayed recall of Set A
	Recall of word-list A
	Questions about purpose of task
Day 2 pm	
Phase 3	24-hour delayed recall of word-list B; presentation of word-list B
	Delayed recall of Set B
	Recall of word-list B

5.2.5 Scoring

For each sequence, the total number of different target actions produced was calculated, as was the number of pairs of actions produced in the target order. For the latter, only the first occurrence of each target action was considered. For example, on the

3-step sequences, if the participant produced all three components in the target order, they would receive credit for three different target actions, and for two correctly ordered pairs of actions (i.e. one point for the pair 1-2, and one point for the pair 2-3). If participants produced actions 1 and 3 in that order, they would receive credit for two different target actions and one correctly ordered pair (i.e. 1 is before 3). However, if they produced the string of actions 3,1,2,3 they would be credited with three different target actions, but with only one correctly ordered pair: 1-2. They would not be credited with the pair 2-3, because they already would have been credited with action 3. This scoring procedure reduces the likelihood of participants receiving credit for production of a sequence by chance or by trial and error.

An additional scoring procedure was applied to the script-based sequences in order to compare the episodic and semantic nature of the sequences. The steps were divided into the following categories: (a) essential script-based steps/pairs (causal, arbitrary). These were steps/pairs that needed to be completed in order to achieve the desired end-state. For example, in making a cup of tea, the following steps were classed as essential script-based: 1. Put tea-bag in teapot; 2. Pour kettle in teapot; 3. Pour teapot in cup. These steps included both causally ordered and arbitrarily ordered steps. Using the making tea example, the kettle could be poured in the teapot before or after the tea-bag is placed in the teapot, therefore this is an arbitrary pair; (b) non-essential script-based (arbitrary-only). These were script-consistent steps but were not necessary components to complete the end-state. For example, using the making tea example, these were steps such as, pour milk in the cup, stir the teapot. Only the arbitrarily ordered steps and pairs were included in this category as they were deemed to be the most 'episodic' in nature; and (c) atypical script-based steps/pairs (causal, arbitrary). These included steps such as, put sugar in teapot and pour cup in teapot. Accuracy of the order of the atypical steps was determined by the presence of the correct prior step in the sequence. For example, pour teapot in cup must occur immediately prior to pour cup in teapot. The scoring procedure was similar to that described above, where in cases of repetitions only the first occurrence of each target action was considered.

The two dependent measures, number of target actions and number of pairs produced, are not independent of one another in that the number of target actions produced affects production of pairs of actions in the target order. Nevertheless, it is possible to earn a high score on the measure of number of different target actions and not

earn a high score on the measure of pairs of actions in the target order. In addition, as it is possible to generate target actions in both causal and arbitrary sequences without generating the correct order, participants were credited with an action regardless of the order in which it occurred. For example, in the causal sequence water transfer, participants were credited with putting their finger on the straw (step 2) regardless of whether they had put the straw in water (step 1).

5.2.6 Analysis

The number of steps and pairs correctly recalled were averaged across sequences within each condition and were converted into percentage correct scores. Separate analyses were conducted for the number of target actions (steps) and sequences (pairs). A significant difference between baseline performance and recall after modelling, in favour of recall, is taken as evidence for memory of the target steps and pairs.

The analysis was conducted in accordance with the statistical procedure described in Section 2.3.2, Chapter 2.

In results Sections 5.3.1, 5.3.2, 5.3.3 the data were analysed using an analysis of variance with a between-subjects factor of group (control, DA) and two within-subjects factors of type[2] (causal, arbitrary) and time (baseline, delay or baseline, immediate, delay), with the appropriate tests of normality and homogeneity of variance. In order to replicate the analysis reported by McDonough *et al.* (1995), all main effects and interactions are reported in Section 5.3.1. To address the effect of delay, only main effects of group and time and interactions with the factor of time are reported in Section 5.3.2 and to address the episodic-semantic dissociation, only main effects of group and type and interactions with the factor of type are reported in Section 5.3.3.

In the results Section 5.3.4, the data were analysed using an analysis of variance with a between-subjects factor of group (control, DA) and two within-subjects factors of type[2] (causal, arbitrary) and condition (with practice, without practice), with the appropriate tests of normality and homogeneity of variance. The memory score was obtained by subtracting baseline performance from delayed recall, thus providing an estimate of delayed memory independent of differences in baseline performance.

[2] Except for script-based arbitrary-only sequences.

All significant interactions are followed up using separate t-tests with Bonferroni correction for multiple comparisons. All findings with a p-value of less than 0.05 are reported and predicted findings with a p-value less than 0.1 are described.

A summary of the results in relation to the predictions are presented in Table 5:20 and Table 5:21 in Section 5.3.5.

5.3 RESULTS

5.3.1 Replication of McDonough et al. (1995)

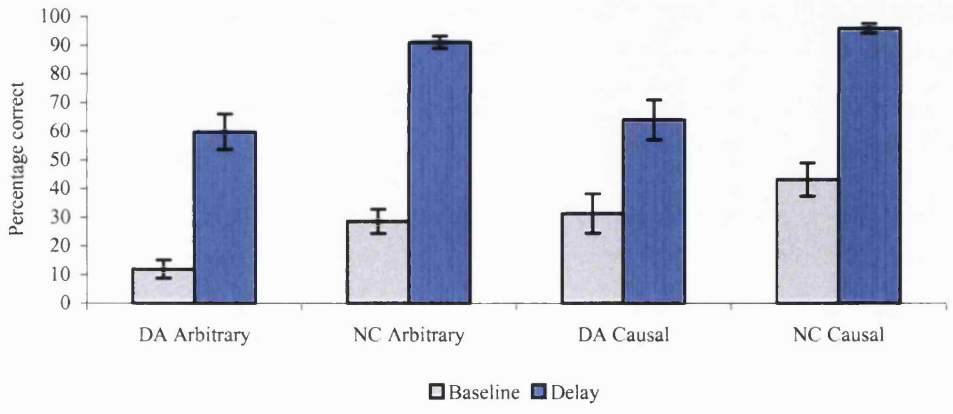
Table 5:2 and Figure 5:1 show the mean (±SEM) percentage of arbitrary and causal target steps correctly recalled by each group at baseline and after a 24-hour delay.

Table 5:2 Percentage of correct steps

	DA	NC
Baseline Arbitrary	11.8 (3.15)	28.5 (4.16)
Delay Arbitrary	59.7 (6.14)	91.0 (2.17)
Baseline Causal	31.3 (6.89)	43.1 (5.79)
Delay Causal	63.9 (6.91)	95.8 (1.62)

Mean (±SEM)

Figure 5:1 Percentage of correct steps



The analysis revealed significant main effects of Group ($F(1,22) = 25.60$; $p < 0.0001$), suggesting that the control group performed better than the DA group, and Time ($F(1,22) = 212.95$; $p < 0.0001$), suggesting that delayed performance was better than baseline performance, and Type ($F(1,22) = 8.5$; $p = 0.008$), suggesting that overall more causal than arbitrary steps were produced. These main effects, as predicted, were qualified by two significant two-way interactions: Group by Time ($F(1,22) = 6.70$; $p = 0.02$) and Type by Time ($F(1,22) = 8.06$; $p = 0.01$). There was no evidence for the predicted Group by Type ($p > 0.1$) or a Group by Type by Time ($p > 0.1$) interactions.

Follow up analysis of the Group by Time interaction revealed that, consistent with the findings reported by McDonough *et al.* (1995), the groups did not significantly differ on baseline performance ($p > 0.0125$[3]), but the control group recalled more target steps than the DA group after a delay ($t(22) = 6.06$; $p < 0.0001$). Further follow-up analysis revealed that both groups produced more target steps at delayed recall than at baseline (NC: $t(11) = -12.42$; $p < 0.0001$; DA: $t(11) = -8.31$; $p < 0.0001$), suggesting memory for the steps, but as predicted this memory effect was larger in the control group (mean difference = 57.6) than in the DA group (mean difference = 40.3).

Follow up analysis of the Type by Time interaction revealed that more causal than arbitrary steps were produced at baseline ($t(23) = -4.10$; $p < 0.0001$) but unexpectedly, not after a delay ($p > 0.1$).

Table 5:3 and Figure 5:2 show the mean (±SEM) percentage of arbitrary and causal target pairs correctly recalled by each group at baseline and after a 24-hour delay.

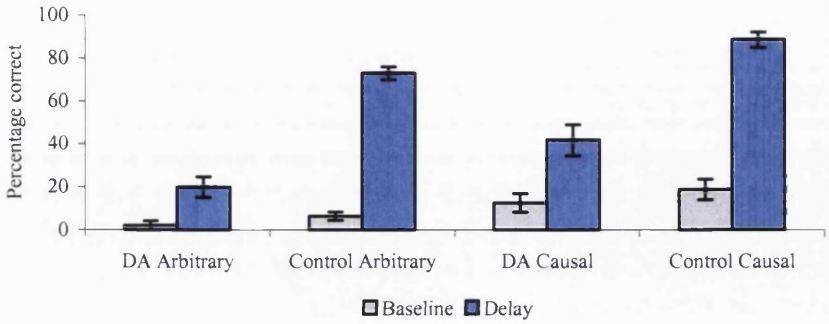
Table 5:3 Percentage of correct pairs

	DA	Control
Baseline Arbitrary	2.1 (2.08)	6.3 (1.88)
Delay Arbitrary	19.8 (4.73)	72.9 (3.01)
Baseline Causal	12.5 (4.35)	18.8 (4.74)
Delay Causal	41.7 (7.27)	88.5 (3.59)

Mean (±SEM)

[3] The p-value with Bonferroni correction is 0.0125 (0.05/4).

Figure 5:2 Percentage of correct pairs



The analysis revealed significant main effects of Group ($F(1,22) = 53.14$; $p < 0.0001$), suggesting that the control group performed better than the DA group, and Time ($F(1,22) = 219.83$; $p < 0.0001$), suggesting that delayed performance was better than baseline performance, and Type ($F(1,22) = 25.88$; $p < 0.0001$), suggesting that overall more causal than arbitrary pairs were produced. There was also a significant Group by Time interaction ($F(1,22) = 52.49$; $p < 0.0001$) and weak evidence for the predicted Type by Time interaction ($F(1,22) = 3.38$; $p = 0.08$). There was no evidence for the predicted Group by Type ($p > 0.1$) or Group by Type by Time ($p > 0.1$) interactions.

Follow up analysis of the Group by Time interaction revealed that, consistent with the findings reported by McDonough *et al.* (1995), the groups did not significantly differ on baseline performance ($p > 0.1$), but the control group recalled more target pairs than the DA group after a delay ($t(22) = 8.69$; $p < 0.0001$). Further follow-up analysis revealed that both groups produced more target pairs after a delay than at baseline (NC: $t(11) = -16.63$; $p < 0.0001$; DA: $t(11) = -5.07$; $p < 0.0001$), suggesting memory for the pairs, but as predicted this memory effect was larger in the control group (mean difference = 68.2) than in the DA group (mean difference = 23.4).

Follow up analysis of the Type by Time interaction revealed that more causal than arbitrary pairs were produced at baseline ($t(23) = -3.70$; $p = 0.001$) and at delayed recall ($t(23) = -4.80$; $p < 0.0001$), but as predicted, the mean difference was greater after a delay (18.8) than at baseline (11.5).

In summary, consistent with the findings of McDonough *et al.* (1995) the groups did not significantly differ in their performance at baseline, and the control recalled more target steps and pairs than the DA group after a delay. However, the patients with DA did still show some memory for steps and pairs after a delay. Like the findings reported by

McDonough *et al.* (1995), the analyses reported in this chapter suggest that more causal than arbitrary target steps were produced at baseline, and that more causal than arbitrary target pairs were produced both at baseline and after a delay. However, unlike McDonough *et al.* (1995) there was no effect of sequence type on the number of target steps produced after a delay, while there was a stronger effect of sequence type on the number of pairs produced after delay compared to baseline. The finding that more causal pairs but not steps were recalled after a delay suggests that the correct recall of the temporal order of causal sequences is not due to an increase in the production of causal compared to arbitrary steps (as discussed in Section 5.2.5).

5.3.2 Effect of delay

5.3.2.1 Three-step novel sequences

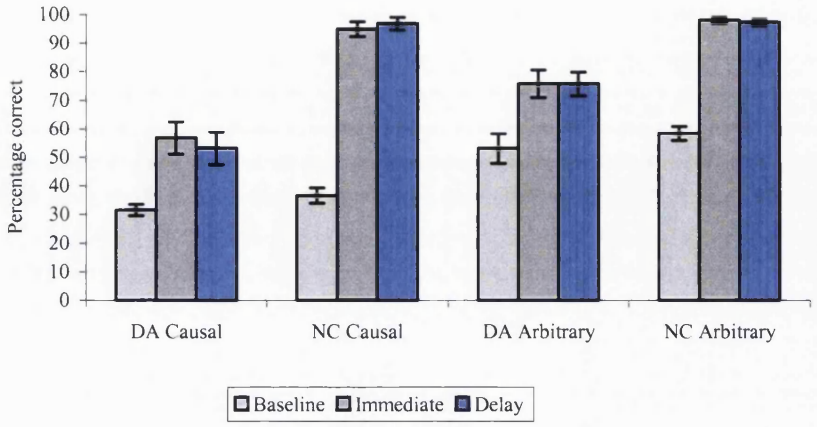
The mean (±SEM) percentage of target steps correctly produced by each group at baseline, immediate recall and after a 24-hour delay are shown in Table 5:4 and Figure 5:3

Table 5:4 Percentage of correct steps

	Baseline	Immediate	Delay
DA causal	31.5 (1.93)	56.6 (5.71)	53.2 (5.70)
NC causal	36.5 (2.70)	94.9 (2.56)	96.8 (2.21)
DA arbitrary	53.0 (5.18)	75.8 (4.80)	75.8 (4.12)
NC arbitrary	58.3 (2.50)	97.9 (1.09)	97.2 (1.18)

Mean (±SEM)

Figure 5:3 Percentage of correct steps



The analysis revealed, as predicted, a significant main effect of Group ($F(1, 21) = 46.08$; $p < 0.0001$), suggesting that overall the control group recalled more steps than the DA group; and a significant main effect of Time ($F(1.51, 31.68) = 181.09$; $p < 0.0001$). Follow up analysis of the main effect of Time, as predicted revealed that overall more target steps were produced immediately after demonstration ($p < 0.0001$) and after a delay ($p < 0.0001$) compared to baseline, but there was no difference between immediate and delayed recall ($p > 0.1$). There was also, as predicted, a significant Group by Time interaction ($F(1.51, 31.68) = 23.88$; $p < 0.0001$).

Follow up analysis of the Group by Time interaction revealed that, as predicted, that the groups did not differ at baseline ($p > 0.1$). However, the DA group was impaired relative to controls at both immediate ($t(11.27) = 6.12$; $p < 0.0001$) and delayed ($t(11.96) = 7.57$; $p < 0.0001$) recall, but there was only slight evidence to suggest that the DA group was more impaired relative to controls at delayed (mean difference = 32.6) than immediate (mean difference = 30.2) recall. An additional follow-up analysis was conducted in order to test whether the DA group showed any evidence of memory following demonstration. The findings indicate that both groups showed evidence of memory following demonstration in that both groups produced significantly more steps at immediate and delayed recall compared to baseline (NC: baseline vs. immediate, $t(11) = -24.29$; $p < 0.0001$; baseline vs. delay, $t(11) = -23.69$; $p < 0.0001$; DA: baseline vs. immediate, $t(10) = -4.6$; $p < 0.0001$; baseline vs. delay, $t(10) = -5.75$; $p < 0.0001$), but the number of steps produced did not differ between immediate and delayed recall in either group (NC: $p > 0.1$; DA: $p > 0.1$). Therefore there was no evidence of forgetting in either

group. However, overall memory was better in the control group than the DA group at both time points.

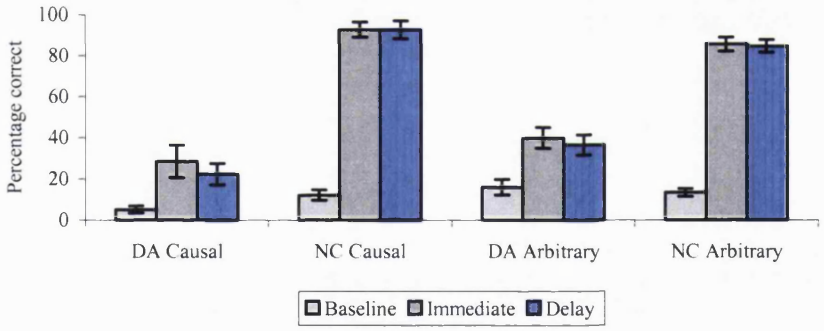
The mean (±SEM) percentage of target pairs correctly produced by each group at baseline, immediate recall and after a 24-hour delay are shown in Table 5:5 and Figure 5:4.

Table 5:5 Percentage of correct pairs

	Baseline	Immediate	Delay
DA causal	5.05 (1.75)	28.5 (7.91)	22.2 (5.19)
NC causal	12.0 (2.54)	92.6 (3.70)	92.6 (4.40)
DA arbitrary	15.9 (3.80)	39.8 (5.01)	36.4 (4.90)
NC arbitrary	13.4 (1.70)	85.5 (3.39)	84.6 (3.07)

Mean (±SEM)

Figure 5:4 Percentage of correct pairs



The analysis revealed, as predicted, a significant main effect of Group ($F(1,21) = 99.23$; $p < 0.0001$), suggesting that overall the control group recalled more pairs than the DA group; and a significant main effect of Time ($F(1.58, 33.08) = 212.53$; $p < 0.0001$). Follow up analysis of the main effect of Time, as predicted revealed that overall more target pairs were produced immediately after demonstration ($p < 0.0001$) and after a delay ($p < 0.0001$) compared to baseline, but there was no difference between immediate and delayed recall ($p > 0.1$). There was also, as predicted a significant Group by Time interaction ($F(1.6,33.8) = 67.7$; $p < 0.0001$).

Follow up analysis of the Group by Time interaction revealed that, as predicted, the groups did not differ at baseline ($p > 0.1$). However, the DA group was impaired

relative to controls at both immediate ($t(21) = 8.80$; $p < 0.0001$) and delayed ($t(21) = 11.05$; $p < 0.0001$) recall, but there was only slight evidence to suggest that the DA group was more impaired relative to controls at delayed (mean difference = 59.3) than immediate (mean difference = 54.9) recall. An additional follow-up analysis was conducted in order to test whether the DA group showed any evidence of memory following demonstration. The findings suggest that both groups showed memory for the pairs following demonstration in that both groups produced significantly more pairs at immediate and delayed recall compared to baseline (NC: baseline vs. immediate, $t(11) = -22.16$; $p < 0.0001$; baseline vs. delay, $t(11) = -25.50$; $p < 0.0001$; DA: baseline vs. immediate, $t(10) = -4.15$; $p = 0.002$; baseline vs. delay, $t(10) = -3.92$; $p = 0.003$), but the number of pairs produced did not differ between immediate and delayed recall in either group (NC: $p > 0.1$; DA: $p > 0.1$). Therefore there was no evidence of forgetting in either group. However, overall memory was better in the control group than the DA group at both time points.

In summary, these findings suggest that the DA group was impaired relative to controls at both immediate and delayed recall, but as predicted not at baseline. However, both groups produced significantly more target steps and pairs after demonstration indicating memory for the steps and pairs, although this memory effect was larger in the control group compared to the DA group. Furthermore, it appeared that memory for the sequences was not much more affected by the delay in the DA group in that the group difference was only slightly larger at delayed than immediate recall. These findings suggest that the DA group, although impaired at both immediate and delayed recall, did not seem to forget much over the 24-hour delay.

5.3.2.2 Scripted sequence

5.3.2.2.1 Script-based typical targets

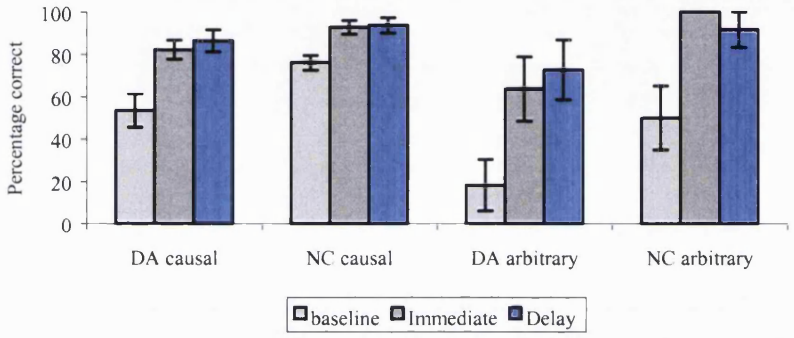
The mean (±SEM) percentage of typical target steps correctly produced by each group at baseline, immediate recall and after a 24-hour delay is shown in Table 5:6 and Figure 5:5.

Table 5:6 Percentage of correct script-typical steps

	Baseline	Immediate	Delay
DA causal	53.4 (7.88)	82.2 (4.53)	86.4 (5.15)
NC causal	76.0 (3.45)	92.7 (3.25)	93.8 (3.61)
DA arbitrary	18.2 (12.20)	63.6 (15.21)	72.7 (14.1)
NC arbitrary	50.0 (15.08)	100.0 (0.00)	91.7 (8.33)

Mean (±SEM)

Figure 5:5 Percentage correct script-typical steps



The analysis, unexpectedly, revealed a significant main effect of Group ($F(1,21) = 10.37$; $p = 0.004$), suggesting that overall the control group produced more target steps than the DA group. There was also a significant main effect of Time ($F(1.37, 28.66) = 23.22$; $p < 0.0001$). Follow up analysis of the main effect of Time, as predicted revealed that more target steps were produced immediately after demonstration ($p < 0.0001$) and after a delay ($p < 0.0001$) compared to baseline, and there was no difference between immediate and delayed recall ($p > 0.1$). It was predicted that this task would be the most 'semantic', and therefore the patients with DA would not significantly differ from controls in the amount of memory shown. As predicted, the Group by Time interaction was not significant ($p > 0.1$).

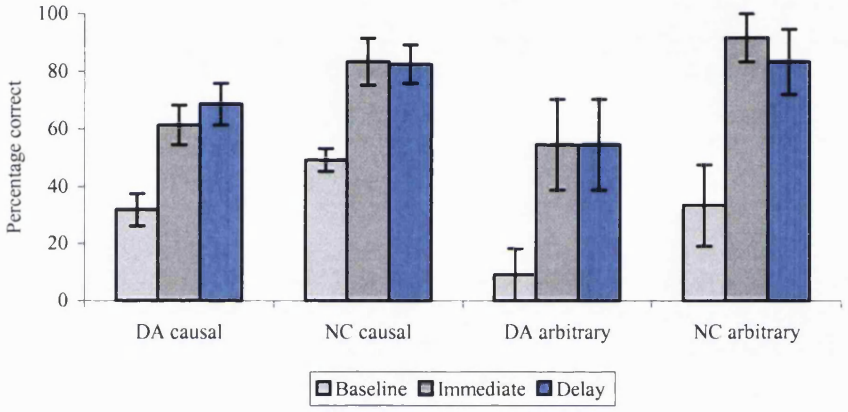
The mean (±SEM) percentage of typical target pairs correctly produced by each group at baseline, immediate recall and after a 24-hour delay is shown in Table 5:7 and Figure5:6.

Table 5:7 Percentage of correct script-typical pairs

	Baseline	Immediate	Delay
DA causal	31.8 (5.67)	61.4 (6.92)	68.6 (7.23)
NC causal	49.2 (3.97)	83.3 (8.10)	82.5 (6.68)
DA arbitrary	9.09 (9.09)	54.6 (15.80)	54.6 (15.80)
NC arbitrary	33.3 (14.20)	91.7 (8.33)	83.3 (11.20)

Mean (±SEM)

Figure 5:6 Percentage of correct script-typical pairs



The analysis, unexpectedly, revealed a significant main effect of Group ($F(1,21) = 10.85$; $p = 0.003$), suggesting that overall the control group produced more target pairs than the DA group. There was also a significant main effect of Time ($F(1.79, 37.67) = 19.49$; $p < 0.0001$). Follow up analysis of the main effect of Time, as predicted revealed that more target pairs were produced immediately after demonstration ($p < 0.0001$) and after a delay ($p < 0.0001$) compared to baseline, but there was no difference between immediate and delayed recall ($p > 0.1$). The Group by Time interaction as predicted was not significant ($p > 0.1$).

In summary, these findings suggest that both groups produced more target steps and pairs after demonstration (both immediate and delay) compared to baseline, indicating memory for the sequences. Furthermore, as predicted, the DA group did not show abnormal forgetting relative to controls of the script-based typical (semantic memory based) steps and pairs, although overall the DA group did not perform as well as controls.

5.3.2.3 Arbitrary targets

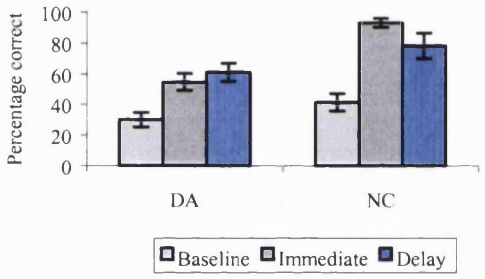
The mean (±SEM) percentage of target steps correctly produced by each group at baseline, immediate recall and after a 24-hour delay is shown in Table 5:8 and Figure 5:7.

Table 5:8 Percentage of correct arbitrary steps

	Baseline	Immediate	Delay
DA	29.9 (4.72)	54.5 (5.72)	61.0 (5.84)
NC	41.3 (5.69)	92.9 (2.84)	78.2 (8.11)

Mean (±SEM)

Figure 5:7 Percentage of correct arbitrary steps



The analysis, as predicted, revealed a significant main effect of Group ($F(1,21) = 19.83$; $p < 0.0001$), suggesting that overall the control group produced more target steps than the DA group. There was also a significant main effect of Time ($F(1.78, 37.27) = 28.59$; $p < 0.0001$). Follow up analysis of the main effect of Time, as predicted revealed that more target steps were produced immediately after demonstration ($p < 0.0001$) and after a delay ($p < 0.0001$) compared to baseline, but there was no difference between immediate and delayed recall ($p > 0.1$). There was weak evidence for the predicted Group by Time interaction ($F(1.78, 37.27) = 3.28$; $p = 0.05$).

Follow up analysis of the Group by Time interaction revealed, as predicted, that the groups did not differ at baseline ($p > 0.1$). However, unexpectedly, the DA group was only impaired relative to controls at immediate recall ($t(14.73) = 6.0$; $p < 0.0001$) and not at delayed recall ($p > 0.1$) recall.

As it was predicted that patients with DA would be impaired on recall of script-arbitrary steps and pairs, another follow up analysis was conducted in order to test whether the Group by Time interaction was caused by recall in the DA group not

differing from baseline (i.e. no memory for the target steps)[4]. The findings suggest that the control group produced significantly more steps at immediate and delayed recall compared to baseline (NC: baseline vs. immediate, $t(11) = -6.71$; $p < 0.0001$; baseline vs. delay, $t(11) = -3.71$; $p = 0.003$), and there was weak evidence to suggest that DA group produced more steps at immediate recall than at baseline (DA: baseline vs. immediate, $t(10) = -3.47$; $p = 0.006$), but the DA group produced significantly more steps at delayed recall compared to baseline ($t(10) = -3.96$; $p = 0.003$). The number of steps produced by both groups did not differ between immediate and delayed recall (NC: $p > 0.1$; DA: $p > 0.1$). Therefore there was no evidence of forgetting in either group. However, overall memory was better in the control group than the DA group at both time points.

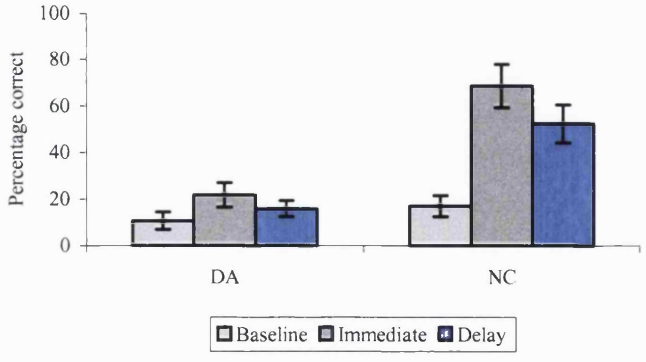
The mean (±SEM) percentage of target pairs correctly produced by each group at baseline, immediate recall and after a 24-hour delay is shown in Table 5:9 and Figure 5:8.

Table 5:9 Percentage of correct arbitrary pairs

	Baseline	Immediate	Delay
DA	10.6 (3.74)	21.7 (5.23)	15.8 (3.46)
NC	17.0 (4.53)	68.6 (9.30)	52.4 (8.21)

Mean (±SEM)

Figure 5:8: Percentage of correct arbitrary pairs



[4] A p-value of 0.006 represents the significant p-value after Bonferroni correction for nine pair-wise comparisons (p-value 0.05/9 = 0.006).

The analysis, as predicted, revealed a significant main effect of Group ($F(1,21) = 16.90$; $p < 0.0001$), suggesting that overall the control group produced more target pairs than the DA group. There was also a significant main effect of Time ($F(1.85, 38.91) = 25.11$; $p < 0.0001$). Follow up analysis of the main effect of Time, as predicted revealed that more target pairs were produced immediately after demonstration ($p < 0.0001$) and after a delay ($p < 0.0001$) compared to baseline, but there was no difference between immediate and delayed recall ($p > 0.05$). As predicted there was a significant Group by Time interaction ($F(1.85, 38.91) = 11.05$; $p < 0.0001$).

Follow up analysis of the Group by Time interaction revealed, as predicted, that the groups did not differ at baseline ($p > 0.1$). The DA group was impaired relative to controls both at immediate recall ($t(17.16) = 4.40$; $p < 0.0001$) and delayed recall ($t(14.74) = 4.10$; $p = 0.001$), and the group difference was larger at immediate (mean difference = 46.9) than at delayed (mean difference = 36.6) recall.

As it was predicted that patients with DA would be impaired on recall of script-arbitrary steps and pairs, another follow up analysis was conducted in order to test whether the Group by Time interaction was caused by recall in the DA group not differing from baseline (i.e. no memory for the target steps). The findings suggest that the control group produced significantly more pairs at immediate and delayed recall compared to baseline (NC: baseline vs. immediate, $t(11) = -6.44$; $p < 0.0001$; baseline vs. delay, $t(11) = -5.52$; $p < 0.0001$), but there was no evidence to suggest that DA group produced more pairs at immediate recall than at baseline ($p > 0.1$) or that delayed recall was better than baseline ($p > 0.1$). The number of pairs produced by both groups did not differ between immediate and delayed recall (NC: $p > 0.006$; DA: $p > 0.1$). Therefore there was no evidence of forgetting in either group.

In summary, these findings suggest that, as predicted, the groups did not differ in their performance at baseline. The prediction that the DA group would be impaired at immediate and delayed recall was partially supported in that the DA group was impaired relative to controls at immediate recall, but the DA group was not impaired at delayed recall of steps, and the group difference was larger at immediate than delayed recall of the pairs. The control group showed evidence of memory for the steps and pairs both immediately after demonstration and after a delay, whereas the DA group showed memory of the steps after a delay and there was a trend at immediate recall but, as

predicted, there was no evidence for memory of the pairs on either memory condition. Neither group showed a significant effect of forgetting over the delay.

5.3.2.4 Script-based atypical targets

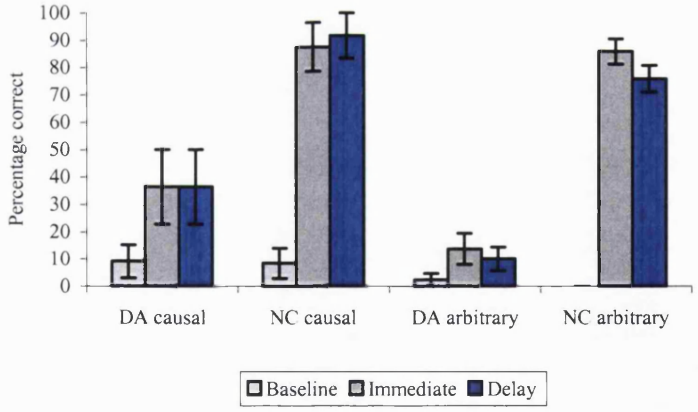
The mean (±SEM) percentage of target steps correctly produced by each group at baseline, immediate recall and after a 24-hour delay is shown in Table 5:10 and Figure 5:9.

Table 5:10 Percentage of correct script-atypical steps

	Baseline	Immediate	Delay
DA causal	9.09 (6.10)	36.4 (13.6)	36.4 (13.6)
NC causal	8.33 (5.62)	87.5 (8.97)	91.7 (8.33)
DA arbitrary	2.27 (2.27)	13.6 (5.72)	10.0 (4.42)
NC arbitrary	0.00 (0.00)	85.8 (4.64)	75.8 (4.92)

Mean (±SEM)

Figure 5:9 Percentage of correct script-atypical steps



The analysis, as predicted, revealed a significant main effect of Group ($F(1,21) = 35.95$; $p < 0.0001$), suggesting that overall the control group produced more target steps than the DA group. There was also a significant main effect of Time ($F(1.30, 27.35) = 119.12$; $p < 0.0001$). Follow up analysis of the main effect of Time, as predicted revealed that more target steps were produced immediately after demonstration ($p < 0.0001$) and after a delay ($p < 0.0001$) compared to baseline, but there was no difference between

immediate and delayed recall ($p > 0.05$). As predicted there was a significant Group by Time interaction ($F(1.30, 27.35) = 47.18$; $p < 0.0001$).

Follow up analysis of the Group by Time interaction revealed, as predicted, that the groups did not differ at baseline ($p > 0.1$). The DA group was impaired relative to controls both at immediate ($t(21) = 6.32$; $p < 0.0001$) and delayed ($t(14.39) = 6.90$; $p < 0.001$) recall, and the group difference was slightly larger at immediate (mean difference = 61.7) than at delayed (mean difference = 60.6) recall.

As it was predicted that patients with DA would be impaired on recall of script-atypical steps and pairs, another follow up analysis was conducted in order to test whether the Group by Time interaction was caused by recall in the DA group not differing from baseline (i.e. no memory for the target steps). Indeed this was the case; there was no evidence to suggest that immediate recall was better than baseline ($p = 0.05$[5]), or that delayed recall was better than baseline ($p > 0.05$), or that immediate recall significantly differed from delayed recall ($p > 0.1$) in the DA group. However, the control group performed better at both immediate ($t(11) = -18.46$; $p < 0.0001$) and delayed ($t(11) = -18.11$; $p < 0.0001$) recall than at baseline, while immediate recall did not significantly differ from delayed recall ($p > 0.1$).

The mean (±SEM) percentage of target pairs correctly produced by each group at baseline, immediate recall and after a 24-hour delay is shown in Table 5:11 and Figure 5:10.

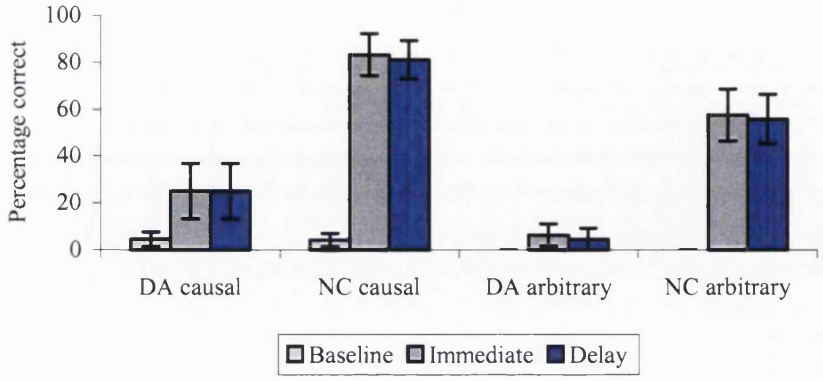
Table 5:11 Percentage of correct script-atypical pairs

	Baseline	Immediate	Delay
DA causal	4.55 (3.05)	25.0 (11.70)	25.0 (11.70)
NC causal	4.17 (2.81)	83.3 (8.88)	81.3 (8.21)
DA arbitrary	0.00 (0.00)	6.36 (4.72)	4.55 (4.55)
NC arbitrary	0.00 (0.00)	57.5 (11.10)	55.8 (10.60)

Mean (±SEM)

[5] A p-value of 0.006 represents the significant p-value after Bonferroni correction for nine pair-wise comparisons (p-value 0.05/9 = 0.006).

Figure 5:10 Percentage of correct script-atypical pairs



The analysis, as predicted, revealed a significant main effect of Group ($F(1,21) = 46.80$; $p < 0.0001$), suggesting that overall the control group produced more target pairs than the DA group; and a significant main effect of Time ($F(1.86, 39.07) = 67.93$; $p < 0.0001$). Follow up analysis of the main effect of Time, as predicted revealed that more target pairs were produced immediately after demonstration ($p < 0.0001$) and after a delay ($p < 0.0001$) compared to baseline, but there was no difference between immediate and delayed recall ($p > 0.05$). As predicted there was a significant Group by Time interaction ($F(1.86, 39.07) = 31.16$; $p < 0.0001$).

Follow up analysis of the Group by Time interaction revealed, as predicted, that the groups did not differ at baseline ($p > 0.1$). The DA group was impaired relative to controls both at immediate recall ($t(21) = 6.20$; $p < 0.0001$) and delayed recall ($t(21) = 6.68$; $p < 0.001$), and the group difference was slightly larger at immediate (mean difference = 54.7) than at delayed (mean difference = 53.8) recall.

As it was predicted that patients with DA would be impaired on recall of script-atypical steps and pairs, another follow up analysis was conducted in order to test whether the Group by Time interaction was caused by recall in the DA group not differing from baseline (i.e. no memory for the target pairs). Indeed this was the case; there was no evidence to suggest that immediate recall was better than baseline ($p > 0.006$[6]), or that delayed recall was better than baseline ($p > 0.006$), or that immediate recall significantly differed from delayed recall ($p > 0.1$). However, the control group performed better at both immediate ($t(11) = -10.46$; $p < 0.0001$) and delayed ($t(11) = -13.06$; $p < 0.0001$)

[6] A p-value of 0.006 represents the significant p-value after Bonferroni correction for nine pair-wise comparisons (p-value 0.05/9 = 0.006).

recall than at baseline, while immediate recall did not significantly differ from delayed recall ($p > 0.1$).

These findings suggest that, as predicted the control group recalled more atypical (episodic-like) steps and pairs after demonstration (both immediate and delay), indicating memory for the sequences, and that delayed recall did not significantly differ from immediate recall indicating memory for the sequences over the 24-hour delay. The DA group was impaired relative to the control at both immediate and delayed recall but as predicted, not at baseline. Further examination of the interaction revealed that the DA group did not perform significantly above baseline either at immediate or delayed recall, indicating as predicted, no memory for the script-atypical sequences (steps and pairs).

5.3.3 Semantic and episodic recall

5.3.3.1 Three-step novel sequences

Table 5:4 and Figure 5:3 show the mean (±SEM) percentage of target steps correctly produced by each group at baseline, immediate recall and after a 24-hour delay.

The analysis revealed, as described in Section 5.3.2.1, that overall the control group recalled more steps than the DA group; and a significant main effect of Type ($F(1, 21) = 46.73$; $p < 0.0001$), suggesting, unexpectedly, that overall more arbitrary than causal steps were recalled. There were also, as predicted, significant interactions of Group by Type by Time ($F(1.47, 30.76) = 6.30$; $p = 0.01$), Group by Type ($F(1, 21) = 8.61$; $p = 0.008$) and Type by Time ($F(1.47, 30.76) = 6.75$; $p = 0.007$). Caution should be applied when interpreting the findings from this task as the control group showed ceiling effects on immediate and delayed recall of causal and arbitrary steps (see Table 5:4 and Figure 5:3).

Follow up analysis of the Group by Type interaction revealed that the control group produced more causal and arbitrary steps than the DA group (Causal: $t(14.52) = 6.92$; $p < 0.0001$; Arbitrary: $t(12.31) = 4.20$; $p = 0.001$), but unexpectedly, the difference between the groups was greater on causal (mean difference = 29.0) than arbitrary (mean difference = 16.3) step recall. This was modified by a Group by Type by Time interaction which occurred because this pattern was significant at immediate ($F(1,21) = 8.89$; $p = 0.007$) and delayed ($F(1,21) = 13.71$; $p = 0.001$) recall but not at baseline ($p > 0.1$).

Follow up analysis of the Time by Type interaction revealed that more arbitrary than causal steps were produced at baseline ($t(22) = 7.66$; $p < 0.0001$), immediate recall ($t(22) = 3.42$; $p = 0.002$) and at delayed recall ($t(22) = 2.94$; $p = 0.008$). The difference between the causal and arbitrary steps was greatest at baseline (mean difference = 21.68), and least at immediate recall (mean difference = 10.7) and delayed recall (mean difference = 11.0).

Table 5:5 and Figure 5:4 show the mean (±SEM) percentage of target pairs correctly produced by each group at baseline, immediate recall and after a 24-hour delay.

The analysis revealed, as described in Section 5.3.2.1, that overall the control group recalled more pairs than the DA group, but no significant effect of Type ($p > 0.1$). There were also, as predicted, a significant interaction Group by Type ($F(1,21) = 13.3$; $p = 0.002$) but unexpectedly, not Group by Type by Time or Type by Time.

Follow-up analysis of the significant Group by Type interaction revealed that the control group recalled more causal ($t(21) = 9.58$; $p < 0.0001$) and arbitrary ($t(21) = 7.50$; $p < 0.0001$) pairs than the DA group but unexpectedly, the mean group difference was larger for causal (47.2) than arbitrary (30.5) pairs.

In summary, these findings suggest that although the DA group was impaired relative to the control group at producing both causal and arbitrary steps and pairs the DA group was, unexpectedly, more impaired at recalling causal than arbitrary steps and pairs.

5.3.3.2 Scripted sequences

5.3.3.2.1 Script-based typical targets

Table 5:6 and Figure 5:5 show the mean (±SEM) percentage of target pairs correctly produced by each group at baseline, immediate recall and after a 24-hour delay.

The analysis, as described in Section 5.3.2.2.1, revealed that overall the control group produced more target steps than the DA group. There was also a significant main effect of Type ($F(1,21) = 5.45$; $p = 0.03$), suggesting that overall, as predicted, more causal than arbitrary steps were produced. There was also, as predicted, a significant Time by Type interaction ($F(1.44, 30.32) = 3.95$; $p = 0.042$). Unexpectedly, the Group by Type interaction was not significant ($p > 0.1$). Due to the lack of variance in the control group on immediate recall of arbitrary steps, the Group by Type by Time interaction was not interpreted.

Follow up analysis of the Time by Type interaction revealed that, unexpectedly, more causal than arbitrary script-typical steps were produced at baseline ($t(22) = 3.03$; $p = 0.006$) but not at immediate or delayed recall.

Table 5:7 and Figure 5:6 show the mean (±SEM) percentage of target pairs correctly produced by each group at baseline, immediate recall and after a 24-hour delay.

The analysis, as described in Section 5.3.2.2.1, revealed that overall the control group produced more target pairs than the DA group, but there was no significant main effect of Type ($p > 0.1$) and unexpectedly the Group by Type by Time, Type by Time and Group by Type interactions were not significant ($p > 0.1$).

In summary, overall the DA group was impaired relative to controls at recalling both steps and pairs. More causal than arbitrary steps were produced at baseline but not at immediate or after a delay, and the DA group was not more impaired at recalling arbitrary than causal steps or pairs.

5.3.3.2.2 Arbitrary targets

Table 5:8 and Figure 5:7 show the mean (±SEM) percentage of target steps correctly produced by each group at baseline, immediate recall and after a 24-hour delay.

As described in Section 5.3.2.3, the analysis revealed that overall the control group produced more target steps than the DA group.

Table 5:9 and Figure 5:8 show the mean (±SEM) percentage of target pairs correctly produced by each group at baseline, immediate recall and after a 24-hour delay.

As described in Section 5.3.2.3, the analysis revealed that overall the control group produced more target pairs than the DA group.

5.3.3.2.3 Script-based atypical targets

Table 5:10 and Figure 5:9 show the mean (±SEM) percentage of target steps correctly produced by each group at baseline, immediate recall and after a 24-hour delay.

As described in Section 5.3.2.4, the analysis, as predicted, revealed a significant main effect of Group ($F(1,21) = 35.95$; $p < 0.0001$), suggesting that overall the control group produced more target steps than the DA group; and as predicted, a significant main effect of Type ($F(1,21) = 5.72$; $p = 0.026$), suggesting that overall more causal than arbitrary steps were produced; but unexpectedly the Group by Type interaction was not significant ($p > 0.1$) nor was the Time by Type interaction ($p > 0.1$). Due to the lack of

variance in the control group's performance on baseline production of arbitrary steps, the Group by Time by Type interaction was not interpreted.

Table 5:11 and Figure 5:10 show the mean (±SEM) percentage of target pairs correctly produced by each group at baseline, immediate recall and after a 24-hour delay.

As described in Section 5.3.2.4, the analysis, as predicted, revealed a significant main effect of Group ($F(1,21) = 46.80$; $p < 0.0001$), suggesting that overall the control group produced more target pairs than the DA group; and as predicted, a significant main effect of Type ($F(1,21) = 6.36$; $p = 0.020$), suggesting that overall more causal than arbitrary pairs were produced; unexpectedly the Group by Type interaction was not significant ($p > 0.1$). Due to the lack of variance in the control and DA groups' performance on baseline production of arbitrary pairs, the Group by Time by Type and Type by Time interactions were not interpreted.

In summary, overall, as predicted, the DA group was impaired relative to controls at recalling both script-atypical steps and pairs. More causal than arbitrary steps and pairs were produced on all three conditions, and the DA group was not more impaired at recalling arbitrary than causal steps or pairs relative to the control group.

5.3.4 Effect of practice

In order to test whether the immediate memory test in the immediate and delayed recall task acted as an additional learning trial, the delayed recall performance was compared between the two conditions, that is delayed-only recall ('without practice') and the delayed recall after an immediate recall trial ('with practice'). Baseline performance was subtracted from the delayed recall performance in order to estimate memory for the target steps and pairs independent of any differences in baseline performance.

5.3.4.1 Three-step novel sequences

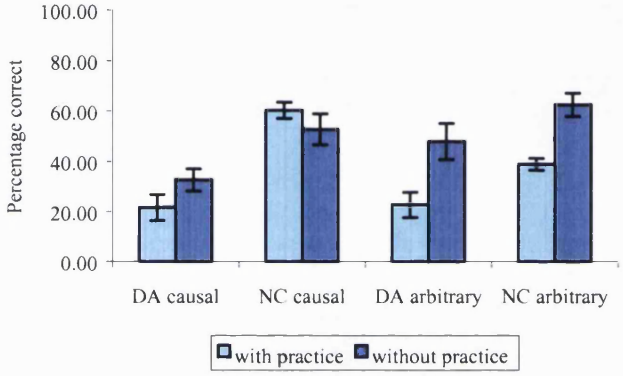
Table 5:12 and Figure 5:11 show the mean (±SEM) percentage of target steps correctly produced by each group at baseline and after a 24-hour delay.

Table 5:12 Percentage of correct steps

	with practice	without practice
DA causal	21.7 (5.17)	32.6 (4.41)
NC causal	60.3 (3.26)	52.8 (6.10)
DA arbitrary	22.7 (5.04)	47.9 (7.19)
NC arbitrary	38.9 (2.37)	62.5 (4.53)

Mean (±SEM)

Figure 5:11 Percentage of correct steps



The analysis revealed significant main effects of Group ($F(1,21) = 22.32$; $p < 0.0001$), suggesting that overall the control group recalled more steps than the DA group, and Condition ($F(1,21) = 15.76$; $p = 0.001$), suggesting that overall recall 'without practice' was better than recall 'with practice'. The Group by Condition interaction was not significant ($p > 0.1$), but the Condition by Type interaction was ($F(1,21) = 22.69$; $p < 0.0001$).

Follow up analysis of the Condition by Type interaction revealed that more arbitrary ($t(22) = -5.94$; $p < 0.0001$), but not causal ($p > 0.1$), steps were recalled on the 'without practice' condition than the 'with practice' condition.

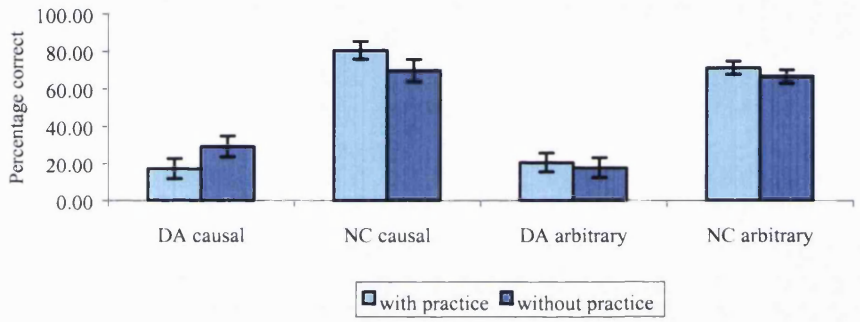
Table 5:13 and Figure 5:12 show the mean (±SEM) percentage of target pairs correctly produced by each group at baseline and after a 24-hour delay.

Table 5:13 Percentage of correct pairs

Pairs	with practice	without practice
DA causal	17.2 (5.48)	29.2 (5.62)
NC causal	80.6 (4.76)	69.8 (5.85)
DA arbitrary	20.5 (5.13)	17.7 (5.43)
NC arbitrary	71.2 (3.50)	66.7 (3.55)

Mean (±SEM)

Figure 5:12 Percentage of correct pairs



The analysis revealed significant main effects of Group ($F(1,21) = 78.15$; $p < 0.0001$), suggesting that overall the control group recalled more pairs that the DA group, but not Condition ($p > 0.1$). The Group by Condition interaction was significant ($F(1,21) = 12.24$; $p = 0.002$), and there was weak evidence for a Group by Condition by Type interaction ($F(1,21) = 4.17$; $p = 0.054$), but not a Condition by Type interaction ($p > 0.1$).

Follow up analysis of the Group by Condition interaction revealed that the control group did show evidence for an effect of practice ($t(11) = 2.85$; $p = 0.02$), in favour of recall 'with practice'. The DA group on the other hand showed weak evidence ($t(10) = -2.10$; $p = 0.062$) for an effect in the opposite direction, in favour of 'without practice'.

Follow up analysis of the Group by Condition by Type interaction (using separate ANOVAs) revealed that this pattern of findings was significant on causal pairs ($F(1,21) = 16.85$; $p = 0.001$), but not on arbitrary pairs ($p > 0.1$).

In summary, these findings suggest that, as expected, overall the control group recall more steps and pairs than the DA group. Furthermore, unexpectedly, both groups recalled more arbitrary steps 'without practice' than 'with practice'. The control group produced more target causal pairs 'with practice' than 'without practice' while the DA

group unexpectedly, produced more target causal pairs 'without practice' than 'with practice'. These findings suggest that the addition of the immediate recall trial may interfere with subsequent recall of arbitrary steps in both groups, and causal pairs in the DA group.

5.3.4.2 Scripted sequences

5.3.4.2.1 Script-based Typical targets

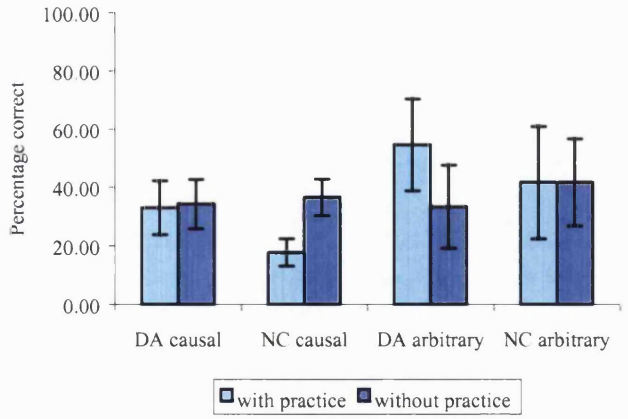
Table 5:14 and Figure 5:13 show the mean (±SEM) percentage of target steps correctly produced by each group at baseline and after a 24-hour delay.

Table 5:14 Percentage of correct script-typical steps

	with practice	without practice
DA causal	33.0 (9.19)	34.2 (8.39)
NC causal	17.7 (4.62)	36.5 (6.26)
DA arbitrary	54.5 (15.70)	33.3 (14.20)
NC arbitrary	41.7 (19.30)	41.7 (14.90)

Mean (±SEM)

Figure 5:13 Percentage of correct script-typical steps



The analysis revealed no significant effects of Group ($p > 0.1$) or Condition ($p > 0.1$) and none of the interactions were significant ($p > 0.1$), suggesting that the immediate recall condition did not act as a practice or interference trial in either group.

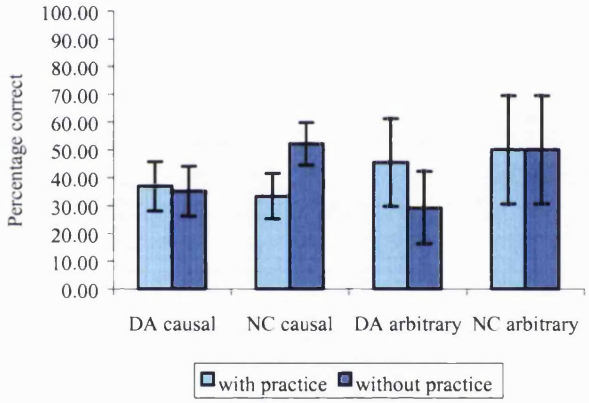
Table 5:15 and Figure 5:14 show the mean (±SEM) percentage of target pairs correctly produced by each group at baseline and after a 24-hour delay.

Table 5:15 Percentage of correct script-typical pairs

	with practice	without practice
DA causal	36.8 (8.86)	35.1 (8.92)
NC causal	33.3 (8.09)	52.1 (7.67)
DA arbitrary	45.5 (15.70)	29.2 (13.00)
NC arbitrary	50.0 (19.50)	50.0 (19.50)

Mean (±SEM)

Figure 5:14 Percentage of correct script-typical pairs



The analysis revealed no significant effects of Group ($p > 0.1$) or Condition ($p > 0.1$) and none of the interactions were significant ($p > 0.1$), suggesting that the immediate recall condition did not act as a practice or interference trial in either group.

5.3.4.2.2 Arbitrary targets

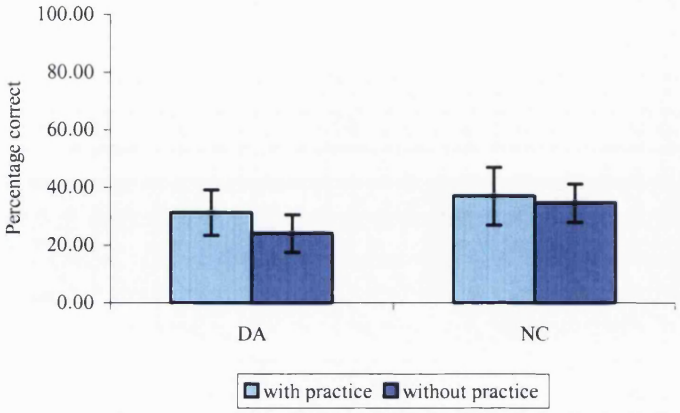
Table 5:16 and Figure 5:15 show the mean (±SEM) percentage of target steps correctly produced by each group at baseline and after a 24-hour delay.

Table 5:16 Percentage correct arbitrary steps

	with practice	without practice
DA arbitrary	31.2 (7.87)	24.0 (6.47)
NC arbitrary	36.9 (9.95)	34.5 (6.66)

Mean (±SEM)

Figure 5:15 Percentage correct arbitrary steps



The analysis revealed no significant effects of Group ($p > 0.1$) or Condition ($p > 0.1$) nor Group by Condition interaction ($p > 0.1$) was not significant suggesting that the immediate recall condition did not act as a practice or interference trial in either group.

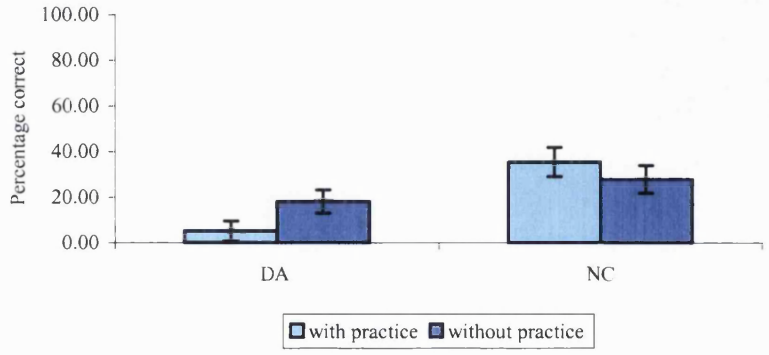
Table 5:17 and Figure 5:16 show the mean (±SEM) percentage of target pairs correctly produced by each group at baseline and after a 24-hour delay.

Table 5:17 Percentage correct arbitrary pairs

	with practice	without practice
DA arbitrary	5.17 (4.30)	18.1 (5.08)
NC arbitrary	35.4 (6.61)	27.8 (6.05)

Mean (±SEM)

Figure 5:16 Percentage correct arbitrary pairs



The analysis revealed a significant main effect of Group ($F(1,21) = 12.93$; $p = 0.002$), suggesting that overall the control group recalled more arbitrary pairs than the DA group. There was no effect of Condition ($p > 0.1$) but there was weak evidence for a Group by Condition interaction ($F(1,21) = 3.48$; $p = 0.08$).

Follow up analysis of the Group by Condition interaction revealed weak evidence to suggest that the DA group recalled more target arbitrary pairs 'without practice' compared to 'with practice' recall ($t(10) = -2.06$; $p = 0.07$), but there was no evidence for a difference between conditions in the control group ($p > 0.1$).

These findings suggest the groups did not differ in their delayed recall of arbitrary steps and neither group showed an effect of practice on recall of steps. However, the control group recalled more arbitrary pairs than the DA group, and the immediate recall trial may have interfered with subsequent delayed recall of arbitrary pairs in the DA group.

5.3.4.2.3 Script-based atypical targets

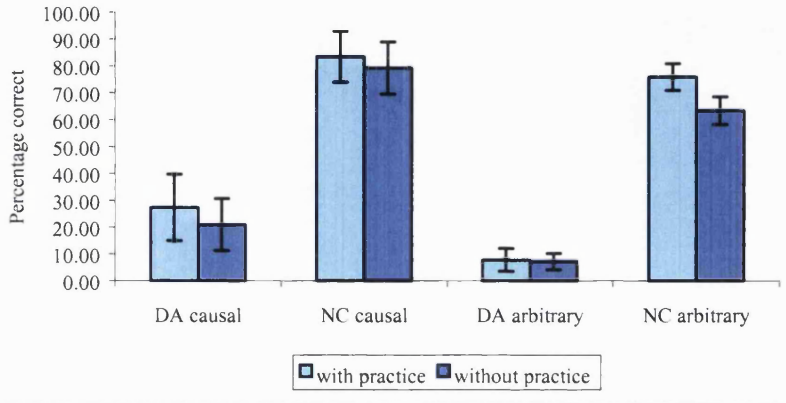
Table 5:18 and Figure 5:17 show the mean (±SEM) percentage of target steps correctly produced by each group at baseline and after a 24-hour delay.

Table 5:18 Percentage correct script-atypical steps

	with practice	without practice
DA causal	27.3 (12.4)	20.8 (9.65)
NC causal	83.3 (9.40)	79.2 (9.65)
DA arbitrary	7.73 (4.23)	7.08 (3.04)
NC arbitrary	75.8 (4.92)	63.3 (5.12)

Mean (±SEM)

Figure 5:17 Percentage correct script-atypical steps



The analysis revealed a significant main effect of Group ($F(1,21) = 93.89$; $p < 0.0001$), suggesting that overall the control group recalled more atypical target steps than the DA group, but not Condition ($p > 0.1$) and there was no evidence for a Group by Condition interaction ($p > 0.1$), suggesting that the immediate recall condition did not act as a practice or interference trial in either group.

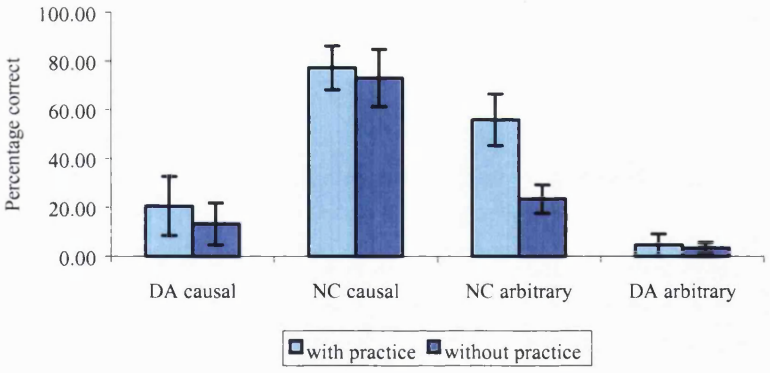
Table 5:19 and Figure 5:18 show the mean (±SEM) percentage of target pairs correctly produced by each group at baseline and after a 24-hour delay.

Table 5:19 Percentage correct script-atypical pairs

	with practice	without practice
DA causal	20.5 (12.10)	13.2 (8.55)
NC causal	77.1 (8.95)	72.9 (11.70)
NC arbitrary	55.8 (10.60)	23.3 (5.82)
DA arbitrary	4.55 (4.55)	3.33 (2.25)

Mean (±SEM)

Figure 5:18 Percentage correct script-atypical pairs



The analysis revealed a significant main effect of Group ($F(1,21) = 60.49$; $p < 0.0001$), suggesting that overall the control group recalled more script-atypical target pairs than the DA group, and Condition ($F(1,21) = 5.06$; $p = 0.035$), where more script-atypical target pairs were recalled 'with practice' than 'without practice'. The Group by Condition interaction was not significant ($p > 0.1$).

These findings suggest that the control group recalled more target steps and pairs than the DA group. Neither group showed an effect of practice on recall of steps, but both

groups recalled more target pairs 'with practice', suggesting that the immediate recall trial may have acted as an additional learning/practice trial.

5.3.5 Summary table of results

Key to tables:

NC = normal control, DA = developmental amnesia, Bl = baseline, Im = immediate recall; Dl = delayed recall; > greater than; < less than; = no difference; * = not applicable; Np = no practice; p = practice; Then for all except the memory and the practice question: Yes = predicted effect; No = not predicted.

Table 5:20 Summary of 'steps' results

Question	Novel 3-step	Script-typical	Script-arbitrary	Script-atypical
Memory?	Yes, Bl < Im/Dl	Yes, Bl < Im/Dl	NC: Yes, Bl < Im/Dl DA: Yes, Bl < Im; Bl < Dl	NC: Yes, Bl < Im/Dl DA: No, Bl = Im = Dl
Immediate vs. Delay?	No, Im = Dl	Yes, Im = Dl	Yes, Im = Dl	Yes, Im = Dl
Immediate NC vs. DA?	No, NC > DA	No, NC > DA	Yes, NC > DA	Yes, NC > DA
Delay NC vs. DA?	Yes, NC > DA	No, NC > DA	No, NC = DA	Yes, NC > DA
Causal NC = DA?	No, NC > DA	No, NC > DA	*	No, NC > DA
Arbitrary NC > DA?	Yes, NC > DA	Yes, NC > DA	Yes, NC > DA	Yes, NC > DA
Practice?	A: Yes, Np > p C: No, Np = p	No, Np = P	No, Np = P	No, Np = P

Table 5:21 Summary of 'pairs' results

Question	Novel 3-step	Script-typical	Script-arbitrary	Script-atypical
Memory?	Yes, Bl < Im/Dl	Yes, Bl < Im/Dl	NC: Yes, Bl < Im/Dl DA: No, Bl = Im = Dl	NC: Yes, Bl < Im/Dl DA: No, Bl = Im = Dl
Immediate vs. Delay?	No, Im = Dl	Yes, Im = Dl	Yes, Im = Dl	Yes, Im = Dl
Immediate NC vs. DA?	No, NC > DA	No, NC > DA	Yes, NC > DA	Yes, NC > DA
Delay NC vs. DA?	Yes, NC > DA	No, NC > DA	Yes, NC > DA	Yes, NC > DA
Causal NC = DA?	No, NC > DA	No, NC > DA	*	No, NC > DA
Arbitrary NC > DA?	Yes, NC > DA	Yes, NC > DA	Yes, NC > DA	Yes, NC > DA
Practice?	NC: Yes, P > Np DA: Yes Np> P	No, Np = P	NC: No, P = Np DA: Yes, Np > P	Yes, P > Np

5.3.6 Awareness of the purpose of study

One DA (DA1) patient said that he was aware that he would be asked to recall the target steps and pairs and that this awareness had occurred to him on the first day of testing. None of the other patients or the controls expressed an awareness of the purpose of the task.

5.4 DISCUSSION

DA has previously been associated with an episodic memory impairment in the presence of relatively preserved semantic memory and an impairment in delayed memory relative to immediate memory (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000), and this was confirmed in Chapter 4. The purposes of this chapter were to replicate the study of McDonough *et al.* (1995) and to further investigate using a nonverbal task, i) memory over a 24-hour delay, ii) the dissociation between episodic and semantic memory; and iii) any effect of practice caused by an immediate recall trial.

Overall the findings were as follows: (a) the results reported in this chapter replicated the findings reported by McDonough *et al.* (1995) in that the patients were impaired relative to controls after a 24-hour delay. However, unlike the study of McDonough *et al.* (1995) patients with DA still showed evidence of some memory after a 24-hour delay; (b) the patients were impaired relative to controls at both immediate and delayed recall, and unexpectedly, delayed recall did not significantly differ from immediate recall; (c) patients with DA were impaired relative to controls at recall of both causal and arbitrary sequences, but there was evidence that they found arbitrary steps and atypical steps within scripted sequences especially hard to remember; and (d) finally, although there was evidence to suggest that the immediate recall trial acted as a practice trial in both groups on one measure and in the control group on another measure, the additional recall trial acted as an interference trial for the DA group on two out of eight measures, and in both groups on one measure. Each of these findings will be discussed in turn.

5.4.1 Replication of McDonough et al. (1995)

McDonough *et al.* (1995) reported the only study to date testing nonverbal recall using deferred imitation in patients with adult-onset amnesia. In their study patients with adult onset amnesia were impaired relative to controls at delayed recall of novel 3-step sequences (steps and pairs), however the groups did not differ at baseline.

The findings reported in Section 5.3.1 replicate the findings reported by McDonough *et al.* (1995), in that the patients with DA were impaired relative to controls at delayed recall of steps and pairs but not at baseline. This impairment in delayed nonverbal recall is consistent with the previous findings of DA (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000). However, there was also evidence to suggest that the DA group did produce more target steps and pairs following demonstration, although this memory effect was smaller compared to the controls. The only hint that the patients with adult-onset amnesia reported by McDonough *et al.* (1995) showed any memory for the event sequences was a significant main effect of assessment (baseline vs. uninstructed recall vs. instructed recall) with a mean number of steps in the expected direction. However, post-hoc follow up comparisons of the two memory conditions versus baseline showed no significant effects. Therefore patients with DA show a better memory at delay compared to that shown by the adult-onset amnesia cases reported by McDonough *et al.*

(1995). This could be due to the differences in extent of injury between these two patient groups. The patients with DA, within the MTL, have selective hippocampal pathology, while the patients reported by McDonough *et al.* (1995) are of mixed aetiology with some patients having KA, a disorder associated with diencephalic and possibly frontal lobe damage. Alternatively, the less severe memory deficit in the DA group might be a consequence of their young age at injury, in that patients with DA may have a less severe amnesia due to the functional reorganisational capacity of the immature brain (e.g. Nelson, 2000). This possibility is discussed in more detail in Section 10.4.2, Chapter 10.

5.4.2 Effect of delay

Previous reports of DA (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000) have suggested that delayed recall is more impaired than immediate recall, and that memory span is unimpaired. Therefore it was predicted that relative to controls, the patients with DA would be more impaired at delayed recall compared to immediate recall of the 3-step sequences. Although there was evidence that immediate memory was relatively less impaired relative to controls than memory after a delay on both 3-step step and pair recall, these differences were very small.

It was also predicted that patients with DA would not be impaired at immediate or delayed memory of script-typical sequences. This prediction was not supported. However, the prediction that the DA group would be impaired relative to controls at both immediate and delayed memory on the other four measures was supported, except for delayed recall of script-based arbitrary steps (see below).

The finding that the DA group was significantly impaired at immediate recall in all conditions is consistent with the immediate memory impairments found in the studies reported in Chapters 2 and 4. Although previous studies of DA have not reported significant impairments in immediate recall in patients with DA on measures of immediate memory span (first trial of a 16-word list; digit and block span), story or design recall (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000), the data reported in these papers suggests a trend in this direction, at least for story and design recall. The finding of immediate memory impairments on the 3-step sequences and the script-based typical sequences may, in part, be due to the demonstration procedure used in the task reported in this chapter. In this task, participants were presented with all eleven sets of sequences before they were permitted to imitate the sequences. It is possible that

remembering eleven sets of sequences exceeds the immediate memory capacity of the DA group, and thus becomes more like remembering a story or a set of designs. This presentation procedure was used for two reasons: i) to replicate the procedure used by McDonough *et al.* (1995); and ii) to limit awareness of the purpose of the task. For example, if immediately after presentation of the first sequence the participant was permitted to imitate the sequence, the participant would realise that he/she was expected to imitate the next demonstrated sequence, thus enabling the participant to recruit rehearsal strategies. However, it is possible that if immediate recall was measured after each demonstration the patients would not be impaired relative to controls, at least on 3-step sequences as short-term memory span is intact in these patients (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000; Vargha-Khadem *et al.*, 2001; Chapter 2).

In order to examine whether the DA group showed evidence of memory for the sequences independently of the control group's performance the performance on immediate and delayed recall was compared to baseline in each group separately. These analyses revealed that the control group produced more target steps and pairs at immediate and delayed recall compared to baseline, and immediate and delayed recall did not significantly differ, on all eight measures. The DA group showed evidence of memory on five of the eight, and immediate and delayed recall did not differ significantly on all of the measures. The finding that neither group showed evidence of forgetting over the 24-hour delay was not predicted on the 3-step novel sequences (steps and pairs) based on the previous reports of the memory profile associated with DA (e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000). However, this may reflect residual episodic memory supporting memory in the patients with DA even after a 24-delay. Indeed the delayed recall findings presented in previous chapters (2 and 4) also indicate some level of memory function after a delay. The reason as to why the delayed recall memory reported in this chapter is not more impaired than immediate recall memory may be a consequence of the meaningfulness of information to-be-remembered. For example, even arbitrarily ordered 3-step sequences using everyday props might be more interesting or meaningful to the patients than word-lists or designs. Furthermore, patients with DA may benefit from the nonverbal nature of this task, in that there was some indication in Chapter 4 that visual memory might be less impaired than verbal memory in these patients.

It was also predicted that the DA group would not show any evidence of memory on the script-arbitrary and script-atypical sequences. This was supported on three of the

four measures. The finding that recall of script-based arbitrary steps was impaired at immediate memory but unexpectedly not at delayed memory in the DA group relative to controls seems to be related to the fact that the control group recalled slightly, but not significantly, more steps immediately after demonstration than after a delay (see Figure 5:7). The control group performance after the delay seemed to fall to a level that was not significantly different to the delayed recall of the patients, but was still significantly different from baseline performance.

In summary, there was no evidence to support the prediction that delayed memory would be more impaired than immediate memory in patients with DA on two of the measures. Instead, neither group showed evidence of forgetting on any of the measure after a 24-hour delay.

5.4.3 Semantic and episodic recall

Based on the discussion in Section 5.1.1, it was predicted that arbitrary sequences and script-based atypical sequences would make the most demands on episodic memory due to their lack of meaningful structure and thus be impaired in DA.

The prediction that memory in the DA group would be more impaired for arbitrary than causal sequences was not supported on any of the measures. Instead it appeared that the DA group was impaired relative to the controls at both causal and arbitrary sequences on all ten measures, including the three-step sequences of McDonough *et al.* (1995). This finding suggests that on these measures, arbitrary sequences are not more 'episodic' than causal sequences.

The only measures to show the predicted Group by Type interaction was 3-step sequences steps and pair recall. However, this interaction was in the opposite direction to that predicted, and was caused by a greater impairment on causal than arbitrary sequences on immediate and delayed recall of the 3-step sequence steps and on all recall conditions of the 3-step sequence pairs. However, the control participants performed close to ceiling on the arbitrary sequences. Therefore, it is possible that this underestimated their performance, in which case the DA group might have been more impaired at arbitrary sequence recall if the controls had been given the opportunity to demonstrate a higher performance.

It was also predicted that overall the DA group would not be impaired on recall of script-typical sequences due to their prior familiarity, and therefore their 'semantic'

nature. Unexpectedly, overall the DA group was impaired relative to controls, including at baseline, immediate and delayed recall. Therefore the DA group did not benefit from script-typical sequences regardless of their causal or arbitrary structure.

As predicted the DA group was impaired relative to the control group at recalling the script-arbitrary sequences (both steps and pairs). The finding that, unlike controls, the DA group did not show any memory for script-arbitrary pairs, that is, performance did not significantly differ from baseline, may reflect that memory for these pairs, as predicted, place a high demand on episodic memory. This may be due to their lack of meaningful temporal order. Furthermore, it appears that the temporal order of the arbitrary sequences is the most demanding, as the DA group showed evidence for memory of the arbitrary steps but not pairs even after a delay. The finding that memory for arbitrary steps and pairs show a different pattern of results strengthens this argument because if no steps were remembered at delay then no pairs could be produced as these two measures are not independent.

The finding that the DA group showed no memory for target atypical script-based sequences (both steps and pairs) may reflect that these sequences are the most 'episodic' in nature. These sequences are entirely novel, and are mostly unusual (e.g. tie dental floss around the toothbrush). One might expect this novelty to render the sequences salient, which may be case in healthy individuals, particularly at immediate recall (e.g. Graesser *et al.*, 1979; Adams and Worden, 1986). However, with the known role of the hippocampus in novelty detection (e.g. Dolan and Fletcher, 1997; 1999) it is possible that these sequences were not remembered by patients with DA due to their hippocampal pathology.

Overall there was no evidence to support the prediction that patients with DA would be more impaired at arbitrary compared to causal sequences. However, there was evidence to suggest that patients with DA were severely impaired at recalling the most 'episodic' sequences, script-arbitrary and script-atypical, showing no memory for the temporal order of these sequences either at immediate or delayed recall relative to baseline.

5.4.4 Effect of practice

Finally, it was predicted that if immediate recall acted as an additional practice or learning trial then delayed recall would be better after a test of immediate recall (with

practice) compared to delayed recall without a test of immediate recall (without practice) in both the DA and control groups.

This was the case on one measure for both groups, script-atypical pair recall, and one measure for the control group, 3-step sequence pair recall. However, on one measure, arbitrary steps of the 3-step sequence, both groups benefited without practice, and on two measures the DA group benefited without practice, suggesting that on these measures the immediate recall trial acted as an interference trial. The immediate recall trial may have acted as an interference trial in that the participant may generate errors, which may then be remembered at subsequent delayed recall. Indeed, as will be discussed in Chapter 6, patients with amnesia are prone to interference effects from errors generated during assessment (e.g. Hayman *et al.*, 1993; Wilson *et al.*, 1994; Hamann and Squire, 1995; Hunkin *et al.*, 1998).

5.4.5 Additional considerations

5.4.5.1 Baseline and ceiling effects

Differences between groups or sequences at baseline combined with ceiling effects may affect predicted interactions. For example, the finding that patients with DA were not more impaired at recalling arbitrary than causal sequences relative to the controls may have been due to the control group producing more arbitrary sequences than the DA group at baseline combined with the finding of ceiling or near ceiling performance after demonstration on this condition, thus the magnitude of the potential memory effect shown by the controls was constrained and therefore underestimated. This pattern of performance only occurred on two of the ten measures, and suggests that if the controls had more scope for performance the predicted memory difference between arbitrary and causal sequences in the patients relative to controls may have occurred.

5.4.5.2 Props and sequences

It was not possible to counter-balance the sequences across Type (causal, arbitrary) due to the temporal order of the sequences being constrained by the props used. However, future studies may benefit from counter-balancing props across sequence type in order to control for differences, such as motivation. For example, the props used in the arbitrary sequences may have been more interesting to play with thus resulted in an

increased performance at baseline and a ceiling effect after demonstration in the control group.

5.4.5.3 Awareness

This task was designed to be a test of unalerted recall in that participants were not told that they would be required to recall the sequences after demonstration. As it is possible that awareness of the purpose of the task may have affected subsequent memory performance due to the participants being able to mentally rehearse the sequences, each participant was asked if he/she was aware of the purpose of the task, and if so when did that awareness occur to them. Only one patient (DA1) indicated any awareness of the purpose of the task. This awareness did not affect subsequent recall in that overall the patient group was impaired relative to controls.

5.4.6 Conclusion

This chapter aimed to examine dissociations between immediate and delayed memory and episodic and semantic associated with DA. The participants were tested for their immediate and/or delayed recall of nonverbal sequences presented incidentally. The findings replicated an earlier study in adult-onset amnesia cases, in that delayed memory for the nonverbal sequences was impaired in the DA group relative to controls. However, unlike the adult-onset amnesic patients reported by McDonough *et al.* (1995), patients with DA showed some evidence for memory of the sequences even after a 24-hour delay. The findings did not support the prediction that immediate memory would be less impaired than delayed recall. Instead despite showing evidence of memory following demonstration on all but the most 'episodic' of the sequences (arbitrary and atypical script-based sequences), the patients with DA were equivalently impaired relative to controls on both memory measures. Furthermore, the findings did not support the prediction that arbitrary sequences would be the most impaired in patients with DA due to their high demand on episodic memory, as the patients were equivalently impaired relative to controls on both arbitrary and causal sequences. Finally, although there was some evidence to suggest that the immediate recall trial acted as an additional practice trial, the addition of the immediate recall trial mostly interfered with subsequent delayed memory in patients with DA.

The finding that the patients showed no evidence of memory for script-arbitrary and script-atypical pairs suggests that these sequences tap into the memory deficits associated with DA. These sequences were designed to be the most 'episodic' due to their novel structure and content, and therefore suggest that the hippocampus is required to support episodic memory. The finding that patients with DA showed some level of memory at immediate recall and after a delay on all of the other measures, suggests some residual memory in these patients. This was predicted on script-typical sequences as these were designed to be the most 'semantic'. Therefore the residual memory in patients with DA suggests that the 3-step novel sequences do not necessarily tap into episodic memory, or tap into episodic memory to a lesser degree than the script-arbitrary and script-atypical sequences. The residual memory demonstrated by patients with DA on this task does not reflect nondeclarative memory, as this was not impaired relative to controls in Chapter 2, but memory is impaired relative to controls on nonverbal imitation. Therefore, nonverbal imitation reflects declarative memory and script-arbitrary and script-atypical sequences more than likely reflect episodic memory. These findings support the multi-system model of declarative memory, in that episodic memory is more impaired relative to other forms of declarative memory. Whether residual memory performance on certain conditions of nonverbal imitation reflect episodic/semantic memory remains to be tested.

6 REPETITION, RELATEDNESS AND SEMANTIC MEMORY

Previous studies of DA have found semantic memory, as measured using tests of intelligence and academic attainments, to be unimpaired (e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000; Baddeley *et al.*, 2001). However, given that these same patients demonstrate severe impairments on delayed recall of recently learned information, an important question is how patients with DA are able to acquire their semantic knowledge base. A recent single case study (Jon) demonstrated impaired recall of information seen in a newsreel video presented only once, but near normal recall of information seen four times, suggesting that repetition may be a key factor (Baddeley *et al.*, 2001). This chapter describes the performance of a group of patients with DA on two learning tasks involving repetition: (a) the newsreel task of Baddeley *et al.* (2001) and (b) a word-list learning task. The word-list learning task also examined the effects of the semantic organisation of the to-be remembered materials, a factor known to affect recall in normal adults. Results show some evidence that repetition enhanced memory in patients with DA, but in neither experiment did repetition enhance memory performance to the level of controls. Both controls and patients with DA significantly benefited from semantic organisation of the to-be-learned materials on immediate memory span and during learning, but only the controls did so during delayed recall.

6.1 INTRODUCTION

Semantic memory is defined as memory for general knowledge and as such is context-free. It includes information such as vocabulary and facts about the world and oneself and can be distinguished from episodic memory – context-rich memories for personally experienced events (e.g. Tulving, 1972). As discussed throughout this thesis, there exits a debate as to whether it is possible to show a dissociation between episodic and semantic memory following damage to the MTL (e.g. Tulving and Markowitsch, 1998; Mishkin *et al.*, 1998; Squire and Zola, 1998). As described in Section 1.6, Chapter 1, the unitary-system model of MTL function holds that both episodic and semantic memory rely on the same MTL regions and thus cannot be differentially impaired following MTL damage (e.g. Squire and Zola, 1998). The multi-system model, on the other hand, holds that the hippocampus is necessary only for episodic memory, and thus episodic memory can be selectively impaired with semantic memory being additionally impaired only with more extensive MTL damage (e.g. Mishkin *et al.*, 1997; 1998; Aggleton and Brown, 1999). The pattern of memory impairment previously reported in patients with DA has been interpreted as evidence in support of this dissociation (e.g. Vargha-Khadem *et al.*, 1997; Mishkin *et al.*, 1998; Gadian *et al.*, 2000). However, the question of how patients with DA are able to acquire their semantic knowledge base remains unclear.

For the purpose of this chapter it is important to distinguish between retrograde and anterograde semantic memory in amnesia. Retrograde semantic memory refers to semantic knowledge acquired before the onset of amnesia, whereas anterograde semantic memory refers to semantic knowledge acquired after the onset of amnesia. Some previous reports of adult amnesia have suggested that semantic memory is preserved following amnesia (e.g. Kinsbourne and Wood, 1975). However, these studies have focused on assessing retrograde semantic memories, such as evidenced by normal intellectual abilities. More recently, investigators have attempted to asses anterograde semantic memory (e.g. Tulving *et al.*, 1991; Hayman *et al.*, 1993; Hamann and Squire, 1995; Bayley and Squire, 2002), and it is these studies that will be discussed here.

Testing the ability to acquire novel information has not been well researched in children with amnesia, partly due to the apparent rarity of the condition. However, in the few reported cases anterograde learning is often assumed from average intellectual

abilities, mathematical and literacy skills (e.g. Wood *et al.*, 1989; Broman *et al.*, 1997; Vargha-Khadem *et al.*, 1997; and Gadian *et al.*, 2000). Consistent with previous reports of DA (e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000), the results in Chapter 4 indicated that the patients with DA who participated in the studies reported in this thesis were not impaired relative to their controls on tests of semantic memory including the comprehension and vocabulary subtests of verbal IQ, academic attainments, the pyramids and palm trees test of semantic association and category fluency, a test of semantic retrieval. The fact that the DA group has acquired an extensive amount of semantic knowledge despite having sustained hippocampal pathology during development suggests that semantic learning is possible under certain conditions.

6.1.1 Effects of repetition

Repetition is known to enhance memory in healthy adults (e.g. Tulving and Madigan, 1970; Baddeley and Longman, 1978) and it has been suggested that repeated exposure increases the likelihood for information to be context-free and therefore semantic (e.g. Baddeley *et al.*, 2001). A number of studies have investigated the effect of repeated exposure on explicit memory in patients with amnesia. For example, Warrington and Weiskrantz (1968) tested recall and recognition of word-lists following one, five or ten learning trials in patients with amnesia. Results showed that although patients were impaired relative to controls, the performance of the patients did improve with increasing repetition, particularly for recognition. In this study, participants were presented with repeated study trials in succession, i.e. massed-practice. Similarly, Holdstock *et al.* (2002) presented case YR, a patient with selective bilateral hippocampal pathology, with word definitions to learn with massed-practice. Memory was tested by cued-recall after each study trial (study-test) and recognition was tested after a delay. YR was unable to recall the definitions, or to recognise which definition was associated with which word, but she was able to discriminate old from new definitions. Thus, using a study-test, massed-practice procedure, YR demonstrated a limited capacity to learn new definitions (recognition of definitions only). It has been demonstrated that distributing study trials over sessions improves learning of information compared to presenting the study trials in succession (Schwartz, 1975; Underwood *et al.*, 1976; Baddeley and Longman, 1978), thus these studies may have underestimated learning ability following amnesia.

Other studies have attempted to teach patients with adult-onset amnesia new information (e.g. novel computer program commands or novel sentences) by distributing the study trials over a few days or weeks (e.g. Glisky and Schacter, 1989; Tulving *et al.*, 1991; Hayman *et al.*, 1993; Hamann and Squire, 1995; Bayley and Squire, 2002). These studies provide evidence both that adults with amnesia are able to learn new information and that repetition is one factor that influences learning. For example, patients with amnesia retained newly acquired information up to delays of ~30 months (Tulving *et al.*, 1991) and the efficiency of their learning improved with increased repetition of the material, as well as with increased meaningfulness of material and the absence or minimisation of pre-experimental and intra-experimental interference (e.g. Hayman *et al.*, 1993; Hamann and Squire, 1995). For example, allowing the patient to repeatedly study the new items before testing memory for the items (study-only) reduced the amount of interference from erroneous responses generated during tests, and resulted in better learning than procedures where memory was tested after each learning trial (study-test; Hayman *et al.*, 1993; Hamann and Squire, 1995). This is consistent with the rehabilitation literature on errorless learning (e.g. Wilson *et al.*, 1994; Hunkin *et al.*, 1998), in that patients with memory disorders learn information better when errors are prevented through repeated study exposure without intervening tests.

A small number of studies have also investigated learning of new information in patients with child-onset amnesia. In one study, new learning of word pronunciations and definitions was assessed in a case of child-onset amnesia (AC; Benedict *et al.*, 1998). Patient AC suffered from herpes encephalitis at 10 years of age that resulted in bilateral MTL damage (more extensive on the right). At time of testing she was 19 years of age, and had an average IQ. Results of the learning phase showed that AC was able to learn all of the correct pronunciations, but she required much longer (78 minutes) to do so than did controls (mean time: 15 minutes). By contrast, even though AC received nearly five times the amount of practice as controls she was unable to learn all of the definitions, reaching a plateau having learned eight of the twelve definitions. At a delayed memory test one week later, AC was able to correctly pronounce eight words, but, unlike controls, was unable to recall or recognise any of the definitions. When tested five weeks post-training she showed the same performance thereby demonstrating retention of oral reading but not word meaning.

A second study attempted to assess the ability of one patient with DA, Jon, (case DA1 in this thesis) to learn novel information from a video with repeated exposure over distributed study sessions (Baddeley *et al.*, 2001). Jon was presented with two videos based on newsreels of events from the years 1937 and 1957. Both of these videos contained information that depicted events that occurred before Jon was born (1977), and therefore information that was likely to be not well known to Jon. Details of this study are described in Section 6.2.1.2. Briefly, one of these videos (1937) was presented four times distributed over a 2-day period, while the other (1957) was presented only once. Both recall and recognition were tested immediately after the final presentation of each video and were re-tested the following morning after a delay of ~18 hours. After one presentation, Jon's immediate recall score was much lower than that of his matched controls. However, after four presentations, Jon's immediate recall score rose considerably, to a level similar to that of his controls. Jon's delayed (overnight) recall after four presentations, although slightly lower than controls, was better than delayed recall after one presentation. His immediate and delayed recognition after one and four presentations was at a similar level to that of his controls, with only delayed recognition after one presentation being slightly below theirs. The recognition performance of Jon and his controls improved slightly with repetition. Jon's performance indicates that his immediate and delayed recall and recognition benefited repeated exposure.

In summary, there is evidence for anterograde learning following amnesia in both adult and child-onset cases, and there is evidence that repetition plays an important role in this process. However, the results are somewhat conflicting in the child-onset cases, with one study providing evidence for a benefit of repetition on delayed memory of factual information (Baddeley *et al.*, 2001) and another study finding evidence only for the learning of pronunciations and not factual information (definitions; Benedict *et al.*, 1998). One reason for these conflicting findings may be related to the extent of pathology, as Jon had relatively selective hippocampal pathology, while AC had extensive MTL pathology. It is possible therefore that the benefits of repetition on factual learning may only be seen in patients with relatively selective hippocampal pathology. Experiments 1 and 2 address this issue in more detail by testing a group of patients with DA associated with relatively selective hippocampal pathology (as revealed on conventional MR scans) and examining the role of repetition in learning of factual information (Experiment 1) and lists of words (Experiment 2).

6.1.2 Effects of semantic organisation

Semantically related words are generally remembered better than unrelated words, at least if the related words are presented in order of category membership (e.g. Channon *et al.*, 1989; Channon *et al.*, 1993; Daum *et al.*, 1995). It is thought that semantically related materials are encoded using complex semantic associations to link two or more items and their study context, leading to superior recall over time relative to recall of unrelated materials (e.g. Channon *et al.*, 2000).

Investigation of encoding and retrieval in patients with adult-onset amnesia has produced consistent evidence with respect to their ability to benefit from semantically related material, but mixed evidence regarding when the effects occur: during encoding, consolidation or retrieval. For example, some authors suggest that the primary deficit in amnesia is an inability to spontaneously encode information at a deep and therefore semantic level (e.g. Cermak *et al.*, 1974; Cermak and Reale, 1978), resulting in extra benefit from semantically related material on memory only under certain conditions (e.g. short list-length, Cermak and Reale, 1978). Others suggest that patients with amnesia, can process and encode semantically related information, but are unable to store and consolidate the information, thereby resulting in a faster rate of forgetting compared to controls (e.g. Isaac and Mayes, 1999a), and thus a benefit of semantically related material at immediate but not delayed recall. A third possibility is that patients with amnesia show no benefit from semantic organisation in learning because of their restricted ability to perform and store the necessary comparative operations needed for the encoding of semantically related materials. This view is supported by one study showing that at both immediate and delayed recall patients with amnesia benefited less from the semantic relatedness of the word-lists than the controls, even when category-related words were clustered together (Channon *et al.*, 2000). However, their results may be due to inclusion of patients who have damage outside the temporal lobes. For example, Korsakoff amnesia can be associated with additional frontal lobe dysfunction (e.g. Torvik *et al.*, 1982; Harper *et al.*, 1987; Kopelman, 1991), which may have contributed to the ineffective encoding of semantically related information (Shallice *et al.*, 1994; Stuss *et al.*, 1994; Tulving *et al.*, 1994).

In summary, most, but not all, studies have found some benefit of semantic organisation on learning and/or recall of verbal information in adult-onset amnesia. The influence semantic organisation has on learning in DA is unknown, but as semantic

memory appears intact in these cases, it might be predicted that they would show a benefit of semantic organisation on learning consistent with controls. Experiment 2 addresses this prediction by examining the influence of semantic organisation on word-list learning in a group of patients with DA.

6.2 EXPERIMENT 1: NEWSREEL TASK

Previous research demonstrates that repetition is an important factor in the formation of anterograde semantic memories in amnesia, and, at least in DA, suggests that patients with amnesia may need more exposure than controls to reach the same total learning score (e.g. Benedict *et al.*, 1998; Baddeley *et al.*, 2001). The purpose of this experiment is to investigate in a larger group of patients than previously reported the role of repetition on immediate and delayed recall and recognition using the newsreel task of Baddeley *et al.* (2001). Based on the previous findings it is predicted that:

(a) Patients with DA will demonstrate a larger benefit from repetition relative to controls, both at immediate and delayed recall. This prediction would be supported by a significant Group (DA, control) by Type (recall, recognition) by Presentation (one, four) interaction, with follow-up analysis demonstrating that patients with DA show the largest difference on recall between one and four presentations.

(b) Patients will not differ from controls at immediate or delayed recognition independent of number of presentations. This prediction would be supported by the absence of significant effects of Group or interactions of Group by Presentation on recognition measures.

6.2.1 Methods

6.2.1.1 Participants

The two youngest participants, patient DA5 and control NC5 did not participate in the newsreel task due to the task being very demanding on attention. In addition, patient

DA11 has difficulty understanding people when they are not facing her and as a result she is unable to use the telephone and view television programs. Therefore, she did not participate in this task. Additionally, data were not available for one of the control participants. Therefore, a total of ten patients with DA and ten controls were included (including Jon (DA1) and the previously reported data for control NC1, Baddeley *et al.*, 2001). All of the participants have been described in detail in Chapter 2. The groups did not significantly differ with respect to age at test, verbal IQ or performance IQ.

6.2.1.2 Procedure

The newsreel task was presented as described by Baddeley *et al.* (2001), with one exception: due to the increase in sample size it was possible to counter-balance the videos across presentations. For example, for patient 1 and control 1, the 1937 video was presented once and the 1957 video was presented four times, whereas for patient 2 and control 2, the 1957 video was presented once and the 1937 video was presented four times. The controls viewed the videos in the same order as the patients.

The administration procedure was as follows: the videos were excerpts from the Pathe Movies newsreels from 1937 and 1957. All of the participants watched the videos with the experimenter present to ensure full attention throughout viewing and so that the film could be stopped by the experimenter at the appropriate point (after ~35 minutes). Participants were instructed to watch the film and give their full attention, as they would be asked questions about the film later on. On Day 1 the participants were shown video A for the first time in the morning and for the second time after their lunch break. As the last task on Day 1, participants were shown their first and only presentation of video B followed by 45 questions for video B (immediate memory test). The participant was given 5 seconds within which to free recall the answer before the examiner read four choices for recognition. The recognition choices were given independent of whether the participant responded to the recall question and independent of their recall accuracy. The questions ranged from specific details such as the names of people shown and the numbers of people involved in specific events, to more general issues mentioned, such as the state of the economy at a particular time. On the morning of Day 2, the participants were again asked the questions for video B (overnight delayed memory test) in the same manner as the evening before. As soon as the questions for video B were completed they were shown their third presentation of video A. At the end of Day 2, video A was shown for

the fourth and last time, and then the 45 questions for video A were asked (immediate memory) in the same manner as described for Video B. The following morning of Day 3 commenced with the questions for video A (overnight delayed memory).

6.2.2 Results

The analysis was conducted in accordance with the statistical procedure described in Section 2.3.2 in Chapter 2 using a four-way mixed-model ANOVA with a between-subjects factor of Group (DA, NC) and within-subjects factors of Type (recall, recognition), Time (immediate, delay), and Presentation (one, four). The dependent measure was percentage correct. All findings with a p-value of less than 0.05 are reported and predicted findings with a p-value less than 0.1 are described.

Table 6:1 and Figure 6:1 and 6:2 show the mean (±SEM) percentage correct for each group on immediate and delayed recall after one and four presentations.

Table 6:1 Immediate and delayed recall

Percentage correct	DA	NC
Immediate recall single	6.1 (1.85)	31.4 (5.00)
Immediate recall four	16.8 (4.90)	42.4 (5.17)
Delayed recall single	9.5 (3.13)	50.8 (4.70)
Delayed recall four	19.1 (4.84)	60.7 (4.65)

Mean (±SEM)

Figure 6:1 Immediate Recall

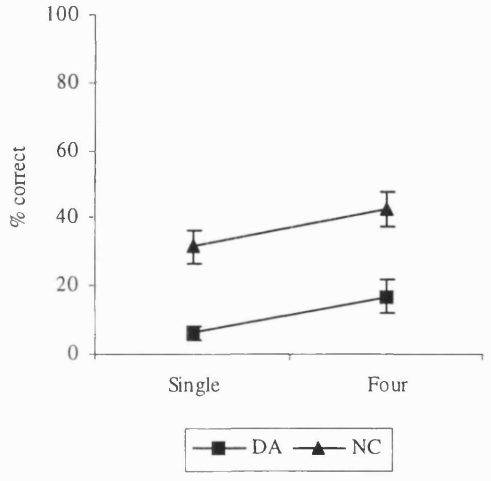


Figure 6:2: Overnight recall

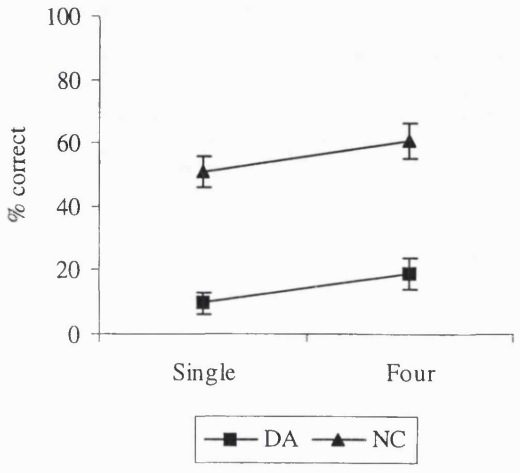


Table 6:2 and Figure 6:3 and 6:4 show the mean (±SEM) percentage correct for each group on immediate and delayed recognition after one and four presentations.

Table 6:2 Immediate and delayed recognition

Percentage correct	DA	NC
Immediate recognition single	41.5 (4.83)	69.7 (3.83)
Immediate recognition four	54.0 (5.34)	78.5 (3.17)
Delayed recognition single	39.8 (3.68)	71.3 (3.83)
Delayed recognition four	54.1 (5.02)	79.9 (3.08)

Mean (±SEM)

Figure 6:3: Immediate recognition

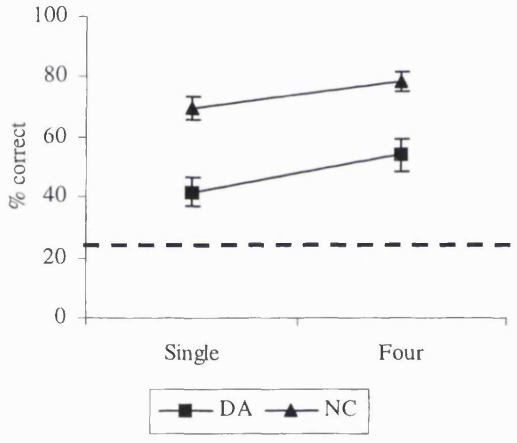
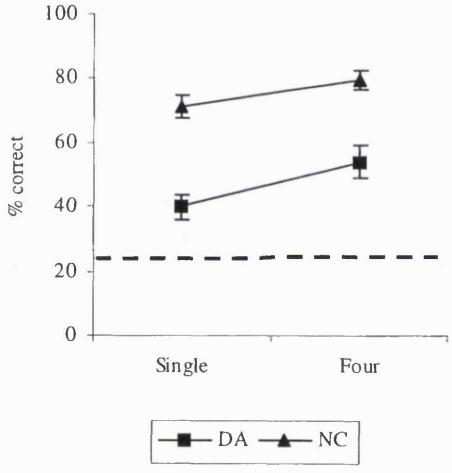


Figure 6:4: Overnight recognition



The dashed line represents chance performance (25%). The recognition memory performance was significantly above chance in both groups ($p < 0.05$).

The analysis revealed significant main effects for all factors[1]. Overall, the control group performed better than the DA group (Group: $F(1,18) = 35.62$; $p < 0.0001$), performance on recognition was better than on recall (Type: $F(1,18) = 422.64$; $p < 0.0001$), memory was better at delayed than immediate testing (Time: $F(1,18) = 33.12$; $p < 0.0001$) and memory was better after four compared to one repetition (Presentation: $F(1,18) = 22.37$; $p < 0.0001$). The analysis also revealed a significant interaction of Group

[1] The findings of this analysis were the same when patient DA1 and control NC1 were removed from the analysis.

by Type by Time ($F(1,18) = 27.93$; $p < 0.0001$). None of the other interactions were significant including the predicted Group by Type by Presentation interaction ($p > 0.1$).

Although Group by Type by Time interaction was not predicted, inspection of the data of Baddeley *et al.* (2001) suggested that it might be caused by a greater improvement in overnight relative to immediate recall in the control group than in the DA group. Follow-up analyses supported this prediction: there was a significant Type by Time interaction only for the control group ($F(1,9) = 96.25$; $p < 0.0001$), which occurred because recall was better at delay than immediate testing ($t(9) = -11.33$, $p < 0.0001$) while recognition did not differ at the two time points ($p > 0.1$). Another way of describing this effect is that the difference in performance between patients and controls was larger on delayed recall (mean difference = 41.48) than on delayed recognition (mean difference = 28.62).

6.2.3 Discussion

The purpose of this experiment was to examine the influence of repetition on immediate and delayed recall and recognition of information learned by video in patients with DA. Based on the preliminary findings of Baddeley *et al.* (2001) it was predicted that (a) patients with DA would show the largest difference on recall between one and four presentations, and (b) that there would be no group differences in recognition regardless of number of repetitions or delay. The results only partially supported the predictions. First, patients with DA were, as expected, impaired relative to controls in recall following one presentation, but, in contrast to predictions, they remained equivalently impaired on recall following four presentations. Second, in contrast to predictions, patients with DA were also impaired relative to controls on recognition both at immediate and delayed testing and following one and four repetitions, although both groups had a recognition memory performance significantly above chance. The patients' impairment in recognition was not so pronounced as that in recall at delayed testing, suggesting that recognition is relatively more preserved than recall in patients with DA.

Overall, performance improved in both patients and controls with repeated presentations, a result that is generally consistent with prior findings in DA (Benedict *et al.*, 1998; Baddeley *et al.*, 2001) and adult-onset amnesia (Warrington and Weiskrantz,

1968; Glisky and Schacter, 1989; Tulving *et al.*, 1991; Hayman *et al.*, 1993; Hamann and Squire, 1995; Bayley and Squire, 2002). The finding that, in spite of this evidence of learning, patients with DA still did not perform as well as controls is also consistent with some previous findings (e.g. Warrington and Weiskrantz, 1968; Benedict *et al.*, 1998), but is inconsistent with the prior report of one patient with DA using the same video task (Baddeley *et al.*, 2001). See Section 6.4 for further discussion of this discrepancy.

The finding that for both groups, recognition performance was better than recall, is also not unexpected as recognition is typically an easier task than recall (e.g. Mandler, *et al.*, 1969; Loftus, 1978). However, the finding that recall appeared to be disproportionately impaired in the DA group after a delay provides support for the view that recognition is relatively preserved in these patients. In other words, the patients' recognition was less affected by delay than was their recall. It is possible that the DA group's recognition performance reflects retrieval of de-contextualised semantic memory for the study material in the form of familiarity-based recognition (i.e. recognition of familiarity without retrieval of the contextual details of the learning episode).

The patients' poorer performance at delayed recall compared to controls appeared to be due to the greater increase in recall overnight by the controls rather than due to increased forgetting overnight in the patients. One explanation is that this reflects more successful consolidation overnight by controls of the study materials. Another explanation is that the immediate recognition test may have differentially affected the groups. One possible effect of this trial, as suggested by Baddeley *et al.* (2001) is that it may act as an extra learning trial. For individuals who were unable to recall the correct response, the recognition test then presented the correct answer as one of four options, and thereby may have served as additional exposure to the correct answer. The patients may either have simply not benefited from this additional exposure, or instead the recognition test may have interfered with their memory by serving as intra-experimental interference, a factor known to have a detrimental effect on learning in adult amnesics (e.g. Hayman *et al.*, 1993; Hamann and Squire, 1995). The fact that patients' performance appeared to remain constant over the delay, rather than to decline, supports the former explanation. Comparing patients' delayed performance with and without immediate tests could more formally test this (see Chapter 5 for this comparison in a nonverbal recall memory test).

Baddeley *et al.* (2001) interpreted their demonstration of overall near-normal recall in Jon following four repetitions of the video as indicating that Jon may have formed context-free semantic memory for the newsreel events with repeated presentation. The results of the current study support this conclusion to the extent that as a group the patients benefited from repetition; however, they do not replicate the prior finding that levels of recall memory were near-normal after four repetitions. One possible explanation is that memory after four repetitions does not reflect context-free semantic memory. In other words, even after four repetitions, memory may still be relatively reliant on episodic processes. If this interpretation is true, then it is possible that Jon shows relatively greater preservation of episodic memory processes than the average patient with DA. Indeed Jon's recall performance is higher than the DA group mean after one (immediate recall: Jon, 16.7%; DA, 4.7%; delayed recall: Jon, 27.8%; DA: 6.8%) and four (immediate recall: Jon, 55.6%; DA, 12.5%; delayed recall: Jon, 51.1%; DA: 15.5%) presentations. One way in which this possibility could be evaluated in future studies is by incorporating a source memory test to the procedure, to allow formal assessment of the extent to which the details of the context of learning are retained after one compared to four repetitions. Another possible explanation for the better performance of Jon compared to the DA group is that Jon acquires semantic memories more quickly than the average DA patient (i.e. requires fewer repetitions). This possibility could be investigated in future studies evaluating whether the DA group as a whole would eventually show near-normal recall if more than four repetitions were given. Finally, Jon's better performance could be related to his verbal IQ (108), which is the highest in the DA group (range excluding Jon: 80 – 105). Indeed a higher IQ may in itself reflect better semantic memory/learning ability in Jon. In order to examine this possible relation between IQ and recall performance in the DA group, a regression analysis was conducted. However, there was no evidence to suggest that immediate ($p > 0.1$) or delayed ($p > 0.1$) recall after one or four presentations was related to verbal IQ performance.

In summary, the results of the present study provide some evidence that repetition facilitates learning in DA and that recognition is relatively less impaired than recall in this group, but the pattern of findings does not exactly replicate those reported by Baddeley *et al.* (2001) with the same task. It appears that as Jon (DA1) demonstrated recall and recognition abilities far superior to those of the DA group, he may represent an example of the higher range in the distribution of abilities associated with DA.

6.3 EXPERIMENT 2: WORD-LIST LEARNING TASK

Previous studies of patients with adult-onset amnesia provide some evidence that their learning and/or memory may benefit from the semantic organisation of to-be-remembered materials (e.g. Warrington and Weiskrantz, 1982; Isaac and Mayes, 1999a). It is not known whether individuals with DA benefit from this factor. Examination of whether semantic organisation influences their learning and/or their later recall can provide evidence as to whether memory impairments are caused by a 'semantic encoding impairment' (e.g. Cermak *et al.*, 1974), an impairment in consolidation (e.g. Isaac and Mayes, 1999a) or both. Thus, in order to determine whether and how patients with DA benefit from semantic organisation, patients were tested in a word-list task based on the CAVLT-2 (Talley, 1993) and that used by Channon *et al.* (1989; 2000). The specific predictions were:

(a) As suggested by Channon *et al.* (2000) the semantic encoding deficit hypothesis (e.g. Cermak *et al.*, 1974) might predict that individuals with normal IQ would be encouraged to semantically process information presented in an organised way. However, according to this hypothesis, patients with amnesia would not be able to spontaneously encode semantically related information when presented in an unorganised way. This would be supported by a significant Group by List interaction with follow up analysis revealing that patients with DA recall more items from a list in which words were clustered together by category (CC) than from a list in which category exemplars were presented randomly (RC list), but unlike controls, would not show any extra benefit on the RC list compared to a list without a category structure (UC list).

(b) By contrast if the consolidation hypothesis (e.g. Isaac and Mayes, 1999a) is true, then patients with DA should benefit from semantic organisation on immediate memory measures, but not on delayed recall or delayed recognition, and should show more forgetting on the semantically related lists compared to the unrelated list.

(c) However, if the relative preservation of semantic memory in DA (Vargha-Khadem *et al.*, 1997; Baddeley *et al.*, 2001), facilitates their new learning, it is predicted that the both groups will show the expected category effects on all the measures: they will remember more from a list in which words were

clustered together by category (CC list) than from a list in which category exemplars were presented randomly (RC list) and more from both of these lists than from a list without a category structure (i.e. each word from a different category; UC list).

(d) In addition, based on prior findings of intact immediate memory span but impaired word-list recall after 20 minutes delay in patients with DA (Vargha-Khadem *et al.*, 1997), a similar general impairment in delayed recall is predicted in the present experiment, but the effect of list should remain.

(e) Finally based on prior findings that cases with DA are not impaired at delayed recognition of word-lists (Vargha-Khadem *et al.*, 1997; Baddeley *et al.*, 2001), a similar pattern of intact delayed recognition is predicted in the present experiment.

6.3.1 Methods

6.3.1.1 Participants

Eleven patients with DA and twelve controls participated in the word-list task due to patient DA4 leaving the study. However, all twelve DA patients and their controls completed the RC word-list. All of the participants have been described in detail in Chapter 2. The groups did not significantly differ with respect to age at test, verbal IQ or performance IQ.

6.3.1.2 Procedure

The general procedure of administration of the word-list tasks followed that of the CAVLT-2 (see Chapter 4). List A of 16 words was read by the experimenter five times and participants were asked to free recall as many words as they could remember after each presentation. Next, List B of 16 words was presented once for recall. Immediately after recall of list B the participants were asked to recall list A (immediate recall). Then after ~20-minute delay they were asked to recall list A (delayed recall) followed by a test of yes/no recognition in which they were asked to indicate whether each of 32 words (16

from List A and 16 distractors) read by the examiner were on list A or not (delayed recognition).

There were three types of word-lists, the CAVLT-2 (as reported in Chapter 4), and two others (see Appendix E) modeled on those used by Channon *et al.* (1989). Each type of word-list included two 16-word learning lists (Lists A and B) and 16 additional distractor words for the recognition test. The three types of lists were: (a) the clustered-categories (CC) word-lists (A (from Channon *et al.*, 1989) and B), each consisted of four items from four categories and were organised according to category membership, that is, all four words in each category were presented in turn. The purpose of this word-list was to test whether category organisation would improve recall. Therefore, to prevent a possible confound from interference from same-category words, the four categories used in List B were different from those used in List A; (b) the category-related randomly organised (RC) lists (A and B of the CAVLT-2) consisted of four items from four categories randomly organised throughout the list. The categories used for these lists were different from those used for the CC lists; and (c) the uncategorised-randomly organised (UC) word-lists (A (based on Channon *et al.*, 1989) and B) each consisted of 16 unrelated words. The target and foils on the recognition lists were ordered according to the target-foil sequence of the CAVLT-2 recognition list, and therefore included some items from the interference list (List B). The distractors of the CC and RC lists were semantically related to the target items. The lists did not differ in word frequency (Francis and Kucera, 1982) and there were an equal number of high and low frequency words within each list.

The three types of word-list were administered over three separate sessions, and the CC and UC lists were counter-balanced between-subjects. The RC word-lists (i.e. the CAVLT-2) was always given first as it was administered as part of the test battery reported in Chapter 4 (the results are also reported there), while the UC and CC word-lists were administered as the filler tasks for the deferred imitation task described in Chapter 5.

The data for all three types of list were used to compute indices based on those standardly computed for the CAVLT-2 as well as additional indices, and percentage correct/raw scores were analysed. The number of correct responses does not include any within-list repetitions. The influence of repetition on learning of the three types of list was assessed by *total learning score* (sum of the number of correct words recalled on each trial A1 to A5), and *rate of learning* (number of correct words recalled on trial A5 minus A1). Immediate memory was assessed by *immediate recall* (number of correct words

recalled on trial A6) and *immediate memory span* (number of correct words recalled on trial A1 plus B1). Delayed memory was assessed by *delayed recall* (number of correct words recalled from List A after ~20 minutes delay) and *delayed recognition* (number of correctly identified words from List A after ~20 minutes delay). Errors were scored as *intrusion errors* (words 'recalled' that were not on the list) and *perseveration errors* (repetition of a correct word previously recalled).

As described in Chapter 4, yes/no recognition tasks are prone to differences in response bias and discrimination between groups and/or conditions (e.g. MacMillan and Creelman, 1991). Therefore, as described in Chapter 4, further analysis of the recognition data was conducted to assess group and condition differences in discrimination (d^1) and response bias (c) between old ("yes") and new ("no") items. Using both hit rate and false alarms, d^1 and c (MacMillan and Creelman, 1991) were calculated separately for each participant.

6.3.2 Results

The analyses were conducted in accordance with the statistical procedure described in Section 2.3.2 in Chapter 2 using mixed-model ANOVAs with a between-subjects factor of group (DA, NC) and a within-subjects factor of list (CC, RC, UC), unless otherwise stated. Follow up analyses of main effects of List and significant interactions were conducted using separate t-tests with Bonferroni correction. All findings with a p-value of less than 0.05 are reported and predicted findings with a p-value less than 0.1 are described.

6.3.2.1 Immediate memory span

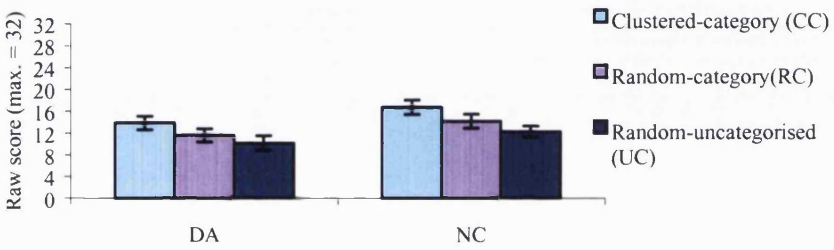
Table 6:3 and Figure 6:5 show the mean (±SEM) raw score for each group on immediate memory span (single trial recall) of each word-list (CC, RC and UC).

Table 6:3 Immediate memory span (Trial A1 + B1)

Raw score	DA	NC
Classified-category (CC)	13.8 (1.2)	16.7 (1.3)
Random-category(RC)	11.5 (1.2)	14.1 (1.3)
Random-uncategorised (UC)	10.1 (1.4)	12.3 (1.0)

Mean (±SEM)

Figure 6:5 Immediate span (Trial A1 + B1)



The analysis (ANOVA) revealed a significant main effect of List ($F(1.84, 38.64) = 11.13$; $p < 0.0001$). Follow up analyses revealed that, as predicted, recall of list CC was better than list UC ($p < 0.0001$) and recall of list CC tended to be better than list RC ($p = 0.059$), but recall of list RC did not significantly differ from recall of list UC ($p > 0.1$).

Neither the main effect of Group ($p > 0.1$) nor the Group by List ($p > 0.1$) interaction were significant.

6.3.2.2 Learning

6.3.2.2.1 Total learning score

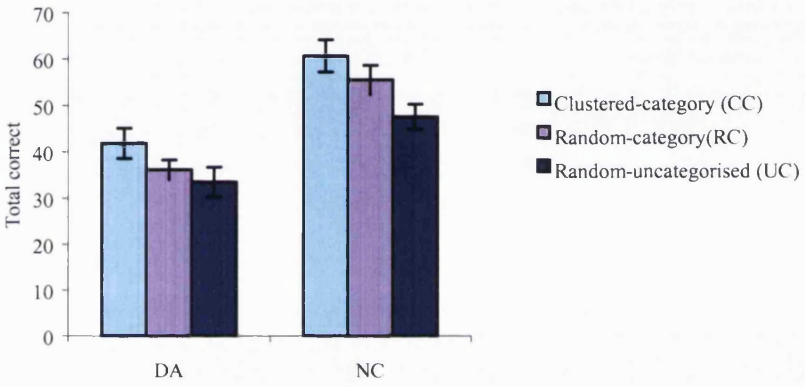
Table 6:4 and Figure 6:6 show the mean (±SEM) raw score for each group on total learning score (trials A1to A5) of each word-list (CC, RC and UC).

Table 6:4 Total learning score Trials 1 to 5

Raw score	DA	NC
Clustered-category (CC)	41.8 (3.3)	60.7 (3.5)
Random-category(RC)	36.1 (2.1)	55.5 (3.1)
Random-uncategorised (UC)	33.5 (3.2)	47.6 (2.7)

Mean (±SEM)

Figure 6:6 Total learning score (Trials 1 to 5)



The analysis (ANOVA) revealed a predicted main effect of List ($F(1.7, 35.77) = 17.84$; $p < 0.0001$). Follow up analysis revealed that, as expected, the learning of list CC was better than UC ($p < 0.0001$), and RC ($p = 0.044$) and the learning of list RC was better than UC ($p = 0.034$). There was also a main effect of Group ($F(1,21) = 20.98$; $p < 0.0001$), which occurred because control group learned more than the DA group across all list types. There was no Group by List interaction ($p > 0.1$).

6.3.2.2.2 Rate of Learning

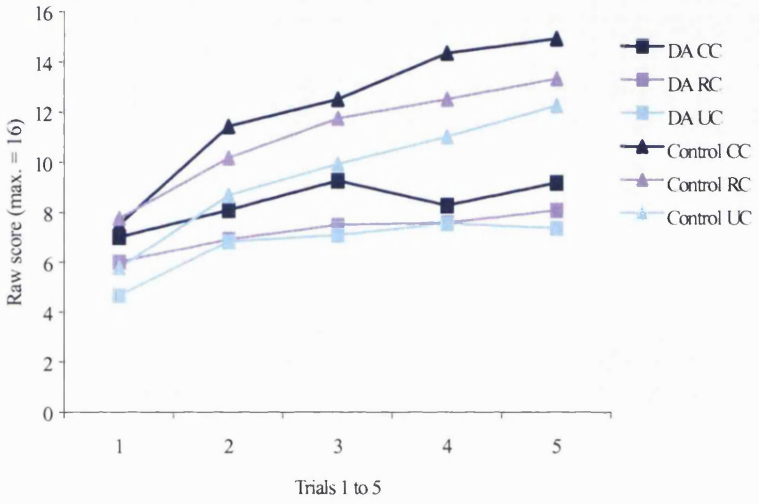
Table 6:5 shows the mean (±SEM) raw score for each group on slope of learning (Trial 5 – Trial 1) of each word-list (CC, RC and UC). Figure 6:7 shows the mean raw score on each learning trial for each group of each word-list (CC, RC and UC).

Table 6:5 Trial 5 minus trial 1

Raw score	DA	NC
Clustered-category (CC)	2.18 (0.67)	7.42 (0.60)
Random-category (RC)	2.08 (0.47)	5.58 (0.72)
Random-uncategorised (UC)	2.73 (0.59)	6.5 (0.51)

Mean (±SEM)

Figure 6:7: Mean raw score correct on five learning trials



In order to establish evidence of learning the number of words correctly recalled on Trial A1 was compared to that correctly recalled on Trial A5 using a mixed-model ANOVA with a between-subjects factor of Group (DA, NC), and within-subjects factors of Trial (trial 1, trial 5) and List (CC, RC, UC).

The analysis (ANOVA) revealed significant main effects for all factors. Overall the control group recalled more than the DA group (Group: $F(1,21) = 19.48$; $p < 0.0001$), Trial 5 was better than Trial 1 (Trial: $F(1,21) = 365.61$; $p < 0.0001$), and List ($F(1.64,34.33) = 20.23$; $p < 0.0001$). Follow up analysis revealed that recall of the list CC was better than list UC ($p < 0.0001$), and RC was better than UC ($p = 0.01$), and recall of list CC tended to be better than recall of list RC ($p = 0.08$).

These main effects were qualified by a significant Group by Trial interaction ($F(1,21) = 83.10$; $p < 0.0001$). None of the other interactions were significant ($p > 0.1$).

Follow up analysis of the significant Group by Trial interaction (using t-tests with Bonferroni correction) revealed no significant difference between the groups on Trial 1 (p

> 0.1), but that the control group recalled significantly more than the DA group on Trial 5 ($t(21) = 6.55$; $p < 0.0001$). Further analysis revealed that although both groups recalled more on Trial 5 than Trial 1 (DA: $t(10) = -7.00$; $p < 0.0001$; NC: $t(11) = -20.20$; $p < 0.0001$), the mean difference was larger in the control group (6.5) than in the DA group (2.3).

6.3.2.3 Immediate recall (after learning trials)

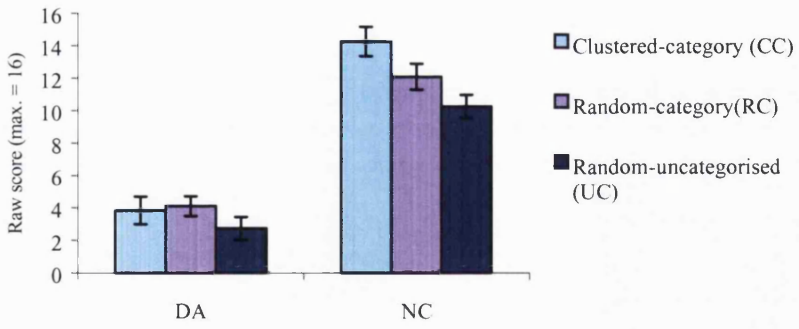
Table 6:6 and Figure 6:8 show the mean (±SEM) of the raw scores for each group on immediate recall of each word-list (CC, RC and UC).

Table 6:6 Immediate recall (trial A6)

Raw score	DA	NC
Classified-category (CC)	3.18 (0.84)	14.3 (0.91)
Random-category(RC)	4.08 (0.61)	12.1 (0.81)
Random-uncategorised (UC)	2.72 (0.70)	10.3 (0.71)

Mean (±SEM)

Figure 6:8 Immediate recall (trial A6)



The analysis (ANOVA) revealed a significant main effects List ($F(1.59,33.36) = 9.46$; $p = 0.001$). Follow up analysis revealed that, as predicted, recall of list CC was better than list UC ($p < 0.0001$) and recall on list RC tended to be better than on list UC ($p = 0.08$), but there was no significant difference between recall of list CC and list RC ($p > 0.1$). There was also a main effect of Group ($F(1,21) = 99.83$; $p < 0.0001$), due to the overall superior performance of the control group.

These main effects were modified by weak evidence for a Group by List interaction ($F(1.59, 21) = 3.55$; $p = 0.05$). Follow up analysis showed that patients with DA performed worse than the controls on all list types (CC: $t(21) = 8.40$; $p < 0.0001$; RC: $t(21) = 7.95$; $p < 0.0001$; UC: $t(21) = 7.53$; $p < 0.0001$) but that this difference was largest for the CC list (mean difference = 10.43) and smaller for the RC (mean difference = 8.00) and UC lists (mean difference = 7.52). Further analysis showed that the control group recalled more on list CC than list UC ($p < 0.0001$), but there was no significant difference between recall on list CC compared to RC ($p > 0.1$) or RC compared to UC ($p > 0.1$), while there were no differences among the lists for the DA group ($p > 0.1$).

6.3.2.4 Delayed memory

6.3.2.4.1 Delayed recall

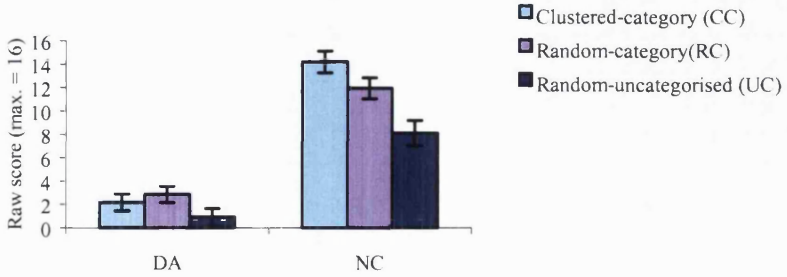
Table 6:7 and Figure 6:9 show the mean (±SEM) raw score for each group on delayed recall of each word-list (CC, RC and UC).

Table 6:7 Delayed recall (A7)

Raw score	DA	NC
Classified-category (CC)	2.18 (0.72)	14.2 (0.92)
Random-category(RC)	2.82 (0.70)	11.9 (0.90)
Random-uncategorised (UC)	0.91 (0.73)	8.08 (1.07)

Mean (±SEM)

Figure 6:9 Delayed recall (A7)



The analysis (ANOVA) revealed a significant main effect of List ($F(1.67, 35.06) = 20.69$; $p < 0.0001$). Follow up analysis revealed that, as predicted, recall of list CC was better than list UC ($p < 0.0001$) and recall on list RC was better than on list UC ($p =$

0.002), but there was no significant difference between recall on list CC and RC ($p > 0.1$). There was also a main effect of Group ($F(1,21) = 87.76$; $p < 0.0001$), due to the overall superior recall by the control group.

These main effects were modified by a Group by List interaction ($F(1.67, 35.06) = 8.11$; $p = 0.002$). Follow-up analysis revealed showed that the DA group were impaired relative to controls on recall of all three list types (CC: $t(21) = 10.11$; $p < 0.0001$; RC: $t(22) = 8.24$; $p < 0.0001$; UC: $t(21) = 5.44$; $p < 0.0001$), but the mean difference between the groups was largest the CC list (mean difference = 11.98) and smaller on the RC (mean difference = 9.08) and UC lists (mean difference = 7.17). Further analysis showed that the control group showed the expected pattern of better recall of list CC than UC ($p < 0.0001$) and a trend for list RC ($p = 0.07$), and better recall of list RC than list UC ($p = 0.02$). The DA group showed weak evidence for the expected advantage of the CC list over the UC list ($p = 0.065$), but showed no other differences.

6.3.2.4.2 Delayed recognition

6.3.2.4.2.1 Total correct

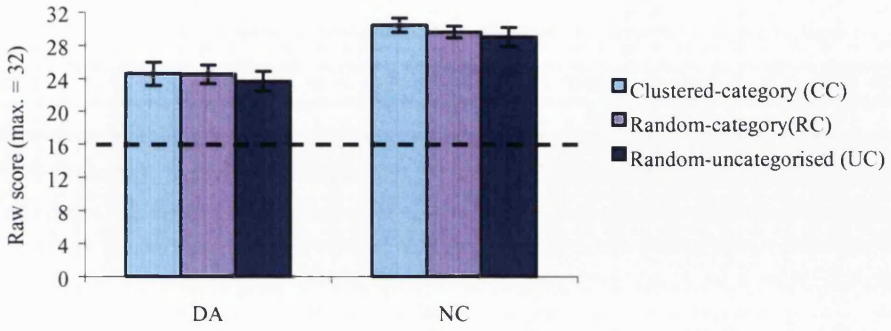
Table 6:8 and Figure 6:10 show the mean (±SEM) total correct for each group on delayed recognition of each word-list (CC, RC and UC).

Table 6:8 Delayed recognition of list A

Raw score	DA	NC
Classified-category (CC)	24.5 (1.42)	30.4 (0.84)
Random-category(RC)	24.5 (1.12)	29.6 (0.71)
Random-uncategorised (UC)	23.6 (1.21)	29.0 (1.15)

Mean (±SEM)

Figure 6:10 Delayed recognition of list A



The dashed line represents chance performance (raw score 16) on word-list recognition. Both groups performed significantly above chance on each word-list ($p < 0.0001$).

The analysis (ANOVA) revealed no evidence for a Group by List interaction ($p > 0.1$), or a main effect of List ($p > 0.1$). However, in contrast to predictions, there was a significant main effect of Group ($F(1,21) = 23.38$; $p < 0.0001$), suggesting that the control group recognised more than the DA group.

6.3.2.4.2.2 Signal detection analysis

In order to assess the participants discrimination sensitivity and their response criterion to old and new items, a d' and c score (Macmillan and Creelman, 1991) was calculated for each participant. A score other than 0 for d' indicates an ability to discriminate between old and new, whereas for c would indicate a response bias. Negative c values arise when the false-alarm rate exceeds the miss rate, and positive c values arise when the false alarm rate is lower than the miss rate (MacMillan and Creelman, 1991).

A majority of the twelve control participants (8 on the RC list, 9 on the UC list and 11 on the CC list) performed at ceiling for either hits or false alarms resulting in no estimate of d' or c. These ceiling effects prevented a between-subjects statistical analysis. However, within-subjects analyses (separate one-way ANOVAs with within-subjects factor of List) were performed on the d' and c scores of the DA group and these revealed no effect of List on either d' or c ($p > 0.1$).

However, as can be seen from Table 6:9 and Table 6:10 below, when d^1 was available, all of the participants, except for DA5 on the UC list, were above 0, indicating some level of discrimination between old and new.

The *c* scores of both the controls and the patients seem to be of a similar magnitude and are not far from 0, where 0 equates to no response bias. Although the *c* scores are small, they are negative for both the controls and the patients. The negative *c* scores suggest that both the control and the DA participants have an increased tendency to give a "yes" response, therefore, the false alarm rate exceeds the miss rate.

Table 6:9 d^l and c scores for the control participants across word-lists

	Classified-category (CC)				Random-category (RC)				Random-uncategorised (UC)			
Name	P hits	P false alarms	d^l	*c*	P hits	P false alarms	d^l	*c*	P hits	P false alarms	d^l	*c*
NC1	1.00	0.00	*	*	1.00	0.00	*	*	0.94	0.00	*	*
NC2	0.81	0.00	*	*	0.88	0.06	2.68	-0.47	0.75	0.00	*	*
NC3	1.00	0.00	*	*	1.00	0.00	*	*	1.00	0.19	*	*
NC4	1.00	0.00	*	*	1.00	0.06	*	*	1.00	0.06	*	*
NC5	0.44	0.19	0.73	-0.31	0.88	0.19	2.04	-0.53	0.50	0.19	0.89	-0.34
NC6	1.00	0.00	*	*	0.94	0.00	*	*	1.00	0.00	*	*
NC7	1.00	0.00	*	*	0.94	1.00	*	*	1.00	0.00	*	*
NC8	1.00	0.00	*	*	0.94	0.00	*	*	0.56	0.25	0.83	-0.41
NC9	1.00	0.00	*	*	0.69	0.19	1.38	-0.44	1.00	0.06	*	*
NC10	0.81	0.00	*	*	0.94	0.19	2.42	-0.56	1.00	0.00	*	*
NC11	1.00	0.06	*	*	0.75	0.00	*	*	0.94	0.19	2.42	-0.56
NC12	0.88	0.00	*	*	1.00	0.00	*	*	0.94	0.00	*	*

P = proportion

* = data not available

Table 6:10: d^l and c scores for the DA participants across word-lists

	Classified-category (CC)				Random-category (RC)				Random-uncategorised (UC)			
Name	P hits	P false alarms	d^l	*c*	P hits	P false alarms	d^l	*c*	P hits	P false alarms	d^l	*c*
DA1	0.75	0.13	1.82	-0.44	1.00	0.19	*	*	1.00	0.19	*	*
DA2	0.88	0.44	1.31	-0.66	0.88	0.38	1.47	-0.63	0.75	0.13	1.82	-0.44
DA3	1.00	0.13	*	*	0.94	0.25	2.21	-0.59	0.69	0.25	1.16	-0.47
DA4	*	*	*	*	0.88	0.06	2.68	-0.47	*	*	*	*
DA5	0.69	0.19	1.38	-0.44	0.69	0.56	0.33	-0.63	0.25	0.25	0.00	-0.25
DA6	0.63	0.19	1.21	-0.41	0.75	0.06	2.21	-0.41	0.69	0.13	1.64	-0.41
DA7	0.75	0.88	-0.48	-0.81	0.50	0.19	0.89	-0.34	0.81	0.00	*	*
DA8	0.88	0.38	1.47	-0.63	0.75	0.38	0.99	-0.56	0.63	0.06	1.85	-0.34
DA9	0.88	0.19	2.04	-0.53	0.88	0.06	2.68	-0.47	0.69	0.19	1.38	-0.44
DA10	0.81	0.50	0.89	-0.66	0.81	0.13	2.04	-0.47	0.69	0.44	0.65	-0.56
DA11	0.56	0.44	0.31	-0.50	0.69	0.50	0.49	-0.59	0.69	0.50	0.49	-0.59
DA12	0.56	0.31	0.65	-0.44	0.69	0.19	1.38	-0.44	0.81	0.31	1.38	-0.56

P = proportion

* = data not available

6.3.2.5 Errors

6.3.2.5.1 Total intrusion errors

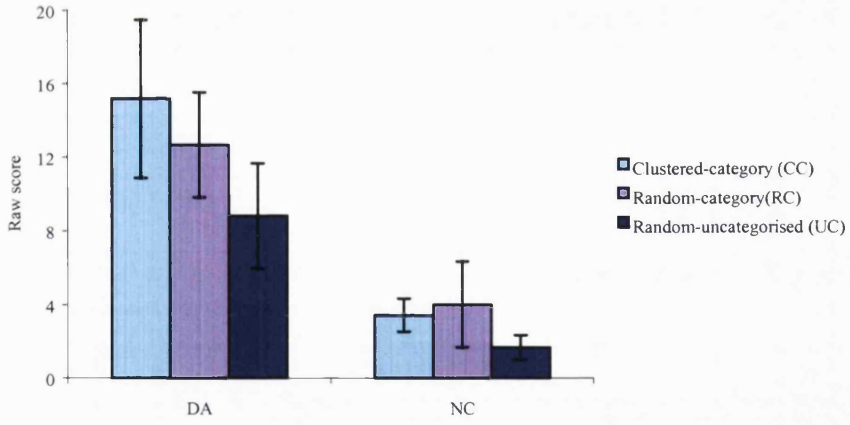
Table 6:11 and Figure 6:11 show the mean (±SEM) raw score for each group on total intrusion errors of each word-list (CC, RC and UC).

Table 6:11 Total intrusion errors (across all recall trials)

Raw score	DA	NC
Classified-category (CC)	15.2 (4.30)	3.42 (0.90)
Random-category (RC)	12.7 (2.86)	4.00 (2.33)
Random-uncategorised (UC)	8.82 (2.85)	1.67 (0.66)

Mean (±SEM)

Figure 6:11 Total intrusion errors



The analysis revealed no evidence for a Group by List interaction ($p > 0.1$), or a main effect of List ($p > 0.1$). However, there was strong evidence for a main effect of Group[2] ($F(1,21) = 11.34$; $p = 0.003$), where the DA group generated more intrusion errors than the control group.

[2] The residuals of list CC had heterogeneous variance therefore the group difference was confirmed using a Mann-Whitney U test ($U = 17.5$; $p = 0.002$).

6.3.2.5.2 Total Perseverative errors

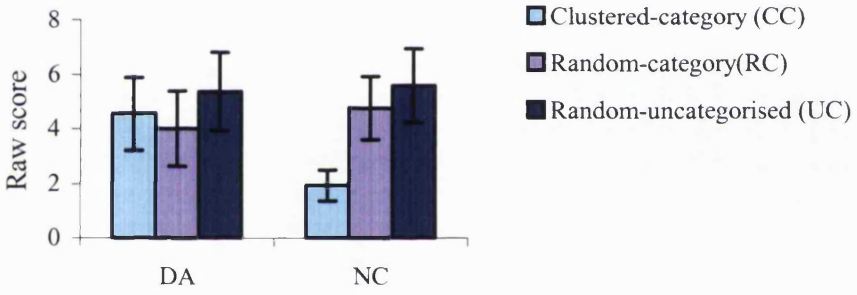
Table 6:12 and Figure 6:12 show the mean (±SEM) raw score for each group on total perseverative errors of each word-list (CC, RC and UC).

Table 6:12 Total perseverative errors (across all recall trials)

Raw score	DA	NC
Clustered-category (CC)	5 (1)	2 (1)
Random-category(RC)	4 (1)	5 (1)
Random-uncategorised (UC)	5 (1)	6 (1)

Mean (±SEM)

Figure 6:12 Total perseverative errors



The analysis revealed no significant effects of Group ($p > 0.1$), List ($p > 0.05$) or Group by List ($p > 0.1$).

6.3.3 Discussion

The aim of this experiment was to determine whether semantic organisation facilitated learning and/or memory for word-lists in patients with DA. The results showed that patients with DA benefited from this organisation during learning (total learning score, and rate of learning), but there was little evidence that it had any effect on their post-learning immediate or delayed recall, or delayed recognition. By contrast, the control group showed consistent effects of semantic organisation, with generally better performance with greater organisation, not only during learning (total learning and rate of learning) but also during recall (immediate memory span and recall, and delayed recall)

but not recognition. Overall, this pattern of results is inconsistent with the semantic encoding deficit hypothesis of amnesia (e.g. Cermak *et al.*, 1974). That is, patients' poor memory does not seem to be explained by an inability to take advantage of semantic organisation during encoding/learning. Instead, the recall results are generally more consistent with the consolidation hypothesis (Isaac and Mayes, 1999a).

6.3.3.1 Immediate memory

In this task there were two measures of immediate memory: immediate span (composite score of recall after single presentations) and immediate recall (recall after 5 presentations and an intervening interference trial).

Based on prior findings demonstrating intact immediate memory span in patients with DA on the CAVLT-2 (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000), it was expected that the DA group would not be impaired on this measure. The results from the immediate memory span measure supported this prediction: patients with DA remembered as many words as controls. Furthermore, against the semantic encoding deficit hypothesis, the recall of both groups benefited to the same extent from the semantic organisation of word-lists, such that both groups recalled more items from the semantically related lists than the unrelated list and recall was the best on the CC list. Although the finding that the patients with DA did not show any extra benefit on recall from spontaneous encoding of the randomly organised (RC) word-list compared to the unrelated (UC) word-list, this was not different to the performance of the control group (no Group by List interaction), suggesting that DA is not associated with a selective semantic encoding deficit. Unlike the immediate recall performance of the patients with adult-onset amnesia reported in the study of Channon *et al.* (2000) these results suggest that patients with DA not only have intact immediate memory span when presented with a supra-span word-list, but also benefit from the semantic relatedness of material at encoding. However, another interpretation is that the results differed between the two studies due to differences in the definition of immediate span. The 'immediate memory span' score reported in this chapter is obtained from the sum of recall after the first presentation of List A and the single presentation of List B, while Channon *et al.* (2000), only analysed recall after the first presentation of List A. To test whether the difference in results between the two studies was due to this methodological difference, the current data were reanalysed using an ANOVA model applied only to the first recall trial of List

A. The results were replicated: no Group difference ($p > 0.1$), a main effect of List ($p < 0.0001$) and no Group by List interaction ($p > 0.1$), thus ruling out the possibility that differences in definition of 'immediate memory span' accounted for the differences in findings.

The results from immediate recall (after 5 learning trials and an intervening interference trial) showed that the patients recalled fewer words than controls on all lists. Also the Group by List interaction revealed that only the performance of the control group benefited from relatedness of the lists. The finding that the DA group did not benefit from the semantic relatedness of the material to be remembered after five learning trials and recall of an interference list, but did show such a benefit on first-trial recall and list learning, suggests that any benefit from semantic encoding is short-lived. This does not support the semantic encoding deficit hypothesis, as this theory might predict that patients with DA should show a benefit on recall from the explicit organisation of the category-organised word-list. However, it is possible that the category-organised word-list is not explicit enough to encourage semantic encoding in patients with DA, and therefore consistent with the semantic encoding deficit hypothesis, patients with DA are unable to engage in spontaneous semantic encoding of the word-lists. This could be tested by informing patients with DA that the word-list is organised by category, to see if the patients benefit further from explicit instructions. For an example of a task that explicitly instructs patients with DA to encode semantically see Chapter 9.

One possible explanation for the poor performance on immediate recall in the DA group is that it was caused by interference. As discussed in the Introduction (Section 6.1.1), learning in patients with adult-onset amnesia is particularly sensitive to interference, and thus the interference word-list trial that occurred just before immediate recall may have particularly affected recall in the patients with DA. In order to examine this, an additional ANOVA was conducted comparing the performance of the groups on recall Trial A5 with that of Trial A6 (i.e. immediate recall of the first list (A) after recall of the interference list (B)). This analysis indicated that the DA group were more prone to interference from the intervening recall of List B, in that there was a significant Group by Trial interaction ($F(1,21) = 43.0$; $p < 0.0001$). Examination of this interaction revealed that although both groups recalled more on Trial 5 compared to Trial 6, this difference was greater in the DA group (mean difference = 4.63) than in the control group (mean

difference = 1.31). However, there was no effect of List ($p > 0.1$), suggesting that interference was not affected by the semantic relatedness of the study lists.

Another factor that may have resulted in poorer immediate recall is the study-test design of the learning trials. As discussed in the Introduction (Section 6.1.1), adults with amnesia tend to learn better in study-only procedures than study-test procedure (e.g. Hayman *et al.*, 1993; Hamann and Squire, 1995). These factors could be assessed in future studies by examining learning of word-lists in a study-only procedure, without interference trials.

Therefore, the findings of an equivalent list effect in controls and patients on immediate memory span do not support the semantic encoding deficit hypothesis, nor do the findings of no list effect in the DA patients on immediate recall. This lack of effect of list on the immediate recall of the patient group could be due to the recall of each list being affected by interference from list B and/or the study-test procedure.

6.3.3.2 Learning

It was expected based on prior findings (Benedict *et al.*, 1998; Baddeley *et al.*, 2001) and the results of Experiment 1 that patients with DA would learn with repetition. The evidence reported in this chapter does lend some support to this prediction, in that the DA group recalled more correct words on Trial 5 than Trial 1, indicating that recall increased with repetition. However, the DA group did not learn at the same rate as the control group and were impaired with respect to their total learning score. The total learning score and rate of learning slope indicated that both groups learned more on the semantically related lists than the unrelated list and that learning was best on the CC list. This demonstrates that both patients and controls benefited from explicit organisation of word-lists during learning, and that patients with DA, like controls, benefited from spontaneous encoding of the randomly organised category related word-list (RC), unlike that predicted by the semantic encoding deficit hypothesis.

6.3.3.3 Delayed memory

It was predicted that delayed recall would be impaired in the DA group relative to controls and indeed this was supported. It was also predicted that despite this impairment, the patients with amnesia would still show an effect of list in the same way as controls, if semantic memory facilitated learning in DA. However, the results were similar to those

reported by Channon *et al.* (2000), such that the control group showed better memory for the semantically related lists compared to unrelated list. In this study, the only hint of an effect of list type on delayed memory was that patients with DA showed a non-significant trend to recall more words from the CC than the UC list, suggesting some evidence for a benefit from semantic relatedness even after a 20 min delay. Overall, the findings are more similar to that predicted by the consolidation deficit hypothesis of amnesia (e.g. Isaac and Mayes, 1999a), with category effects being most pronounced during learning and weak or absent at delayed memory testing. Furthermore in support of the findings of Isaac and Mayes (1999a), the patients with DA showed greater forgetting relative to controls on the semantically related lists compared to the unrelated list.

Based on previous findings of relatively preserved recognition in patients with DA (e.g. Vargha-Khadem *et al.*, 1997; Baddeley *et al.*, 2001) it was predicted that the DA group would not be impaired relative to the control group on measures of recognition. Analysis of the total recognition score revealed that, although both groups performed significantly above chance, in contrast to predictions, the DA group was impaired relative to controls at recognition across all word-lists and neither group demonstrated any benefit from the relatedness of the lists. Examination of the proportion of hits and false alarms revealed that most of the control participants performed at ceiling, thus the degree of impairment in the patients with DA may even have been underestimated. The results of the signal detection analysis showed that both groups were able to accurately discriminate old from new items, and that the difference in recognition scores was not due to a difference between the groups in response bias (both groups had an increased tendency to respond "yes" and therefore generate an increase in false-alarms). Moreover, at least for the DA group (the controls were not analysed due to ceiling effects), there was no evidence to suggest that discrimination sensitivity or response criterion differed among the lists.

The finding that the recognition performance of the DA did not benefit from the semantic relatedness of the word-lists might be expected given that there was only weak evidence for such an effect on delayed recall (see above). However, the finding that the control group benefited from the semantic relatedness of the word-lists at delayed recall but not at recognition was unexpected. One possible reason for this is that the control group performed close to ceiling on the delayed recognition test. Therefore, this ceiling

effect might have underestimated any effect of list organisation on the performance of the control group.

6.3.3.4 Errors

Analysis of the types of errors made showed that the DA group produced more intrusion errors but not more perseverative errors than controls. The increase in intrusion errors in the DA group suggests that they have an increased tendency to confabulate. One possibility is that this is an indication of frontal lobe dysfunction, as patients with frontal dysfunction show increased confabulation (e.g. for a review see Schnider, 2001). Another possibility is that the increased intrusion errors reflect a memory strategy, such that the patients generate as many items as possible in the hope of producing some targets. The fact that patients did not produce more perseveration errors than did controls shows that they are able to remember items previously generated during the recall trial. Interestingly, this finding is different to that of category fluency, reported in Chapter 2. In the category fluency task, patients with DA produced more perseverative errors than controls. It was hypothesised in Chapter 2 that this may reflect that the patients have difficulty monitoring previously generated category-related items. However, this explanation is not supported by the findings reported here, as based on this explanation it would be predicted that patients with DA would show increased perseverative errors, particularly on the CC word-list.

6.3.3.5 Summary of word-list task

In summary, the findings of this experiment do not support the 'semantic encoding deficit' hypothesis of Cermak *et al.* (1974), in that immediate memory span, total learning score and rate of learning slope benefited from semantically related material in both patients with DA and controls to the same degree, even when required to spontaneously encode the semantic associations during learning, although patients were generally impaired relative to controls at learning the lists. Instead, these data offer some support for the consolidation/storage deficit hypothesis proposed by Isaac and Mayes (1999a) in that, unlike controls, patients with DA only showed weak evidence of benefiting from semantically related material after a 20-minute delay, and showed the greatest forgetting of the semantically related lists compared to the unrelated list. In relation to previous studies of DA, these data support the prediction that patients with DA can benefit from

the semantic relatedness of the to-be-remembered material, however, this is only at immediate memory span, total learning score and rate of learning slope.

6.4 GENERAL DISCUSSION: LEARNING IN DEVELOPMENTAL AMNESIA

The purpose of the experiments reported in this chapter was to investigate the roles of repetition and semantic organisation on learning and memory in patients with DA, with an aim to understand how these patients are able to acquire their relatively normal semantic knowledge base. One important finding that was consistent across both experiments is that patients with DA are able to learn new information: they were able to recall both factual information (Experiment 1) and words from a list (Experiment 2) even after a delay, and they were able to recognise previously learned information after a delay at a level greater than chance. However, the main evidence that patients benefited from repetition was that in both experiments, the DA group recalled more after repeated learning trials than on the first learning trial, although the patients' memory performance was still below that of controls. Given the impairments these same patients show in tests of episodic memory (see Chapter 4), these results do lend some support to Tulving's (1995) theory that some new memories can be acquired in the presence of a severe episodic memory deficit. The general conclusion from both experiments is that, while patients with DA do show evidence of new learning, they consistently score lower than controls (the only measure not to show a difference was immediate memory span in Experiment 2).

As described in Chapters 2 and 4, the DA group shows evidence of anterograde semantic learning with respect to average IQ and academic attainments, and they do not significantly differ from controls on tasks of semantic association and retrieval. Thus, they clearly can learn information about the world post-injury in a natural context. If this is the case, why did they appear to learn so slowly in the current experiments? One possible explanation for this persisting difference between the groups is that control participants have the advantage of using both episodic and semantic memory when remembering information, while patients are limited to semantic memory processes. Thus, episodic memory could still have contributed to controls' remembering even after repetitions, thereby elevating their performance relative to the group with DA. Another

possible explanation is that patients with DA simply learn more slowly and would require more repetitions than used in the present experiments (four in Experiment 1; five in Experiment 2) to show the benefits of repetition and to reach a total learning score (Experiment 2) and delayed memory similar to controls. This possibility could be tested in future experiments that use a larger number of repetitions. One additional factor that may facilitate learning in the natural environment, that was not examined in the current experiments, is repeated exposure to information in a variety of contexts. In the current experiments, the context of learning remained fairly constant across repetitions (varying only by time of day in Experiment 1). In a more natural context, learning, for example, that a pyramid is associated with a palm tree and not a fern tree (Pyramids and Palm Trees test, Chapter 4), may reflect evidence of learning that has occurred in many different contexts over time (e.g. lessons at school, reading books, watching television programs). This could be examined in future studies in which learning trials are presented across different spatio-temporal contexts and sensory modalities.

Baddeley *et al.* (2001) have suggested that an increase in memory performance with increasing presentations is evidence for semantic learning, in that memory (greater than memory span) for information after a single presentation makes more heavy demands on episodic memory, whereas memory after four presentations does less so. The results from their case study of Jon (DA1) using the newsreel task support this view: Jon's recall was impaired after one, but not four, repetitions of the newsreel video. However, the group of patients tested with the same task in the present study in Experiment 1 did not show the same pattern and remained impaired on recall even after four repetitions. The only evidence for a beneficial effect of repetition was that there was an overall improvement in performance after four repetitions.

The main evidence that repetition enhanced patients' memory in the word-list task (Experiment 2) is that the DA group recalled more on Trial 5 than Trial 1. The finding that the DA group with repeated exposure did not achieve a level of performance equivalent to controls in either of these experiments may be due to the nature of the tasks. The newsreel task was originally designed by Baddeley *et al.* (2001) with Jon's interests in mind, that is, current affairs. It is possible that the DA group as a whole may not have found the material very interesting and as a result of low motivation may have not attended well during viewing the videos. Although this would apply to both the patients and controls, it is possible that motivational factors play a key role in learning in patients

with amnesia due to learning requiring more effort in this group. This could be addressed by using material that is interesting for the whole group to learn. In a similar way the word-list task may not have been as easy to learn as other real-life associations (e.g. a pyramid is associated with a palm tree and not a fern tree; Pyramids and Palm Trees test) as the material may not have been meaningful to the patients. Moreover, the word-list task used a study-test design with massed practice, both factors that may hinder learning.

Although the level of learning demonstrated in these experiments is not a good as that predicted, this anterograde learning is greater than that demonstrated by YR, a patient with bilateral hippocampal pathology sustained in adulthood (Holdstock *et al.*, 2002). This greater capacity to learn new information in patients with DA may be a consequence of their early age at injury, and thus functional reorganisational capacity (e.g. Pascalis and de Haan, 2002), the development of better learning strategies or more selective pathology.

During learning of the word-list (total learning score and rate of learning), the DA group benefited from the semantic-relatedness of the information to be remembered, even when required to spontaneously make associations, and this was not different to the benefit experienced by controls (as indicated by no significant Group by List interaction). Similarly, in Chapter 2 analysis of the total learning score of related and unrelated word-pairs suggested that both the DA group and controls benefited from the semantic associations between the word-pairs. These findings suggest that like controls, patients with DA engaged in semantic encoding and formed semantic associations among the study items. These results argue against the 'semantic encoding deficit' hypothesis of amnesia (Cermak *et al.*, 1974). Instead, the DA group show abnormal forgetting over time independent of semantic organisation of the material and therefore a consolidation deficit, as the benefit of semantic organisation was only significant on immediate memory span (first learning trials), total learning score and rate of learning, but not on immediate recall (after an interference trial) and delayed recall.

While the results of this study are consistent with prior studies in showing some evidence of new learning in amnesia, there remains a debate as to whether this learning is due to intact semantic memory (Tulving *et al.*, 1991; Hayman *et al.*, 1993), residual episodic memory (e.g. Hamann and Squire, 1995) or nondeclarative memory (Benedict *et al.*, 1998; Bayley and Squire, 2002). For example, Benedict *et al.* (1998) interpret patient AC's learning of new oral reading as evidence of procedural learning, and argue and that her inability to recall and recognise any definitions demonstrates an inability to acquire

new semantic memories. However, further tests of nondeclarative memory for the words are needed to support this conclusion. For example, as suggested by the authors, a word recognition test would assess whether AC had formed a lexical store of the studied words, i.e. a representation of the word without its meaning. Alternatively, testing AC's ability to pronounce similar sounding words to those that she had studied would demonstrate whether she was able to transfer and adapt her newly learned skills. Moreover, the fact that in Experiments 1 and 2 patients with DA showed evidence of memory on explicit tests (recall and recognition) suggests that not all new semantic learning in patients with amnesia is due to procedural learning. Along these lines, Baddeley *et al.* (2001) have argued that the improvement in Jon's recall to near-normal levels with repeated exposure is evidence of preserved ability to acquire new semantic memories i.e. that he was able to formulate de-contextualised 'semantic' memories of the information through repetition. At a neuroanatomical level, it is argued that Jon's intact parahippocampal region can support new semantic learning (Mishkin *et al.*, 1998; Baddeley *et al.*, 2001). This is also supported by the significant relationship between semantic memory performance and grey matter density in the parahippocampal region in patients with DA, as reported in Chapter 4. However, another interpretation is that this learning reflects the effects of residual episodic memory. The results of the present experiments cannot rule out this rival hypothesis. Future studies in which the neural correlates of new learning in DA are examined using functional MRI could begin to address this issue by investigating whether the parahippocampal regions in fact mediate new learning.

6.4.1 Conclusion

There was limited evidence in Experiment 1 and 2 that individuals with DA learn with repetition, in that although performance increased with repetition, performance did not reach the level of controls. In Experiment 2 semantic organisation of the to-be remembered words facilitated immediate memory span, total learning score and rate of learning in both the DA group and controls, even when required to make spontaneous associations in the case of learning. However, unlike in controls, semantic organisation had no significant effect on patients' delayed recall. The results thus provide some evidence in support of the view that repetition may facilitate formation of de-contextualised semantic memories in patients with DA, but provide only weak evidence

for the possibility that semantic organisation of materials during learning facilitates formation of long-term semantic memories in these patients.

7 RECALL VERSUS RECOGNITION

As discussed in Section 1.7.3.1, Chapter 1, there is some debate as to whether both recall and recognition are impaired following damage to MTL structures (e.g. Aggleton and Shaw, 1996; Reed and Squire, 1997). A recent study of Jon (DA1, Baddeley *et al.*, 2001) suggested that DA may be associated with spared recognition in the presence of impaired recall, and proposed that intact parahippocampal regions may provide the neural substrate for preserved recognition.

This chapter assesses the performance of a group of patients with DA and a group of matched controls on a standardised test of recall and recognition enabling direct comparison between these types of memory (Doors and People task, Baddeley *et al.*, 1994). The results suggest that although the DA group is impaired relative to controls on recall and recognition memory, recall is more impaired than recognition, supporting the multi-system model of MTL function. Although recall performance did not significantly relate to hippocampal abnormality, verbal recognition was correlated with a reduction in grey matter density in the parahippocampal region and the hippocampal region. In addition, there was evidence of a relationship between visual recognition and hippocampal grey matter density. This will be discussed in more detail in Section 7.4.2

7.1 INTRODUCTION

Huppert and Piercy, (1979) were one of the first to suggest that amnesia may be associated with relatively preserved recognition in the presence of a deficit in recall. Although other studies confirmed this dissociation (e.g. Volpe *et al.*, 1983; 1986), it is possible that observed dissociations were due to differences in task difficulty (Mandler *et al.*, 1969) between recall and recognition memory tests. Thus a 10% decrease in recall may not be equivalent to a 10% decrease in recognition accuracy (Loftus, 1978).

In attempts to overcome these inequalities, authors began to equate the performance of control participants to that of the patients on recognition, and then compare recall performance between the two groups (e.g. Hirst *et al.*, 1986; 1988; Haist *et al.*, 1992). However, the studies came to different conclusions. Hirst *et al.* (1986; 1988) found that recall was impaired in patients relative to controls despite being matched on recognition performance, suggesting a recall-recognition discrepancy, in favour of recognition. Haist *et al.* (1992) found, however, that recall did not differ between the groups when matched on recognition performance. One possible reason for the discrepancies between these studies may be the different methods used to match performance of patients with amnesia and control subjects. To address this, Haist *et al.* (1992), in their second experiment, used the same forced-choice recognition task and matching procedure as described by Hirst *et al.* (1988). Despite this additional task, the authors found no group difference in recall when matched on recognition performance. Other possible reasons for the discrepant findings may be location of pathology. As noted by Haist *et al.* (1992), three of the six patients reported by Hirst *et al.* (1988) had amnesia resulting from a ruptured anterior communicating artery aneurysm. It is therefore possible that the impaired recall performance was due to additional frontal lobe dysfunction (e.g. Janowsky *et al.*, 1989; Squire, 1992). Alternatively, as noted by Haist *et al.* (1992), the patients in their study had lower recognition scores than the patients reported in Hirst *et al.* (1988). The patients reported by Haist *et al.* (1992) were of mixed-aetiology and two of the patients with non-Korsakoff amnesia had diencephalic damage. The reduced recognition performance in this group may have been due to additional damage to the thalamic nuclei, regions thought to be involved in recognition memory (e.g. Aggleton and Brown, 1999).

In studies of patients with fornix damage or relatively selective hippocampal damage, recall is typically found to be more impaired than recognition (e.g. Aggleton *et al.*, 2000; Holdstock *et al.*, 2000a). Moreover, recognition memory in these patients is sometimes in the normal range (e.g. Aggleton and Shaw, 1996) although this is not always the case (e.g. Reed and Squire, 1997).

To enable direct comparison between recall and recognition, Baddeley and colleagues devised a test of visual and verbal recall and recognition equating task difficulty (The Doors and People Test, 1994). This was achieved by making the recognition task difficult (using distractor items that are similar to the target) and the recall task easy (meaningful stimuli presented over three learning trials), and also by using scaled scores.

7.1.1 Adult-onset hippocampal pathology and the Doors and People test

The Doors and People test has been administered to patients with fornix damage or relatively selective hippocampal damage and, as before, the findings are inconsistent across different studies. Some of these studies have found recognition to be preserved relative to recall (e.g. Aggleton *et al.*, 2000; patient YR in Holdstock *et al.*, 2000a), whereas others have found impairments in both recall and recognition (e.g. patients AB, LJ and PH in Manns and Squire, 1999; patient VC in Cipolotti *et al.*, 2001; 7 patients in Manns *et al.*, 2003b). However, none of the studies reporting impairments in both measures quantitatively analysed structures outside of the MTL, but assumed the integrity of other brain regions based on visual inspection alone. Yet, as demonstrated in Chapter 3, conventional MR techniques may not be sufficient in detecting the full extent of pathology associated with amnesia.

Furthermore, case VC (Cipolotti *et al.*, 2001), a patient who had hippocampal volumes (~45%) of a similar reduction to YR (~46%, Holdstock *et al.*, 2000a) and yet a recognition impairment similar to the patients reported by Manns and Squire (1999) and Manns *et al.* (2003b), also had mild volume reduction in the left parahippocampal cortex, and amygdala damage was reported on conventional MR imaging. This additional damage may have contributed to the recognition memory impairment, as the parahippocampal cortex is known to be involved in recognition memory (e.g. for a review see Aggleton and Brown, 1999; Brown and Aggleton, 2001), and damage to the amygdala

may include additional damage to the entorhinal cortex (e.g. Amaral, 1999), a region also involved in recognition memory (e.g. Meunier *et al.*, 1993).

An alternative possibility for the differences in findings reported in patients with adult-onset hippocampal pathology, could be the extent and location of bilateral hippocampal volume reduction (Manns and Squire, 1999: 22-34%; Holdstock *et al.*, 2000a: ~46%; Cipolotti *et al.*, 2001: ~45%; Manns *et al.*, 2003b: 10-45%). The smaller hippocampal volume reduction in the patients reported by Manns and Squire (1999) and in some of the patients reported by Manns *et al.* (2003b) compared to YR (Holdstock *et al.*, 2000a) may have resulted in greater recognition impairments. For example, according to the findings of Baxter and Murray in the monkey, (2001a; 2001b; but see Zola and Squire, 2001) smaller hippocampal volume reduction can result in greater impairments in recognition possibly due to partial hippocampal lesions adversely affecting the activity of connected structures that are more important for recognition memory, such as the rhinal cortices. Alternatively, according to recent findings from studies using fMRI, there is functional segregation along the anterior-posterior axis of the hippocampus (e.g. Strange *et al.*, 1999), suggesting that differences in the location of hippocampal pathology may be associated with different memory profiles.

7.1.2 Child-onset hippocampal pathology and the Doors and People test

Recall and recognition memory, as tested using the Doors and People test, has been reported in two patients with amnesia associated with selective hippocampal pathology sustained early in development. Broman *et al.* (1997) presented case MS, a patient who sustained relatively selective hippocampal pathology following a hypoxic-ischaemic episode between 7 and 8 years of age. MS was administered the Doors and People test at 27 years of age. He obtained overall scaled scores at floor for both recall and recognition memory and thus showed no discrepancy in performance on the two measures. Although MS is presented as a case with selective hippocampal pathology, the extent of his pathology has not been quantified with either volumetric measurements or with whole-brain quantitative analyses, such as voxel-based morphometry. Based on his medical history (cardiac arrest at age 7 years 6 months and respiratory arrest at 8 years followed by epilepsy) it is possible that MS has pathology extending beyond the hippocampus (e.g. Bachevalier and Meunier, 1996; Markowitsch, *et al.*, 1997; Reed *et al.*,

1999; Caine and Watson, 2000; Grubb *et al.*, 2000), which may account for his severely impaired memory performance.

The recall and recognition performance of patient Jon (DA1), was also assessed using the Doors and People test (Baddeley *et al.*, 2001). Jon's performance was compared to that of two age-, sex-, and IQ-matched controls. For visual and verbal recall, Jon scored between the 1st and 5th percentile, indicating severe impairments, while he scored between the 50th and 75th percentile, i.e. within the normal range, on the verbal and visual recognition subtests. A possible reason for Jon's recall-recognition discrepancy may be that, consistent with animal models of amnesia (e.g. Mishkin *et al.*, 1997; 1998; Aggleton and Brown, 1999; Aggleton and Pearce, 2001; Brown and Bashir, 2002), intact parahippocampal regions support recognition memory.

7.1.3 Memory function in relation to extent of MTL abnormality

As discussed in Chapter 4 some authors have found a relationship between memory impairment and hippocampal pathology, such that decreases in hippocampal volume are associated with impaired recall memory performance (e.g. Isaacs *et al.*, 2000; Kopelman *et al.*, 2001; Vargha-Khadem *et al.*, 2001). Some studies, in humans, have found evidence to suggest that hippocampal volume reduction may also be associated with recognition memory impairments (e.g. Cahn *et al.*, 1998; Jernigan *et al.*, 2001; Kopelman *et al.*, 2001). In monkey studies, the role of the hippocampus in recognition memory is a topic of lively debate. Some authors have found no relationship between extent of hippocampal pathology and recognition memory (e.g. Zola *et al.*, 2000; Zola and Squire, 2001), while others have found evidence to suggest an inverse relationship (e.g. Baxter and Murray, 2001a; 2001b), such that the greater the reduction in hippocampal volume the better the recognition performance. Several possible mechanisms for this inverse relationship were proposed by the authors, including that partial hippocampal lesions could adversely affect, through abnormal electrical activity, the activity of connected structures that are more important for recognition, such as the rhinal cortex.

According to the multi-system model of MTL function, the parahippocampal region supports some aspects of recognition memory, such as familiarity-based item recognition, independently of the hippocampus (e.g. Mishkin *et al.*, 1997; Aggleton and Brown, 1999; Brown and Aggleton, 2001; Brown and Bashir, 2002). In humans, the

relationship between degree of pathology in the parahippocampal region and memory performance is less well researched compared to the relationship with the hippocampus partly due to a limited number of patients with selective lesions to the parahippocampal region reported in the literature, and due to volume measurements in these regions being less well established compared to the methods used to measure hippocampal volumes (e.g. it is difficult to reliably define the boundaries of the cortices within the parahippocampal region). However, Mayes *et al.* (1999) and Holdstock *et al.* (2002) presented patient JL, a patient with greater volume reduction in the right compared to the left perirhinal cortex, as well bilateral damage to the superior, middle and inferior temporal gyri, but not the hippocampus. JL's neuropsychological profile indicated normal performance on tests of recall and recognition (Doors and People test), suggesting that these may not depend on the perirhinal cortex in humans. Animal studies, on the other hand, have found a significant relationship between damage to the perirhinal cortex and recognition memory (DMNS), suggesting that the greater the volume reduction, the greater the recognition impairment (e.g. Baxter and Murray, 2001).

7.1.4 Summary

In summary, it appears that the role of the hippocampus in recognition memory remains controversial. There is evidence to support both the unitary-system model of MTL function (e.g. Squire and Zola, 1998), that the hippocampus and parahippocampal region supports both recall and recognition memory (e.g. Broman *et al.*, 1997; Manns and Squire, 1999; Cipolotti *et al.*, 2001; Manns *et al.*, 2003b), and the multi-system model of MTL function (e.g. Mishkin *et al.*, 1997; Aggleton and Brown, 1999), that recognition memory can be supported by extra-hippocampal structures (Aggleton *et al.*, 2000; Holdstock *et al.*, 2000a; Baddeley *et al.*, 2001). It is possible that, consistent with the multi-system model of MTL function, patients who demonstrate impairments in both recall and recognition memory (e.g. Broman *et al.*, 1997; Manns and Squire, 1999; Cipolotti *et al.*, 2001; Manns *et al.*, 2003b) have pathology extending beyond the hippocampus. Indeed in some of these patients more extensive pathology has been suggested by the authors themselves (e.g. Cipolotti *et al.*, 2001). However, without confirmation from quantitative MR imaging techniques (e.g. volume measurements and voxel-based morphometry), this remains a hypothesis.

It seems that a greater decrease in hippocampal volume is associated with greater recall memory impairment (but possibly, at least in the monkey, lesser recognition deficit). An increase in pathology in the parahippocampal region seems to be associated with an increase in recognition memory impairment. These relationships will be examined in this chapter using hippocampal T_2 values, hippocampal volumes, and voxel-based morphometry (VBM). As T_2 values and volume measurements of the parahippocampal region are not available for the patients reported in this thesis, the relationship between recognition memory performance and pathology in the parahippocampal region will be investigated using VBM only.

7.1.5 Specific aims and predictions

This chapter aims to establish whether relatively selective hippocampal pathology (as revealed on conventional MRI) sustained in early development is associated with a recall-recognition discrepancy in favour of recognition. To this end the Doors and People test was administered to a group of patients with DA and matched controls.

Based on the discussion above it is predicted that:

(a) Patients with DA will show impaired recall and spared recognition memory relative to controls.

(b) Patients with DA will not show a verbal-visual memory discrepancy, due to the hippocampal pathology being bilateral in patients with DA.

(c) Consistent with both models of MTL-function, impairments in recall memory in the patient group will be associated with extent of hippocampal pathology, while according to the multi-system model, recognition memory performance in the patient group will be associated with extent of abnormality in the parahippocampal region but not the hippocampus.

7.2 METHODS

7.2.1 Participants

The details of the participants are reported in Chapter 2. Briefly, the groups did not differ significantly ($p > 0.1$) on age at test, verbal IQ or performance IQ.

7.2.2 Procedure

The Doors and People test was administered in the same way to all participants according to the published manual (Baddeley *et al.*, 1994), and therefore the test procedure will be described only briefly here. The test consists of four subtests: verbal recall, visual recall, verbal recognition, and visual recognition. The subtests are described in the order in which they were administered.

Verbal recall (People test): Four colour pictures were presented on separate cards for 3 seconds each. Each card depicted a photograph of a person together with a printed name and occupation. After viewing the fourth picture, participants were immediately asked to recall each name cued by the occupation (e.g. "What is the name of the doctor?"). This procedure (presentation of four pictures and cued recall) was repeated until all four names were correctly recalled or up to a maximum of three times. Errors were not corrected. Finally, delayed cued recall of the names was tested after the second subtest (visual recognition) was administered (~10 minutes later).

Visual recognition (Doors test): This subtest consisted of two study-test blocks. In the study phase of the first block, participants viewed photographs of 12 doors each presented for 3 seconds on separate sheets, accompanied by an appropriate but ultimately unhelpful label, for example "this is a church door". Immediately thereafter, participants viewed 12 arrays of four doors, each array on a separate sheet, and tried to identify the door from the study list. By ensuring that the items within each array all have the same label (e.g. church doors), the role of verbal labelling was minimised. This same test was repeated with a second block consisting of 12 photographs of doors presented in exactly the same way as the first study-test block, but with foils that were more similar to the doors on the study list than on the first block.

Visual recall (Shapes test): Participants copied each of four simple line drawings, resembling crosses. They then tried to draw the four shapes from memory. This procedure (presentation of four simple designs and recall from memory) was repeated until all four shapes were correctly recalled or up to a maximum of three times. Errors were not corrected. For the second and third trials, participants viewed the shapes but did not copy them. Delayed recall of the shapes was tested after the fourth subtest (verbal recognition) was given (~10 minutes later).

Verbal recognition (Names test): This subtest consisted of two study-test blocks. In the study phase of the first block, 12 female names (both a first name and a surname)

were presented on separate cards for 3 seconds each, and the experimenter read them out loud. Immediately thereafter, participants saw 12 lists of four names, each list presented on a separate card, and tried in each case to select the name from the study list. All four names in each group used the same first name and the same initial letter for the surname. This same test was repeated with a second block consisting of male names presented in exactly the same way as the first study-test block, but the foils and the names from the study list differed only in one syllable of the surname.

7.2.3 Scoring

The Doors and People test enables raw scores to be converted into scaled scores for each subtest. Ten of the patients obtained raw scores below the range for which the testing manual provides normative data for scaled scores. This combined with the finding that two control participants obtained overall scaled scores at floor, prevented an accurate estimate of the recall-recognition discrepancy score (i.e. the difference between overall recall scaled score and overall recognition scaled score is converted to a discrepancy scaled score). This may be due to the lack of normative data for participants under the age of sixteen years or due to the Doors and People test being insensitive to low raw scores. Therefore, for the purpose of group comparisons, raw scores for each subtest were converted to percentage correct scores and the data were analysed in a mixed model ANOVA as described in Section 7.3.1.1.

7.2.4 Memory function in relation to extent of MTL abnormality

Linear regressions were conducted in order to examine the relationship between hippocampal abnormality and memory performance in the DA group. The hippocampal abnormality was measured using volumetrics and T_2 values as described in Chapter 3. As left and right hippocampal volumes (Pearson correlation: 0.82; $p = 0.006$) and T_2 values (Pearson correlation: 0.71; $p = 0.01$) were highly correlated, an average volume and T_2 value was calculated in order to obtain bilateral measures of hippocampal abnormality. The relationship between bilateral hippocampal volume and memory was then examined using separate linear regressions with each memory measure (percentage correct) and with age at scan as a covariate; the same analysis was repeated with the bilateral hippocampal T_2 value. Age at scan was included as a covariate because the patients with DA were not matched on age at test.

The VBM analysis was conducted in accordance with the procedure described in Section 3.2.3.4 Chapter 3, except that a the correlation with the memory factors listed above was calculated in the DA group only. That is, only intra-group values were entered into the design with age at scan as a covariate. Significance was determined in accordance with the method described in Section 3.2.3.4, Chapter 3. To apply small volume correction in the hippocampal and parahippocampal region a sphere with a radius of 15 mm centred at ±27, -15, -15 (encompassing many regions in the MTL) was used in order to obtain a conservative correction.

7.3 RESULTS

The data are analysed in three ways. First, in order to compare the performance of the all twelve patients with DA to that of matched controls, a between-subjects analysis of variance was conducted using percentage correct[1]. This analysis was conducted in accordance with the procedure described in Section 2.3.2, Chapter 2.

Second, in order to compare the previously reported performance of Jon with the group of eleven patients with DA, and that of other patients reported in the literature (Broman *et al.*, 1997; Manns and Squire, 1999; Aggleton *et al.*, 2000; Holdstock *et al.*, 2000a; Cipolotti *et al.*, 2001) scaled scores were calculated and included in Table 7:2. Scaled scores have a mean of 10 and a standard deviation of 3, therefore the normal range is 4-16 scaled scores (10±2SD). Scaled scores are reported for two reasons: i) the age at test varies across studies and therefore percentage correct scores may be confounded by age effects which cannot be adjusted for across tests; ii) in some studies control participants' raw scores were not reported, and therefore scaled scores provided the only frame of reference.

Finally, the data were also analysed in order to explore relationships between memory performance and hippocampal and parahippocampal integrity.

[1] The results did not change when Jon and his control NC1 were excluded from the group analysis.

7.3.1 Memory performance

7.3.1.1 The Doors and People subtests

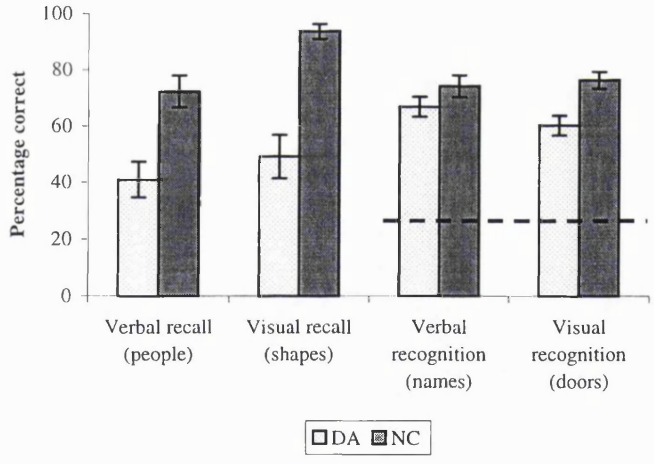
Table 7:1 and Figure 7:1 show the mean (±SEM) percentage correct for patients with DA and controls on each of the four subtests.

Table 7:1 The Doors and People subtests

	DA	NC
Verbal recall (people)	41.0 (6.29)	72.2 (5.64)
Visual recall (shapes)	49.1 (7.66)	93.5 (2.61)
Verbal recognition (names)	66.7 (3.60)	74.0 (3.88)
Visual recognition (doors)	60.1 (3.46)	76.0 (3.00)

Mean (±SEM)

Figure 7:1 The Doors and People subtests



The dashed line represents chance performance (25%) on recognition tests. Recognition performance was significantly above chance in both groups on verbal recognition ($p < 0.0001$) and visual recognition ($p < 0.0001$).

An ANOVA with a between-subjects factor of Group (DA, NC), a within-subjects factors of Task (recall, recognition) and Type (verbal, nonverbal) revealed a significant

main effect of Group ($F(1,22) = 30.14$; $p < 0.0001$)[2], suggesting that overall the control group performed better than the DA group. Unexpectedly there was no main effect of Task ($p > 0.1$) but there was a main effect of Type ($F(1,22) = 6.25$; $p = 0.02$), suggesting that performance on visual memory measures was better than on verbal memory measures. As predicted the Group by Task interaction was significant ($F(1,22) = 12.26$; $p = 0.002$), but unexpectedly, the Group by Type ($F(1,22) = 4.83$; $p = 0.039$) and Type by Task ($F(1,22) = 12.14$; $p = 0.002$) interactions were also significant. As predicted the Group by Task by Type interaction was not significant ($p > 0.1$).

Follow up analysis of the predicted Group by Task interaction revealed that the control group performed better than the patients with DA on recall memory ($t(22) = 5.30$; $p < 0.0001$) and recognition memory ($t(22) = 2.77$; $p = 0.011$), but, as predicted, the mean group difference was larger on recall (37.85) than recognition (11.63).

Follow up analysis of the unexpected Group by Type interaction revealed that the control group performed better than the patients with DA on verbal memory ($t(22) = 3.43$; $p = 0.002$) and visual memory ($t(22) = 6.53$; $p < 0.0001$), but the mean group difference was larger on visual (30.21) than verbal memory (19.27). Further follow up analysis revealed that although the patients with DA did not show a discrepancy ($p > 0.1$), the control participants performed better on the visual than on the verbal memory subtests ($t(11) = -3.89$; $p = 0.003$).

Follow up analysis of the Type by Task interaction revealed that visual recall was better than verbal recall ($t(23) = -3.42$; $p = 0.002$), but there was no significant difference between visual and verbal recognition ($p > 0.1$).

7.3.1.2 Across study comparisons

Table 7:2 shows the scores for the recall and recognition indices of the Doors and People test. The recall index is a composite scaled score of verbal (people) and visual (shapes) recall subtests, and the recognition index is a composite scaled score of verbal (names) and visual (doors) recognition subtests. The scaled scores have a mean of 10 and a standard deviation of 3. These indices allow the comparison of recall and recognition performance across studies using individuals differing in age. When scaled scores were

[2] Tests of homogeneity of variance revealed that the variance between the groups was not homogeneous on the visual recall (shapes) subtest. Therefore the main effect of group was confirmed with a Mann-Whitney U test ($U = 13.5$; $p < 0.0001$).

not reported in the original articles cited, scaled scores were obtained using the Doors and People test manual. Some of the raw scores were below the range for which the testing manual provides normative data for scaled scores, and therefore these were assigned the lowest possible scaled score and are indicated by the < sign. Only the data of the three patients with selective hippocampal pathology were included from the study reported by Manns and Squire (1999) and only the three patients with fornix damage were included from the study reported by Aggleton *et al.* (2000). The data reported by Manns *et al.* (2003b) were not included for comparison, as details were not available from the original article.

Table 7:2 Mean or individual scaled scores (percentile) for the recall and recognition indices of the Doors and People test

	Recall shapes + people	Recognition doors + names
DA n = 11 (Jon (DA1) removed)	4 (1-5%)	5 (5%)
Baddeley *et al.* (2001) Jon n = 1	<3 (<1%)	11 (50-75%)
Broman *et al.* (1997) n = 1	<3 (<1%)	<3 (<1%)
Manns and Squire (1999) n = 3	3 (1%)	3 (1%)
Aggleton *et al.* (2000) n = 3	3 (1%)	5 (5%)
Holdstock *et al.* (2000a) YR n = 1	3 (1%)	13 (75-90%)
Cipolotti *et al.* (2001) VC n = 1	4 (1-5%)	<3 (<1%)

In comparison to the performance of Jon (Baddeley *et al.*, 2001), the eleven patients with DA performed at a level similar to his on recall memory, but not as well as him on recognition memory. Possible reasons for Jon's better recognition memory will be discussed in more detail in Section 7.4. However it is worth noting here that this was not related to any differences in IQ or age at test, as there was no significant relationship between recognition memory and verbal IQ, performance IQ or age at test within the patient group ($p > 0.1$).

As shown in the table, all of the patients reported in the literature (Broman *et al.*, 1997; Manns and Squire, 1999; Aggleton *et al.*, 2000; Holdstock *et al.*, 2000a; Baddeley *et al.*, 2001; Cipolotti *et al.*, 2001), and the DA group, perform at a similar level on recall memory. Jon and patient YR (Holdstock *et al*, 2000a) perform the best on recognition memory, and show the largest discrepancy between recall and recognition memory (8 and

10 point difference respectively), while the group of patients with DA perform like the patients with fornix damage reported by Aggleton *et al.* (2000).

7.3.2 Memory function in relation to extent of MTL abnormality

In order to examine the relationship between memory performance in the DA group and hippocampal abnormality, separate linear regression analyses were conducted with bilateral hippocampal volumes and bilateral hippocampal T_2 values as independent measures and with verbal recall, visual recall, verbal recognition, visual recognition (percentage correct) as dependent measures. VBM correlation analyses were also conducted in order to examine the relationship between hippocampal and parahippocampal region grey matter density and memory performance in the DA group. Age at test was included as a covariate in all analyses.

7.3.2.1 Hippocampal volumes and memory performance in the DA group

The results of the linear regression analyses are shown in Tables 7:3.

Table 7:3 Bilateral hippocampal volumes and memory performance in the DA group

Percentage correct	R Square	β (confidence interval)	t	df	p-value
Verbal recall (people)	0.68	0.00054 (-0.04, 0.05)	0.31	2, 6	0.77
Visual recall (shapes)	0.59	0.026 (-0.03, 0.08)	1.14	2, 6	0.30
Verbal recognition (names)	0.17	-0.016 (-0.05, 0.02)	-1.06	2, 6	0.33
Visual recognition (doors)	0.13	-0.0034 (-0.04, 0.04)	-0.21	2, 6	0.84

None of the regression analyses reached significance.

7.3.2.2 Hippocampal T_2 values and memory performance in the DA group

The results of the linear regression analysis are shown in Table 7:4.

Table 7:4 Bilateral hippocampal T_2 values and memory performance in the DA group

Percentage correct	R Square	β (confidence interval)	t	df	p-value
Verbal recall (people)	0.16	-0.12 (-2.33, 2.10)	-0.12	2, 9	0.91
Visual recall (shapes)	0.08	-0.12 (-3.0, 2.74)	-0.08	2, 9	0.94
Verbal recognition (names)	0.23	-0.87 (-2.09, 0.34)	-1.62	2, 9	0.14
Visual recognition (doors)	0.22	-0.66 (-1.84, 0.52)	-1.27	2, 9	0.24

None of the regression analyses reached significance.

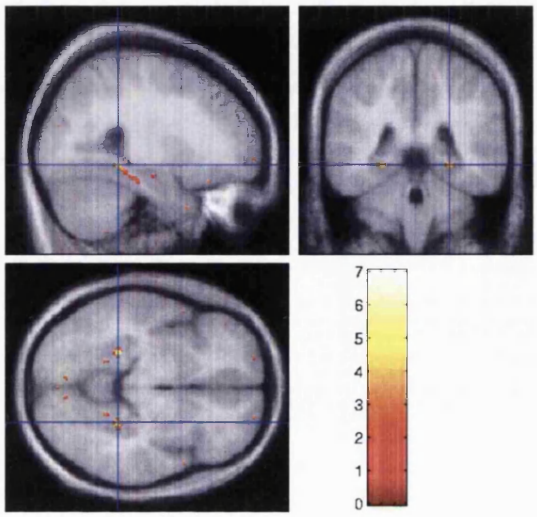
7.3.2.3 VBM correlation with memory performance in the DA group

Neither recall measure correlated significantly with hippocampal or parahippocampal grey matter density, but both recognition measures did. Verbal recognition correlated significantly with grey matter density in the parahippocampal region at a corrected level and in the hippocampal region at an uncorrected level, suggesting that a decrease in grey matter density in these regions was associated with a decrease in verbal recognition memory performance. Visual recognition correlated significantly only with hippocampal grey matter density, suggesting that a decrease in grey matter density in the region of the hippocampus was associated with a decrease in visual recognition memory performance.

Figure 7:2 shows the correlation between grey matter density in the parahippocampal region and verbal recognition (whole-brain corrected, WBC). Figure 7:3 shows the correlation between grey matter density in the hippocampal region and verbal recognition (predicted uncorrected, PUC). Figure 7:4 shows the correlation between grey matter density in the hippocampal region and visual recognition (small volume corrected, SVC).

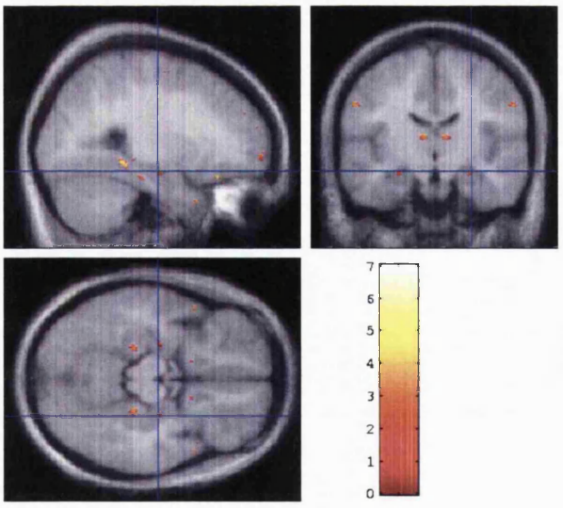
Parahippocampal region and verbal recognition

Figure 7:2 Parahippocampal region ± 26, -40, -8 (4mm; WBC: z = 5.73; p = 0.006)



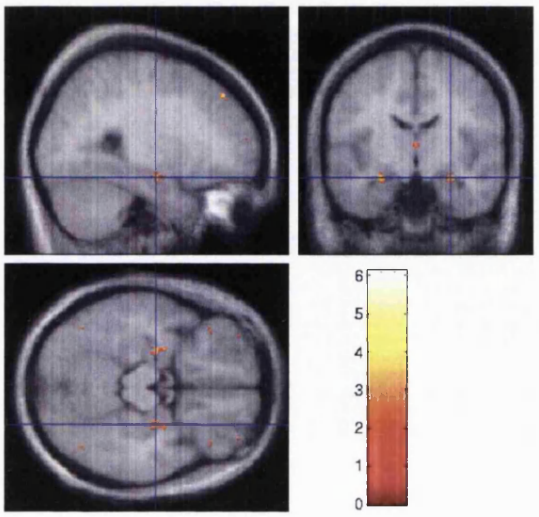
Hippocampal region and verbal recognition

Figure 7:3 Hippocampal region ± 27, -14, -15 (4mm; PUC: z = 3.47; p < 0.0001)



Hippocampal region and visual recognition

Figure 7:4 Hippocampal region ± 27, -10, -16 (4mm; SVC: z = 4.61; p = 0.023)



7.4 DISCUSSION

This chapter aimed to establish whether DA was associated with impaired recall but preserved recognition memory, a recall-recognition discrepancy. This chapter also aimed to establish whether recall and recognition memory was associated with the integrity of the hippocampus and parahippocampal region. The findings reported in this chapter supported the prediction that patients with DA would be impaired on recall memory, but this did not correlate significantly with hippocampal abnormality. There was also evidence to suggest that recognition memory was impaired in patients with DA relative to controls, but as predicted, this was less impaired than recall memory suggesting some evidence for a recall-recognition discrepancy. There was evidence to suggest that verbal recognition memory was associated with the integrity of the parahippocampal and hippocampal regions, and visual recognition was associated with the integrity of the hippocampal region.

7.4.1 Memory performance

It was predicted, based on the bilateral pathology associated with DA, that these patients would not show a discrepancy between visual and verbal memory. This

prediction was supported, but the analysis also suggested that the control group performed better on visual than verbal memory. As percentage raw scores and not scaled scores were included in the analysis it is possible that the discrepancy in the control performance reflects differences in task difficulty between visual and verbal memory measures normally accounted for by scaled scores. This is somewhat supported by the finding that both groups performed better on visual than verbal recall memory measures. However, as the overall discrepancy was only found in the performance of the control group, and as both groups showed a better performance on visual recall, these differences between visual and verbal memory do not affect the main finding of interest, that recall memory was more impaired than recognition memory in the DA group relative to controls.

The finding that patients with DA were impaired on visual and verbal recall measures was predicted by both models of MTL function, and is consistent with reports of adult-onset hippocampal pathology (e.g. Manns and Squire, 1999; Holdstock *et al.*, 2000a; Cipolotti *et al.*, 2001; Manns *et al.*, 2003b) and previous reports of child-onset hippocampal pathology (e.g. Broman *et al.*, 1997; Baddeley *et al.*, 2001). However, the additional finding that, despite visual and verbal recognition being impaired relative to controls, the impairment in recognition was less than that in recall is consistent with the multi-system model of MTL function. The impairment in recognition memory, although not predicted, possibly reflects the additional benefit of intact episodic memory in the control group.

This relatively preserved recognition compared to recall performance is similar to that of one adult-onset case of selective hippocampal pathology (YR, Holdstock *et al.*, 2000a) and a previously reported case of DA (Jon, Baddeley *et al.*, 2001), but is different to that reported by some studies which show equivalent impairments in both recall and recognition memory (e.g. Broman *et al.*, 1997; Manns and Squire, 1999; Cipolotti *et al.*, 2001). However, as shown in Table 7:2 both YR and Jon showed a larger discrepancy between recall and recognition than the group of patients with DA. Indeed both YR and Jon had overall recognition memory scaled scores within the normal range, whereas the group of patients with DA (excluding Jon) had a mean overall recognition memory scaled score 1.3 standard deviations lower than the normal population mean, but greater than that of the patients reported by Broman *et al.* (1997), Manns and Squire (1999), and Cipolotti *et al.* (2001). As explained in Section 7.2.3, low mean scaled scores in the group of patients with DA may be a consequence of some of the members of the group being

younger than the age range of the scaled norms and/or floor effects. Thus the use of scaled scores might have underestimated the performance of the group of patients with DA.

Despite this potential underestimation in performance, the patients with DA had the same overall recognition memory scaled score as that of the patients reported by Aggleton *et al.* (2000) who had fornix damage. Fornix damage is thought to result in a similar memory profile to that of hippocampal damage as the fornix is the principal efferent pathway between the hippocampus and the diencephalon (e.g. Aggleton *et al.*, 2000). These findings demonstrate the range of performance that is associated with reportedly selective hippocampal pathology.

Interestingly, in a recent study by Yonelinas *et al.* (2002) a similar range of performance was found when comparing recall with recognition in a group of fifty-six mild hypoxia patients with suspected selective hippocampal pathology. Although they did not administer the Doors and People test, they attempted to equate recall and recognition by scaling the performance of the patients to that of the mean and standard deviation of a control group (z-scores). These findings revealed that although a majority of the patients were more impaired at recall than recognition, some patients were more impaired on recognition than recall and others were not impaired on either (see Figure 1b, Yonelinas *et al.* 2002). It is difficult to assume that all of the cases had selective hippocampal pathology without structural imaging data on these patients. However, these results further highlight the variability in recall and recognition memory performance associated with hypoxia cases.

One possible reason for the variability in performance of different patients is variable damage to structures that support recognition memory, such as the parahippocampal region (e.g. for reviews see Aggleton and Brown, 1999; Brown and Aggleton, 2001). Indeed mild pathology in the left parahippocampal cortex has been reported in patient VC (Cipolotti *et al.*, 2001) and bilaterally in the parahippocampal region in one patient (PH, see Manns and Squire, 2001) reported in Manns and Squire (1999). Therefore, YR and Jon may have parahippocampal regions that are more intact than those of the group of patients with DA. This is discussed in more detail below.

Other reasons for this range in performance in patients with reportedly selective hippocampal pathology could be differences in the location of hippocampal pathology (e.g. Strange *et al.*, 1999), or hypoactivity in other memory structures (e.g. Warburton *et*

al., 2001; Jenkins *et al.* 2002). These alternative possibilities will be discussed in more detail in Chapter 10.

7.4.2 Memory function in relation to extent of MTL abnormality

Hippocampal volumes, T_2 values, and grey matter density did not relate to recall performance in patients with DA. As discussed in Chapter 4, these findings may reflect a lack of statistical power in the analysis caused by small sample size and lack of dynamic range in hippocampal measures and/or behavioural scores. Nor was there any relationship between grey matter density in the parahippocampal region and recall memory. The most significant correlation between verbal recognition and grey matter density was seen in the parahippocampal region, but there was also a suggestion of a correlation in the hippocampal region. In addition, there was evidence of a relationship between visual recognition memory performance and hippocampal grey matter density indicating that a reduction in performance is associated with a reduction in grey matter density. Unfortunately, unambiguous interpretation of the combined findings in terms of the multi-system or the unitary-system model is difficult. The findings that both hippocampal and parahippocampal grey matter density show correlations with recognition memory performance appear broadly inconsistent with the multi-system model. However, the fact that the most significant and extensive (see Figure 7:2) correlation with verbal recognition was seen in the parahippocampal region perhaps indicates that some elements of both the unitary-system model and the multi-system model are helpful, in that both hippocampal and parahippocampal regions play a role in recognition memory, with the parahippocampal region more dominant.

7.4.3 Conclusion

In conclusion, the findings suggest that although the DA group is impaired at both recall and recognition relative to the controls, this impairment is larger for recall than recognition memory performance. These findings are broadly consistent with the multi-system model of MTL function. The examination of the relationship between memory performance and extent of MTL abnormality was complicated by the lack of power in the analyses; hence the main prediction that recall memory performance would be associated with hippocampal abnormality was not supported. The correlation of recognition memory performance with grey matter density in the parahippocampal and/or hippocampal regions

are interesting and reflect the need for further neuroimaging analysis in a larger group of patients.

8 ITEM VERSUS ASSOCIATIVE RECOGNITION

Previous studies of DA, have reported an impairment on multi-trial tasks of object-place and voice-face associative recognition but not one trial single item or intramodal associative recognition tasks (Vargha-Khadem *et al.*, 1997). These findings suggest that the hippocampus supports cross-modal and object-place associative recognition, but not single item or intramodal associative recognition, consistent with the multi-system model of MTL function (e.g. Mishkin *et al.*, 1997; Aggleton and Brown, 1999). The first experiment reported in this chapter aimed to replicate these findings in a larger group of patients with DA than previously reported, relative to a group of matched controls, using the same tasks of single item and associative recognition (one trial and multi-trial) described by Vargha-Khadem *et al.* (1997). Experiment 2 aimed to further examine the role of the hippocampus in object-place memory using a newly devised task of one trial object-place recognition memory. Whilst the results of Experiment 1 largely replicated the previous findings, deficits were also found on the multi-trial intramodal associative recognition task involving unfamiliar faces and place-only recognition. Furthermore, in Experiment 2, the patients with DA were impaired at recognising the location of objects (both object-place and place-only recognition memory) when presented with single arrays for study and subsequent recognition after a two-minute delay. These findings suggest that the hippocampus is required for some types of associative recognition when the memory load is high, but also for object-place associative recognition independent of size of memory load.

8.1 INTRODUCTION

As discussed in Chapter 1, declarative memory is subserved by the MTL and its cortical connections (e.g. Squire and Zola, 1991; Eichenbaum *et al.*, 1994; Mishkin *et al.*, 1997; Aggleton and Brown, 1999, but see Gaffan *et al.*, 2002). However, the specific contribution of the different components of the MTL system to declarative memory remains unclear. Some authors propose that the MTL-cortical circuit functions as a unitary system supporting both single item and associative recognition memory (e.g. Stark and Squire, 2000; 2001; 2003; Stark *et al.*, 2002). Others propose that the parahippocampal region supports single item and intramodal associative recognition memory but that the hippocampus plays a special role in object-place and other cross-modal associative recognition memory (e.g. Sutherland and Rudy, 1989; Kroll *et al.*, 1996; Vargha-Khadem *et al.*, 1997; Aggleton and Brown, 1999; Mayes *et al.*, 1999; 2001; 2002; Brown and Aggleton, 2001).

8.1.1 Animal studies of recognition memory

As described in Chapter 1, animal imaging and recording (*c-fos* and electrophysiology) studies have suggested that the parahippocampal region supports single item and intramodal (e.g. object-object stimulus pairs) associative recognition (e.g. Zhu *et al.*, 1995; Brown and Xiang, 1998; for a review see Brown and Aggleton, 2001), while the hippocampus reportedly plays a special role in supporting object-place associative recognition (e.g. Brown and Xiang, 1998; Wan *et al.*, 1999).

Animal lesion studies provide converging evidence for the notion that the parahippocampal region can support single item (e.g. Murray *et al.*, 1989; Meunier *et al.*, 1993; Gaffan, 1998; Gaffan *et al.*, 2000; but see Zola *et al.*, 2000) and intramodal associative recognition memory (e.g. Spiegler and Mishkin, 1981; Murray *et al.*, 1993). However, the role of the hippocampus in object-place recognition memory is not supported by recent lesion studies (Belcher *et al.*, 2000; Lowther *et al.*, 2001; Malkova and Mishkin, 2003). For example, the findings of Malkova and Mishkin (2003) suggest that one trial object-place associative recognition can be supported by structures other than the hippocampus. Indeed in the latter study of only monkeys with combined parahippocampal, presubiculum and parasubiculum (posterior parahippocampal cortices) lesions were impaired on a task of one trial two-pair object-place associative recognition

memory. Lesions to the parahippocampal cortex alone or to the hippocampus, parasubiculum and presubiculum did not result in such impairments. The deficit observed in previous studies of monkeys with hippocampal lesions (e.g. Parkinson *et al.*, 1988; for a review see Gaffan, 1998; Murray *et al.*, 1998; Hamstead *et al.*, 2001) thus apparently resulted from additional combined injury to the posterior parahippocampal cortices.

8.1.2 Adult human studies of recognition memory

Human imaging studies, using cross-category stimulus pairs such as house-face (e.g. Henke *et al.*, 1997) or colour-object (Yonelinas *et al.*, 2001) have reported increased activation in the hippocampus and parahippocampal region during the encoding (Henke *et al.*, 1997) and retrieval (Yonelinas *et al.*, 2001) of pairs relative to single items. Furthermore, Stark and Squire (2000) reported increased hippocampal activation during the retrieval of target (old) items (objects, words) and associations (study = object, test = word) relative to foils (new), but hippocampal activation was not greater in the associative compared to the single item recognition task. These findings suggest that both the hippocampus and parahippocampal region are involved in the encoding (Henke *et al.*, 1997) and retrieval (Yonelinas *et al.*, 2001) of cross-category pairs, and the retrieval of single items (Stark and Squire, 2000).

In relation to object-place recognition, there is evidence to suggest activation of both the right hippocampus and parahippocampal cortex during the encoding and retrieval of topographical memory including object-place recognition (for a review see Maguire, 1997). In a recent PET study, Kohler *et al.* (2002) also found evidence to suggest increased activation in the parahippocampal cortex bilaterally (but more on the right than left) during the encoding and retrieval of spatial scenes, whereas the hippocampus contributed to the recognition of novel scenes but not scene details. Together, these human imaging findings suggest that the parahippocampal region and hippocampus are involved in single item and cross-category (including object-place) encoding, but that the hippocampus may additionally play a special role in scene recognition memory.

A problem with imaging studies of healthy controls is that activation in a structure does not necessarily mean that task performance is dependent on the function of that structure. Studies of patients with hippocampal lesions possibly provide a better indication of whether specific memory functions are dependent on the hippocampus.

However, behavioural studies of patients with selective hippocampal lesions report inconsistent findings. For example, some studies have found that single item recognition is impaired following bilateral hippocampal damage (e.g. Manns and Squire, 1999; Stark *et al.*, 2002; Stark and Squire, 2003) while others have not (e.g. Kroll *et al.*, 1996; Mayes *et al.*, 1999; Holdstock *et al.*, 2000a; 2000b; Mayes *et al.*, 2001). As discussed in Chapters 1 and 7, there are a number of possible reasons for these conflicting findings, including differences in the extent and location of hippocampal pathology, and/or extent of pathology in the parahippocampal region. Another possible reason may be differences in the performance of the control participants. For example, although Stark and Squire (2003) attempted to replicate the methodology used by Kroll *et al.* (1996), the control participants reported by Stark and Squire (2003) performed better than did the control participants reported by Kroll *et al.* (1996). These findings suggest that the impaired performance in patients relative to controls reported by Stark and Squire (2003) may be due to the high performance of the control group.

In a recent study, Stark *et al.* (2002) assessed the performance of four patients with selective bilateral hippocampal pathology sustained in adulthood on tests of one trial single item and associative yes/no recognition. The single item recognition task involved studying ten pictures of either faces or houses, and associative recognition involved studying ten house-face pairs. In the first experiment, both the controls and patients were given one study trial and a recognition test after a brief delay. The results indicated that the patients were impaired at both single item and associative recognition relative to controls. In a second experiment the patients were given eight study trials for both single item and associative recognition after which their performance did not differ significantly from that of the control group in the first experiment, and both groups performed better at single item than associative recognition. These findings suggest that associative recognition was more difficult than single item recognition for both patients and controls, but they do not support a selective role for the hippocampus in cross-category associative recognition.

In the report of Stark *et al.* (2002), participants were required to make yes/no judgements to indicate whether an item (or pair of items) was previously studied. Unlike the forced-choice recognition paradigm (where the participant is presented with more than one alternative) this paradigm is prone to differences between participants' response criterion, and therefore to response bias (e.g. Macmillan and Creelman, 1991). As

described in Chapter 4, response bias can be estimated from the proportion of correct hits and false alarms. A difference in response bias may account for differences in performance between groups or conditions.

Based on the results reported by Stark *et al.* (2002) it was possible to estimate the response bias index for patients and controls on single and associative recognition tasks (see Chapter 4 for calculation procedure). Visual inspection of response bias indicated that single items (controls: 0.06; patients: -0.03) elicited less response bias than associations (controls: -0.08; patients: -0.12) in both groups (Experiment 1). However, with increased study exposure (Experiment 2), the patients showed a response bias similar to that of controls on single items (controls: 0.06; patients: 0.04), but unlike that of controls on associative recognition (controls: -0.08; patients: -0.28). This increase in negative bias in the patients indicates an increased tendency to respond "yes" and resulted in more hits but also false alarms. These findings suggest that, although there was no group difference and no Group by Condition interaction when accuracy of performance was measured, the patients made more false alarms on associative recognition after increased study exposure compared to single item recognition relative to controls, suggesting the patients had particular difficulty with associative recognition memory.

Forced-choice recognition may provide a better estimate of differences in recognition performance between groups and conditions due to it being less influenced by differences in response bias (Macmillan and Creelman, 1991). However, even studies using forced-choice recognition have reported inconsistent results. Thus, adult-onset bilateral hippocampal pathology led to impaired performance on single item forced-choice recognition in the study reported by Manns and Squire (1999), but preserved performance in the study reported by Holdstock *et al.* (2000a; 2000b).

8.1.3 Developmental human studies of recognition memory

To date there has been only one study reported in the literature comparing single item with associative recognition in patients with child-onset bilateral hippocampal pathology (Vargha-Khadem *et al.*, 1997). In this study, three patients with child-onset bilateral hippocampal pathology were unimpaired on single item, one trial and multi-trial intramodal associative (e.g. word-word) forced-choice recognition relative to controls, yet were impaired on multi-trial voice-face and object-place paired associative forced-choice

recognition[1] (Vargha-Khadem *et al.*, 1997). These findings were taken as evidence to support the multi-system model of MTL function, suggesting that the parahippocampal region can support some forms of recognition memory, whereas the hippocampus is necessary to support cross-modal and object-place associative recognition memory (e.g. Mishkin *et al.*, 1997).

According to the findings of Malkova and Mishkin (2003), the reported deficits in object-place recognition memory associated with DA may be due to more extensive damage than first thought, extending to the posterior parahippocampal cortex. Although this can not be ruled out, a preliminary study by Schoppik *et al.* (2001) suggested that the entorhinal, perirhinal and parahippocampal cortex volumes of five DA patients (including Jon, one of the original three cases reported by Vargha-Khadem *et al.*, 1997) were within the normal range.

There are a number of other possible reasons for the discrepant results between the two studies (Vargha-Khadem *et al.*, 1997; Malkova and Mishkin, 2003), including the fact that the monkeys reported by Malkova and Mishkin (2003) sustained their lesion in adulthood, and received pre-operative training. Also, there are differences in task methodology, including list-length. For example, in the study of Malkova and Mishkin (2003) the monkeys were only required to remember two object-place pairs at a time, whereas in the study reported by Vargha-Khadem *et al.* (1997) the patients with DA were required to remember twenty object-place pairs over multiple learning (study-test) trials. Therefore, it is possible that the hippocampus is only required for object-place recognition memory when a large number of pairs are to be remembered (high memory load) over a number of learning trials. Indeed the longest multi-trial reported list-length presented to monkeys with hippocampal lesions is only ten object-place pairs (e.g. Belcher *et al.*, 2000).

The purpose of the experiments reported in this chapter is to: a) attempt to replicate the findings of Vargha-Khadem *et al.* (1997) in a larger group of patients with age-, sex- and IQ-matched controls (Experiment 1), and b) test in the same patients whether object-place recognition is impaired with short list-lengths (Experiment 2).

[1] In one trial presentation, the participant is presented with the target pairs once for study and once for test; in multi-trial presentation, the participant is presented with the target pairs once for study and is given up to ten test trials with feedback or until the participant has reached a criterion of 90% correct.

8.2 EXPERIMENT 1: ONE TRIAL AND MULTI-TRIAL RECOGNITION

To date, only three patients with DA have been tested on item and associative recognition tasks (Vargha-Khadem *et al.*, 1997). In the study of Vargha-Khadem *et al.* (1997) the performance of these three patients (one of whom was a child at the time of testing) was compared to adult controls. Given the theoretical issues outlined above, the study reported in this chapter was carried out to further investigate the role of the hippocampus in recognition memory. Item and associative recognition was tested in a larger group of patients with DA using forced-choice one trial and multi-trial recognition tasks of visual familiar (famous faces), visual unfamiliar (unknown faces), verbal familiar (real words), verbal unfamiliar (unknown words), voice-face, object-only, place-only, and object-place recognition.

Based on the discussion above and previous findings of DA (Vargha-Khadem *et al.*, 1997) it is predicted that if the hippocampus is only required for object-place and other cross-modal associative recognition then:

(a) The DA group will be unimpaired on single item recognition, one trial associative recognition, and multi-trial intramodal associative recognition, place-only and object-only recognition memory tasks.

(b) The DA group will be impaired relative to controls on multi-trial voice-face and object-place recognition memory tasks.

(c) The DA group will be impaired relative to controls on the first trial of voice-face and object-place recognition memory tasks.

8.2.1 Methods

8.2.1.1 Participants

Eleven[2] patients with DA and twelve controls took part in the one trial tasks, and eleven[3] patients with DA and twelve controls took part in the object-place multi trial task. The participants have been described in full in Chapter 2 and therefore will not be

[2] Patient DA4 did not participate in any of the one trial tasks.
[3] Patient DA8, did not participate in object-place associative recognition.

described in detail here. Briefly, the groups did not differ significantly on age at test ($p > 0.1$), verbal IQ ($p > 0.1$) or performance IQ ($p > 0.1$).

8.2.1.2 Procedure

The tasks were administered to the DA group in a randomised order. The control group received the tasks in the same order as the patient group. The tasks were presented on a computer and were administered over two 3-hour sessions. The responses of the participants were coded automatically by the computer, and output log files were saved for subsequent analysis. The participants were given regular breaks between tasks in order to limit effects of fatigue.

8.2.1.2.1 One trial recognition

8.2.1.2.1.1 Single item recognition

One trial verbal familiar (real words): The participants were shown a series of 12 words (abstract words of medium frequency selected from Paivio *et al.*, 1968), ~5 seconds per word (inter-stimulus interval of ~3 seconds), and were told that they would be required to remember them later on and therefore should pay close attention to the words. Once all twelve words had been presented, the participants were shown two words, one target and one foil and were asked to indicate which item had been seen before. The participants were given ~12 seconds within which to make a response, if no response was made a 'please choose' prompt appeared on the screen. Once a response was made, the computer sounded a tone, although this did not differentiate between correct and incorrect responses. They were presented with 5 lists in total.

One trial verbal unfamiliar (nonwords): The procedure was the same as that described for verbal familiar, except that the participants were shown 5 lists of 12 nonwords consisting of bisyllabic pronounceable words.

One trial visual familiar (famous faces): The participants were shown a series of 12 famous faces, ~5 seconds per face (inter-stimulus interval of ~ 3 seconds). Each face in the list was of the same person but the photographs depicted the same person in a different pose and expression and sometimes with a different hairstyle. Again, the participants were informed prior to study that they would be asked to remember the faces later on. Immediately after viewing the twelfth face, the participants were shown two

faces, one target and one foil; again these were images of the same person. The participants were required to indicate which item they had seen previously. Other procedures were the same as before.

One trial visual unfamiliar (unknown faces): The procedure was the same as that described for the visual familiar task, except that participants were shown different views of an unknown face. They were given 5 lists of 12-items, each list containing a new person.

8.2.1.2.1.2 Associative recognition

One trial verbal familiar associative recognition (real word pairs): The participants were shown 6 pairs of real words for study, one after the other. The first word of the pair was presented for ~5 seconds before the second word appeared on the right, together with the first for an additional ~5 seconds (inter-stimulus interval of ~5 seconds). The participants were informed they would be required to remember the pairs later on. Immediately after study, the participants were presented with the test phase. For test, the stimulus word of each pair was presented together with two words for choice, one above the other, the correct response word and an incorrect one taken from the same list. To accomplish this, each response word was used twice, once with its own stimulus word and once with another. The participants were asked to indicate which item on the right (above or below) went with the item on the left. The positions of the target/foil (i.e. above/below) were randomised across trials. They were presented with 10 6-pair lists in total. Other procedures were as before.

One trial verbal unfamiliar associative recognition (non-word pairs): The procedure was the same as that described for verbal familiar associative recognition except that the lists consisted of nonword pairs. There were again 10 6-pair lists in total.

One trial visual familiar associative recognition (famous faces): The participants were presented with a series of 6 pairs of famous faces, each image depicting the same person in a different pose and expression and sometimes with a different hairstyle. Each image (including the foil) was of the same person from different angles/time periods. The participants were asked to indicate which item (above or below) had previously been presented with the image on the left. There were again 10 6-pair lists in total, each with a different famous face. Other procedures were as before.

One trial visual unfamiliar associative recognition (unknown faces): The procedure was the same as that described for visual familiar associative recognition, except that each of the 10 6-pair lists contained images of a different unknown face.

8.2.1.2.2 Multi-trial associative recognition

Multi-trial verbal unfamiliar associative recognition (non-word pairs): Participants were shown a series of 20 nonword pairs for study (each a bisyllabic pronounceable nonword). The first nonword of the pair was presented for ~5 seconds on the left of the screen before the second nonword appeared on the right, together with the first, for an additional ~5 seconds (inter-stimulus interval of ~5 seconds). They were informed that they would be required to remember the pairs later on. Immediately after all 20-pairs had been shown, the participants were giving the test phase. In this test phase and all succeeding trials, one of the study items was presented together with two items for choice, the correct response item and the incorrect one was taken randomly from the study list. The locations of the target and foil (above and below) was randomised across trials. The participant was asked to indicate which of the two on the right was previously shown with the one on the left. The participants were given ~12 seconds within which to make a response, if no response was made a 'please choose' prompt appeared on the screen. Once the participant made a response they received feedback from the computer (a recorded voice) indicating whether they were correct or incorrect. The test phase continued either until the participant reached the criterion of 90% correct criterion or until 10 test trials were administered.

Multi-trial visual unfamiliar associative recognition (unknown face pairs): The procedure was the same as that described for the multi-trial verbal unfamiliar associative recognition task, except that participants were shown 20-unknown face pairs. Other procedures were the same as above.

Multi-trial voice-face associative recognition: The participants were informed that they would be shown a face and at the same time hear a voice saying: "Hello, I am sorry that I didn't get to meet you. I hope you remember me." They were told that each face would be presented with that particular persons voice and that they would be asked about them later on. The participants were then presented with 20 voice-face pairs. All of the pairs were female. The voice recording began ~1 second before the face appeared on the screen allowing the face and voice to be presented together for ~ 4 seconds (inter-

stimulus interval of ~ 5 seconds). Immediately after the study presentation the participants were shown two faces on the screen (above and below), while simultaneously, they heard one voice and were asked to indicate which face was previously shown with that voice. Both of the faces shown had been presented before, but only one face was presented with that voice. The participants were given ~12 seconds within which to make a response; if no response was made a 'please choose' prompt appeared on the screen. Once the participant made a response they received feedback from the computer (in text on the screen) indicating whether they were correct or incorrect. The test pair remained on the screen with the feedback for ~ 6 seconds. The test phase continued either until the participant reached the 90%-correct criterion or until 10 test trials were administered.

Multi-trial object-place associative recognition: The participants were informed that they would be shown an object on the far right of the screen and that object would then also appear in one of forty circles presented in an irregular but fixed array that occupied the remainder of the screen (see Appendix F). They were informed that they would be asked to name each object as it appeared, and later on would be asked about the objects and their location. The participants were then presented with 20 object-place pairs. First an object was presented on the far right of screen and simultaneously one of the 40 circles was highlighted for ~ 4 seconds. Then the object also appeared in the highlighted circle for ~ 4 seconds (inter-stimulus interval of ~ 3 seconds). Thus, twenty of the circles were never occupied. All 20 objects were colour photographs of common everyday objects and could be easily labeled verbally. Immediately after the study presentation the participants were shown two objects on the far right of the screen (above and below), and simultaneously they were shown a highlighted circle and were asked to indicate which object (above or below) was previously shown in that circle. Both objects had previously been presented, but only one object had previously been shown in that location. The participants were given ~12 seconds within which to make a response; if no response was made a recorded 'please choose' prompt was given by the computer. Once the participant made a response they received feedback from the computer (again by a recorded voice) indicating whether they were correct or incorrect. The stimuli remained on the screen for ~ 3 seconds after a response made, and then the display of unlit empty circles appeared for ~ 5 seconds before the next object was presented. The test phase continued either until the participant reached the 90%-correct criterion or until 10 test trials were administered.

Immediately after completion of the object-place test phase, participants were shown two objects (one above the other, one old and one new) and were asked to indicate which object had been shown during study (object-only recognition). For this test, each of the 20 objects was shown with a visually similar foil. The participants were given ~12 seconds within which to make a response; if no response was made a 'please choose' prompt was given by the computer in text in the middle of the screen. Although the participants received verbal feedback after each response they were given only one test trial. Next, the participants were shown two highlighted circles (one target, one foil) and were asked to indicate which of the two circles had previously been occupied in the study phase (place-only recognition). Again, although the participants were given feedback, they were only given one test trial.

8.2.2 Results

The data were analysed in accordance with the analysis plan outlined in Section 2.3.2, Chapter 2. For one trial recognition tasks, mixed-model ANOVAs with a between-subjects factor of Group (DA, NC) and within-subjects factors of Familiarity (familiar, unfamiliar) and Modality (verbal, visual) were conducted. Significant interactions were followed up with separate t-tests correcting for multiple comparisons. All findings with a p-value of less than 0.05 are reported and predicted findings with a p-value less than 0.1 are described. Overall, the results did not change when the three previously reported cases were removed from the analysis (i.e. DA1 (Jon), DA2 (Beth) and DA10 (Kate), Vargha-Khadem *et al.*, 1997)

8.2.2.1 One trial recognition

8.2.2.1.1 Single item recognition

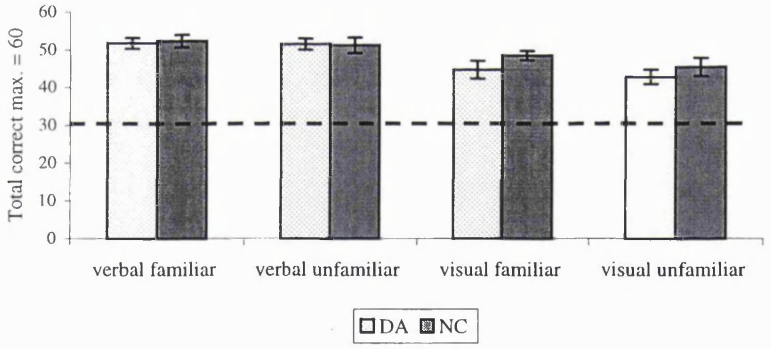
Table 8:1 and Figure 8:1 show the mean (±SEM) total number correct (maximum = 60) on single item recognition for the DA and control groups.

Table 8:1 One trial single item recognition (mean ±SEM)

Total correct (raw score)	DA	NC
Verbal familiar (real word)	51.8 (1.5)	52.3 (1.7)
Verbal unfamiliar (nonword)	51.5 (1.5)	51.1 (2.0)
Visual familiar (famous face)	44.6 (2.4)	48.4 (1.2)
Visual unfamiliar (unknown face)	42.7 (1.9)	45.3 (2.4)

Mean (±SEM)

Figure 8:1 Single item recognition



Dashed line represents chance performance of 30 correct. The recognition memory performance of both groups was significantly above chance on all measures ($p < 0.0001$).

The analysis (ANOVA) revealed as predicted, no evidence for a main effect of Group ($p > 0.1$). There was a significant main effect of Familiarity ($F(1,21) = 25.25$; $p < 0.0001$), suggesting that performance was better for familiar than unfamiliar items, and Modality ($F(1,21) = 7.84$; $p = 0.011$), suggesting that performance was better for verbal than visual items. None of the interactions were significant ($p > 0.1$).

8.2.2.1.2 Associative recognition

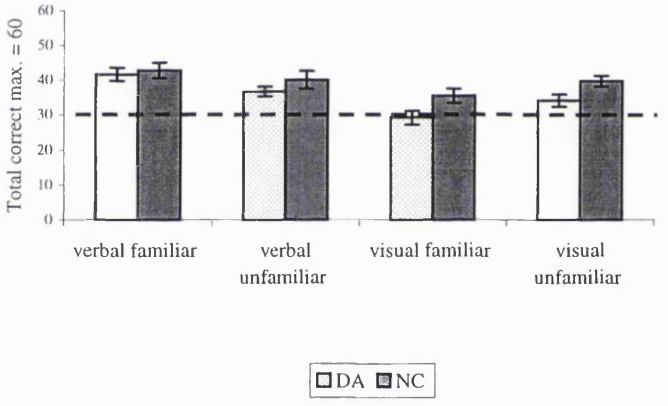
Table 8:2 and Figure 8:2 show the mean (±SEM) total number correct on one trial associative recognition in the DA and control groups.

Table 8:2 One trial associative recognition

Total correct (raw score)	DA	NC
Verbal familiar (real words)	41.6 (1.9)	42.8 (2.2)
Verbal unfamiliar (nonwords)	36.6 (1.4)	40.0 (2.5)
Visual familiar (famous faces)	29.2 (1.9)	35.4 (2.1)
Visual unfamiliar (unknown faces)	34.1 (1.8)	39.7 (1.5)

Mean (±SEM)

Figure 8:2 One trial associative recognition



The dashed line represents chance performance of 30 correct. The recognition memory performance of the control group was significantly better than chance on all measures ($p < 0.05$). The recognition memory performance of the DA group was significantly better than chance on all of the measures ($p < 0.05$), except for visual familiar associative recognition memory ($p > 0.1$).

The analysis (ANOVA) revealed, as predicted, no evidence for a main effect of Group[4] ($p > 0.05$). There was a significant main effect of Familiarity ($F(1,21) = 24.24; p < 0.0001$), suggesting that performance was better for familiar than unfamiliar pairs. There was no main effect of Modality, but unexpectedly the Familiarity by Modality interaction

[4] The variance of the residuals was heterogeneous in the visual unfamiliar associative recognition condition. Therefore the lack of significant group difference was confirmed using a Mann-Whitney U test ($p > 0.1$)

was significant ($F(1,21) = 15.36$; $p = 0.001$). None of the other interactions were significant.

Follow up analysis of the interaction revealed that performance was better on verbal than visual familiar associative recognition ($t(22) = 6.25$; $p < 0.0001$), but there was no significant difference between verbal and visual unfamiliar associative recognition ($p > 0.1$).

8.2.2.2 Multi-trial associative recognition

In these tasks participants were presented with test trials until criterion was reached or for a maximum of 10 trials. Therefore, three scores were derived from the data: number of trials to reach criterion (maximum of 10), total number of errors across all test trials, and number of errors made on the first test trial. The number of errors made on the first test trial was calculated because on this trial participants can succeed before they have made any errors on that pair. Patients with DA may be prone to interference from previously erroneous responses (e.g. Hayman *et al.*, 1993; Hamann and Squire, 1995), and therefore the first test trial provides a measure of recognition independent of interference, akin to the one trial associative recognition tasks, but with a list-length of 20-pairs.

Separate independent samples t-tests were conducted unless there was evidence of heterogeneity of variance between the groups, in which case nonparametric Mann-Whitney U tests were conducted. All other details of the analyses are the same as that described in Section 2.3.2, Chapter 2.

8.2.2.2.1 Number of trials to reach criterion

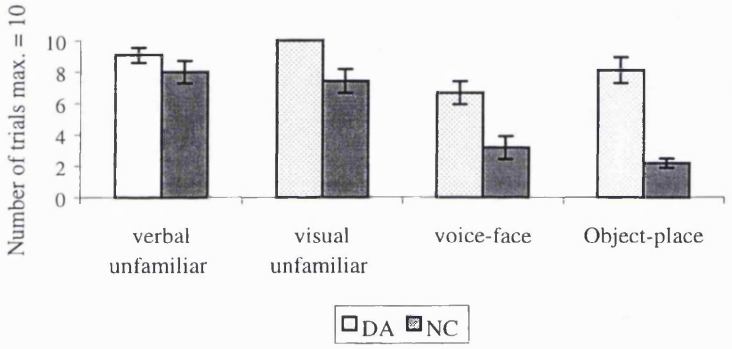
Table 8:3 and Figure 8:3 show the mean (±SEM) total number of trials taken to reach criterion in the DA and control groups.

Table 8:3 Number of trials to reach criterion

Number of trials (max = 10)	DA	NC
Verbal unfamiliar (nonword)	9.1 (0.5)	8.0 (0.7)
Visual unfamiliar (unknown faces)	10.0 (0.0)	7.4 (0.8)
Voice-face	6.7 (0.7)	3.2 (0.7)
Object-place	8.1 (0.8)	2.2 (0.3)

Mean (±SEM)

Figure 8:3 Number of trials to reach criterion



As predicted, the analysis revealed that the control group took significantly fewer trials to reach criterion compared to the DA group voice-face ($t(22) = -3.39$; $p = 0.003$) and object-place ($t(12.57) = -6.75$; $p < 0.0001$) recognition memory but not on verbal unfamiliar associative recognition memory ($p > 0.1$). However, unexpectedly the control group took fewer trials to reach criterion compared to the DA group on face-face recognition (Mann-Whitney U test: $U = 30$; $p = 0.002$).

As seen from Table 8:3 and Figure 8:3, there was no variance in the performance of the DA group on the visual unfamiliar associative recognition task, and therefore caution must be taken when interpreting this statistical analysis. All of the patients with DA required 10 test trials indicating that this was the most difficult condition for all patients, but it is possible that ceiling effects may have underestimated the performance of the DA group.

8.2.2.2.2 Total errors

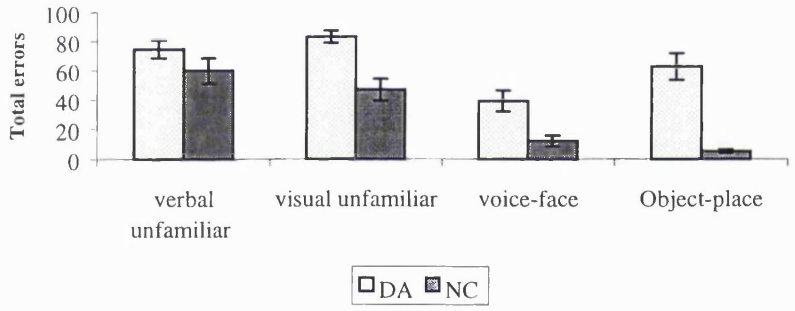
Table 8:4 and Figure 8:4 show the mean (±SEM) total number of errors made on multi-trial associative recognition tasks by the DA and control groups.

Table 8:4 Total errors

Total errors	DA	NC
Verbal unfamiliar	74.8 (6.2)	60.0 (8.7)
Visual unfamiliar	83.1 (4.1)	47.0 (7.4)
Voice-face	39.1 (7.1)	12.3 (3.7)
Object-place	62.8 (9.05)	5.3 (1.2)

Mean (±SEM)

Figure 8:4 Total errors



It was not possible to test whether the performance of the participants was different from chance, as the number of trials and therefore potential for errors varied between participants.

As predicted, the error analysis revealed no effect of Group on verbal unfamiliar associative recognition ($p > 0.1$), but the control group made significantly fewer errors compared to the DA group on voice-face ($t(16.60) = -3.36; p = 0.004$) and object-place ($t(10.35) = -6.29; p < 0.0001$) recognition. Unexpectedly, the control group also made significantly fewer errors compared to the DA group on visual unfamiliar associative recognition ($t(17.19) = -4.26; p = 0.001$).

8.2.2.2.3 Total errors on first trial

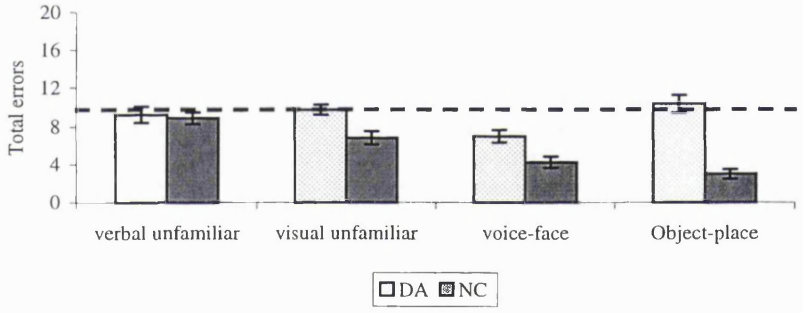
Table 8:5 and Figure 8:5 show the mean (±SEM) total number of errors made on the first trial of the multi-trial associative recognition tasks by the DA and control groups.

Table 8:5 Total errors on first trial

Total errors (first trial)	DA	NC
Verbal unfamiliar	9.3 (0.8)	8.9 (0.6)
Visual unfamiliar	9.8 (0.5)	6.8 (0.7)
Voice-face	7.0 (0.7)	4.3 (0.6)
Object-place	10.4 (1.0)	3.0 (0.5)

Mean (±SEM)

Figure 8:5 Total errors on first trial



The dashed line represents chance performance of 10 errors. A score significantly below 10 errors indicates performance above chance. The recognition memory performance of the control group was significantly better than chance on all measures ($p < 0\ 05$) except for verbal unfamiliar associations ($p > 0.05$). The recognition memory performance of the DA group was better than chance only on one measure, voice-face recognition ($p = 0.001$), and was not different from chance on any of the other measures ($p > 0.05$).

The analysis revealed, as predicted, no effect of Group on verbal unfamiliar associative recognition ($p > 0.1$), but the control group made significantly fewer errors than the DA group on voice-face ($t(22) = -3.07$; $p = 0.006$) and object-place ($t(21) = -7.13$; $p < 0.0001$) recognition. Unexpectedly, the control group also made significantly

fewer errors than the DA group on visual unfamiliar associative recognition ($t(19.87) = -3.42$; $p = 0.003$).

8.2.2.2.4 Total errors on object-only and place-only

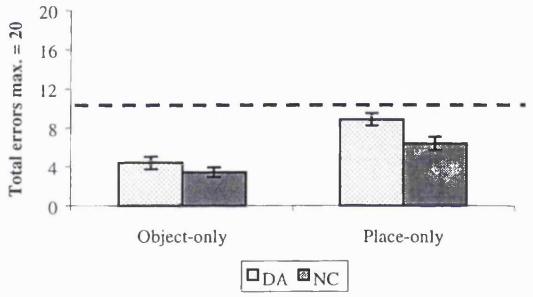
Table 8:6 and Figure 8:6 show the mean (±SEM) total number errors made on the object-only and place-only recognition tasks by the DA and control groups.

Table 8:6 Total errors on object-only and place-only

Total errors	DA	NC
Object-only	4.36 (0.70)	3.42 (0.50)
Place-only	8.81 (0.64)	6.33 (0.70)

Mean (±SEM)

Figure 8:6 Total errors on object-only and place-only



The dashed line represents chance performance of 10 errors. The recognition memory performance of control group was significantly better than chance on both measures ($p < 0.0001$). The recognition memory performance of the DA group was better than chance on the object-only measure ($p < 0.0001$), but not on the place-only measure ($p > 0.05$).

The analysis revealed, as predicted, no effect of Group on object-only recognition memory ($p > 0.1$), but unexpectedly, the control group made significantly fewer errors than the DA group on place-only recognition memory ($F(1,21) = 6.75$; $p = 0.017$).

8.2.2.3 Original analysis reported by Vargha-Khadem et al. (1997)

In order to test whether the differences between the findings reported in this chapter and those reported by Vargha-Khadem *et al.* (1997) were due to the different analyses used, the analysis method reported by Vargha-Khadem *et al.* (1997) was also applied to the data. Unrelated t-tests with Bonferroni correction for multiple comparisons ($p = 0.05/16 = 0.003$) replicated the main analyses reported in this chapter. There was no evidence for group effects on one trial single item and associative recognition or multi-trial verbal unfamiliar associative recognition ($p > 0.1$) but there was evidence for a group difference on multi-trial visual unfamiliar (trials: $t(22) = -3.43$; $p = 0.002$; errors: $t(22) = -4.26$; $p < 0.0001$), voice-face (trials: $t(22) = -3.39$; $p = 0.003$; errors: $t(22) = -3.36$; $p = 0.003$) and object-place (trials: $t(12.57) = -6.75$; $p < 0.0001$; errors: $t(10.35) = -6.29$; $p < 0.0001$) associative recognition, where the control group took fewer trials to reach criterion and made fewer errors. The results of the control tasks place-only and object-only were not reported in the original paper. However, when analysed using the same method with correction ($p = 0.05/18 = 0.0028$) as used by Vargha-Khadem *et al.* (1997), there was no evidence for Group effects on either object-only recognition memory ($p > 0.1$), or place-only recognition memory ($p = 0.017$).

8.2.3 Discussion

This experiment aimed to test whether relatively selective hippocampal pathology is associated with a specific deficit in cross-modal and object-place recognition, leaving single item and intramodal recognition intact. The results supported this prediction, in that the groups did not differ on any of the one trial single item or intramodal associative recognition tests, but patients were impaired relative to controls on voice-face and object-place recognition. However, unexpectedly, impairments were also demonstrated on the multi-trial visual unfamiliar (faces) and the place-only recognition tests.

Both groups performed above chance on each condition of the single item recognition tests suggesting that both groups were able to perform the task. Although the groups mainly performed above chance on the one trial associative recognition tests, the DA group did not perform above chance on the one trial recognition of visual familiar

associations (famous faces). This suggests that although there was no significant difference between the groups on this measure, the patients with DA found visual familiar associative recognition the most difficult. There was some evidence to suggest differences in task difficulty on the single item recognition tasks, such that both groups showed better recognition of familiar than unfamiliar items, and verbal recognition was better than visual recognition. However, these differences in task difficulty did not affect the groups differently (i.e. no significant Group by Familiar or Group by Modality interactions). There was a significant Familiarity by Modality interaction on the one trial associative recognition tests, suggesting that recognition performance was better for verbal than visual familiar associative recognition. Again, however, this difference in difficulty did not differ between the groups (i.e. no Group by Familiarity by Modality interaction). Together these findings suggest that unlike the prediction of the unitary-system model of MTL function (e.g. Squire and Zola, 1998), one trial single item and intramodal associative recognition can be supported by structures other than the hippocampus.

It was also predicted that the DA group would not be impaired relative to controls on the multi-trial intramodal associative learning tasks. However, analysis of the number of trials taken to reach criterion and the total number of errors made on the multi-trial associative recognition tasks suggested slightly different findings from those reported by Vargha-Khadem *et al.* (1997). Unlike the three DA patients reported by Vargha-Khadem *et al.* (1997), the DA group was impaired relative to controls on the number of trials taken to reach criterion on the visual unfamiliar (face-face) associative recognition task. The DA group performed at ceiling on this condition whereas the control group did not, suggesting that all of the patients with DA had particular difficulty with this task. This was confirmed by the analysis of the total number of errors made, in that the control group made significantly fewer errors than the patients with DA. Statistical analysis of the remaining conditions confirmed the findings of Vargha-Khadem *et al.* (1997), in that the control group took fewer trials to reach criterion and made fewer errors than the DA group on voice-face and object-place associative recognition but there was no significant difference between the groups on unfamiliar verbal associative recognition.

It is of interest to compare the deficit of the DA group on voice-face recognition with a finding reported by Murray and Gaffan (1994) in the monkey. In this study, monkeys with amygdala and entorhinal cortex lesions were required to associate sound tones with letters (visual-auditory recognition). These monkeys were impaired at this task

suggesting the entorhinal cortex and amygdala support cross-modal associative recognition. The stimuli used in the studies with monkeys are of course different from those used with the DA group. Tones and letters are not ethologically meaningful to monkeys, whereas voices and faces are meaningful stimuli to humans. It may be that the more meaningful stimuli used in this Experiment rendered the task hippocampal dependent. Alternatively, the findings of Murray and Gaffan (1994) can be reconciled with the findings reported here on the supposition that lesions to the entorhinal cortex disconnect the hippocampal input and effectively act as a hippocampal lesion. Indeed the entorhinal cortex provides the hippocampus with most of its afferents (Amaral *et al.*, 1987; Witter and Amaral, 1991) and so is commonly considered an essential structure for hippocampal function.

In order to test whether the hippocampus was also required for one trial object-place and cross-modal associative recognition, and whether the group differences found on multi-trial associative recognition were due to factors other than list-length (e.g. inability to respond to feedback), performance was analysed on the first test trial of the multi-trial tasks. Statistical analysis of the number of errors made on this first trial confirmed the findings of the total number of errors made across all trials. The control group performed above chance on all of the measures except for verbal unfamiliar associative recognition memory, while the DA group did not differ significantly from chance on any of the measures except for voice-face recognition. The findings indicate that both groups had difficulty with verbal unfamiliar associative recognition on which they did not differ, but that they differ on the three other associative recognition conditions, including voice-face recognition. Thus, it appears that the impairments in patients with DA on the multi-trial tasks are not accounted for by the necessity to respond to feedback, and are more likely a consequence of the high memory load (i.e. 20 pairs to be remembered).

This interpretation is supported by the finding that the patients with DA were not impaired relative to controls on the one trial (6-pairs) version of the visual unfamiliar condition but were impaired on the first trial of the multi-trial (20-pairs) version. However, there was no difference between the patients with DA and controls on either the one trial (6-pairs) version of the verbal unfamiliar condition or first trial of the multi-trial (20-pairs) version. Although both conditions require the participant to discriminate between a target and foil taken from the same study list, the visual unfamiliar condition

requires the participants to discriminate between two photographs of the same person, whereas the verbal unfamiliar condition involves discriminating between two unique nonwords. Therefore, relying on familiarity-based recognition may not prove to be a successful strategy in the visual unfamiliar condition but may be adequate in the verbal unfamiliar condition. Alternatively, this might suggest a greater right than left hippocampal abnormality (e.g. Morris *et al.*, 1995; Crane and Milner, 2001), but this was not supported in the analysis of left and right hippocampal volume reduction (see Chapter 3), which showed equal reduction on both sides.

Finally, analysis of the control tasks for the object-place condition suggested that the control group performed significantly above chance on both while the DA group only performed significantly above chance on object-only recognition. Furthermore, the control group made significantly fewer errors than the DA group on the place-only but not the object-only condition, suggesting that the DA group had specific difficulty recognising the previously presented locations. These findings affect the interpretation of the object-place data, as specific impairments in place recognition and not necessarily the object-place associations per se may cause impairments on the object-place associative recognition task. This will be discussed in more detail in Section 8.4.2.

In an attempt to determine whether difference between the findings reported in this chapter and those previously reported by Vargha-Khadem *et al.* (1997) were due to the type of analyses used, the analysis method reported by Vargha-Khadem *et al.* (1997) was also conducted. Generally this analysis confirmed the findings reported in this chapter and suggested that the additional findings reported in this chapter are not due to the analysis used.

8.3 EXPERIMENT 2: ONE TRIAL SINGLE ARRAY RECOGNITION

As discussed in the Introduction to this chapter, there is evidence from both animal and human studies to suggest that some associative recognition tasks involving spatial information (e.g. object-place), but not single item recognition, require the hippocampus (e.g. Vargha-Khadem *et al.*, 1997; Mayes *et al.*, 1999). Although there is evidence in the literature to contradict this claim, these opposing studies are open to the criticisms of: damage extending beyond the hippocampus may impair single item recognition (e.g.

Manns and Squire, 1999); difference in response bias between groups and conditions (e.g. Stark *et al.*, 2002); and the list-length being too short to demonstrate an impairment in the monkey (Malkova and Mishkin, 2003).

In order to address the question of list-length, a further test of forced-choice object-place recognition was conducted. This task attempted to determine whether patients with DA would be impaired at object-place associative recognition memory and place-only recognition memory when only a single 3-stimulus array is presented for study and is tested after only a short delay.

It is predicted that, if DA is associated with selective hippocampal injury and that the hippocampus plays a special role in object-place and more generally spatial recognition then:

(a) Patients with DA will be impaired on object-place and place-only recognition memory when tested two minutes after the presentation of a single 3-stimulus array.

(b) Patients with DA will not be impaired on object-only recognition or recognition of an array with new objects in new places (object and place).

8.3.1 Method

8.3.1.1 Participants

Eleven[5] patients with DA and twelve controls took part in this study. The participants have been described in full in Chapter 2 and therefore will not be described in detail here. Briefly, the groups did not differ significantly on age at test ($p > 0.1$), verbal IQ ($p > 0.1$) or performance IQ ($p > 0.1$).

8.3.1.2 Stimuli

The stimulus arrays consisted of three objects variously positioned on a three by three grid. The objects were common everyday objects that could be easily labeled verbally. Two identical arrays were presented at study, and one of these was altered at

[5] Patient DA4 did not participate in this study.

test. The altered or new arrays (targets) differed from the study array in one of four possible ways (conditions): object-place (two objects switched place); object and place (two objects were replaced by new objects in new places); object-only (two objects were replaced by two new objects in the same place as study); place-only (two objects were moved to two new places). See Appendix G for an example of the object-place condition. Therefore in each new array in the test phase only one object was of the same identity and in the same location as that in the study array. This 'study-constant' location was unique to each trial in each condition forcing the participant to scan the array in order to determine which test array was the target. The participants were presented with ten trials in each condition (forty trials in total) presented in a randomised order, i.e. not blocked by condition. Each study and test trial presented trial unique stimuli.

8.3.1.3 Procedure

This task was administered as an active recognition component to a visual-paired comparison task not reported in this thesis. The participants were informed that they would be shown two identical 3-object arrays side-by-side on the computer screen, and that they would be required to identify a new stimulus array after a short delay. At study they were presented with two identical stimulus arrays side-by-side on the computer screen and were given 5 seconds to look at them. Then after a two-minute delay they were shown two 3-object arrays, one identical to the array presented at study and one new array (target). The side of screen presentation of the 'new' and 'old' arrays was randomly ordered. Participants were asked to point to the new target. The examiner clicked whichever mouse button corresponded to the array chosen by the participant and the computer recorded responses. No feedback was given.

8.3.2 Results

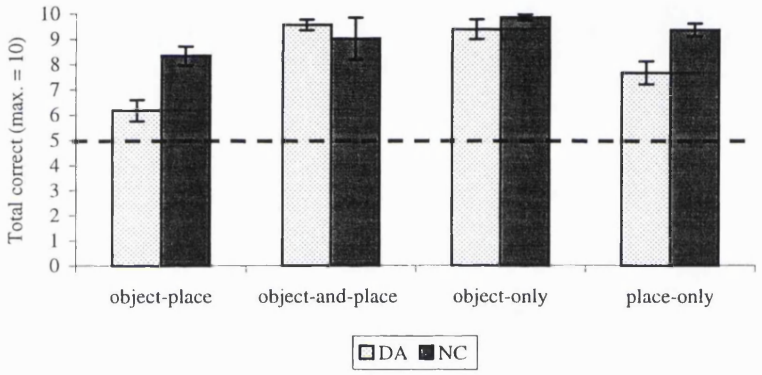
The data were analysed in accordance with the analysis plan outlined in Section 2.3.2, Chapter 2. Separate independent samples t-tests were conducted unless there was evidence of heterogeneity of variance between the groups, in which case nonparametric Mann-Whitney U tests were conducted. All findings with a p-value of less than 0.05 are reported and predicted findings with a p-value less than 0.1 are described.

Table 8:7 One trial array recognition

(maximum = 10)	DA	NC
Object-place	6.18 (0.42)	8.33 (0.38)
Object-and-place	9.55 (0.21)	9.00 (0.83)
Object-only	9.36 (0.39)	9.83 (0.11)
Place-only	7.64 (0.45)	9.33 (0.26)

Mean (±SEM)

Figure 8:7 One trial array recognition



The dashed line represents chance performance of 5 correct. Both groups performed significantly above chance on all measures ($p < 0.05$).

The analysis revealed that the control group performed better than the DA group on object-place recognition ($t(21) = 3.82$; $p = 0.001$) and place-only recognition ($t(21) = 3.34$; $p = 0.003$), but not object-and-place recognition ($p > 0.1$). Tests of variance revealed that variance between the groups was heterogeneous on object-only recognition ($p = 0.019$), therefore a Mann-Whitney U test was conducted to test for differences between the groups on performance. The Mann-Whitney U test indicated no significant difference between the performance of the groups on object-only recognition ($p > 0.1$).

These findings are consistent with the multi-trial recognition tests, in that the DA group was impaired at object-place and place-only recognition.

8.3.3 Discussion

This experiment attempted to test whether selective hippocampal pathology is associated with specific spatial recognition memory deficits even with a short list-length.

The findings of this experiment suggest that selective hippocampal pathology is indeed associated with specific impairments in spatial memory (both object-place and place-only). Although both groups performed above chance on all measures, the patients with DA were impaired at identifying a new (i.e. recognising the old) array of three objects after a two-minute delay when the location of the objects were switched (object-place), and when the location of the objects was changed (place-only). However, the recognition memory of the patients with DA did not differ significantly from that of controls when only the object identity was changed (object-only) or when both the object identity and location was new (object and place).

These findings, which confirm those of Experiment 1, suggest that the hippocampus may be required for general spatial recognition memory but not object identity recognition. This is consistent with some models of hippocampal function in the animal literature (e.g. Gaffan, 1998; Gaffan *et al.*, 2001; Brown and Aggleton, 2001) and is consistent with some studies of human amnesia (e.g. Mayes *et al.*, 1999). However, these findings are inconsistent with those of Malkova and Mishkin (2003) and suggest that the hippocampus is required for object-place and place-only recognition memory even when one array is to be remembered over delays as short as two minutes. Reasons for these inconsistent findings will be discussed in Section 8.4.2.

8.4 GENERAL DISCUSSION

The findings reported in this chapter largely replicated those of Vargha-Khadem *et al.* (1997), in that single item and one trial intramodal associative recognition was preserved in patients with DA and multi-trial voice-face and object-place recognition was impaired relative to controls (Experiment 1). However, additional impairments were seen in this group of patients with DA. These included the recognition of twenty visual unfamiliar associations both after the first learning trial and after multiple learning trials,

and recognition of places, both when tested with list-lengths of twenty items and when tested with a list-length of one 3-item array after a relatively short delay (Experiment 2).

The multi-trial task deficits are not likely to be due to the errorful-learning nature of the task (i.e. learning from feedback) because the same pattern of results was shown on the first test trial of the multi-trial tasks. The finding that recognition memory of 20 unfamiliar face-face, and 20 voice-face paired-associates was impaired both after the first and multiple learning trials suggests that the hippocampus may only be required for memory of associations between unfamiliar visual stimuli or ones with a high memory load. Furthermore, object-place associative recognition and place-only recognition memory were also impaired when the participants were required to remember a single stimulus over a short delay, suggesting that the hippocampus may be required for spatial memory independent of list-length and therefore of memory load.

8.4.1 A comparison with other studies of recognition

Unlike the findings of Stark *et al.* (2002), the patients with DA were unimpaired relative to controls on single item recognition tasks. There are differences between the methodologies of these two studies. For example, in the task of Stark *et al.* (2002) participants were required to make yes/no choices at test, whereas in the tasks reported in Experiment 1 and 2, participants were required to choose the target item from two alternatives (forced-choice). It is possible that the unimpaired recognition of the DA group compared to the impaired performance of the amnesic patients reported by Stark *et al.* (2002) is a result of the two-alternative forced-choice procedure. Forced-choice recognition may be relatively easier than yes/no recognition because the participant can make a judgement based on the comparable familiarity of the two test items. However, studies comparing forced-choice with yes/no recognition performance in healthy controls and patients with amnesia have not found evidence to suggest a difference in performance accuracy or the level of familiarity-based recognition between the two types of test (e.g. Khoe *et al.*, 2000). It is also possible that the group differences reported by Stark *et al.* (2002) were a consequence of differences in response bias (see Introduction).

Alternatively, the unimpaired performance in the DA group relative to controls may be supported by intact parahippocampal regions (e.g. Mishkin *et al.*, 1997; 1998; Aggleton and Brown, 1999; Brown and Aggleton, 2001). Although parahippocampal volumes are not reported in this thesis, preliminary studies by Schoppik *et al.* (2001) have

suggested normal volumes in this region in five patients with DA. However, the patients of Stark *et al.* (2002) although reported to have relatively selective hippocampal pathology, did have a small degree of volume reduction reported in the parahippocampal region (GW = 15%, LJ = 6%, MJ = 3%).

Finally, another possible reason why the DA patients did not show an impairment on single item recognition could be that their somewhat preserved recognition abilities are due to functional reorganisation and/or the development of compensatory strategies due to their child-onset pathology (e.g. Nelson, 2000). Although it is not possible to completely rule this out through the studies reported in this thesis, some studies of adult-onset amnesia have also reported intact single item recognition (e.g. Mayes *et al.*, 1999; 2001; Holdstock *et al.*, 2000a; 2000b).

The amnesic adults reported by Stark *et al.* (2002) were also impaired at associative recognition when given one study-test trial of 10 house-face pairs. The task used by Stark *et al.* (2002) involved nonverbal pairs of items from different semantic categories and therefore may be analogous to the voice-face and object-place associative recognition conditions used here, as these consist of stimuli from different processing modalities/streams. Despite task procedure differences, the findings of impairments in the DA group on voice-face and object-place associative recognition are consistent with the findings reported by Stark *et al.* (2002) on house-face associative recognition. The finding that patients with hippocampal damage (both adults and DA) are impaired at cross-category/modality associative learning is also consistent with the finding of increased hippocampal activation when encoding (Henke *et al.*, 1997) and retrieving (Yonelinas *et al.*, 2001) cross-category pairs and scenes (e.g. Kohler *et al.*, 2002).

8.4.2 Object-place recognition

The finding of an impairment in object-place recognition in patients with DA relative to the control group is consistent with findings from some monkey studies (e.g. Gaffan, 1994; 1998; Brown and Xiang, 1998; Murray *et al.*, 1998; Hamstead *et al.*, 2001) and the performance of a patient with adult-onset selective hippocampal pathology, YR (Mayes *et al.*, 1999). In addition the finding that place-only recognition was impaired, although inconsistent with the previously reported findings of Vargha-Khadem *et al.* (1997), is consistent with the findings in studies of monkeys with hippocampal lesions (e.g. Parkinson *et al.*, 1988; Angeli *et al.*, 1993). Together these findings suggest that the

hippocampus is necessary for spatial memory including object-place associations even when only a single 3-stimulus array is to be remembered over a relatively short delay.

However, a recent study by Malkova and Mishkin (2003) found that monkeys with lesions restricted to the hippocampus, i.e. not including the parahippocampal cortex, parasubiculum or presubiculum (posterior parahippocampal region), were not impaired at object-place (2-pair list length) or place-only one trial recognition when tested after a 6-second delay. However, monkeys with lesions to the posterior parahippocampal region were impaired at both one-trial object-place and place-only recognition. These findings suggest that the posterior parahippocampal region support spatial memory including object-place recognition.

Whether the performance of patients with DA is associated with additional damage to the posterior parahippocampal region remains to be addressed and is beyond the remit of this thesis. However, as already mentioned, preliminary volumetric analysis of the entorhinal, perirhinal and parahippocampal cortex of five patients with DA (the recognition performance of three of these are reported in this chapter), indicated normal volumes (Schoppik *et al.*, 2001). Furthermore, the preserved object-only recognition demonstrated by patients with DA is consistent with findings of preserved item recognition in monkeys with hippocampal lesions (e.g. Murray and Mishkin, 1998; Buckmaster *et al.*, 1999) and suggests intact functioning of the perirhinal cortices (for a review see Brown and Aggleton, 2001). It seems unlikely that the injury associated with DA involves the hippocampus, parahippocampal cortex, parasubiculum and presubiculum but not the perirhinal cortex as there is no reason to suspect that their aetiology (as described in Appendix A) would be associated with this particular pattern of damage to the MTL structures.

The findings reported in this chapter suggest either that the DA group have extra-hippocampal damage extending to the posterior parahippocampal cortex, or that in humans, the hippocampus is required for object-place and place memory even at very short delays with very low memory loads. Volume measurements of the posterior parahippocampal cortex in patients with DA may help to disentangle these hypotheses.

Although Malkova and Mishkin (2003) present a convincing case for the role of the posterior parahippocampal region in spatial memory, it remains to be seen whether a direct replication of the tasks reported in this chapter (list-length of 20 locations, spatial alterations in 3-item arrays) would be preserved in monkeys following selective

hippocampal lesions. It would also be of value to compare the performance of patients with DA to that of monkeys with similar lesions sustained early in development using the same tasks in order to test whether differences in the developmental nature of the disorder could account for differences in recognition performance. Furthermore, it is possible that the difference between the findings reported in this chapter and those of Malkova and Mishkin (2003) are due to the difference in delay between study and test. That is, it is possible that the hippocampus is only required for object-place and place-only recognition when the delay exceeds a few seconds. This hypothesis could be tested by administering a test of object-place and place-only recognition to monkeys with hippocampal lesions after a longer delay, and to patients with DA after even shorter delays.

Finally, it is of interest to consider whether the deficit in spatial memory demonstrated by patients with DA reflects an allocentric or egocentric spatial memory deficit (e.g. Holdstock *et al.*, 2000a; Kessels *et al.*, 2001; King *et al.*, 2002). The place component of this study could be defined as either allocentric or egocentric. The location of the object can be specified either in relation to the other 39 circles (allocentric view), or in relation to the observer whose position does not change between study and test (egocentric view). Therefore, it is possible for participants to apply either an allocentric or egocentric strategy to this task. However, impairment in the DA group could be the result of deficient allocentric spatial memory only (e.g. King *et al.*, 2002), which forced them to rely on an egocentric strategy, since the control group may have utilised both strategies and thus performed more effectively. This could be investigated in more detail in the DA group using a task like that reported by King *et al.* (2002), which manipulates task dependence on either ego- or allocentric spatial memory strategies.

8.4.3 Conclusion

In relation to theories of hippocampal function, these findings suggest that patients with DA demonstrate a different profile from that of the adults described by Stark *et al.* (2002), in that one-trial single item recognition is preserved. Although the methodology between the two studies differ, it is possible that the preserved performance demonstrated by patients with DA is a consequence of somewhat preserved familiarity-based recognition. This may be supported by intact parahippocampal cortices (Meunier *et al.*, 1993; Mishkin *et al.*, 1997; 1998; Aggleton and Brown, 1999). Furthermore, the

parahippocampal region may support one-trial intramodal associative recognition. The structural and functional integrity of the parahippocampal region, particularly the posterior parahippocampal cortex, needs to be confirmed with volumetric measurements and fMRI studies in order to assess this hypothesis.

9 RECOLLECTION VERSUS FAMILIARITY

Previous studies of patients with DA have suggested that recognition memory may be relatively preserved following bilateral hippocampal injury sustained in childhood (Vargha-Khadem *et al.*, 1997; Baddeley *et al.*, 2001). Furthermore, a study of a single case, Jon (DA1), using event related potentials suggested that familiarity-based recognition memory might be preserved, whereas recollection-based recognition might be impaired (Düzel *et al.*, 2001). This chapter describes a study that manipulated the levels-of-processing (LOP) at encoding (Craik and Lockhart, 1972) followed by an old/new recognition memory test. As DA is thought to result in impaired recollection-based but preserved familiarity-based recognition it was predicted that patients with DA would show a reduced LOP effect with impaired recognition of deep but not shallow encoded items relative to controls. An overall analysis of correctly recognised deep, shallow and rejected new items revealed that both groups showed a LOP effect and the control group performed more accurately than the DA group in all conditions. Thus there was no difference between the groups in the magnitude of the LOP effect. These findings suggest that DA may be associated with residual recollection-based recognition memory, although this is impoverished relative to controls.

9.1 INTRODUCTION

As discussed in Section 1.7.3 in Chapter 1, recognition is thought to comprise of two levels of awareness, recollection and familiarity (e.g. Atkinson and Juola, 1973; Mandler, 1979; Jacoby, 1983; Tulving, 1985a; 1985b; Yonelinas, 1994; Aggleton and Brown, 1999). Recollection-based recognition is accompanied by retrieval of details about the specific study event, while familiarity-based recognition is accompanied by a feeling of familiarity about the item without retrieving specific details of the study event. According to the memory model proposed by Tulving (1983, 1985a), retrieval from episodic (autonoetic) memory is associated with remembering (recollection) and retrieval from semantic (noetic) memory is associated with knowing (familiarity), and retrieval from either system is independent. In support of this, in a recent review of the literature Yonelinas (2002) found many examples of task manipulations that effect recollection more than familiarity (e.g. the LOP paradigm, Gardiner *et al.*, 1996; Yonelinas *et al.*, 1998), familiarity more than recollection (e.g. changing the perceptual characteristics of an item between study and test, e.g. Gregg and Gardiner, 1994; Toth, 1996), or both equivalently (e.g. increasing study duration, Dewhurst and Anderson, 1999; Jacoby *et al.*, 1999).

As discussed in Section 1.7.3.1, Chapter 1, although recollection-based and familiarity-based recognition memory are thought to be subserved by the MTL and its cortical connections, the precise role of these structures in recognition memory remain under debate. As discussed throughout this thesis neuroanatomical models of memory can be divided into two types: unitary-system models and multi-system models. The unitary-system model of MTL function proposes that both the hippocampus and parahippocampal region support both recollection and familiarity (e.g. Squire and Knowlton, 1995). This model was recently supported by Manns *et al.* (2003b) who found that patients with relatively selective hippocampal pathology were impaired at both "remember" and "know" judgements. However, an alternative multi-system model proposed by Aggleton and Brown (1999) suggests that familiarity-based recognition is dependent on the perirhinal-medial dorsal thalamic circuit, whereas recollection-based recognition is dependent on the hippocampal-anterior thalamic circuit. This model, like others, (e.g. Mishkin *et al.*, 1997) proposes that a dissociation between recollection and familiarity-based recognition memory can occur following damage restricted to the hippocampus.

Indeed as described in Section 1.7.3.2, Chapter 1, there is a great deal of evidence from animal studies to support this (for reviews see Brown and Aggleton, 2001; Brown and Bashir, 2002) and recently human lesion studies have demonstrated similar findings. For example, persevered familiarity-based recognition (as indicated by "know" responses and receiver-operating characteristic (ROC) curves) has been found in patients with lesions restricted to the hippocampus (suspected based on hypoxic-ischaemic aetiology, e.g. Yonelinas *et al.*, 2002), whereas both recollection- and familiarity-based recognition ("remember" and "know" responses) have been shown to be impaired in patients with more extensive MTL pathology (Knowlton and Squire, 1995; Lazzara *et al.*, 2001).

9.1.1 Neuroimaging evidence for recollection and familiarity

Further evidence for a dissociation between recollection-based and familiarity-based recognition memory in humans, can be seen in studies using event related potentials (ERP) and other imaging methods such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET).

In an attempt to identify the neural correlates associated with recollection and familiarity, studies have compared ERPs evoked by 'remember vs. know' judgements (e.g. Smith, 1993; Düzel *et al.*, 1997; Rugg *et al.*, 1998b), 'deep vs. shallow' processing (e.g. Rugg *et al.*, 1998a; 1998c) and 'word vs. nonword' recognition (e.g. Curran, 1999). LOP studies have identified three ERP components (e.g. Düzel *et al.*, 1997; Rugg *et al.*,1998c): a late-positive going left parietal ERP component peaking at ~600 ms post-stimulus onset (LPC), associated with correctly recognised deep items compared to shallow or new items (recollection component); a frontal-central waveform peaking at ~400 ms post-stimulus onset (N400) that was more positive for correctly recognised items than for new items or old words misclassified as new (familiarity component); and a further parietal component around 300-500 ms post-stimulus onset that was more positive for old compared to new items independent of accuracy or level of processing, possibly reflecting implicit memory.

In relation to theories of recognition, an important observation to note is that the familiarity-based component (N400) was present independent of deep/shallow processing, remember/know judgement or word/nonword items, suggesting that recollected items are also accompanied with this familiarity component in healthy individuals (e.g. Rugg *et al.*, 1998c; Curran, 1999).

Although ERP studies have good temporal resolution they do not provide detailed information about the structural location of activation due to recording from the scalp. fMRI and PET studies have identified regional activation/cerebral blood flow differences between 'deep vs. shallow' encoding (e.g. Kapur *et al.*, 1994; Grady *et al.*, 1998; for a review see Buckner *et al.*, 2000), 'deep vs. shallow' retrieval (e.g. Rugg *et al.*, 1997; Rugg *et al.*, 1998a) and 'remember vs. know' judgements (e.g. Henson *et al.*, 1999; Eldridge *et al.*, 2000), suggesting different structural regions are involved in recollection and familiarity. Moreover, some of these studies have identified increased hippocampal activation/cerebral blood flow with the recognition of deep relative to shallow encoded items (e.g. Rugg *et al.*, 1997; 1998a), "remember" relative to "know" responses (e.g. Eldridge *et al.*, 2000) and "remember" relative to "new" response (Henson *et al.*, 1999). Therefore the hippocampus may play a special role in recollection.

9.1.2 LOP as a test of recollection and familiarity

In 1972, Craik and Lockhart published an influential paper suggesting that remembering is a by-product of cognition and what determines what is to be remembered is not the intention to remember per se, but the extent to which events are attended, processed and organised. Craik and Lockhart's (1972) LOP theory postulates that the more deeply an item is processed the better it will be remembered, with information processed in superficial sensory terms (e.g. attending to type script) giving rise to relatively short-term traces, and phonological processing (e.g. rhyming) producing a more intermediate trace, while deep semantic processing (e.g. category membership) produces the most durable learning, hence a LOP effect.

Studies manipulating LOP in healthy participants suggest that meaning-based (i.e. deep processing) compared to perceptual-based processing (i.e. shallow processing) at encoding increases both recollection and familiarity, but that recollection is more sensitive to the effect than familiarity. For example, a large number of studies using process estimation measures (e.g. remember/know paradigm, ROC procedure) have found that deep processing leads to a large increase in recollection and a smaller but consistent increase in familiarity (e.g. Gardiner, 1988; Toth, 1996; Khoe *et al.*, 2000).

LOP manipulations seem to influence explicit recognition but not implicit perceptual priming tasks (e.g. Challis and Brodbeck, 1992; Craik *et al.*, 1994; Mulligan, 1999). However, a few studies have found evidence to suggest that deeper encoding

increases subsequent conceptual priming in healthy participants (e.g. for a review see Challis and Brodbeck, 1992), and to a lesser degree in patients with amnesia, (e.g. Jenkins *et al.*, 1998; but see Lazzara *et al.*, 2001). It has been suggested that this LOP effect is due to the contribution of explicit memory (e.g. Challis and Brodbeck, 1992; Hamann and Squire, 1996) or lexical processing (for a discussion see Jenkins *et al.*, 1998).

9.1.3 LOP effects in patients with amnesia

In order to examine the role of the MTL-cortical circuit, described in Section 1.2, Chapter 1, in recollection-based and familiarity-based recognition memory, a number of studies have tested patients with amnesia using the LOP paradigm (e.g. Cermak and Reale, 1978; Meudell *et al.*, 1980; Yonelinas *et al.*, 1998; Lazzara *et al.*, 2001). These studies have found that although overall recognition memory performance was lower than that found in controls, patients with amnesia showed a LOP effect when memory was tested shortly after study.

It is unclear as to what might be supporting the LOP effect in patients with amnesia. One suggestion, proposed by Yonelinas *et al.* (1998), is that the LOP effect found in patients with amnesia is supported by short-lived recollection processes. Indeed many studies of amnesia report recollection to be more impaired than familiarity, but not eliminated in amnesia (for a review see Yonelinas, 2002). In addition, in some of these studies memory for deep encoded items was more impaired relative to controls than shallow encoded items, hence a reduced LOP effect in patients relative to controls (e.g. Meudell *et al.*, 1980; Yonelinas *et al.*, 1998). If shallow items reflect familiarity-based recognition then the reduced LOP effect might indicate preserved familiarity-based recognition as familiarity-based recognition is influenced by LOP albeit to a lesser degree than recollection-based recognition. These studies included groups of patients with mixed aetiology, patients without magnetic resonance imaging (and therefore possibly damage greater than suspected based on aetiology), or patients with damage to both the hippocampus and parahippocampal region, and/or in some cases diencephalic regions. A better model for addressing the MTL contribution to recollection/familiarity might be to test patients with restricted hippocampal lesions, as these patients according to the multi-system model of MTL function would be impaired at recollection but not familiarity-based recognition.

In order to examine whether familiarity-based recognition was preserved in patients with selective hippocampal lesions, Lazzara *et al.* (2001) compared the performance of patients with hypoxia-ischaemia (and therefore suspected selective hippocampal pathology) with that of patients with more extensive MTL lesions. The results confirmed their prediction; patients with more extensive MTL pathology were impaired on familiarity estimates (collapsed across both deep and shallow) relative to the hippocampal lesioned patients. Unfortunately, the authors did not compare these separate groups to a control group so it is unknown whether the patients with the more selective hippocampal lesions were not different from controls on these measures. However, a subsequent study by Yonelinas *et al.* (2002) suggests that these same patients with suspected selective hippocampal lesions were not impaired relative to controls on estimates of familiarity. Also, Lazzara *et al.* (2001) collapsed deep and shallow items, therefore it is not possible to compare the magnitude of the LOP effect between patients with more selective hippocampal lesions and those with more extensive MTL lesions.

No known studies of LOP effects on subsequent recognition in patients with confirmed selective hippocampal lesions sustained in adulthood have been reported to date. However, in a recent study, the effect of deep encoding (living/nonliving or abstract/concrete judgements) on subsequent recognition has been reported using ERPs with Jon, a case of DA (Düzel *et al.*, 2001). In the old/new recognition test Jon's behavioural performance was reduced compared to controls (69.3% hits versus 88.3%, respectively). In controls, correctly recognised "old" words (hits) elicited more positive ERPs in both the N400 and LPC time windows compared to correct rejections. Jon's ERPs were also more positive in response to correctly recognised "old" compared to correct rejections, but this was only evident in the N400 time window. That is, unlike controls Jon did not show the LPC, recollection-based component. Furthermore, Jon showed more positive ERP waveforms for unrecognised "old" words (misses) than correct rejections at frontocentral and left posterior temporal electrodes (similar to the 'implicit' component described by Rugg *et al.*, 1998c). These findings suggest that although deep encoding facilitates recollection-based and familiarity-based recognition in control participants, a recognition impairment was evident in Jon, presumably because of his inability to benefit from the normal effect of deep encoding on recollection. However, this study did not test recognition of shallow encoded items, therefore a comparison between the magnitude of LOP effects between Jon and his controls was not permitted.

9.1.4 Specific aims and predictions

Based on the discussions above, is it concluded that both recollection and familiarity are influenced by LOP whereby memory is greater for deep compared to shallow encoded items (e.g. Toth, 1996). However, this effect is stronger for recollection than familiarity-based recognition (e.g. Yonelinas, 2002).

This study aims to test whether DA is associated with intact familiarity-based recognition but impaired recollection-based recognition (consistent with the multi-system model of MTL function) as measured by a reduced LOP effect in recognition accuracy relative to controls. A LOP paradigm was used as opposed to a remember/know paradigm for two reasons: (i) preliminary work with patient Jon (DA1) suggested that patients with DA might have difficulty understanding remember/know task instructions; (ii) EEGs were also recorded during task performance, therefore to be consistent with other studies that recorded EEGs a LOP paradigm was used. The LOP paradigm involves an incidental learning task with simple instructions suitable for young participants.

It is predicted that:

(a) If patients with DA have intact familiarity-based but impaired recollection-based recognition they will show a reduced LOP effect relative to controls, with impairments in subsequent recognition of deep but not shallow items (a Group by Condition interaction).

9.2 METHOD

9.2.1 Participants

Ten[1] patients diagnosed with DA and twelve controls participated in this study. Details of the participants can be found in Chapter 2. The groups did not differ on age at test ($p > 0.1$), performance IQ ($p > 0.1$) or verbal IQ ($p > 0.1$).

[1] Patient DA4 did not take part in this phase of the study. Patient DA7 was excluded from the analysis, as he was unable to accurately recall the button presses after the recognition task. See Section 9.2.3.

9.2.2 Stimuli

In the following study, pictorial items were presented for study and test. Pictures were used in this study to ensure that memory would be independent of reading ability, and therefore appropriate for low functioning participants as well as young children. Also word frequency effects influence the LOP effect (Duchek and Neely, 1989) and these can vary by age (Troia *et al.*, 1996). A pilot study indicated a LOP effect with pictorial stimuli (Takeoka *et al.*, unpublished data).

The stimuli were 200 different colour pictures (height = 80 mm, width = 100 mm) of everyday objects presented on a grey background. Each image had a white letter S or number 5 (front size = 10) presented on a black background superimposed on or near it, as shown in Appendix H. The stimuli were counterbalanced across participants so that each picture (excluding practice items) appeared equally often as a shallow, deep or new item.

9.2.3 Procedure

Study phase: The participant was instructed to fixate on the black cross (+) in the centre of the screen and that familiar objects would briefly appear one at a time, each of which would have a letter S or number 5 superimposed on or near it. The participants were told that just before each picture presentation the cross would turn red and they would hear an auditory instruction of either "indoor, outdoor" or "S or five" through a set of speakers. If the participant heard the former, s/he was required to press one of two buttons to indicate whether the object is typically found inside or outside (deep encoding). If the participant heard the latter, s/he would have to press one of the two buttons to indicate which of the two characters was superimposed or near the object (shallow encoding).

Generally participants found it easier to associate the first presented instruction with their right hand. Therefore, when the hand responding to each of the choices was counter-balanced across the participants so were the order of instructions. For example, for one order of instructions, "indoor, outdoor" or "S or five", the right-hand button corresponded to "indoor" and "S" and the left-hand button corresponded to "outdoor" or "five". For the alternative order of instructions, "outdoor, indoor" or "five or S", the right-

hand button corresponded to "outdoor" and "five" and the left-hand button corresponded to "indoor" or "S".

The study phase consisted of three blocks: a practice block of 20 trials and two study trials of 60 trials each. In each block half of the trials were presented for deep encoding and half were presented for shallow encoding and these conditions occurred randomly within each block. The practice block was administered twice for five of the DA patients (DA2, DA5, DA7, DA10, DA11) to ensure that they were confident with the task instructions. The participants were re-administered the full set of instructions in between the two study blocks. The stimulus duration was 1000 ms and the experimenter[2] controlled inter-stimulus interval by clicking a mouse following a response from the participant in order for the next trial to proceed. This was done to ensure that the participant made responses before the next trial proceeded. The black fixation cross was presented for 1500 ms before the encoding instruction was heard. At no point during the study phase were the participants informed that they would be required to remember the pictures later on, therefore, this was an incidental memory task.

Test phase: Immediately following the two study blocks, the experimenter explained that there would be a test of recognition of the items presented in the two study blocks. In the test phase, the 120 pictures presented for study and 60 new pictures were presented in a random order.

The presentation of the stimuli during the test phase was the same as during the study phase except that: (a) the stimuli no longer had the characters S or 5 superimposed on them; (b) the auditory instruction they heard before they saw the picture on the screen was "old or new"; and (c) the pictures were presented for 500 ms[3] (see Appendix H).

The test phase consisted of a practice block of the 20 trials previously seen in the practice study block and 3 test blocks of 60 trials. The participants were given a practice test block to ensure that they were able to remember the button presses required for the recognition test. This practice block was administered twice for four of the DA patients (cases DA2, DA7, DA10, DA12).

[2] Except for case DA1; the inter-stimulus interval was self-paced by the participant using the space bar. The self-paced procedure proved effective when piloted with healthy participants, however, after administration to this patient it was decided that this would be too demanding for some of the other DA patients.

[3] A pilot study of the task with healthy participants indicated a more convincing LOP effect with the shorter stimuli presentation of 500 ms.

During each of the test blocks, one third of the items were those deeply studied during the study phase, one third were those shallowly studied and one third were new items not previously seen. The participant was told that if they thought the picture was presented previously they should press the "old" key, while if they thought it was new they should press the "new" key. As the order of instruction was counterbalanced across participants so was the key press. The participants were encouraged to press either key even if they were to guess. Again the experimenter controlled the inter-stimulus interval to ensure that a response was made. To ensure participants understood the task instructions, the experimenter paused the task (by not clicking the mouse) during and between each test block and reminded all participants of the key presses. Finally, after completing the task, the participants were asked which button corresponded to "old" and which to "new" to test whether they had remembered the keys during the recognition task. Only one patient, case DA7, did not accurately recall the button presses and therefore this patient was excluded from the main analysis.

9.3 RESULTS

The behavioural data were analysed according to the description provided in Section 2.3.2, Chapter 2. All findings with a p-value of less than 0.05 are reported and predicted findings with a p-value less than 0.1 are described.

9.3.1 Test phase

9.3.1.1 Percentage correct at test

A mixed design analysis of variance was conducted with a between-subjects factor of group (DA, control) and within-subjects factor of condition (deep-hits, shallow-hits, new-hits).

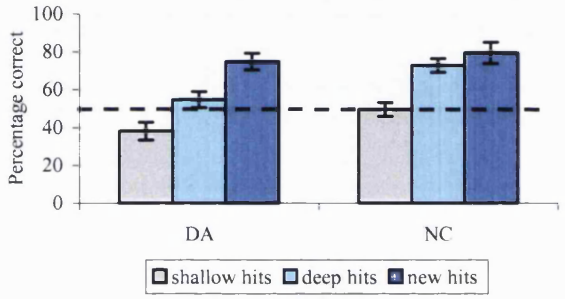
Table 9:1 and Figure 9:1 show the mean (±SEM) percentage of correctly recognised deep and shallow previously studied items (old) and the mean (±SEM) percentage of correctly rejected new items.

Table 9:1 Percentage correct at test

	DA	NC
Shallow hits	38.1 (4.7)	49.5 (3.6)
Deep hits	54.6 (4.2)	72.8 (3.7)
New hits	74.8 (4.4)	79.4 (5.6)

Mean (±SEM)

Figure 9:1 Percentage correct at test



The dashed line represents the number correct by chance (50%). Separate one-samples t-tests revealed that the performance of the control group was significantly above chance on new items ($p < 0.0001$) and deep items ($p < 0.0001$), but did not significantly differ from chance on shallow items ($p > 0.1$). The performance of the DA group was significantly above chance on new items ($p < 0.0001$) and did not significantly differ from chance on deep items ($p > 0.1$), but performance was significantly below chance on shallow items ($p = 0.03$).

The analysis (ANOVA) revealed a significant main effect of Group ($F(1,20) = 15.56$; $p = 0.001$), suggesting that the control group performed better than the DA group. There was also a significant main effect of Condition ($F(1.5,30.9) = 23.98$; $p < 0.0001$), suggesting that, as predicted, more deep than shallow items were recognised ($p < 0.0001$) and more new items were correctly rejected than both deep ($p = 0.04$) and shallow ($p < 0.0001$) items were correctly recognised. Unexpectedly, the Group by Condition interaction was not significant ($p > 0.1$).

9.3.1.2 Signal detection

As described in Chapter 4, yes/no recognition tests are prone to differences in response bias between participants and conditions (e.g. MacMillan and Creelman, 1991;

Yonelinas, 1994). Therefore, a signal detection analysis was conducted (for a description see Chapter 4). Using both hit rate and false alarms (MacMillan and Creelman, 1991), d^l (discrimination sensitivity) and c (response criterion) was calculated separately for each participant and averaged across the groups to compare the ability of the patients with DA and their controls to discriminate between old and new items (d^l) and their response criterion (c).

Table 9:2 shows the mean (±SEM) proportion of hits (collapsed across deep and shallow) and false alarms (respond "old" when correct response is "new") for both patients with DA and their controls. These proportions were used to estimate d^l and c in accordance with the calculations reported in Macmillan and Creelman (1991, for details see Chapter 4). A score other than 0 for d^l indicates an ability to discriminate between old and new items, whereas for c indicates a response bias. Negative c values arise when the false-alarm rate exceeds the miss rate (a tendency to give "old" responses), and positive c values arise when the false alarm rate is lower than the miss rate (a tendency to give "new" responses).

Table 9:2 Proportion of hits and false alarms

	DA	NC
Hits	0.47 (0.04)	0.61 (0.03)
False alarms	0.25 (0.04)	0.21 (0.06)
d^l	0.65 (0.10)	1.22 (0.21)
c	0.41 (0.12)	0.29 (0.11)

Mean (±SEM)

Only one control participant, NC8, performed at ceiling on correct rejections of new items, resulting in no false alarms. Therefore, it was not possible to calculate the d^l and c for this control case and she was excluded from the analysis.

As shown in Table 9:2, both patients and controls have a mean d^l above zero, indicating some level of discrimination sensitivity in both groups. Tests of homogeneity revealed that the variance between the groups differed on d^l, therefore a nonparametric Mann-Whitney U test was conducted. This analysis revealed that there was evidence to suggest that the control group tended to be more sensitive to discriminating (d^l) old from new items than patients with DA ($p = 0.051$).

It is also shown in the table (Table 9:2) that both groups have a positive *c* score, indicating a tendency to give a "new" response. An independent samples t-test revealed that the groups did not significantly differ on *c* ($p > 0.1$).

9.3.2 Study phase

To determine whether any LOP effect or differences between patients and controls could be accounted for by differences in performance at study, a mixed-design analyses of variance was carried out with a between-subjects factor of group (DA, control) and within-subjects factor of level of processing (deep, shallow).

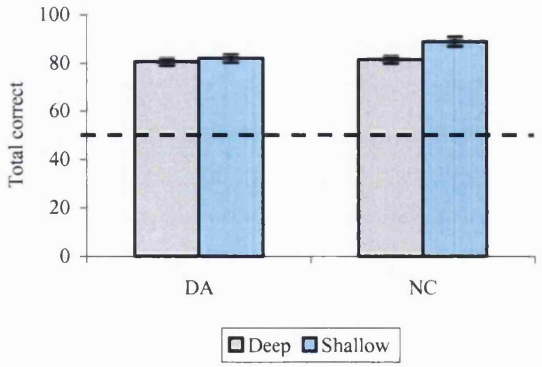
Table 9:3 and Figure 9:2 show the mean (±SEM) percentage correct deep and shallow study judgements for the control and DA groups.

Table 9:3 Percentage correct at each level of encoding

	DA	NC
Deep	80.6 (4.8)	81.5 (1.9)
Shallow	82.0 (5.7)	88.9 (2.5)

Mean (±SEM)

Figure 9:2 Percentage correct at each level of encoding



The dashed line represents the number correct by chance (50%). Separate one-sample t-tests revealed that both groups performed significantly above chance on both conditions ($p < 0.0001$).

The analysis (ANOVA) revealed, as expected, no significant main effect of Group ($p > 0.1$), but unexpectedly, revealed a main effect of Condition ($F(1,21) = 5.33$; $p =$

0.031), suggesting that more shallow than deep items were judged correctly. As predicted, the Group by Condition interaction was not significant ($p > 0.1$).

9.4 DISCUSSION

The aim of this study was to test whether DA is associated with intact familiarity-based recognition but impaired recollection-based recognition as measured by a reduced LOP effect in recognition accuracy relative to controls. It was predicted that patients with intact familiarity-based recognition would show an impairment in subsequent recognition of deep but not shallow items (a Group by Condition interaction). This prediction was not supported by the results reported in this study. Instead, both groups showed a LOP effect, but the magnitude of this effect did not significantly differ between the groups. These findings suggest that although recognition performance is impaired in patients with DA relative to controls (both deep and shallow recognition memory was lower than that of controls) the LOP effect is not impaired.

The finding of a LOP effect in the control group is consistent with other studies (e.g. Craik and Lockhart, 1972; Craik and Tulving, 1975; Gardiner, 1988; Gardiner *et al.*, 1996; Toth, 1996; Yonelinas *et al.*, 1998). As deep encoding is thought to influence recollection-based recognition more than familiarity-based recognition, this increased memory for deep relative to shallow items in controls likely reflects recollection-based recognition (e.g. Yonlinas, 2002). Therefore, one possible explanation for the finding of a LOP effect with a similar magnitude in the patient group compared to controls is that patients with DA have residual recollection-based recognition memory (e.g. Yonelinas *et al.*, 1998).

A recent study found that patients with amnesia showed LOP effects on measures of recollection, familiarity and conceptual priming (Lazzara *et al.*, 2001). Lazzara *et al.* (2001) found that the recognition performance of the patients was impaired relative to controls for "remember" responses and "familiarity" estimates, but performance on the conceptual priming task did not differ between the groups. Importantly, similar to the findings reported in this chapter, there was no Group by Condition interaction on any of these measures. These findings suggest that like that of controls, the LOP effect in patients with amnesia can be supported by recollection, familiarity and conceptual

priming. However, the finding, in this chapter, that overall recognition performance was reduced in patients relative to controls suggests that the processes that contribute to recognition in patients with DA are not as efficient as those in the control group. It is difficult to conclude which processes support the LOP in the patients with DA as this study did not include additional estimates of recollection and familiarity (e.g. remember/know responses, ROC procedure, ERP). Therefore further investigation is needed in order to confirm the contribution of recollection and familiarity to the LOP effect in patients with DA. However, the LOP effect possibly reflects the contribution from both recollection-based and familiarity-based recognition and possibly conceptual priming, albeit less efficient than that of controls, as if only one of these processes was impaired, particularly recollection, there should be a reduced LOP effect compared to that of controls.

The results of the main analysis of variance also indicated that the patients with DA were impaired relative to the control group at correct rejection of new items. However, both groups performed better on correct rejections than deep and shallow recognition memory. This finding suggests that patients and controls found it easier to correctly identify new items than to recognise old items. In order to correctly reject new items the participant must experience a memory of the study event to decide that the item was not presented. In patients this increase in novelty discrimination relative to recognition of old items might indicate residual function of the hippocampus and/or preserved function of the parahippocampal region. For example, human imaging studies have shown increased activation in the hippocampus in response to novelty discrimination (e.g. Dolan and Fletcher, 1997; 1999) and animal imaging studies have shown that neurons in the perirhinal cortex increase activation in response to novel stimuli (e.g. Zhu *et al.*, 1995). The better performance in the control group relative to the patients might reflect more efficient function of these structures in novelty detection.

However, a participant may also achieve a high correct rejection score if they show a bias towards giving a "new" response on an old/new recognition test. Although this seems plausible in the DA group given the poor recognition of old items (as indicated by the significant main effect of Group and weak evidence for a group difference on d^{l}), and the finding that the DA group responded consistently below chance on shallow recognition, this was not confirmed by an analysis of c, an index of response bias. This analysis indicated that although the DA group showed an increased bias towards giving

"new" responses, this was also true for the controls, and there was no evidence of a group difference. This is consistent with the finding that both groups performed better on the correct rejection of new items relative to correct recognition of old items and that both groups performed significantly above chance on the correct rejection of new items. However, this does not explain the group difference in performance on correct rejections, suggesting that differences other than response bias must account for the group difference on percentage correct rejections. One possibility, as mentioned above, is the functional integrity of the MTL structures.

A chance analysis also revealed that the performance of the DA group did not significantly differ from chance on recognition of deep items, indicating, as expected, poor recognition of deep items, but the control group performed above chance on the recognition of deep items, suggesting good recognition of these items. The performance of the control group, however, did not significantly differ from chance on recognition of shallow items, indicating poor recognition of shallow items, whereas in patients with DA, performance was below chance on recognition of shallow items suggesting that patients with DA responded to shallow items as if they were new items. This suggests that the LOP effect found in the two groups, although of a similar magnitude is possibly associated with different processes. That is, in the control group, recognition of deep items is good, whereas recognition of shallow items, although poor, did not differ from chance. The patients with DA on the other hand, performed no different from chance on recognition of deep items, but systematically respond to shallow items as if they were new. This may be associated with differences in discrimination sensitivity or response bias between the groups on the different conditions. Unfortunately, due to the test procedure it was not possible to calculate measures of discrimination sensitivity (d^1) or response bias (c) for each condition (i.e. deep versus shallow), as there was no means of measuring the number of false alarms representing deep compared to shallow items.

Another possible reason for a difference between the recognition of deep and shallow items at test is due to differences at study. If judgements are easier to make in one encoding condition than another it is possible that participants would spend less time looking at the easier items and therefore may encode the items to a lesser degree. This in turn may affect the LOP effect, as the condition in which judgements were easier to make would be encoded to a lesser degree and therefore would be associated with poorer recognition. In order to determine whether the encoding conditions differed in difficulty

the accuracy of the study responses were analysed. The results suggested that the groups did not differ in their judgements, and performance on both conditions was above chance, but that both groups found it easier to make shallow (S/5) than deep (indoor/outdoor) judgements. This might cause subsequent recognition of the shallow items to be impaired due to less encoding, in which case, this may enhance the LOP effect. This might explain why performance was so low on shallow recognition in the control group. However, it cannot explain any differences or lack there of between the groups at test because the encoding effect was the same for both groups.

9.4.1 Unitary versus multi-system models of MTL function

As predicted by the unitary-system model, recognition of both deep and shallow items is impaired in patients with DA relative to controls. However, as predicted by the multi-system model patients with DA show a LOP effect, although contrary to the prediction of the multi-system model, this LOP effect is not reduced relative to controls. Therefore, the findings reported in this chapter do not selectively support either model of MTL function.

It is difficult to determine what processes account for the LOP effect in patients with DA without additional measures of recollection and familiarity (e.g. ROC curves, remember/know judgements). However, it may be that the remaining hippocampal tissue can support some degree of recollection in this group of patients with DA, hence a preserved LOP effect but impaired recognition.

9.4.2 Limitations of the LOP paradigm

Although as mentioned in the Introduction to this chapter, there are a number of studies that find a LOP effect in controls and patients with amnesia, there are also a number of limitations with the LOP theory. One limitation is that there is no generally accepted way of independently measuring LOP, i.e. the level of processing is determined by performance at retrieval, where a good performance is assumed to reflect deeper encoding. One independent measure of the LOP effect on retrieval is the use of the ERP technique. This technique has demonstrated two components associated with LOP, separated by latency and topography; the LPC component and the N400 component. Studies have suggested that the LPC and N400 components are associated with accurate recognition of deep encoded items, whereas only the N400 component is associated with

accurate recognition of shallow encoded items. Therefore, ERP studies may help to dissociate between recollection and familiarity contributions to LOP effects.

A further limitation is that the LOP theory does not specify the relevant retrieval conditions. For example, a study by Morris *et al.* (1977) found that the level of accuracy at retrieval was influenced by the retrieval condition, where semantic encoding resulted in better retrieval than rhyming when participants were given a "old/new" test, but rhyming resulted in better retrieval when participants were required to judge on the basis of rhyme (i.e. does the test item rhyme with a previously presented study items). In relation to the findings reported in this chapter, the findings of Morris *et al.* (1977) suggest that recognition of the shallow items might be improved if the test conditions were made to be similar to the shallow study conditions. This may be achieved if the test pictures were to also display the symbols S or 5 as they did in the study phase (in the current experiment the symbols were removed at test).

9.4.3 Conclusion

The findings presented in this chapter confirmed the prediction that the patients with DA would be impaired on recognition of deep items. However, unexpectedly, the patients did not show a reduced LOP effect in that they were not more impaired at recognition of deep compared to shallow items. Instead their performance was impaired overall compared to controls. It is possible that these findings indicate that patients with DA have residual recollection abilities. Another possible reason for these findings is that the preserved LOP effect in the DA group reflects familiarity-based recognition memory for the deep encoded items and a severely impaired recognition of the shallow items. However, this will need to be confirmed using other process estimation paradigms, such as the remember/know paradigm, ROC procedure, and ERP studies, under conditions where recognition of shallow items is above chance. In relation to theories of long-term memory organisation these findings suggest that patients with DA show some level of recollection-based recognition, and therefore do not selectively support either the unitary or multi-system model of MTL function.

10 GENERAL DISCUSSION

The studies reported in this thesis aimed to further characterise the memory profile associated with bilateral hippocampal pathology sustained in childhood, DA. To this end, three potential dissociations in memory were examined in detail, episodic versus semantic memory, recall versus recognition memory, and recollection versus familiarity-based recognition memory.

Twelve patients participated in the studies reported in this thesis. These are described in detail in Chapter 2. All patients had evidence of bilateral hippocampal pathology, sustained during the course of development, as revealed on conventional MR imaging, and all had intellectual abilities in the average range despite severe everyday memory difficulties. A control group was also included for comparison, matched to the patient group on age, sex, and verbal IQ in order to account for possible confounding factors in the between-subjects analyses.

This chapter aims to summarise the general findings of the studies reported in this thesis. Possible reasons for the findings will be given in relation to models of memory organisation and the neuropathology associated with DA. Next, future directions for the study of DA will be suggested, and finally a general conclusion will be drawn.

10.1 DISSOCIATIONS IN MEMORY

As described in Chapter 1, amnesia is a disorder of long-term declarative memory that occurs in the absence of any other obvious signs of intellectual, short-term memory or nondeclarative memory dysfunction. Many theories for the possible causes of this profile have been postulated over the years (e.g. Warrington and Weiskrantz, 1970; Cermak *et al.*, 1974; Warrington and Weiskrantz, 1982; Squire and Zola, 1998; Tulving and Markowitsch, 1998; Isaac and Mayes, 1999a; 1999b).

Current models of amnesia agree that episodic memory is impaired, but there is disagreement as to whether all aspects of anterograde declarative memory is impaired. According to Squire and colleagues (e.g. Squire, 1987; 1992; 1994; Squire and Knowlton, 1995; Squire and Zola-Morgan, 1991; 1996; 1998; Manns and Squire, 2002) amnesia is associated with impairments in both episodic and semantic memory, and recall and

recognition, whereas according to Tulving and colleagues (Tulving 1985a; 1995; 2001; 2002; Tulving and Markowitsch, 1997; 1998) an episodic memory impairment does not necessarily equate to an impairment in semantic memory. As described in Section 1.6, Chapter 1, neuroanatomical models have been postulated to account for the amnesia profile. The neuroanatomical models of Squire and colleagues (Squire and Zola-Morgan, 1991; 1996) propose that the MTL, a region typically damaged in patients with amnesia, functions as a unitary system, supporting all forms of declarative memory. Thus dissociations in anterograde memory are not possible following selective MTL damage, while additional damage to the frontal lobes may be associated with a disproportionate impairment in episodic memory and free recall. The alternative view, held by Mishkin and colleagues (Mishkin *et al.*, 1997; 1998) and Aggleton and colleagues (Aggleton and Brown, 1999; Brown and Aggleton, 2001) is that the hippocampus is necessary for episodic memory, while the parahippocampal region can support semantic memory and familiarity-based recognition memory, hence a multi-system model of MTL function.

This section will begin with a discussion of the findings in relation to the general dissociations associated with amnesia, such as declarative versus nondeclarative memory, immediate versus delayed memory and visual versus verbal memory. Next, the findings reported in this thesis will be discussed in relation to the dissociations predicted by the multi-system model of MTL function, namely, episodic versus semantic memory, recall versus recognition, item versus associative recognition, and recollection versus familiarity-based recognition.

10.1.1 Declarative versus nondeclarative memory

Although both the unitary-system and multi-system models of MTL function predict nondeclarative motor skill learning to be unimpaired previous studies suggested that DA may be associated with additional damage to basal ganglia (Gadian *et al.*, 2000; Salmond *et al.*, 2000a; 2000b). The findings presented in Chapter 2 suggested that the patients were unimpaired relative to controls on a test of motor skill learning. This functional preservation was confirmed by the MR findings presented in Chapter 3, in that there was no evidence of basal ganglia structural abnormality in patients with DA relative to controls.

10.1.2 Immediate versus delayed recall memory

Tests of verbal and nonverbal immediate recall memory demonstrated that patients with DA were not impaired on tests of memory span (Chapters 2, 4 and 6), but were impaired relative to controls on tests of immediate memory when memory was greater than memory span (Chapters 2, 4, 5, 6). Although previous studies of DA did not report such deficits (e.g. Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000), closer examination of the data reported in these studies suggests a trend in this direction. Furthermore, preliminary findings comparing early- (up to 1 year of age) with later-onset (6–14 years) cases with DA found that later-onset cases were more impaired than early-onset cases at immediate recall of stories and paired associates but there was no difference between the two groups at delayed recall (Vargha-Khadem *et al.*, 2001).

It is interesting to note that when presented with a supra-span word-list of sixteen items (Chapters 4 and 6), patients with DA, like controls, recalled the same number of items as would be expected from memory span on the first recall trial. However, when presented with a supra-span story of approximately twenty-three pieces of information (e.g. WMS-a, Chapter 2), patients with DA were impaired relative to controls because the amount of story information retrieved by controls, but not patients, exceeded memory span. This possibly reflects impairments in the 'episodic memory buffer', the temporary store that interfaces with long-term and short-term memory (e.g. Baddeley, 2000; Baddeley and Wilson, 2002). This buffer is thought to be involved in the retrieval of integrated information over short delays (e.g. Prabhakaran *et al.*, 2000). Immediate story recall can be considered as recall of integrated information, which possibly accounts for the difference in recall between patients and controls.

Although immediate memory was found to be impaired, patients with DA generally showed the expected pattern of delayed recall memory being more impaired than immediate recall memory (Chapter 2, 4, 6), suggesting abnormal forgetting and thus supporting the consolidation/storage deficit of amnesia (Isaac and Mayes, 1999a; 1999b).

Despite these recall memory impairments patients with DA generally performed above zero, suggesting that they were able to remember something of the information studied even after an overnight delay as shown in Chapter 5, and Experiment 1 of Chapter 6. This may reflect that patients with DA have residual episodic memory (see Section 10.1.4), or that they are able to remember the gist of the information to be remembered, possibly related to their preserved semantic anterograde memory (Chapter 4).

Memory for the gist of the information to be remembered is often associated with false memory in normal controls (e.g. Schacter *et al.*, 1996a), which may account for the findings of increased intrusions errors (confabulations) during word-list recall in patients relative to controls (Chapters 4 and 6).

Generally patients with DA showed evidence of increased interference effects on subsequent recall (Chapters 4, 5 and 6), consistent with the increased susceptibility to interference hypothesis of amnesia (e.g. Warrington and Weiskrantz, 1970). Interference was possibly caused by the opportunity to produce errors in the study-test design (Hayman *et al.*, 1993; Hamann and Squire, 1995), or in the presentation of additional information to be remembered prior to testing recall. This increased susceptibility to interference is probably indicative of their episodic memory impairments, reflecting an inability to remember where and when the information was learned.

10.1.3 Visual versus verbal memory

It was predicted based on their bilateral pathology that patients with DA would not be differentially impaired on visual versus verbal memory (e.g. Moscovitch, 1979; Kim *et al.*, 2003). In general this was supported across the studies reported in this thesis. However, Chapter 4 indicated evidence to suggest a visual-verbal discrepancy in favour of visual memory in patients with DA, but not in controls, while, in contrast, Chapter 7 indicated a discrepancy in favour of visual memory in the control group but not in patients with DA. As these findings are inconsistent it is possible to conclude that the DA group did not show a systematic discrepancy between visual and verbal memory.

10.1.4 Episodic versus semantic memory

Both the unitary-system and multi-system model of MTL function postulate that hippocampal pathology will be associated with an episodic memory deficit. This was confirmed in Chapters 2 and 4, and was further supported in Chapter 5, in that patients with DA showed the greatest impairments on the most 'episodic' components of a nonverbal recall task. The models of MTL function, however, conflict with respect to semantic memory following amnesia. Chapter 2 indicated that all patients had intellectual abilities in the average range, likely to have been acquired post-injury onset in most of the patients studied due to their young age at injury. This preserved semantic memory was confirmed in Chapter 4, in that the patients were unimpaired relative to controls on

measures of semantic association and retrieval, general knowledge of vocabulary and everyday situations, and academic attainments. Furthermore, Chapter 6 found some evidence to suggest that learning in patients with DA benefited from repeated exposure (de-contexualised memory), and the semantic organisation of material. However, this benefit did not result in them demonstrating immediate or delayed recall memory at the same level as controls. Moreover, when semantic memory was investigated in more detail (Chapter 5), it appeared that the patients' preserved semantic memory did not enable them to recall the more 'semantic' components of a nonverbal recall task to the level of controls. However, they were able to recall at least some of these items, and there was a suggestion that they were able to remember them better than the more 'episodic' components of the sequences.

One possible reason for the discrepancy between a preserved semantic knowledge base but impaired semantic learning as tested in the laboratory is that the preserved semantic knowledge base reflects gradual learning over a number of years supported by the parahippocampal region or other neocortical structures (e.g. McClelland *et al.*, 1995), which is difficult to imitate in the laboratory due to time constraints. Furthermore, the superior performance of the controls on the laboratory-based tasks possibly reflects the additional contribution of episodic memory, available to a greater extent than in the patients with DA.

In relation to previous studies of amnesia, the finding that patients with DA have acquired a semantic knowledge base is inconsistent with some studies of anterograde semantic acquisition in adult-onset cases with selective hippocampal pathology (Cipolotti *et al.*, 2001; Manns *et al.*, 2003a), but consistent with others (e.g. Verfaellie *et al.*, 2000; Holdstock *et al.*, 2002). Even some patients with more extensive MTL lesions demonstrate intact vocabulary and factual post-morbid acquisition (e.g. Kitchener *et al.*, 1998). Furthermore, the finding that learning benefited to some degree from repetition (Chapter 6) is consistent with some studies of patients with adult-onset amnesia associated with more extensive MTL pathology (e.g. Tulving *et al.*, 1991; Hayman *et al.*, 1993). However, the anterograde semantic memory of adult-onset patients, even those with selective hippocampal lesions, is limited compared to that of patients with DA (see Holdstock *et al.*, 2002). Therefore, it is possible that the relatively preserved semantic memory in patients with DA is a consequence of their young age at injury and therefore increased capacity for reorganisation and/or development of learning strategies, or

selectivity of injury within the MTL. Irrespective of the differences between the amount of anterograde semantic memory capacity available to patients with adult-onset amnesia compared to DA, combined these findings indicate that semantic memory is supported by structures outside of the hippocampus and in some cases, outside of the MTL (e.g. Tulving *et al.*, 1991; Hayman *et al.*, 1993; Kitchener *et al.*, 1998).

In patients with DA, one candidate is the parahippocampal region and its connections with other structures in the memory circuit. Indeed, this is suggested by a significant correlation between semantic memory and grey matter density in the parahippocampal region (Chapter 4). However, the finding that learning as tested in the laboratory was not at the same level as controls suggests that patients with DA may require more effortful learning in order to achieve the same level of semantic memory as controls.

An alternative hypothesis is that the preserved performance on the tests of semantic memory reported in Chapter 4 reflect nondeclarative memory processes (e.g. Ostergaard and Squire, 1990). Although this may be the case for some of the measures of academic attainments, such as reading ability (e.g. Ostergaard and Squire, 1990), this seems unlikely for the vocabulary definition and comprehension tasks, as these measures require retrieval of factual knowledge about the world (e.g. Tulving, 1972; Tulving and Markowitsch, 1998).

A further alternative hypothesis is that semantic memory is acquired in the presence of residual episodic memory (e.g. Hamann and Squire, 1995; Squire and Zola, 1998). Although this seems plausible given that patients with DA did not score zero on most measures of episodic memory (Chapters 2, 4, 6, 7), this does not account for the findings that patients with DA do not significantly differ from controls on measures of semantic association and retrieval, but do differ from controls on measures of episodic memory (Chapter 4 and 5). That is, if residual episodic memory supported semantic memory then both episodic and semantic memory should be impaired to the same extent (Squire and Zola, 1996); this clearly is not the case from the studies reported in Chapter 4.

According to the unitary-system model proposed by Squire and colleagues (e.g. Squire and Zola, 1998) episodic memory may be differentially affected compared to semantic memory if there is additional frontal lobe pathology. This was not supported by the generally unimpaired performance of the patients with DA on tests of executive

function, thought to be subserved by the frontal lobes, reported in Chapter 2, or the whole-brain MR analysis reported in Chapter 3.

Thus, overall, patients with DA showed intact semantic memory and retrieval relative to controls, and showed an ability, though reduced, to learn new information, while they showed severe impairments in episodic memory. This dissociation is not predicted by the unitary-system model, and is unlikely to be accounted for by additional damage in other memory-related areas such as the frontal lobes. The possibility that the relatively preserved semantic abilities are mediated by parahippocampal regions remains the most plausible hypothesis.

10.1.5 Recall versus recognition memory

Both the unitary-system and multi-system models agree that episodic recall memory will be impaired following hippocampal damage. This was supported by the findings reported in Chapters 2, 4, 5, 6 and 7. However, the models differ in their predictions regarding recognition memory. The unitary-system model predicts that recognition will be impaired, while the multi-system model predicts that recollection-based recognition will be impaired but familiarity-based recognition will be preserved following hippocampal pathology.

Although recognition memory was also impaired in patients with DA (Chapters 4, 6, 7, 8, 9), this was to a lesser degree than recall memory (Chapter 7). The impairment in recognition memory may reflect the additional contribution of episodic memory (recollection) to the controls' performance. However, the better recognition compared to recall memory in the patients with DA suggests some evidence for intact familiarity-based recognition.

These findings offer some support for the multi-system model of MTL function, and possibly reflect intact functioning of the parahippocampal region (e.g. Mishkin *et al.*, 1997; 1998; Aggleton and Brown, 1999). Unfortunately, from the correlation analyses, as reported in Chapter 7, it was not possible to disentangle the evidence for or against either model of MTL function, as there was evidence to support both the multi-system and unitary-system model. Functional imaging studies may help to determine the contribution of the hippocampus and parahippocampal region to recognition memory.

The finding of a recall-recognition discrepancy in patients with DA is consistent with some studies of adult-onset patients with selective hippocampal damage (Holdstock

et al., 2000a; Mayes *et al.*, 2002). However, other studies have found evidence to suggest that both recall and recognition is impaired following selective hippocampal pathology sustained in adulthood (e.g. Manns and Squire, 1999; Manns *et al.*, 2003b) and childhood (e.g. Broman *et al.*, 1997). It is possible that the patients reported in these studies had additional damage to regions outside of the hippocampus that may normally support recognition. However, without additional whole-brain MR analysis of these cases, this remains to be tested.

10.1.6 Item versus associative recognition memory

The unitary-system model would predict that hippocampal pathology would be associated with impairments in both item and associative recognition memory (e.g. Stark *et al.*, 2002), whereas the multi-system model would predict that item recognition and some intramodal associative recognition memory might be preserved following selective hippocampal damage (e.g. Vargha-Khadem *et al.*, 1997). This was tested in the studies reported in Chapter 8. In support of the multi-system model of MTL function, patients with DA, compared to controls, showed preserved recognition memory for single items and intramodal associations when the list-length was short, and impaired recognition of cross-modal associations when list-length was long. Furthermore, object-place associative recognition was impaired when a single 3-stimulus array was to be remembered after a short delay. These findings support the view that single item recognition can be supported by structures other than the hippocampus, and further suggest that the hippocampus plays a special role in object-place recognition. Although this is consistent with other studies of human amnesia (e.g. Mayes *et al.*, 1999), it is not possible, at this stage, to rule out the contribution of additional injury to the posterior parahippocampal cortex in patients with DA; a structure thought to support object-place recognition in the monkey (Malkova and Mishkin, 2003). Volume measurements of these structures may help to test this hypothesis.

10.1.7 Recollection versus familiarity-based recognition memory

The unitary-system model predicts that both recollection and familiarity-based recognition are impaired following selective hippocampal injury (e.g. Manns *et al.*, 2003b), whereas the multi-system model predicts that intact parahippocampal regions can support familiarity-based recognition (e.g. Aggleton and Brown, 1999).

The findings in Chapters 4, 6, 7, 8, 9 suggest that recognition, although impaired in patients with DA relative to controls, is better than that predicted by the unitary-system model. In an attempt to address whether this relatively preserved recognition memory was associated with intact familiarity-based recognition, Chapter 9 presented a study that manipulated the levels-of-processing (LOP). Unexpectedly, both patients with DA and controls showed a LOP effect to a similar degree, but overall the patients with DA were impaired relative to controls. One possible reasons for patients with DA showing a LOP effect of similar magnitude to controls is that it reflects recollection-based memory in the patients with DA. This will need to be investigated in more detail under conditions where recognition of shallow items is above chance, at least in controls, before firm conclusions can be drawn.

10.1.8 Evidence for unitary-system or multi-system model of MTL function?

The findings of the studies generally support the predictions of the multi-system model of MTL function: episodic memory was more impaired than semantic memory (Chapter 4), recall memory was more impaired than recognition memory (Chapter 7), cross-modal recognition memory was impaired but item recognition memory was not (Chapter 8). The only inconclusive finding was that of recollection-based recognition compared to familiarity-based recognition (Chapter 9). Although the findings by and large support the multi-system model, some aspects of semantic and recognition memory were not as good as that of controls (Chapters 4, 5, 6, 7, 8, 9). Possible reasons for this are given below.

10.2 BRAIN-BEHAVIOUR RELATIONSHIP

The MR findings presented in Chapter 3 confirmed the presence of bilateral hippocampal grey matter reduction and further suggested abnormality in the remaining hippocampal tissue (T_2).

Furthermore, damage was also found in the thalamus (decrease) and white matter (increase) in patients with DA compared to controls. The additional damage to the thalamus although difficult to localise possibly includes the pulvinar, ventral thalamic nuclei, and the medial dorsal nucleus. Only the medial dorsal thalamic nucleus is thought

to be involved in memory, due to its connections with the perirhinal (Aggleton and Brown, 1999) and orbitofrontal cortex (e.g. Groenewegen, 1988). It has been suggested that the medial dorsal thalamic nucleus is involved in familiarity-based recognition (for a review see Aggleton and Brown, 1999). Therefore, impairments in this area might contribute to the relatively poor recognition memory demonstrated by this group of patients with DA (Chapters 4, 6, 7, 8, 9). Furthermore, this circuit may be important for anterograde semantic learning (e.g. Mishkin *et al.*, 1998; Baddeley *et al.*, 2001) and therefore damage to this area might additionally contribute to the relatively poor learning demonstrated by patients with DA in Chapter 6.

The white matter abnormalities in patients with DA may further contribute to the memory profile demonstrated in the studies reported in this thesis. White matter abnormalities may reflect aberrant pathways connecting structures within the memory circuit and beyond, and therefore may be associated with inefficient connectivity between structures. These findings are possibly associated with the developmental nature of this disorder but need to be confirmed with other measures of white matter integrity, such as diffusion tensor imaging (DTI, Basser *et al.*, 1994; Eriksson *et al.*, 2001)

Although there was no evidence of additional damage to the surrounding parahippocampal region revealed on whole-brain (VBM) analysis, there was evidence that semantic memory performance (Chapter 4) and verbal recognition (Chapter 7) correlated significantly with this region. These significant correlations indicated that a decrease in performance was associated with a decrease in grey matter density in this region. Furthermore, it is possible that the function of this region may be adversely affected by the damaged hippocampus; for example, in the rat, damage to the hippocampus was associated with hypoactivity in the perirhinal cortex (Warburton *et al.*, 2001). This may also contribute to the reduced recognition memory and semantic learning demonstrated in patients with DA relative to controls.

Therefore, there are a number of possible neuroanatomical explanations for the profile observed in patients with DA. Whether the aetiology associated with DA is the cause of additional abnormalities in the thalamus and white matter, or whether these are a consequence of early hippocampal pathology affecting the later development of these regions is unclear. However, what is clear is that the cognitive profile associated with DA can not be considered as being solely associated with selective hippocampal abnormality when one considers the whole brain and not just the MTL. More importantly these studies

suggest that conventional imaging alone is not adequate to provide a full account for the neuropathology associated with amnesia. However, further neuroimaging investigations, such as volumetrics of the parahippocampal region and DTI, are needed in order to confirm these findings.

10.3 IS JON AN ATYPICAL CASE OF DA?

Previous studies of Jon have reported preserved recognition memory and learning with repetition (Baddeley *et al.*, 2001). These findings were not replicated in Chapters 6 and 7. Therefore the question arises, is Jon an atypical case of DA? Although Jon seems to consistently perform at the higher range of the DA group performance, the data do not suggest that Jon is atypical of the group, in that he appears to be on one end of a continuum rather than an outlier. Another single case study of child-onset hippocampal pathology has been reported in the literature who performs at the opposite extreme to Jon, case MS (Broman *et al.*, 1997). Both of these single case studies (Jon, Baddeley *et al.*, 2001; MS, Broman *et al.*, 1997) are informative in that they represent two extremes of the possible outcome following bilateral hippocampal pathology sustained in childhood, but a group study enables the common memory profile to be determined.

10.4 ADDITIONAL CONSIDERATIONS

So far it seems that the memory profile associated with DA supports the multi-system model more so than the unitary-system model, and that damage beyond the hippocampus may account for some of the unexpected deficits in semantic learning and recognition memory. However, there are additional considerations to take into account when interpreting the memory profile associated with DA.

10.4.1 Heterogeneity within the DA group

The patients included in the studies reported in this thesis were of mixed aetiology and had different ages at injury. Moreover, they differed on other dimensions as well, with some cases being born preterm, some cases suffering from epilepsy, and some cases

suffering from psychiatric problems, such as depression. All of these factors could contribute to the memory profile reported in the studies of this thesis. Although such additional considerations are likely to be present in most group studies of patients with amnesia (e.g. Yonelinas *et al.*, 2002), they may account for some of the unexpected findings. For example, although a majority of the patients suffered hypoxic-ischaemic episodes, these were of varying degrees and occurred at different ages, and therefore may be associated with different outcomes (e.g. Volpe, 2001). Furthermore, premature birth is also associated with episodic memory impairments (e.g. Isaacs *et al.*, 2000). Epilepsy may also be a confounding factor in this study, as memory problems have been associated with seizure activity (e.g. Guerreiro *et al.*, 2001). Finally, psychiatric problems, such as depression have been associated with memory problems (e.g. Porter *et al.*, 2003) and may also have influenced motivational factors during testing. However, none of these factors alone have been associated with episodic memory problems as profound as those seen in the group of patients reported in this study. Moreover, despite such diversity within the group of patients on these factors, the patients were homogenous in their performance on the memory tasks, suggesting that the common factor among them, bilateral hippocampal abnormality, accounted for the episodic memory profile.

Future studies could address each of these additional considerations in turn, by testing a homogenous subset of patients, or by comparing the functional and structural profile with the relevant control groups.

10.4.2 Developmental nature of disorder

Another important consideration when interpreting the data reported in this thesis is whether the memory profile associated with DA is due to the developmental nature of the disorder (e.g. Nelson, 2000; Pascalis and de Haan, 2000), or whether this profile is also applicable to adult-onset cases with selective bilateral hippocampal pathology.

For example, some authors suggest a role for the hippocampus and MTL in the later development of other structures in the memory circuit (e.g. Pascalis and de Haan, 2000). Indeed a number of animal studies have found subsequent structural and neurochemical abnormalities in the frontal lobe following lesions to the hippocampus and other MTL structures early in development (e.g. Bertolino *et al.*, 1997; Saunders *et al.*, 1998; Hanlon and Sutherland, 2000). These findings suggest that the profile associated with DA may be peculiar to patients with bilateral hippocampal pathology sustained in

childhood due to influence of early injury on the development of later maturing structures, and/or the reorganisational capacity of the immature brain.

In relation to adult-onset cases, there is some evidence to suggest that this profile is not restricted to developmental cases. For example, other studies have reported relatively intact post-morbid semantic knowledge acquisition in patients with adult-onset hippocampal pathology (e.g. Verfaellie *et al.*, 2000; Holdstock *et al.*, 2002), albeit limited compared to that in patients with DA, and others have found evidence of intact recognition (e.g. Mayes *et al.*, 1999; 2001; Holdstock *et al.*, 2000a; 2000b). However, identical measures have not always been used, except for the Doors and People test (Baddeley *et al.*, 2001; Holdstock *et al.*, 2000a; Chapter 7); therefore direct comparisons of performance across studies is not possible.

As discussed in detail in Chapter 7, a comparison of findings from the Doors and People test (Baddeley *et al.*, 1994) across studies indicated that on tasks of recognition patient YR (Holdstock *et al.*, 2000a) performed better than the group of patients with DA, but showed a similar performance to that of Jon (Baddeley *et al.*, 2001). If Jon's recognition performance represents the higher range of performance associated with DA, then the recognition performance of patient YR also falls in this high range, and therefore is not atypical compared to that of the patients with DA. If this is the case then the profile associated with DA reflects the profile associated with hippocampal pathology and not the developmental nature of this disorder. However, this remains to be tested by assessing patients with adult-onset bilateral hippocampal pathology on the same tasks as those reported in this thesis.

10.5 FUTURE STUDIES AND DIRECTIONS

The findings of the studies reported in this thesis generated a number of questions that deserve further examination.

Generally it was found that although patients with DA were unimpaired on measures of immediate memory span, they were impaired on measures of immediate memory for information above memory span capacity. This possibly reflects interference effects, introduced by the methodological design of the tasks employed in this thesis. This could be examined in more detail by limiting the amount of opportunity for

interference from previously generated errors, or additional information to be learned. In addition, impaired immediate recall memory may be associated with an impaired 'episodic memory buffer' (Baddeley, 2000). Although this is a relatively new concept, a possible test of its function could be to assess the patients' ability to retrieve integrated information over short delays (e.g. Prabhakaran *et al.*, 2000).

Although Chapters 4, 5 and 6 attempted to address the episodic-semantic memory dissociation, and therefore the different predictions of the unitary-system and multi-system models, these chapters did not successfully tap into how patients with DA have acquired their extensive semantic knowledge. In order to address this, a future study could attempt to teach patients with DA novel information longitudinally, manipulating the amount of exposure (repetition), meaningfulness of the material, and levels of interference. These types of studies in patients with adult-onset amnesia have found that each of these factors can have marked effects on performance (e.g. Tulving *et al.*, 1991; Hayman *et al.*, 1993; Hamann and Squire, 1995), possibly explaining the relatively poor level of learning found in Chapter 6 of this thesis.

Longitudinal studies of patients with aetiologies suspected to be associated with DA, such as hypoxia-ischaemia, would enable a better understanding of the developmental trajectory of amnesia in childhood. It is known that episodic and semantic memory have different developmental trajectories (e.g. Perner and Ruffman, 1995; Nelson, 1995; 1997; Wheeler *et al.*, 1997). Therefore, a longitudinal study of how these abilities develop in children with hippocampal injury would be of theoretical importance. In relation to this, as mentioned above, comparisons between patients with adult-onset and child-onset selective hippocampal pathology, using the same measures, may help to determine the effect of age at injury, and whether the profile associated with DA is a consequence of the developmental nature of the disorder.

Another unexpected finding was that recognition memory, although less impaired than recall, was not preserved in patients with DA relative to controls (Chapters 4, 6, 7, 8, 9). Future studies could further assess recognition memory in patients with DA using fMRI studies in order to identify the neural correlate associated with recognition memory. Based on the findings of Maguire *et al.* (2001) it is possible that patients with DA would activate a different network from controls on tasks of recognition memory. In relation to this, as suggested by animal imaging studies following lesions to the memory circuit (e.g.

Warburton *et al.*, 2001; Jenkins *et al.*, 2002), PET studies may identify regions of hypoperfusion during task performance.

Although not addressed in this thesis, the role of the hippocampus in retrieval of retrograde memory is an area of equivalent contention to that of anterograde memory (as discussed in Chapter 1). Future studies could examine retrograde memory in patients with DA of older age at onset. Unfortunately, this was not possible in the patient group reported in this thesis due to a majority of the patients being of a young age at injury. However, case studies would be possible given the later onset in some of the members of the group. Such studies could investigate the patients' retrieval of retrograde personal and public events and facts relative to that of controls, in order to test whether the retrieval of episodic but not semantic memory is dependent on the hippocampus (e.g. Nadel *et al.*, 2000; Rosenbaum *et al.*, 2001).

Finally, an important direction for future research is to study how best to help these patients cope with their episodic memory impairments. Although these patients attend/attended mainstream school and in some cases technical college, they rarely go on to study at university or to obtain employment. The investigation of rehabilitation techniques, such as memory strategies (deep encoding, as suggested in Chapter 9), or repeated exposure over distributed sessions (as suggested in Chapter 6), may help these individuals further their education and independence.

10.6 CONCLUSION

The studies reported in this thesis set out to examine the role of the hippocampus in declarative memory, in relation to two models of MTL function, the unitary-system model and the multi-system model. It is apparent from this discussion that the syndrome of DA generally supports the predictions of the multi-system model of MTL function, although not conclusively, in that patients with DA showed impairments on some aspects of semantic memory and recognition memory.

The fact that there are two directly opposing models of MTL function highlights the complex role this region plays in memory. The study of DA further emphasises the complexity of the hippocampus and its interactions with other structures in the memory circuit. Thus amnesia should not be considered as the product of the dysfunction of one

'memory centre', but instead should be considered as the dysfunction of the 'memory circuit', particularly when the memory disorder is developmental.

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APPENDIX A: SUMMARY OF MEDICAL HISTORY

DA1 (Jon in Vargha-Khadem *et al.*, 1997; Case 4 in Gadian *et al.*, 2000) was delivered prematurely at 26 weeks of gestation, following a twin pregnancy. His co-twin died from apnoeic attack at age 3 days. The surviving twin weighed 940 g at birth and suffered from breathing problems that required intubation at 15 minutes, but spontaneous breathing was established 30 minutes later. Blood pH was 7.28. He did well, despite some brief apnoetic attacks, until age 3 weeks, when more severe and repeated attacks required intubation and positive pressure ventilation for 1 week. He was suspected to have enterocolitis and had stormy periods with multiple episodes of severe apnoea, again necessitating intubation and positive pressure ventilation, and he was transferred to an intensive care unit for the next 3 weeks. Thereafter, he improved steadily. He walked alone at 16 months and spoke short sentences by 2 years. At 3 years 10 months, he had an unconfirmed convulsive episode in association with cold and cough. He was always somewhat clumsy, but developed with no other motor abnormalities. Memory problems were first noticed by the family around the age of five to six years.

DA2 (Beth in Vargha-Khadem *et al.*, 1997; Case 1 in Gadian *et al.*, 2000) was born to a mother with insulin-dependent diabetes mellitus following a pregnancy complicated by polyhydramnios. Labour was induced at 37 weeks and birth weight was 5060 g. Delivery was difficult following slow progression of labour and foetal distress with cardiac deceleration down to 80 beats per minute. Shoulder dystocia resulted in injury to the right branchial plexus. There was no heartbeat at birth, and she was immediately intubated. She underwent cardiac massage and intracardiac administration of adrenalin before being resuscitated after 7 – 8 minutes. The Apgar score was 0 at birth and 5 minutes after birth, and 8 at 10 minutes. Two hours after resuscitation, she had a generalised seizure, and such attacks recurred sporadically for 3 days despite treatment with anticonvulsants. She was initially floppy, with absent Moro and grasp reflexes. Within two weeks, however, she had made a good recovery, although the brachial plexus injury resulted in permanent impairment of the right arm and hand due to partial loss of the nerve function deriving from the fifth and sixth cervical nerve roots. Development was normal, except for poor motor skills, possibly related to mandatory dominant use of the left hand, and no other neurological problems were evident after the neonatal period. Memory problems were first noticed by the family around the age of five to six years.

DA3 (Case 2 in Gadian *et al.*, 2000) was delivered at 42 weeks following a normal pregnancy. His birth weight was 5200 g. Delivery was difficult, with shoulder dystocia. There was no heartbeat at birth and he was apnoeic for 10 minutes, requiring external cardiac massage and intracardiac injection of adrenalin. His heartbeat was regular at 20 minutes, but he had gasping respiration until then. Blood pH was 7.14 with a base excess of −18.9 mEq on day 1. Breathing became regular at 25 minutes and he was ventilated for 2 days. DA3 had recurrent neonatal convulsions during the first days before being discharged home at 2 weeks. There were no further problems until age 6, when he had some brief vacant episodes, and at age 7 years he had three generalised tonic or tonic-clonic seizures. Memory problems were first noticed by the family around 6 to 7 years of age.

DA4 (Case 3 in Gadian *et al.*, 2000), a non-identical twin, was born with umbilical cord around his neck. He was not ventilated in the neonatal period. Labour was said to be delayed and he was said to have lacked oxygen for 20 minutes. He was placed in a special care unit for 2.5 weeks and he had three major seizures in the first 36 hours of life. Development was apparently normal, but there was a tremor of the hands, especially on writing, pale optic disks (6/6 vision bilaterally) and mild inco-ordination. He currently attends a specialist school for children with speech and language difficulties. Age at onset of memory impairment is unknown.

DA5 was delivered via c-section following induction due to foetal bradycardia. She weighed 2660 g and had an Apgar score of 1 at one minute, her heart beat was below 100. She was intubated and resuscitated and transferred to intensive care on a ventilator. She displayed abnormal cycling movements of the arms, and was administered anti-convulsant medication. She was breathing on her own by the second day and was extubated. By day 9 she was alert, well and there were no further seizures. Memory problems were first noticed by the family around 2 to 3 years of age.

DA6 was born at 32 weeks gestation and weighed 4 lbs, 6 oz. On her second day of life she experienced significant respiratory distress which required intubation and ventilation for seven days followed by low-flow oxygen for 16 days. She had two neonatal blood transfusions and experienced mild jaundice. Her developmental milestones were reported to be within the normal limits. Memory difficulties were noted around age 4 years, as were underdeveloped motor skills and letter reversals.

DA7 (Case 5 in Gadian *et al.*, 2000) was born at 33 weeks of gestation. During pregnancy his mother had high blood pressure and pre-eclampsia. Congenital heart disease (ventricular septal defect) was noted a few days after birth. At 11 weeks, he was placed in an intensive care unit because of pneumonia with several respiratory arrests that required assisted ventilation for 4 days; seizures were reported. He was hospitalised five further times during his first year because of multiple respiratory arrests and dyspnoeic attacks. His development was mildly delayed; he walked at 18 months, could say sentences of three or four words by 2 years 2 months, and was clumsy. He had seizures with temporo-occipital spike focus, which developed at 7-8 years. Age at onset of memory impairment is unknown.

DA8 was born full-term through normal delivery. Although she was born with the umbilical cord around her neck and was purple at the time, she was not kept in special care. She had an episode of meningitis at four months of age and some prolonged febrile seizures at 2 years 6 months (she stopped breathing during these). She has had a seizure disorder since this time, with marked auras and seizures that are complex partial in nature. Seizure duration ranges from 20 seconds to 1 minute. Telemetry investigations in March 1999 revealed that seizures start over the left hemisphere and become regional over the left temporal lobe. Seizures sometimes spread to the right hemisphere. She is unable to speak during a seizure and afterwards suggesting left hemisphere involvement. Current medication is Tegretol Retard, Lamotrigine and Carbamazepine. Age at onset of memory impairment is unknown.

DA9 was born at 38 weeks with no neonatal problems and a normal delivery. At the age at 4 years 6 months he experienced an unconfirmed seizure, but was reported to have episodes of absence from a very early age. Reportedly during seizures he would be unresponsive for a few seconds and would stare blankly and stop any activity. On recovery, he would return to normal after about 15 minutes. The EEG showed that seizures would start over the occipital region and spread over both hemispheres. His seizures were managed with Epilem until September 2001. He is currently seizure free and off medication. Age at onset of memory impairment is unknown.

DA10 (Kate in Vargha-Khadem *et al.*, 1997) was born after a normal pregnancy. As an infant, she developed eczema and sometime between the ages of three and four she developed asthma. Some of her attacks required hospitalisation. She was an average student until the age of 9, when she was accidentally administered a toxic dose (400mg

for 3 days) of theophylline, a drug with which she was being treated for asthma. An acute episode of seizures, unconsciousness, and respiratory arrest ensued, from which she showed good physical recovery but which left her profoundly amnesic. Subsequently, at age 17, she developed temporal lobe epilepsy, which is well controlled with Carbamazepine.

DA11 was diagnosed as having a slow growing inoperable tectal plate tumour, with secondary hydocephalus at the age of 9 years. She had a shunt inserted and during an operation in 1994 to clear the shunt that had become blocked, she suffered interventricular bleeding and contracted severe meningitis. She had respiratory failure and required intensive care. Subsequent to this she suffered severe cognitive impairment specifically affecting her expressive speech. Whilst she made a good physical recovery, when she was first seen for a neuropsychological evaluation in 1995, she complained of impaired hearing (although her audiological report was normal) and memory difficulties. At time of assessment (2002) DA11 demonstrated auditory comprehension difficulties, she seemed to only understand a conversation when the speaker spoke directly to her face-to-face. As a consequence of this difficulty she is unable to use the telephone or watch movies.

DA12 was born at term gestation. Birth weight was appropriate for gestational age. Pregnancy, labor and delivery were uncomplicated. His early medical history was unremarkable until he reached age 8 years old in 1991. Then he was diagnosed with Type I (Insulin-Dependent) diabetes mellitus. At age 9 years 6 months he experienced a severe hypoglycaemic episode that resulted in a seizure lasting up to 30 minutes and loss of consciousness. After that time his family recalls 5 or 6 similar episodes in which he remained unconscious for about 5 to 10 minutes secondary to hypoglycaemia before treatment was started. Though he and his family kept meticulous records of insulin doses and glucose monitoring for several years, the records ceased when they turned over the management of DA12's diabetes to him. His memory problems were suddenly noticed in October 1998 (15 years 5 months) on a specific morning as he prepared to go to school. His mother could point out a drop in his grades during that term and recount stories about his inability to remember music he was studying as verification of the sudden onset. She could not recall any precipitating incidents in terms of hypoglycaemic episodes, seizures, illness or other complications. Given the previous history of extreme reactions to hypoglycaemia, the poor monitoring of glucose levels and insulin doses during

adolescence, and the morning manifestation of symptoms, it is possible that he suffered a severe hypoglycaemic attack during the night. Such episodes are frequent in Type I diabetes and may be difficult to recognize because of the Somogyi (or Smogyi) Effect, also known as "rebound". In this condition, a high level of glucose (sugar) in the blood follows an extremely low level, usually occurring after an untreated insulin reaction during the night, and is caused by the release of stress hormones to counter low glucose levels. The high morning glucose levels confuses the individual into thinking he needs more rather than less insulin. An alternative hypothesis is that the earlier hypoglycaemia resulted in damage that became clinically obvious later in development.

APPENDIX B: VOLUNTEER QUESTIONNAIRE

DETAILS OF ADULTS WHO MAY PARTICIPATE IN A RESEARCH STUDY

Name of adult _____DOB_____

Gender: Male / Female Name of College _____

Home Address_____

Daytime Contact No/ email address_____

Is English your first language? YES/ NO

If not, please specify the following:

First language: _____

Fluency out of 10 for first language: _____

Fluency out of 10 for English: _____

Do you any documented learning difficulties, such as dyslexia, dyspraxia, etc. If yes please describe:_____

_____

Do you have any neurological condition, such as epilepsy. If yes please describe:_____

_____

_____

Have you ever received speech and language therapy or occupational therapy. If so please give brief details and approximate dates:_____

_____

Have you ever been assessed by another Psychologist and completed tests, such as IQ tests. If so please give any results reported:_____

_____

Please inform us of your GCSE/A-level results: _____

_____

APPENDIX C: INFORMATION AND CONSENT FOR STUDY

INFORMATION FOR PATIENTS

We invite you to take part in a clinical research study at the Great Ormond Street Hospital for Children and the Institute of Child Health, University of London.

1. Title of Project

Developmental Amnesia and Other Early Memory Disorders

2. The Aim of the Study

Our main aim is to find out more about the development and neurological basis of childhood memory disorders.

3. Why is the study being done?

Our main aim is to understand more about the brain regions that are important for remembering, but we also hope that this work will provide guidance for people who have memory difficulties of one type or another. You have been chosen as a possible participant in this study because we are interested to determine whether individuals with your type of medical history experience any difficulties with memory.

4. How is the Study to be Done?

You will be asked to carry out simple paper-and-pencil tasks and visual tests. Some of our tests are designed to be done by computer. We will always describe what we will be doing before starting the tests and give you an idea of what specific aspect of brain function we are evaluating. The psychological testing will be carried out by Dr. de Haan and by other psychologists working under the direction of Dr. de Haan & Prof. Vargha-Khadem.

You will undergo a scan that gives pictures of your brain. The brain scanner uses a magnetic field and radio waves to produce detailed pictures of your brain. These pictures will show us if there are any abnormal regions of the brain. In order to obtain these pictures it is necessary that you lie inside a magnet that is shaped as a cylinder tube. You need to stay very still during the scan process for the brain scanner to get an accurate picture. The total scanning time may be as long as 2-3 hours depending on what we are trying to find out In some cases, we may ask you to carry

out simple tasks, such as looking at objects in a computer screen, or thinking of things you have done in the past.

Additionally we may carry out some studies looking at the electrical signals of your brain while you carry out some very simple tasks. These are painless procedures.

If you wish we will help you to arrange transport for your visits to us. We will reimburse you all your travel expenses and any incidental expenses you may incur during your visits with us. We will schedule the appointments when you are able to come in and will provide you with an estimate of how many visits will be required. Most children need 3-4 sessions and each session can last from 1.5-3 hours.

5. Are there risks and discomforts?

If you are awake while in the scanner (you might fall asleep!), you will hear a thumping noise created by movements inside the magnet. Also you may become uncomfortable because you will be lying in a confined space and will be asked not to move your head. To avoid too much movement we may ask you to put on a special mask. If you do not like the feeling of being confined for too long or do not like the noise, you can ring a bell and the staff will come to take you out of the scanner right away.

6. What are the potential benefits?

This research project may not bring any immediate benefits to you. However we hope that in due course the information we obtain from this research project will help children's educational development and quality of life.

7. Who will have access to records?

Access to the case/research records will be available to all of the collaborators working under the research project and to a representative of the Ethics Committee.

8. Do I have to take part in the study?

No. If you decide now or at a later stage that you do not wish to participate in this research project, that is entirely your right and will not in any way prejudice your present or future treatment.

9. 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 you wish to comment in another way, please contact the Chairman of the Research Ethics Committee, by post via the Research and Development Office, Institute of Child Health, 30 Guilford St., London, WC1N 1EH, or if urgent by telephone on (0207) 242 9789 ext. 2620 and the Committee administration will put you in contact with him.

10. Researcher who will have contact with the family:

Miss Anna Adlam

11. Details of how to contact the researcher

Contact Miss Anna Adlam at:

The Wolfson Centre

Institute of Child Health

Mecklenburgh Square

London WC1N 2AP

Telephone: (0207) 837 7618 ext. 2992.

CONSENT FOR STUDY

Great Ormond Street Hospital for Children NHS Trust and
Institute of Child Health Research Ethics Committee

Consent form for Parents of Participants of Research Studies

Title: Developmental Amnesia and Other Early Memory Disorders

NOTES FOR PARENT:

1. You have been asked if your child would like to take part in a research study. The person organising that study is responsible for explaining the project to you before you give consent.
2. Please ask the researcher any questions you may have about this project, before you decide whether you wish your child to participate.
3. If you or your child decides, now or at any other stage, that you do not wish to participate in the research project, that is entirely your right, and if you are a patient it will not in any way prejudice any present or future treatment.
5. If you have any complaints about the way in which the 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 you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via The Research and Development Office, Institute of Child Health, 30 Guilford Street, London, WC1N 1EH or if urgent, by telephone on 020 7905 2620 and the committee administration will put you in contact with him.

CONSENT

I, the parent/guardian of _____, agree that the Research Project named above has been explained to me to my satisfaction, and I agree for my child to take part in this study. I have read both the notes written above, and understand what the research study involves.

SIGNED [Parent] **DATE**

_____ _____

SIGNED [Researcher] **DATE**

_____ _____

APPENDIX D: DEFERRED IMITATION ACTION SEQUENCES

Set A
3-step causal

Water transfer
put straw in water
put finger on straw
transfer water to empty cup

Bernoulli effect
dryer on
balloon in air stream
rotate dryer

Magnet
turn cup over
clip on magnet
pull string

Tuning fork
lid on box
hit fork on table
put handle on lid

Set A
3-step arbitrary

Sound tone
pour water from one to other
hit fork on new
hit fork on old

Muller-Lyre demonstration
make long
make short
interchange straw

Drawing a star
fold paper
cut corners
draw star

Balance coins
one coin at one end
one coin at other
balance ruler on block

Set B
3-step causal

Money box
open box
Remove inner tray
put paper through slot

Popper
lift lid
Ball in side hole
Push popper

Magic box
pen box
remove eraser
erase picture

Electric circuit
batt 1 to bulb 1
bulb 1 to bulb 2
bulb 2 to batt 2
switch on

Set B
3-step arbitrary

Etcher-sketcher
erase picture
draw around magnet
spin magnet on table

Dancing clown
hat on clown
bang symbol
make him dance

Put tools away
put tools away
sit man in truck
hang weight on hook

Feed Rabbit
put on eyes
lift ears
feed carrots

Scripted sequences

Changing batteries
open clock
change direction of battery
close clock
play with buttons
open torch
replace batteries
close torch
shine on hand

Playing a tape
put tape in player
press play
switch micro on
say 'hello, hello'
put wire in back of machine
press stop
rewind tape with finger

Driving a car
key in ignition
turn key
turn driving wheel
flick lights
pick up phone
will be there in 5
turn speed dial
beep horn
remove keys
put glasses on wheel

Scripted sequences

Make a cup of tea
look in kettle
1 t-bag in t-pot
pour milk in cup
look in kettle
pour kettle in pot
sugar in pot
stir pot
t bag in cup
pour pot in cup
pour cup in pot

Brushing teeth
roll t-paste from bottom
put paste on brush
brush teeth at top
brush teeth at bottom
pour mouthwash on brush
stand brush in holder
cut off dental floss
tie floss around brush

Shopping
switch on
2 food on conveyor
move conveyor belt
scan 2 food
scan credit card
type number
swipe money
unlock drawer
put money in drawer
switch off

APPENDIX E: WORD-LISTS

CLUSTERED-CATEGORIES (CC)

Trial 1: I'm going to read a list of words to you. I want you to listen carefully, because when I'm finished, I want to repeat as many words you can remember. It doesn't matter in what order you repeat them. Do you understand?
Trial 2: I am now going to read the same list to you again. When I am finished, please tell me as many words as you can remember, including the words you said the first time. Do you understand?
Trial 3-5: I'm going to say the words again. Tell me all the words you can remember, including the words you've said before.

List A	Trial A1	Trial A2	Trial A3	Trial A4	Trial A5
Fox					
Monkey					
Eagle					
Donkey					
Brass					
Steel					
Bronze					
Copper					
Bean					
Cabbage					
Pea					
Celery					
Cliff					
River					
Tree					
Hill					

Correct _____

Intrusions _____

Interference Trial: Now I'm going to say a different list of words. This time I want you to tell me just the words from this second list.
Immediate Recall Trial: Now tell me all the words from the first list again, the ones I said five times. Tell me just the words from the first list.
Delayed Recall Trial: Remember those word lists that you learned before? Tell me all the words from the first list again.
Recognition Trial: Now I am going to read a list of words to you. Listen carefully. After I read each word, I want you to tell me whether or not that word was in the first list that you learned. If the word was in the first list, say "Yes". If it wasn't, say "No". Do you understand?

List B	Trial B1	Immediate Recall A6	Delayed Recall A7	Recognition List	Recognition Trial
Shoe				Strawberry	Y N
Jacket				Copper	Y N
Scarf				Cave	Y N
Dress				Hill	Y N
Sunshine				Lake	Y N
Fog				River	Y N
Lightening				Fox	Y N
Snow				Bronze	Y N
Peach				Jacket	Y N
Plum				Cabbage	Y N
Strawberry				Dress	Y N
Cherry				Tree	Y N
Table				Spoon	Y N
Chair				Monkey	Y N
Stool				Steel	Y N
Bed				Bean	Y N
				Gold	Y N
				Pea	Y N
				Tin	Y N
				Table	Y N
				Eagle	Y N
				Cliff	Y N
				Plum	Y N
				Celery	Y N
				Dish	Y N
				Sunshine	Y N
				Stool	Y N
				Brass	Y N
				Cherry	Y N
				Donkey	Y N
				Fork	Y N
				Saucer	Y N

Stop time _____ Start time _____

Correct _____

Intrusions _____

Recognition Accuracy:
(32 – no. of errors)

Immediate Memory Span:
(Trial 1 + Interference)

Level of learning:
(trials 3 +4 +5)

Total Intrusions:
(all trials except recognition trials)

UNCATEGORISED-RANDOMLY ORGANISED WORD-LIST (UC)

Trial 1: I'm going to read a list of words to you. I want you to listen carefully, because when I'm finished, I want to repeat as many words you can remember. It doesn't matter in what order you repeat them. Do you understand?
Trial 2: I am now going to read the same list to you again. When I am finished, please tell me as many words as you can remember, including the words you said the first time. Do you understand?
Trial 3-5: I'm going to say the words again. Tell me all the words you can remember, including the words you've said before.

List	Trial A1	Trial A2	Trial A3	Trial A4	Trial A5
Dance					
Tent					
Ladder					
Foam					
Pipe					
Harvest					
Cardboard					
Ball					
Flame					
Money					
Comb					
Fan					
Leather					
Game					
Document					
Sponge					

Correct _____

Intrusions _____

Interference Trial: Now I'm going to say a different list of words. This time I want you to tell me just the words from this second list.
Immediate Recall Trial: Now tell me all the words from the first list again, the ones I said five times. Tell me just the words from the first list.
Delayed Recall Trial: Remember those word lists that you learned before? Tell me all the words from the first list again.
Recognition Trial: Now I am going to read a list of words to you. Listen carefully. After I read each word, I want you to tell me whether or not that word was in the first list that you learned. If the word was in the first list, say "Yes". If it wasn't, say "No". Do you understand?

List B	Trial B1	Immediate Recall A6	Delayed Recall A7	Recognition List	Recognition Trial
Carpet				Shark	Y N
Guitar				Ball	Y N
Ring				Tunnel	Y N
Tea				Sponge	Y N
College				Map	Y N
Mother				Game	Y N
Star				Dance	Y N
Field				Cardboard	Y N
Chapel				Guitar	Y N
Medicine				Document	Y N
Shark				Tea	Y N
Chicken				Money	Y N
Pen				Clock	Y N
Purple				Tent	Y N
Hotel				Harvest	Y N
Soap				Flame	Y N
				Shop	Y N
				Comb	Y N
				Puppet	Y N
				Pen	Y N
				Fan	Y N
				Leather	Y N
				Medicine	Y N
				Ladder	Y N
				Bag	Y N
				College	Y N
				Hotel	Y N
				Pipe	Y N
				Chicken	Y N
				Foam	Y N
				Bottle	Y N
				Chalk	Y N

Stop time_____ Start time_____

Correct _____
Intrusions _____

Recognition Accuracy:
(32 – no. of errors)

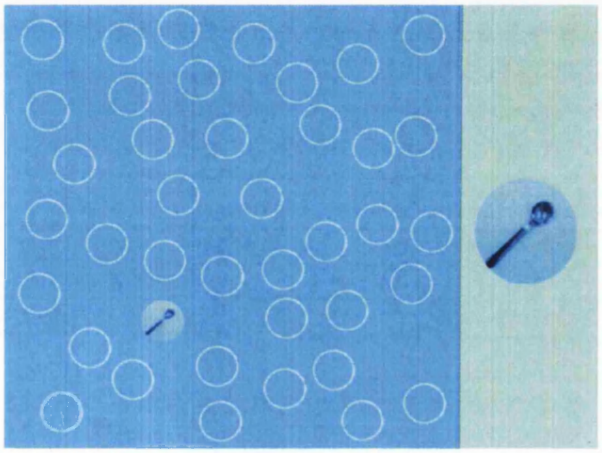
Immediate Memory Span:
(Trial 1 + Interference)

Level of learning:
(trials 3 +4 +5)

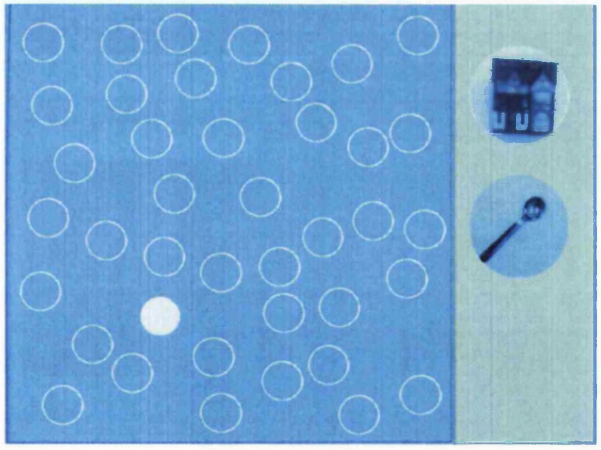
Total Intrusions:
(all trials except recognition trials)

APPENDIX F: MULTI-TRIAL OBJECT-PLACE ASSOCIATIVE RECOGNITION

Study (20-pair list)



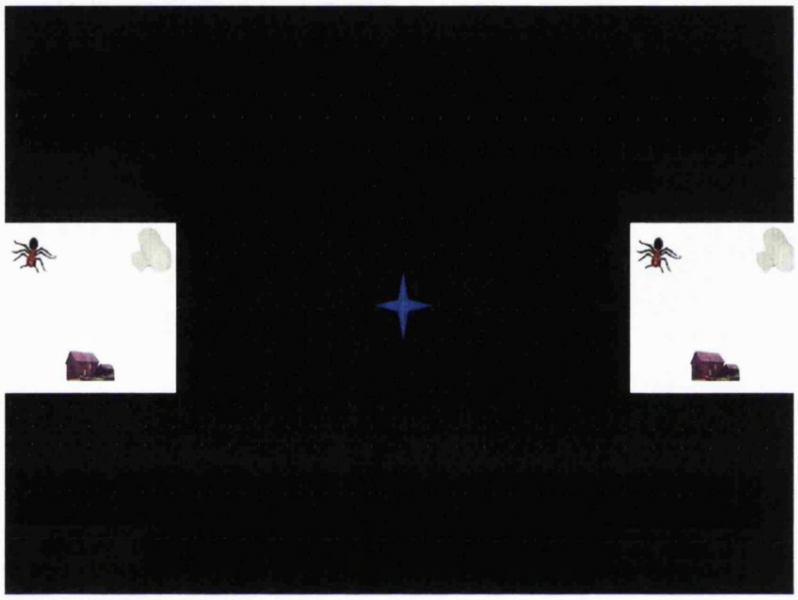
Test (all pairs, criterion 90% correct)



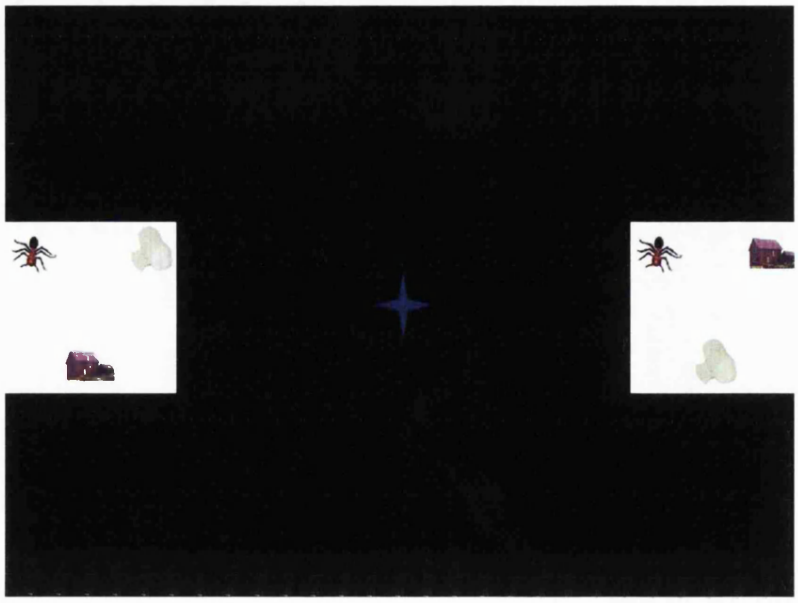
APPENDIX G: 3-STIMULUS ARRAY

OBJECT-PLACE

Study phase (two identical 3-item arrays).

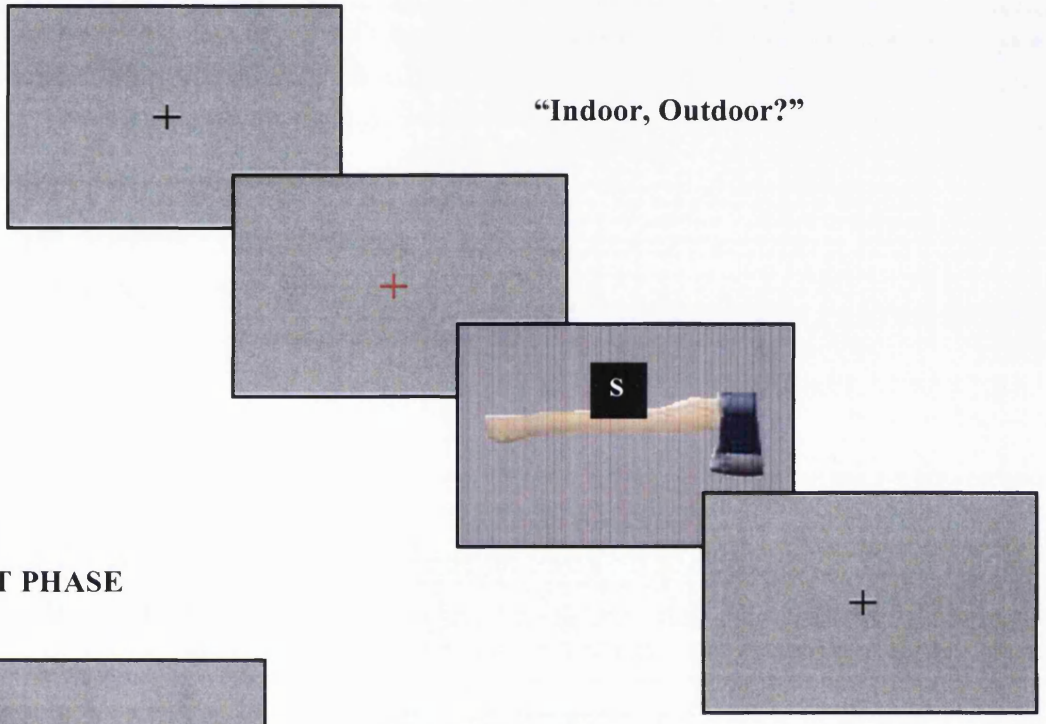


Test phase (one new array (target), one old array (foil)).

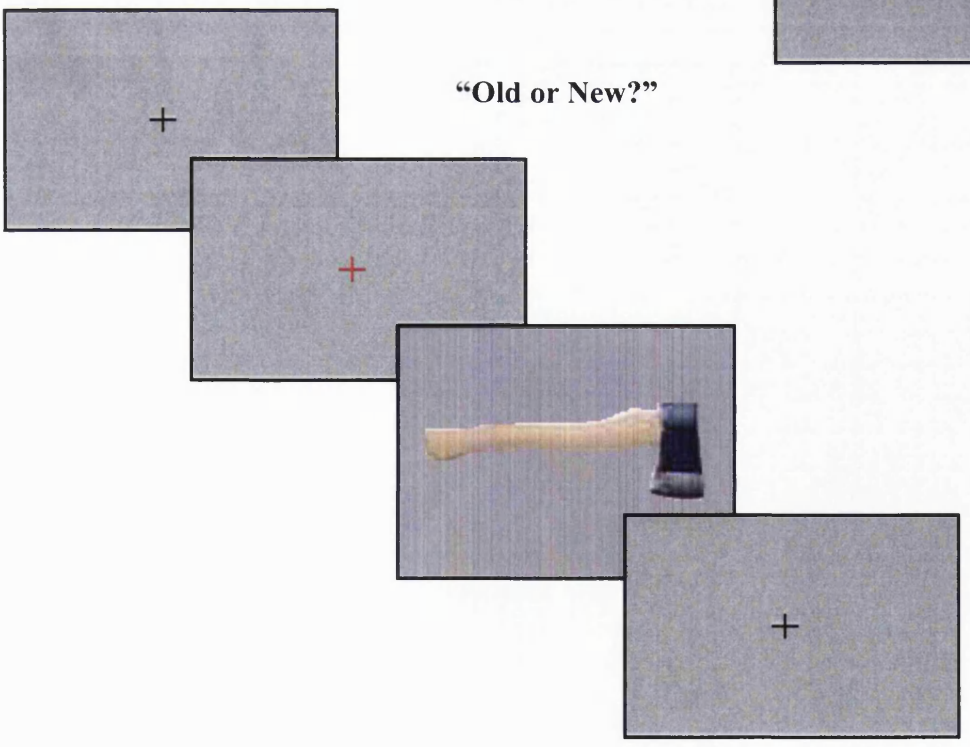


APPENDIX H: LEVELS-OF-PROCESSING PARADIGM

STUDY PHASE



TEST PHASE



APPENDIX I: PRINCIPAL COMPONENT ANALYSIS

There are several neuropsychological tests presented in chapters 2 and 4, some of which are presumed to test the same underlying (latent) variable, for example, immediate verbal recall. Under this assumption the test results should be highly correlated. Principal component analysis (PCA) was used to pull out this single common component from the set of scores. This should provide a better measure of the single underlying process (as represented by the first principal component) since it removes the noise (contained within the remaining principal components).

The resulting factor scores were used in subsequent regression calculations with the extent of MTL abnormality as the independent variable. The advantages of this method are: a) PCA provides an improved measure of the underlying process e.g. immediate verbal recall; b) it provides a formal method for reducing the dimensionality of the problem and, consequently, reduces the number of regression calculations required to investigate the relationship between MTL abnormality and immediate verbal recall. The PCA calculation was performed using the correlation matrix. An initial scaling of the variables has no effect on the correlation matrix and, consequently, has no effect on the PCA results. For this reason variables were entered into the PCA without prior scaling (weighting).