Episodic Memory across the Life Span: Evidence from Infancy, Childhood, Adults and Amnesia.

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Abstract

It is vital to examine changes in hippocampal-dependent memory across the life-span, in order to understand both its ontogeny and subsequent decline with healthy aging. To the authors' knowledge, earlier research has not used the same methodology to assess episodic memory processes in children and adults, yet comparisons in performance between these groups have been made regardless. Equally, there is a lack of robust evidence to indicate that episodic memory paradigms employed with young children are hippocampal-dependent. In this thesis, I aimed to address these important issues by assessing memory performance across the life-span in children aged 7.5-months-old to 8-years-old (n= >500), young adults aged 18-25 years (n= >60), older adults aged 54-77 years (n= >60) and patients with selective hippocampal damage aged 52-75 years (n=5). Two tasks were used; 1) a deferred imitation task which measured memory for action sequences and 2) a faces and places task which measured memory for face-scene associations via eye-tracking and/or explicit recall. Comparisons between patients and adult controls permitted me to infer whether these paradigms are measuring hippocampal-dependent processes. Both tasks contained conditions that did not rely on instructions, in order to permit valid comparisons to be made between pre-verbal infants and adults and determine at what age task performance becomes adult-like and exceeds that of patients.

When patient performance was examined on both tasks relative to adult controls, patients demonstrated significantly poorer memory for the action sequence (deferred imitation task) and significantly worse recall for face-scene associations (faces and places task). These findings suggest that both tasks appear to index hippocampal-dependent memory processes and the integrity of the hippocampus is needed to support successful performance. Subtle distinctions were found between memory for action information and memory for temporal order information across childhood. While both types of memory became adult-like by 4-years-old and remained relatively stable from this age onwards, memory for actions increased more incrementally with age from approximately 2-years-old whereas temporal order memory emerged more sharply around 4-years-old.

Alongside supporting episodic memory, the hippocampus plays a specialised role in the processing of scenes (Hassabis & Maguire, 2007) and spatial memory (O'Keefe & Nadel, 1979). In order to examine whether hippocampal scene processes may be influencing memory development, memory for face-scene associations was assessed in all age groups when scene viewing perspective either remained the same or was shifted slightly between learning and test. We examined whether participants could tolerate the change in scene perspective, i.e. recognise that it is the same place albeit the view of the scene has shifted slightly, to retrieve the previously formed association between that scene and a face. While all groups aged between 7.5-month-old to 4-years-old, with the exception of 3-year-olds, demonstrated eye movements veridical of remembering face-scene pairs when scene view remained constant within a trial, this behaviour was eradicated when scene perspective was shifted between learning and test in all groups with the exception of 4-year-olds. Shifting scene perspective between learning and test had a detrimental effect on memory for previously presented face-scene pairs in older adults and to a more significant extent in patients with selective

hippocampal damage. In contrast, shifting scene perspective between learning and test did not impact on recall for face-pairs in young adults and children aged 5-8 years.

In addition to age-related increases in memory across childhood, the acquisition of developmental milestones may also facilitate memory development. Previous literature has tentatively linked the attainment of independent locomotion (IL) with greater memory retrieval flexibility in infancy (Herbert et al., 2007), with suggestion that the greater experience in varying spatial contexts that accompanies this milestone may be providing scaffolding to support episodic memory processes (Rovee-Collier & Cuevas, 2009). Therefore, I aimed to not just explore age-related differences in memory performance within my tasks, but assessed whether attaining IL in early infancy provides mnemonic benefits compared to peers who develop this ability later in the first year. Performance was compared between infants who had achieved IL and age-matched non-locomotive peers (NIL) at 7.5-months-old. A sub group of these infants returned to participate when aged 9-months-old and performance was compared between infants who had acquired IL by 7.5 months of age compared to age-matched peers who only recently acquired this milestone. DI performance in 9-month-olds who had acquired IL by 7.5 months of age significantly outperformed their age-matched peers who only recently acquired IL (i.e. IL was acquired between 7.5-9 months of age). Furthermore, only those infants who had acquired IL by 7.5-months-old demonstrated eye-movements veridical of remembering previously presented face-scene pairs.

This collection of findings are discussed in terms of how using the same hippocampal-dependent memory task across the life-span can inform current understanding of the developmental trajectory of this specific form of memory. I reflect upon how the additional onus of the hippocampus in spatial processing may be fundamentally intertwined with episodic memory development and how the acquisition of spatial knowledge through attaining IL may be providing a scaffold for this type of memory development in early childhood.

Acknowledgments

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1. Chapter 1. General Introduction

1.1 *Episodic Memory in Adults*

Episodic memory can be defined as our memory of past events set in specific spatial-temporal contexts, also referred to as '*what-where-when*' memory (Tulving, 1972). In this first section, I outline current understanding of the neural underpinnings of episodic memory in adults, principally the hippocampus and how selective memory impairments occur as a result of injury to this neural region. Subsequently, I discuss current theories of hippocampal function and how episodic memory may be fundamentally intertwined with other functions subserved by the hippocampus.

1.1.1 Neural Correlates of Episodic Memory

1.1.1.1 Anatomy of the Episodic Memory System

The medial temporal lobe (MTL) contains a collection of cortical regions including the hippocampal formation, the perirhinal cortex (anterior parahippocampal gyrus) and the parahippocampal cortex (posterior parahippocampal gyrus). The hippocampal formation consists of two laminae folded inside one another: the dentate gyrus (DG) and the hippocampus proper (containing the four Cornu ammonis subfields; CA1-CA4) along with the subiculum, presubiculum, parasubiculum and the entorhinal cortex (see figure 1.1). The hippocampal formation can also be subdivided into sections in addition to its distinct subfields. Using the uncal apex as a mid-point, the hippocampal horizontal axis can be divided into anterior and posterior regions (Poppenk et al., 2013). More discrete divisions along the horizontal axis can also be made, referred to as the hippocampal head, body and tail (Duvernoy, 2005). Hippocampal subfields are distributed differently along the horizontal axis. The anterior portion of the hippocampus is dominated by CA1 and the subiculum, while the posterior portion contains greater clusters of DG and CA3 neurons (Zeidman & Maguire, 2016).

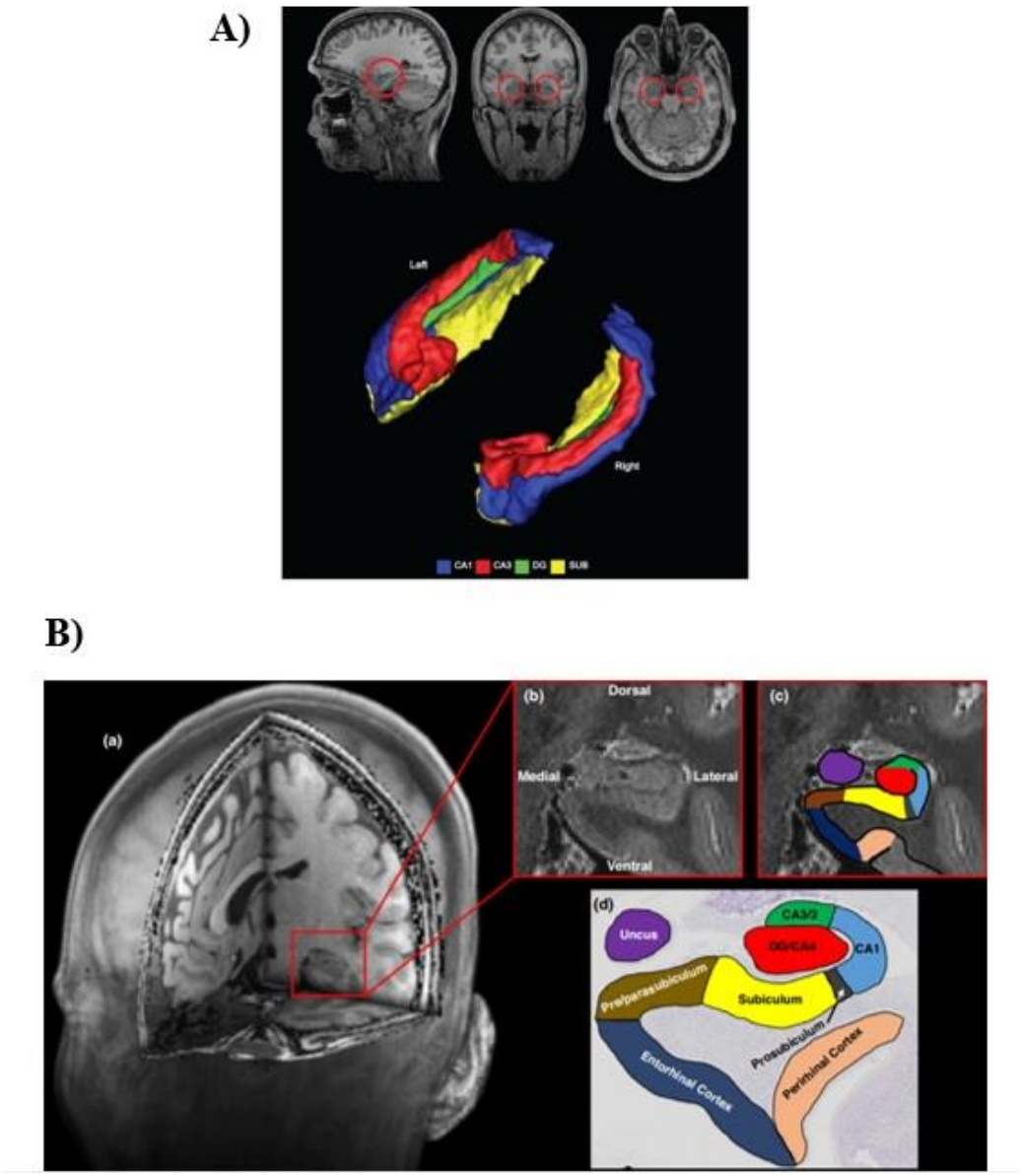

Figure 1.1 Images of the human hippocampus from neuroimaging.

A) The human hippocampi circled in red (top section) displayed from sagittal (left), coronal (middle) and axial (right) views from a structural MRI scan. Bottom section shows three-dimensional images for two example hippocampi with key subregions indicated *(blue = CA1; red= CA3; green= dentate gyrus; yellow= subiculum*). Taken from Mullally & Maguire (2013). **B)** Selection of images presenting the location and structure of the hippocampal formation. Taken from Dalton & Maguire (2017).

There are several neuroanatomical pathways in which information is received and distributed in the hippocampal formation (Insausti, Amaral & Cowan, 1987; Jábes and Nelson, 2015). Information from the neocortex arrives at the hippocampal formation predominantly through the entorhinal cortex, however there is evidence for direct connections between the hippocampus and subcortical regions via the fornix (Aggleton & Brown, 1999; Insausti et al., 2017). Once information has reached the entorhinal cortex, it can be processed by the hippocampus through different parallel routes (see figure 1.2A). The trisynaptic pathway

involves the neo-cortical information being passed through the main hippocampal subfields, first reaching the dentate gyrus, followed by the CA3 subfield, reaching the CA1 subfield and lastly the subiculum (Jabes & Nelson, 2015; denoted by the green lines in figure 1.2A). This information is then sent back to the entorhinal cortex to be projected to other neural regions, thus forming a functional loop of processing (see figure 1.2B). Alternatively, the entorhinal cortex can also project directly between different hippocampal subfields, with these pathways being referred to as entorhino-hippocampal circuits (Insausti & Amaral, 2012). Direct entorhinal projections to the CA1, CA2, CA3 and subiculum subfields have been documented, which can process information separately from the more complex trisynaptic circuit (Chrobak & Amaral, 2007). The bidirectional connectivity between the entorhinal cortex and the CA1 (and subiculum) is referred to as the monosynaptic pathway (Nakishiba et al., 2008; denoted by red lines in figure 1.2A).

A) **B)**

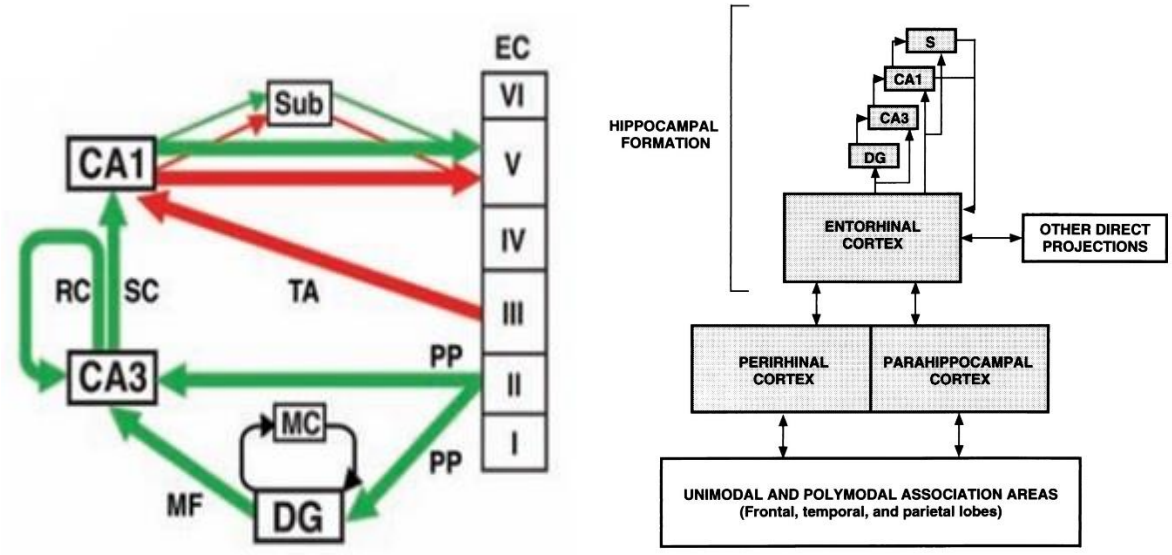

Figure 1.2 Diagrams of medial temporal lobe memory pathways.

A) Pathways within the hippocampal formation. Taken from Nakishiba et al. (2008). Note. Sub= subiculum; SC= Schaffer collateral pathway; RC= CA3-recurrent collateral; MF= mossy fibers; MC= mossy cells; PP= perforant pathway and TA= temporoammonic pathway. **B)** Pathways extending beyond the hippocampus. Taken from Squire & Zola-Morgan (1996).

1.2 *Episodic Memory Disruption with Hippocampal Damage*

Early case studies demonstrated the crucial role of the hippocampus in episodic memory and firmly established that memory is not a unitary system. The seminal case of patient HM, who underwent bilateral resection of the MTL to alleviate severe epilepsy, provided instrumental

insight into the neural correlates of diverse types of memory (Scoville & Milner, 1957). Surgical intervention involved almost complete resection of the hippocampus and entorhinal cortex, along with the adjacent parahippocampal gyrus (Annese et al., 2014). Post-surgery, while HM was able to learn novel skills (Milner et al., 1968), the patient was unable to form new memories of personal experiences and also experienced temporally graded retrograde amnesia for memories of this kind (for a period spanning 3-11 years post-surgery; Milner et al., 1968; Corkin, 1984). Hence, HM demonstrated distinct long-term memory deficits as a result of MTL (particularly hippocampal-entorhinal cortex) damage.

Subsequent cases of severely amnesic patients with hippocampal damage also emphasized that only selective forms of long-term memory are underpinned by this neural region. Scoville & Milner (1957) demonstrated that bilateral resection of the MTL in a cohort of eight patients with psychotic disorders resulted in persistent anterograde amnesia for episodic events with memory for technical skills remaining intact. Critically, the severity of memory impairments experienced by these patients reflected the degree of hippocampal resection, with greater anterograde amnesia observed (and in some cases retrograde amnesia) for experienced events found in individuals that underwent the largest amount of surgical resection. Equally, the case of patient KC illustrated that diffuse traumatic brain injury incurred to the hippocampus bilaterally and in areas extending into the neocortex resulted in selective long-term memory impairment for both pre-morbid and post-injury personally experienced events (Tulving et al., 1988). As KC's retrograde amnesia was more profound than HM's and he had more diffuse injuries that extended beyond the MTL into the neocortex, this case emphasized that the extent of damage within and beyond the MTL is reflective of the degree of memory impairments experienced.

Later cases where patients have incurred more selective damage to the hippocampus also mirrored the impairments observed in Scoville & Milner's cohort and patient KC. Selective bilateral hippocampal damage is very rare but can occur as a result of pathologies such as anoxia, ischemia and types of limbic encephalitis like voltage-gated potassium channel complex antibody associated limbic encephalitis (VGKCC_LE) (Clark & Maguire, 2016). VGKCC-LE is a rare autoimmune condition (Reid, Foley, & Willison, 2009). In the acute and subacute stages of this inflammatory disorder, patients present with seizures, behavioural and sleep disturbances, abnormal signal changes within the medial temporal lobe or hippocampus

during MRI scanning and widespread cognitive impairment (Reid et al., 2009; Butler et al., 2014). Following treatment, recovered patients can continue to have selective anterograde episodic memory deficits (Buckley, et al., 2001). Case studies of patients with hippocampal atrophy as a result of VGKCC_LE have reported that these patients demonstrate selective anterograde amnesia on standardised neuropsychological assessments of memory, such as story recall and word list learning (Butler et al., 2014), and exhibit deficits in their ability to bind together information during encoding and retain these associations over delays (Pertzov et al., 2013). Damage to specific hippocampal subfields has also been documented within this disorder; selective bilateral atrophy to the CA3 subfield has been reported in patients with VGKCC_LE (Miller et al., 2017), which was found to result in severe anterograde amnesia for episodic events.

1.2.1 Key Theories of Hippocampal Function

While it is beyond the scope of this thesis to describe all theoretical accounts of hippocampal function here (and in great detail), I have outlined key perspectives that are of particular relevance to this thesis.

1.2.1.1 Consolidation Theory/Declarative Theory

In the 1980's, behavioural studies of non-human primates with hippocampal lesions provided further evidence for the existence of diverse forms of memory, with subjects displaying memory impairments for previously seen objects as a result of damage to the hippocampal formation, while skill-based memories remained intact (Squire, 2004). The distinction between spared and impaired memory as a result of hippocampal damage in both early human and animal research led to a central theory of long-term memory termed consolidation/declarative theory (Squire, 1992; Squire et al., 2004). This theory was based on the multiple memory systems model (Tulving, 1985; Squire & Zola-Morgan, 1996). This model proposes there are two major forms of long-term memory, declarative and non-declarative (see figure 1.3). Tulving (1972) first proposed that the declarative memory system could be further divided into two distinct subtypes; semantic memory (memory of facts not derived from personal experience) and episodic memory. Non-declarative memory is an umbrella term encompassing memory of procedural skills, nonassociative learning and acquired as a result of priming and classical conditioning (Squire & Zola-Morgan, 1996).

Declarative memories are argued to be explicitly remembered and expressed, while non-declarative memories are argued to be implicitly retrieved and produced (Squire, 1992).

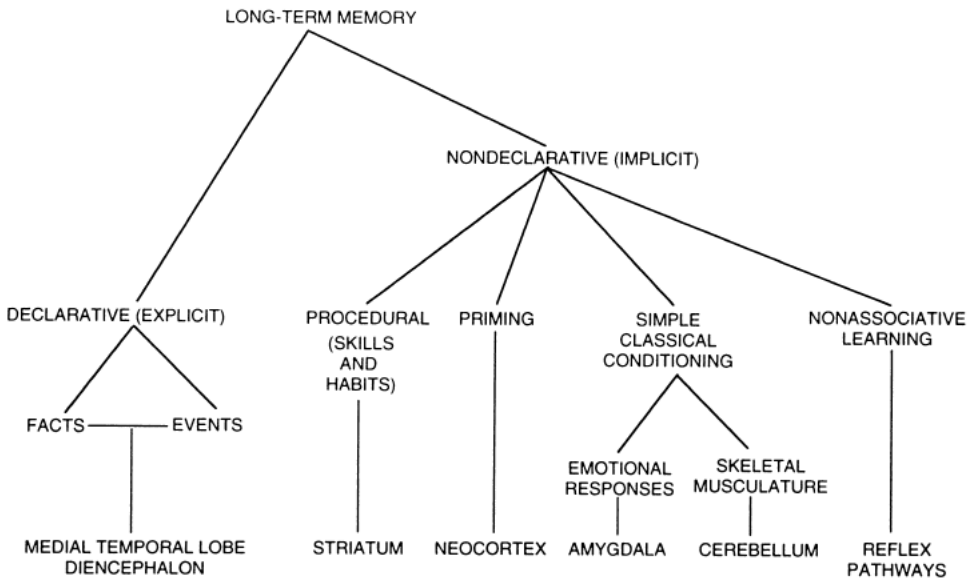

Figure 1.3 Taxonomy of different long-term memory systems and the neural structures postulated to support them in mammalian brains.

Taken from Squire & Zola-Morgan, (1996).

Based on the early studies of human amnesia (discussed in section 1.1.2) and non-human primates with hippocampal lesions, one of the major assumptions of consolidation/declarative theory is that the MTL principally supports memory, with the hippocampus being selectively involved in declarative memory (encompassing both episodic and semantic memory). Alongside episodic memory deficits, declarative theorists propose that semantic memory is disrupted in patients with hippocampal damage, based on results where amnesic patients were found to greatly impaired in their knowledge for news events and learning new semantic information post-injury (Reed & Squire, 1998; Gabrieli, Cohen & Corkin, 1988; Manns et al., 2003).

Previous research has reported that once information has been processed by the hippocampus, it is projected back to the neocortex, along with other neural areas (Squire & Zola-Morgan, 1996; see figure 1.2B). In line with this, consolidation/declarative theory proposes that communication between the MTL and neocortex is needed for long-term memory consolidation and argues that this interaction results in consolidated memories becoming

independent of the MTL after a prolonged period of consolidation (Squire, Stark & Clark, 2004). The idea that the MTL does not permanently store long term memories, (and that these are stored in the neocortex instead), was based on evidence that patients with hippocampal damage were found to be able to retrieve remote memories for autobiographical events that occurred 11-30 years prior (Bayley et al., 2003; Manns et al., 2003). Recent work by Kitamura et al. (2017) has increased current understanding of long-term memory consolidation in the rodent brain when learning a context-specific event. During a contextual fear paradigm, where rodents formed a memory representation of an environment before associating that context with receiving an electrical shock, neo-cortical pre-frontal neurons were generated rapidly through input from the hippocampal-entorhinal cortex circuitry at initial learning. With increasing time, pre-frontal neurons functionally matured while hippocampal neurons became muted. Thus these findings provide evidence for the vital role of the hippocampus in long-term memory consolidation, with the hippocampus facilitating recent memory storage and long-term memory consolidation arising due to hippocampal-neocortical interaction and subsequent prefrontal cortex storage.

In a similar vein, since remote memories are argued to be stored independently of the hippocampus, consolidation/declarative theory also suggests that retrograde memory impairment observed in patients with selective hippocampal damage will be temporally graded (Squire et al., 2004). Supporters of this theory propose that hippocampal damage impairs recent memory while more remote memories (acquired a long time before hippocampal injury) are preserved, with this view largely based on amnesia studies whereby patients demonstrate retrograde amnesia for memories acquired in the decade prior to their injury only while earlier memories remained intact (Milner et al., 1968; Corkin, 1984).

Consolidation/declarative theory remains one of the dominant views of hippocampal function in the literature. However, evidence for the role of the hippocampus in spatial processing (see section 1.1.3.3) and the mental construction of visual scenes (see section 1.1.3.5) has led other authors to generate theories of hippocampal function which amass the many disparate functions of the hippocampus into one coherent theory. Moreover, there is contention as to whether patients with selective hippocampal damage can successfully acquire new semantic memories, with studies reporting that patients with this specific injury can acquire novel semantic knowledge (Westmacott & Moscovitch, 2001; Holdstock et al., 2002). Lastly, there

is a collection of findings which debate declarative theorists' claims that remote memories are stored independently of the hippocampus and thus retrograde memory impairment in patients with hippocampal damage is only limited to recent as opposed to remote memories. Studies which have examined autobiographical memory for events that occurred in early life (and so would be classified as remote memories) have observed retrieval deficits for these memories in patients with hippocampal damage (Viskontas et al., 2000; Cipolotti et al., 2001). Equally, functional neuroimaging studies of healthy adults have detected hippocampal recruitment while engaging in memory retrieval for early autobiographical events (Maguire et al., 2001a; Maguire & Frith, 2003), with the vividness of the episodic memory- not age of memory- being found to produce the highest levels of hippocampal activation (Gilboa et al., 2004; Addis et al., 2004a). Thus, these findings contradict consolidation/declarative theory, in that the hippocampus appears to be involved in episodic retrieval regardless of the age of the memory. Overall, the assumptions of declarative theory remain to be contested, particularly by advocates of later theories such as Transformation Hypothesis (Winocur & Moscovitch, 2011) which argues that the medial temporal lobe differentially supports episodic and semantic memory and that the hippocampus plays a role in episodic memory retrieval regardless of the remoteness of the memory.

1.2.1.2 Recollection- vs. Familiarity-based Recognition

There are divergent opinions in the literature as to whether damage to the hippocampus results in impairments of recognition memory (Mayes et al., 2007; Squire et al., 2007; Brown et al., 2010). The process of recognition is argued to occur either through recollection of previous stimuli and their specific contexts or through detecting familiarity in the absence of memory for the context in which the stimuli was encountered (Aggleton & Brown, 1999). Applying this principle to the recognition of episodic events, episodic memory is argued to require recollective processes, as memory for the contextual features in which an event took place is required to enable rich episodic memory retrieval.

One of the key theories of recognition memory, referred to as dual process theory, argues that recollection-based recognition is subserved by the hippocampus, whereas familiarity-based recognition is performed by the perirhinal cortex (Aggleton & Brown, 1999; Brown et al., 2010). This is based upon findings where patients with selective bilateral hippocampal damage demonstrate recognition memory similar to that of controls when familiarity-based

recognition can be used, however are significantly impaired when recollection-based recognition is required (Holdstock et al., 2002; Yonelinas et al., 2002; Mayes et al., 2003; Bastin et al., 2004). A tool that has been frequently used to assess the processes underlying the dual processes argued to underpin recognition memory is the analysis of receiver operating characteristics (ROC), which consists of plotting the relationship between the proportion of correctly recognised target items ('hits') and the proportion of incorrectly recognised lure items ('false positives') as confidence in responses varies (Yonelinas, 1997). Previous research has documented that the shape of the ROC relates to the measured contribution of recollection and familiarity during a given recognition task, with familiarity judgments resulting in a curved symmetrical line (as the target and lure familiarity distributions have equal variance), recollection judgments presented as a straight, asymmetrical line and judgments which feature both recollection and familiarity depicted by a curvilinear line that is asymmetrical (Yonelinas & Parks, 2007; see figure 1.4A). When ROC has been applied to examine recollection and familiarity processing during recognition, patients with hippocampal damage have been found to demonstrate a curved, symmetrical ROC curve indicative of an absence of recollection-based recognition processing (Yonelinas et al., 1998; Aggleton et al., 2005), which contrasts with the asymmetrical curve observed in healthy controls (see figure 1.4B).

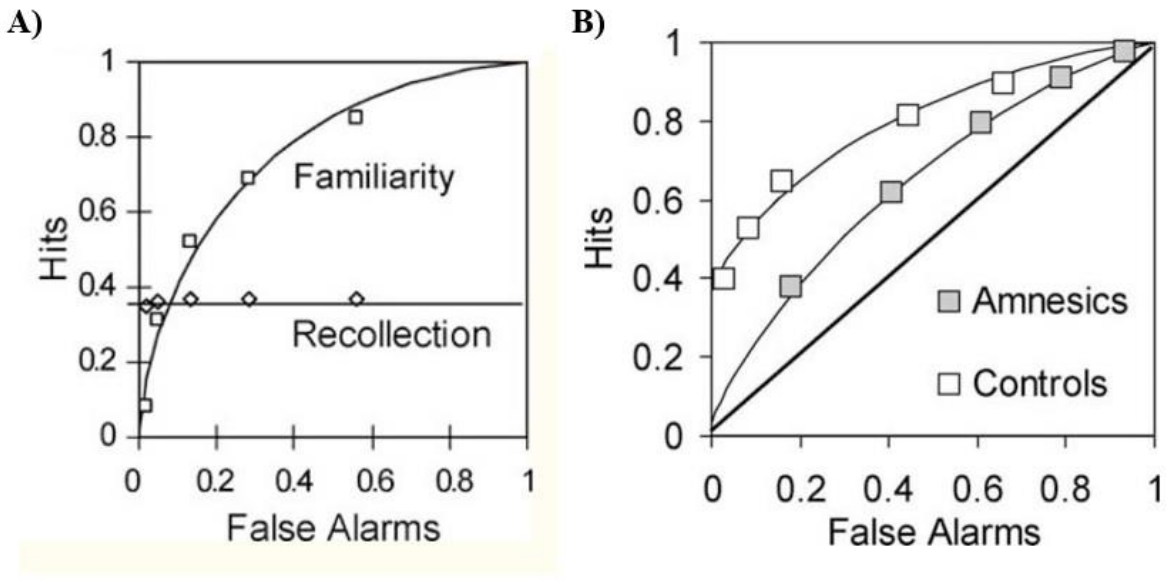

Figure 1.4 Receiver-operating characteristic (ROC) curves present during recognition memory.

A= Differences in ROC curves when making recollection-based judgments and familiarity-based judgments during recognition memory tasks. Taken from Yonelinas et al. (2010).

B= Differences between amnesic patients with medial temporal lobe damage and healthy controls in their ROC curve during a recognition memory test. Taken from Yonelinas et al. (1998).

Studying recognition memory performance in patients with selective perirhinal cortex damage has also provided supportive evidence for dual-process theory. Bowles et al. (2007) reported the case of patient NB who had undergone surgical resection of the left anterior temporal lobe to treat intractable epilepsy. While almost all of the perirhinal cortex had been resected, the hippocampi were left intact. Applying ROC analysis, patient NB demonstrated preserved recollection-based recognition but was substantially impaired on memory judgments involving familiarity-based recognition (inferred from an asymmetrical and relatively flat ROC curve).

In contrast, a body of work has demonstrated both recollection- and familiarity-based recognition to be impaired in patients with damage that is restricted to the hippocampus (Reed & Squire, 1997; Manns & Squire, 1999; Manns et al., 2003; Wais et al., 2006; Jeneson et al., 2010), with these researchers advocating that the hippocampus underpins both these forms of recognition memory but that the disruption observed is dependent on the strength of the memory i.e. recollective processes reflect stronger memory traces (referred to as the single process model; Wixted & Squire, 2004). A recent study by Merkow et al. (2015) assessed recognition for objects in patients undergoing intracranial electroencephalographic monitoring for epilepsy. When measuring high frequency activity (HFA) in the brain (which refers to a spatiotemporally precise signal of neural activation), the authors reported hippocampal HFA during the recognition test that predicted memory performance and was present during both performance that was seen to reflect recollection and familiarity (assessed via response latency).

Alterative perspectives propose that the recruitment of the hippocampus in recognition memory is dependent on the stimulus involved (Mayes et al., 2007), with only memory for between-domain associations disrupted by hippocampal lesions (Mayes et al., 2004; Mayes & Montaldi, 2007). The neural underpinnings of recognition memory remains to be a fiercely debated topic within the literature.

1.2.1.3 Cognitive Map Theory

Electrophysiological research in non-human animals conducted in the 1970's first demonstrated that the hippocampus supports another cognitive function; namely the processing of space and spatial memory. Seminal work conducted by O'Keefe and colleagues

demonstrated the existence of cells in rat hippocampi (termed 'place cells') that allow the brain to create a mental map of an individual's surrounding environment, which they can then use to navigate themselves through space (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978). O'Keefe and colleagues observed that when a rat first encounters a location in a novel environment, several neurons, i.e. place cells, begin firing. However, when a rat moves to a different location, a different set of place cells elicit firing instead (O'Keefe & Dostrovsky, 1971; O'Keefe & Conway, 1978). The authors noted that each time the rat returned to a location, the same cluster of place cells would begin firing; hence, suggesting that place-specific firing occurs within the hippocampus that appears to relate to neural reconstruction of the animal's memory for that location (O'Keefe et al., 1998).

This research led to the formation of 'cognitive map theory' which advocates that the animal hippocampus supports the representation of their previously visited environments which they can then use as a basis for memory and spatial navigation (O'Keefe & Nadel, 1979). Moreover damage inflicted to the rodent hippocampi results in impairments in spatial navigation and place learning (Morris et al., 1982; Sutherland & Rudy, 1988; Jarrad, 1993). This theory is incongruent with declarative theory in that cognitive map theory postulates that the hippocampus is predominantly concerned with the functional role of place cells.

Later work identified a network of other cells within the medial entorhinal cortex that work in collaboration with place cells to encode location information (Rowland et al., 2016). Grid cells were discovered in medial entorhinal cortex that also encode location information (Fyhn et al., 2004). Like place cells, grid cells fire in response to a rat changing position within its environment. However, each individual grid cell has multiple firing fields, with these multiple fields within the neuron forming a triangular array (i.e. 'grid') that map the entire environment available to the rodent (see figure 1.5; Hafting et al., 2005; Moser et al., 2008).

Additionally, other types of cells within the medial entorhinal cortex and adjacent pre- and parasubiculum have been to found to represent spatial orientation and position in the rodent brain. Head direction (HD) cells have been found to code directional information (Ranck, 1985; Tang et al., 2016), in addition to border cells which code for an animal's location relative to geometric borders in their environment (Solstad et al., 2008) and speed cells that

code for an animal's running speed i.e. how fast they navigate their environment (Kropff et al., 2015). These cells, in addition to place cells, map space in a co-ordinated manner. For instance, if an animal rotates in a location, HD cells code this change in direction and place and grid neurons modify their firing in response to this change in head direction cell activity (Sargolini et al., 2006).

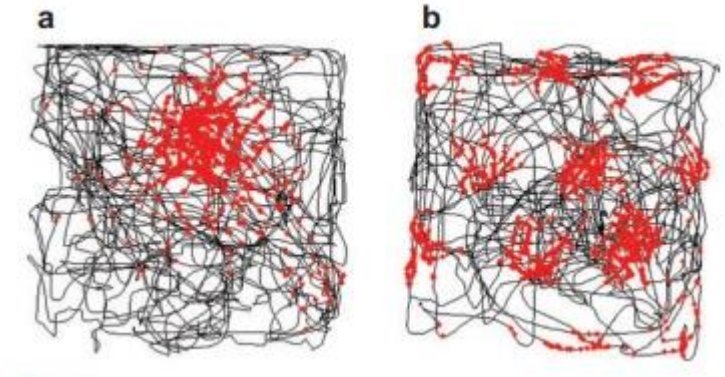

Figure 1.5 Differences in firing patterns of place cells and grid cells in rodents.

A) Place cells in hippocampus that have a single firing location. **B)** Grid cells in the medial entorhinal cortex, with each cell possessing numerous firing fields in a grid-like array representing the entire environment available to the rodent. Taken from Moser et al. (2008).

Human neuroimaging has demonstrated hippocampal activation when adults are learning a virtual town layout from viewing film footage of travelling through it and when verbally describing routes through a real city (Maguire et al., 1996). Furthermore, place cell firing has now been recorded in vivo in the human hippocampi when participants are navigating through a virtual environment (Ekstrom et al., 2003), with evidence suggesting this activity is specifically localised to the posterior CA1 subfield (Suthana et al., 2009).

Hassabis and colleagues (2009) have also provided pioneering evidence that the human hippocampus represents spatial locations as specific clusters of neuronal firing and that these groups of voxels observed during fMRI could be used to accurately predict a participant's location in a virtual reality environment. During fMRI, participants performed a virtual reality spatial navigation task which involved virtually moving between two different environments (a blue room and a red room), each containing four target locations positioned in each corner of the room. Participants were required to navigate to a given location using a key-pad and to press a button once they had reached the desired location. Once the button had been pressed,

the participant's view on-screen was changed to mimic looking downwards at the floor at that location, denoted by a rug. This view was presented for 5 seconds, to isolate the neural response to that specific location with fMRI, before the view-point returned to the horizontal position and the participant continued with the task. The authors analysed the data using multivariate pattern analysis to determine whether specific voxels (i.e. units of brain tissue containing thousands of neurons) within the hippocampus were able to discriminate between the target locations in a given room, and thus show evidence of clusters of neural activation specific to a spatial location. Indeed, Hassabis et al. observed that large numbers of voxels in the body-posterior region of the hippocampus accurately discriminated the location of the participant. Later electrophysiological and functional neuroimaging research has also identified the presence of grid cells in vivo within the human entorhinal cortex while navigating through a virtual reality environment (Doeller et al., 2010; Jacobs et al., 2013).

1.2.1.4 Relational Theory

An alternative perspective of how the hippocampus is involved in long-term memory is relational theory (Cohen & Eichenbaum, 1993). This view follows the principles of the multiple memory systems model (Tulving, 1985; Squire & Zola-Morgan, 1996), in that long-term memory can be subdivided into declarative and non-declarative types; although these are referred to as 'relational' and 'procedural' memory by relational theorists. Applying this principle, relational memories are argued to be represented by the MTL, especially the hippocampus, and reflect the outcomes of processing different elements of a given learning experience (Cohen & Eichenbaum, 1993). Specifically, the hippocampus is argued to support the binding together of the discrete elements of experienced events into sequences of memory representations. These representations are then integrated into a network of relational memories, whereby all possible relations between discrete elements of events are stored (see figure 1.6; Eichenbaum, 2004). By arranging memory representations in this way, the hippocampus is argued to allow flexible memory retrieval by permitting access to this network and flexibly recombining the discrete elements of episodic memories to apply them to novel situations an individual finds themselves in. This process enables both memories of specific contextual information (episodic content) and general semantic content to be compared and inferences to be made among indirectly related events, referred to as 'representational flexibility' (Eichenbaum, 1997). In contrast, relational theorists argue that procedural memories are supported by neocortical processes, are inflexible in nature and only relevant to specific tasks (Cohen & Eichenbaum, 1993).

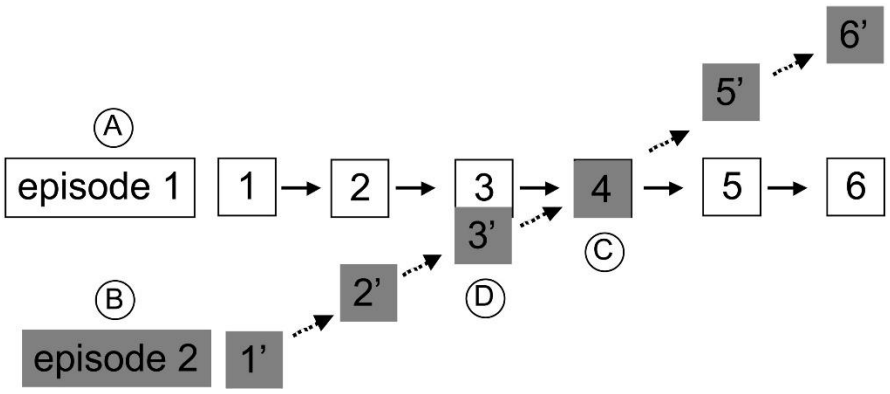

Figure 1.6 Theoretical representation of a relational memory network.

In this example, a network consists of two different episodic memories (A and B), with each depicted as a sequence of elements (1–6) that represent the content of an event. C refers to an element that contains the same features in both episodic memories, with D depicting an element that contains only some of the common information across both memories. Therefore, flexible recall of either episode can occur when elements 3 and 4 are individually encountered, depending on the situation that the individual finds themselves, i.e. representational flexibility Taken from Eichenbaum (2004).

Critically, relational theory accounts argues that the hippocampus is responsible for forming associations between discrete elements of an experienced event in general (Konkel et al., 2008). This view therefore conflicts with cognitive map theory (O'Keefe & Nadel, 1979), in that the hippocampus does not have a selective role in spatial memory but that memory for spatial contexts is just a component of a relational memory network.

1.2.1.5 Scene Construction Theory

While relational theory has attempted to reconcile the theoretical accounts of how the hippocampus is implicated in both episodic memory and spatial abilities, by arguing that the hippocampus plays a general role in binding all discrete elements of an event with spatial context simply being one of these elements, other accounts have outlined how the spatial role of the hippocampus may play a role in episodic memory processes. Episodic memory in everyday life consists of recalling the scene in which the encoded event took place (Burgess, Maguire & O'Keefe, 2002). For example, when retrieving a memory of when you last saw a friend you may recall where you saw them (in a restaurant) and where you were positioned (at a table, opposite your friend) as well as other episodic content of your memory e.g. what you ate. Research has indicated that the hippocampus plays a role in scene construction, i.e. the formation of novel or familiar scenes in one's mind (Hassabis & Maguire, 2009). It has been reported that the ability to mentally construct spatially-coherent scenes (whether these are

fictional or possible future events) is impaired in patients with hippocampal damage (Hassabis et al., 2007; Mullally et al., 2012) and visualised scenes are like a collection of fragmented and incoherent images rather than a clear mental representation of a past or fictional event in these patient cohorts (Hassabis et al., 2007). Furthermore, the application of fMRI during studies with healthy adults has documented hippocampal engagement during tasks where participants are imagining fictitious scenes and future scenarios (Addis et al., 2007; Hassabis et al., 2007a; Zeidman et al., 2014). This led to the proposal that the primary role of the hippocampus is to facilitate the construction of atemporal spatially-coherent scenes, which in turn may provide a foundation for a variety of cognitive procedures such as spatial navigation, episodic memory and imagining the future (Hassabis & Maguire, 2007; 2009); referred to as scene construction theory (SCT).

However there is a conflict in the literature regarding whether the hippocampus does support scene construction, with some authors maintaining that the role of the hippocampus is mnemonic and not required for the mental representation of scenes (Squire et al., 2010). Kim et al. (2015) reported that whilst patients with hippocampal amnesia demonstrated impairments on tasks assessing episodic memory, they exhibited intact performance comparable to controls on spatial tasks, including a measure of scene construction. However, the authors do note that the patients produced less accurate and detailed versions of previously viewed scenes compared to controls. Equally, sufficient functioning in residual hippocampal tissue may enable some patients with bilateral hippocampal damage to engage in rudimentary scene construction (Maguire et al., 2010a; Mullally, Hassabis & Maguire, 2012).

A recent study by McCormick et al. (2017) aimed to determine the exact role of the hippocampus in scene processing by examining performance when participants had to identify either semantic or constructive violations within images of scenes when mnemonic demand was absent. Patients with selective bilateral hippocampal damage were impaired in their ability to detect whether scenes were constructively possible or impossible, but matched control performance when judging the semantic possibility of scenes. These results along with aforementioned neuroimaging data suggest that the hippocampus plays a central role in forming representations of spatial scenes and the authors propose that this function may act as a scaffold for subsequent memory processes.

1.2.1.6 The Hippocampus and Memory for Temporal Context

A key hallmark of episodic memory is that the spatiotemporal context of events is processed in combination with the events themselves when forming a memory for a particular experience (Tulving, 1972). Both spatial and temporal context are important components of episodic memories. As outlined above in section 1.1.3.3, neurons within the hippocampal formation are specifically involved processing spatial environments, with a great deal of scientific focus placed on the role of the hippocampus in memory for spatial context. In the last decade, greater empirical attention has now been given to examining the role of the hippocampus in temporal context memory (for a review, see Palombo & Verfaelli (2017)).

Impairments in the ability to remember temporal order information surrounding events has been observed in adults with hippocampal damage. Mayes et al. (2001) observed that despite demonstrating recognition of previously learnt word pairs that did not significantly differ from the performance of controls, a patient with hippocampal damage was unable to remember the order in which the words were previously presented. Furthermore, Dede et al. (2016) conducted a study whereby patients with hippocampal damage and healthy controls were given a tour of a university campus which included 11 distinct events taking place. When memory for the experience was probed via narrative descriptions following the tour, patients recalled fewer episodic details than controls (e.g. which objects they had seen and where each of the events had taken place). Critically, while control participants described the events in the order in which they had occurred during the tour, the order in which patients recalled the events did not correspond to the order in which they happened. Collectively, these studies suggest that as patients with hippocampal damage are able to remember individual items/events but are unable to reproduce information concerning their temporal context, difficulties in binding together the temporal information with memory for the event itself may underpin patients' impairments.

There is also suggestion in the literature that the hippocampus is involved in processing time even when the task used is not considered a measure of episodic memory. For instance, Palombo et al. (2016) employed a task whereby patients with medial temporal lobe damage and controls were required to provide judgments about the length of time that had elapsed at different points while watching a nature-based video. Patients were impaired in their temporal assessments when the time elapsed exceeded four minutes or more relative to controls, with

this group difference not observed for durations of 90 seconds or less. Of note, a subset of the patients had focal hippocampal damage and it was found that these patients did not significantly differ from the patients with more widespread medial temporal lobe damage; both sets of patients' temporal judgments were impaired when time elapsed >4 minutes.

Regarding the neural correlates of temporal order memory, there is now accumulating evidence that rodent CA1 is involved in coding temporal sequences (Gilbert et al., 2001; Hunsaker et al., 2006; Mankin et al., 2012), with the discovery of 'time cells' that fire when an animal is at a specific moment in a temporally structured episode parallel to 'place cell' activity in response to previously encountered space (Macdonald et al., 2011; Eichenbaum, 2014). Discrete patterns of CA1 activation occurs when processing non-spatial associations between stimuli e.g. when encoding the order in which a sequence of odours were presented, with authors suggesting that the CA1 plays a general role in forming temporally structured associations between events occurring in a given episode (Kesner et al., 2010; Langston et al., 2010; Allen et al., 2016).

In terms of theories for how the hippocampus may underpin temporal order memory, Eichenbaum and colleagues propose that hippocampal time cells encode a temporal context (through representing the temporal information present with an event with a distinct pattern of neural firing) that gradually develops over time and allows experiences to be bound together to form memory for temporally organised experiences (Eichenbaum, 2013; Howard & Eichenbaum, 2015). Paz et al. (2010) provided evidence that the human hippocampus codes temporal order in a successive manner to permit the gradual formation of memory for the temporal order of events. In this experiment, single cell recording were obtained in the human hippocampus while participants viewed presentations of video clips of famous characters completing different activities. To test whether temporal order memory emerged gradually, each video was presented six times in a pseudorandomised order. Paz et al. found that the firing rate of neurons in response to a video clip at any given time rapidly became correlated with subsequent firing rate of neurons when the same clip was presented again. Equally, when examining overlaps in activity between consecutive time segments for each video clip, the neural activity at a given time was found to predict successive firing activity. From these findings, some authors suggest that the hippocampus forms memories of temporally structured events from representations of experiences in time (Schiller et al., 2015).

In accordance with relational theory (section 1.1.3.4 above), an extension of this view is that the hippocampus encodes various contextual information about an experienced event including both spatial and non-spatial information, with temporal order information falling into the latter category (Eichenbaum & Cohen, 2014; Schiller et al., 2015). The hippocampus then enters these representations into a network of relational memories, where all possible relations between discrete elements of events are stored thus supporting the formation of a wide variety of 'cognitive maps' to capture all contextual information present during events (Schiller et al., 2015).

1.2.2 Mechanistic Models of Hippocampal Subfield Functions

There is mounting evidence that individual hippocampal subfields play distinct roles in memory and differ in their retention rates (Gilbert et al., 2001; Yassa & Stark, 2011; O'Reilly et al., 2012). Retention of information in the CA1 subfield requires repeated exposures, reflecting a gradual learning process (Nakashiba et al., 2008). In comparison, memories are formed by the DG and CA3 in as little as one exposure (Kesner et al., 2008; Nakashiba et al., 2008). This information is largely attained from non-human animal electrophysiological experiments and theoretical models, due to the challenges of measuring hippocampal subfield activity in vivo in humans (Mullally, 2015) and the differences in protocol used when attempts have been made to analyse human in vivo data (Bonnici et al., 2012). It is beyond the scope of this thesis to discuss the vast literature outlining hippocampal subfield functionality. However, a brief overview is provided here for two types of hippocampal processing that are of particular relevance to this thesis and which have been linked to specific subfields.

1.2.2.1 Pattern Completion and Pattern Separation

To avoid confusing memories and to permit successful storage and retrieval of distinct but overlapping events, the hippocampus is argued to perform two complimentary processes. Pattern separation refers to the process by which distinct representations are assigned to specific events by transforming similar memories into highly dissimilar and non-overlapping patterns of activation (Norman, 2010). This reduction in overlap between similar memories is needed in order to accurately remember similar memories as separate from one another. The ability to correctly differentiate between previous encountered and perceptually similar novel stimuli is thought to represent the behavioural outcome of pattern separation (Yassa & Stark, 2011). Pattern completion refers to the retrieval of encoded memories when presented with

partial cues (McNaughton & Morris, 1987; Norman & O'Reilly, 2003). Distinct subfields within the hippocampal formation are argued to support pattern separation and pattern completion processes (Norman & Reilly, 2003). The DG and CA3 subfields are both linked to pattern separation while the CA3 subfield is reported to support pattern completion (Marr, 1971; Leutgeb et al., 2004; 2005; Hunsaker & Kesner, 2013).

It is proposed that when faced with novel stimuli that are highly similar to previously encountered stimuli, the DG performs pattern separation by disaggregating cortical inputs received from the entorhinal cortex through amplifying minor differences between these inputs. This is argued to be accomplished by the entorhinal cortex input being dispersed onto a more extensive layer of the sparsely firing granule cells within the DG so that each granule cell is only carrying a small fraction of the total entorhinal input (Treves et al., 2008). The DG then projects this information to the CA3 cells downstream (Treves et al., 2008). Cells within CA3 are highly controlled by other CA3 cells (via recurrent interconnected pyramidal cells) which forms the CA3 'autoassociation network' (McNaughton & Morris, 1987). Thus, pattern separation leads to the creation of distinct memory representations within the CA3 region and allows us to successfully encode and retrieval memories of distinct but overlapping events. Due to the high interconnectivity within CA3 neurons, this subfield is postulated to re-establish stored patterns of action when presented with degraded or partial cues (i.e. that are similar to stored memories); thus, the CA3 subfield is argued to support pattern completion processes (Norman & O'Reilly, 2003). Pattern completion is important as we rarely encounter the perceptually identical experience twice and therefore must be able to apply stored memories to similar experiences.

In rodents, the ability to discriminate between similar spatial contexts is impaired following lesions of the DG, indicative of pattern separation deficits (Gilbert et al., 2001; Goodrich-Hunsaker et al., 2008; Hunsaker & Kesner, 2008). Equally, CA3 lesions or CA3 receptor inhibition disrupts rats' ability to utilise available cues to find the location of objects to obtain a food reward, i.e. pattern completion impairments (Nakazawa et al., 2002; Gold & Kesner, 2005; Kesner & Warthen, 2010). Regarding evidence for pattern separation and completion processes in the human hippocampi, behavioural performance combined with high-resolution functional neuroimaging or electrophysiological recordings have produced significant findings which appear to generally corroborate animal data. Of note, due to the difficulty is

segmenting the hippocampal subfields with precision, studies often analyse activity within the DG and CA3 subfields collectively. Using mnemonic similarity tasks (whereby participants are tested on their ability to recognise previously studied items along with correct rejection of perceptually similar unstudied items i.e. lures), neuroimaging studies with humans have demonstrated similar levels of activity in the DG/CA3 regions when viewing previously presented items and when presented with highly similar lures (Bakker et al., 2008; Lacy et al., 2011). Similar levels of activity in the DG/CA3 areas suggests that the lure items are being processed as novel representations, and therefore distinct from the previously viewed items, indicative of pattern separation occurring. Additionally, Baker et al. (2016) demonstrated that a patient with selective DG damage was impaired in their ability to discriminate between perceptually similar experiences, which parallels the deficits observed in rodents with selective DG lesions (e.g. Gilbert et al., 2001).

A recent study by Dimsdale-Zucker et al. (2018) employed a virtual reality task whereby participants were first familiarised with two houses (i.e. spatial contexts). Participants then passively navigated through houses in a series of virtual reality videos in which they encountered a variety of objects. Critically, each object was only shown once in a single video and in only one of the houses. Therefore, each video, set within a specific spatial context (i.e. house 1 or house 2) in which unique objects were encountered, formed an episodic context Following this task, participants completed an object recognition task with fMRI whereby participants were required to differentiate between previously seen items presented without their episodic context and novel items. Note the CA2, CA3 and DG were not examined separately but were segmented collectively. Multi-voxel pattern similarity analysis of fMRI data demonstrated that the CA1 elicited more similar patterns of activity when presented with objects that shared an episodic context (i.e. were in the same house shown in the same video) relative to objects belonging to different episodic contexts. In comparison, the CA2/CA3/DG subfields represented objects that fell within the same episodic context as more dissimilar, i.e. elicited different patterns of activity between these objects. The authors suggest that these distinctions in activation patterns across subfields are reflective of diverse processes, with the CA1 representing similarities across items in the same episodic context, i.e. pattern completion, and the CA2/CA3/DG denoting differences between items that overlap in their episodic context, i.e. pattern separation.

Neuroimaging studies have also supplied evidence for the role of the CA3 subfield in pattern completion processes. Chen et al. (2011) used a paired association task to demonstrate CA3 involvement during retrieval of previously encoded pairs of items when presented with a partial cue. Participants were asked to study house-face pairs before a recall test wherein one half of a given pair was presented and participants were required to identify whether the item presented on-screen was the other half of the pair. Functional neuroimaging revealed CA3 activation when participants correctly selected the item that completed the pair, indicative of CA3 involvement in humans when required to engage in pattern completion.

Moreover, Chadwick et al. (2014) observed a relationship between activation patterns of the CA3 subfield and episodic recall of overlapping events. Participants were first shown four video clips depicting two different events that were each presented in two different spatial contexts and therefore contained highly overlapping content. Participants were then scanned using fMRI while recalling each video clip numerous times, in order to determine whether recall of one video would lead to the co-activation of the other videos and to deduce the neural response to this recall. Critically, only the CA3 subfield demonstrated a significant degree of co-activation between overlapping episodic representations at recall, i.e. indicating pattern completion had occurred. Additionally, this indicated that overlapping events were not represented by completely distinct neuronal representations in the CA3, which may suggest that, due to the high similarity between the studied videos, pattern separation processes had partially failed. Moreover, participants were asked whether they were aware of the similarities across the four videos during retrieval to obtain a measure of subjective confusion. A significant positive correlation was observed between the degree of CA3 overlapping activation and subjective confusion, suggesting that greater difficulty in deducing similarities between videos is linked to higher levels of overlap in representations of these events in the CA3. Additionally, participants with a larger CA3 subfield demonstrated lower levels of both subjective confusion and overlapping activations within the CA3. Thus, these findings overall demonstrate individual differences in episodic recall for overlapping events that appear to be related to the size and processing of the CA3 subfield.

Collectively, these findings indicate that the CA3 and DG subfields are linked with pattern separation while the CA3 region also supports pattern completion. Therefore, these

differential subfield functions may contribute to episodic memory processing in a complimentary manner in the human hippocampus (Dimsdale-Zucker et al., 2018).

1.2.3 Summary

Overall, there is sizeable evidence that both episodic and spatial memory abilities are reliant on the hippocampus. Although all the theoretical perspectives outlined above each afford some explanation for how the hippocampus supports episodic memory, none of them provide a complete account that concurs with all the existing data.

1.2.3.1 Task-dependent Processes within the Hippocampus

A recent study by Dalton et al. (2018) suggests that there may be multiple processing circuits within the hippocampus that are recruited depending on task requirements. Participants completed six different mental construction tasks during fMRI, whereby they were seated in front of a blank screen and required to mentally construct the following stimuli in their mind's eye one at a time; a fixation cross (while listening to non-sense phrases), simple objects (while listening to simple descriptions of those objects), a 2D grid, a 3D grid, objects placed on a 2D grid (construct array condition) and objects placed on a 3D grid (construct scene condition); see figure 1.7. This allowed the authors to determine the neural correlates of mental construction for each of conditions and importantly determine whether the neural correlates of performance differed between conditions where objects were either presented in space requiring scene construction (construct scene condition) or when no scene construction was demanded (construct array condition). A selective region of the anterior hippocampus (containing the pre/parasubiculum; see Dalton & Maguire (2017) for a discussion of the role of these hippocampal regions in scene processing) was engaged in scene construction tasks, along with the parahippocampal cortex, retrosplenial cortex and posterior cingulate cortex. In comparison, array construction (i.e. only engaging the construction of multiple objects) more strongly recruited the entorhinal cortex, perirhinal cortex, posterior regions of the early visual cortices and activation within the left posterior and left entorhinal cortex bordering the anterior medial hippocampus. Variances in neural recruitment between the construct array and construct scene conditions could not be accounted for by differences in task engagement (assessed via eye-tracking to measure visual attention), encoding of the different stimuli types (examined via a surprise recognition memory test at the end of the study) or strength of mental imagery (tested by asking how vivid mental construction was).

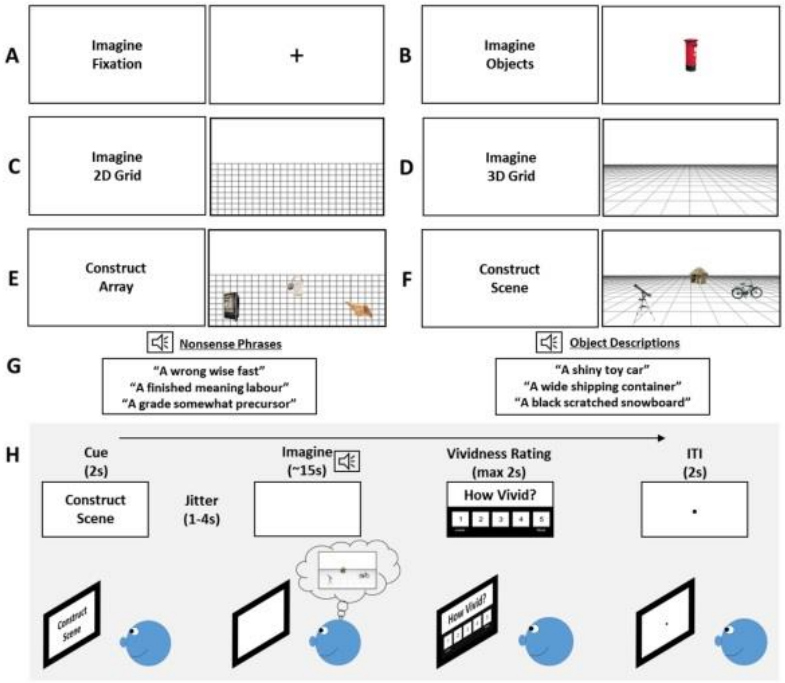

Figure 1.7 Experimental design employed in Dalton et al. (2018).

A-F= each of the different mental imagery tasks. **G=** Examples of nonsense phrases and object descriptions used. **H=** example of time line for a single trial.

As differentiable portions of the hippocampus were recruited for scene construction or associative processing that did not require scene construction, Dalton et al. argue that uni-functional accounts of hippocampal function should be reassessed. Considering these findings, one could infer that episodic memory may be the end product of collaborations between the varying functions of the hippocampus.

Furthermore, due to the wide-spread connectivity of the hippocampus, this neural structure does not subserve memory in isolation. Neuroimaging studies have consistently demonstrated activation in a key set of neuroanatomical structures during episodic retrieval (Cabeza et al., 2000; Spreng et al., 2009). These structures include the prefrontal cortex (PFC), posterior parietal cortex, retrosplenial cortex and medial temporal lobe structures, including the hippocampus and parahippocampal cortex (Spiers et al., 2001; Nyberg et al., 2003; Svoboda et al., 2006; Andrews-Hanna et al., 2014). Of particular note, it is argued by many researchers in the field that the crucial role of the PFC in episodic memory is to facilitate strategic retrieval of memories, by supporting top-down memory processing (Eichenbaum, 2017). The PFC is also argued to facilitate long-term memory retrieval, by acting as a memory consolidation hub beyond the hippocampus to integrate new memory representations in the

context of pre-existing schemas, i.e. our cognitive frameworks that allow us to organise and interpret information (Benoit et al., 2015; Moscovitch et al., 2016). Overall, episodic memory is a complex, multifaceted construct that may arise through collaborations between the different functions of the hippocampus and its elaborate connectivity in the brain.

1.3 *The Ontogeny and Decline of Episodic Memory*

There is widespread agreement that atrophy in the hippocampal formation, through neuropathology or acquired brain injury, results in episodic memory deficits. When considering when episodic memory first emerges in humans and the developmental trajectory of these processes across the life-span, there is less consensus. To establish the age at which episodic memory appears to develop and subsequently declines in older adults, one must consider that the process of successfully forming, retaining and retrieving episodic events requires a number of cognitive computations to take place. When contemplating the ontogeny and decline of episodic memory development, one should consider how these distinct computations emerge and develop throughout childhood in order to pave the way for the emergence of adult episodic memory and how these processes may be impacted with healthy ageing. In this section, I first outline current understanding of the neuromaturational development of the hippocampal formation and existing evidence for the development of diverse memory functions throughout early childhood that are argued to support episodic memory processing. Consequently, I will discuss evidence for the impact of healthy ageing on episodic memory in adults.

1.3.1 Hippocampal-dependent Memory in Childhood

1.3.1.1 The Maturational Trajectory of the Hippocampal Formation

A series of studies by Lavenex and colleagues have provided a wealth of information about the structural and functional development of the hippocampal formation in the rhesus macaque monkey (Amaral & Lavenex, 2007; Jábes et al., 2011). Specifically, the subfields of the hippocampal formation and their functional connectivity follow diverse developmental trajectories throughout early life. At birth, the hippocampal formation, particularly the dentate gyrus (DG) is immature both in structure and function. CA1 is one of the earliest subfields to reach maturity and appears to be adult-like in volume and gene expression by 6 months of age in macaques (Lavenex & Banta Lavenex, 2013), which is argued to correspond to

approximately 2 years of age in humans (Fortman et al., 2001). However, individual layers of the CA1 region also reach maturity at different rates, with the most superficial layer (stratum lacunosum-moleculael) that connects directly with the entorhinal cortex maturing the earliest.

The DG and CA3 subfields appear to possess the most protracted developmental trajectories (Jábes et al., 2011). Firstly, there are different patterns of maturation within the CA3 region. Circuitry connecting CA3 directly with the entorhinal cortex emerges earlier, with proximal neuronal connectivity between the CA3 and DG developing at a slower rate. The maturation of mossy fiber projections from the CA3 to the DG cells and projections of the DG to the polymorphic layer follow a later and more protracted developmental trajectory. Slow pruning of synapses in the macaque DG emerge after 5 months of age (Eckenhoff & Rakic, 1991). These regions appear to only reach adult levels in volume and gene expression after 1 years old in macaques, which corresponds to approximately 4-years-old in humans (Fortman et al., 2001). Thus, entorhino-hippocampal circuits, particularly bidirectional connectivity between the entorhinal cortex and the CA1, appear to develop earlier in the macaque brain compared to the more complex trisynaptic circuitry (Jábes & Nelson, 2015).

Evidence from post-mortem data has increased our understanding of specifically how these neural structures develop in humans. In accordance with non-human primate data, myelination of the hippocampal subfields show differential rates of development, with the DG specifically demonstrating protracted maturation that extends well into adolescence (Arnold & Trojanowski, 1996; Ábraháms et al., 2010). The DG subfield appears to be adequately mature by 20-24 months old to permit some neural communication via the trisynaptic circuitry, however synaptic pruning only reaches adult-like levels after 4-5 years old (Bauer, 2007).

1.3.1.2 Memory Feats in Early Infancy

Soon after being born, infants are capable of remarkable mnemonic feats (Mullally & Maguire, 2014). Three-four days post-partum, infants recognise their mother's face and voice (DeCasper & Fifer, 1980; Bushnell et al., 1989; Bushnell, 2001) and after 8-10 days infants can distinguish their mother's breast milk from that of another woman (MacFarlane, 1975). Thus, evidence of recognition memory is present very early in an infant's first days of life.

Attempting to measure hippocampal-dependent memory processes during infancy is challenging, largely due to 1) paradigms must not require explicit responses and 2) it is difficult to know whether infant variants of adult memory measures are hippocampal-dependent. For a more detailed discussion, see section 1.3.2 below. Early attempts to measure hippocampal memory in infants typically employed visual preference paradigms, with the most commonly used involving visual paired comparison (VPC). VPC methodology was originally developed by Robert Fantz to assess visual perception in young infants and was subsequently modified to investigate visual recognition memory (Fantz, 1964). VPC tasks measure recognition as a function of habituation and novelty preferences, based on the notion that humans decrease their visual attention to previously-seen images (habituation) and thus elicit a preference to novel images. In typical VPC tasks, infants are familiarised to a visual stimulus, e.g. a black and white pattern, and then are simultaneously presented with the familiar stimulus and a novel stimulus at test. Recognition of the familiar stimulus is inferred if the infant spent significantly longer fixating on the novel stimulus (i.e. showing a novelty preference) than the familiar stimulus (Fagan, 1971).

Employing this paradigm, infants as young as 3 days old can elicit preferential looking to a novel stimulus compared to a familiar stimulus following a 2 minute retention interval (Pascalis, 1994). Numerous studies had showed evidence that infants aged between 3-6 months old are capable of recognising diverse stimuli types (e.g. faces, black and white shapes, letters), with age-related increases in the ability to retain these memories over increasing delays (ranging from 2 minutes to 24 hours) and with older infants requiring less stimulus exposure during familiarisation to elicit novelty preference compared to younger infants (Fagan, 1971; Rose, 1983; Colombo et al., 1988; Pascalis et al., 1998). Interestingly, a series of experiments have found that longer retention intervals (e.g. retention intervals over 1 month compared to 1 minute or 24 hours) produced preferential looking of the familiarised stimuli in infants aged 3 months, indicative of long-term recognition memory for such stimuli (Bahrick & Pickens, 1995; Courage & Howe, 1998). Thus, manipulating retention interval in VPC tasks appears to impact how recognition of previously encountered stimuli presents itself. Overall, very young infants are able to encode visual stimuli, store this representation for relatively long durations of time and use this representation to recognise the stimuli as familiar when they encounter it again in the near future.

1.3.1.3 Memory for Basic Associations

The ability to learn basic associations between an action and an event has been extensively studied in early infancy, using a variety of different paradigms. Among these methodologies, operant conditioning tasks have been widely employed. The mobile conjugate reinforcement task (Rovee-Collier et al., 1980) assesses an infant's ability to remember that kicking will cause an over-hanging mobile to move (see figure 1.8) and is typically used in infants aged 2-6 months old. In this task, a baseline measurement of an infant's rate of kicking is taken when laid in a crib with a mobile hanging above. Next, infants are exposed to a training phase whereby a ribbon is tied around their ankle which connects to the mobile. Infants learn that kicking their leg to which the ribbon is tied will result in the mobile moving. At test, the ribbon is disconnected from the mobile and the experimenters record the rate of kicking that the infant elicits. The rate of kicking elicited at baseline and test is compared, with successful recognition of the mobile (and retention of the association between kicking and consequent mobile movement) being inferred if the proportion of kicking at test significantly exceeds that observed at baseline.

Using this paradigm, age-related increases in the ability to learn the association between the mobile and kicking behaviour have been consistently found between 2-6 months old, with older infants requiring less training to learn the association and retaining the association for a longer durations compared to younger infants (See figure 1.9; Sullivan et al., 1979; Rovee-Collier, 1984; Davis & Rovee-Collier, 1983; Rovee-Collier et al., 1985; Hill et al., 1988).

As infants become progressively more active and capable of independent locomotion, mobile conjugate reinforcement tasks become inappropriate. Rovee-Collier and colleagues devised another operant conditioning task that could be used with infants aged 6-24 months, termed the train task (see figure 1.8; Hartsthorn & Rovee-Collier, 1997). Infants were exposed to a miniature train set and the amount of times that they spontaneously pressed a lever within the apparatus was recorded to obtain a baseline level of lever presses. Infants then underwent training to learn that pressing the lever would result in the train moving around the track. At test, the lever was disconnected and the experimenters recorded the number of lever presses that the participant elicited. Retention for the association between the lever press and train movement was inferred if the number of lever presses elicited after training significantly exceeded those at baseline. Using this task, again age-related increases as observed in the

amount of time in which the association between the lever press and the train can be retained, with older infants being able to retain the association across significantly longer delays than younger infants (see figure 1.9; Hartsthorn & Rovee-Collier, 1997; Hartsthorn et al., 1998).

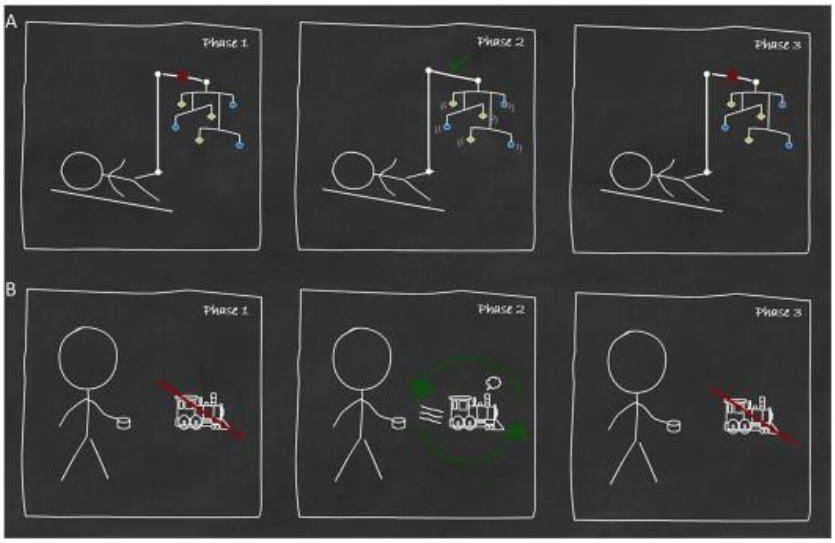

Figure 1.8 Overview of infant operant conditioning tasks.

A) The mobile conjugate reinforcement task; infants are first exposed to an over-hanging mobile whereby the ribbon tied around their ankle does not elicit movement of the mobile (phase 1). In phase 2, infants learn that kicking will cause the ribbon around their ankle to move the mobile. At phase 3, the ribbon is disconnected from the mobile and memory for the action and its consequence (i.e. kicking will move the mobile) is measured by comparing the incidence of kicking between phase 1 and phase 3. **B)** The operant train task; infants are exposed to a train set inclusive of non-functional lever (phase 1). Baseline frequency at which infants press the lever is recorded. At phase 2, infants learn that pressing the lever will cause the train to move around the track. At phase 3, the lever is disconnected and memory for the action and its consequence (i.e. pressing the lever will move the train) is measured by comparing the incidence of lever presses between phase 1 and phase 3. Taken from Mullally & Maguire, 2014.

Furthermore, imitation paradigms have been frequently used to examine how recall for associations between objects and actions develops in early infancy (Hayne, 2004). In these tasks, the experimenter demonstrates an action/multiple actions on a cue (e.g. a puppet). The experimenter then presents the infant with the cue either immediately (elicited imitation) or after a delay period (deferred imitation), and records how many previously demonstrated actions the infant reproduces. Retention is typically inferred when reproduction of correct actions is significantly higher in infants who previously observed the actions being imitated compared to infants who were not shown the demonstration (i.e. naïve controls).

Using deferred imitation paradigms, research has found that infants aged 6-9-months-old can significantly outperform naïve peers in the number of correctly imitated actions after a 24

hour delay (Meltzoff, 1988; Collie & Hayne, 1999); thus demonstrating evidence of memory retention for previously seen action-object associations. Age-related increases are observed in the number of correctly recalled actions and retention duration, with older infants reproducing significantly more actions over longer delay periods than younger infants (see figure 1.9; Bauer & Mandler, 1989; Barr et al., 1996; Herbert & Hayne, 2000).

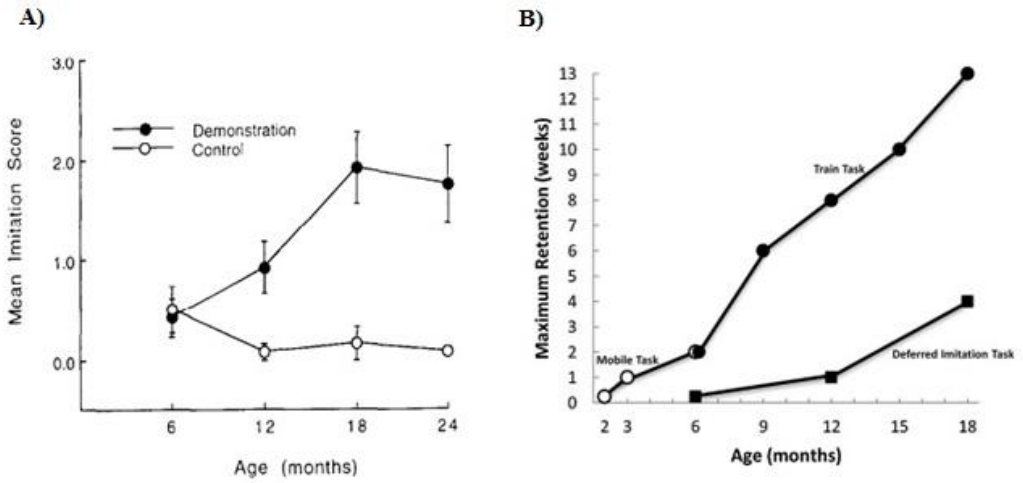

Figure 1.9 Increases observed in infant memory for associations between actions and events across the first two years of life.

A) Deferred imitation task performance examined across 6-24 month olds using a three-step action sequence. *Note.* Demonstration = infants who viewed the sequence at learning; naïve = infants not shown the sequence at learning. Taken from Barr et al., 1996. **B)** Memory retention rate on different infant paradigms (mobile conjugate reinforcement task; operant train task; deferred imitation) across the first two years of life. Taken from Rovee-Collier & Cuevas, 2009.

1.3.1.4 Memory for 'what-where-when' Information

While very young infants can form and retain basic associations, the ability to encode and retain the contextual information underpinning these associations appears to emerge later in childhood (Ghetti, 2017). The ability to bind together the components of an experienced event, for instance '*what*' happened with '*where*' and '*when*' it occurred, is argued to be a defining characteristic of episodic memory (Olson & Newcombe, 2013). The nature of these binding operations appear to follow individual developmental trajectories, with discrete developmental time courses dependent on the type of association being formed and retained (Edgin et al., 2014; Ghetti, 2017). While some studies have examined recall for '*what*' '*where*' and '*when*' memory separately, others have attempted to track the development of these distinct episodic components simultaneously using the same task.

The ability to form and retain basic item-spatial associations (i.e. the '*what-where*' of memory) has been consistently shown to emerge between the ages of 22-25 months, when toddlers can successfully locate a reward hidden in one of several possible locations in an open-field arena (Newcombe et al., 1998; Ribordy et al., 2013). When children aged 16-36 months old were asked to search for buried objects hidden in a sandbox after they had been moved to the opposite side of the sandbox to which they had been when the objects were hidden, only children aged 24 months and over were able to use distal visual landmarks to locate hidden objects (Newcombe et al., 1998). Distal visual cues refer to elements in the environment which can be used to inform spatial judgments e.g. the position of furniture relative to a hiding location. The availability of these cues can be manipulated e.g. by using opaque curtains to hide space surrounding the open-field arena. This result suggests that the ability to use distal cues enables children from 24 months old and above to create basic allocentric spatial representations of their environments.

The robustness of memory for where an object has been hidden has been shown to increase gradually with age. Ribordy et al. (2013) also examined the ability to locate a reward hidden under a plastic cup in the presence of 3 other potential locations in 18 month olds to 5 year olds (figure 1.10). Participants were able to perform the search in the presence of local cues (i.e. cues within the participant's immediate vicinity in the arena that marked the location of a reward) in the form of a red cup, or with no local cues present (and thus the participant must rely on allocentric spatial memory). The study found that when local cues were present, all groups were able to locate the hidden rewards. However, when these local cues were absent, only children aged 25 months old and over could successfully locate the reward. Additionally, children's ability to engage in more complex allocentric spatial processing was examined, by determining participant's ability to successfully locate multiple hidden rewards when a larger number of decoy locations are present (to locate 3 rewards within 18 potential reward locations). When local cues were present, children aged 25-41 months old were able to successfully locate the rewards when more locations were introduced. However, only children aged 42 months (i.e. 3.5-years-old) and above were able to find the rewards with no cues present and thus effectively engage in discriminating spatially-similar locations. Hence, these findings suggest that basic allocentric spatial learning emerges in the second year of life, with significant age-related increases in the ability to process and retrieve more complex allocentric spatial information observed between the ages of 24-42 months old.

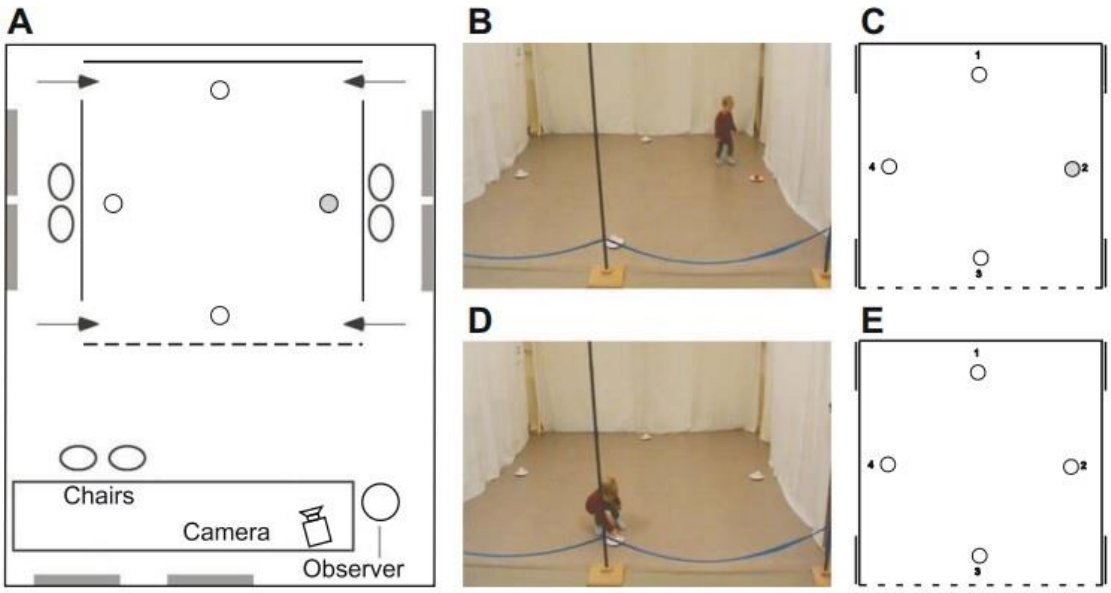

Figure 1.10 Example of a basic allocentric search task used in Ribordy et al. (2013).

Participants are required to locate a hidden reward under a choice of 4 location (denoted by cups). *Note*. **A)** depiction of the testing room and arena used; **B)** example of a participant in the area during the local cue condition (red cup present); **C)** depiction of arena during local cue condition; **D)** example of a participant in the arena during the no cue (allocentric spatial) condition; **E)** depiction of the arena during the no cue (allocentric spatial) condition.

When examining recall for temporal order information within events (‘*what-when’* memory), evidence using imitation paradigms has demonstrated that towards the end of their first year of life, infants are able to reproduce multi-step sequences in the correct order (Barr et al., 1996). However, in these instances, infants were tested on their recall for events constrained by enabling relations, which refers to actions performed on an object whereby the reproduction of later actions in the sequence is dependent on preceding actions being performed first. In the study by Barr et al., to replace a glove onto a puppet’s hand, the infant must have first removed the glove. Hence, enabling actions may inflate memory for the action sequence, due to the reproduction of actions presented early in the sequence potentially cueing recall for actions later in the sequence. Indeed, infants aged 13-20 months elicit superior recall for enabling as opposed to arbitrary-related actions following delays ranging from 24 hours to 2 weeks (Bauer & Hertsgaard, 1993; Barr & Hayne, 1996; Bauer et al., 1998; 2000). Therefore, measuring recall for previously seen arbitrarily-related actions may provide more genuine evidence for the ability to successfully recall temporal order of events.

Indeed, research indicates that successful temporal order recollection of arbitrarily-related events emerges later in childhood and continually develops (see chapter 3 section 3.1). Bauer and colleagues (1998) examined age-related changes in the ability to reproduce previously

seen arbitrarily-related actions in 16, 22 and 28 month old infants. When the ability to reproduce three-step action sequences in the correct order was tested either immediately or after a 2 week delay, only children aged 22 months and above could reproduce the actions significantly above chance when recall was tested immediately. However, only 28-month-olds were able to reproduce the actions following a 2 week delay. Hence, age-related increases in the ability to recall arbitrarily-related action sequences in the correct order are observed throughout toddlerhood.

However, there are caveats that need to be acknowledged when interpreting the findings of Bauer et al. (1998). Firstly, deferred imitation after the 2 week delay may be confounded by having the children complete the action sequences immediately after modelling, referred to as elicited imitation. This allowed the children to practice the sequence and thus could have facilitated memory for the sequences at the later testing period. While the authors propose that memory for arbitrary temporal sequences is present at 28 months, these infants only elicit a mean temporal ordering score of 1.29 out of a possible score of 2. Therefore, performance is not at ceiling and we do not know how the performance of these infants compares to older children and adults.

Previous studies which have employed the use of a hide and seek paradigm to assess memory retention for the individual components of an event where a child observes a toy being hidden in a room, have also reported differences in preschool children for recall of '*when*' the toy was hidden. In a study by Hayne & Imuta (2011), children aged 3- and 4-years-old completed a task whereby they first hid three teddies around the participant's house with the experimenter, with each teddy placed in a separate location. Following a 5 minute delay, children were verbally asked to recall *what* toy was hidden *where* and *when* this toy hidden (i.e. in which order). After the verbal recall test, children were asked to find the toys. 4-year-olds reported more information overall than 3-year-olds during the verbal recall test. When behavioural recall of the hiding event was assessed, 4-year-old children recalled '*when*' the hiding event had taken place significantly more often than 3-year-old children whilst the ability to recall '*what*' toy and '*where*' that toy was hidden did not significantly differ between groups (Hayne & Imuta, 2011).

Using a hide and seek paradigm, Cuevas et al. (2015) also reported that the lowest levels of recall for the hiding event related to the order in which toys were hidden within 3-year-old participants, and that although a significant increase in temporal order recall was observed when children were assessed again at 4-years-old, memory for order (i.e. '*when*' memory) was still poorer relative to memory for the '*what*' and '*where*' information of the event. Taken together, evidence from hide and seek paradigms suggests that although 3-year-old children can elicit memory for content and spatial context of previously observed events, it is not until 4 years of age that children begin to successfully recollect the temporal information of events experienced. Although as highlighted above, we do not know from these studies how the temporal order memory of 4-year-olds compared to that of adults.

The ability to bind together the '*what*' content of an event with its contextual details (i.e. the '*where*' and '*when*' information) also improves between the ages of 3-7 years (Ghetti, 2017; Scarf et al., 2017). Employing eye-tracking, Pathman & Ghetti (2014) demonstrated age-related increases in children aged 7 and 10 years compared to young adults for temporal memory underpinning events (see figure 1.11). Participant's first encoded sequences of 4 objects presented one at a time on-screen. At retrieval, a previously shown object was presented on-screen (cue) before three additional objects appeared. Participants were to identify which of the three objects had been previously presented after the cue. The two distractor objects presented with the target object was dependent on the trial condition. On temporal order trials, the two distractors were from the same sequence as the cue and target. During temporal context trials, the distractors belonged to different studied sequences (i.e. a different temporal context). Lastly, in the recognition condition, the distractors were novel objects. Correct memory judgments were found to significantly increase as a function of age, with 10-year-olds performing significantly better than 7-year-olds and worse than young adults. When eye-movements were examined during retrieval, young adults and 10-year-olds elicited disproportionate viewing of the correct items seconds before providing judgments regarding temporal order. Thus, in these age groups, eye movement behaviour appears to be veridical of underlying temporal order memory. In contrast, 7-year-olds failed to elicit this pattern of eye movement behaviour. Interestingly, when 7-year-olds were separated by accuracy of responses at retrieval, 7-year-olds who scored more highly in accuracy for their memory judgments did show evidence of this preferential looking behaviour. Thus, these findings suggest that age-related increases are observed in middle childhood for temporal order memory, which are indexed by eye movement behaviour.

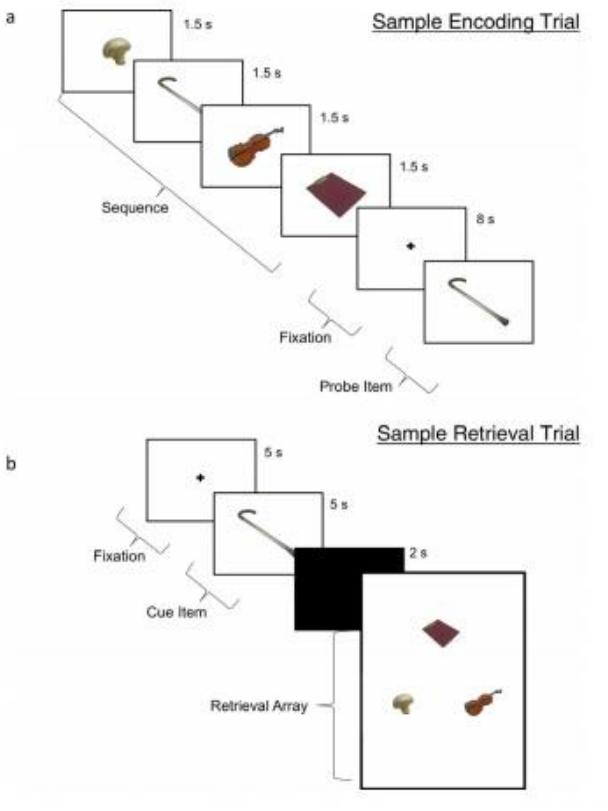

Figure 1.11 Temporal order task used in Pathman & Ghetti (2014).

A) Encoding phase where the participant is asked to state the ordinal position of the probe item. **B)** Retrieval phase where the participant selects the item that came immediately after the cue item during encoding.

In summary, this collection of findings suggest that the ability to successfully bind content and contextual information of events and retain these representations continues to develop across later childhood and into adolescence, with some authors proposing that age-related changes in relational memory may contribute to overall maturation of episodic memory in early childhood (Olsen & Newcombe, 2014).

1.3.2 Episodic Memory Decline with Healthy Ageing

1.3.2.1 Age-related Anatomical Changes to the Hippocampus

Studies of normal ageing in humans have revealed that the hippocampal formation appears to be particularly vulnerable to the effects of ageing. Neuroimaging and post-mortem data has revealed decreases in hippocampal volume as a function of age from 16 years to 99 years (Simić et al., 1997; Fjell et al., 2014), with studies reporting greater hippocampal volume loss in older adults relative to younger adults in both cross-sectional (Jack et al., 1997) and longitudinal studies (Scahill et al., 2003). Note these studies corrected for overall intracranial

volume. Regarding specific subfield volume loss, CA1 subfield volume reductions have been observed with healthy ageing (Mueller et al 2007; Mueller & Weiner, 2009; Wisse et al., 2014). Some studies have provided evidence for DG volume reduction with increasing ageing (Mueller & Weiner, 2009; Wisse et al., 2014; Pereira et al., 2014), while others do not provide evidence of age-related changes in DG volume (Mueller et al., 2007; Shing et al., 2011). Therefore, there does not seem to be consensus as to whether ageing results in hippocampal subfield loss (see Grady & Ryan, 2017; figure 1.12).

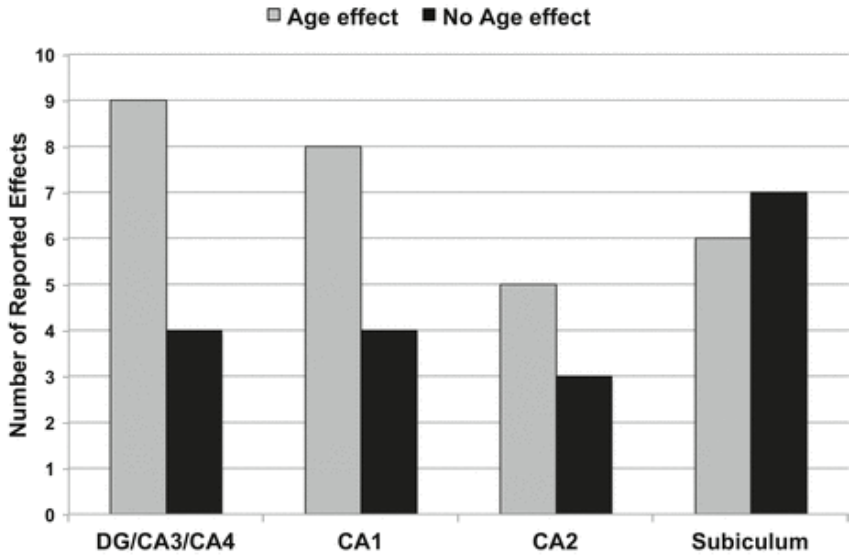

Figure 1.12 Summary of data that has examined age-related differences in hippocampal subfield volume, performed by Grady & Ryan (2017).

Note grey bars depict the number of papers demonstrating age-related reduction in volume for each subfield. Black bars indicate number of papers reporting no age difference.

1.3.2.2 Changes to Episodic Memory Proficiency with Ageing

While episodic memory deficits are observed in patients who incur damage to the hippocampal structures, decline in both the encoding and retrieval of episodic events as a result of normal ageing is also evidenced in the literature (Nyberg, 2017). A large body of work predominantly conducted by Naveh-Benjamin and colleagues has demonstrated that older adults show deficits in their ability to bind item-context information and successfully recollect these associations relative to younger adults (Spencer & Raz, 1995; Old & Naveh-Benjamin, 2008). Specifically, older adults have been found to demonstrate poorer recognition of previously encoded picture pairs (Naveh-Benjamin et al., 2003; Ratcliffe & McKoon, 2015), object-location pairings (Johnson, 1996; Bastin & Van der Linden, 2005; Plancher et al., 2008) and object-temporal associations (Plancher et al., 2008; Cheke, 2016)

compared to younger adults. These findings offer support for the associative-deficit hypothesis (Naveh-Benjamin, 2000), which postulates that poorer episodic memory observed in old age results from deficits in binding together and retaining associations between single units of information.

Some sources have reported that decline in memory proficiency can begin as young as 20-30 years of age in healthy adults (Salthouse, 2003; 2009). Performance on standardised neuropsychological measures of long-term memory have also been found to reach peak performance around the mid-twenties, with short-term memory performance identified as reaching optimal level in late adolescence (Hartshorne & Germine, 2015). However, large-scale longitudinal studies note that significant age-related decline in episodic memory appears to begin from approximately 60-years-old (Rönnlund et al., 2005). Individual differences such as level of education attained and degree of physical activity engagement have been found to play a role in the onset and degree of memory deterioration (Josefsson et al., 2012).

As outlined in section 1.2.2.1, structural changes in the hippocampus have been found to occur with normal ageing. Research has reported associations between the degree of episodic memory decline and the preservation of hippocampal structure and function in ageing populations, with small hippocampal volume in older adults being correlated to poorer verbal recall (Kramer et al., 2007; Chen et al., 2010; Ezzati et al., 2016). Functional neuroimaging has demonstrated that older adults show less hippocampal activation during episodic encoding and retrieval compared to younger adults (Daselaar et al., 2003; Persson et al., 2012; Salami et al., 2012; Pudas et al., 2013). Previous work has implicated the CA1 subfield in particular in forming associations between items and spatial or temporal contexts (Suthana et al., 2009). As outlined in section 1.2.2.1, CA1 subfield volume reductions have been observed with healthy ageing (Mueller et al 2007; Mueller & Weiner, 2009; Wisse et al., 2014). Therefore, decreased ability to remember item-context associations with ageing may be reflective of CA1 subfield loss.

Another important hippocampal function that has been found to decrease in proficiency with ageing is pattern separation (Yassa & Stark, 2011). Shing et al. (2011) demonstrated a significant association between DG/CA3 volume in older adults and performance on a

mnemonic similarity task designed to measure pattern separation. In this experiment, participants first encoded word pairs before being presented with a recognition test for such pairs. At test, participants were either presented with previously encoded pairs (targets), re-paired words from encoding (lures) and novel word pairs. The study found that larger DG/CA3 subfield volume was significantly correlated with greater recognition for previously encoded pairs, i.e. they were more able to correctly discriminate targets from lures and novel pairs than individuals with smaller DG/CA3 subfield volumes.

In summary, age-related decreases in the structural and functional integrity of the hippocampal formation appear to result in episodic memory decline. Considering the vast body of literature outlined above in section 1.2.1 that demonstrates how distinct episodic memory abilities grow during childhood and how these processes then decline with ageing, it appears that episodic memory may follow an inverted U-shaped developmental trajectory. However, it is difficult to investigate this apparent age-related trajectory as tasks used in the child development literature vary enormously from those used in the ageing literature.

1.4 *Issues with Current Understanding of Episodic Memory Development*

Existing literature suggests that the key building blocks of episodic memory appear to follow diverse developmental trajectories. As highlighted above, various methodologies have been used to measure the development of these abilities which differ according to the age of participants used and it is largely unknown whether these tasks are accurately measuring hippocampal memory processes. Regarding the mechanisms behind the emergence of rudimentary episodic memory processes in early infancy, neuromaturational perspectives postulate that the development of distinct episodic memory functions reflects the protracted maturation of the neural regions that support them. However, there is incongruous evidence which proposes that additional factors related to an individual's life experiences can influence the development of hippocampal-dependent memory. In this section, I will highlight issues regarding previous assessment of episodic memory processes in childhood, specifically the use of a wide range of highly diverse methodologies which in most cases have little evidence to confirm that such tasks index hippocampal-dependent processing. Finally, I present the conflicting neuromaturational and ecological perspectives surrounding episodic memory development.

1.4.1 Diverse Methodologies Employed

While extant literature indicates that episodic memory processes develop throughout infancy and childhood, there is ambiguity as to what age children acquire different elements that contribute to a mature episodic memory system due to substantial differences in tasks used. Tasks used to assess episodic memory abilities differ greatly depending on the age of participants (see table 1.1). This means that any comparisons made between children of differing ages, and accompanying inferences regarding hippocampal-dependent memory development, are limited in their empirical integrity.

To the author's knowledge, very few studies have tracked memory performance across diverse ages using the same methodology or experimental design. See chapter 2 table 2.1 for further discussion of how when using the same deferred imitation paradigm across age groups, distinct differences exist between tasks. Examples in the literature which have utilised the same task across different age groups have either focused on discrete developmental periods, e.g. 6-24 months old (Barr et al., 1996) or on 3-5 year olds (Hayne & Imuta, 2011). Tasks used with older children typically rely on instructions. Hence, comparisons between older children and pre-verbal infants are not suitable. Fundamentally, performance on a task tapping episodic memory processes has not been tracked across the lifespan from infancy to old age within current literature.

Table 1.1 Diverse paradigms used to explore episodic memory functions across childhood.

Note. Y= yes; N=no.

Ability	Paradigm used	Age groups examined	Verbal instructions present? Y/N
Recognition Memory	Visual paired comparison (Fagan, 1971; Pascalis & de Schonen, 1994)	3 days old +	N
	Mobile conjugate reinforcement (Rovee-Collier et al., 1980)	2-6 months old	N
	Operant train task (Hartsthorn & Rovee-Collier, 1997; Hartsthorn et al., 1998)	6-24 months old	N
Non-spatial relational memory	Deferred Imitation (Barr et al., 1996; Bauer et al., 1998)	6-28 months old	Y with infants aged ≥16 months
Allocentric spatial memory	Open-field arena spatial memory tasks (Newcombe et al., 1998; Ribordy et al., 2015)	16 months- 4 years old	Y
Episodic memory	what-where-when tasks (Hayne & Imuta, 2011; Lee et al., 2016; Scarf et al., 2017)	3 years old +	Y
	Verbal recall tasks (Fivush et al., 1987; Tustin & Hayne, 2016)	2 years old +	Y

1.4.2 Task Reliance on the Hippocampus

Debates have arisen over whether memory tests are accurately measuring hippocampal-dependent memory in infancy (Richmond & Nelson, 2007). Due to the lack of functional neuroimaging data in infants and young children, we do not have sufficient evidence to correlate the emergence of different episodic memory processes to maturation of hippocampal structures in early childhood (Mullally, 2015); an important issue which needs to be addressed in future research to further our understanding of how disparate memory processes may be subserved by specific neural regions (Mullally & Maguire, 2014). Several authors in the field have proposed that the protracted development of episodic memory across childhood and into adolescence is reflective of hippocampal formation maturation (Lavenex & Banta Lavenex, 2013; Jábes & Nelson, 2015; Gómez & Edgin, 2016). To make valid inferences about neural development from behavioural performance, we need to ensure that tasks are accurately measuring hippocampal-dependent memory processes.

To ascertain whether infant tasks are valid measures, researchers have developed criteria, termed 'filters', which must be met in order to declare that a task is correctly indexing hippocampal memory (see table 1.2). Squire & Schacter (2002) proposed 'the amnesic filter' which argues that a task is only hippocampal-dependent if performance on that task is impaired in patients with hippocampal amnesia. However, only a handful of studies have endeavoured to employ infant paradigms in studies of patients with hippocampal amnesia. Using imitation-based tasks, patients with adult-onset hippocampal damage are significantly impaired in their reproduction of previously demonstrated action sequences compared to age-matched controls and also do not elicit significantly greater action reproduction than controls who had not been shown the action demonstrations (McDonough et al., 1995). This result is also observed in adults with developmental amnesia (i.e. who incurred hippocampal damage perinatally or very early in childhood) albeit to a lesser extent in terms of recall deficits experienced (Adlam et al., 2005). For more detailed discussion, see chapter 2 section 2.1.

Equally, the visual paired comparison task (VPC) has been employed with patients with adult-onset hippocampal damage (McKee & Squire, 1993). Adults were first familiarised to pictures showing different backgrounds before being presented with a familiar picture alongside a novel picture. Patients with hippocampal damage looked significantly less at the novel picture compared to controls, both when the retention interval was 2 minutes and 1 hour long. At both testing periods, patients divided their looking time between the familiar and novel image approximately 50:50, suggesting that they were unable to recognise the familiar picture and thus failed to elicit the novelty preference looking behaviour. Furthermore, in a subsequent verbal recognition test, patients performed significantly worse compared to controls at correctly identifying the novel pictures and the amount of looking time devoted to the novel pictures during the VPC task was positively correlated with better recognition memory performance. These findings are also supported by a later study reporting a lack of novelty preference elicited during the VPC task in a patient with selective hippocampal damage, even after brief delays of 5 and 10 seconds (Pascalis et al., 2004). However, as evidence has suggested that extra-hippocampal regions are involved in familiarity-based recognition memory (Aggleton & Brown, 1999), there is conjecture as to what the role of the hippocampus is during VPC tasks, with some authors postulating novelty preference deficits arising from hippocampal damage may underpin VPC task impairments observed in these patients (Richmond & Nelson, 2007).

These findings, combined with the fact that infants aged 6-9 months old demonstrate evidence of memory retention on such tasks (e.g. Collie & Hayne, 1999), led to the view that infants as young as 6 months of age are demonstrating hippocampal-dependent memory processes (Hayne, 2004). However, one critical factor that needs to be acknowledged in these studies, with the exceptions of McKee & Squire (1993) and Pascalis et al., (2004), is that the tasks used with adult participants vary substantially from those employed with infant cohorts. These key differences include methodological aspects such as the stimuli and action sequences used (McDonough et al., 1995; Adlam et al., 2005). To the author's knowledge, there are no existing studies which compare infant and adult performance using identical methods. This is problematic when attempting to determine whether performance observed in young infants on such memory tasks is essentially reflecting hippocampal-dependent memory processes.

Table 1.2. Comparison of infant memory paradigms regarding evidence as to whether they meet the requirements of the amnesic filter.

Note. Y= yes; N=no; N/A= refers to tasks that are inappropriate to be administered to adult cohorts; asterisks indicate instances where although patients with hippocampal damage have elicited deficits on these tasks relative to matched controls, different task versions have been used with adults and infants.

Paradigm	Pass the amnesic filter? **Y/N**
Deferred Imitation	**Y*** (McDonough et al., 1995; Adlam et al., 2005)
Visual paired comparison (VPC)	**Y** (McKee & Squire, 1993; Pascalis et al., 2004)
Operant conditioning tasks: Mobile conjugate reinforcement & Train task	**N/A**

* Different tasks used with infants and adults

1.4.3 Age- versus Experience-related Memory Development

Early views of memory development postulated that the two main branches of long-term memory, declarative and non-declarative memory (figure 1.3), emerge at different rates

during development (Nadel & Zola-Morgan, 1984; Schacter & Moscovitch, 1984). These authors argued that prior to the age of 9 months, memory feats demonstrated by infants are supported by perceptual priming processes or a result of learned habits/skills that are not consciously recalled; hence classified as non-declarative memory. This form of memory is argued to be available from birth and includes motor behaviours that we learn without awareness, e.g. how to pull oneself up on a piece of furniture to reach an object. At 9-months-old, infants are then argued to gain access to their declarative memory system, including rudimentary episodic-like memory functions which are dependent on the hippocampus and are consciously recollected. This view was largely grounded from studies where non-human primates and humans with hippocampal damage could successfully perform non-declarative memory feats, such as skill learning (Scoville & Milner, 1957; Milner, 1962; Malamut et al., 1984; Zola-Morgan & Squire, 1984), coupled with evidence that only infants aged approximately 9 months and over had been found to successfully retain memories for action events following substantial delays relative to naïve peers (Meltzoff, 1988), on tasks which patients with hippocampal damage demonstrated memory deficits (McDonough et al., 1995). Hence, 9-months-old was regarded as the critical age at which hippocampal-dependent declarative memory processes begin to emerge (Nadel & Zola-Morgan, 1984; Schacter & Moscovitch, 1984). This account, referred to as the neuromaturational account, has subjugated the infant memory literature for decades.

With more recent research providing evidence that the hippocampal structures underpinning declarative memory are structurally immature at 9-months-old (see section 1.2.1.1) and younger infants demonstrating the ability to retain associations over delays (Barr et al., 1996), the neuromaturational account is not comprehensive enough to explain these results. Recently, Jábes & Nelson (2015) attempted to link the emergence of different memory functions with the maturation of individual subfields within the hippocampal formation (see figure 1.13). The authors propose that early maturation of the CA1 subfield and its connectivity with the entorhinal cortex by approximately 2-years-old (Lavenex & Banta Lavenex, 2013) may support the emergence of rudimentary episodic memory functions that are observed in infants aged under 2 years. These authors argue that this basic associative memory processing becomes more complex around 2-4-years-old, which corresponds to the estimated time period where DG and CA3 functions are argued to be functionally mature enough to support more complex computations (Bauer, 2007). Finally, these authors propose that due to the protracted

maturation of the DG into adolescence (Ábraháms et al., 2010), this results in episodic memory being the last memory function to emerge.

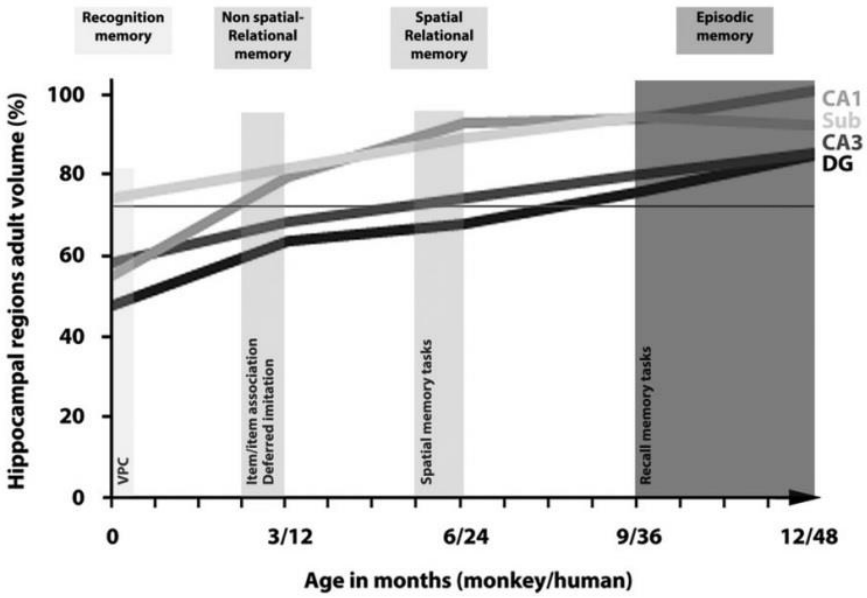

Figure 1.13 Visual representation of the parallel development of the hippocampal regions in monkeys and the emergence of different memory functions in humans.

Note. One year in monkeys corresponds to 4 years in humans (Fortman et al., 2001). Note. *DG= dentate gyrus; Sub= subiculum. Taken from Jábes & Nelson (2015).*

While theories concerning the ontogeny of episodic memory appear to largely focus on relating the emergence of episodic memory functions to underlying hippocampal formation development, a body of literature suggests that other factors besides neural maturation may be facilitating increases in rudimentary episodic memory in early life (Rovee-Collier & Cuevas, 2009).

A collection of studies have consistently shown that exposing young infants to two stimuli before receiving training to elicit a specific action with one of the stimuli has been found to increase the infant's ability to reproduce the target action when the other stimulus is presented at test. Boller (1997) exposed 6 month old infants to study and test contexts simultaneously (the contexts consisted of different coloured cloth panels that were both placed over the crib) during the learning phase of a MCR task. Only infants who had been exposed to the contexts simultaneously were able to successfully apply the memory of the target action when there was a change experienced between study and test. Similarly, Barr, Marrott & Rovee-Collier (2003) conducted a deferred imitation study in which 6-month-old infants were exposed to

two puppet stimuli across a 7 day period before watching the experimenter perform a sequence of actions on puppet A. After a 24 hour delay, only infants who have been pre-exposed to the two stimuli were able to imitate target actions on puppet B (see figure 1.14). Thus, indicating that greater experience with a variety of different contexts and cues will result in the ability to produce memory feats earlier in infancy and more 'flexible' memory in terms of cues that can be used for retrieval.

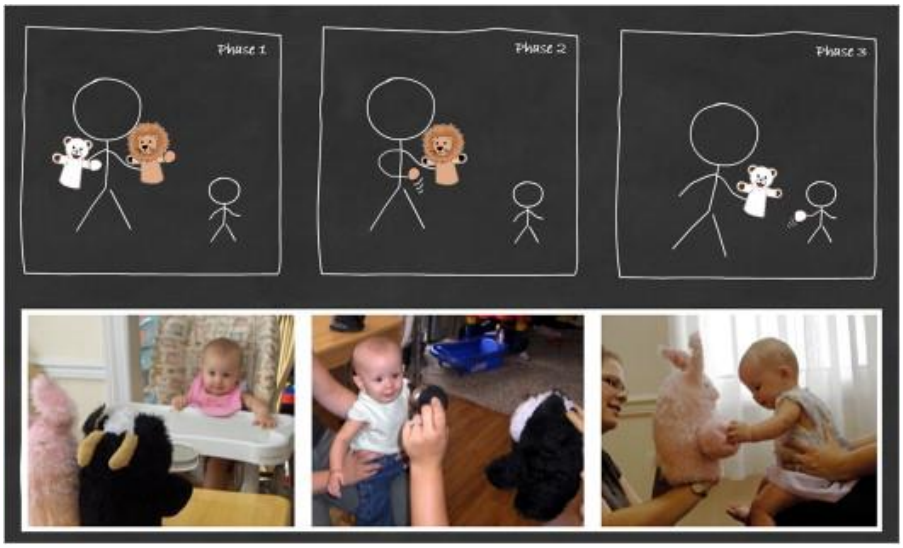

Figure 1.14 Deferred imitation task with sensory preconditioning (SPC) used in Barr et al. (2003).

In phase 1, the experimenter exposes the infant to two puppet stimuli. During phase 2, the experimenter performs the target actions on puppet A. In phase 3, the infant is presented with puppet B and retention of the target actions is determined by the number of correct actions reproduced by the infant. Taken from Mullally & Maguire (2014).

This observation contrasts with the memory retrieval flexibility of young infants that are not provided with this greater experience with differing contexts at encoding; research indicates that young infants aged ≤ 12-months have highly specific memory retrieval for associations, whereby changes to the cue or context between encoding and test will disrupt memory retrieval. For instance, Hayne et al. (1997) observed that varying levels of changes to a puppet stimulus used in a typical deferred imitation task could be tolerated to successfully reproduce previously modelled actions on that cue, dependent on the infant's age. Twelve-month-olds could successfully reproduce actions when the colour of the puppet was changed between encoding and test, however only 18-month-olds can retrieve the action events when the shape of the puppet is also altered and only 21-month-olds could successfully reproduce the actions when greater visual differences in puppet stimuli existed between encoding and test (e.g. very

different facial features). It is essential that the specific details of an event are remembered to ensure that correct memories are retrieved based on cues present to the infant. However, it is also important to be able to retrieve memories for events in the presence of related but different cues, as we rarely experience the same event again in the exact perceptual context. This is a necessary ability to allow us to apply our past experiences to future scenarios where although the situation is not perceptually identical to the learning event, the content of the learning event is relevant for this novel scenario.

The observation that increasing an infant's experience with different contextual information facilitates more flexible memory retrieval was based upon seminal work examining sensory preconditioning (SPC) with pre-weaning rat pups, largely conducted by Spear and colleagues (Spear, 1973). A typical SPC paradigm involves three phases of learning; 1) two stimuli are paired together and the subject is exposed to them, 2) the subject is trained to elicit a specific response with one of the stimuli and then finally 3) memory for the specific response is tested using the other stimulus. If the subject has successfully performed the target response on the other stimulus, it is inferred that the subject was able to form an association between the two stimuli at the preconditioning phase and so this association enabled them to apply their memory of the learned response to the other stimuli (Chen et al., 1991). There is a large body of evidence that pre-exposing rat pups to two distinct odours or tastes enabled the pups to apply learned responses more flexibly to different cues (e.g. Lavin, 1976; Rescorla, 1980; Chen et al., 1991).

Another critical observation by Spear and colleagues was that SPC is more rapidly acquired in juvenile rats compared to adults, with the authors proposing that young infants learn more rapidly than older children and adults as they need to acquire information about the world around them quickly to inform their current needs (Kucharski & Spear, 1984; Spear et al., 1994). In contrast, adults and older children already have a more robust knowledge base and so this type of exuberant associative learning may not be needed. Therefore, providing an infant with greater experience of diverse contexts and cues may allow them to more rapidly accumulate this knowledge. Indeed, the developmental representational flexibility hypothesis argues that memory performance is dependent on the retrieval cues being matched to the infant's developmental ability and their accrued knowledge base (Hayne, 2006).

A perspective that resonates with this line of thinking is termed ecological theory (Rovee-Collier & Cuevas, 2009) which proposes that inflexibility in memory retrieval during early infancy is driven by a lack of knowledge about the world. Equally, Richmond & Nelson (2007) argue that using SPC within infant memory paradigms enables an infant to establish prior knowledge which a novel event can then be inserted into. By possessing a network of knowledge for related events, an infant can then use this information to flexibly retrieve memory for an event in different scenarios. These authors are therefore suggesting that inflexible memory retrieval in young infants is a result of a dearth of knowledge networks for a memory to be inserted into. Therefore, infants who are able to acquire knowledge about the world around them through experiences should demonstrate more flexible memory retrieval. This poses the question, what kinds of experiences occur within the first year of life that could assist young infants with acquiring information more rapidly?

A major developmental milestone that occurs towards the end of an infant's first postnatal year is the acquisition of independent locomotion. A variety of cognitive benefits have been associated with the acquisition of independent locomotion (IL), such as increases in social skill development (Clearfield, 2011; Anderson et al., 2013) and spatial cognition (Anderson et al., 2013; Gerhard & Schwarzer, 2018). However do these benefits lend themselves to episodic memory?

A key study by Herbert and colleagues (2007) provided a tentative link between IL attainment and superior memory retrieval flexibility in 9-month-old infants (see chapter 4 section 4.1 for a comprehensive account of this study). A deferred imitation paradigm was used to assess memory for a previously modelled action event following a 24 hour delay in crawling and non-crawling infants. Performance was examined when the cue and context (i.e. room) remained the same between learning and test or when a different cue was presented in a different context at test. Herbert et al. reported that while both groups could produce the actions to a significantly greater extent than their peers who were naïve to the action (i.e. not shown the demonstration of the target action), only crawling infants were found to significantly outperform their naïve counterparts when the cue and context differed between learning and test. These results suggest that the acquisition of IL may be facilitating greater memory retrieval flexibility in the first year of life. However, to the author's knowledge, this

topic has been largely neglected in the child development and memory literature for over a decade.

1.5 *Thesis Aims*

Reflecting upon the vast body of literature discussed above, several issues were identified:

1. There appears to be a dearth of research which has adequately tracked the development of specific episodic memory functions across the life-span, using the same tasks with participants of varying age.

2. Available tasks used with young children are argued to measure episodic memory functions dependent on the hippocampus. However, evidence is lacking to support this assumption; comparisons made between performance of infants and adults with hippocampal damage are based on studies where very different methodologies have been employed. Equally, due to the challenges in determining the neural correlates of task performance in very young children, it is difficult to establish whether tasks used with pre-verbal infants are indexing hippocampal-dependent memory.

3. While there is tentative evidence in the literature to suggest that independent locomotion may facilitate memory retrieval in infancy, there have been little efforts to investigate whether the acquisition of this developmental milestone may provide scaffolding for the emergence of more advanced episodic memory functions.

In an attempt to address these issues, the current thesis aimed to track performance on two previously used infant memory paradigms across the life-span, employing tasks which can be used with both pre-verbal infants and adults. The paradigms applied were a deferred imitation task (Chapters 2 and 3) and a face-scene association eye-tracking task (Chapter 5).

Performance on both tasks was assessed in a cohort of patients with selective hippocampal damage as a result of voltage-gated potassium channel complex antibody associated limbic encephalitis (VGKCC_LE). This enabled me to deduce whether performance on infant tasks are supported by the hippocampus and also allowed crucial comparisons to be made between patient performance and that of all age groups (see chapters 2, 3 and 5). In the absence of

access to neuroimaging techniques, performing comparisons between patient and child group's performance allowed inferences to be made regarding at what age children can significantly outperform patients on these tasks and thus show evidence of robust episodic memory abilities.

Lastly, this thesis aimed to establish whether earlier acquisition of independent locomotion is linked to superior memory for previously learnt associations in the first year of life compared to infants who acquire this milestone later in their first year (see Chapter 4 and 6). This line of investigation allowed me to explore whether experiences in early life arising from the acquisition of developmental milestones, such as the attainment of independent locomotion, may be influencing memory development besides age-related increases in memory purported to occur due to neuromaturational changes in the brain.

2. Chapter 2. Deferred imitation as a valid index of hippocampal-dependent memory processes.

Chapter 2 Summary

Deferred imitation (DI) is one of the most widely used measures of non-verbal hippocampal-dependent memory in infancy, largely due to the fact that patients with hippocampal amnesia are impaired on adult versions of these paradigms (McDonough et al., 1995). However, to the author's knowledge, previous research has not examined both infant and patient performance utilising the same memory task, nor have they directly compared performance using a DI paradigm in healthy young and older adults to examine age-related memory decline in recollection. In analysis 1, performance during an infant DI task was compared between 7.5-month-old infants along with patients with selective hippocampal damage and age- and IQ-matched healthy older adults. In analysis 2, performance was compared between all adult cohorts and a group of young adults. Participants were shown a three-step sequence on a puppet and presented with this cue again after a 30 minute delay in order to determine whether the participant could spontaneously demonstrate the sequence of actions. Within the adult cohorts, participants were then asked if they could specifically demonstrate the sequence of actions previously shown to them on the puppet. Recognition memory for the action sequence and additional events embedded in the demonstration video was also examined within adults; with patients demonstrating preserved familiarity-based recognition whilst exhibiting recollection-based memory impairments consistent with dual-process models of hippocampal function. Crucially, we found evidence that our infant task does appear to index hippocampal memory processing; patients demonstrated impaired task performance relative to healthy controls. Furthermore, young adults elicited significantly better performance compared to older adults; thus demonstrating that this infant task is sensitive to age-related memory decline. Although infants imitated significantly more previously shown actions relative to naïve age-matched peers, infant performance did not significantly differ from that of patients and lacked the proficiency of healthy adults. Further work is needed to pinpoint the neural correlates underlying this similar performance in our patient group and infants.

2.1 *Introduction*

The ability to imitate observed behaviours of others is a critical mechanism by which humans learn. Within the first year of postnatal life infants experience a period of rapid learning, with imitation acting as a crucial modality for infants to acquire new skills and information about the world around them (Piaget, 1962; Hayne, 2004). Successful imitation following a delay relies heavily on the individual's capacity to form and retain mental representations of observed behaviours or events, which can be then used to reproduce such behaviours in a similar future scenario. This ability refers to a specific form of imitation, termed 'deferred imitation'. In a typical infant deferred imitation task, the experimenter performs a sequence of actions on an object (e.g. the experimenter removes a glove from a puppet's hand, shakes the hand and replaces the glove; Barr, Dowden & Hayne, 1996). Following a delay, the infant is presented with the object again and their ability to spontaneously reproduce the sequence of actions is assessed. Retention is typically inferred if the performance of infants who had previously watched the demonstration of the action sequence significantly exceeds that of age-matched infants who had no prior viewing of the demonstration. As recall of the previously seen sequence is based on a single demonstration period where the infant was not permitted to practice the actions, deferred imitation performance is not seen to be a product of simple motor practice and argued to rely on hippocampal-dependent memory (Nelson, 1995).

Due to the challenges of assessing hippocampal-dependent memory in pre-verbal infants (see section 1.3.2), evidence that the hippocampus is supporting performance during infant deferred imitation was lacking. Efforts have been made in adult literature to apply the 'amnesic filter' to deferred imitation paradigms, i.e. examining task performance in patients with hippocampal damage to establish whether tasks are hippocampal-dependent memory (see section 1.3.2). Applying an adult version of the deferred imitation paradigm, McDonough and colleagues (1995) reported that patients with hippocampal damage were impaired in their memory for sequences of actions compared to age-matched controls, including whether the target actions were performed in the correct order. Patients viewed the experimenter modelling several three-step action sequences on different objects and their ability to reproduce the action sequences, both spontaneously when simply presented with the objects and when instructed to perform previously demonstrated sequences, was assessed following a 24-hour delay. When amnesic patient performance was compared to that of controls who had not been shown the action sequences modelled, akin to the measure of retention used within infant paradigms, patients also did demonstrate significantly greater performance than these

control participants. These findings were interpreted by the authors as evidence that successful performance on deferred imitation tasks used with infants is subserved by the hippocampus. This view, coupled with the findings that infants aged 6-9 months old can produce significantly more previously modelled actions after a 24-hour delay than age-matched infants who did not see the actions being modelled (Meltzoff, 1988; Collie & Hayne, 1999), lead to the notion in the literature that some rudiments of hippocampal-dependent memory are in place as young as 6 months of age in human infants. Thus, deferred imitation paradigms became a widely-used measure of hippocampal-dependent memory in infancy (Hayne, 2004).

However, a crucial issue is that the deferred imitation tasks utilised in the study by McDonough et al. (1995) with adult participants differed considerably from those used in typical infant tasks. For instance, participants were required to perform sequences of actions such as reproducing the Bernoulli Effect using a balloon and hairdryer. The Bernoulli Effect refers to the principle that air pressure decreases inside a stream of flowing air and so air within the stream will be moving faster than surrounding air. This effect then leads to the phenomenon whereby objects placed within a column of air will become trapped there. In McDonough et al., participants were required to turn on a hairdryer, place a balloon in the air stream, and then tilt the hairdryer to demonstrate that the balloon remains captured in the airstream. This action sequence is therefore notably different from those used with infants. Yet, regardless of this discrepancy, this was interpreted in the literature as evidence that infant deferred imitation tasks are supported by the hippocampus. Moreover, the amnesic patient sample in McDonough et al. contained individuals who did not have selective hippocampal damage. 4/7 patients had a diagnosis of Korsakoff syndrome; a condition which typically results in damage beyond the hippocampus, such as the frontal lobe and thalamus, and cognitive difficulties in addition to episodic memory impairments like executive dysfunction (Brion et al., 2014; Kopelman, 2015). In the remaining three amnesic patients, only two patients had confirmed volume reduction in the hippocampal formation using magnetic resonance imaging (MRI), outlined in different papers (Squire, Amaral & Press, 1990; Polich & Squire, 1993). However, volume reductions were observed beyond the hippocampal formation in one of these patients (e.g. reductions in size within the parahippocampal gyrus). Note this neuroimaging was conducted in the early 1990's whereas more advanced and high-resolution imaging is available now. Hence, additional cognitive deficits (arising from damage beyond the hippocampal formation) may have led to poor task performance within

this specific patient cohort to a greater extent than within individuals with selective hippocampal damage only.

A more recent study by Adlam et al. (2005) did assess performance of developmental amnesic patients with selective bilateral hippocampal damage, using the same adult deferred imitation task completed in McDonough et al. (1995). This study replicated the findings of McDonough et al., in that patients reproduced significantly less action sequences than controls after 24 hours. However, the patients in this study had developmental amnesia resulting from brain injury acquired early in life (ranging from perinatal to 15-years-old) and it was noted that patients produced significantly more actions at test than at baseline, indicative of retaining some memory for the action sequences. Acquiring hippocampal damage at a younger age may have permitted residual hippocampal functioning in this group of patients compared to adult-onset amnesic patients, possibly due to the greater neuronal plasticity in the developing brain and thus potential for functional reorganisation of neural circuitry required to remember the action sequences. Nonetheless, the task utilised in Adlam et al. still differed substantially from the type of deferred imitation task used in infant studies. Thus to date, no previous research has directly compared infants and patients with adult-onset selective hippocampal damage in their performance using the same deferred imitation task. Without this research, evidence is lacking to accurately determine whether infant deferred imitation tasks are valid measures of hippocampal memory processing.

As discussed in chapter 1 section 1.2.2, decline in episodic memory proficiency is observed in normal ageing, with changes to the hippocampal structure and function reported in older adults (Nyberg, 2017). There is evidence that poorer episodic memory in older adults largely arises due to ageing negatively impacting the ability to bind the content and contextual information of events together compared to younger adults (Naveh-Benjamin, 2000). For instance, Cheke (2016) used a treasure-hunt task to determine whether older adults would be impaired in their memory for the different elements of a hiding event compared to young adults. During a computerised task, participants were instructed to hide food items within two complex scenes, with a food item being placed within each scene on two occasions. Following 5-minute intervals, recall for what items, where the items were placed and when the items were placed (i.e. on the first or second occasion) was assessed along with participants' ability to bind these individual elements of the hiding event together. Young

adult recall for the hiding events was significantly greater overall. However, when memory for the individual elements of the hiding event were examined, older adults only showed significantly lower recall for when items were hidden. Thus, these findings suggest that difficulties in recalling contextual information of events observed in older adults may be more specifically related to temporal ordering of such events.

The lack of intersection between child memory development and ageing research makes it difficult to draw accurate comparisons between infant and adult task performance. Using the same deferred imitation task with both infants and adults would permit us to make valid inferences as to how infant performance compares to that of adults in their ability to recollect content and temporal information of a previously seen event. Equally, to the author's knowledge, the studies by McDonough et al. (1995) and Adlam et al. (2005) are the only examples of deferred imitation used to assess memory in healthy adults. Therefore, young and older adult performance has not been directly compared using the same deferred imitation task. This would provide further insight into the apparent reduction in the ability to recall temporal contexts of events with healthy ageing (Cheke, 2016) and inform our knowledge regarding the developmental trajectory of memory for action sequences. Thus, examining task performance across the life-span is important to validly track changes in hippocampal-dependent memory from its ontogeny to later decline.

Alongside the challenges of determining whether infant tasks are accurately measuring hippocampal-dependent memory and how to validly compare infant and adult recollective abilities (also discussed in section 1.3.1), diverse types of deferred imitation tasks have been used within the first two years of postnatal life (see table 2.1). Varying task parameters between studies poses further challenges in our ability to draw inferences regarding how this form of memory develops during infancy. Differences in findings between studies which utilise cohorts of the same age may be a result of task methodology influencing memory performance. The use of instructions may provide older groups an unfair memory advantage and makes comparisons between preverbal infants and adults impossible. Equally, it may be difficult to deduce changes in mnemonic abilities arising from increasing age during infancy from changes in performance arising from the use of different task parameters between studies.

Moreover, tasks which measure deferred reproduction of a single action (e.g. Meltzoff, 1988) do not permit the assessment of temporal order recall. Although memory for certain aspects of the singular event can be assessed (e.g. the ability to bind the action event to the item or the ability to bind the event to the physical context in which it is presented); these tasks fail to examine infants' ability to bind and recall the temporal context of events that make up an experienced episode. Considering that temporal information of an event contributes to the rich and intricate nature of episodic memories (Tulving, 2002); efforts should be made by experimenters to permit the assessment of this defining element of episodic memory within their research methodology.

In order for the developmental trajectory of memory recall for action sequences to be accurately tracked across childhood and into adulthood, effort must be made to 1) utilise the same task across all ages that is suitable for pre-verbal groups, 2) assess memory for arbitrarily associated actions to reduce the likelihood of memory inflation (see section 1.2.1.4) and 3) permit the assessment of memory recollection that truly constitutes elements of an episodic event i.e. assessing memory for actions but also temporal order information of such sequence.

Table 2.1 Common types of deferred imitation tasks used within the infant memory literature and their methodological parameters.

Study	Age of Infants	Stimuli Used	N of Actions in Sequence	N of Demonstrations at Learning	Retention Interval	Enabling or Arbitary Actions	Temporal Order Information Assessed
Meltzoff (1988)	9 months	3 x novel objects created by experimenter e.g. plastic egg filled with metal nuts to create rattle sound	1 per each object (3 in total)	3 (20 sec period) per object	24hrs	N/A	N/A as single action each time
Meltzoff (1995)	14 & 16 months	4 x novel objects created by experimenter e.g. collapsable plastic cup to be pressed down upon to trigger collapse	1 per each object (4 in total)	3 (20 sec period) per object; extra condition included where imitation of actions assessed immediately after demonstration	2 months & 4 months	N/A	N/A as single action each time
Barr, Dowden & Hayne (1996)	6, 12, 18 & 24 months	one of two hand-held animal puppets	3	3 (20-30 sec period)	24hrs	Enabling	Yes (but constrained by enabling actions)
Barr & Hayne (1996)	18 months	2 x novel objects created by experimenter e.g. a plastic frog secured to a metal spring which could 'jump' between two boards that acted as platforms	3 per each object (6 in total)	1 per object (90 sec period in total); extra condition included where imitation of actions assessed immediately after demonstration	1 week	Both enabling and arbitary sequences (counter-balanced between each object)	Yes
Collie & Hayne (1999)	6 & 9 months	**A)** 6x novel objects secured to an 'activity board' e.g. an owl that could be removed from a tree and contained a button press on its torso	1 per each object (3/6 completed in total per participant)	6 per object (2-3 min period in total)	24hrs	Enabling	Not reported
		B) 12x novel objects secured to an 'activity board'; 6 of which presented in experiment A	1 per each object (6/12 completed in total per participant)	6 per object (3-4 min period in total)	24hrs	Enabling	Not reported

Note. N= number; sec= seconds; min= minutes; hrs= hours; N/A= not applicable.

The current chapter aimed to determine whether performance on an infant deferred imitation task is a reliable index of hippocampal memory processing and to validly compare infant performance with that of patients with selective hippocampal damage and healthy adults using the same task. We assessed memory retrieval for a three-step sequence of arbitrarily related actions following a short delay, both for memory of specific actions that were modelled and the temporal ordering of those actions.

In analysis 1, performance was examined in adult patients with selective hippocampal damage, age- and IQ-matched older adults and infants aged 7.5-months-old to determine whether deferred imitation reflects hippocampal processing. This particular age was selected for the infant participants as it is argued that between 6-9 months infants begin to reproduce previously modelled actions following a delay. However, enabling action sequences and/or one-step action sequences were predominantly utilised within this literature to arrive at this conclusion. Thus, we wanted to examine infants' capacity to reproduce arbitrarily associated actions in a multi-step sequence at this critical age. Firstly, we aimed to establish whether impairments are present within patient performance, both compared to matched controls who had seen the action sequence being demonstrated and who had not viewed the sequence (i.e. naïve controls), which would indicate that spontaneous recall for a sequence of events (as assessed in infant paradigms) does rely on hippocampal functioning. Secondly, group comparisons of spontaneous recall, i.e. without the use of instructions, allowed us to directly compare infant, adult and patient memory. This allowed us to fairly test different hypotheses regarding whether similarities or differences between infant and patient performance may be reflecting rudimentary hippocampal processing.

In analysis 2, patient and older adult performance was compared with that of young adults, to examine whether memory for the action sequence declines as a result of ageing. We also completed additional analyses to rule out different confounds which could be influencing memory. This includes task engagement (via the overall number of actions produced regardless of memory accuracy) and recall for the action sequence when instructed to reproduce the sequence to examine the role of instructions. Finally, we examined recognition memory for the action sequence and events that occurred during encoding with our adult groups. This task was included for two reasons. Firstly, it enabled us to check that the patients had remembered the event taking place, i.e. they remembered being asked to watch a video,

and to determine if memory errors were related to the overall event or specifically related to the action sequence. Secondly, it allowed the comparison of patient recognition memory with healthy younger and older adults, to determine the nature of any observed memory impairments within older adults with and without hippocampal damage, i.e. whether any apparent deficits are related to recollective and/or recognition memory processes. This further information is important as the role of the hippocampus in recognition memory for events is fiercely debated in the literature (see chapter 1 section 1.1.3.2).

2.2 *Method*

2.2.1 Participants

Patients with Hippocampal Damage

Five patients (3 males, 2 females) with voltage-gated potassium channel complex limbic encephalitis (VGKCC_LE) that resulted in selective hippocampal damage took part in the study. VGKCC-LE is a rare autoimmune condition with a prevalence of about 1 in 400,000 (Reid, Foley, & Willison, 2009). There are three types of VGKCC_LE, with the anti-LGI antibodies subtype resulting in the most selective hippocampal atrophy (see section 1.1.2). Patients had a mean age of 67.6 years (SD = 9.6 years; range = 52-75 years) and were recruited via the Cognitive Clinic at the Royal Victoria Infirmary, Newcastle upon Tyne. Average pre-morbid intelligence (assessed using Wechsler Test of Adult Reading (WTAR); Wechsler, 2001) was 113. Patients provided informed consent and Newcastle upon Tyne Hospitals NHS Foundation Trust Research and Development committee granted ethical approval.

These participants formed part of a larger cohort of VGKCC_LE patients (n = 7) who underwent neuropsychological assessment within a study by Lad et al. (in prep). Neuropsychological testing identified that all patients exhibited significant impairment of anterograde memory when examined using the Story Recall test (taken from the British-normed BIRT Memory and Information Processing Battery (BMIPB, Coughlan, Oddy & Crawford, 2007) and memory deficits specific to recall when examined using the Doors and People test (Baddeley et al., 1994). Patients also demonstrated significant deficits in retrograde memory for autobiographical events that had occurred in young adulthood or

recently, assessed using the Autobiographical Incident Schedule (Kopelman, Wilson & Baddeley, 1989). Evidence of hippocampal atrophy in one or both structures was obtained using structural MRI scanning prior to initial neuropsychological evaluation, with this damage being relatively specific to the hippocampus as opposed to parahippocampal structures. For individual patient summaries and neuropsychological assessment results, see appendix A.

Older Adults

Sixty older adults (23 males, 37 females) were recruited as age- and IQ-matched controls to the patient cohort and to determine the effects of healthy ageing on task performance. This group had a mean age of 65.4 years (SD= 6.1, range= 54-77 years) and did not possess significant medical problems, including neurological and psychiatric conditions. Average pre-morbid intelligence was 117. Mann-Whitney U tests revealed no significant differences between the patients and older adult controls in both age (U= 103, z=-1.159, p=.261) and intelligence (U= 93, z=-1.327, p=.184). Control participants were recruited from Newcastle University Institute of Neuroscience participant database and Voice North, Newcastle upon Tyne and were compensated with payment for their time.

Young Adults

Sixty-two young adults (9 males, 53 females) were recruited. This group had a mean age of 19.4 years (SD= 1.6, range= 18-25 years) and did not possess significant medical problems, including neurological and psychiatric conditions. Average intelligence was 115 and young adults did not significantly differ in IQ from the patient cohort (t (39) = .448, p=.656). Participants were recruited from Newcastle University Institute of Neuroscience participant database and Newcastle University School of Psychology Undergraduate research participation scheme. Participants were compensated with payment or course credits for Undergraduate Psychology students.

Infants

Data was obtained for 60 infants (35 females, 25 males) with mean age of 32.93 weeks/7.58 months (months SD=1.4). Infants who took part had no significant medical problems, were born within two weeks (+/-) of their due date and had an Apgar score above 7 at birth. An additional three infants had been tested, however they were not included in the data set due to

failing to touch the puppet at test. Infants were recruited from local nurseries, children's centres and via social media advertisements. Infants received a certificate and gift for participating and parents were reimbursed for travelling expenses. Parents provided informed consent for their child to participate and ethical approval was granted by the Faculty of Medical Sciences Ethics Committee at Newcastle University.

2.2.2 Apparatus & Stimuli

All participants were tested using a puppet which was obtained from a company specialising in unique toys, to reduce the likelihood that participants had seen the puppet before. The puppet consisted of a lamb, measuring 15cm in width by 26cm in height (see figure 2.1). The puppet was modified by the researcher to contain elements specifically for the task. Firstly, it had a removable glove on its left hand (the same colour as the puppet's fur on that hand). The puppet also had ribbons on the back of its head and a square flap on its body that when lifted revealed a small plastic animal.

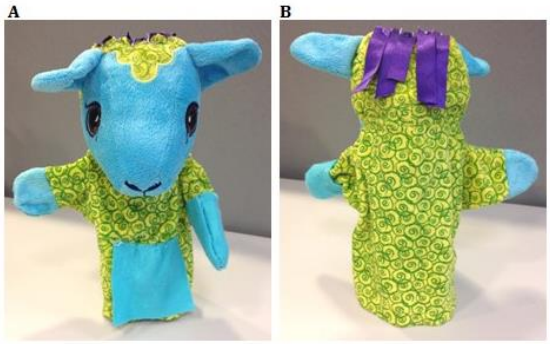

Figure 2.1 Puppet used in deferred imitation task

The three target action elements are visible (flap, gloved hand, ribbons).

A Sony CX240E HD video camcorder mounted upon a tripod was used to record task performance, to ensure participant performance was rated accurately and to enable the assessment of interobserver reliability.

2.2.3 Procedure

In accordance with previous imitation studies, within each of the infant, young adult and older adult groups, n=20 participants were randomly assigned to the naive condition. The procedure for this condition was identical to the spontaneous reproduction test, whereby the participant was presented with the puppet without prior viewing of the action sequence and the

experimenter recorded any actions performed on the stimulus within 90 seconds from the participant first touching it. This data was then utilised to determine whether participants that had viewed the demonstration of the action sequence produced significantly more actions than age-matched participants who were naïve to the action sequence; an analysis that is typically performed within imitation studies to infer memory retention.

The remaining n≥40 participants within each group and the patient cohort completed the experimental condition of the task. Firstly, participants were shown a sequence of arbitrarily related actions modelled on the puppet. Following a retention interval of approximately 20-30 minutes, during which participants took part in a different task presented in chapter 5, all participants then took part in the spontaneous reproduction test. All adult groups then completed instructed reproduction and recognition tests to assess their memory for the previously demonstrated action sequence. See figure 2.2 for study protocol.

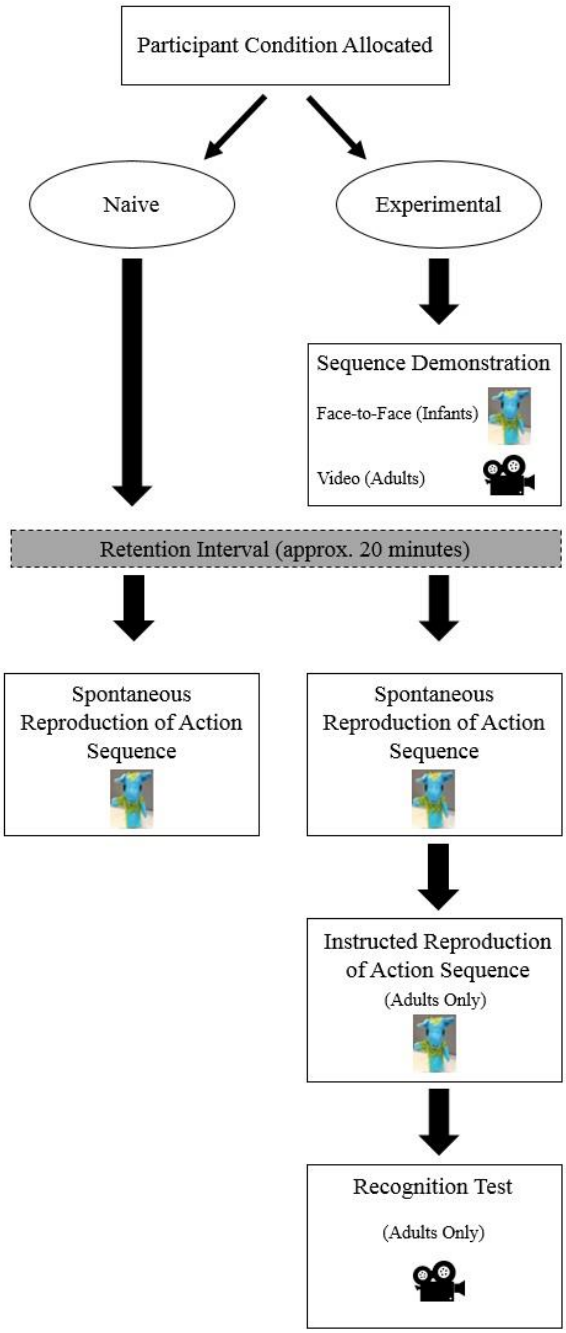

Figure 2.2 Study protocol for deferred imitation tasks.

Participants are allocated to either the experimental condition (who observe the demonstration of the action sequence) or the naïve condition. *Note* all participants within the patient cohort were assigned to the experimental condition; during the retention interval, participants completed the faces and places task presented in chapters 5-6.

Demonstration of Action Sequence

In accordance with typical infant deferred imitation paradigms (e.g. Barr et al., 1996), each participant was shown a three-step sequence of actions performed on the puppet. Infants were shown a face-to-face demonstration of the action sequence, whilst adult groups viewed a video version of the demonstration. Video demonstration was used with adult participants to

permit the assessment of recognition of other events that had occurred in the video besides the demonstration of the action sequence (see *Recognition Test*) and to determine whether the patients possessed any memory for content within the video. Equally, using face-to-face demonstration may have been perceived as strange by adults and so video demonstration was considered more appropriate. Additional testing with adult participants observed no significant differences in memory recall between adults who had viewed the face-to-face demonstration and adults who had viewed the video demonstration (see appendix B).

Face-to-face Demonstration: The infant was seated on their parent's knee and the experimenter knelt in front of them with the puppet held out of the infant's reach. When the experimenter had their attention, she demonstrated the sequence of arbitrarily related actions on the puppet; 1) the experimenter shook the puppet's hand 2) she moved the puppet's ribbons in a forwards and backwards motion, and 3) she lifted a flap to reveal a plastic animal on the puppet's body. This took 10 seconds per sequence iteration and the experimenter performed the sequence three times to the infant (30 seconds in total), placing the puppet behind her back between sequence iterations. The ordering of the actions was counter-balanced across participants. The experimenter did not verbally describe the actions or label the stimuli at any time. Parents were also instructed not to speak during the demonstration and to not verbally describe what the experimenter had done/refer to the puppet during the rest of the experiment. If an infant disengaged during the demonstration, the experimenter used the infant's name or said '*look at me*' to engage their attention again. Participants were unable to touch the puppet or practice the actions at any time (observation-only task).

Video Demonstration: A video was recorded by the researcher and presented using the software OGAMA (OpenGazeAndMouseAnalyzer) version 4.2. Adult participants were seated in front of a computer before the experimenter provided the participant with the following instruction: "*In this study we are interested in how memory develops and changes over time, including how babies learn and remember. To do this we bring babies into the baby lab with their parents. I am going to show you a video of Baby Flynn visiting our lab. The video has no sound and lasts roughly 2 minutes. Please watch the video as closely as you can".* The experimenter then played the video. The video consisted of a parent bringing their infant into the Child Development Lab at Newcastle University whereby they interacted with the experimenter in several ways. To begin, different events occurred such as the

experimenter obtaining written consent from the parent and the experimenter giving the infant a toy shaker (see figure 2.3). After these events, the experimenter knelt in front of the infant and demonstrated the three-step sequence of actions on the puppet following the exact procedure used in the face-to-face demonstration of the action sequence (see figure 2.3). The video contained no sound and lasted 2 minutes 48 seconds in total, with the demonstration of the action sequence lasting 30 seconds.

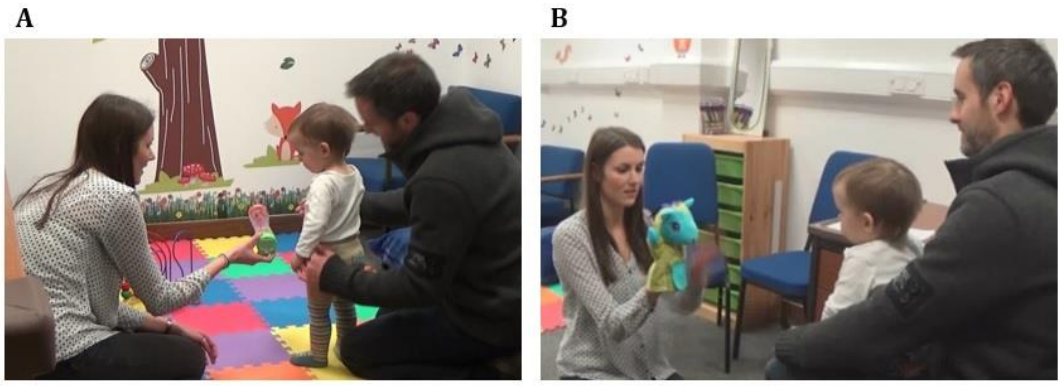

Figure 2.3 Snap-shots of the video footage for A) an event and B) the experimenter performing the sequence of actions.

Recall Test

Recall for the sequence of actions was examined in two ways; spontaneous reproduction and instructed reproduction. Infants were assessed solely on spontaneous reproduction.

Spontaneous Reproduction: Infants were seated on their parent's lap and the experimenter knelt in front of the child but this time with the puppet within their reach. The infant was allowed 90 seconds from first touching the puppet, to perform the correct sequence of actions, which was measured using a stopwatch. The experimenter remained silent during the testing phase and did not prompt the child in any way. With adult participants, the procedure was the same with the exception that when the researcher held the puppet out within the participant's reach, they asked *"Could you please interact with the puppet in whatever way comes naturally to you, handle it as you wish"* to enable the task to be adult appropriate.

Instructed Reproduction: Firstly, the experimenter asked the participant if they had seen the puppet before to clarify that they remembered the cue being shown previously, before giving them the following instruction: "*Do you remember when I interacted with the puppet I performed some actions on it. If I hold out the puppet to you like I did before, can you demonstrate what these actions were please?"* The participant was given 90 seconds from first touching the puppet to perform the sequence of actions. Once they were finished, the experimenter then asked *"Great, so were those actions performed in that order?"* If the participant answered no, the experimenter asked them to specify the order.

Recognition Test

Within the adult groups, recognition of the sequence of actions and other events that occurred in the demonstration video was assessed. The first section of the task involved presenting participants with short video clips of the experimenter performing an action on the puppet. Half of the clips were actions previously presented in the video (i.e. 'true' actions) and half were novel (and so 'false') actions (see figure 2.4). The novel actions consisted of the experimenter 1) waving the puppet, 2) patting the puppet on the head and 3) removing the puppet's glove. The ordering of the actions was pseudo-randomised with six trials shown in total (3 true; 3 false). Participants were seated in front of a computer and were given the following instruction: "*Now you will see a series of video clips, each of an experimenter performing an action on the puppet. Your task here is very simple. It is simply to decide whether you saw this action in the video of baby Flynn's visit to the lab or not. Simply respond Yes or NO aloud. I'm also going to ask you to rate how confident you are in your answer – from 'not confident at all' to 'very confident'. The response options will be presented on screen. Please respond as quickly and as accurately as possible*." The experimenter then asked the participant "*Was this action performed in the video you watched earlier?*" and "*How confident are you in your answer?"* after each trial, before proceeding to the next trial by pressing the space bar.

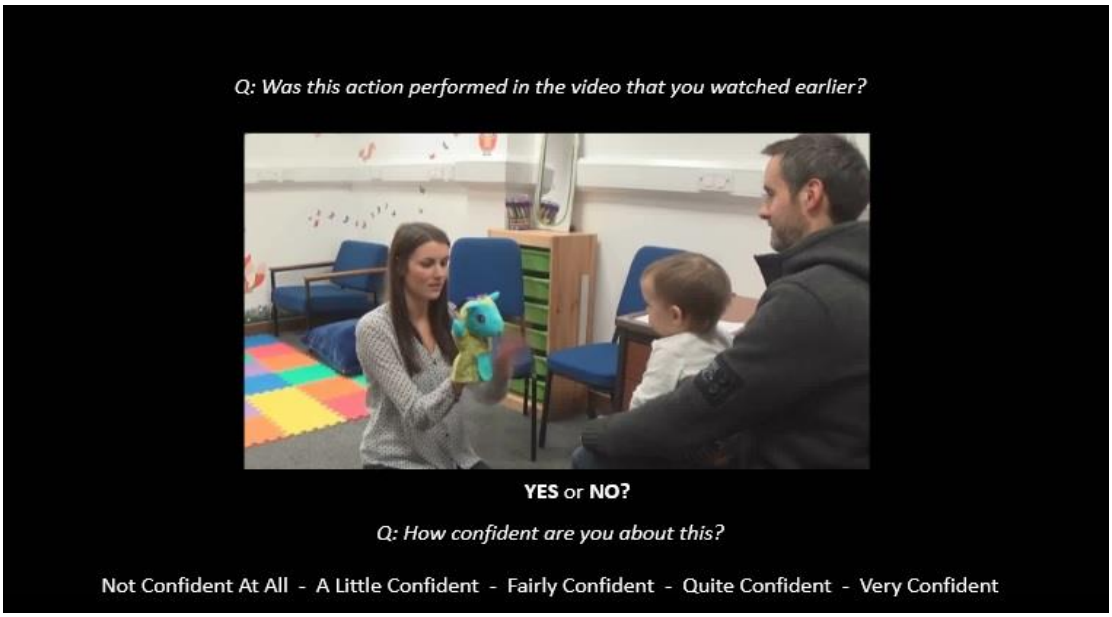

Figure 2.4 Example of an action recognition trial.

In the second section of the task, recognition of other events that occurred during the video was examined by presenting still images of events; half of which were true and taken from the video footage and half of which were false and did not occur in the video (see figure 2.5). Again, the ordering of the images was pseudo-randomised, with six trials shown in total (3 true events; 3 false events). Participants were given the following instruction: "*Now what I'm going to do is to present a series of pictures. Some of these pictures are taken from the video of Baby Flynn's lab visit that you watched earlier and some are of footage of Baby Flynn's lab visit that you did NOT see earlier. Your task is simply to decide if each picture was taken from the video that you watched earlier (YES) or if it was NOT (NO). I will also ask you to rate your confidence in your response. Please respond as quickly and as accurately as possible."* The experimenter then pressed the space key to navigate through the trials, asking the participant for their response on each trial.

Figure 2.5 Example of an event recognition trial.

2.2.4 Statistical Analysis

Video Coding

All videotaped sessions were scored in the same manner. Firstly, the experimenter recorded all behaviours performed by the participant on the puppet during the 90-second test period. The number of correctly imitated actions was recorded including which actions were performed and the order in which they were performed. The experimenter also noted any extra behaviours (i.e. false actions) that the participant performed. Participants were only given credit for the first time they performed an action, therefore producing a score between 0-3 for correct actions present. When scoring whether the correct actions present were produced in the same order in which they were previously demonstrated, a scoring system was used whereby the participant received a score of between 0-3 for temporal ordering ability (see table 2.2). This coding system followed a strategy whereby the correct sequence (i.e. all three actions performed in the correct order) was coded as 'ABC' and received a score of three. The experimenter noted the order in which the participant had performed the correct actions in terms of the string they produced and then compared this to the correct sequence. For example, if a participant produced the actions in the following order: second action, third action; this would equate to the participant performing 'BC'. As the participant had successfully reproduced the end of the sequence order correctly but failed to produce the first action, this would amount to a score of two.

This scoring method was selected as it appeared to be a fair way to reward reproduction of the first action in the sequence in comparison with temporal order scoring strategies employed in previous literature. For example, Barr & Hayne (1996) used a scoring system whereby temporal order memory for a three-step action sequence was determined by dividing the sequence into two segments. Participants were awarded one point for correctly reproducing the first two target actions in the correct order (i.e. 'AB') and one point for correctly reproducing the last two target actions in the correct order (i.e. 'BC'). Therefore, participants could receive a maximum temporal ordering score of two if they produced all of the actions in the correct order. Notably, this method does not award credit for correct reproduction of the first target action when the second target action is not reproduced. Hence, the scoring system presented in table 2.2 was used to address this.

A limitation of the approach used in this thesis is that action reproduction and temporal order reproduction scores are correlated, with action reproduction score influencing correct temporal ordering score. However, it is difficult to score temporal order memory in a valid and systematic way that is not confounded by action reproduction. Previous examples of scoring strategies used in infant deferred imitation studies (e.g. Barr & Hayne, 1996) also contain this confound.

Table 2.2 Scoring system used when recording whether correct actions were performed in the correct order (temporal ordering ability).

Note minimum score of 0, maximum score of 3.

Actions Imitated	Score awarded
First	1
Second	0
Third	0
First then third	1
First then second	2
Second then third	2
Second then first	0
Third then first	0
Third then second	0
First, second then third	3
First, third then second	1
Second, third then first	2
Second, first then third	0
Third, first then second	0
Third, second then first	0

Interobserver Reliability

40% of the videotaped sessions were also scored by an independent observer who was naïve to the aims of the experiment. The second observer coded the videos in the exact manner outlined above. Consistency between observers was then calculated, in terms of the percentage of agreement between observers and inter-rater reliability analysis using Cohen's Kappa (κ) statistic.

Spontaneous and Instructed Reproduction

To examine group differences in the number of correctly imitated actions and whether these actions were performed in the correct order, Kruskal Wallis tests were used followed by pairwise comparisons using Mann-Whitney U tests due to data being not normally distributed. Bonferroni correction was applied to correct for conducting multiple comparisons. Each experimental group was compared to their age-matched naïve group in terms of the mean number of correct action performed. Equally, between-group comparisons were made for both the mean number of correct actions performed and mean correct temporal ordering score.

Recognition of Actions and Events

For each adult participant, the following variables were calculated by summing the responses elicited when recognition memory for actions presented during the demonstration video was tested: number of correctly recognised actions/ true hits (i.e. responding 'yes' when a previously presented action was shown again); number of false-positive responses (i.e. responding 'yes' when a novel action was presented). To determine recognition for events occurring within the demonstration video, the following variables were calculated: number of correctly recognised events; number of falsely recognised events. Mixed ANOVA tests were conducted to establish whether significant effects of group (young adults, older adults, patients) and response type (true hits, false positives) existed in recognition of actions and recognition of events. Where relevant, post-hoc pairwise comparisons were completed to determine any group differences using Independent t-tests. Furthermore, confidence ratings were examined between-groups in terms of confidence in responses during the action recognition task and event recognition task. Confidence was also examined within each task when confidence ratings were separated into those provided for correct items and false items. As confidence ratings consisted of ordinal data, Kruskal-Wallis tests were employed to examine whether group effects were present for the following dependent variables: overall

action confidence; true action confidence; false action confidence; overall event confidence; true event confidence; false event confidence. Where significant effects of group were observed, pairwise comparisons were made between groups using Mann-Whitney U tests.

2.3 *Results*

2.3.1 Interobserver Reliability

The percentage of agreement between the two observers was 95.8% for the number of correct actions recorded and 97.9% for temporal ordering score awarded. Equally, Cohen's κ yielded strong inter-rater reliability between observers in both the number of correct actions recorded ($\kappa = .960$, $p<.0001$) and temporal ordering score awarded ($\kappa = .868$, $p<.0001$). As these κ coefficients exceeded .80, this indicates that interobserver consistency was outstanding (Landis & Koch, 1977).

2.3.2 Analysis 1

Firstly, we compared patient performance during *spontaneous reproduction* of the action sequence with age-matched controls who had also seen the demonstration of the action sequence and age-matched controls naïve to the sequence. This was to determine whether performance on a task used with infants (i.e. that measures spontaneous memory recall) is impaired in patients with hippocampal damage compared to age-matched controls; thus, permitting inferences to be made regarding whether infant deferred imitation tasks are subserved by hippocampal processes. We also compared infants who had seen the sequence being demonstrated with naïve age-matched infants, to determine whether evidence of memory retention was present in the former group. Critically, we directly compared task performance between patients and infants, in order to infer whether infants are showing some evidence of hippocampal-dependent memory abilities.

Kolmogorov-Smirnov tests revealed that the dependent variables (mean number of correctly imitated actions; mean temporal ordering score) were not normally distributed when data normality was examined within each group ($p<.0001$). Since normality was violated and differences in sample size were large when group comparisons were made with the patient group, non-parametric tests were used.

Correct Actions Performed

A significant effect of group was observed for the mean number of correctly imitated actions during spontaneous reproduction (χ^2 (4) = 45.734, p<.0001). From subsequent Mann-Whitney U-tests, we replicated previous literature in that infants who viewed the demonstration of the action sequence imitated significantly more correct actions on average that naïve age-matched infants who had not previously observed the action sequence (figure 2.6A; U = 234.0, z= -2.774, p=.006, r= -.36). Equally we replicated previous studies (McDonough et al., 1995; Adlam et al., 2005), in that our patients did not perform significantly different from naïve age-matched older adults who had not seen the action sequence (U = 31.0, z= -1.374, p=.169, r= -.28; see Figure 2.6B) and exhibited a trend to produce significantly less actions that age-matched controls who had seen the actions demonstrated (U = 53.5, z= -1.852, p=.064, r= -.28). In contrast, older adults who had seen the actions demonstrated reproduced significantly more correct actions than older adults naïve to the demonstration (U = 101.0, z= -4.935, p<.0001, r= -.64).

When making the vital comparison between infant and patient performance (figure 2.6C), we did not observe a significant difference between these groups in the number of correctly imitated actions (U = 90.5, z= -.370, p=.712, r= -.06). These results remain statistically significant when Bonferroni correction is applied to control for multiple comparisons (alpha value of 0.01 adopted). This suggests that although infants aged 7.5-months-old show evidence of memory retention for the demonstrated actions compared to naïve peers, the infants performed similar to patients with hippocampal damage.

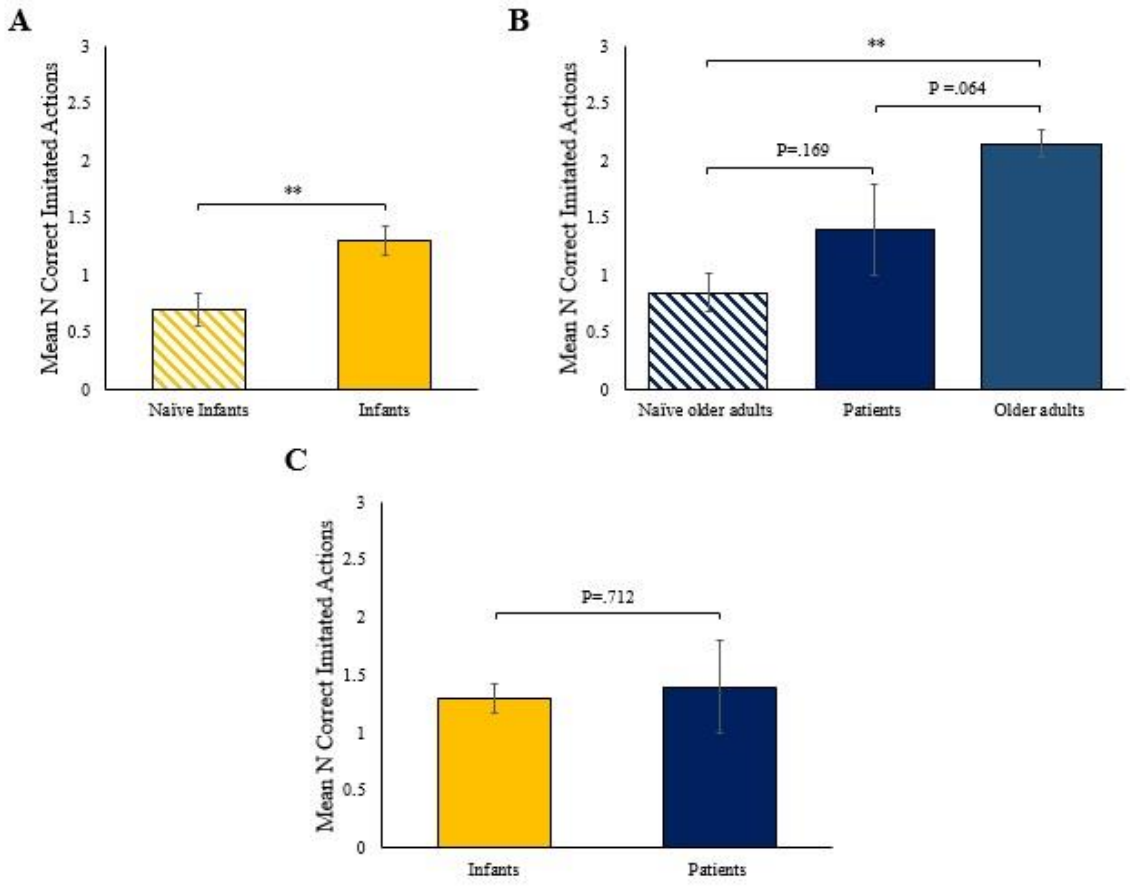

Figure 2.6 Group differences in the mean number of correctly imitated actions during spontaneous reproduction.

Comparisons between **A)** the performance of infants who had seen the action demonstration with their naïve age-matched counter-parts; **B)** patient and older adult performance compared to naïve age-matched older adults and **C)** comparing infant and patient performance in correct reproduction of previously demonstrated actions. *Note.* Error bars depict standard error of mean. Asterisks denote significant differences between groups; * = p<.05, ** = p<.01.

Temporal Ordering of Actions

When examining the ability to reproduce correct actions in the order in which they were previously demonstrated (figure 2.7), a significant effect of group was observed (χ^2 (2) = 6.000, p=.049), although it is noted that the alpha value obtained is very close to exceeding 0.05. We also did not observe a significant difference in performance between the patients and 7.5-month-old infants (U = 85.0, z= -.627, p=.531, r= -.09). Although older adults demonstrated significantly greater temporal ordering ability than infants (U = 575.0, z= -2.434, p=.015, r= -.27), their performance did not significantly differ from that of patients (U = 85.0, z= -.609 p=.542, r= -.09). These findings withstand Bonferroni correction (when alpha value of 0.016667 adopted).

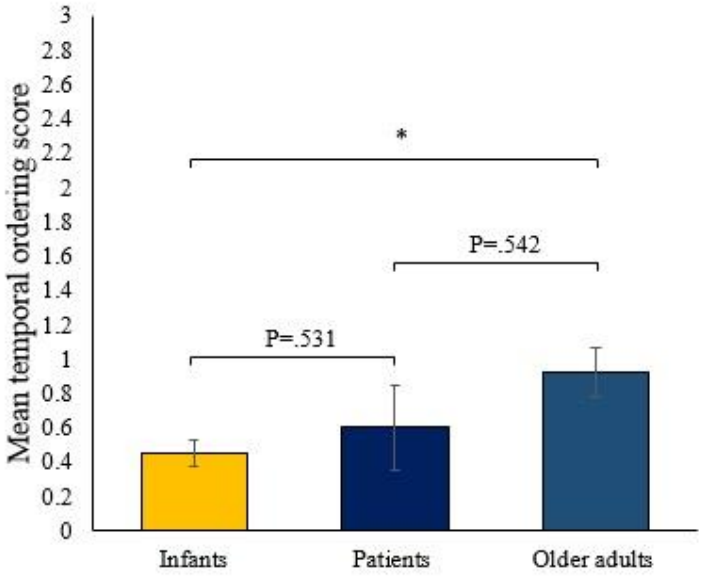

Figure 2.7 Group differences in mean temporal ordering of correctly imitated actions during spontaneous reproduction.

Note. Error bars depict standard error of mean. Asterisks denote significant differences between groups; * = p<.05, ** = p<.01.

2.3.3 Analysis 2

Performance was compared during both spontaneous and instructed recall between all adult groups, in order to examine whether age-related decreases in memory for the action sequence are observed and whether poorer memory in the patient cohort is related to hippocampal damage rather than strictly ageing.

2.3.3.1 Spontaneous Reproduction of Action Sequence

Kolmogorov-Smirnov tests revealed that the dependent variables (mean number of correctly imitated actions; mean temporal ordering score) were non-normally distributed when data normality was examined within each group (p values ranging from p<.0001 to p=.026). Since normality was violated, non-parametric tests were used.

Correct Actions Performed

When determining significant memory retention, young adults performed significantly more correct actions than age-matched naïve controls (figure 2.8A; U = 96.5, z= -5.086, p<.0001, r= -.65). A significant effect of group was observed for spontaneous action reproduction (χ^2

(2) = 7.446, p=.024). From pairwise tests, younger adults reproduced significantly more correct actions than patients (U = 36.5, z= -2.605, p=.009, r= -.38). However young adult performance did not significantly differ from older adult performance for action reproduction (U = 664.0, z= -1.471, p=.141, r= -.19). These findings withstand Bonferroni correction (when alpha value of 0.016667 adopted). These results suggest a decline in memory recall for the action information as a result of hippocampal insult, rather than strictly ageing.

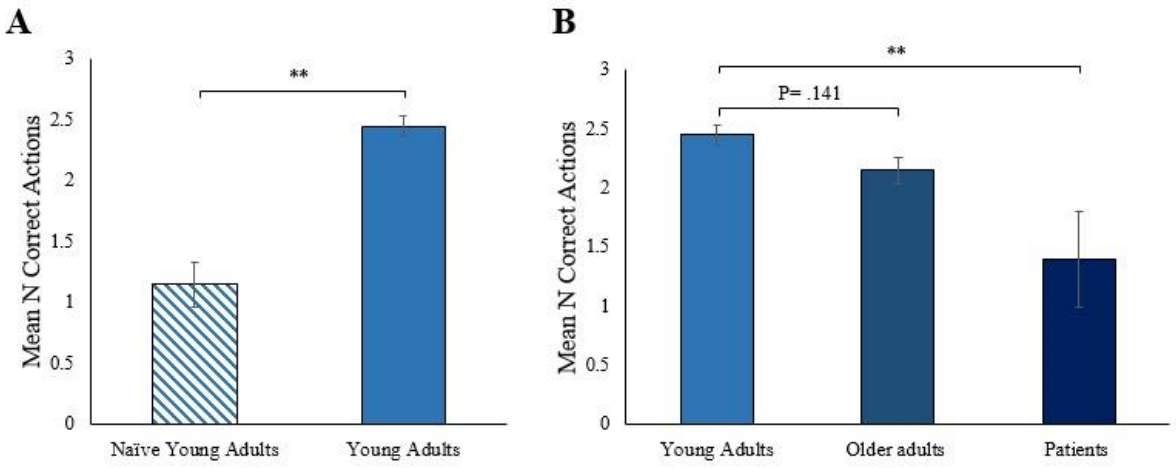

Figure 2.8 Group differences in the mean number of correctly imitated actions during spontaneous reproduction in adults.

Comparisons between **A)** the performance of young adults who had seen the action demonstration with their naïve age-matched counter-parts; **B)** young adult, older adult and patient performance in correct reproduction of previously demonstrated actions. *Note*. Error bars depict standard error of mean. Asterisks denote significant differences between groups; * = p<.05, ** = p<.01.

Temporal Ordering of Actions

Regarding whether actions were performed in the correct temporal order, young adults did not significantly differ in their performance from older adults (U = 674.5, z= -1.360, p=.174, r= -.15), nor patients (U = 68.0, z= -1.317, p=.188, r= -.19). Therefore, again we failed to observe significant differences between adult groups and the patient cohort for spontaneous reproduction of temporal order information.

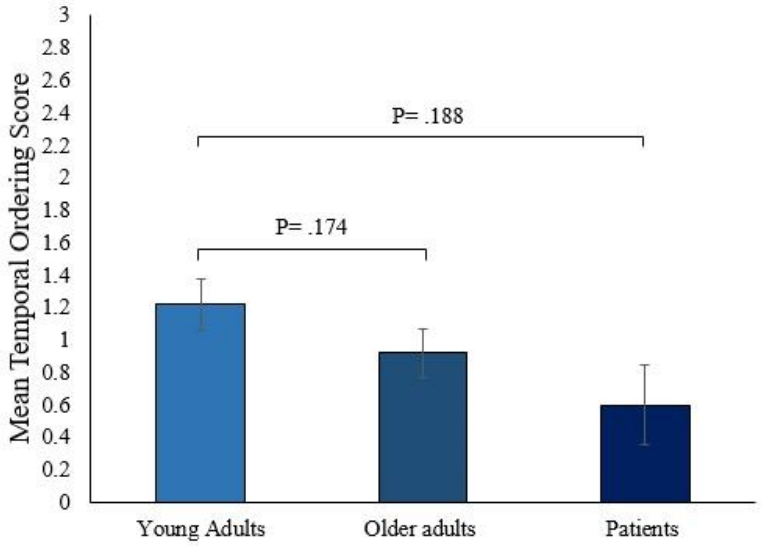

Figure 2.9 Mean temporal ordering score between adult groups during spontaneous reproduction.

Error bars depict standard error of mean.

2.3.3.2 Instructed Reproduction of Action Sequence

Again Kolmogorov-Smirnov tests revealed that the dependent variables were not normally distributed when data normality was examined within each group ($p<.0001$). Since normality was violated, non-parametric tests were used.

Correct Actions Performed

When instructed to reproduce the previously demonstrated actions, we observe performance similar to that in the spontaneous reproduction condition; memory recall for action information appears to decline with healthy ageing and hippocampal damage. A significant effect of group was observed (χ^2 (2) = 15.920, $p<.0001$). Young adults reproduced significantly more actions than older adults (U = 528.0, z= -3.143, p=.002, r= -.35) and patients (U= 28.5, z= -3.436, p=.001, r= -.50). Whilst older adults appear to have poorer memory for actions previously demonstrated than younger adults, there was a trend for their performance to be better than that of age-matched patients with hippocampal damage (U = 52.0, z= -1.870, p=.061, r= -.28). These findings withstand Bonferroni correction (when alpha value of 0.016667 adopted).

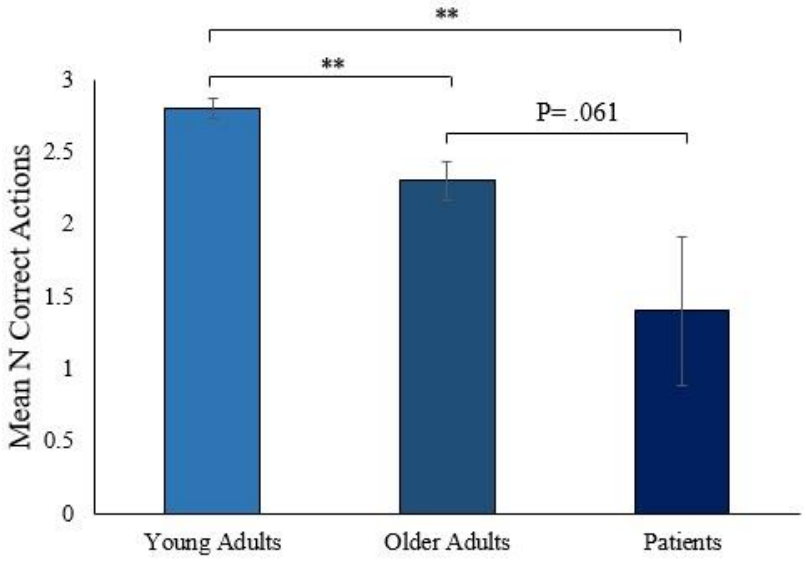

Figure 2.10 Group differences in the mean number of correctly imitated actions during instructed reproduction.

Note. Error bars depict standard error of mean. Asterisks denote significant differences between groups; * = p<.05, ** = p<.01.

Temporal Ordering of Actions

When instructed to reproduce the correct actions in the order in which they were previously demonstrated, a significant effect of group was observed (χ^2 (2) = 16.449, p<.0001). We now observe that young adults produce significantly more temporal order information than both older adults (U= 489.0, z= -3.328 p=.001, r= -.37) and patients (U = 21.5, z= -3.357, p=.001, r= -.49). Although older adults visibly reproduce more correct temporal order information than patients, this difference in performance is not statistically significant (U = 63.5, z= -1.394, p=.163, r= -.21). These findings withstand Bonferroni correction (when alpha value of 0.016667 adopted).

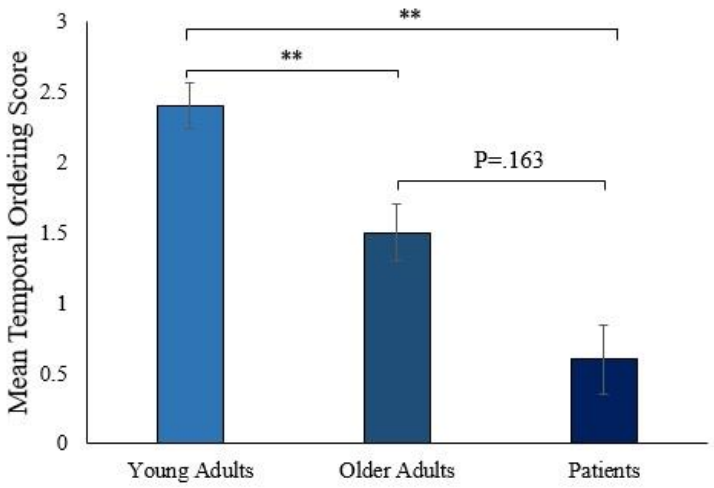

Figure 2.11 Group differences in the mean temporal ordering score during instructed reproduction

Error bars depict standard error of mean. Asterisks denote significant differences between groups; * = p<.05, ** = p<.01.

2.3.4 Additional Analyses

In order to rule out any confounds that could be affecting memory performance, level of task engagement and differences in adult performance between uninstructed and instructed recall were examined. Additionally, recognition memory for the actions and events presented during the demonstration were also assessed in the adult groups.

2.3.4.1 Task Engagement

To ensure that differences in action reproduction between experimental groups and naïve groups were not a result of poorer task engagement within naïve groups, we examined the total number of actions elicited (correct + false actions) between each experimental group and their naïve counterparts. Note patient performance was compared to age-matched naïve older adults. No significant differences were observed between naïve infants and experimental group infants in total number of actions elicited (U = 61.0, z= -1.420, p=.156, r= -.18). Young adults assigned to the experimental condition did not elicit significantly more actions overall than naïve young adults (U = 363.0, z= -.599, p=.549, r= -.08). Both older adults (U= 299.50, z= -1.620, p=.105, r=-.21) and patients (U= 44.50, z= -.383, p=.701, r=-.08) assigned to the experimental condition did not elicit significantly more actions overall than the naïve older adults. Thus, all groups engaged with the task similarly. We may infer that differences in performance between experimental groups and their naïve counterparts are due to memory retention and not willingness to handle the puppet.

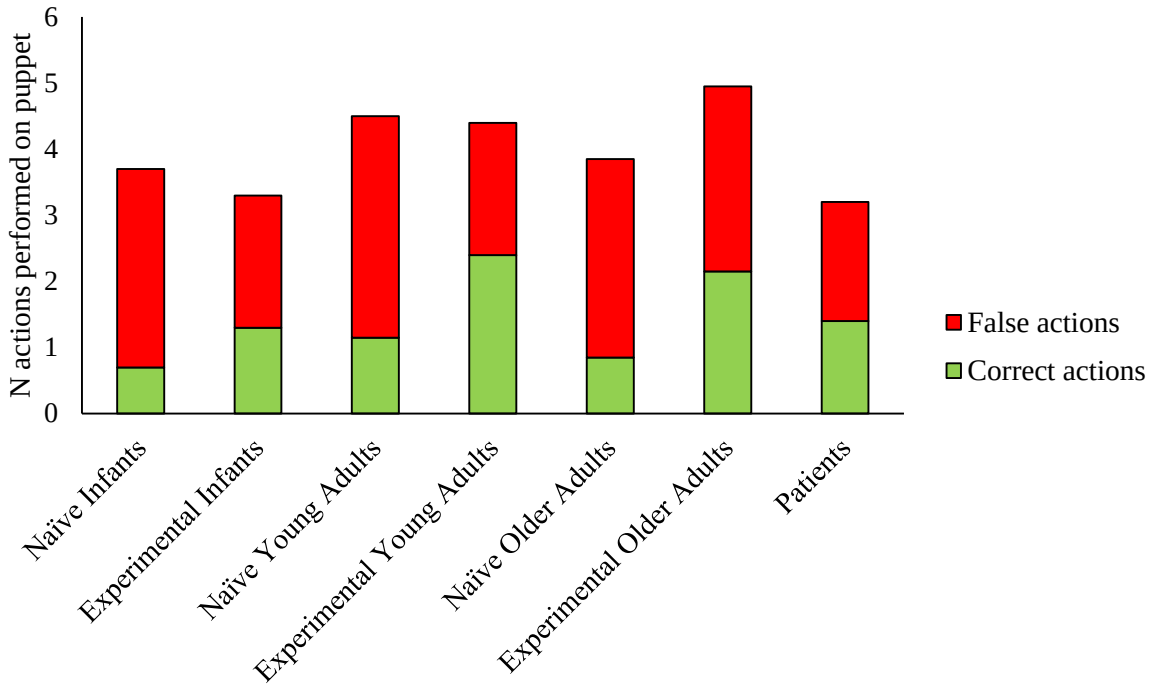

Figure 2.12 Overall mean number (N) actions performed on puppet, separated into correct actions and false actions within each group.

Comparisons were made between experimental groups and naïve groups.

2.3.4.2 Spontaneous vs. Instructed Reproduction

When we compare performance between spontaneous and instructed reproduction, we observed that patients performed exactly the same regardless of task instruction (figure 2.13). When comparing reproduction of action information between spontaneous and instructed conditions, a significant increase in correct action reproduction with instructions was only observed within the young adult group (see figure 2.13A; z= -2.904, p=.004, r= -.32). Examining within-group differences in production of correct temporal order information between conditions (figure 2.13B), both young adults (z= -4.147, p<.0001, r= -.45) and older adults (z = -2.629, p=.009, r= -.29) showed a significant increase in temporal ordering ability when instructed to reproduce the action sequence in the same order in which the experimenter demonstrated it to them.

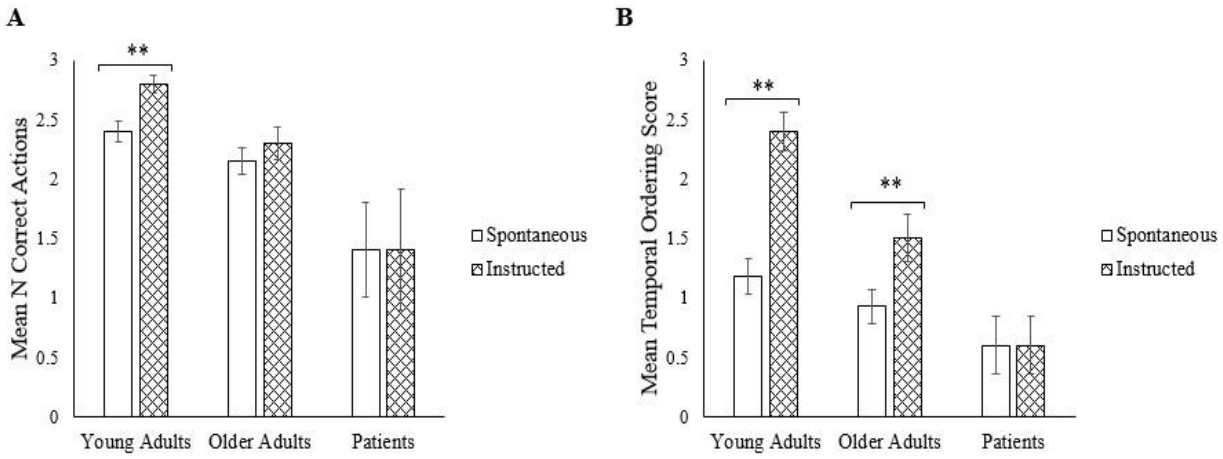

Figure 2.13 Comparisons between spontaneous and instructed reproduction in A) mean number of correctly imitated actions and B) correct temporal ordering of actions imitated within groups.

Error bars depict standard error of mean. Asterisks show significant differences at p<.05 level (*) and p<.01 level (**).

2.3.4.3 Recognition of Video Content

Action Recognition

When examining the accuracy of memory for actions presented during the demonstration video (Figure 2.14), a 2x3 mixed ANOVA (response type: true, false x group: young adults, older adults, patients) revealed a significant effect of response type ($F(1, 81) = 294.943$, $p<.0001$). Overall, participants recognised significantly more correct actions than false actions. We observed a significant effect of group ($F(2, 81) = 7.272$, $p = .001$) and equally a significant interaction between response type and group ($F(2, 81) = 10.186$, $p<.0001$). When the nature of this interaction was explored with pairwise post-hoc comparisons, patients elicited significantly more false responses than both older adults ($t(42) = -3.040$, $p=.004$, $r= .43$) and young adults ($t(43) = -5.683$, $p<.0001$, $r= .66$). Therefore, this indicates that recognition accuracy for actions previously demonstrated appears to be impaired in patients with hippocampal damage, specifically in that they elicit a larger degree of false memory compared to age-matched controls and young adults.

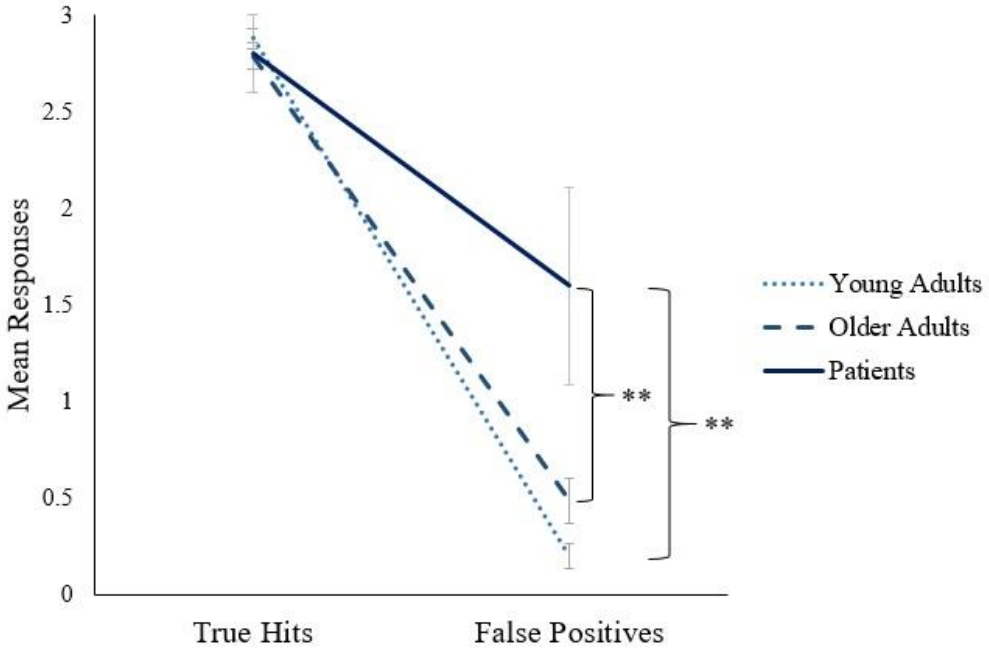

Figure 2.14 Group comparisons in accuracy of recognition memory for actions presented in the demonstration video.

The mean number of correct (true hits) and incorrect (false positives) responses are examined. Note. Error means indicate standard error of mean and asterisks denote significant differences between groups (* p<.05, ** p<.01).

Event Recognition

However, when comparing adult groups in their memory accuracy for events presented during the demonstration video (figure 2.15), interestingly we do not observe impairments in patient performance. A 2x3 mixed ANOVA (response type: true, false x group: young adults, older adults, patients) revealed a significant effect of response type ($F(1, 82) = 597.286$, $p<.0001$), with all groups eliciting more correct responses than false responses. However, we did not observe a significant effect of group ($F(1, 82) = 1.541$, $p=.220$), nor an interaction between response type and group ($F(2, 82) = .647$, $p=.526$). Thus, patients are performing equally as well as both younger and older adults and demonstrate robust recognition memory for individual events that were previously presented at demonstration.

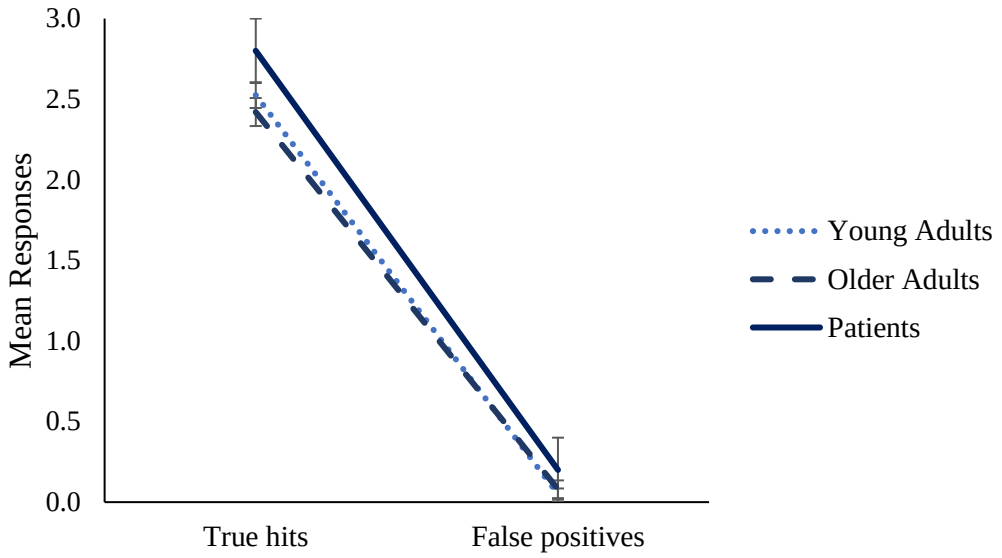

Figure 2.15 Group comparisons in accuracy of recognition memory for events presented in the demonstration video.

The mean number of correct (true hits) and incorrect (false positives) responses are examined. Note. Error means indicate standard error of mean.

Confidence Ratings

To determine participants' confidence in their responses during the action recognition task, confidence ratings were compared between-groups in terms of their confidence in their responses for correct actions, false actions and overall confidence during the task (see table 2.3).

Table 2.3 Confidence ratings provided during the action recognition task.

Confidence ratings are presented as mean confidence when providing judgments for true actions, false actions and overall confidence. Range and standard deviation (SD) also indicated.

		Young Adults (n=40)	Older Adults (n=40)	Patients (n=5)
Confidence for Actions	True Actions			
	Mean	3.708	3.561	3.067
	SD	0.363	0.580	0.693
	Range	1.830	2.330	1.670
	False Actions			
	Mean	3.306	3.149	3.133
	SD	0.630	0.801	0.650
	Range	3.000	2.670	2.330
	Overall Actions			
	Mean	3.492	3.338	3.000
	SD	0.406	0.606	0.972
	Range	1.830	2.330	1.670

No significant effects of group were observed for confidence ratings during true action responses (χ^2 (2) = 3.570, p=.168, r=-.04), false action responses (χ^2 (2) = .370, p=.831, r=-.004) and overall confidence (χ^2 (2) = 1.707, p=.426, r=-.02). Mean confidence ratings across groups fell between the confidence level 3 '*fairly confident'* and the confidence level 4 '*quite confident*'. Therefore, groups appear to rate their confidence in their responses similarly during action recognition.

When confidence ratings were examined during the event recognition task (see table 2.4), significant effects of group were observed for confidence ratings during true event responses (χ^2 (2) = 7.264, p=.026, r=-.09), false event responses (χ^2 (2) = 7.311, p=.026, r=-.09) and overall confidence (χ^2 (2) = 8.874, p=.012, r=-.11). Mean confidence ratings across groups fell between the confidence level 3 '*fairly confident'* and the confidence level 4 '*quite confident*'. However, when Bonferroni correction was applied to correct for multiple tests (alpha level of 0.017 adopted), only an effect of group remains for overall confidence during event recognition. Pairwise comparisons completed using Mann-Whitney U tests indicated that overall event recognition confidence did not significantly differ between patients and young adults (U= 93.0, z= -.254, p=.820, r=-.04) and between patients and older adults (U= 60.0, z= -1.487, p=.117, r=-.22). Older adults were significantly more confident overall in their event recognition responses relative to young adults (U= 493.0, z= -2.880, p=.004, r=-.32).

Table 2.4 Confidence ratings provided during the event recognition task.

Confidence ratings are presented in terms of mean confidence when providing judgments for true events, false events and overall confidence. Range and standard deviation (SD) also indicated.

		Young Adults (n=40)	Older Adults (n=40)	Patients (n=5)
Confidence for Events	True Events			
	Mean	3.485	3.675	3.467
	SD	0.449	0.468	0.691
	Range	1.670	2.000	1.670
	False Events			
	Mean	3.723	3.838	3.600
	SD	0.438	0.653	0.723
	Range	1.670	4.000	1.670
	Overall Events			
	Mean	3.609	3.756	3.533
	SD	0.366	0.403	0.431
	Range	1.500	2.000	1.000

2.4 *Discussion*

This chapter aimed to determine whether infant deferred imitation tasks are a reliable index of hippocampal memory processing. To determine this, we compared task performance between patients with compromised hippocampal circuitry with healthy adults and infants using as similar methodology as possible to see the extent to which this test captures hippocampal processing. Patients with selective hippocampal damage acquired from VGKCC_LE did not significantly differ in their performance from naïve age-matched controls that had not seen the action sequence modelled previously. Applying the principle that recollection of the action sequence in the group that had viewed the sequence at demonstration should significantly exceed that of the control group naïve to the modelled sequence, our finding suggests that insufficient memory retention for the actions previously modelled was observed in the patients. There was a trend for patients to elicit significantly less actions than older adults, with young adults spontaneously reproducing significantly more correct actions than the patients. However, these results need to be interpreted with caution, as group sizes are unequal with a particularly low sample size for the patient group. Referring to the amnesic filter criteria (Squire & Schacter, 2002); we can tentatively infer that the integrity of the hippocampal formation is needed to successfully retain memory for a sequence of actions within infant deferred imitation paradigms. Therefore, previous arguments that postulate nonverbal deferred imitation paradigms correspond to verbal reports of hippocampal-dependent memory appear to be valid (e.g. Hayne, 2004).

Fundamentally, we have directly compared infant and patient performance on the same task when no instructions to imitate the sequence are provided; a crucial comparison that was absent from prior research. Previous literature has suggested that as 1) patients with hippocampal damage exhibit memory deficits on adult deferred imitation tasks and 2) infants can outperform naïve peers on infant deferred imitation tasks, then infants are demonstrating rudimentary hippocampal memory (McDonough et al., 1995). Despite our findings corroborating both of the above assumptions, we also found that 7.5-month-old infants did not perform significantly different from patients with a compromised hippocampus, in both the number of correctly imitated actions and whether those actions reproduced were in the correct order. Thus, these findings suggest that the neural circuitry underpinning infant performance at this age may be similar to the spared hippocampal circuits of patients with hippocampal damage.

One could speculate that similarities in performance between the patients and infants may exist due to residual functioning remaining in the patient group that corresponds to rudimentary hippocampal functioning in the infant brain at this age. For instance, the early emergence and structural development of the entorhinal cortex and CA1 hippocampal subfield connectivity, which appears to develop between the ages of 0-6 months in monkeys (Jabès et al., 2011) and equivalent age of 0-24 months in human infants (Fortman et al., 2001), is postulated to permit rudimentary associative memory processes (Jabès & Nelson, 2015). Alternatively, these findings may suggest that performance in both groups may be subserved by neural substrates outside of the hippocampal formation. Future research should endeavour to utilise high-quality structural neuroimaging within both patients and infants of this age, as a means of empirically testing these speculations.

Moreover, we also observed a significant decline in recollection of the action sequence with healthy ageing. Older adults showed significant memory retention for the actions previously modelled compared to naïve age-matched peers (and thus showed evidence of substantial retention for the action sequence). However, older adults reproduced significantly fewer actions compared to young adults both for spontaneous and instructed recall. Equally, older adults did not significantly differ from patients in their reproduction of actions and the correct temporal ordering of those actions during both spontaneous and instructed reproduction, although older adult mean performance on these measures is visibly higher and trends are observed for action reproduction. These findings are consistent with previous literature, which reports age-related deficits in forming inter-item and item-context associations (Old & Naveh-Benjamin, 2008a), which are deficits also observed in patients with hippocampal amnesia but to a lesser extent in healthy older adults (Grady & Ryan, 2017). These findings, coupled with the fact that young adults remembered significantly more correct actions than the patients, suggests that decline in task performance arises with ageing, as would be predicted by age-related structural changes to the hippocampus (see section 1.2.2.1).

When analysing healthy controls' performance in their spontaneous recall of temporal order information, these results were surprising. Both young and older adults did not significantly outperform patients with hippocampal damage, nor was a significant difference observed between young and older adult performance. Although it can be noted that there are trends present in the data and visually mean performance is as one would expect, i.e. the highest

performance achieved by young adults, followed by older adults and then the patients. It may be that spontaneous recall for temporal order information of the sequence event could be impacted in adults by the strangeness of interacting with a puppet stimulus (e.g. shyness). Equally, without direct instructions to perform the actions in the correct order, adults might not have realised that this is a task requirement. Examining healthy adults' performance when instructed to reproduce the temporal ordering of the actions seems to support this hypothesis; when provided with instructions to produce the action sequence in the same order in which the experimenter modelled the sequence, young adults significantly outperform patients and older adults in both the number of correct actions reproduced and the order of their reproduction. Equally, older adults now exhibit trends to outperform the patients in both action and temporal order reproduction. Correct temporal order reproduction significantly increased in both young and older adults when instructed to perform the action sequence compared to when spontaneous reproduction of the action sequence was assessed (i.e. with no instruction to do so); a behaviour that was not observed within the patient group. Therefore, this also suggests that the oddity of spontaneous reproduction using puppet stimuli or lack of awareness of task goal may have decreased temporal order recall within the healthy control groups. Future applications of the deferred imitation paradigm could use alternative stimuli to the puppets, which are more adult-appropriate but still engaging to infants and young children.

Critically, the hippocampal patient group were unable to increase their recall further when instructions were provided. If the patients are remembering fewer actions compared to healthy controls (albeit marginally when compared to the older adult controls), logically if one remembers fewer actions then it is more difficult to remember the temporal order, i.e. if recall for certain actions in a sequence are omitted. The spontaneous vs. instructed reproduction comparison could not be conducted with pre-verbal infants. Therefore, we do not know how the lack of instructions could have impacted upon infants' performance. Future work should endeavour to devise tasks that can more adequately assess temporal order recall in both young children and adults, whilst ensuring that advantage is not given to language-proficient groups over e.g. pre-verbal infants. Previous research has successfully employed eye-tracking methodology to assess temporal ordering memory in children, with suggestion that preferential looking bias can be used as an indicative measure of temporal order memory (Pathman & Ghetti, 2014; outlined in section 1.2.1.4). Perhaps employing methodologies like

these in pre-verbal infants could shed light as to whether deferred imitation paradigms used with these age groups could be underestimating infant temporal order memory.

In this chapter, we also explored recognition memory accuracy for actions and events previously presented at encoding within the demonstration video. The inclusion of this task allowed us to check 1) that the patients had not forgotten the video completely by test and 2) to examine how recall for actions within an action sequence may differ from recognition memory for such actions and how recognition memory for action sequences may differ from memory for single events. This provided a further opportunity to examine mnemonic abilities across our adult groups and to determine whether patients exhibited unimpaired recognition memory, in accordance with dual-process theories of memory which argue that whilst recollection is compromised with hippocampal damage, recognition should be spared (Yonelinas, 2002). Within the recognition task, we noted differences in patient performance when comparing recognition of actions and recognition of events that were not observed in healthy young or older adults.

When comparing adults' ability to recognise single events that occurred within the demonstration video (e.g. whether the experimenter handed the infant a toy rattle), patients performed equal to both young adults and older adults and their performance was almost at ceiling. Therefore, in contrast to their observed impairments in recollection of the action-sequence during spontaneous and instructed reproduction, patients with selective hippocampal damage elicited robust memory when deciding if they recognised a single event as having occurred previously. This difference in task performance, with recognition memory appearing to be spared whilst recollection is impaired in this patient group, is consistent with dual-process models (Aggleton & Brown, 1999; Yonelinas, 2002). See section 1.1.3.7. Thus, we contribute to this body of literature with our finding that patients with selective hippocampal damage as a result of VGKCC_LE do not exhibit recognition-based deficits on a behavioural measure of memory for single events.

However, when comparing groups in their ability to correctly recognise actions that were previously demonstrated, we observe very different performance within the patients. All groups with the exception of the patients performed very well (at/almost at ceiling across

groups). Poor accuracy in correctly recognising previously modelled actions was observed within the patients, with this group producing significantly more false alarms than all other groups i.e. they incorrectly identified significantly more false actions as been previously modelled. As the patients were able to successfully recognise whether single, visually and temporally distinct events had occurred previously in the demonstration video, perhaps the patients are unable to rely on familiarity-based recognition when judging whether actions had been demonstrated previously, due to the actions shown being very similar and thus having a great deal of feature level overlap. Therefore, if the patients are unable to use familiarity-based recognition to distinguish between the novel (i.e. false) actions and highly similar previously shown actions, this may mean that they have to engage in recollection-mediated recognition which they have difficulties with.

This notion is in line with the complementary learning systems model of recognition (Norman & O'Reilly, 2003; Norman, 2010), that argues that recognition memory is subserved by hippocampal-based recollection in situations where familiarity-based recognition is ineffective, specifically when very similar targets and lures are shown one at a time and participants must identify if an item was presented previously. Previous studies examining recognition of items in a patient with selective hippocampal damage have reported that - whilst patient YR demonstrated relatively spared recognition memory for items across various tests (Mayes et al., 2002) - if the test required discriminating between previously presented target items and lures which were visually highly similar, patient YR was impaired relative to controls (Holdstock et al., 2002).

A mechanism that may underpin this recollection-mediated false recognition is the use of gist-based memory retrieval (Reyna & Brainerd, 1995). Gist-based false recognition refers to incorrect recognition of items that are highly similar to previously encoded items, as a result of failure to retrieve the specific details of an event but just the 'gist' of what occurred during that event episode (Brainerd & Reyna, 1998). Therefore, if the patients are unable to rely on familiarity-based recognition and also have impairments in their recollection-mediated recognition due to their hippocampal injury, they may be forced to rely on gist-based retrieval, resulting in their high rate of falsely recognised actions.

There is also evidence that false alarms to novel items may not simply arise as a result of gist-based false recognition, but as a result of ineffective pattern separation (Gutchess & Schacter, 2012; see section 1.1.4.1). Pattern separation refers to the ability to effectively encode the unique features of an event (e.g. which actions occurred within a sequence) while understanding how they differ from previously formed memory representations (Lee, Johnson & Ghetti, 2017). This process appears to rely on the DG and CA3 subfield within the hippocampal formation (Bakker et al., 2008; Lacy et al., 2011), with the ability to correctly discriminate between previously viewed events and similar novel events during behavioural tasks being considered a hallmark of this process (Yassa & Stark, 2011). The finding that false recognition of items is akin to control performance in a patient with hippocampal damage when dissimilar targets and lures are used (Holdstock et al., 2002), may also indicate that patients with hippocampal injury possess intact recognition memory when pattern separation is not required. Therefore, difficulties experienced in distinguishing novel actions from previously viewed actions in adults with hippocampal injury in our study may arise as a result of inability to adequately engage in pattern separation. Further research is necessary to verify the neural correlates of this false recognition observed in patients with hippocampal damage when it appears that familiarity cannot be relied upon, in order to determine whether this false recognition occurs as a result of ineffective pattern separation and so reliance on gist-based strategies, which consequently fail in situations where stimuli are visually similar.

Additionally, we measured recognition confidence during both action and event recognition. Confidence ratings have been applied in previous literature to indicate whether familiarity-based recognition is being used as opposed to recollection-based recognition (Yonelinas, 2002). It has been argued that high confidence ratings reflect recollection-based recognition responses, as confidence should be greater due to actively recollecting the contextual details of an event. On the other hand, familiarity-based recognition may vary in familiarity strength, i.e. a stronger or weaker feeling of an event being familiar but lacking the specific contextual details that underpins recollection. Therefore, previous literature argues that low confidence ratings are reflective of weak familiarity-based recognition but high confidence recognition responses could be indicative of either strong familiarity-based recognition or recollection-based recognition (Migo et al., 2012). As all groups provided confidence ratings that fell within the ranges of '*fairly confident*' to '*quite confident*' for both action and event recognition responses (which are middle-high range responses on the confidence Likert scale), it is difficult to make inferences regarding whether subjects' confidence ratings may be

indicative of recollection- or familiarity-based recognition. Group differences were not observed for any of the different areas of confidence ratings (true items, false items, overall confidence), with the exception of older adults providing significantly higher confidence ratings for overall event recognition responses compared to younger adults (although note mean overall event confidence fell within the same Likert scale range in each group). If patients are using familiarity-based recognition as speculated above, as their confidence ratings are relatively high this would suggest that their familiarity-based recognition is relatively strong (as weak familiarity-based recognition should have resulted in low confidence ratings, which we did not observe).

Making inferences regarding the basis of recognition memory using confidence ratings should be tentatively employed, because relying on subjective reports may be problematic in terms of accuracy and subject self-awareness. Equally, research has reported that remember/know procedures frequently employed to determine whether familiarity or recollection is supported recognition memory are dissociable from confidence ratings (Yonelinas, 2002). In remember/know task, participants introspect about the basis of their memory judgments and decide whether they recognise items due to remembering (recollection-based) or from knowing (familiarity-based) (Tulving, 1985). Evidence suggests that recognition confidence ratings are not equivalent to remember/know responses (Gardiner & Java, 1991; Rajaram, 1993). Therefore, caution should be taken when interpreting the basis of recognition memory using recognition confidence.

In conclusion, this study aimed to compare infant, adult and patients with hippocampal damage in their performance on the same measure of hippocampal-dependent memory, using as similar methods as possible across all groups. We provided considerable evidence that memory for an action sequence assessed in typical infant deferred imitation paradigms is supported by hippocampal processing, due to poorer recollection of the action sequence being observed in patients with hippocampal damage. Our results may imply that preserved familiarity-based recognition processing is present in our patients with selective hippocampal damage whilst recognition that may require recollective-based processing is impaired. In accordance with previous research, infants aged 7.5-months-old exhibit evidence of rudimentary memory for an action sequence; however, this is highly similar to performance of

patients with a compromised hippocampal system and significantly lower in proficiency compared to healthy adults.

Further work is needed in order to pinpoint the neural correlates underlying this similar performance in our patient group and infants, to determine whether this limited memory retention elicited by infants of this age relies on hippocampal circuitry that have retained residual function in the patient group or is subserved independently of the hippocampus. Equally, performance using the same DI task should be tracked across the life-span, in order to ascertain at what age children demonstrate adult-like memory for an action sequence. Therefore, the next step in this thesis is to determine when memory for an action sequence becomes adult-like in function and performance exceeds that of patients with hippocampal damage, in order to make inferences regarding the anatomical and functional development of the hippocampal circuitry in childhood (chapter 3).

3. Chapter 3. Age-related changes in deferred imitation of action sequences across the life span.

Chapter 3 Summary

It is vital to examine changes in hippocampal-dependent memory across the life-span, in order to understand both its ontogeny and decline with aging. To the author's knowledge, previous research has not used the same methodology to assess memory of this kind in children and adults, yet comparisons in performance between these groups have been made regardless. In chapter 2, a deferred imitation task measuring memory for a previously modelled three-step action sequence was used with 7.5-month-old infants, young and older adults and a cohort of patients with selective hippocampal damage. While the task appears to index hippocampal-dependent memory processes (deduced from performance impairments in patients relative to adult controls); 7.5-month-olds' performance did not significantly differ from the patients and lacked the proficiency of healthy adults. In this chapter, the same task was utilised to measure performance cross-sectionally across childhood. Performance was examined in children aged 9-months-old to 8-years-old and compared to healthy adult and patient memory, in order to determine at what age children demonstrate adult-like memory for action sequences. Previous literature has indicated that memory for the discrete components of an event develops at different time points in childhood, with temporal order memory found to emerge later than memory for spatial contexts and the event itself. Thus, memory retrieval of actions and the correct temporal order in which they occurred was examined separately. Memory for actions appears to emerge between the ages of 2-4 years; children aged 2 and 3 years significantly outperform infants and match the 4-year-olds' and older adults' performance. However, only children aged 4-years-old and above perform equally as well as younger adults and demonstrated performance that significantly exceeds patients with selective hippocampal damage. Examining temporal order memory, again children aged over 4-years-old elicited performance that did not significantly differ from younger adults. All groups aged ≤3 years demonstrated poor temporal order recall, indicative of an absence of temporal ordering ability prior to the age of 4 years. When older children and adults were instructed to reproduce the action sequence, adult-like memory recall for both action and temporal order information was evident from 4-5 years. Equally, accurate action recognition was observed from ≥4 years. Our results are generally consistent with the literature which argues memory for a sequence of arbitrary events appears to be rudimentary during infancy, becomes adult-like in function by 4-years-old and later declines with aging.

3.1 *Introduction*

An important component of episodic memory or '*what-where-when*' memory (Tulving, 1972) is the ability to remember the temporal contexts of events (i.e. '*when*' memory). While infants aged 6-months-old and above can form and retain basic associations between an action and an object (Collie & Hayne, 1999), i.e. '*what*' information about an episodic event, the ability to encode and recollect the temporal information about an experience ('*when*' information) appears to emerge later in childhood (see section 1.2.1.4). Using different paradigms, previous literature has demonstrated that the ability to remember '*what*' happened during an event and '*where*' it happened does not significantly differ between 3 and 4-year-olds (Hayne & Imuta, 2011; Cuevas et al., 2015). In contrast, temporal order memory for an event, i.e. '*when*' an event had taken place, was recalled to a significantly greater extent in 4-year-olds compared to 3-year-olds in these studies (Hayne & Imuta, 2011; Cuevas et al., 2015). However, as noted in Cuevas et al. (2015), even at 4 years of age memory recall for this temporal information appears to be less robust than recall for other elements of the event.

Further increases in the proficiency of temporal context event memory are observed from preschool age into adolescence (Ghetti, 2017). Scarf et al. (2017) examined whether children aged between 3-6 years could accurately recall the order in which they visited five different locations either immediately after their visit or following a 30-minute delay. Children were required to place five pictures depicting the visited locations on a paper timeline in the order in which they were visited, as a way of reducing the language demand on younger participants. 5- and 6-year-old children were significantly more accurate in their ordering of the locations visited than the younger children and all groups except the 3-year-old children performed significantly above chance. The authors also conclude that as memory performance did not differ as a function of delay, the differences in performance between the age groups may be attributed to encoding failures rather than retention failures. Therefore, it may be inferred that children's ability to bind events and temporal contexts into a memory representation appears to emerge from 4-years-old and continues to improve into middle childhood.

Behavioural evidence that indicates memory for the temporal context of events emerges around 4-years-old is consistent with neuromaturational accounts of hippocampal memory development. As outlined in section 1.2.1.1, distinct subfields within the human

hippocampus (and the computations they support) appear to possess different maturational trajectories. Authors have hypothesised that maturation of specific subfields may underlie the emergence of different hippocampal-dependent memory processes and have made inferences regarding how performance of infants and children on behavioural episodic memory measures appears to reflect this protracted anatomical development (see section 1.3.3). Jábes & Nelson (2015) propose that early maturation of the CA1 subfield and its connectivity with the entorhinal cortex may support the emergence of rudimentary episodic memory functions that are observed in infants aged 2 years and under, such as the ability to reproduce previously demonstrated actions after a delay (Barr et al., 1996) and basic memory for spatial locations (Ribordy et al., 2013).

These authors argue that memory processing then becomes more complex in accordance with the maturation of the DG and CA3 subfields that make up the trisynaptic hippocampal circuitry, which follow prolonged developmental time courses extending into adolescence. More remarkable memory feats, e.g. more complex spatial location memory (Ribordy et al., 2015; 2017), appear to emerge from 42 months (3.5 years) onwards. This corresponds to the estimated time period where DG and CA3 functions are argued to be structurally mature enough to support more complex computations (Ábraháms et al., 2010). Finally, these authors propose that due to the protracted maturation of the DG into adolescence, this results in adult-like episodic memory being the last memory function to emerge. This view is consistent with existing findings that argue memory for events and the recall of their spatio-temporal contexts appears to emerge at around 4 years of age and increases incrementally throughout childhood (Scarf et al. 2017).

However, there are some clear issues when attempting to determine at what age the ability to recollect temporal context information about events first emerges and becomes adult-like in function. Firstly, the tasks used to measure this concept vary enormously within the literature (as outlined in section 1.3.1). Paradigms used with young infants, such as deferred imitation, are very different in terms of task demands compared to paradigms used with older children, such as the hide and seek paradigm employed by Hayne & Imuta (2011) which contains cognitive demands such as language and motor skill requirements that are unsuitable for use with pre-verbal and very young infants.

Equally, there is a large gap in the literature regarding deferred imitation performance between 2-year-olds and participants aged 11-26 years, with the latter group found to perform at/or near ceiling when instructed to recollect action sequences (Adlam et al., 2005). Without assessing task performance between toddlerhood and young adulthood, we are unable to determine how this memory for action sequences develops with age. Whilst performance on deferred imitation tasks appears to stabilise between the ages of 18-24 months old, toddlers reproduce on average less than 2/3 target actions and thus their performance is not at ceiling (Barr et al., 1996).

The results of chapter 2 established that while 7.5-month-old infants can significantly outperform naïve age-matched peers in their recall of previously imitated actions, their performance was not adult-like and did not significantly differ from that of adults with selective hippocampal damage. Recall of temporal order information at 7.5-months-old was very poor and thus we do not know how memory for temporal contexts underpinning action events develops across childhood. This chapter aimed to determine at what age children begin to demonstrate adult-like memory for action sequences using the deferred imitation task outlined in chapter 2. Equally, we assessed at what age children's performance significantly exceeds that of patients, as this would allow inferences to be made regarding underlying hippocampal functional development.

3.2 *Method*

3.2.1 Participants

Data was obtained for a total of 415 children aged between 9-months-old to 8-years-old. See table 3.1 for group statistics. Twenty-seven additional children were tested however data was not obtained due to the child not touching the puppet at test (9-months-old n=1, 1-years-old n= 7, 2-years-old n= 5, 3-years-old n= 14). Children who took part had no significant medical problems. Children aged 4 years and under were recruited from local nurseries, children's centres and via social media advertisements. These children were tested within the Cognitive Development Lab at Newcastle University and received a certificate and gift for participating. Parents were reimbursed for travelling expenses. Children aged 4 years and over were tested in local primary schools once the experimenter was granted permission from school staff and signed parental consent forms were obtained. These children were tested in a separate

classroom and received a sticker for participating. All parents provided informed consent for their child to participate and ethical approval was granted by the Faculty of Medical Sciences Ethics Committee at Newcastle University.

Table 3.1 Descriptive statistics separated by age group for child participants tested.

Age Group (total n= 415)	Mean age in weeks (*SD*)	Gender (F/M)
9 months (n= 59)	41.1 (*1.9*)	35 F, 24 M
1 years (n= 47)	63.7 (*17.7*)	25 F, 22 M
2 years (n= 66)	109.3 (*12.8*)	34 F, 32 M
3 years (n= 53)	159.8 (*16.8*)	28 F, 25 M
4 years (n= 60)	214.4 (*13.3*)	29 F, 31 M
5 years (n= 21)	265.1 (*17.2*)	13 F, 8 M
6 years (n= 45)	319.6 (*13.3*)	21 F, 24 M
7 years (n= 29)	369.8 (*24.9*)	17 F, 12 M
8 years (n= 35)	426.4 (*14.5*)	17 F, 18 M

Note data from infants aged 7.5-months-old, patients with hippocampal damage, older adults and young adults derived from Chapter 2 are presented within the results below, to permit comparisons across the life span.

3.2.2 Apparatus

The apparatus was identical to that described in Chapter 2 section 2.2.2.

3.2.3 Procedure

Due to testing in primary schools, only children aged 9 months to 4 years were randomly allocated to the naive condition (total n=85; 9-month-olds n=19, 1-year-olds n=13, 2-years-old n=20, 3-years-old n=18, 4-years-old n=15). As outlined in Chapter 2 section 2.2.3, participants assigned to the naïve condition were not shown the sequence of actions. These participants were simply given the puppet and the number of actions they produced were recorded.

The remaining children were assigned to the experimental condition which observed the action sequence being demonstrated. The demonstration procedure was identical to that described in Chapter 2 section 2.2.3, with all child groups observing the face-to-face

demonstration of the action sequence. Following the retention interval, children aged 2 years and under completed spontaneous recall only due to language limitations at these ages. Children aged 3 years and above completed both spontaneous and instructed reproduction tests, however slightly more age-appropriate instructions were utilised for instructed reproduction. The experimenter held the puppet within the child's reach and gave the following instruction: "*So when I was playing with the puppet before what did I do to him? Can you show me what I did to the puppet?"* The child was again allowed 90 seconds from first touching the puppet to elicit the action sequence. If the child performed some actions on the puppet, the experimenter asked *"So what did I do first? What did I do next? What did I do last?"* These questions were adapted to the child's initial response to avoid prompting them or confusion, e.g. if they only performed two actions the experimenter would only enquire about the ordering of those two actions. Additionally, a temporal order language task was completed by 3- and 4-year-old participants (see appendix C). This task was used to check whether any differences observed between these age groups in their instructed recall of the action sequence may be a result of age-related differences in their understanding of temporal order language (e.g. understanding what position in a sequence the term 'first' refers to, etc.)

Additionally, children aged 3 years and above then completed a face-to-face version of the recognition test outlined in Chapter 2 section 2.2.3 which assessed recognition of the actions only. The experimenter knelt in front of the child with the puppet on her hand and once she had the child's attention, the experimenter gave the following instruction: "*So I'm going to play with the puppet now, I want you to tell me whether I did this to the puppet when I played with him the first time. If I did this before, I want you to give me a thumb's up (experimenter demonstrated thumbs up) but if it's something new that I show you I want you to give me a thumb's down (experimenter demonstrated thumbs down)".* The experimenter also clarified that the child could simply state '*yes*' or '*no*' too before performing the following actions on the puppet: 1) patted puppet's head, 2) lifted flap, 3) removed glove, 4) moved ribbons in forwards and backwards motion, 5) shook hand and 6) moved puppet from side to side. After each action, the experimenter asked *"Did I do this when I played with the puppet before?"* and recorded the child's response. These actions performed are identical to those presented in the adult version of the recognition test, including the order in which they were performed.

3.2.4 Statistical Analysis

All data was scored and analysed in the exact manner described in Chapter 2 section 2.2.4. Results are presented in two sections. In analysis 1 (section 3.3.2), the crucial comparisons are made between groups during spontaneous reproduction of the action sequence. This analysis allowed us to perform between-group comparisons on action reproduction and temporal order reproduction across all age groups when language demands were not present. In the additional analyses section (section 3.3.3), performance is compared in children aged ≥3 years and adults on their instructed reproduction and action recognition performance. Level of task engagement (assessed via overall action production during the spontaneous and instructed tasks, i.e. correct and false action production) was compared between naïve and experimental groups in order to exclude differences in task engagement as a potential memory confound.

3.3 *Results*

3.3.1 Interobserver Reliability

17% of video recordings were scored by two observers. Again, the percentage of agreement between scorers was high and inter-rater reliability examined by Cohen's κ fell between moderate to outstanding consistency (see table 3.2).

Table 3.2 Inter-rater reliability statistics when scoring between the two independent observers was compared using percentage (%) of agreement and Cohen's Kappa (κ).

Variable coded in video	% agreement	Cohen's k	p value
Spontaneous actions	94.90%	0.95	p<.0001
Spontaneous temporal ordering	94.90%	0.89	p<.0001
Instructed actions	90%	0.71	p<.0001
Instructed temporal ordering	96%	0.88	p<.0001

3.3.2 Analysis 1- Spontaneous Reproduction of Action Sequence

Kolmogorov-Smirnov tests revealed that the dependent variables were not normally distributed (mean number of correctly imitated actions ($D(450) = .250$, $p<.0001$); mean temporal ordering score ($D(450) = .261$, $p<.0001$)). This was also the case when these

variables were examined separately per group (p values ranging from p<.0001 to p=.008). Since normality was violated, non-parametric tests were used.

Correct Actions Reproduced

Memory retention for the previously demonstrated actions was compared between participants who watched the demonstration of the action sequence (experimental participants) and those who did not (naïve participants) within each age group, using Mann-Whitney U tests. We observed that children aged 9-months-old to 4-years-old produced significantly more correct actions than their naïve age-matched groups (figure 3.1; p<.0001 for all comparisons made and thus survived Bonferroni correction for multiple comparisons). Therefore, we can infer that all children under the age of 4 years displayed significant memory retention for actions previously seen relative to naïve peers.

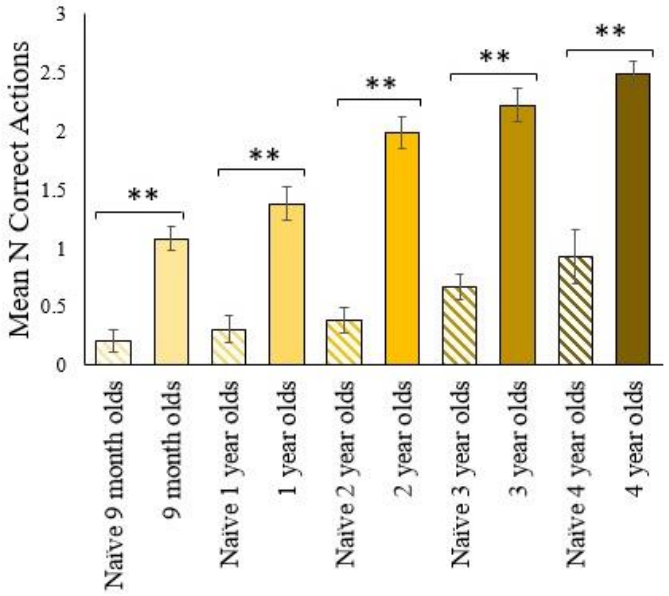

Figure 3.1 Comparison of experimental groups with their naïve counterparts in the mean number of correctly imitated actions during spontaneous reproduction.

Error bars show standard error of mean. Asterisks represent group differences that are significant at * p<.05 and ** p<.01.

When we examined group differences in memory for actions previously seen from infancy to adulthood (figure 3.2); we observe a gradual increase in recall for correct actions as a function of age that then stabilises across middle childhood and appears to decrease in older adults and adults with hippocampal damage. Firstly, a Kruskal Wallis test revealed a significant effect of

group for correct action reproduction (χ^2 (12) = 163.620, p<.0001). Pairwise comparisons revealed a prominent increase in action reproduction at 2 years of age; 2-year-olds reproduced significantly more actions than infants aged <1 years (respectively 7.5-month-olds: U = 538.50, z = -3.352, p = .001, r= -.34; 9-month-olds: U = 411.00, z = -4.551, p<.0001, r= -.47; 1-year-olds: U = 493.50, z = -2.822, p = .005, r= -.32) and did not significantly differ in performance from 3-year-olds (U = 610.00, z = -1.207, p =.228, r= -.14). At 3-years-old, children did not significantly differ from young adults in correct action reproduction (U = 561.50, z = -.985, p = .325, r= -.12). 4-year-olds reproduced significantly more actions than 2-year-olds (U = 677.50, z = -2.767, p = .006, r= -.34) and this was the first age group that reproduced significantly more actions than the patients (U = 37.5, z =-2.666, p = .008, r= -.40); although note that this latter result fails to remain statistically significant when Bonferroni correction was applied to adjust for multiple comparisons (alpha level of 0.007 adopted). Therefore, this suggests that by 3-4 years, children are beginning to show adult-like memory for previously seen actions.

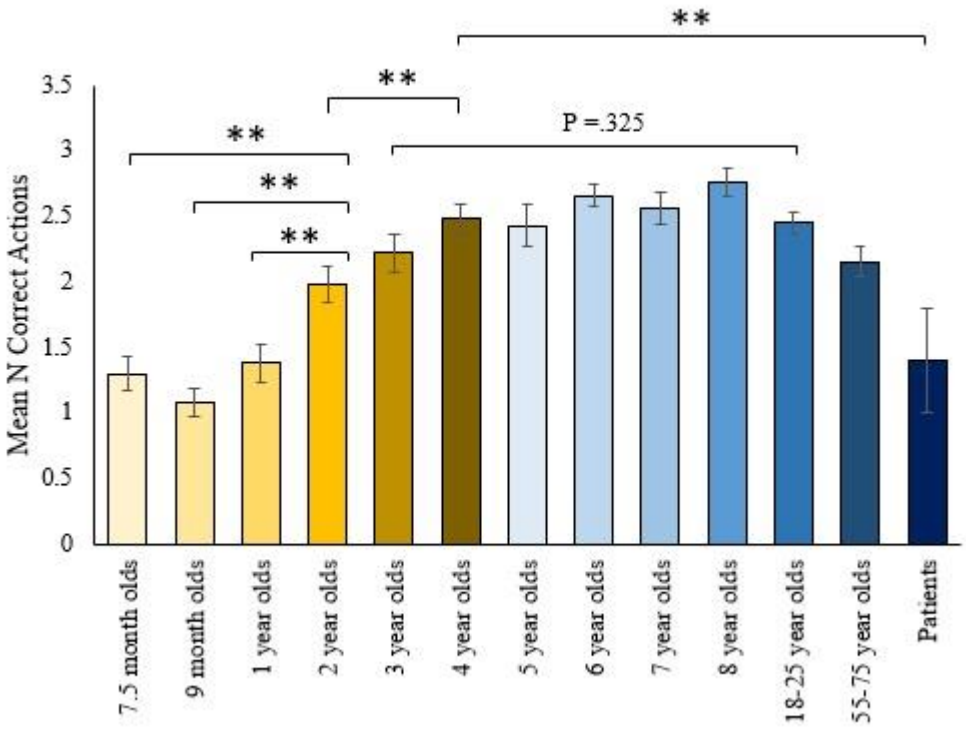

Figure 3.2 Spontaneous reproduction of actions previously demonstrated compared across all experimental groups.

Error bars show standard error of mean. Asterisks represent group differences that are significant at * p<.05 and ** p<.01.

Temporal Ordering of Actions

When group comparisons are made in terms of temporal ordering accuracy (figure 3.3), here we observe patterns in performance that appear to differ from action reproduction accuracy. Firstly, like action reproduction, a significant effect of group was observed for mean temporal order score (χ^2 (12) = 71.517, p<.0001). Performance is very poor in all infant groups including 2-year-olds; we failed to observe a gradual increase in correct recall in temporal order information but rather performance appears to increase more abruptly from the age of 4 years onwards. Whilst, performance does not significantly differ between 3-year-olds and 4-year-olds (U = 553.00, z = -1.532, p = .126, r= -.17), the 4-year-olds produced significantly more actions in the correct order than 2-year-olds (U = 663.00, z = -2.756, p = .006, r= -.30). It is at 4 years of age that recall of correct temporal ordering information does not significantly differ from young adult performance (U = 841.00, z = -.183, p = .854, r= -.02). Unexpectedly, it can be observed that mean temporal ordering scores are higher in all child groups aged 5-8 years than in the young adult group. 8-years-olds reproduced significantly more correct actions in the correct order than young adults (U = 438.50, z = -2.772, p = .006, r= -.31) and patients (U = 30.5, z = -2.406, p = .016, r= -.38). Note when Bonferroni correction is applied, the difference observed between patients and 8-year-olds in temporal ordering performance does not remain statistically significant. Due to young adults, who should possess optimal adult memory, performing significantly worse than 8-year-old children; these findings suggest that perhaps spontaneous recall for an action sequence when not instructed to perform the actions in the correct order may not be accurately capturing temporal order memory in adult groups.

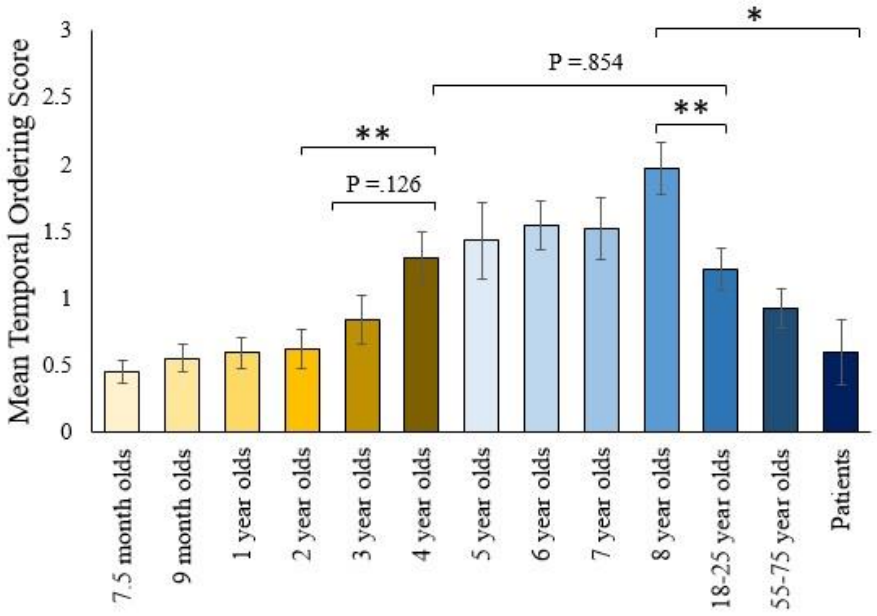

Figure 3.3 Group differences in mean temporal ordering score during spontaneous reproduction of action sequence.

Error bars show standard error of mean. Asterisks represent group differences that are significant at * p<.05 and ** p<.01.

Overall, we observed different patterns of performance in action reproduction and temporal order reproduction during spontaneous recall (see figure 3.4 for a visual depiction of these patterns). Memory for action information appears to emerge and begin to resemble adult-like performance around 3-years-old, with a gradual increase in performance observed across early infancy. Memory for action information then appears to remain relatively stable across middle childhood. In contrast, temporal ordering memory is poor (a score of less than 1) prior to the age of approximately 4 years, with a more abrupt increase observed in temporal ordering ability from 4-years-old.

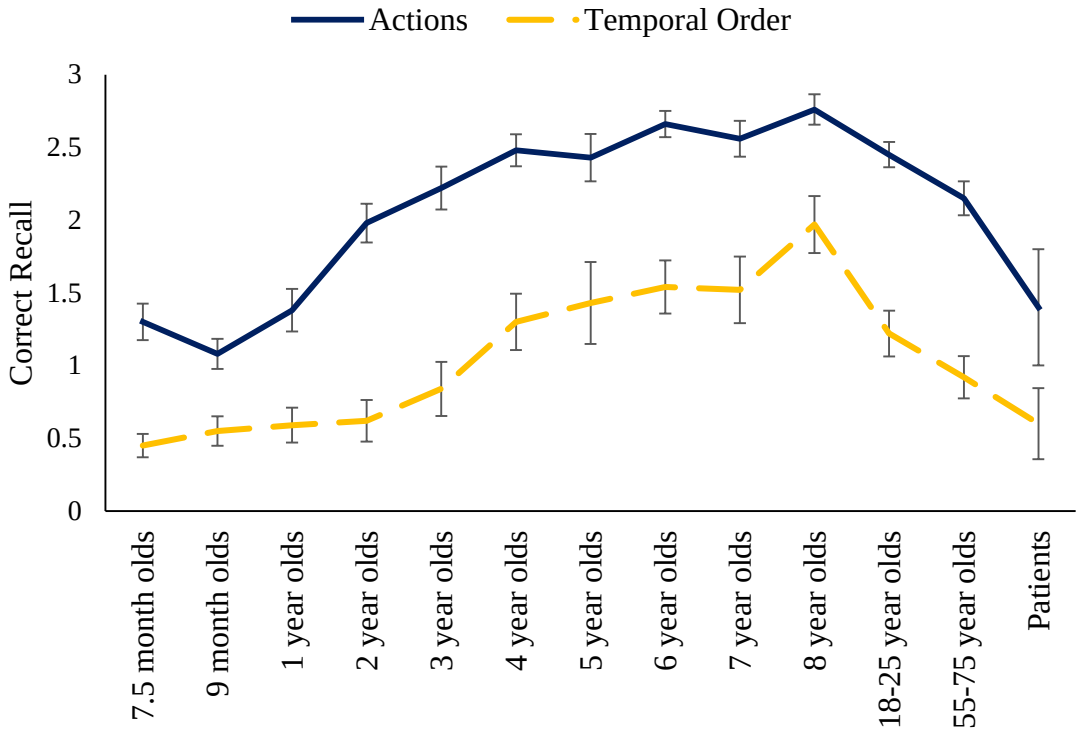

Figure 3.4 Illustration of differences in spontaneous reproduction of actions (solid line) and temporal order information (dashed line) across all experimental groups.

Error bars show standard error of mean.

3.3.3 Additional Analyses

Further analyses were conducted to establish whether introducing instructions would influence task performance in more language proficient children aged ≥3 years and to also provide comparisons between children and young adults to establish when performance appears adult-like. Task engagement was also assessed between naïve and experimental child groups to rule this out as a potential memory confound. Lastly, action recognition memory was compared across all groups aged ≥3 years.

3.3.3.1 Instructed Reproduction of Action Sequence

Again, the dependent variables (mean number of correctly imitated actions; mean temporal ordering score; mean verbal temporal ordering score) were non-normally distributed (Kolmogorov-Smirnov tests yielded p values from $p<.0001$ to $p=.016$) and so non-parametric analysis was used.

Correct Actions Reproduced

A Kruskal Wallis test revealed a significant effect of group for correct action reproduction (χ^2 (8) = 68.503, p<.0001). When instructed to reproduce actions that were previously demonstrated (figure 3.5), we observed that from the age of 4-years-old, children produced significantly more correct actions than 3-year-olds (U = 377.5, z= -2.246, p=.025, r= -.27) and patients (U = 39.5, z = -2.746, p = .006, r= -.40). Moreover, 4-year-olds' action reproduction did not significantly differ from young adults (U = 761.0, z= -1.017, p= .309, r= -.11). These findings, coupled with the results in spontaneous reproduction, suggest that at 4 years children are beginning to elicit adult-like memory for previously seen actions. At 4-years-old this memory recall appears to exceed that of patients with hippocampal damage and thus may reflect the engagement of more mature hippocampal-dependent memory processing.

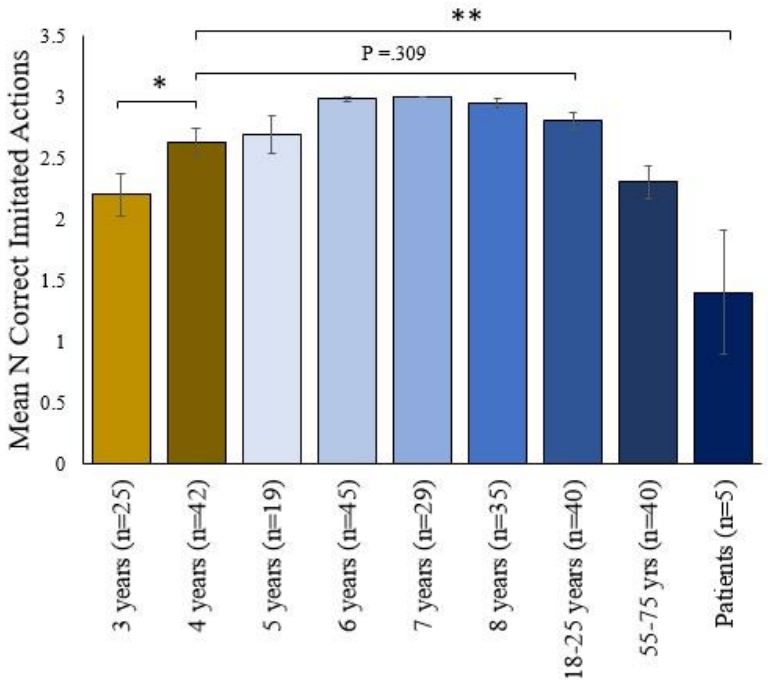

Figure 3.5 Group differences in instructed reproduction of previously demonstrated actions.

Error bars show standard error of mean. Asterisks represent group differences that are significant at * p<.05 and ** p<.01.

Temporal Ordering of Actions

A Kruskal Wallis test revealed a significant effect of group for correct temporal order reproduction (χ^2 (8) = 80.124, p<.0001). Children performed significantly worse than young adults until the age of 5 years (figure 3.6A; U = 306.0, z = -1.435, p = .151, r= -.18). It is also

at this later age of 5 years that children obtain significantly greater temporal ordering scores than patients (U = 18.0, z = -2.217, p = .027, r= -.44).

As outlined in section 3.2.3, children were asked a follow-up question in order to establish whether instructed reproduction of temporal ordering ability may be impacted by children's ability to understand what is being asked of them, i.e. to perform the actions in the order in which they were modelled at demonstration. Temporal ordering score elicited to this follow-up question was then analysed in conjunction with the adults groups' original temporal ordering scores. Again, we observed a significant effect of group (χ^2 (8) = 80.124, p<.0001).

When children are verbally asked if the action sequence that they have reproduced was performed in that order previously (see figure 3.6B), here we observed that children aged 4-years-old and above do not significantly differ in their temporal ordering ability from young adults (U = 689.5, z = -.139, p = .889, r= -.02) and demonstrate significantly better performance than patients (U = 16.5, z = -3.294, p = .001, r= -.52). This suggests that 4-year-olds can recollect temporal information about the action sequence that is not significantly different from that of young adults, but perhaps not emphasizing the need to reproduce the actions in the correct order at initial instructed reproduction may be resulting in their lower temporal ordering score obtained prior to verbal assessment of order.

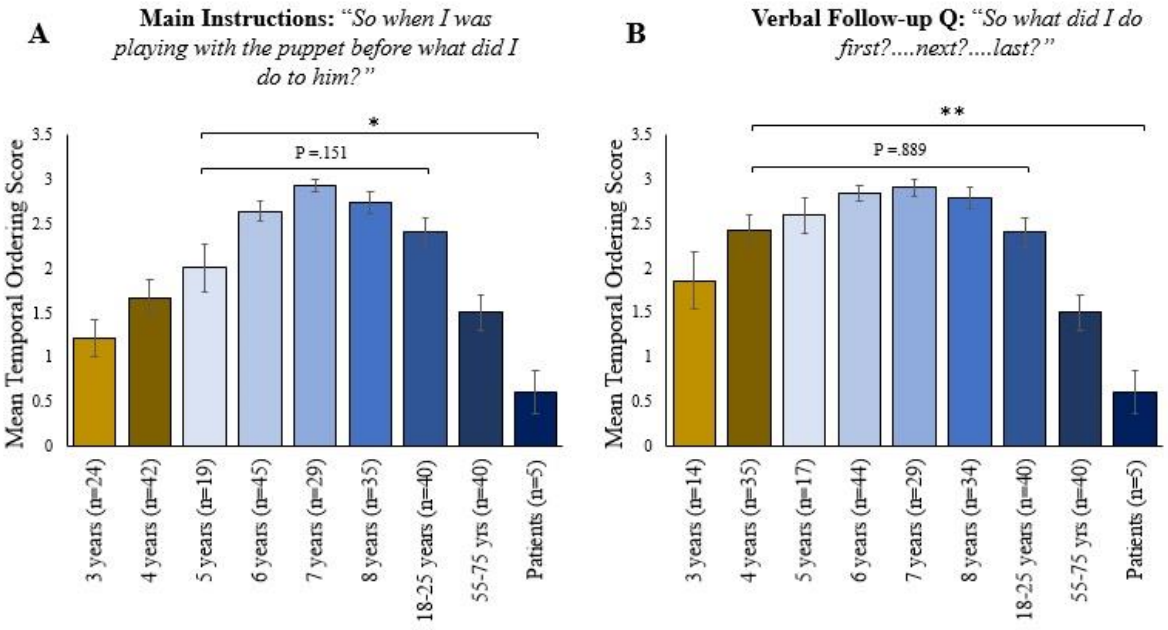

Figure 3.6 A) Group differences in the correct ordering of reproduced actions during instructed reproduction and B) correct ordering of these actions when the experimenter probed temporal order with a follow-up question.

Error bars show standard error of mean. Asterisks represent group differences that are significant at * p<.05 and ** p<.01.

3.3.3.2 Comparison between Spontaneous and Instructed Reproduction

Pairwise comparisons within-groups using Wilcoxon Signed Rank tests (adopting an alpha level of 0.0045 to apply Bonferroni correction) revealed that action reproduction only significantly increased between spontaneous and instructed reproduction within the 6-year-old group (z =-2.968, p=.003, r= -.32) and the 7-year-olds (z =-2.973, p=.003, r= -.39).We note from analysis presented in Chapter 2 (section 2.3.4.2) that young adults also reproduce more actions when instructed to do so (z =-2.904, p=.004, r= -.33).

When examining the effect of instructions on correct temporal order reproduction (figure 3.7B), we observe that there is a significant increase in performance between spontaneous and instructed reproduction within-groups aged 6-8 years (6-year-olds: z= -4.407, p<.0001, r= -.47; 7-year-olds: z= -3.703, p<.0001, r= -.49; 8-year-olds: z= -3.095, p=.002, r= -.37) that is not seen in younger children or patients. Analysis presented in Chapter 2 (section 2.3.4.2) also shows that temporal ordering performance increases with the use of instructions in both young adults (z =-4.147, p<.0001, r= .46) and older adults (z =-2.629, p=.009, r= -.29).

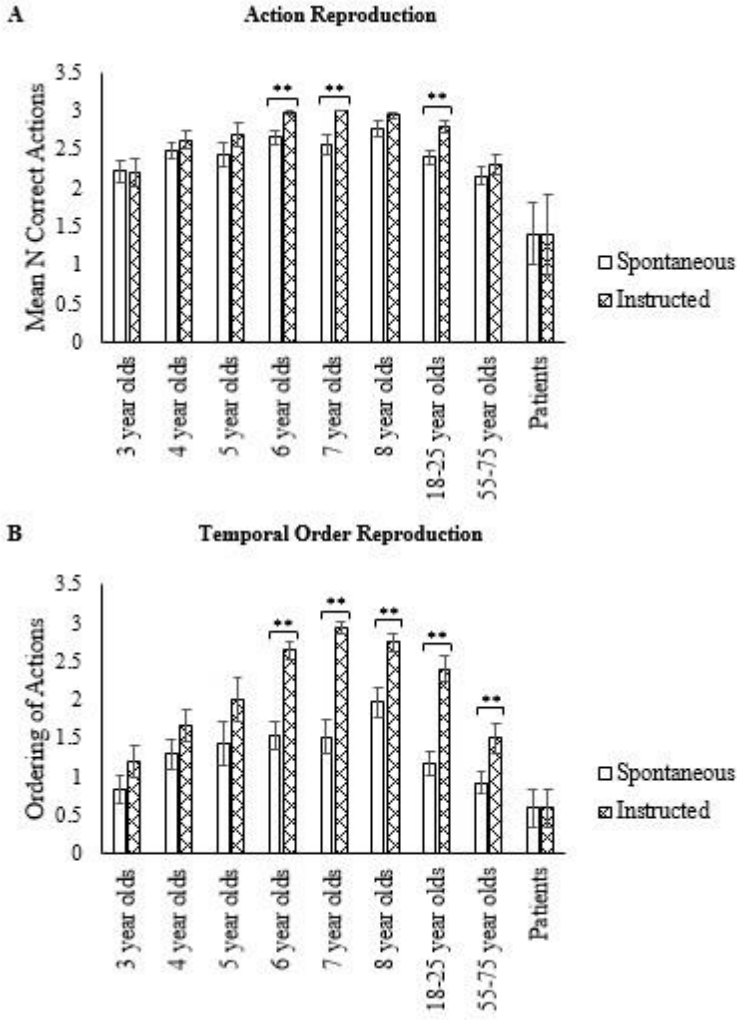

Figure 3.7 Comparison within-groups in performance when examining reproduction type (spontaneous; instructed) for A) reproduction of actions and B) reproduction of temporal order information.

Error bars depict standard error of mean. Asterisks denote significant differences within groups at * p<.05 and ** p<.01.

3.3.3.3 Task Engagement

Pairwise comparisons were made using Mann-Whitney U tests to establish whether differences in spontaneous action production differed between child groups and their naïve age-matched counterparts, followed by Bonferroni correction (alpha level of 0.01 adopted). This analysis is in line with that performed in chapter 2 section 2.3.4.1 to ensure that differences in action reproduction between experimental groups and naïve groups (presented in figure 3.1 above) were not a result of poorer task engagement within naïve groups. Note this analysis is not performed for children assigned to the experimental condition aged 5+ as they did not have a naïve group to complete this comparison.

Significant differences in overall action production (true and false actions) were not observed between experimental and naïve participants within 9-month-olds (U= 252.5, z= -1.624, p=.104, r=-.22), 2-year-olds (U=444.0, z=-.403, p=.687, r=-.05), 3-year-olds (U=231.0, z=-1.187, p=.235, r=-.17) and 4-year-olds (U=241.5, z=-1.577, p=.115, r=-.21). 1-year-olds in the experimental group were found to produce significantly more actions overall compared to their naïve counterparts (U=85.0, z=-3.305, p=.001, r=-.48). However, this suggests that the 1-year-olds assigned to the experimental condition were engaged in the task perhaps more so that their naïve group and thus is not an issue when interpreting memory retention by comparing experimental groups to their naïve counterparts above in section 3.3.2.

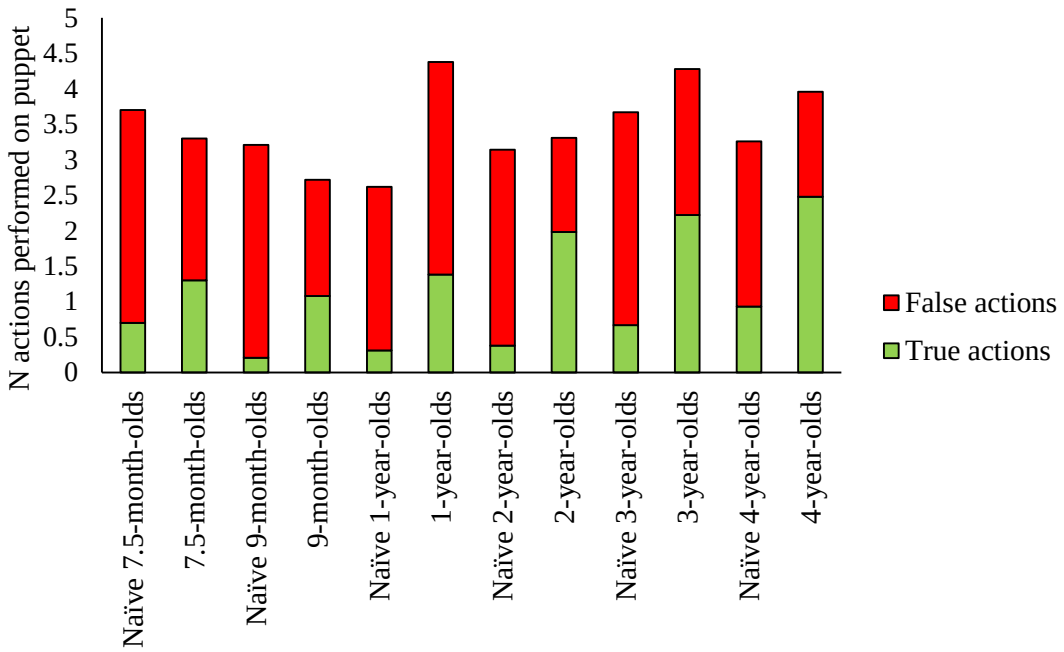

Figure 3.8 Overall mean number (N) actions performed on puppet, separated into correct actions and false actions within each age group (naive and experimental).

3.3.3.4 Recognition of Actions

When we compare children and adults in their ability to recognise previously shown actions (Figure 3.9), a mixed 2x9 ANOVA (2 response accuracy types (correct and false) x 9 groups) revealed a significant effect of group ($F(8, 243) = 4.401$, $p<.0001$). Overall participants elicited more correct recognition (i.e. true hits; Mean = 2.86; SEM = .028) than false recognition (Mean = .50; SEM = .049), $F(1, 243) = 1542.101$, $p<.0001$. There was also a significant interaction observed between group and response accuracy ($F(8, 243) = 7.609$,

p<.0001). When pairwise comparisons were made using Tukey HSD tests to examine the nature of this interaction, we observed that patients produced significantly more false responses than all groups with the exception of 3-year-children (p=.774). Children aged 3-years-old are showing poor recognition memory for previously seen actions, which is similar to impairments in performance observed in patients with hippocampal damage.

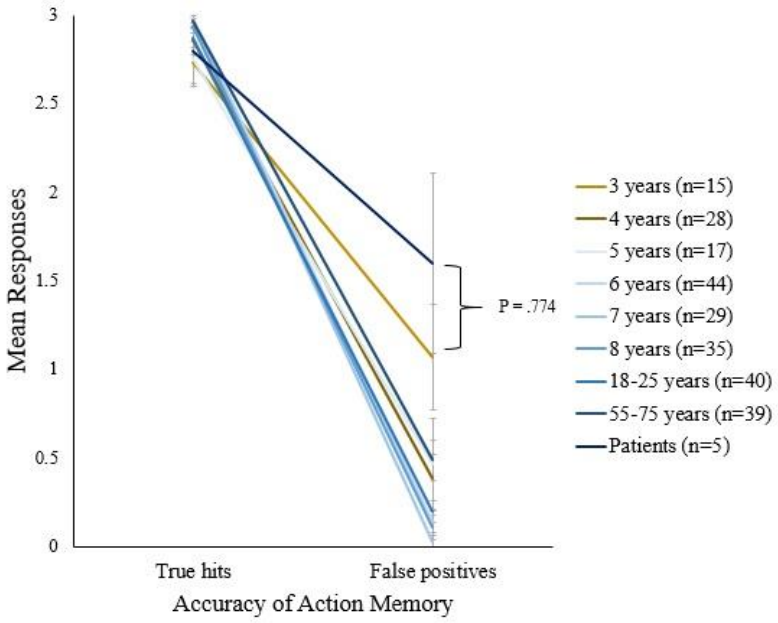

Figure 3.9 Group differences in accuracy of recognition memory for actions previously presented, when the mean number of correct (true hits) and incorrect (false positives) responses are examined.

Error bars indicate standard error of mean.

3.4 *Discussion*

This chapter aimed to examine the development of memory for a sequence of actions across the life span, assessed via deferred imitation. Measuring spontaneous reproduction of a previously modelled action sequence, we observed distinct findings for action reproduction relative to temporal order reproduction. At 2 years of age, children began to demonstrate significantly more correct actions than younger age groups. This finding concurs with previous research which has shown older infants within their second year of life demonstrate significantly more previously modelled actions than younger infants (Barr et al., 1996; Herbert & Hayne, 2000a). Action reproduction was then shown to increase further between the ages of 3-4 years; 3-year-olds' action reproduction did not significantly differ from young adults and at 4-years-old children significantly reproduced more correct actions than patients with selective hippocampal damage. When instructed to reproduce the previously demonstrated actions, children aged 4 years and over significantly outperform patients and

match young adult performance. Thus, it can be inferred from these findings that adult-like memory recollection for previously modelled actions begins to emerge at approximately 2-years-old and becomes increasingly more accurate between the ages of 2-4 years.

Examining the developmental trajectory for correct temporal ordering of the actions during spontaneous reproduction, this ability appeared to follow a slightly different pattern to that observed for correct action recall (figure 3.4). We observed that temporal order recall was very poor in children aged ≤2 years, with no incremental increase in performance observed with increasing age. An abrupt increase in correct temporal ordering of actions can then be observed around the age of 4 years; 4-year-old children significantly produced more actions in the correct order than all groups aged 2 years and under and matched young adult performance. This recall for temporal ordering of actions then appears to be relatively stable across the ages of 5-7 years, followed by an increase in performance at 8-years-old. Thus, across infancy to middle childhood, spontaneous recall of actions and recall for temporal ordering of those actions appear to follow quite different developmental courses.

An unanticipated finding was that young adult spontaneous temporal order performance does not significantly differ from that of the patients and was significantly worse compared to 8-year-olds. When hypothesising why young adults may be eliciting temporal ordering ability that is not greater than that of children, it may be the case that spontaneous recall for the action sequence where participants are simply told to interact with the puppet in any way that comes naturally to them could seem a strange request for adults and possibly make them feel shy or hesitant to interact with the puppet. Equally, a lack of direct instruction to model the sequence may meant that adult temporal ordering performance is not accurately captured by spontaneous reproduction. Examining young adult performance when instructed to reproduce the temporal ordering of the actions seems to support this hypothesis; young adults perform significantly more actions in the correct temporal order during the instructed condition compared to the spontaneous condition. When provided with instructions, young adults significantly outperform patients and also child cohorts do not reproduce significantly more correct temporal order information than young adults. Therefore, using spontaneous recall within a deferred imitation task may not accurately capture temporal order memory in adults.

Moreover, instructed recall for temporal order does not significantly exceed patients nor match young adults until 5 years of age. However, when the experimenter verbally checks whether the instructed recall produced is the same as that shown to them at demonstration, 4-year-olds significantly reproduce more correct temporal order information than patients and their performance does not significantly differ from that of young adults. The increase in the temporal ordering performance of 4-year-olds when follow-up questions are used to clarify action order may also suggest that language used in the tasks could be underestimating memory for temporal order in this age group. In terms of children younger than 4 years, this finding begs the question as to whether spontaneous temporal ordering ability also does not accurately capture performance in younger children too. Within all groups aged 5 years or over, with the exception of patients, significant increases are observed in the ability to recollect temporal information about the action sequence when given instructions compared to spontaneous recollection. Therefore, it may also be the case that spontaneous recall may also underestimate temporal order memory in children too.

From these results, uncertainty exists as to whether spontaneous reproduction of an action sequence used in typical infant deferred imitation paradigms accurately captures temporal ordering ability. More robust measures could be used in future research in order to ensure that comparisons between age groups are truly reflective of age-related differences in temporal ordering ability. Indeed, previous research has successfully employed the use of eye-tracking to measure memory for object-temporal associations in children and adults (Pathman & Ghetti, 2014; see section 1.2.1.4). Evidence has suggested that eye movements appear to be veridical of implicit hippocampal-dependent memory (Hannula et al., 2007), with eye-tracking successfully employed to study non-verbal cognitive processes from early infancy (Gredebäck, Johnson & von Hofsten, 2009). Perhaps more accurate measures of temporal ordering ability that can be validly applied across the life span (i.e. from preverbal infants to adults) should be utilised in future.

Overall, while acknowledging the caveats outlined in the preceding paragraphs, we observed that memory for actions and memory for the temporal context of those actions appear to follow slightly different developmental trajectories. Whilst memory for actions appears to emerge gradually and stabilises over middle childhood, temporal order recall seems to appear more abruptly at 4 years of age. These results converge with previous studies employing

different methodologies that have also documented that memory for the temporal context of associations emerges at 4 years (Hayne & Imuta, 2011; Cuevas et al., 2015) and continues to develop into middle childhood and beyond (Scarf et al., 2017).

Furthermore, our results which suggest 4 years appears to be a critical age for the emergence of more adult-like temporal order memory are consistent with current knowledge regarding the development of hippocampal circuitry and the processes these neural regions perform (see section 1.2.1.1). Literature suggests that the emergence of more advanced hippocampal-memory processes, such as retention of temporal order information and the ability to bind and retain multiple components of an event to form context-rich episodic memories, occurs due to the development of more complex trisynaptic circuitry within the hippocampal formation (Gomèz & Edgin, 2016). Recent research by Lee, Ekstrom & Ghetti (2014) has also documented age-related increases in the volume of the right CA3 and DG in children aged 8-14 years, with volume in these neural substrates being positively associated with episodic memory performance. Therefore, the development of this more complex hippocampal circuitry extends into later childhood and adulthood. Regarding the specific mnemonic functions of regions within the hippocampal circuitry, the CA1 subfield has been shown to support the forming of temporal and spatial sequences in both rodents and human adults (Chen, Cook & Wagner, 2015; Sellami et al., 2017). However, there is evidence that these sequential associations require multiple exposures to be subsequently encoded in the CA1 subfield of rodents (Nakashiba et al., 2008). In comparison, the DG and CA3 regions within the trisynaptic pathway have been shown to support higher level allocentric spatial memory and the effective encoding of the unique associations between different features of that event (pattern separation; see section 1.1.4.1), both in adult neuroimaging studies (Bakker et al., 2008; Lacy et al., 2011) and rodent studies (Leutgeb et al., 2007).

Relating our findings to current knowledge regarding the ontogeny of more complex hippocampal circuitry and the memory processes they underpin, this may explain distinctions in the emergence of adult-like memory for action information and temporal order information we observed in our age groups. Perhaps the maturation of the monosynaptic pathway and emergence of trisynaptic connectivity is facilitating the increase in memory for action information that we observed at 2 years of age. However, a greater degree of maturation of the trisynaptic circuit in later childhood may be needed to support more complex processing

of episodic events including the ability to recollect temporal order information surrounding events after just one encoding exposure.

Furthermore, increases in the ability to recollect temporal order event information may reflect developmental changes in the prefrontal cortex that occur later in childhood (Ofen et al., 2007; Ghetti & Bunge, 2012). As outlined in section 1.1.5, the prefrontal cortex has been found to support control processes, i.e. strategic control of memory processing, which can aid episodic memory encoding and recollection (Cabeza et al., 2003; Mitchell & Johnson, 2009). If older children are able to engage in control processes and process information in a strategic manner, due to greater prefrontal cortex maturation, this may enable them to elicit superior memory for events and their temporal context. Equally, the prefrontal cortex has been found to play a crucial role in recall of temporal information that compliments hippocampal recall for other components of an experienced event e.g. spatial information. Ekstrom et al. (2011) applied fMRI while participants navigated a virtual reality town and encoded the spatial locations of different shops and the order in which they appeared in the simulation. While similar hippocampal activation was observed when retrieving spatial and temporal information, greater prefrontal cortex activation was present during temporal order memory retrieval. Moreover, deactivation of the pathway between the dorsal hippocampal CA1 subfield and medial prefrontal cortex in the rodent brain has been found to selectively disrupt temporal order memory judgments (Barker et al., 2017). These studies demonstrate that the prefrontal cortex plays a role in memory retrieval for temporal order information surrounding events. Therefore, perhaps greater prefrontal cortex maturation in older children may be providing the benefit of better temporal order memory with increasing age in childhood.

When comparing groups in their ability to correctly recognise actions that were previously demonstrated (section 3.3.3.4), we observe very different performance within the patients. All groups with the exception of 3-year-olds and the patients performed very well (at/almost at ceiling). Akin to the patient group, 3-year-olds demonstrated poor accuracy in correctly recognising previously modelled actions as a result of producing significantly more false alarms than all other groups i.e. they incorrectly identified significantly more false actions as been previously modelled. From this result we would assume that children aged $\leq$3 years would also elicit this pattern of recognition, however this was unable to be tested due to language constraints in younger groups.

In chapter 2, we observed that the patients were able to successfully recognise whether single, visually distinct events had occurred previously in the demonstration video but were impaired relative to controls when they were required to determine whether visually-similar target and lure actions had been previously presented. From this finding it was inferred that perhaps the patients are unable to rely on familiarity-based recognition when judging whether actions had been demonstrated previously (a process argued to be supported outside of the hippocampal formation; Aggleton & Brown, 1999), due to the actions shown being very similar and thus having a great deal of feature level overlap. Therefore, when forced to rely on recollection-based recognition subserved by the hippocampus, this results in the poor recognition accuracy observed in the patients. As the 3-year-old children are demonstrating recognition memory for single actions that is extremely similar to the performance of the patients, this may suggest that 3-year-olds are unable to use familiarity-based recognition to distinguish between the novel (i.e. false) actions and highly similar previously shown actions which may result in retrieval failure when required to engage in recollection-mediated recognition.

Moreover, high rates of false recognition may arise as a result of using gist-based memory retrieval (Reyna & Brainerd, 1995). Gist-based false recognition can be defined as the incorrect recognition of lure items that are perceptually similar to previously encountered items, as a result of failure to retrieve the specific details of an event but just the 'gist' of what occurred during the event (Brainerd & Reyna, 1998). When examining recognition of previously presented words in children aged 6- and 9-years-old, Reyna & Kiernan (1994) observed that the presentation of lures which were highly semantically similar to the targets cued the gist memories of targets, as opposed to verbatim (i.e. specific and detailed) memories of presented targets. Brainerd & Reyna (1998) have also postulated that verbatim based retrieval places larger demands on memory (as specific information about events must be retained) and thus verbatim memories become inaccessible at a faster rate and are more prone to forgetting than gist memories. Perhaps false recognition in the 3-year-olds arose as a result of reliance on gist-based memories for the actions that occurred, due to faster deterioration of verbatim memories and as the high similarity between target and false actions meant that gist-based memory for actions presented was cued.

Alternatively, the high rate of false alarms to novel items in the 3-year-olds may have arose as a result of ineffective pattern separation (see section 1.1.1). This process appears to be

supported by the DG and CA3 subfields within the hippocampal formation (Bakker et al., 2008). Lee et al. (2014) reported that in older children aged 8-14 years old, DG and CA3 volume was found to be negatively associated with greater false item recognition. Whilst there are relatively few studies examining the development of pattern separation in younger children, Ngo, Newcombe & Olson (2018) examined pattern separation abilities in children aged 4-6 years and young adults using a task where participants first encoded pictures depicting different objects and subsequent recognition of previously shown objects was examined when presented alongside a highly similar object at test. The study found that 4-year-olds consistently recognised lures as previously shown, with increases in the ability to discriminate between previously shown objects and lures between the ages of 4-6 years. Equally, 6-year-olds did not correctly distinguish between previously viewed objects and lures above chance whilst young adults did. These studies taken in conjunction may suggest that age related increases in DG and CA3 maturity could be underpinning the ability to accurately distinguish previously viewed objects from highly similar novel objects.

Further research is necessary to verify the neural correlates of this false recognition observed in 3-year-old children when it appears that familiarity cannot be relied upon, in order to determine whether this false recognition occurs as a result of ineffective pattern separation and so reliance on gist-based strategies, which consequently fail in situations where stimuli are visually similar.

In conclusion, this chapter has demonstrated age-related differences in memory for a sequence of actions cross-sectionally across the life-span. Using a deferred imitation paradigm, distinctions between spontaneous action memory and temporal order memory recall were observed between age groups. Memory for actions appeared to emerge between the ages of 2-4 years. Only children aged 4-years-old or over performed equally as well as younger adults and significantly outperformed the patient group. In contrast, all age groups under 3 years performed very poorly on temporal ordering recall. Again, only children aged 4 years and above demonstrated temporal order recall that did not significantly differ from that of young adults. Therefore, while memory for action events appears to emerge gradually throughout the first two years of life, temporal ordering memory does not appear to be evident prior to the age of 4 years. When instructed to reproduce the previously seen action sequence, action memory and temporal ordering memory performance significantly exceeds that of the patient

group between the ages of 4-5 years. Accuracy of recognition memory for actions previously presented also appears to be adult-like from the age of 4-years-old.

Generally, our results are consistent with the literature which argues memory for a sequence of arbitrary events appears to be rudimentary during infancy, begins to resemble adult-like function by 4-years-old and later declines with aging and hippocampal damage. An area of research which has also received relatively little attention is how developmental milestones (and the cognitive benefits that may accompany them) could be playing a role in memory development in early life. Subsequently in chapter 4, I explore whether the acquisition of independent locomotion may be providing later mnemonic benefits for deferred imitation of action sequences.

4. Chapter 4. Moving towards Memory I: Does independent locomotion attainment facilitate memory retrieval for an action sequence in the first postnatal year of life?

Chapter 4 Summary

Independent locomotion (IL) is a major developmental milestone in the latter half of an infant's first year of life. Coincidentally, memory for basic associations appears to emerge around 6-9-months of age, specifically the ability to reproduce previously modelled action following a delay (Collie & Hayne, 1999). Over a decade ago, Herbert et al. (2007) observed that crawling 9-month-olds demonstrated greater memory retrieval for a previously seen action when retrieval cues differ from those present at learning compared to their non-crawling peers. This study associated the acquisition of IL in infants with more flexible memory retrieval. In this chapter, memory for a three-step action sequence was compared between 7.5-month-old infants who had attained IL and their non-locomotive peers (NIL), in order to assess whether this developmental milestone may be influencing changes in memory in the latter half of the first year. Memory was examined using a deferred imitation task whereby the cue and room present at learning either remained the same or were different at test. Performance was also assessed in a follow-up study when aged 9-months-old in a sub-cohort of these infants. At follow-up, memory performance was compared between infants who had acquired IL by 7.5-months-old (IL-IL infants) and infant who developed IL between 7.5-9-months-old (NIL-IL infants). Significant differences were not observed between groups when aged 7.5-months, both in action reproduction and correct temporal ordering. However in the subgroup assessed later when 9-months-old, infants who had attained IL at an earlier age (IL-IL) reproduced significantly more actions than infants who had only recently acquired this developmental milestone (NIL-IL). These findings tentatively hint that the acquisition of IL may be providing some mnemonic benefits in early infancy.

4.1 *Introduction*

Independent locomotion (IL) is a major developmental milestone in the latter half of an infant's first year of life. Attainment of this milestone is mainly referred to as the onset of crawling, which typically acquired around the ages of 7.5-9-months-old (Benson, 1993; Adolph et al., 2011). However, IL can also be achieved through bottom-shuffling and slithering on one's stomach using hands or feet to propel oneself forwards. When an infant first begins to move independently, they are able to enhance their knowledge of the world around them and increase their understanding of how events can occur in a variety of different contexts. Previous literature has linked the attainment of IL with developmental increases in spatial cognition, social signalling and language skills (Campos et al., 2000; Iverson, 2010), with some authors suggesting these changes arise due to the greater visual input acquired through moving oneself through their environment (Iverson, 2010; Kretch et al., 2014).

As outlined in section 1.1.3.3, the hippocampus supports another cognitive function besides episodic memory: the processing of spatial contexts. Research suggests that experience with self-produced locomotion is positively related to performance on spatial search tasks in human infants (Anderson et al., 2013). Studies which have compared the performance of 7.5-9.5 month old infants that are either crawling, non-crawling or non-crawling with experience using a walker have demonstrated that the more crawling experience an infant has, the better their ability to locate a hidden object when its learned hiding location is altered (Horobin & Acredolo, 1986; Kermoian & Campos, 1988). Equally, following training to use a motorised mobility device, a 7-month-old infant with substantial motor deficits resulting from spina bifida demonstrated significant increases in cognitive functioning including memory performance by 12-months-old which improved at a rate greater than the infant's chronological age (Lynch et al., 2009). This collection of findings imply that self-produced locomotion may be providing infants with cognitive benefits. However, do these benefits lend themselves to episodic memory processes? If the attainment of IL is associated with improvements in spatial memory underpinned by the hippocampus, then one could hypothesise that increases in other forms of memory supported by the hippocampus could also occur with achieving this developmental milestone. Therefore, this chapter sought to determine whether the acquisition of IL may be influencing the development of hippocampal memory processes in early infancy.

In chapter 2, 7.5-month-old infants reproduced significantly more previously modelled actions compared to age-matched infants who had not seen the actions being demonstrated, indicative of memory retention for the action sequence after a delay. Previous deferred imitation studies have also observed that infants aged 6-9 months old can reproduce a previously modelled action following a 24 hour delay, compared to age-matched peers who had not seen the target action modelled (Meltzoff, 1988; Collie & Hayne, 1999). Herbert, Gross & Hayne (2007) assessed whether differences in memory existed between crawling and non-crawling 9-month-old infants using a deferred imitation paradigm. Infants were first presented with one of two wooden animal stimuli, in the shape of a cow or duck (figure 4.1A). The experimenter demonstrated the target action to the infant which consisted of pressing a button that made an animal noise and caused LED lights in the animal's eyes to flash. Following a 24 hour delay, infants' ability to successfully imitate the target action was assessed. Infants could be presented with the same stimulus in the same room in which they had been shown the action demonstration, referred to as the 'no change' condition. Alternatively, infants could be assigned to the 'change' condition, whereby the infant was presented with a different stimulus in a different room. Allocation to these experimental conditions was counter-balanced both within- and between-groups according to crawling status. An additional group of infants (half who were crawling; half who were non-crawling) were recruited that did not see the action demonstration and served as naïve controls. This is the equivalent of naïve participants included in chapter 2. Naïve participants were simply presented with one of the stimuli and the experimenter recorded whether or not they performed the target action. In the no change condition, both crawling and non-crawling infants reproduced the target action significantly more than their naïve control group. However, only crawling infants could significantly outperform their naïve control group in completing the target action when tested with the different stimulus in the different context (figure 4.1B). The authors concluded that the onset of IL is associated with superior performance in the ability to flexibly apply memory for an event to a different situation.

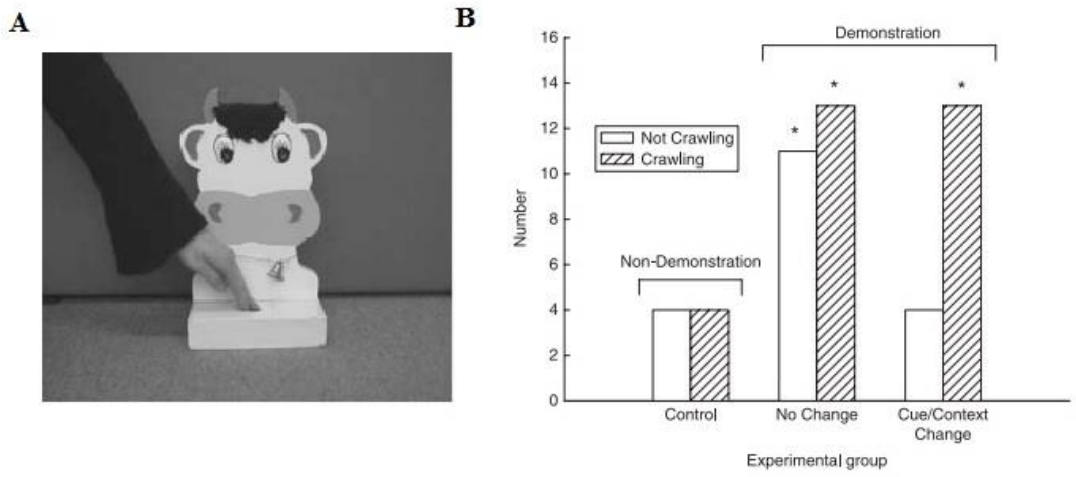

Figure 4.1 A) Example of one of the stimuli used in Herbert et al. (2007). **B)** The number of infants in Herbert et al. that performed the target action following a 24 hour delay.

However, a direct statistical comparison between the crawling and non-crawling infants in the demonstration condition was not reported; each experimental group were simply compared to controls matched on crawling status who did not see the action demonstration prior to test. The crucial comparison between crawling and non-crawling infant performance is absent. Nonetheless, these findings tentatively imply that crawling attainment may be facilitating the ability to retrieve a memory for an action when different cues are present.

It is important to be able to retrieve memories for events in the presence of related but different cues as we rarely experience the same event again in the exact perceptual context. The ability to recall memories from retrieval cues that are not identical to the encoding cues is essential in order for us to apply past experience to future situations that are not perceptually equivalent to the learning incident (Barr & Brito, 2013). Retrieving memories despite changes to the cues originally present at encoding is referred to as representational flexibility (Eichenbaum, 1997). However, one must note that a balance must be achieved between memory specificity and flexibility in order to prevent retrieval errors. Remembering the specific details of the event is important to ensure that correct information is retrieved but a degree of retrieval flexibility is needed to allow past experiences to inform new situations. Conversely, too much flexibility will result in overgeneralisation and recovery of memories inappropriate to the context in which the individual finds themselves.

As outlined in section 1.3.3, studies have shown that infants aged ≤ 12-months have highly specific memory retrieval for associations, whereby changes to the cue or context between encoding and test will disrupt memory retrieval. Using mobile conjugate reinforcement paradigms (Rovee-Collier & Sullivan, 1980), cues, such as the mobile and colour of cot bedding used, must remain the same between learning and test in order for the target action (kicking to move the mobile) to be successfully reproduced by infants aged 2-6 months (Hayne et al., 1986; Butler & Rovee-Collier, 1989; Shields & Rovee-Collier, 1992). Furthermore, retrieval of multi-step action sequences when the cue and context is changed at test is disrupted until 21-months-old using deferred imitation paradigms. 12-month-olds can successfully retrieve an action sequence when the colour of the puppet used is changed between encoding and test, however only 18-month-olds can retrieve the action events when the shape of the puppet is also altered (Hayne et al., 1997; Hayne et al., 2000). When larger visual differences in puppet stimuli exist between encoding and test, such as very distinct facial features, only infants' aged 21-months-old can successfully retrieve the action sequence (Hayne et al., 1997). Thus, cues that can retrieve memories for previously experienced events appear to be highly specific in infants under the age of 2 years, with age-related increases in this ability observed across this developmental period.

To explain these age-related increases in memory retrieval flexibility, the developmental representational flexibility hypothesis (Hayne, 2006) argues that memory performance is reliant on the retrieval cues being matched to the infant's developmental ability and knowledge base. Learmonth, Lamberth & Rovee-Collier (2004) assessed memory for a sequence of actions when the context could be changed in two ways between encoding and test. Firstly the demonstration sequence was performed in front of the infant in a certain room on a specific mat. At test, the mat could differ but the room remained the same, the room could differ while the mat remained the same or both the mat and room could differ. 6-month-olds could tolerate either a change in mat or a change in room and still successfully imitate the target actions, however changing both impaired their memory retrieval. In contrast, 9-month-olds were able to tolerate both a change in mat and room and successfully reproduce the target actions. Although Learmonth et al. do not specify whether infants in their 9-month-old group have achieved IL, Herbert et al. (2007) have demonstrated that crawling experience at 9-months-old appears to enhance memory retrieval for an action event in the presence of two changes to contextual cues (i.e. a change to the cue and room used). Relating these finding to

Hayne's theory, the onset of IL may be an experiential mechanism or antecedent for this age-related increase in memory retrieval flexibility across infancy. Independent locomotion may perform this role by increasing an infant's knowledge base of the world around them.

The proposed role of experience in enhancing the flexibility of memory retrieval is supported by studies demonstrating that increasing experience in different contexts at learning allows infants to elicit greater memory retrieval for previously seen actions than assumed possible for their age. When infants aged 3-6 months learn a target memory across different contexts and with different cues (e.g. that kicking one of their legs will move an overhead mobile with several types of mobiles), the disruption typically caused by changing the proximal cues present between memory encoding and retrieval is decreased (Greco, Hayne & Rovee-Collier, 1990; Rovee-Collier, Greco-Vigorito & Hayne, 1993). Equally, exposing young infants to two stimuli before receiving training to elicit a specific action with one of the stimuli has been found to increase the infant's ability to reproduce the target action when the other stimulus is presented at test (Boller, 1997; Barr et al., 2003). This is referred to as sensory preconditioning (SPC) and is based on the work of Spear and colleagues who first demonstrated this increase in memory retrieval cues following SPC in pre-weaning rat pups (Spear, 1973; section 1.3.3).

Intriguingly, SPC appears to be more rapidly acquired and effective in juveniles compared to adult rats (Kucharski & Spear, 1984; Heyser et al., 1990). Spear and colleagues theorised that SPC may be more effective during infancy, as infants are constantly learning about the world around them and so SPC is a mechanism in which they can acquire associations and knowledge quickly in a unitized way to inform their current needs. However in adulthood, this type of processing may be markedly different once they possess a substantial body of knowledge (Spear, McKinzie & Arnold, 1994).

In line with this work, Rovee-Collier (1996) suggested that infants younger than 6-months-old may demonstrate this heightened sensitivity to context as a functional adaptation in anticipation of developing IL; before infants are able to move themselves around their environment, they must be able to learn where specific stimuli can be located and at what time, in order to acquire knowledge which can inform their subsequent locomotion. Thus

holding events in specific contextual representations may prevent infants from moving themselves to an incorrect location as this would be counterproductive. Once infants have gained experience in a variety of different contextual environments, these associations between different cues and events may be entered into a complex mnemonic network (Rovee-Collier & Cuevas, 2009). As this network grows with the more experience an infant gains, this body of associations becomes increasingly interconnected and as a result permits more flexible memory retrieval. As IL and associative memory abilities are both developing greatly across the infant's first two postnatal years, perhaps only once an infant has obtained a well-established knowledge base then they are able to demonstrate greater memory flexibility and allocentric spatial processing that we observe in older children and adults.

To summarise, research suggests human infants first begin to demonstrate rudiments of hippocampal-dependent memory, including memory for sequences of events, in the latter half of their first year. In chapter 2 we established that when memory for a sequence was examined after a short delay, 7.5-month-olds reproduced significantly more actions than naïve peers; indicative of memory retention. Utilising different infant memory paradigms, there is considerable evidence that increasing an infant's experience of different contexts and environments allows them to retrieve memories of associations in situations that differ from the original learning context at an earlier age (Amabile & Rovee-Collier, 1991; Barr et al., 2003). Furthermore, there is a suggestion in the literature that developing the ability to crawl appears to enable infants to apply memory of a previous event to a different physical context, thus demonstrating less rigid memory retrieval compared to non-crawling infants of the same age (Herbert et al., 2007). Therefore, chapter 4 aimed to examine whether there are significant differences in memory performance between infants who have acquired IL and their non-locomotive peers, in order to further shed light on whether this developmental milestone is acting as an antecedent to changes in memory that emerge in the latter half of an infant's first year.

The deferred imitation task used in chapter 2 was employed but with a distinct methodological alteration. Infants first observed the experimenter performing a three-step action sequence on one of two puppets at learning. At test, the puppet and testing environment could either remain the same as those present at learning, termed the 'same' condition, or

these cues could be different i.e. the 'different' condition. This methodological manipulation allowed us to determine whether differences in memory for a previously modelled action sequence would exist between infants who have achieved independent locomotion (IL) and infants who have not attained this milestone (NIL), both when the retrieval cues remained the same or differed from the encoding cues. Considering the findings of Herbert et al. (2007), it was hypothesised that infants who had achieved IL would reproduce significantly more actions in the different condition (i.e. when the puppet and testing room used were changed at test) than their non-locomotive peers. However, as memory flexibility is not required for the same condition (as both puppet and testing room remain the same), group differences were not anticipated for performance in this condition.

Task performance was examined at 7.5-months-old (when the onset of IL may first emerge), with a subset of this cohort participating in the tasks again at 9-months-old. A total of 95 participants are presented for 7.5-month-old infants in this chapter, with 32/95 of these data sets being presented previously in chapter 2. These 32 infants were all allocated to the 'same' condition. Performance was compared between infants who took part in both phases of the experiment, to assess whether any increases in memory performance between ages are seen with acquisition of IL and if infants who have been self-locomotive for longer have a mnemonic advantage over their peers who acquired this milestone later.

A difference between this chapter and Herbert et al. is that we did not restrict IL to the acquisition of crawling, but included other forms of self-locomotive behaviours which would permit an infant to successfully explore their environment (and thus reap the proposed benefit of greater memory flexibility). The rationale for expanding the criteria for IL is in line with literature that argues that the greater and more varied an infant's early experiences are, the more memory representations have been formed which can then be applied to different experiences (Cuevas et al., 2006), which may be achieved by other self-locomotive behaviours besides crawling.

Another important difference between this chapter and Herbert et al. (2007) was that we assessed memory performance longitudinally between the critical ages of 7.5-9-months-old. This allowed us to track task performance within the key period in which both IL and memory

for previously modelled actions are argued to emerge, in order to determine whether developmental changes within this period may be influencing memory ontogeny in the first year of life.

4.2 *Method*

4.2.1 Participants

Infants who took part had no significant medical problems, were born within 2 weeks (+/-) of their due date and had an Apgar score above 7 at birth. Infants were recruited from local nurseries, children centres, via poster advertisements and social media. Infants received a certificate and a small gift for participating and parents were awarded travelling expenses. All parents provided informed consent for their child to participate, infants were accompanied by their parent at all times and ethical approval was granted by the Faculty of Medical Sciences Ethics Committee at Newcastle University.

The current study contained two testing phases; phase 1 took place when infants were aged 7.5-months-old and phase 2 was a follow-up when infants were aged 9-months-old. At phase 1, infants were grouped by those who had achieved independent locomotion (IL) and those who had not (NIL). At phase 2, infants were grouped at follow-up by those who had originally achieved IL at phase 1 (IL-IL) and those who had attained this developmental milestone between phase 1 and attending follow-up at 9-months-old (NIL-IL). Locomotion status was established initially from parental report prior to taking part in the study and this was confirmed by the experimenter during participation. There were no discrepancies found between parental report and experimenter observation. Infants were deemed to have achieved IL if they were able to move themselves independently for a distance ≥1 metre using any of the following modes of locomotion: crawling, slithering on their stomach using hands or feet to propel themselves forwards or bottom shuffling. Infants who did not meet this criteria were not deemed to have achieved independent locomotion (NIL); this included the attainment of motor functions like rolling and sitting independently.

In phase 1, infants took part when aged approximately 7.5-months-old (+/- 2 weeks). In total, 105 infants attended appointments to participate in the study. Of these infants, n=95

contributed data for the deferred imitation task (10 additional infants took part but were excluded from analysis as they did not touch puppet at test). Infants who had successfully contributed data in phase 1 were invited back to participate in phase 2 when aged approximately 9-months-old (+/- 2 weeks). 68/95 infants tested at 7.5-months-old attended follow-up appointments when aged 9-months-old. 40/68 infants completed the task at both phases of the study. See table 4.1 for a summary of the participants that contributed data during both phases of the study.

Table 4.1 Descriptive statistics for participants that contributed data to the current study, separated by phase 1 and phase 2.

Phase 1 participants (total n=95)		
Group	Gender	Mean age (*SD*)
IL (n=52)	29 F 23 M	7.82 (*.314*)
NIL (n=43)	26 F 17 M	7.72 (*.391*)
Phase 2 participants (total n=40)		
Group	Gender	Mean age (*SD*)
IL-IL (n=21)	12 F 9 M	9.35 (*.290*)
NIL-IL (n=19)	12 F 7 M	9.54 (*.473*)

Note. Mean age in months; SD= standard deviation; IL= independent locomotion acquired group at phase 1; NIL = group that had not acquired independent locomotion at phase 1; IL-IL= infants who had acquired independent locomotion at phase 1 when tested at phase 2; NIL-IL = group that had previously not acquired independent locomotion at phase 1 but have now attained this at phase 2.

4.2.2 Stimuli

The puppet stimulus outlined in chapter 2 was used, along with another puppet in order to create a pair of stimuli (see figure 4.2A). This second puppet consisted of a pink and yellow rabbit that possessed the same modifications as the lamb puppet to enable the experimenter to demonstrate the target actions: a flap that could be lifted to reveal a plastic animal underneath, a removable glove on one of the puppet's hands and purple ribbons sewn onto the back of the puppet's head that could be moved.

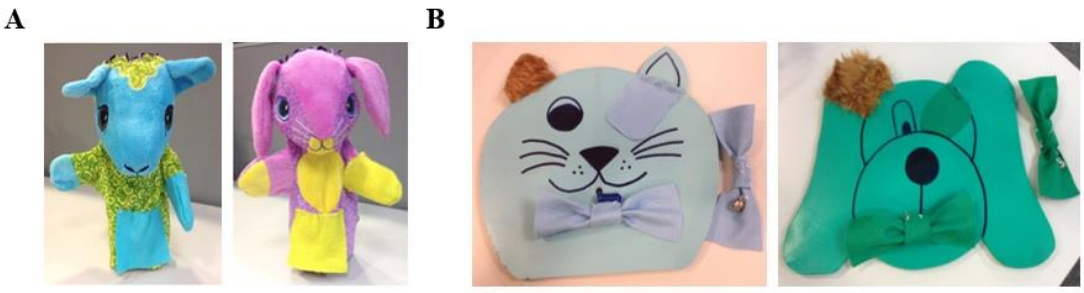

Figure 4.2 A) Puppet stimuli and **B)** Board stimuli used in the current study during the deferred imitation task.

To enable participants to be tested at two points in time during the current study (i.e. at phase 1 and again at follow-up), an additional pair of stimuli were created by the experimenter. These consisted of brightly coloured boards in the shape of a cat and a dog (see figure 4.2B). Each board measured 26cm in width and 23cm in height and contained specific features that were used by the experimenter to demonstrate the target actions during the task: a furry ear (which could be stroked), a felt eye-patch (which could be lifted) and a bow-tie attached to a spring (which could be shaken). The stimuli used (puppets or boards) was counter-balanced between phases so that an infant was tested with a different stimuli set at each study phase.

4.2.3 Procedure

In both phases, the study began with the encoding phase of the deferred imitation task, whereby the experimenter performed the action sequence on either a puppet or board stimulus in the exact manner outlined in section 2.2.3. During phase 1, infants were randomly assigned to either the demonstration condition (n=65) whereby they observed the demonstration of the action sequence upon arrival at the child development lab, or the naïve control condition (n=30) where the action sequence was not shown. In the naïve condition, infants simply interacted with the experimenter in the lab in the absence of being shown the action sequence (depicted on figure 4.3 as a hatched box). Assignment to demonstration or control condition was divided equally within locomotion groups. The infant and their parent were then escorted to the eye-tracking lab where a different task was administered in the retention interval (the faces and places eye-tracking task). This task procedure and results obtained are subsequently outlined in chapter 5. The testing phase of the deferred imitation task then took place (approximately 25-30 minutes after demonstration).

Whilst the procedure for the demonstration of the action sequence remained the same as that presented in chapter 2, the procedure at test differed (see figure 4.3). Participants who had seen the action sequence modelled on a puppet at encoding (referred to as puppet A) in the child development lab could then be assigned to one of two conditions at test. If assigned to the *same condition*, the same cue (puppet A) and context (the child development lab) were presented when assessing spontaneous reproduction of the action sequence at test. If assigned to the *different condition*, a different cue (the other puppet i.e. puppet B) would be presented at test and reproduction would be examined in a different context (within the eye-tracking lab). This manipulation enabled us to assess whether simultaneously changing the cue and context associated with the episodic event (i.e. the action sequence) at encoding would disrupt memory recall and critically, whether infants who have acquired independent locomotion (IL group) will demonstrate differential disruption due to this change compared to infants who have yet to acquire independent locomotion (NIL group). The experimenter recorded whether the infant successfully demonstrated the previously modelled action sequence. Infants assigned to the naïve condition were simply presented with either the puppet or board at test and the experimenter recorded any actions performed within 90 seconds from first touching the stimulus.

Parents also completed a measurement of average pre-morbid intelligence (assessed using Wechsler Test of Adult Reading (WTAR); Wechsler, 2001) and questionnaires regarding their child's developmental progress (see appendix D). This included questions concerning their child's attainment of different milestones alongside personal information like details of medical conditions.

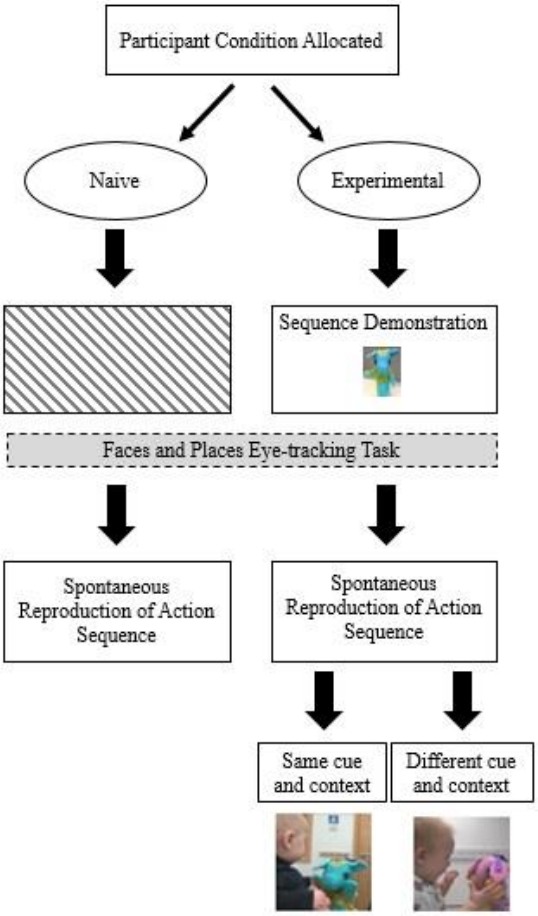

Figure 4.3 Study Protocol.

This procedure was repeated with participants who returned in phase 2, however a different pair of stimuli were used to prevent practice effects. Only infants who had participated in the demonstration condition of the task in phase 1 returned at follow-up. Therefore, there were no naïve control group participants in phase 2.

4.2.4 Statistical Analysis

Spontaneous reproduction of the actions and the order in which they were performed in was scored in the same manner outlined in section 2.2.4. All videotaped sessions were scored by the experimenter and 50% of these recordings were scored separately by an independent researcher. The independent researcher was naïve to the aims of the study, participant condition allocation and IL status. Consistency between observers was then calculated, in terms of the percentage of agreement between observers and inter-rater reliability analysis using Cohen's Kappa (κ) statistic.

Between-group comparisons were then completed, in order to establish whether differences in performance existed between infants who had acquired IL and infants who had not (or had achieved this milestone later in phase 2), and also whether changing the cue and context at test affected memory retention for the action sequence both within- and between-groups. Where data normality had been violated, non-parametric tests were used. Bonferroni correction was applied where multiple comparisons were made.

To further investigate whether attaining IL enhanced memory recollection, a Spearman Rho correlation was conducted to assess whether a relationship existed between the duration of locomotion experience attained with the IL group in weeks and the mean number of correctly imitated actions. This analysis was also repeated to examine whether an association existed between duration of locomotion experience attained and mean temporal ordering score. Nonparametric correlational analysis was used due to the data for duration of locomotion experience being negatively skewed.

4.3 *Results*

4.3.1 Interobserver Reliability

The percentage of agreement between the two observers was 92% for the number of correct actions recorded and 99% for temporal ordering score awarded. Cohen's κ yielded strong inter-rater reliability between observers in both the number of correct actions recorded ($\kappa = .87$, $p<.0001$) and temporal ordering score awarded ($\kappa = .96$, $p<.0001$).

4.3.2 Phase 1

4.3.2.1 Preliminary Analyses

When grouped by locomotion status (IL; NIL), independent t-tests revealed no significant differences between groups in terms of age in months ($t(93) = 1.477$, $p=.143$) and parental WTAR ($t(49) = -.060$, $p=.952$). Kolmogorov-Smirnov tests revealed that the dependent variables (mean number of correctly imitated actions; mean temporal ordering score) were not normally distributed when data normality was examined within each group ($p<.0001$). Since normality was violated, non-parametric tests were used for subsequent analysis.

4.3.2.2 Effects of Stimuli Set Used

To determine whether the stimuli type used (puppets; boards) impacted task performance, within-group comparisons were made using Mann-Whitney U-tests. In the IL group, there was no significant difference in the number of correctly imitated actions when using puppets (mean= 1.22, SD= .801) compared to boards (mean= 1.44, SD= .875; U= 293.5, z= -.880, p= .379, r= -.12). Equally, a significant difference did not exist in mean temporal ordering score within this group when using puppets (mean= .87, SD= .911) or boards (mean= .58, SD= .895; U= 142.0, z= -.683, p= .494, r= -.11). Within the NIL group, no significant difference was observed in the number of correctly imitated actions when using puppets (mean= .95, SD= .785) compared to boards (mean= 1.38, SD= .669; U= 165.5, z= -1.726, p= .084, r= -.26); however, there is a trend for the NIL infants to reproduce more correct actions when using the board stimuli compared to the puppet stimuli. Moreover, no significant difference was found in mean temporal ordering score when using puppets (mean= .63, SD= .876) compared to boards (mean= .86, SD= .795) within the NIL group (U= 78.0, z= -1.245, p= .213, r= -.23). Therefore, stimuli types were collapsed for all subsequent analyses.

4.3.2.3 Mean Number of Correctly Imitated Actions

7.5-month-old performance not separated by locomotion status

To determine whether changing the cue and context between encoding and test effected reproduction of the correct actions in 7.5-month-old infants regardless of locomotion status, we compared performance between the same and different demonstration conditions (figure 4.4A). No significant difference in the mean number of actions reproduced was found between conditions (U= 524.5, z= -.050, p= .960, r= -.01). This finding is intriguing as previous literature indicates that infants aged 7.5-months-old are not able to successfully retrieve memory for actions when the cue and context at test differed from those presented at encoding. Thus, our findings suggest that changing the cue and context did not affect task performance at an earlier age than previously postulated.

Furthermore, we examined whether infants at 7.5-months-old regardless of locomotion group could successfully show evidence of memory retention for the actions compared to infants who had not previously seen the actions demonstrated (figure 4.4B). Indeed, when

demonstration condition was collapsed, infants within the demonstration condition performed significantly more actions compared to naïve peers (U= 585.0, z= -3.398, p= .001, r= -.35).

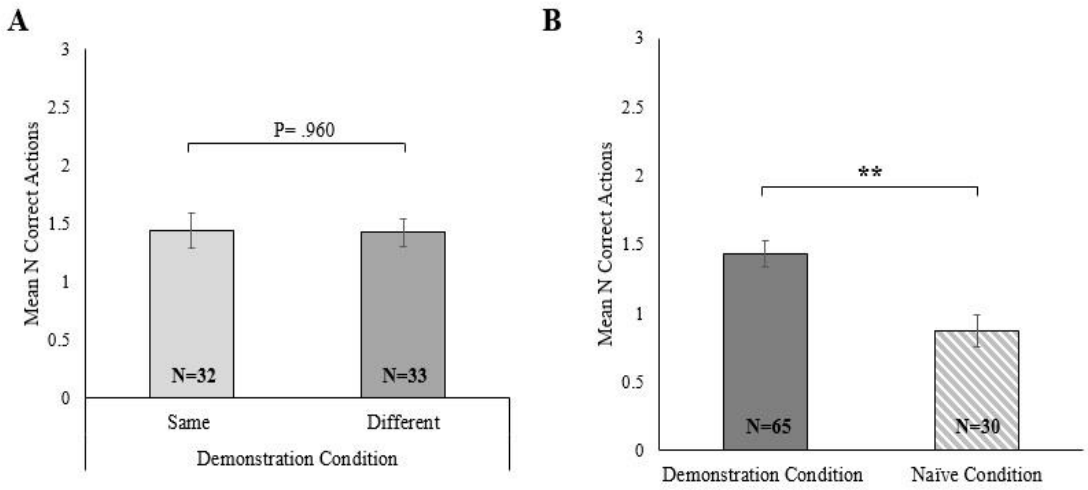

Figure 4.4 Mean number of correctly imitated actions performed by 7.5-month-old infants when **A)** separated into the two demonstration conditions (same; different) and **B)** when demonstration condition is collapsed.

Note. Error bars depict standard error of mean. Asterisks denote significant differences between groups; ** = p<.01.

Performance when separated by locomotion status

To determine whether acquisition of IL impacted upon reproduction of previously seen actions, first comparisons were then made between IL infants and NIL infants in the mean number of correctly imitated actions when infants had previously seen the action sequence demonstrated during encoding (figure 4.5A). No significant difference was observed between IL infants (Mean= 1.53, SD= .874) and NIL infants (Mean= 1.33, SD= .816) when the cue and context had remained the same between encoding and test (U= 119.5, z= -.322, p= .747, r= -.06). Equally, no significant difference was observed between IL infants (Mean= 1.53, SD= .612) and NIL infants (Mean= 1.29, SD= .726) when the cue and context differed between encoding and test (U= 100.5, z= -1.315, p= .188, r= -.23). When demonstration condition is collapsed, we still do not observe a significant difference between locomotion groups in the mean number of correctly imitated actions (U= 449.0, z= -1.047, p=.295, r= -.13).

Moreover, IL infants that had seen the action sequence demonstrated previously performed significantly more actions than peers that were naïve to the action sequence (U= 155.0, z= -2.879, p= .004, r= -.40; see figure 4.5B). NIL infants that had seen the action sequence demonstrated previously did not significantly produce more correct actions than peers that were naïve to the action sequence (U= 137.0, z= -1.856, p= .064, r= -.29). This result cannot be attributed to differences in performance in the naïve condition between locomotive groups; naïve IL infants did not significantly differ in action reproduction from naïve NIL infants (U= 110.0, z= -.095, p=.924, r= -.02). Note though there is a trend for NIL infants in the demonstration condition to produce more actions than their naïve counterparts. Nonetheless, this finding suggests that infants who have acquired locomotion (IL) at 7.5-months-old appear to elicit evidence of memory retention (in that they significantly outperform naïve peers), which is not observed to the same extent in infants who have not achieved independent locomotion (NIL). Note all significant differences observed remain when Bonferroni correction is applied.

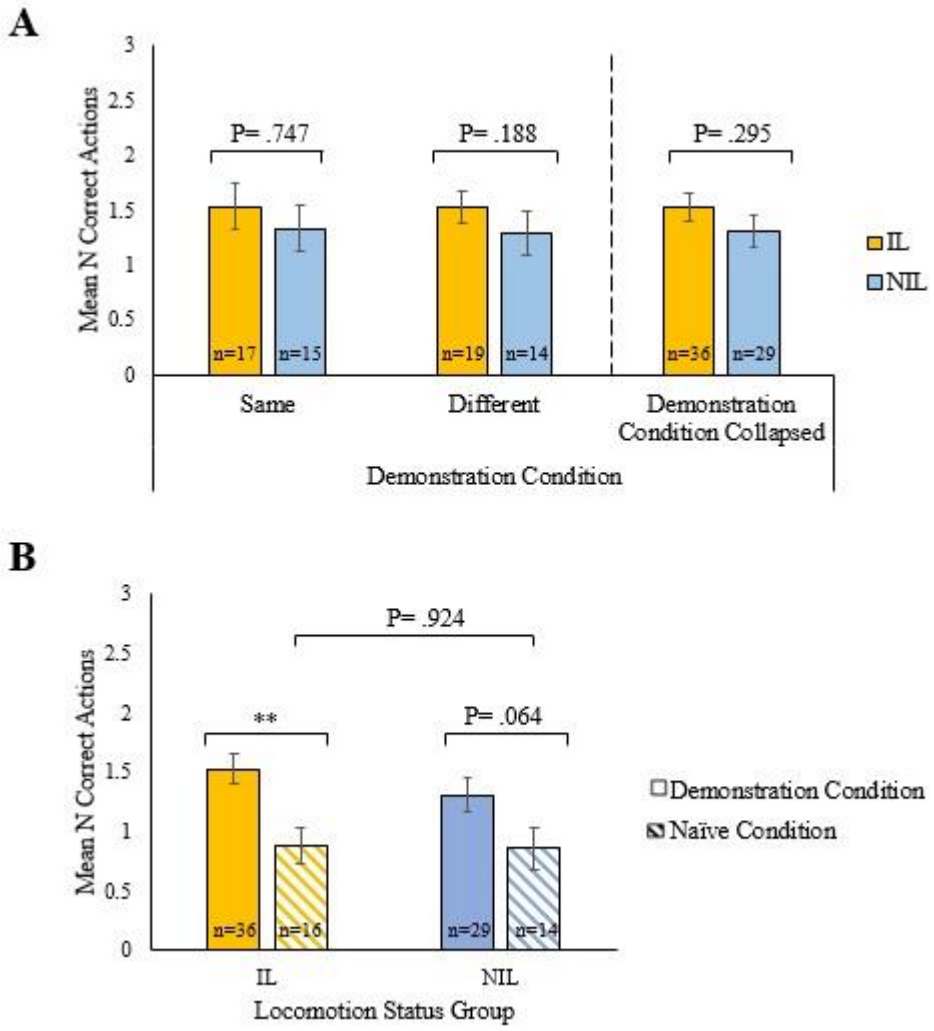

Figure 4.5 Group comparisons in the mean number (N) of correctly imitated action at 7.5-months-old when demonstration condition (same; different) is analysed separately or is collapsed.

Note. Error bars depict standard error of mean. Asterisks denote significant differences between groups; ** = p<.01.

Within the IL group, there was a significant moderate positive correlation observed between the number of correctly imitated actions and the duration of IL experience obtained in weeks (r_S = .381, p = .022; see figure 4.6). Thus, correct action recollection appears to increase as the length of IL experience obtained increases in the group of infants who have achieved this milestone by 7.5-months-old.

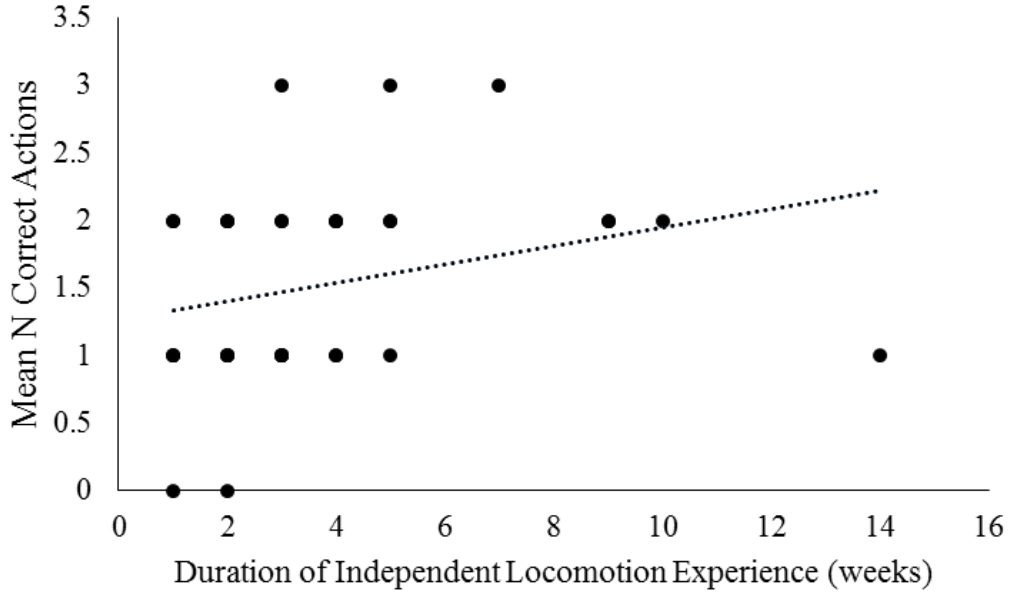

Figure 4.6 Correlation observed between the number of correctly imitated actions and the duration of independent locomotion experience obtained (in weeks) within the IL group.

4.3.2.4 Temporal Order of Actions

No significant differences were observed overall between 7.5-month-olds assigned to the same condition (M=.64, SD=.909) and those assigned to the different condition (M=.68, SD=.846) in their temporal ordering performance (U= 496.5, z=-.448, p=.634, r=.06). Equally a significant difference in temporal ordering performance was not observed between IL infants (M=.62, SD=.977) and NIL infants (M=.67, SD=.859) during the same condition (U=116.0, r=-.471, p=.634, r=-.08). A significant difference was not observed in temporal ordering performance between IL infants (M=.74, SD=.903) and NIL infants (M=.61, SD=.789) during the different condition (U=130.0, z=-.117, p=.907, r=-.02). Therefore, demonstration condition was collapsed for subsequent group comparisons.

Assessing temporal ordering performance between-groups, there was no significant difference observed between IL infants (M=.68, SD=.927) and NIL infants (M=.64, SD=.812) in temporal ordering score (U= 504.5, z= -.250, p= .802, r= -.03). Equally, no relationship was found between duration of locomotion experience acquired and mean temporal order score within the IL group (r_s= .195, p=.294). Acquisition of IL does not appear to offer mnemonic advantage in temporal ordering ability compared to peers who have not achieved this milestone by 7.5-months-old.

4.3.3 Phase 2 (Follow-up)

4.3.3.1 Preliminary Analyses

In the subgroup of infants who took part in both phases of the study, there were no significant differences observed between groups in age during phase 1 (t (38) = -.302, p=.765), nor at phase 2 (t (38) = 1.582, p=.122), or in parental WTAR (t (27) = .369, p=.715).

4.3.3.2 Mean Number of Correctly Imitated Actions

As only a subset of infants that participated at phase 1 attended phase 2, analysis for performance during phase 1 was examined again specifically for this subset of infants. No significant differences were observed between groups in the mean number of correct actions imitated during phase 1; IL-IL and NIL-IL performed exactly the same (U= 199.5, z=.000, p=1.000). Therefore, the trend for the IL group to be performing slightly more actions than the NIL group in phase 1 is not present within this subgroup (see figure 4.7). When comparing performance at phase 2, IL-IL infants performed significantly more correct actions than NIL-IL infants (U= 125.5, z= -2.146, p=.032, r= -.34). This result may suggest that the acquisition of IL earlier may have a downstream effect resulting in greater memory recall for actions previously learnt later at phase 2 when aged 9-months-old.

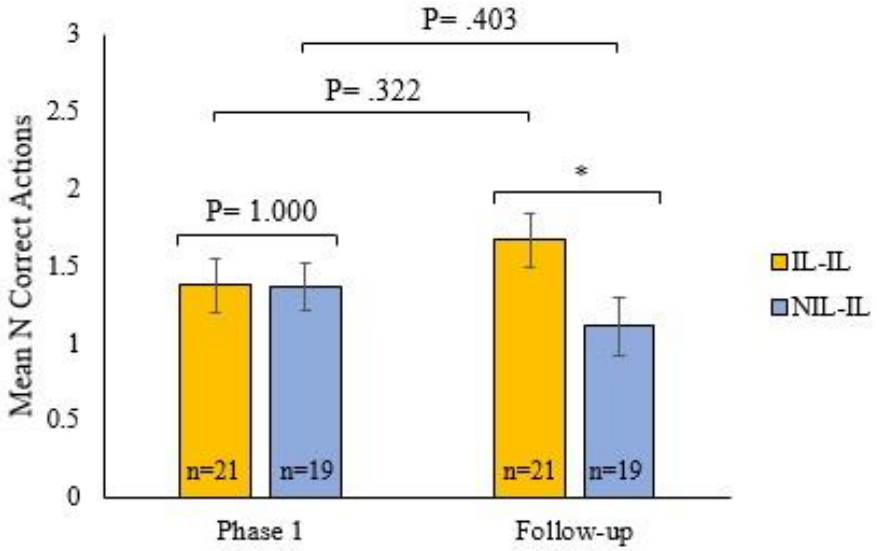

Figure 4.7 Mean number of correctly imitated actions at phase 1 and follow-up for infants when split into groups by locomotion status (NIL-IL; IL-IL).

Error bars present standard error of mean, asterisks denote significant differences; * p<.05. NIL-IL= infants who had not attained independent locomotion at phase 1 but acquired this milestone by phase 2. IL-IL= infants who had achieved independent locomotion at phase 1.

No correlation was observed between the duration of locomotion experience attained (in weeks) by 9-months-old at phase 2 and the mean number of correctly imitated actions overall in this subsample of infants (r_s = .114, p=.483). Equally when infants were split by locomotion group (NIL-IL; IL-IL), no correlation was observed between these variables for both the NIL-IL group (r_s = -.038, p=.877) and IL-IL group (r_s = -.043, p=.853). This may suggest that the apparent greater memory recall for actions observed in the IL-IL group may not be simply attributed to duration of locomotion experience obtained.

4.3.3.3 Temporal Order of Actions

No significant differences were observed between groups in temporal ordering score both at phase 1 (U= 183.0, z= -.502, p= .615, r= -.08) and phase 2 (U= 146.5, z= -1.560, p= .119, r= -.25). Within IL-IL infants we can see a visible increase in mean temporal ordering score between phases 1 and 2 within this sub-cohort of infants (see figure 9). However, this increase is merely a trend (z= -1.814, p=.070), although the strength of this effect is moderate (r= -.40).

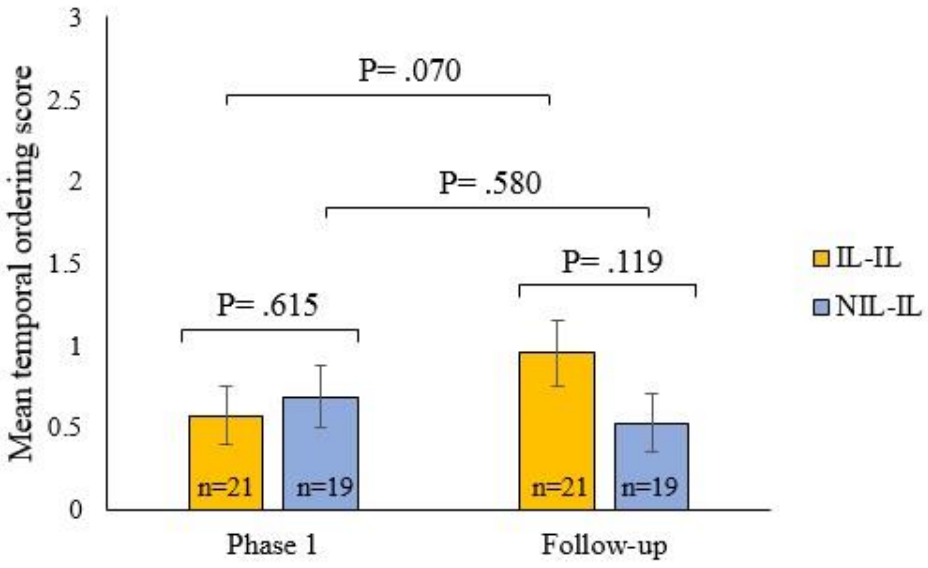

Figure 4.8 Mean temporal order score performance elicited during phase 1 and follow-up, separated by locomotion group (NIL-IL; IL-IL).

Note. Error bars present standard error of mean.

When assessing whether a relationship exists between the duration of locomotion experience attained (in weeks) by phase 2 and temporal ordering score in this infant subsample, again no significant correlation was not observed (rs= .088, p=.589). Equally when infants were split

by locomotion group, neither the NIL-IL group (rs= -.018, p=.943) nor the IL-IL group (rs= .012, p=.957) demonstrated a correlation between duration of locomotion experience attained and mean temporal ordering score.

4.4 *Discussion*

Over a decade ago, research associated the acquisition of IL in young infants with more flexible memory retrieval (Herbert et al., 2007). The current study aimed to determine whether differences existed in memory performance between 7.5-month-old infants who had acquired this developmental milestone and their non-locomotive peers, and to then examine whether earlier acquisition of IL provided later mnemonic advantages when aged 9-months-old.

Using a deferred imitation paradigm, we observed differences in correct action reproduction when infants were separated by locomotion status. At 7.5-months-old, infants who had acquired IL reproduced significantly more correct actions than naïve peers. In contrast, there is only a trend for non-locomotive (NIL) infants of this age to reproduce significantly more actions than their naïve counterparts. Although there is a hint in the data that the IL group are demonstrating better reproduction of the target actions than the NIL group, significant group differences were not found. However, when performance is tracked within a subgroup of infants who participated both when aged 7.5-months-old and 9-months-old, infants who have attained IL for the longest amount of time (the IL-IL group) reproduced significantly more correct actions than infants who acquired this milestone later (the NIL-IL group) at 9-months-old. Hence, these results tentatively suggest that earlier acquisition of IL may facilitate greater memory retrieval for previously seen actions later in the first year of life. When examining memory for temporal order, no differences were observed between groups at either phase of the study. This was expected as chapters 2 and 3 have demonstrated that recall for temporal order of action sequences does not emerge until later in childhood.

As there was not robust evidence that this memory advantage is present when IL has only been recently acquired at aged 7.5-months-old, this suggests that it is not the acquisition of IL per se that results in mnemonic benefits. To determine whether the duration of locomotion experience is the impetus behind greater memory retrieval in the IL groups, the relationship

between the number of weeks of locomotion experience attained and the mean number of correctly imitated actions was examined at both phases of the study. At phase 1, we observed a significant positive correlation between duration of locomotion experience in weeks and the number of correct actions reproduced. This suggests that IL experience (and the postulated increase in knowledge that accompanies this) may be assisting memory recall at this age, consistent with theories proposed by Rovee-Collier and colleagues (Rovee-Collier, 1996; Rovee-Collier & Cuevas, 2009). However, we did not observe a significant correlation between locomotion experience and action reproduction at phase 2. As all infants have acquired IL by phase 2 and the duration of IL experience gained by the NIL-IL group at phase 2 did not differ from the experience that the IL-IL group has possessed at phase 1 (approximately 4 weeks experience), this may explain why no differences were observed between groups at this point. Experience obtained may result in mnemonic advantages in the imminent future and as infants in the NIL-IL group have only recently achieved IL, perhaps they have yet to reap the proposed benefits.

In a similar vein, previous literature has demonstrated associations between acquisition of later forms of IL and other cognitive abilities, such as independent walking attainment and significant increases in productive and receptive language (Walle & Campos, 2014). The physical process of walking provides the infant with richer visual input of their surrounding environment compared to crawling infants; walking infants are able to see the world around them from an upright position compared to crawling infants who are viewing the floor while locomoting unless they periodically stop and crane their neck to view their surroundings (Kretch et al., 2014). Equally, infants who are walking can travel faster and farther than crawling infants and subsequently may engage in more social interactions with caregivers as a consequence, e.g. by reaching caregivers placed in more distal locations (Campos et al., 2000). Therefore, independent walking may provide greater opportunities for learning than crawling. A recent unpublished dissertation (Eason, 2018) examined deferred imitation performance using the task outlined in chapter 2 in relation to the development of independent walking in children aged 1-4 years. Although this study only observed a significant positive correlation between task performance (both correct action and temporal order reproduction) and duration of independent walking experience attained when age was not accounted for; intriguingly, children who had crawled earlier also walked independently at an earlier age. Male temporal order memory was also found to be significantly correlated with walking

experience duration when age was accounted for. Considering these findings in relation to prior research, perhaps crawling is providing a framework of knowledge which is built upon further with the attainment of independent walking and accompanying increases in experience. The apparent mnemonic advantages observed in infants that acquired IL earlier in this chapter may also extend to later walking ability. Longitudinal research exploring the association between memory performance and the development of different forms of IL is needed to shed light on this theory.

Interestingly, we have found that infants at 7.5-months-old regardless of locomotion status performed almost identically between the same and different conditions. Altering the stimuli and environmental context between encoding and test did not significantly change retrieval of correct actions compared to when these cues remained the same. Our results are inconsistent with previous literature which suggests infants at this age should have memory performance disrupted by changing both the cue and context at test compared to when these variables are kept the same (Hayne et al., 1997; Hayne et al., 2000). Although Learmonth et al. (2004) reported that while 6-month-old infants could tolerate either a change in stimuli or a change in environment to successfully retrieve a target action, only infants aged 9-months-old could tolerate changing both. Therefore, the results of Learmonth et al. suggested that at some point between 6-9 months old, infants gain the ability to retrieve memory for target actions when both cue and context differ from encoding conditions. The current study therefore appears to narrow the proposed window for this emergence of greater mnemonic flexibility. It appears to be between the ages of 6-7.5 months old that infants first begin to demonstrate the ability to flexibly retrieve a memory for a sequence of actions using a different cue and context.

Methodological limitations that could potentially have impacted on the magnitude of differences in performance observed between groups were noted. The duration of retention interval used (30 minutes) was shorter compared to previous studies applying deferred imitation paradigms (e.g. 24 hours: Barr et al., 1996; Collie & Hayne, 1999; Herbert et al., 2007). This shorter retention period was employed to prevent subject attrition which may have occurred due to the practicalities of bringing young infants in for study participation on two consecutive days. A greater retention interval (and thus greater memory storage demand) may have highlighted differences between groups more clearly. Furthermore, there was a

trend for the mean number of imitated actions to be slightly higher when using the board stimuli compared to the puppet stimuli. Although the researcher equally distributed the use of each stimuli type both within- and between groups, to ensure that any differences observed between group performances were due to memory retrieval alone and not the stimuli used, the use of two different stimuli types will be avoided in future studies.

As discussed in chapter 1 (section 1.1.3.3), the hippocampus plays a pivotal role in spatial memory. The act of independent locomotion enables the individual to move themselves through space and thus this individual must be able to process spatial contexts accurately in order to successfully locomote through their environment. It is proposed by some authors that this increase in knowledge of the world around us provides young infants with scaffolding to support better memory for experienced events (Rovee-Collier & Cuevas, 2009). Chapter 4 demonstrates evidence of mnemonic advantages in infants that acquire independent locomotion earlier in their first postnatal year of life, compared to their peers who acquire this ability later. These findings are discussed in more detail in chapter 7 (section 7.7) regarding how the role of the hippocampus in processing space may be influencing memory following the onset of independent locomotion.

Overall, this research re-establishes empirical attention to how the acquisition of developmental milestones like IL could be facilitating the development of greater memory retrieval in infancy, when this line of investigation appears to have been largely neglected in the infant literature for over a decade. If the earlier acquisition of independent locomotion does provide some mnemonic advantages by 9-months-old, this begs the questions 1) at what age do these benefits continue to exist and 2) when do infants who acquired this developmental milestone later in life catch up? These are important questions which future research should endeavour to answer, in order to increase our understanding of how environmental experience, and particularly increases in spatial processing abilities acquired from navigating independently through space, may influence the developmental trajectory of hippocampal-dependent memory processes.

5. Chapter 5. When memories are more than a sum of their parts: Face-scene memory representations in infancy, children, adulthood and amnesia.

Chapter 5 Summary

Employing eye-tracking, the ability to encode face-scene pairings and retain these associations has been demonstrated in both infants and adults, with patients with hippocampal damage failing to elicit eye-movements indicative of remembering the pairings. Applications of this paradigm in older children has revealed a pattern of results that suggest this expression of memory for face-scene associations follows a non-linear developmental trajectory. Using a modified version of the faces and places task (Hannula et al., 2007), this chapter assessed memory for face-scene pairs in children aged 7.5-month-old-8 years, young adults, older adults and a cohort of patients with selective hippocampal damage. For 50% of trials, the view-point of the test scene was identical to that presented at learning (identical-perspective trials). For remaining trials, the view-point of the test scene was shifted between learning and test (shifted-perspective trials), which aimed to mimic what occurs when a viewer turns their eyes slightly when viewing a scene. We examined whether participants could tolerate the change in scene perspective, i.e. recognise that it is the same place albeit the view of the scene has shifted slightly, to retrieve the previously formed face-scene association. Firstly, eye movement behaviour was examined in six groups of children aged 7.5-months-old to 4-years-old along with young and older adults to investigate age-related differences in implicit recall of the pairings. All groups, with the exception of 3-year-olds, elicited preferential looking towards the correct face during identical-perspective trials; however the time course and consistency of this behaviour varied across groups. Only 4-year-olds and adult groups demonstrated looking behaviour indicative of remembering the face previously paired with the test scene during shifted-perspective trials. Secondly, memory for the pairings was examined via explicit recall in children aged 5-8 years and adult groups. Shifting scene perspective between learning and test had a detrimental effect on memory for previously presented face-scene pairs in older adults and patients. Memory for shifted-perspective trial pairs was significantly worse than memory for identical-perspective trial pairs in the explicit recall of older adults and patients, with patients also performing significantly worse than adult controls in memory for pairs during identical-perspective trials. Explicit performance matched that of young adults by 5-years-old, for both trial types. Similar to young adults, no differences in recall of face-scene pairs between identical and shifted trials was observed from 5-8 years. Overall these findings suggest that changes in task performance with increasing age in childhood may not follow simple linear progression, but instead may reflect differences in cognitive processing underpinning memory performance at distinct ages. Memories for face-scene pairings may not simply be a sum of their parts, but could rely on scene construction abilities also subserved by the hippocampus.

5.1 *Introduction*

Challenges exist when attempting to measure memory for episodic events across the life-span. A key difficulty lies in the construction of tasks that can measure this type of hippocampal-dependent memory process in both verbal and non-verbal populations, i.e. from pre-verbal infants to language proficient adults. To tackle this issue, tasks must not be reliant on instructions. A solution is the application of eye-tracking, with this methodology being successfully employed to study non-verbal cognitive processes from young infants to adults (Gredebäck, Johnson & von Hofsten, 2009; Feng, 2011). Duration of fixation during eye movement behaviour is argued to parallel looking time measures in previously used infant habituation paradigms, such as visual paired comparison (see section 1.2.1.2). Eye-tracking is considered to be more precise than habituation paradigms, in that data is not reliant on human observers using techniques like video recordings and stopwatches that can be biased by human error and inaccuracy (Oakes, 2012). However it is acknowledged that eye-tracking possesses its own challenges, particularly when this technique is used with young children. Adequate calibration is required in order to ensure accurate data and this calibration is dependent on the ability of the participant to stay still and keep their head within the range of the eye-tracker. Nonetheless, eye-tracking has been found to provide an 'online' measure for the time course of various cognitive processes across the life span (Feng, 2011).

Employing eye-tracking, Hannula et al. (2007) used a task referred to as the 'faces and places' paradigm in which participants viewed arbitrarily paired faces and scenes before being presented with three faces superimposed onto one of the scenes viewed previously (see figure 5.1). Participants were instructed to commit the faces and scenes to memory prior to learning. At test, adult controls elicited rapid disproportionate viewing of the face which had previously been paired with that scene during learning in comparison with the other equally familiar faces. This looking bias was elicited 500-750 ms post-stimulus onset and occurred more than 1000 ms prior to explicit response when asked to identify the face that was shown with that scene earlier. Critically, these patterns of eye movements were not elicited by patients with hippocampal damage. The notion that eye movements are veridical of hippocampal-dependent memory for item-scene relations has been supported by research employing fMRI, where hippocampal activation while viewing a previously presented scene was found to predict subsequent disproportionate viewing of the face which had been presented with that scene earlier, even when explicit retrieval was incorrect in adults (Hannula & Ranganath, 2009).

This evidence has crucial implications, in that eye-tracking methodology can be effectively utilised to study hippocampal-dependent binding processes in participants who are unable to verbally declare their memories, like infants and young children. Indeed, Richmond & Nelson (2009) demonstrated that 9-month-old infants elicited disproportionate viewing of the face that was previously paired with a scene two study trials back when using the faces and places paradigm. The time course of this looking bias also matched that reported in adult controls in Hannula et al (2007) in that this behaviour occurred rapidly in the first 1000 ms post-stimulus onset.

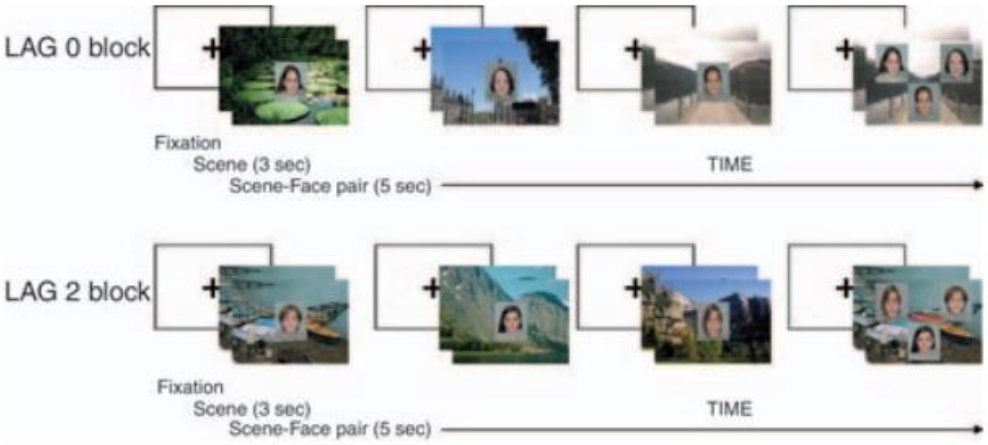

Figure 5.1 The faces and places eye-tracking task used to measure the presence of eye movements veridical of memory for face-scene pairings.

In this example, the top row depicts lag 0 trials and the bottom row depicts lag 2 trials. Each trial block contains three study trials (displaying a face-scene pair), before a test trial which presents a scene with the face it was previously paired with alongside two equally familiar faces. Preferential looking elicited to the face previously paired with the test scene is taken as evidence of memory for the face-scene pair. Taken from Richmond & Nelson (2009).

However, inconsistencies exist in this literature regarding the age at which infants demonstrate eye movements veridical of hippocampal associative memory. While Richmond & Nelson (2009) report that this ability is present from 9-months-old, this eye movement behaviour was absent in 12-month-olds (Richmond & Power, 2014). In a further study, 6-month-old infants were found to elicit preferential looking towards an object previously paired with a scene within the first 1000 ms when such scene was presented again after a 10 second delay but not for immediate recall (Chong et al., 2015). The authors noted that when they had applied strict eye-tracking data inclusion criteria used in previous studies (Richmond & Nelson, 2009; Richmond & Power, 2014), infants had only elicited eye movements towards the correct object during the first 500 ms post-stimulus onset when the test scene was

presented immediately after learning, with no evidence of preferential looking was observed after a 10 second delay.

Adding further perplexity to the picture, Koski et al. (2013) demonstrated that 4-year-old children only elicited eye movement behaviour indicative of remembering the face that was previously paired with the test scene when their explicit verbal recall was correct. Preferential looking also occurred later in the test trial, at approximately 3000 ms post-stimulus onset. This eye movement behaviour was absent when 4-year-olds provided incorrect responses when asked to identify the face previously paired with the test scene (figure 5.2). Therefore, older infants and children appear to lose the ability to produce eye movements veridical of remembering previously presented face-scene pairs and when this behaviour is present, it is far less rapid compared to younger infants.

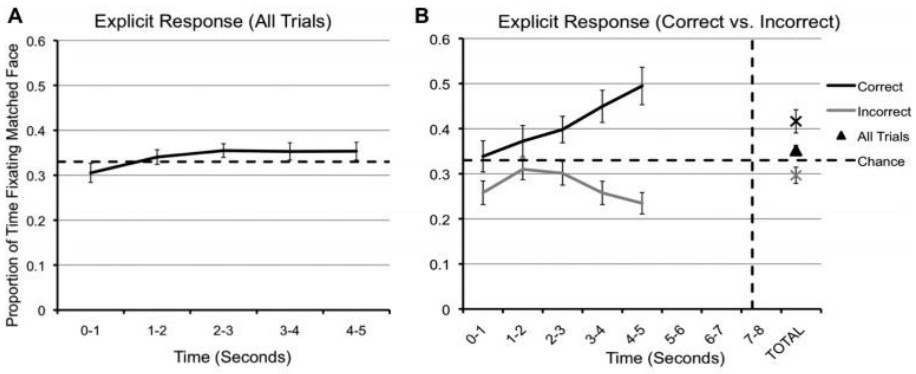

Figure 5.2 Performance of 4-year-olds during the faces and places eye-tracking task in Koski et al. (2013).

A) Proportion of time spent fixating on the correct face during all test trials regardless of whether participants explicitly identified the correct face. **B)** Proportion of time fixating on the correct face when test trials are separated into those where the participants explicitly identified the correct face and test trials where the participant gave an incorrect response.

Recently, Liu (2015) investigated the ability to express memory for face-scene associations through preferential looking and a subsequent recognition test in 7-8-year-olds and young adults. Young adults elicited preferential viewing of the correct face that was significantly above chance across all time bins, with this looking behaviour occurring very early at 250 ms post-stimulus onset. 7-8-year-olds also demonstrated preferential looking falling significantly above chance for all time bins, however this looking behaviour occurred slightly less rapidly at 500 ms post-stimulus onset. Young adults also elicited significantly greater viewing of the

correct face even when later recognition response was incorrect compared to the children. Therefore, by 7-8 years, children are beginning to elicit eye movements more characteristic of adult-like performance.

Overall, this collection of eye-tracking studies indicate that the time course of eye movements veridical of hippocampal binding processes fluctuates across early and middle childhood and does not appear to follow a linear developmental trajectory. Therefore, the rapid onset of preferential looking in very young infants and adults may be underpinned by memory computations that are different from those employed by older children who demonstrate a lack of/ late onset of preferential looking.

A prominent issue with this body of literature is that there are methodological differences between studies (see table 5.1). Particularly of note, studies with older children and adults use instructions and also feature explicit recall for studies face-scene pairs during the task (Hannula et al., 2007; Koski et al., 2013; Liu, 2015). Therefore, it is unfair to make comparisons between preverbal infant and older children/adults' performance when the use of instructions may be enhancing memory in older groups.

Table 5.1 Summary of existing studies which have employed the faces and places eye-tracking task.

Study	Pairings used	Age group(s)	Instructions given?	Lag type	Looking preference present?	Timing of looking preference	Looking preference independent of correct explicit response?	Control for multiple comparisons?
Chong et al. (2015)	toy-scene	**6 months old**	N/A	Lag 0; Lag 2	Yes	*strict data inclusion criteria* - lag 0: 0-500 ms lag 2: none *full sample included*- lag 0: none lag 2: 0-4000 ms	N/A	Yes
Richmond & Nelson (2009)	face-scene	**9 months old**	N/A	Lag 0; Lag 2	Yes	lag 0: 0-250 ms 500-1000 ms lag 2: 500-1000 ms	N/A	No
Richmond & Power (2014)	face-scene	**6 months old & 12 months old**	N/A	Lag 0; Lag 2	Yes- 6 months only	lag 0: 250-500 ms lag 2: none	N/A	No
Koski et al. (2013)	face-scene	**4 years old**	Yes	Lag 0; Lag 1; Lag 2	Yes- correct trials only	3000-5000 ms; no differences between lag	No	No
Liu (2015)	face-scene	**7-8 years old & young adults** (mean age= 20.6 years)	Yes	Does not specify; lag 1 in figure example	Yes	7-8 years: 500-5000 ms young adults: 250-5000 ms	No	Yes
Hannula et al. (2007)	face-scene	**Young adults** ('university students') **& patients with adult-onset hippocampal amnesia**	Yes	Does not specify	Yes- young adults	Young adults: 500-2000 ms patients: none	Yes- young adults	Yes

Applying the faces and places eye-tracking paradigm used in Hannula et al. (2007), the first aim of this chapter was to examine performance on this task across the life span when no instructions were provided to memorise the face-scene pairs. Memory for face-scene pairs was examined from 7.5-months-old-8 years and within young adults, older adults and patients with selective hippocampal damage. This was to permit valid comparisons between the looking behaviour of preverbal infants and more language proficient groups (i.e. older children and adults). Equally, this chapter aimed to determine at what age young children

demonstrate eye movement behaviour that is more congruent with that of adults and investigate how the time course of this looking behaviour progresses with increasing age.

The faces and places task requires the ability to bind together the face and scene in order to remember which face was previously paired with the test scene, with relational memory theorists arguing that the hippocampus is needed for binding together arbitrarily occurring components of an experience (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). Age-related changes in the ability to bind together items and their contexts are observed across the life span (Naveh-Benjamin, 2000; Ghetti, 2017). Thus, we would anticipate that variances between age groups in their memory for the face-scene pairs may arise due to differences in their ability to bind together the distinct parts of the event, i.e. the face and scene stimulus simultaneously present.

However, a large body of evidence indicates that the hippocampus may play a more specialised role in the processing of scenes which appears to exceed this straightforward function of binding items with the scenes or contexts in which they occur. In a series of experiments, Lee and colleagues have demonstrated that the integrity of the hippocampus is required to successfully discriminate between visual scenes where there is a large degree of overlap or when the viewing perspective of a target scene has been altered. In Lee, Bussey et al. (2005) patients with selective hippocampal damage and controls were presented with three images of stimuli on-screen and were required to determine which of the bottom two images in the array was the most similar to the top image (figure 5.3A). The bottom images were morphed versions of the top image with feature overlap between images consisting of between 0-49%. Images belonged to five different categories: faces, objects, outdoor scenes, abstract art and colours. Patients were unimpaired at correctly selecting the most similar image within all categories of stimuli, with the exception of scene images. Performance was significantly impaired when discriminating between images of scenes in the patient cohort, with the number of errors made increasing as the percentage of feature overlap increased.

Similarly, a deficit in the ability to discriminate between scenes when view-point has been altered has been documented in patients with hippocampal damage. In Lee, Buckley et al. (2005), patients with selective hippocampal damage and controls took part in an oddity task

whereby participants were asked to select the odd-one-out from an array of stimuli (figure 5.3B). Stimuli consisted of either virtual reality indoor scenes or unfamiliar human faces and two trial types were used. In same-view trials, three identical images of the same scene or face were presented in conjunction with an image of a different scene or face. In different-view trials, three different view-points of the same scene or face were shown along with another view-point of a different scene or face. Thus, for participants to correctly identify the odd-one-out during scene trials, they must be able to process numerous spatial relations between the individual elements in the scene. Patients with hippocampal damage were severely impaired when discriminating between scenes presented from different view-points to identify the correct odd-one-out. However, this impairment was not observed when patients were viewing scenes from the same view-point and during any condition when using face stimuli.

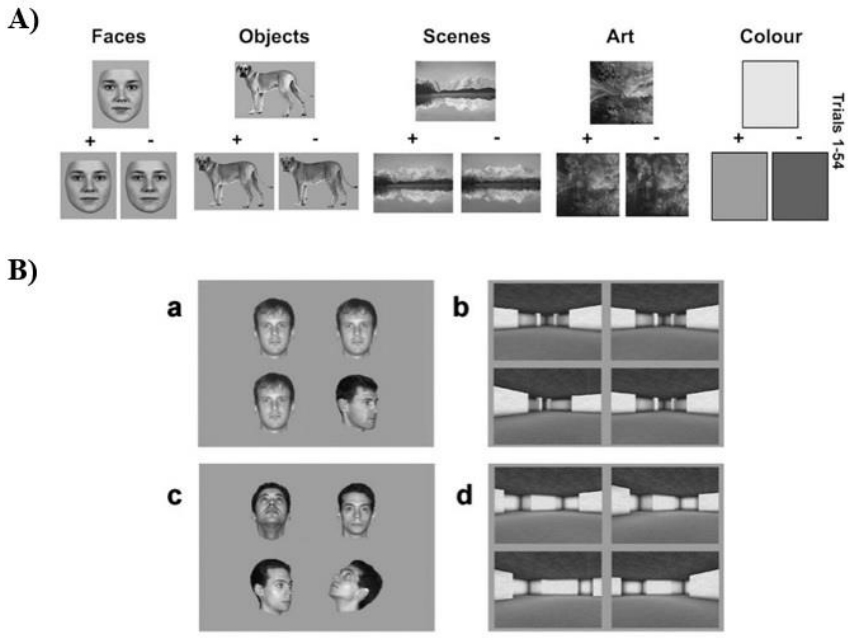

Figure 5.3 Stimuli used to investigate the ability to discriminate between visual images when a large degree of overlap is present in **A)** Lee, Bussey et al. (2005) and **B)** Lee, Buckley et al. (2005).

A= Examples of trials where participants are required to decide which of the two bottom images is the most similar to the top original image for each of the stimuli types. (+) indicates correct response; (-) indicates incorrect response. **B=** Examples of trials where participants determined which image out of a set of four images was the odd-one-out. a) and b) depict same-view trials where three identical images of the same face or scene are presented with a different face or scene. c) and d) depict different-view trials where three different view-points of the same face or scene are shown with a different face or scene.

Equally, deficits in the ability to recognise object or LED light locations in environments where the scene view-point has been shifted have been documented in cases of developmental (King et al., 2002) and adult-onset selective bilateral hippocampal damage (Holdstock et al., 2000). Holdstock et al. (2000) compared the performance of patient YR with matched

controls on a spatial memory task that distinguished between egocentric and allocentric spatial processing abilities. Participants were shown a LED light illuminate briefly in one of numerous potential locations on a board. After delays of either 5, 20 or 60 seconds, participants were asked to indicate where the light had been present on the board. Participants were tested in an egocentric condition, whereby they remained in the same position when they viewed the light at learning, or in an allocentric condition where they moved to another position around the board prior to indicating the light's location. In the egocentric location, patient YR was not impaired relative to controls in her recall of the light locations across all delay periods. In contrast, while patient YR could correctly recall the light location in the allocentric condition following a 5 second delay, YR was significantly impaired relative to controls in accurately recalling the light location following 20 and 60 second delays. Thus, YR demonstrated a selective impairment in recollection of allocentric spatial information across very brief delays, with the reproduction of egocentric spatial information not significantly differing from matched controls.

A later study by King et al. (2002) also demonstrated this greater impairment in allocentric spatial memory compared to egocentric spatial memory in patient Jon. Jon and matched controls viewed objects being successively placed in locations within a virtual reality town square. After a 5 second delay, recognition memory for the object locations was assessed by presenting a target object in the location it had been presented in at learning along with foils (i.e. identical objects to the target object in other locations). Critically, the view-point at test could remain the same or could be shifted (140° shift in perspective; figure 5.4). On same trials, the list length of objects presented was either 4, 7, 10 or 13 objects whereas on shifted trials the list length of objects ranged from 1-5 and 7 objects. Intriguingly, Jon's performance on same trials was equal or better than controls up to list lengths of 7 objects, with his accuracy reducing with increases in list lengths beyond this number. In contrast, Jon performed at chance for recognising a single object location during the shifted perspective trials and was markedly impaired relative to controls on this trial type. Again this study demonstrated deficits in recognition of object locations when view-point is shifted between learning and test even across very short delays following bilateral hippocampal damage.

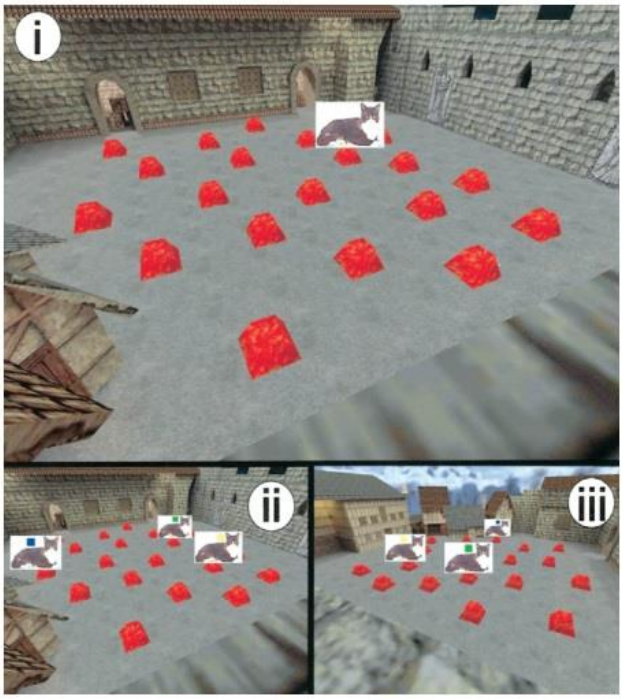

Figure 5.4 Task employed in King et al. (2002) to examine memory for object locations within a virtual reality town square when view-point remained the same or was shifted between learning and test.

i= learning phase; ii= test trial presented from the same view; iii= test trial presented from shifted view.

A theoretical perspective specifically relates the deficits experienced by individuals with hippocampal damage in remembering view-independent locations as a result of an inability to construct spatially-coherent scenes in the mind's eye, referred to as scene construction theory (SCT; Hassabis & Maguire, 2007; see section 1.1.3.5). Based on functional neuroimaging studies that have demonstrated increased hippocampal recruitment during tasks which involve imagining fictitious scenes in the mind's eye in healthy controls (Hassabis, Kumaran & Maguire, 2007; Zeidman et al., 2014), SCT proposes that the hippocampus is critically involved in creating internal representations of scenes which can then be used as a foundation to support recollection of episodic events. Therefore, applying SCT, performance on any task which requires an internal representation of a scene to be formed should be substantially impaired in individuals with bilateral hippocampal lesions (Maguire & Mullally, 2013). Indeed, patients who have sustained such damage have been found to produce more fragmented and less spatially-coherent fictitious scenes compared to matched controls (Hassabis et al., 2007; Mullally et al., 2012a).

A phenomenon that is argued to index scene construction ability is the boundary extension effect, which refers to the notion that when we first encounter a visual scene we construct an internal representation of that scene that extends beyond the image we have in front of us (Intraub & Richardson, 1989; Intraub, 1997). This process is argued to occur as we understand that space and scenes continue beyond the borders of our available visual field and thus is an adaptive process to enable the perceptual experience of a continuous world around us. This phenomenon then leads to a specific memory error, termed the boundary extension error, whereby we remember seeing more of a scene than was previously viewed and so are more likely to experience a physically identical version of the original scene as more close-up but a wider angle version of such scene as more similar or identical to the original scene (Intraub, 2007). As the extrapolation of scenes beyond the borders of a view relies on intact scene construction ability, commitment of the boundary extension error is therefore argued to be indicative of scene construction processes.

The boundary extension effect has been documented in children as young as 3-months-old (Quinn & Intraub, 2007), and found to occur to a greater extent in middle childhood and in older adults relative to young adults (Seamon et al., 2002). Critically, Mullally et al. (2012) demonstrated an absence of the boundary extension error in patients with selective bilateral hippocampal damage across a variety of different boundary extension measures. In a drawing task, patients failed to reproduce scenes from memory which contained more background than the original scene they had studied (figure 5.5). During a rapid serial visual presentation task, when presented with an identical version of a scene shown seconds earlier, patients identified only one third of scenes as 'closer' which was significantly less than healthy controls (who declared 61.1% as 'closer'). Mullally et al. also employed a haptic task whereby participants were blindfolded and instructed to study a selection of items presented in a rectangular border (i.e. a scene) using touch alone and thus no visual input. While remaining blindfolded, the border of the scene was removed and participants were asked to place borders around the items to match the boundaries of the previous scene. The boundary extension error therefore occurs if the participant places the borders of the scene so they are significantly larger in distance from the items (and so more background is included in the scene) than in the original scene. Again, patients failed to produce this boundary extension error and their performance was significantly different from controls whom misplaced the borders at larger distances from the items. Lastly, a scene probe task was employed whereby participants were shown a picture of a visual scene and asked questions describing the scene e.g. outlining objects

present in the scene and describing the type of place depicted in the scene. Patients were unimpaired relative to controls in their responses to these questions. However, when they were asked to describe what the scene might be like beyond the borders of its current view, patients were impaired in their ability to mentally step back and visualise what might come into view if the scene were extended. Overall, these findings indicated that patients were impaired relative to controls in their ability to construct visual scenes beyond the borders of a photograph.

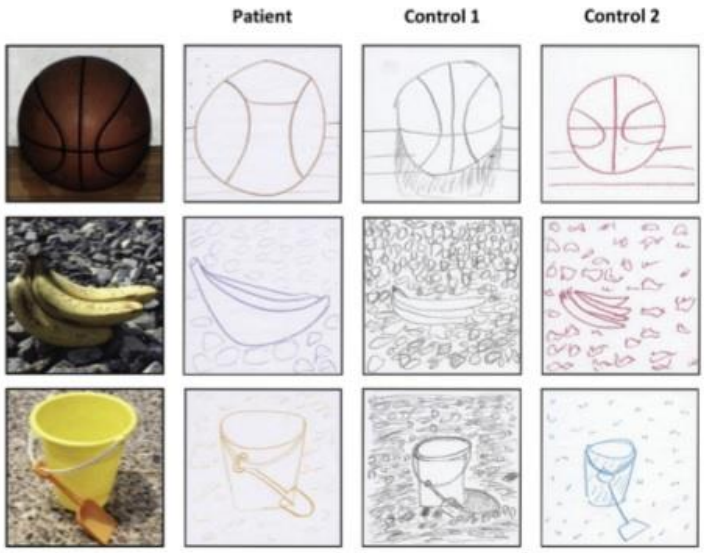

Figure 5.5 Example drawings of a patient and two controls during the boundary extension drawing task within Mullally et al. (2012).

Controls' drawings clearly demonstrate more background than was present in the original image on the far left, indicative of the boundary extension error. In contrast, patients show significantly less boundary extension.

This collection of studies illustrates a selective deficit in the ability to construct internal representations of scenes and extensions of those scenes in patients with hippocampal damage. Applying this research and the assumptions of SCT, perhaps the inability to generate spatially-coherent scenes may underpin the deficits in discriminating between different view-points of the same scene observed in previous literature. If patients with hippocampal lesions are constructing fragmented representations of space and are not extrapolating beyond the borders of such scenes (as indicated by lack of boundary extension error), this may result in the inability to recognise scenes from different view-points. Memories that rely on the hippocampus, such as remembering face-scene associations, may be reliant on more than a sum of their parts, including the ability to construct representations of scenes in the mind.

Therefore, this chapter aimed to also investigate whether the ability to construct extended versions of visual scenes in the mind's eye plays a role in the remembering of face-scene associations. To test this aim, the faces and places task employed in this chapter contained an important manipulation. For 50% of trials, the view-point of the test scene was identical to that presented at learning (identical-perspective trials). For the remaining trials, the view-point of the test scene was shifted between learning and test (shifted-perspective trials). This shift in scene perspective aimed to mimic what occurs when a viewer moves their head/eyes slightly when viewing a scene. The purpose of this modification was to examine whether participants could tolerate the change in scene perspective (i.e. recognise that it is the same place albeit the view of the scene has shifted to the right slightly), to retrieve the previously formed association between that scene and a face. This manipulation allowed us to further previous research to determine whether hippocampal injury causes greater disruption to memory for face-scene associations when participants are required to extrapolate beyond the borders of an image. As differences in scene construction ability are reported across the life-span (as indexed by degree of boundary extension error made; Seamon et al., 2002), we examined whether memory performance on shifted-perspective trials was significantly different compared to identical-perspective trial performance both within- and between- all age groups. This included examining at what age children begin to demonstrate successful and/or adult-like performance on shifted-perspective trials and whether a significant effect of ageing is observed within older adults.

In light of these study aims, three important comparisons were made. Firstly, explicit memory for the previously learnt face-scene pairs was examined between children aged 5-8 years, young adults, older adults and patients when participants had not been instructed to remember the pairings at learning. This would allow us to investigate whether patients with selective hippocampal damage exhibit deficits in their memory for face-scene pairs relative to young and older adults; indicative of this task being reliant on hippocampal memory processes. Making between-group comparisons in memory for shifted-perspective trials allowed us to determine whether healthy ageing and/or hippocampal damage results in poorer memory for face-scene pairs when scene perspective has been shifted between learning and test. Comparisons were also made between the performance of children and all adult groups in order to establish when explicit recall of face-scene pairings becomes adult-like, for both identical-perspective and shifted-perspective trials. Equally, the performance of the child groups was compared to that of the patients, to allow inferences to be made regarding whether

children are demonstrating memory that appears to rely on the hippocampus (as inferred by performance that significantly exceeds that of the patients).

Secondly, eye-movement behaviour during the uninstructed faces and places eye-tracking task was examined in children aged 7.5-months-old to 4-years-old, younger adults and older adults. Note eye-movement data was not obtained for the patient cohort and 50% of older adults due to eye-tracker recording inaccuracies (see section 5.2.4). The presence of eye movements veridical of remembering face-scene pairings (i.e. by denoting preferential looking to the correct face at test) was assessed in the absence of instructions to remember the pairings, in order to determine whether adult cohorts will produce looking behaviour indicative of memory for the face-scene pairs without instructions and so valid comparisons can be made between adult and child performance. Through examining eye movement behaviour in children under 4 years during the modified faces and places task, we could attempt to shed light on the inconsistencies within previous literature regarding the developmental trajectory of looking behaviour indicative of hippocampal-dependent memory processes and investigate at what age children begin to demonstrate successful and/or adult-like performance on shifted-perspective trials.

Lastly, eye movement behaviour and explicit memory recall for face-scene pairs when participants were directly instructed to remember the pairings was examined in all adult cohorts (additional analyses). By administering both the uninstructed and instructed versions of the tasks, we could also examine the effect of instructions on memory performance within our adult groups.

5.2 *Methods*

5.2.1 Participants

Adults with Hippocampal Damage

5 patients with voltage-gated potassium channel complex limbic encephalitis (VGKCC_LE) that resulted in selective hippocampal damage took part in the study. For patient demographics see chapter 2 section 2.2 and appendix A.

Older Adult Controls

Thirty older adults (13 males, 17 females) were recruited as age- and IQ-matched controls to the patient cohort and to determine the effects of healthy ageing on task performance. Participants had a mean age of 65.1 years (SD = 5.7; range = 54-76 years) and did not possess significant medical problems, including neurological and psychiatric conditions. Average intellectual functioning assessed using WTAR was 117 (SD = 4.7). No significant differences were observed between the patients and older adult controls in both age ($t(33) = -.900$, $p = .374$) and IQ ($t(33) = 1.267$, $p = .214$).

IQ-matched Young Adults

Forty-eight young adults (7 males, 41 females) were recruited to examine task performance within a cohort typically assumed to possess optimal memory ability (mean age = 20.1 years; SD = 2.1; range = 18-25 years). Average IQ assessed using WTAR was 115 (SD = 3.7). Young adults did not significantly differ in their IQ compared to both patients ($t(34) = -.507$, $p = .616$) and older adults ($t(59) = 1.795$, $p = .078$). All control participants were recruited from Newcastle University Institute of Neuroscience participant database, Voice North and Newcastle University School of Psychology undergraduate research participation scheme. Participants were compensated with payment or course credits for undergraduate Psychology students.

Infants & Children

A total of 386 children aged from 7.5-months-old to 8-years-old participated (see table 5.2 for individual group descriptive statistics). An additional 82 children had participated however they were not included in the final data set due to: n= 31 lost to inadequate calibration/unable to calibrate during eye-tracking (n=13 7.5-month-olds, n= 10 9-month-olds, n=2 1-year-olds, n=2 2-year-olds, n=3 3-year-olds and n=1 4-year-olds), n= 47 lost to fussiness (e.g. not wanting to sit in the car seat, disengagement from the task, etc.; n=18 7.5-month-olds, n=13 9-month-olds, n=5 1-year-olds, n=5 2-year-olds, n= 4 3-year-olds and n=2 4-year-olds) and n=4 lost to eye-tracking equipment failure (all 9-month-olds).

Children aged ≤4 years were recruited from local nurseries, children's centres and via social media. These participants attended an appointment within the Cognitive Development Lab, Newcastle University, to complete the study. Parents provided informed consent for their child to participate, with each child receiving a certificate and gift for participating and parents were reimbursed for travelling expenses. Children aged ≥5 years were recruited from two local primary schools within the Newcastle upon Tyne area and participated in the study in an allocated slot during their school day. Distribution of study participation forms and information sheets to parents was performed by teaching staff. Permission to collect data on school premises was obtained from the head teacher of each school. Detailed information sheets and consent forms were provided for parents to review and complete. Only children for whom we had received signed consent forms back were allowed to participate. The experimenter also explained to each participant on the day that they were free to withdraw from the study at any time. Ethical approval was granted by the Faculty of Medical Sciences Ethics Committee at Newcastle University.

Table 5.2 Individual group descriptive statistics for child participants.

Note. SD= standard deviation.

Group *(n)*	**Mean age in weeks *(SD)***	**Gender (M/F)**
7.5 months (n=60)	33.0 (*1.086*)	21M 39 F
9 months (*n=58*)	40.61 (*1.820)*	20 M 38 F
1 years (*n=40*)	59.00 (*11.481*)	18 M 22 F
2 years (*n=36*)	106.38 (*13.102*)	15 M 21 F
3 years (*n=37*)	165.76 (*26.551*)	16 M 21 F
4 years (*n=37*)	214.60 (*12.556*)	16 M 21 F
5 years (*n=12*)	270.83 (*15.573*)	5 M 7 F
6 years (*n=41*)	318.51 (*11.608*)	21 M 20 F
7 years (*n=31*)	368.68 (*24.531*)	13 M 18 F
8 years (*n=34*)	427.03 (*14.292*)	17 M 17 F
Total n= 386		**Total M=162 Total F=224**

5.2.2 Stimuli

5.2.2.1 Faces and Places Eye-tracking Task

We utilised the 'Faces and Places' eye-tracking paradigm employed in previous studies with both infants (Richmond & Nelson, 2009) and adults with hippocampal damage (Hannula et al., 2007), to measure whether eye movements that are indicative of relational memory processing existed within each of our cohorts.

Each trial consisted of three study trials followed by one test trial (see figure 6). During study trials, a scene was presented for 3000 ms followed by a face superimposed on top of that scene (i.e. a face-scene pair) for an additional 5000 ms. A different face was presented with each study trial. During the test trial, one of the previously presented scenes was displayed for 3000 ms followed by the three previously presented faces superimposed on top of the scene for a further 5000 ms. The scene presented on the test trial was either from study trial 2 (lag 1; i.e. with one intervening study trial; figure 5.6A) or from study trial 1 (lag 2; i.e. with two intervening study trials; figure 5.6B). This allowed us to examine whether the length of the delay between presentation of the scene at study and test impacted on participant's ability to recognise the face previously paired with that scene. Each trial was preceded by a white fixation cross presented at the centre of the screen for 250 ms on a black background. The position of the correct face (i.e. the face that was previously paired with that scene at study) was counterbalanced across trial blocks so that it could be presented in either the left, right or bottom position within the test trial. The trial block duration was 32 seconds.

Critically, within the task, there were two types of trials. 50% of the trial blocks were the same as those used in Hannula et al., (2007), whereby the scene displayed at test remained the same as the version of that scene presented previously at study. These are referred to as *identical-perspective* trials (figure 5.6A). For 50% of the trial blocks, we made an important modification to the test scene. In *shifted-perspective* trials blocks, the scene presented at test was a shifted view of a previously presented study scene (figure 5.6B). The shifted test scene overlapped 63% on average with the original version of the scene previously presented at study, however the scene now contained a region with novel content (measuring on average 378 pixels x 762 pixels and so equating to 37% of the scene). This shift in scene perspective aimed to mimic what occurs when a viewer moves their head/eyes slightly when viewing a

scene. The purpose of this modification was to examine whether participants would recollect the faces previously paired with these test scenes despite this change in scene perspective. The four conditions (2 lags x 2 scene perspectives) were presented in a random order.

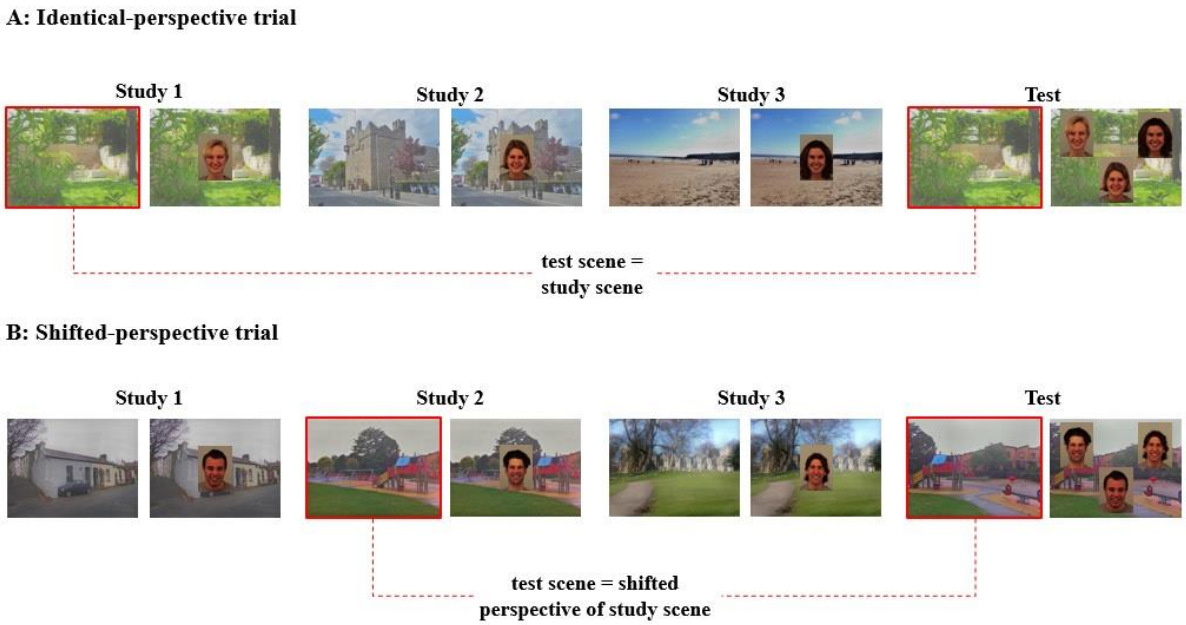

Figure 5.6 Example of identical-perspective (A) and shifted-perspective (B) trial blocks.

Each block consisting of three study trials of face-scene pairs followed by a test trial showing a previously presented scene plus the three faces previously shown in that block. The identical-perspective trial block is presented at lag 2 and the shifted-perspective trial block is presented at lag 1 within this example, however lag type was distributed equally within trial types. At test, the faces were superimposed over the scene in the left, right or bottom location with face position counter-balanced across trial blocks.

To create 24 trials (12 uninstructed trials; 12 instructed trials), 72 images of scenes and 72 faces were used (3 scenes x 3 faces per trial block). Images of indoor and outdoor scenes (1024 pixels x 762 pixels; RGB images) were obtained from the internet (n = 54) or photographed by the researchers (n = 18). Faces were selected from the Karolinska Directed Emotional Faces database (KDEF; Lundgvist et al., 1998), well-validated face stimuli (Goeleven et al., 2008). The faces (n = 48; 24 females; 24 males) consisted of the face and neck of an individual denoting a happy facial expression and wearing a grey plain t-shirt. An additional 24 (12 female; 12 male) face stimuli were selected from the Radboud Faces Database (RaFD), another validated face stimuli set (Langner et al., 2010). These images consisted of an individual with a happy facial expression and wearing a black t-shirt. Each face (562 pixels x 762 pixels) was then paired with a scene. This was performed in a pseudo-randomised manner so that an equal number of male and female faces were paired with indoor

and outdoor scenes. Face-scene pairs were then arbitrarily arranged into sets of three to form 24 trials, with each trial containing faces belonging to the same gender and scene location type (e.g. all indoor scenes). 50% of these trials also contained a fourth scene which consisted of the shifted perspective of one of the three scenes in that trial, which was presented as the test scene during shifted-perspective trials. These trials were programmed into two tasks, each task containing 12 trials, using the software SR Research Experiment Builder.

The SHINE toolbox (Willenbockel et al., 2010) was applied to scene images, using the *sfMatch* function to equate the amplitude spectrum of each scene image with the average spectrum across the set of scene images within each trial block, whilst preserving the amplitude distribution across orientations to ensure image quality was retained. Note that the toolbox was adapted for colour (RGB) images by separately normalizing each colour channel. This normalization process controls for differences in low-level stimulus attributes like luminance, contrast and spatial frequency that participants may use as mnemonic cues, to differentiate between scenes during the task. Face images were not SHINEd.

5.2.2.2 Explicit Memory Tests

To assess explicit memory retrieval of the face-scene pairs following each of the eye-tracking tasks, two memory tests were created; one which contained all the test trials for the uninstructed task and one which contained all the test trials for the instructed task. The explicit memory tests were presented using the software OpenGazeAndMouseAnalyzer (OGAMA) v4.2. Within each test, the test trials were displayed one at a time, with the experimenter asking the participant to identify the face that was previously paired with that scene and pressing the space bar to navigate through the trials. The presentation order of the test trials was randomised within each test.

5.2.3 Apparatus

Eye movement data was obtained at a sampling rate of 500 Hz using the EyeLink 1000+ eye-tracker in remote mode with a 16mm lens and a target sticker placed in the centre of the participant's forehead. Participants were calibrated using a 5-point calibration sequence. The tasks were presented on a 21.5-inch monitor with a refresh rate of 60Hz and a resolution of 1920 x 1080 pixels. Explicit memory tests were presented on the same computer or on a HP Pavilion laptop with a resolution of 1366 x 768 pixels.

5.2.4 Procedure

Participants aged ≤4 years completed the uninstructed faces and places task only, with eye-movement data recorded (see figure 5.7). Participants were seated in a car seat (or on their parent's lap if this was not possible), 50-70cm away from the eye-tracker. A small target sticker was placed on the participant's forehead. The experimenter manipulated the camera until it accurately detected the participant's pupil and corneal reflection from their right eye (left was used if there was difficulty detecting the right). Eye movements were then calibrated and validated by presenting cartoon stars that appeared in a calibration sequence. Due to the limited amount of time that young child participants would tolerate testing conditions, these participants viewed a maximum of eight trials (2x lag 1 identical; 2x lag 1 shifted; 2x lag 2 same; 2x lag 2 shifted). Participants were given no instructions but simply asked to *"watch the images of faces and scenes presented on screen".* Drift corrections were performed between trial blocks (using a cartoon star with sound to attract attention) and calibration was repeated if eye-tracking became inaccurate.

Adult groups completed the tasks in the following order: uninstructed eye-tracking task, uninstructed explicit recall task, instructed eye-tracking task, instructed explicit recall task (see figure 5.7). Adults were seated on a desk chair at the computer station, 50-70cm away from the eye-tracker. Again, a small target sticker was placed on the participant's forehead and the experimenter performed calibration and validation. For adults, the maximum number of trials was 12 (i.e. 3x lag 1 identical; 3x lag 1 shifted; 3x lag 2 same; 3x lag 2 shifted) within the uninstructed task and 12 trials within the instructed task. In the uninstructed task, adult participants were given no instructions but simply asked to *"attend to the images of faces and scenes presented on screen".* All older adults watched the trials on-screen but only 15/30 older adults provided EyeLink eye-tracking data which is included in this chapter. The other half of the older adults group, plus the patients, performed the task using an alternative eye-tracker (The Eye-Tribe Tracker Pro). However, this data was found to be unreliable. This was primarily due to poor calibration, arising from the eye-tracker not tolerating thick glasses lens and as we were unable to re-calibrate participants during the task used with this eye-tracker (OGAMA v4.2 does not permit re-calibration), which led to large periods of missing data within participant's data sets. Therefore, eye-tracking data obtained for these older adult participants and the patients is not presented. All adult participants then completed the uninstructed explicit memory test. Where possible, participants were then asked whether they had *"noticed the background shifted on some trials?"* and their response was recorded.

Following completion of the uninstructed tasks, adult participants then completed the instructed tasks (see figure 5.7). Participants were given the following instructions: *"I'm now going to show you a series of scenes paired with faces. I want you to study them, committing each pair to memory so that you would be able to identify the match between a particular face and background scene when it appears again onscreen"*. Participants completed the eye-tracking task before the instructed explicit memory task was administered.

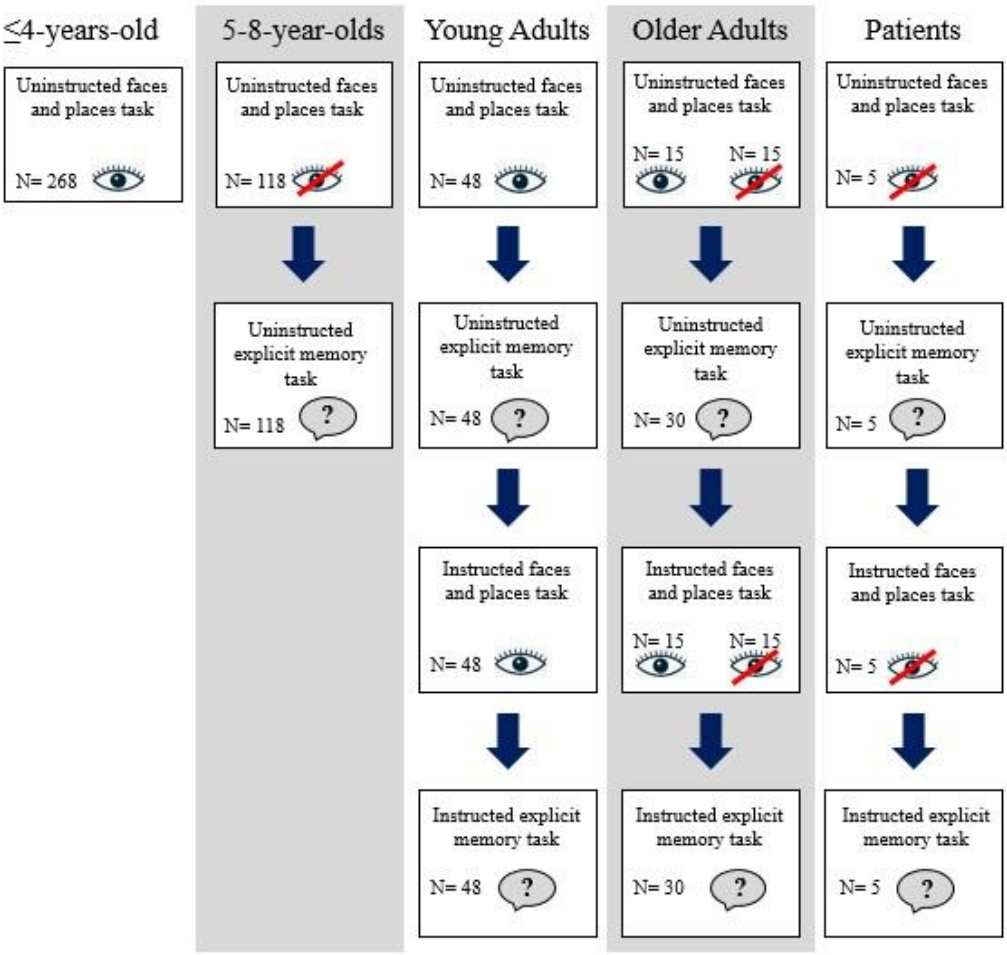

Figure 5.7 Experimental procedure for different participant groups.

Participants could complete a maximum of four tasks; uninstructed faces and places eye-tracking task; uninstructed explicit memory test; instructed faces and places eye-tracking task; instructed explicit memory test. Note. Eye icon depicts eye-tracking data obtained during task; eye icon with red slash indicates eye-tracking data not obtained; speech bubble icon with question mark indicates verbal response acquired.

5.2.5 Statistical Analyses

5.2.5.1 Explicit Memory Tests (Children aged 5-8 years, Young Adults, Older Adults, Patients)

When assessing memory for the face-scene pairs, within-group comparisons for the proportion of correctly identified pairs between identical-perspective and shifted-perspective trial types were made. Between-group effects in the correct identification of face-scene pairings was also examined. This analysis was completed using Wilcoxon signed-rank and Mann-Whitney U tests due to data not being normally distributed.

5.2.5.2 Uninstructed vs. Instructed Explicit Recall (Young Adults, Older Adults, Patients)

The proportion of correctly remembered face-scene pairs during the explicit memory test was examined between uninstructed and instructed tasks conditions in order to establish whether instructions (and so direction to engage in top-down processing) or practice was resulting in this difference in performance. Within each group, the overall proportion of correctly remembered face-scene pairs were calculated. Secondly, performance on individual test trials was scored (1 for correct response, 0 for incorrect response). Performance was then averaged across blocks of 3 or 4 consecutive trials throughout both the uninstructed and instructed explicit memory tests. As data was not normally distributed, Wilcoxon Signed Ranks tests were conducted within groups to establish whether differences in performance existed between each block of trials. This analysis was repeated when trials were separated into identical-perspective and shifted-perspective trials.

5.2.5.3 Eye Movement Behaviour (Children ≤4 years, Young Adults, Older Adults)

A. Inclusion Criteria and Areas of Interest (AOIs)

We applied inclusion criteria to the eye-tracking data based on that used in Chong et al. (2015). For each participant and trial block, we included data in which (1) there was accurate calibration for that trial block; (2) participants looked at both the scenes and faces within each scene during the study and test trial; and (3) participants looked at the faces during the test trial ≥ 1500 ms as a way of ensuring sufficient task engagement. These criteria were adopted to avoid the use of too stringent looking time criteria, as this could particularly bias infant samples to include only participants who take longer to encode, compared to older participants who may engage in faster visual processing and thus more rapid attentional disengagement. Eye-tracking data which met the inclusion criteria were initially processed by

programming areas of interest (AOIs) around the scene and face stimuli presented on-screen. The duration of fixations devoted to each AOI were summed to produce an overall raw looking time (ms) devoted to that AOI.

B. Preferential Viewing of the Correct Face

To determine if participants elicited looking behaviour indicative of remembering the face-scene pairs, we examined whether participants spent significantly longer looking at the face that was previously paired with the test scene. Firstly, the duration of fixations devoted to the three faces were summed. The amount of looking time devoted to the correct face was then divided by this value to obtain the proportion of looking time directed at the correct face for that trial. This proportion of looking time devoted to the correct face was calculated for each successive 250 ms time bin for all test trials (e.g. 0-250 ms, 250-500 ms and so on), to assess the temporal emergence of preferential looking to the correct face. If a participant had missing data for a given 250 ms time bin, the average proportion of looking time that the participant devoted across the time bins within that test trial was interpolated to fill in that missing data point.

Functional data analysis (FDA; Ramsay & Silverman, 1997) was used to increase statistical power to find periods during which looking time directed to the correct faces were greater than chance (i.e. 33%). For this analysis, we interpolated the time bin data with a continuous function. Subsequent analyses were then performed on a single function as opposed to a series of time points. Therefore, multiple comparisons were not performed and thus correction was not necessary. Firstly the time bin data was converted to functional data using B-spline basis functions of order 4 with 12 bases to create a smooth curve of best fit to the data. Based on the functional data, the upper and lower critical t-values (95% confidence interval) were calculated around a reference value. The reference value consisted of the mean proportion of looking time across all time bins across all samples. Time bins whose t-value was greater/less than these critical values were considered significant (two-tailed t-test). This analysis was performed within-groups to determine whether participants devoted a greater proportion of looking time to the correct face that significantly exceeded chance and the time-course of any preferential looking elicited. An alternative version of this analysis was also performed using one-tailed t-tests for independent samples, to examine whether differences in performance were observed between lag types. See appendix E for an example of analysis performed.

C. Scene Viewing Behaviour

We also examined whether differences in looking behaviour existed when viewing identical-perspective and shift-perspective scene previews prior to the faces appearing at test. We assessed whether participants could detect the novel region of scenes during shifted-perspective test trials. To determine this, an AOI was placed around the novel region within each shifted-perspective trial test scene, with a spatially equivalent AOI placed within identical-perspective trials test scene where no manipulation had occurred as a control (Fig 5.12A). The mean proportion of looking time devoted to this AOI was calculated by deducting the sum of fixation times attributed to this AOI from the sum of fixation durations elicited to the whole scene. Furthermore, AOIs were placed around the faces and remaining scene region during shifted-perspective test trials where three faces were superimposed over the test scene (Fig 5.12A). Again, the mean proportion of looking time devoted to the different AOI regions was produced by dividing the looking time devoted to each AOI by the total looking time devoted to all three AOIs. Between- and within-group comparisons were made in terms of the amount of looking time devoted to the novel region or unchanged region when viewing the scene again at test (to determining participant's ability to recollect the scene and thus detect the change to the shifted-perspective scenes), and furthermore whether this looking behaviour changed when the faces were then presented with the test scene (i.e. if looking behaviour to the faces at test was negated by viewing the novel scene region during shifted -perspective trials). Data was skewed and so non-parametric tests were used for all analyses (within-group comparisons: Wilcoxon signed-ranks, between-group comparisons: Kruskal-Wallis tests and Mann-Whitney U-tests).

5.2.5.4 Debrief Question Analysis (Young Adults)

Additional analysis was completed to determine whether differences existed between adults who detected the shift in scene view during shifted-perspective trials and those who did not notice this change during uninstructed trials. Adult participants were grouped by those who had noticed the shift and those who had not. Eye-movement behaviour and explicit recall of face-scene pairs during uninstructed tasks was then compared between these two groups. Between-subject functional data analysis was employed to determine whether differences existed between these groups in their looking behaviour directed to the correct face at test. Independent t-tests were employed to compare the number of correctly remembered face-scene pairs between these groups.

5.3 *Results*

5.3.1 Uninstructed Explicit Memory Test

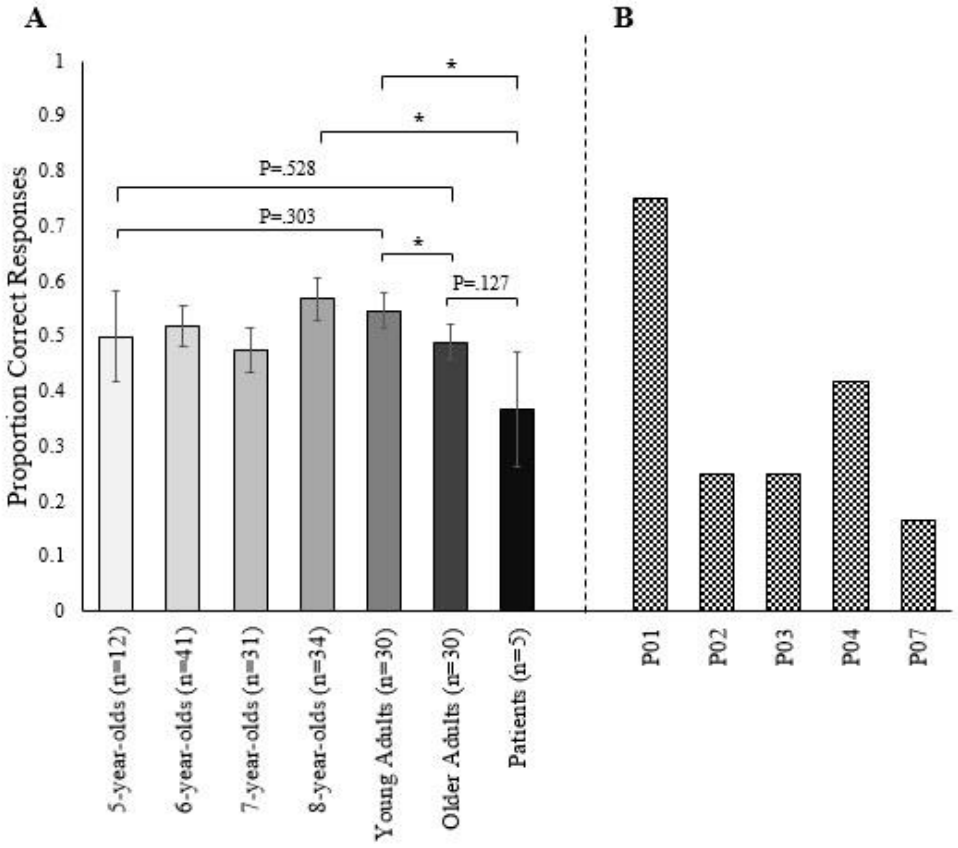

Figure 5.8 Group differences in overall uninstructed explicit recall of face-scene pairs.

A) Overall mean proportion of correctly identified face-scene pairs during the uninstructed memory test and **B)** Individual patient scores for total proportion of correctly identified face-scene pairs. Error bars depict standard error of mean. Asterisks denote significant differences where * p<.05.

When testing overall memory for face-scene pairs when identical- and shifted-perspective trials are collapsed (see figure 5.8A), we observe significantly greater recall performance in young adults compared to patients (U= 48.0, z= -2.297, p= .022, r= -0.34) and older adults (U= 486.0, z= -2.426, p= .015, r= -0.28). This suggests an overall decline in recall for face-scene pairs with healthy ageing and hippocampal damage. Although note these differences are low to medium in effect size. We observed that 5-year-olds were able to match older adult (U= 157.5, z= -.631, p= .528, r= -.09) and young adult performance (U= 232.5, z= -1.031, p=.303, r= -.13). However, it was not until 8-years-old that children could significantly identify more correct pairs than patients (U= 38.5, z= -2.006, p= .045, r= -.32).

Markedly, we did not observe a significant difference between older adult and patient performance (U= 43.0, z= -1.525, p= .127, r= -0.26). When viewing individual patient performance (figure 5.8B), P01 demonstrated superior memory performance compared to the other patients (SD = .48 above the patient group mean). Considering this unanticipated finding, this analysis was repeated with P01's data excluded. With this exclusion, we now found that patients' performance was significantly lower than older adults (U = 15.0, z = -2.434, p = 015, r= -0.42). It is still at 8-years-old that children remembered significantly more pairs than the patients, even with the exclusion of P01 (U= 13.5, z= -2.667, p=. 008, r= -.43).

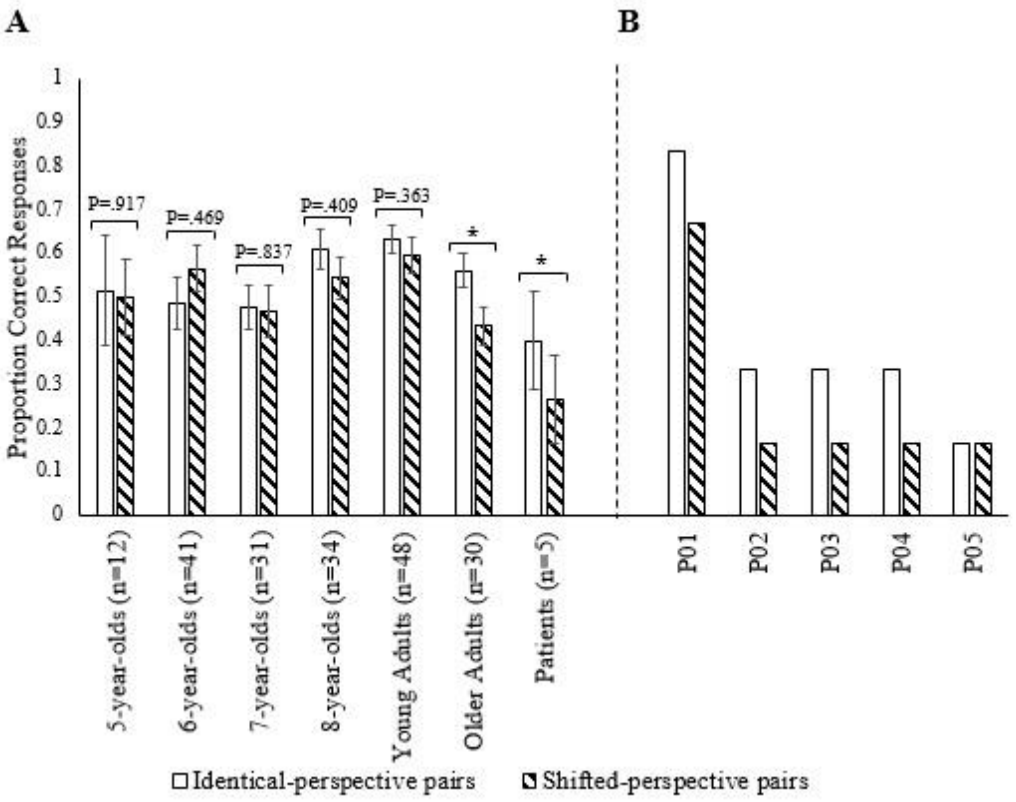

Figure 5.9 Group differences in uninstructed explicit recall of face-scene pairs when separated by trial type. **A)** Mean proportion of correctly identified face-scene pairs when performance is separated into identical-perspective and shifted-perspective trial pairs and **B)** Individual patient scores for correctly identified face-scene pairs separated by scene perspective type. Error bars depict standard error of mean. Asterisks denote significant differences where * p<.05.

When we examined whether shifting the perspective of a scene at test impacted on subsequent memory retrieval for the face previously associated with that scene, here we observed clear distinctions in memory performance within-groups (figure 5.9A). Critically, memory for pairs presented was significantly worse during shifted-perspective trials compared to identical-

perspective trials in both older adults (z= -2.520, p=.012, r= -0.46) and patients (z= -2.000, p=.046, r= -0.89). This was not observed within 5-year-olds (z= -.105, p= .917, r= -.03), 6-year-olds (z= -.725, p= .469, r= -.11), 7-year-olds (z= -.205, p= .837, r= -.04), 8-year-olds (z= -.826, p= .409, r= -.14) nor young adults (z= -.910, p=.363, r= -0.13). Hence, these results suggest that ageing and damage to hippocampus specifically impacts on the ability to remember associations between faces and scenes when scene perspective has been modified.

Moreover, young adults remembered significantly more face-scene pairs during shifted-perspective test trials than both patients (U = 42.5, z = -2.397, p = .017, r= -0.33) and older adults (U= 493.0, z= -2.370, p= .018, r= -0.27). This finding, combined with the result that patients and older adults elicit poorer memory for face-scene pairs during shifted-perspective trials compared to identical-perspective trials, may advance support for the hippocampus being attuned to tasks that require spatial processing, due to differences in memory being observed between trials that require additional spatial processing alongside memory retrieval (i.e. shifted-perspective trials) compared to trials where scenes presented are identical at learning and test (i.e. identical-perspective trials).

Although older adults demonstrate poorer memory for face-scene pairs during shifted-perspective trials compared to young adults, differences did not exist between these groups in performance on identical-perspective trials (U= 587.5, z= -1.394, p=.163, r= -0.16). In addition, young adults demonstrated significantly better recall for pairs during identical-perspective trials than patients (U= 56.5, z= -1.973, p=.048, r= -0.27; although this difference was low in effect size which may reflect low sample size within the patient cohort). These results suggest that although healthy ageing possibly reduces older adults' ability to remember face-scene associations when the scene perspective has been shifted at test, their memory performance does not appear to be largely different from that of younger adults when the scene view remained the same.

Again, we did not observe a significant difference in memory between patients and older adults when performance was examined separately for both identical-perspective (U=41.5, z=-1.619, p=.105, r= -0.27) and shifted-perspective trial pairs (U=40.0, z=-1.688, p=.091, r= -0.29). P01 performed much better than the other patients (SD = .43 above the patient group

mean for identical-perspective and SD = .40 above the patient group mean for shifted-perspective trials), although note that P01 exhibited better memory for identical-perspective compared to shifted-perspective pairs in accordance with the other patients (figure 5.9B). When P01's data is excluded, patients demonstrate significantly poorer memory compared to the older adult group in both the identical-perspective pairs (U= 14.5, z=-2.497, p=.013, r= -0.43) and shifted-perspective pairs (U=16.0, z=-2.409, p=.016, r= -0.41). Thus, these findings suggest that task performance is significantly impacted by hippocampal damage compared to age-matched controls both with and without scene perspective manipulation occurring at test, with the exception of P01.

5.3.2 Uninstructed Eye Movement Behaviour

5.3.2.1 Data Inclusion

The inclusion criteria for fixation data outlined above was applied to the raw eye-tracking data. Table 5.3 displays trial data contributed by each group. Note the percentage of trials watched within the child groups is similar to those observed in previous developmental studies that have used eye-tracking paradigms (e.g. Richmond & Nelson, 2009: 55%; Richmond & Power, 2014: 48%).

Table 5.3 Individual group data for number (n) of test trials included in analysis. Note. SD= standard deviation.

Group	% Trials Included	Mean N trials included (*SD*)
7.5-months-old	43.75%	3.50/8 trials (*1.900*)
9-months-old	50.25%	4.02/8 trials (*1.959*)
1-years-old	41%	3.28/8 trials (*1.826*)
2-years-old	47.63%	3.81/8 trials (*2.039*)
3-years-old	48.63%	3.89/8 trials (*1.712*)
4-years-old	57.75%	4.62/8 trials (*2.165*)
Young Adults	98.42%	11.81/12 trials (*0.607*)
Older Adults	96.08%	11.53/12 trials (*1.600*)

5.3.2.2 Attention during Learning

Looking time during study trials was >60% for all groups, in terms of attending to the scenes presented alone (7.5-month-olds: 74.20%, 9-month-olds: 69.51%, 1-year-olds: 67.47%, 2-year-olds: 71.59%, 3-year-olds: 72.71%, 4-year-olds: 71.92%, young adults: 87.19%, older adults: 87.93%) and the face-scene pairs (7.5-month-olds: 67.11%, 9-month-olds: 60.04%, 1-

year-olds: 60.08%, 2-year-olds: 65.46%, 3-year-olds: 69.82%, 4-year-olds: 69.93%, young adults: 89.91%, older adults: 90.19%). Thus, all groups showed evidence of attention during study trials.

To determine whether any subsequent within-group differences observed in looking behaviour at test between identical-perspective and shifted-perspective trials could be attributed to differences in the amount of attention devoted at learning, the proportion of total looking time devoted to face-scene pairs at study was compared between identical-perspective and shifted-perspective trials (see table 5.4). Wilcoxon Signed-Ranks tests were used due to data being positively skewed. No significant differences were observed in looking time elicited to identical-perspective and shifted-perspective face-scene pairs at study, with the exception of 1-year-olds and 2-year-olds that devoted significantly more attention on-screen during identical-perspective trials compared to shifted-perspective trials. However, when Bonferroni correction is applied to correct for multiple comparisons (alpha level of 0.00625 adopted), these differences cease to remain significant. Hence, these results suggests that any within-group differences observed in looking behaviour between identical-perspective and shifted-perspective test trials cannot be attributed to the amount of attention devoted at learning.

Table 5.4 Within-group comparisons for the mean proportion of attention devoted to face-scene pairs at learning during identical-perspective and shifted-perspective trials.

Note. Bold font denotes significant differences in the proportion of looking time devoted to face-scene pairs between the two trial types ($p<.05$).

Group	Proportion looking time identical-perspective pairs (*SD*)	Proportion looking time shifted-perspective pairs (*SD*)	Wilcoxon Signed-Ranks Statistics
7.5-months-old	.70 (*.175*)	.65 (*.186*)	Z=-1.667, p=.097, r=-.22
9-months-old	.62 (*.164*)	.58 (*.215*)	Z=-1.339, p=.181, r=-.18
1-years-old	.64 (*.168*)	.56 (*.199*)	Z=-2.309, **p=.021**, r=-.37
2-years-old	.69 (*.158*)	.63 (*.167*)	Z=-2.391, **p=.017**, r=-.39
3-years-old	.72 (*.142*)	.69 (*.146*)	Z=-.852, p=.394, r=-.14
4-years-old	.71 (*.169*)	.69 (*.165*)	Z=.913, p=.361, r=-.15
Young Adults	.91 (*.039*)	.89 (*.063*)	Z=-.918, p=.359, r=-.13
Older Adults	.90 (*.044*)	.89 (*.042*)	Z=-1.224, p=.221, r=-.32

5.3.2.3 Preferential Viewing of the Correct Face

Firstly, we performed functional data analysis within-groups to examine whether the proportion of looking time devoted to the correct face at test significantly differed depending on lag for each of the trial types (identical-perspective, shifted-perspective). Once time-bin data was converted into functional data for each trial type, the critical value for establishing one-tailed independent samples comparisons was calculated around a reference value from the functional data. Within each trial type, the difference between lags in the proportion of looking time elicited to the correct face was then compared to the critical t value obtained. From this analysis, no significant differences in looking time were observed between lag type in both identical-perspective and shifted-perspective trials. This was the case within all groups. Therefore, lag types were collapsed for all subsequent analyses.

Identical-Perspective Trials

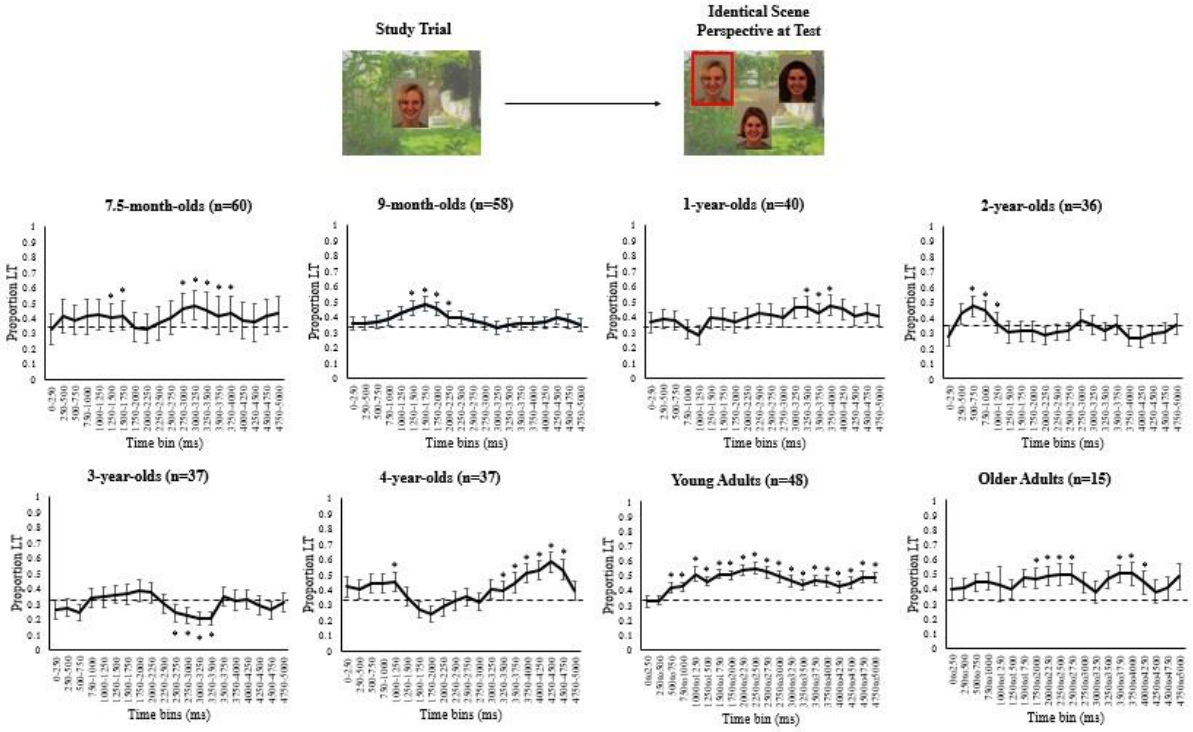

Figure 5.10 Mean proportion of looking time (LT) devoted to correct face (example outlined in red) during test trials on identical- perspective trials, separated into 250 ms time bins.

Bins where the proportion of looking time exceeds the higher critical t-value during functional analysis are marked by asterisks. Chance performance (.33) is indicated by the dashed line. Error bars indicate standard error of the mean.

During identical-perspective trials, young adults devoted most of their looking time to the correct face at test; preferential looking directed to the correct face emerged early and endured

throughout test trials (500-5000 ms). Preferential looking elicited towards the correct face was observed in the eye movement behaviour of older adults, which was clustered into two discrete time periods (1750-2750; 3500-4250 ms). Thus, adults demonstrate eye-movements indicative of implicitly remembering face-scene associations when instructions to memorise the associations were not provided.

All child groups, with the exception of 3-year-olds, demonstrated preferential looking towards the correct face at test. However, the time course of this looking behaviour appears to differ with age. 7.5-month-olds showed preferential looking to the correct face during two distinct time bins within the identical-perspective trials (1250-1750 ms; 2750-4000 ms). 9-month-olds devoted preferential looking towards the test face early on during the test trials (spanning 1250-2250 ms). 1-year-olds showed preferential looking towards the end of the test trials (spanning 3250-4000 ms). Preferential looking was observed early during the test trials in 2-year-olds (spanning 500-1250 ms). 4-year-olds elicited preferential looking towards the correct face at test during the time bin spanning 1000-1250 ms and later on in the test trial (3250-4750 ms). In contrast, 3-year-olds elicited eye movements that were significantly lower than the lower critical t value for time bins spanning 2500-3500 ms.

Shifted-Perspective Trials

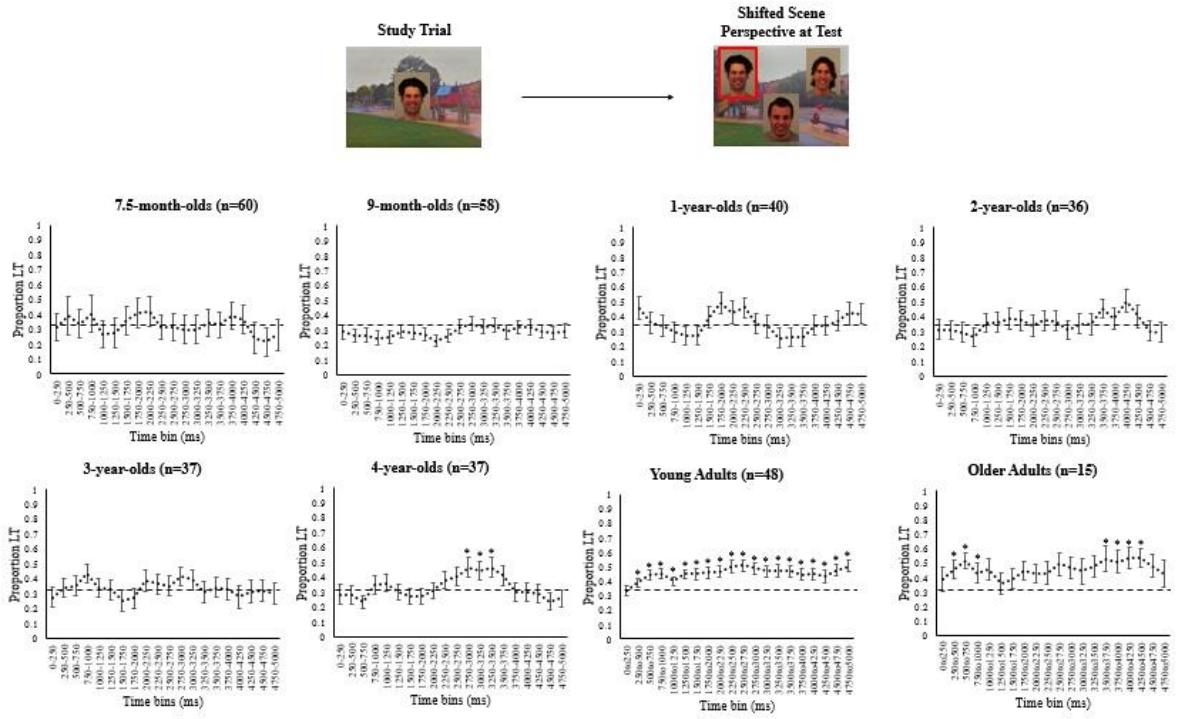

Figure 5.11 Mean proportion of looking time (LT) devoted to correct face (example outlined in red) during test trials on identical- perspective trials, separated into 250 ms time bins.

Bins where the proportion of looking time exceeds the higher critical t-value during functional analysis are marked by asterisks. *Note*. Chance performance (.33) is indicated by the dashed line. Error bars indicate the standard error of the mean.

During shifted-perspective trials, young adults elicited significant preferential looking towards the correct face during the majority of time bins at test (250-5000 ms). Older adults elicited preferential looking sporadically during two clusters of time bins which were present very early post-stimuli presentation (250-1000 ms) and towards the end of the shifted-perspective test trials (3500-4500 ms). Therefore, we can infer that adult groups demonstrated eye movements indicative of successfully remembering the face that was previously paired with the test scene, both when the scene perspective remains identical to its presentation at study (figure 5.10) and when the scene perspective is shifted at test.

In contrast, preferential looking towards the test face that significantly exceeded chance was observed only within the looking behaviour of 4-year-olds (spanning 2750-3500 ms) within the child groups. Shifting the perspective of a scene between study and test seems to eradicate preferential looking to the correct face in children under 4 years.

5.3.2.4 Scene Viewing Behaviour

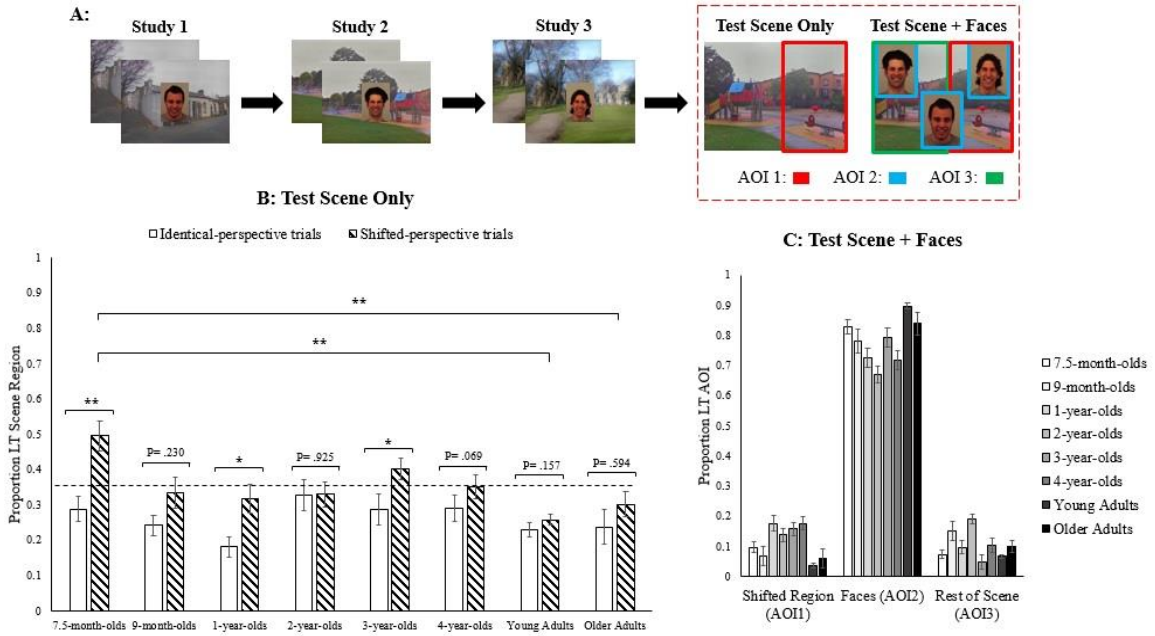

Figure 5.12 Analysis of scene viewing behaviour during the uninstructed faces and places task.

A: Areas of interest (AOIs) used to calculate the proportion of looking time devoted to AOI 1) the novel region (equivalent scene region on identical-perspective trials where no shift in scene view has occurred), AOI 2) the faces and AOI 3) the rest of the scene content during test trials **B:** Mean proportion of looking time (LT) devoted to the novel region during shifted-perspective trials and to the equivalent region during identical-perspective trials, when the test scene is presented alone. **C:** Mean proportion of looking time devoted to different AOI regions when faces superimposed over test scene during shifted-perspective trials. Asterisks mark group differences significant at * p<.05 and ** p<.01. Error bars indicate the standard error of the mean. Dashed line on B depicts the proportion of scene filled by novel region on average (approximately 37% of total scene).

One question that arises from the failure to associate the faces and shifted-perspective test scenes in children under 4 years may be that they regard this shifted-perspective as a depiction of an entirely novel scene, and hence the face-scene association is no longer relevant. To test this, we explored within-groups whether looking behaviour differed between the identical-perspective and the shifted-perspective test scenes; specifically, in the region containing the novel scene content (approximately 37% of total scene when scene presented alone, see figure 5.12A). A looking bias towards the novel region in the shifted-perspective trials relative to the equivalent region in the identical-perspective trials was observed within 7.5-month-olds (Z = -3.206, p =.001, r= -0.45), 1-year-olds (Z= -2.528, p= .011, r= -0.43) and 3-year-olds (Z= -2.361, p= .018, r= -.39). This bias was not present in 9-month-olds (Z= -1.200, p= .230, r= -0.20), 2-year-olds (Z= -.094, p= .925, r= -.02), 4-year-olds (Z= -1.818, p= .069, r= -0.30), young adults (Z = -1.415, p =.157, r= -0.20) or older adults (Z = -.534, p =.594, r= -0.14). When Bonferroni correction was applied (alpha level of 0.00625 adopted), differences in

preferential looking observed within the 1-year-olds and 3-year-olds cease to remain significant. When this looking bias directed to the shifted region in 7.5-month-olds was compared to adult viewing of this region, 7.5-month-olds elicited significantly greater viewing of the novel shifted region than both adult groups (young adults: $U = 627.0$, $z = -4.073$, $p < .0001$, $r = -0.41$; older adults: $U = 185.0$, $z = -2.681$, $p = .007$, $r = -0.34$).

To rule out the possibility that children under 4 years are unable to associate the faces and shifted-perspective test scenes due to the novel region biasing their attention at test (and so reducing their viewing of the faces), the proportion of looking time devoted to the three AOIs presented on-screen during shifted-perspective test trials was plotted (see figure 5.12C). All groups directed the majority of their looking behaviour to the face stimuli. Thus, it does not appear likely that the failure to associate the faces and shifted-perspective test scenes in children under 4 years is due to the novel shifted scene region biasing their attention away from the faces at test.

5.3.2.5 Debrief Question Additional Analysis

Furthermore, we were interested in determining whether differences existed between adults who detected the shift in scene view during shifted-perspective trials and those adults who did not notice this change, with the aim of shedding light on why our infant cohort devoted a greater proportion of viewing of the region of change at test during shifted-perspective trials (and thus are correctly viewing this scene region as novel) but are unable to elicit preferential looking towards the face previously paired with that scene. Data was obtained for n=40 young adults. However, data was only obtained for n=10 older adults and so this analysis was not conducted with older adults due to low group sizes obtained. When asked whether participants had "*noticed the background shifted on some trials?"* 60% of older adults and 50% of younger adults did not notice the shifted scene view.

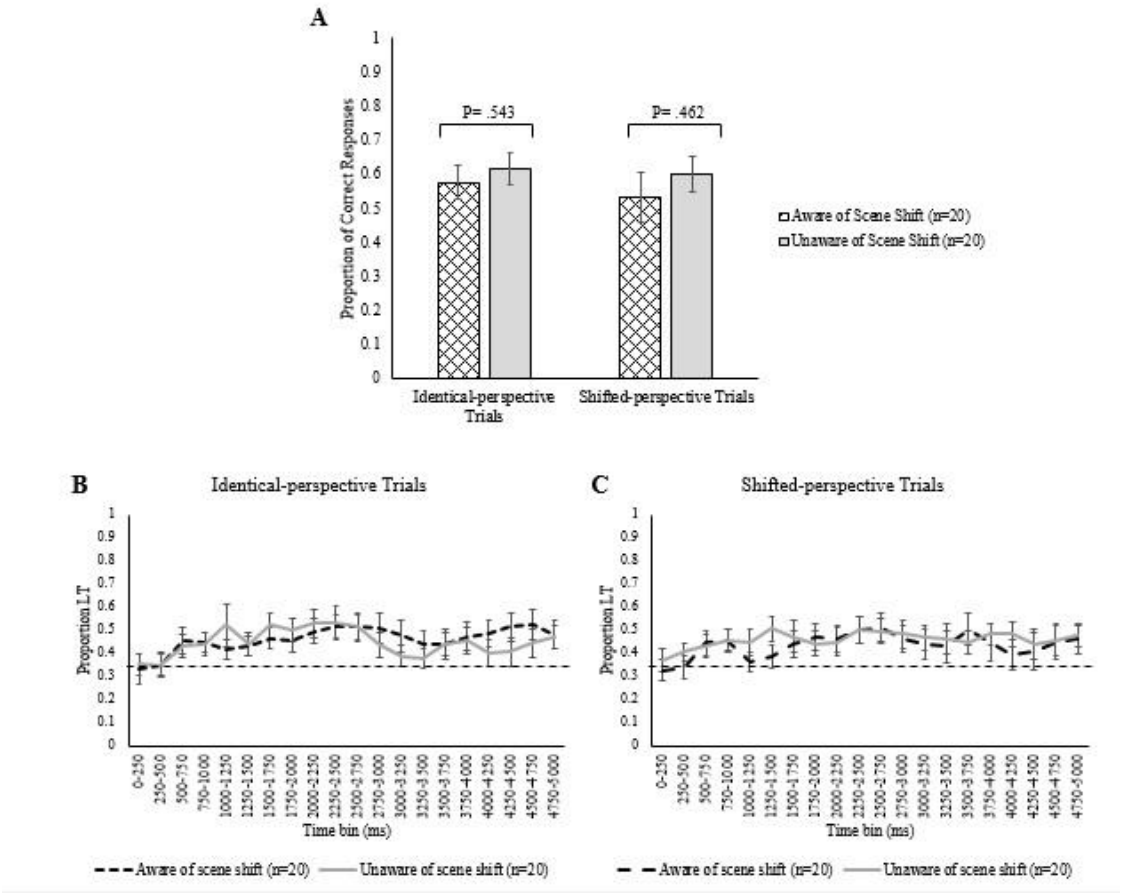

Figure 5.13 Analysis of uninstructed recall performance in young adults, separated into those who did or did not notice the shift in scene view.

A) Mean proportion of correctly identified face-scene pairs during the uninstructed explicit memory test, separated into young adults who detected the shift in scene view during shifted-perspective trials (n=20) and those who were not aware of this change (n=20). Proportion of looking time devoted to the correct face at test during the uninstructed eye-tracking task, separated into performance on identical-perspective trials **(B)** and shifted-perspective trials **(C).** Dashed line depicts chance (.33) looking proportion. Error bars depict standard error of mean.

When performance on the uninstructed explicit memory test was examined between younger adults who were aware of the shift in scene view and those who were not, significant differences were not observed between groups in the proportion of correctly remembered pairs during both identical-perspective ($t(38) = -.613$, $p=.543$, $d= -.19$) and shifted-perspective trials ($t(38) = -.743$, $p=.462$, $d= -.24$). Equally, between-subject functional analysis did not reveal significant differences between groups across any time bin and either trial type. Therefore, these results suggest that awareness of the change in scene view does not appear to influence young adults' ability to elicit preferential looking towards the correct face previously paired with a scene or explicit recall of face-scene pairings.

5.3.3 Additional Analyses

5.3.3.1 Instructed Eye Movement Behaviour

Functional data analysis was used to examine within groups whether proportion of looking time devoted to the matching face at test significantly differed depending on lag for each of the trial types. Within each group, no significant differences were observed between lag types for the proportion of looking time devoted to the correct face during identical-perspective trials. However, during shifted-perspective trials older adults elicited significant differences in looking behaviour dependent on lag across time bins spanning 3750-4250 ms (figure 5.14). Therefore, lag was collapsed for subsequent analyses with the exception of the shifted-perspective trials for the older adult group.

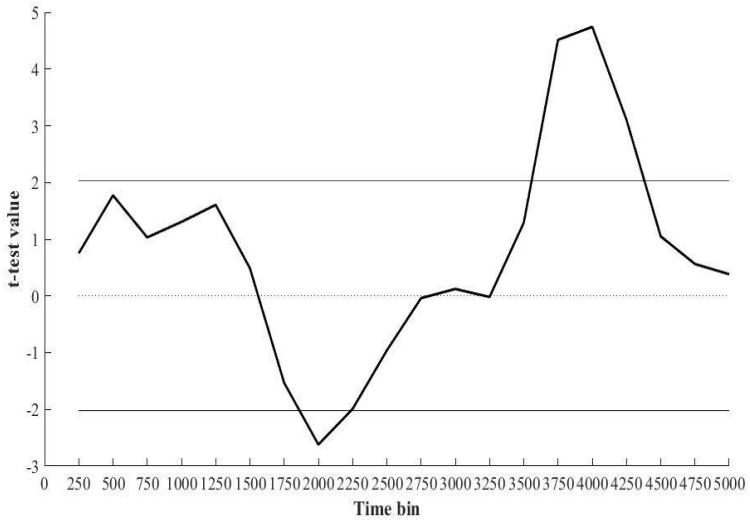

Figure 5.14 Mean functional proportion of looking time devoted to match face as a function of time bin during shifted-perspective trials in the older adult cohort.

The curve represents the value of the t-statistic as a function of time. The solid horizontal lines represent two-tailed critical values for the t distribution. *Note.* Significant differences in looking time between lag types are observed due to one-tailed between-subject t-values exceeding the higher critical t statistic value across time bins spanning 3750-4250 ms.

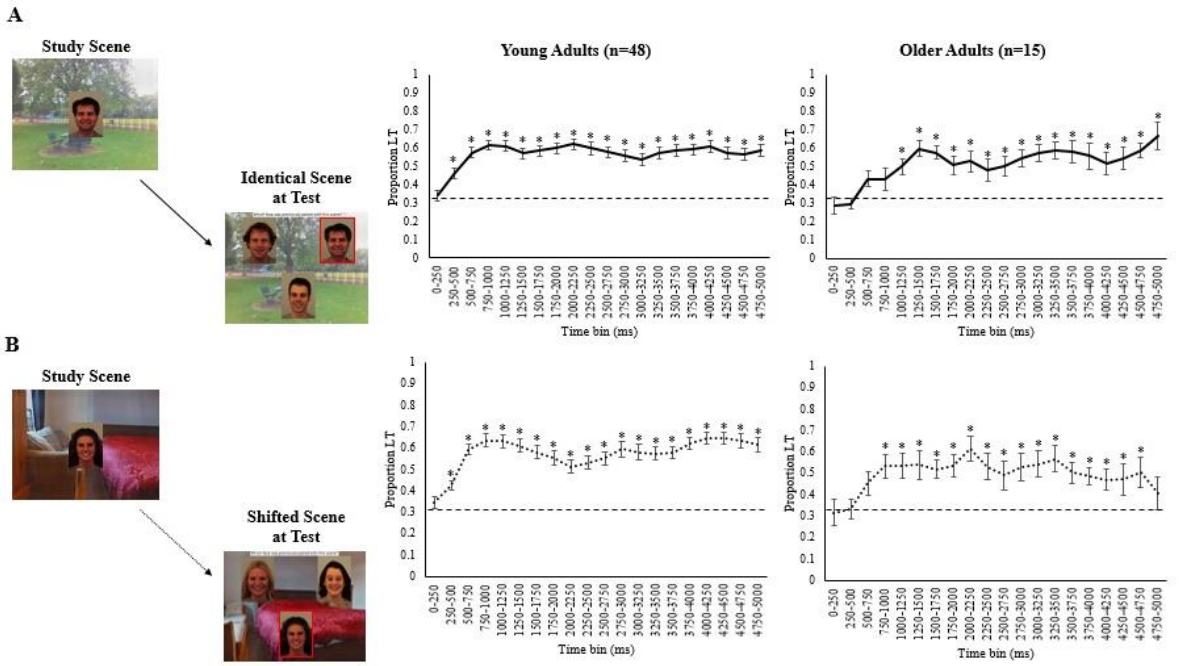

Figure 5.15 Mean proportion of looking time (LT) devoted to correct face during test trials on identical-perspective trials (A) and shifted-perspective trials (B) when participants were instructed to remember face-scene pairs during study.

Following instructions to memorise the face-scene pairs during learning, both groups elicit preferential looking towards the correct face at test for the majority of the test trial duration during both identical-perspective (figure 5.15A) and shifted-perspective trials (figure 5.15B). However, it can be noted that this preferential looking behaviour has a slightly later onset post-stimulus presentation within the older adults (1000 ms post-stimulus onset for identical-perspective trials and 750 ms post-stimulus onset for shifted-perspective trials) compared to younger adults (250 ms post-stimulus onset for both trial types). Considering differences were observed in looking behaviour as a function of lag on shifted-perspective trials in older adults (figure 5.14), performance on these trials was analysed separately by lag in this group (figure 5.16).

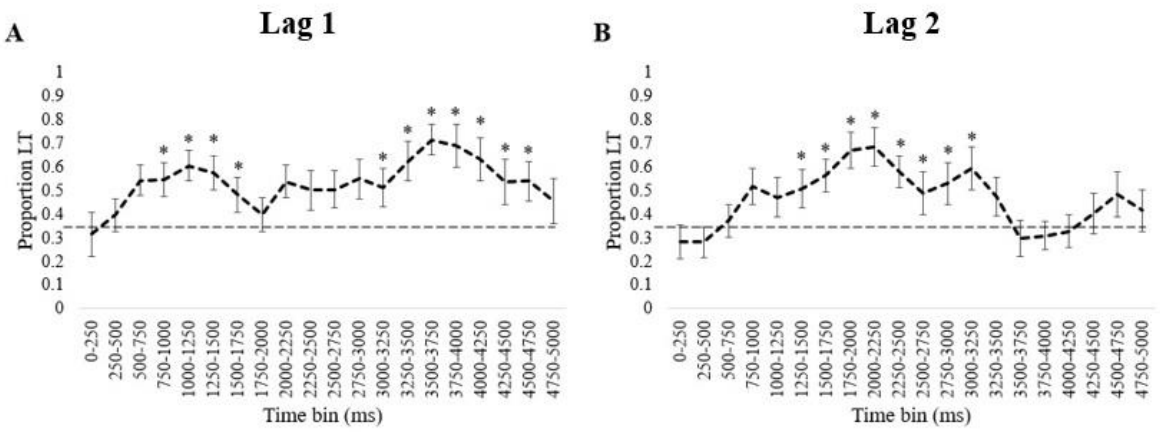

Figure 5.16 Mean proportion of looking time (LT) devoted to correct face during shifted-perspective test trials when the test scene was previously presented at a lag of 1 (A) or a lag of 2 (B) within older adults.

Bins where the proportion of looking time exceeds the higher critical t-value during functional analysis are marked by asterisks. *Note*. Chance performance (.33) is indicated by the dashed line. Error bars indicate the standard error of the mean.

When the test scene was previously presented one study trial back (lag 1; figure 5.16A), older adults elicited preferential looking towards the correct face at two discrete time periods (750-1750 ms and 3000-4750 ms). In comparison, when the test scene had been presented two study trials back (lag 2; figure 5.16B), preferential looking occurs in one more prolonged time period spanning 1250-3250 ms post-stimulus onset.

5.3.3.2 Instructed Explicit Memory Test

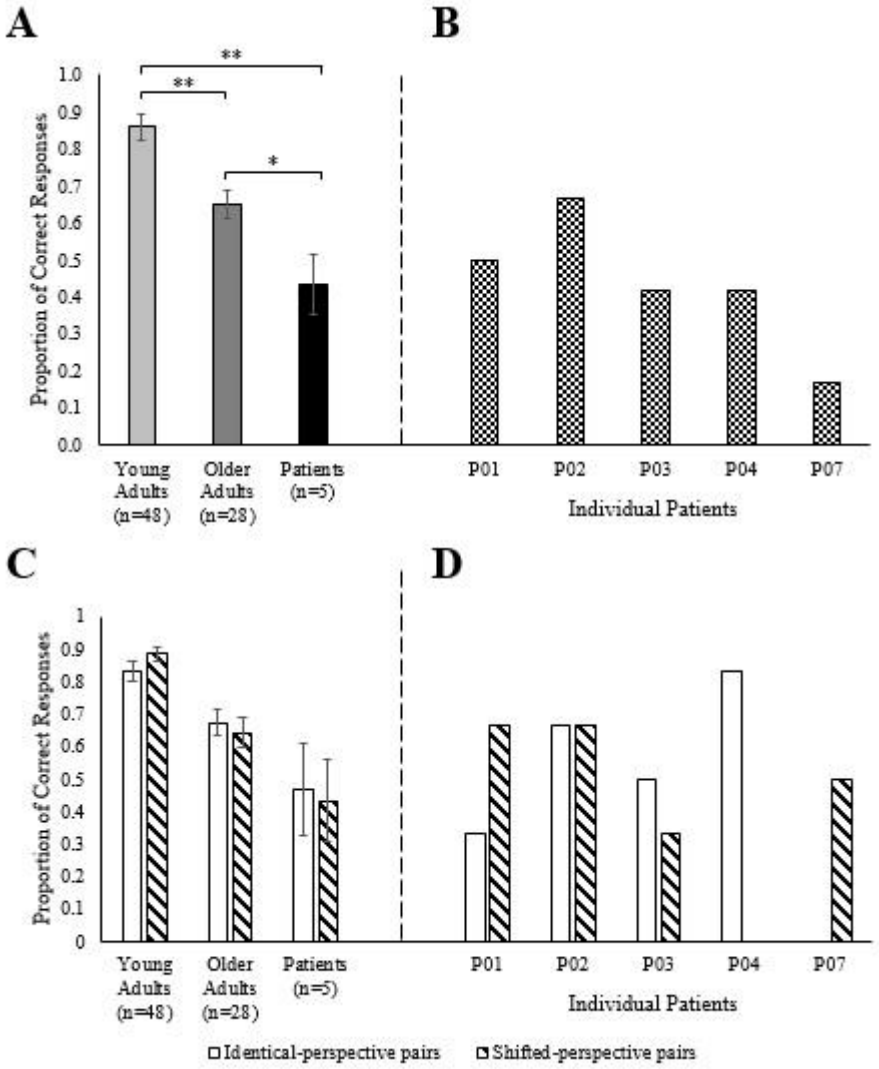

Figure 5.17 Instructed explicit recall for face-scene pairs.

A: Mean proportion of correctly identified face-scene pairs during instructed explicit memory test within groups (young adults; older adults; patients). **B:** Individual patient scores for correctly identified pairs. **C:** Mean proportion of correctly identified face-scene pairs when separated into identical-perspective and shifted-perspective trials. **D:** Individual patient scores for correctly identified pairs when split by trial type. Note error bars depict standard error of mean. Asterisks indicate significant differences; * = p<.05, ** = p<.01.

When adults were instructed to memorise the face-scene pairs at learning, we now observe no differences in the proportion of correctly identified face-scene pairs between identical-perspective and shifted-perspective trials within groups (figure 5.17C; young adults: z=-1.791, p=.073, r= -.26; older adults: z=-.513, p=.608, r= -.10; patients: z=0, p=1.000). Therefore, instructing participants to memorise the face-scene pairs during learning appears to eradicate the difference in memory recall between scene perspectives conditions observed previously when no instructions are given.

In terms of overall memory for face-scene pairs (figure 5.17A), young adults demonstrated significantly better memory than both older adults (U=161.5, z= -3.950, p<.0001, r= -.52) and patients (U= 7.5, z= -3.230, p=.001, r= -.55). Young adults also remembered significantly more identical-perspective pairs than both older adults (U= 366.50, z= -3.407, p=.001, r= -.39) and patients (U= 34.0, z= -2.754, p=.006, r= -.38), and significantly more shifted-perspective pairs than both older adults (U= 286.5, z= -4.340, p<.0001, r= -.50) and patients (U= 11.5, z= -3.548, p<.0001, r= -.49). Therefore, we still observe a significant impact on memory for face-scene pairs regardless of scene perspective condition with healthy ageing and hippocampal damage, even when instructions are provided to memorise the pairs at learning.

Surprisingly when examining patient performance, it can be observed in figure 5.17B and 5.17D that there is varying performance between individual patients. After receiving instructions to remember the pairings during learning, no significant differences can be observed between patient and older adult performance in correctly identifying face-scene pairs presented during identical-perspective trials (U= 43.0, z= -1.389, p=.165, r= -.24) and shifted-perspective trials (U=41.5, z=-1.463, p=.143, r= -.26). Although older adult controls remembered significantly more correct pairs overall than the patients (U= 29.0, z= -2.093, p=.036, r= -.36).

5.3.3.3 Comparison of uninstructed versus instructed explicit memory performance

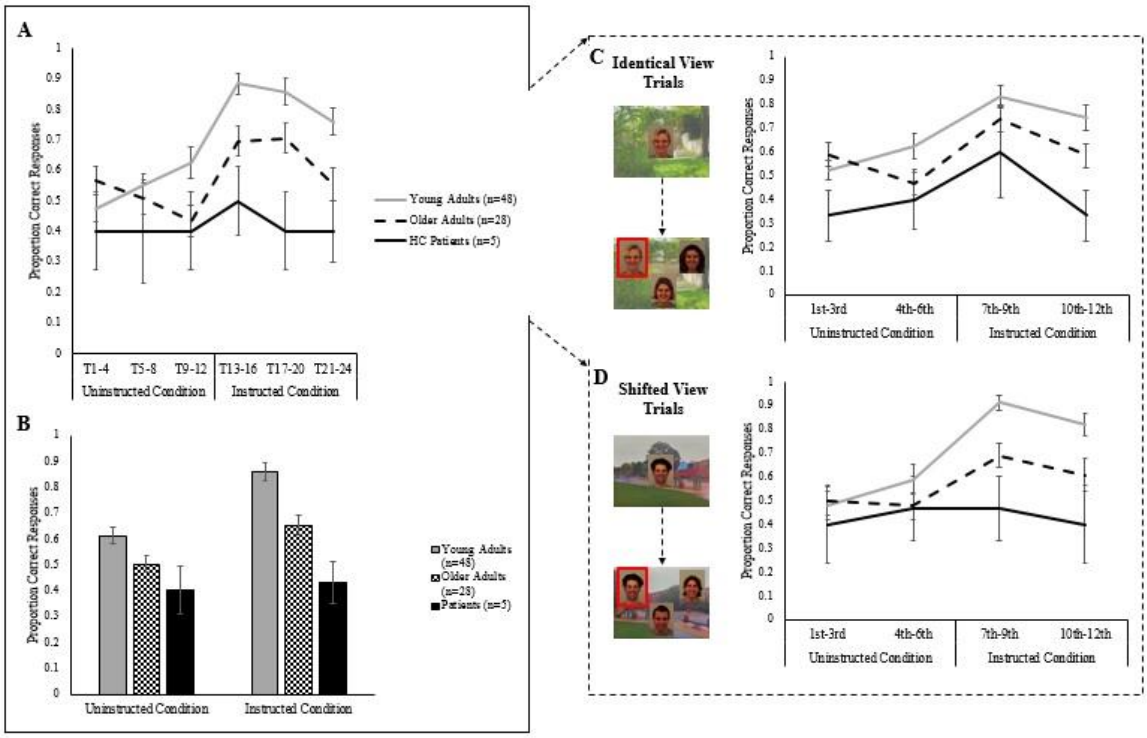

Figure 5.18 Comparison of uninstructed versus instructed memory performance in adults.

A) Mean proportion of correctly identified face-scene pairs across consecutive blocks of trials during uninstructed pairings and instructed pairings, separated by group. **B)** Overall mean proportion of correctly identified face-scene pairs during the uninstructed task and instructed task within groups. Mean proportion of correct responses across trial blocks in the order in which they were presented, separated by group and by trial type (**C:** Identical-perspective trials, **D:** Shifted-perspective trials). Error bars depict standard error of the mean. T= trial number.

Wilcoxon Signed Rank tests were employed to examine whether differences in the proportion of correct responses exist within groups as participants proceed through blocks of trials, regardless of trial type (figure 5.18A). Intriguingly, no significant differences in performance were observed between any of the blocks of trials as patients progressed through the tasks. In contrast, a significant increase in performance is observed between the last block of uninstructed trials (T9-12) and the first block of instructed trials (T13-16) in both the young adults (z=-3.269, p=.001, r= -.47) and older adults (z= -3.093, p=.002, r= -58). Furthermore, a significant decrease in performance is observed between the middle block (T17-20) and last block (T21-24) of instructed trials, again in both young adults (z=-2.144, p=.032, r= -.31) and older adults (z= -2.497, p=.013, r= -.47). Thus, we can assume that practice effects are not occurring, due to no significant increases in performance being present as participants are progressing through the trials. The observed significant decrease in performance during the

last block of instructed trials within the control groups could indicate fatigue. We can see that the increase in performance within the control participants observed in the instructed condition is simply due to instructions provided. Interestingly this effect of instructions does not appear to exist within the patient cohort.

Furthermore, when examining the proportion of correct responses given separately by trial type, again no significant differences are observed between any of the blocks of trials within the patients. Examining the proportion of correct responses denoted during identical-perspective trials (figure 5.18C), we observe again a significant increase in task performance between the last block of uninstructed trials and the first block of instructed trials within the young adults ($z= -2.506$, $p=.012$, $r= -.36$) and within the older adults ($z= -3.740$, $p<.0001$, $r= -.68$). We also observe a significant decrease in task performance within the older adult group between the first and last block of the instructed trials ($z= -1.987$, $p=.047$, $r= -.38$), which is perhaps indicative of fatigue. Furthermore, when examining task performance elicited during shifted-perspective trials (figure 5.18D), we also observe a significant increase in performance between the last block of uninstructed trials and the first block of instructed trials both within the young adults ($z= -3.619$, $p<.0001$, $r= -.52$) and older adults ($z= -2.378$, $p=.017$, $r= -.45$). As this significant increase in performance is again restricted solely to the change in instructions given, our findings indicate that increases in task performance between uninstructed and instructed conditions is due to the acquisition of instructions and not practice effects as a result of completing consecutive trials.

5.4 *Discussion*

Using a modified version of the faces and places task, this chapter demonstrated key differences between-groups in their implicit and explicit memory for face-scene pairs. When examining explicit memory for face-scene pairs in the uninstructed task (section 5.3.1), adult controls demonstrated retention of previously viewed face-scene associations when no instructions were provided to memorise the pairings. Younger adults identified significantly more correct pairs overall than both older adults and patients; indicating an effect of ageing and hippocampal damage on task performance. Surprisingly, patient P01 demonstrated different (and superior) performance compared to the remaining patient cohort. When P01 was excluded from analysis, older adults demonstrated significantly greater memory for the

pairs compared to the patients. These findings indicate a decline in recall for face-scene pairs with healthy ageing, concurring with previous literature which demonstrates a decrease in the ability to form and retain relationships between items and their contexts with increasing age in older adults (Naveh-Benjamin, 2000; Plancher et al., 2010). Equally, these results are in agreement with Hannula et al. (2007), in that patients with selective hippocampal damage elicited poorer recall of face-scene pairs compared to healthy controls, and resonates with relational memory theory (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001) as patients appear unable to form associations between simultaneously occurring items.

Another key finding of this chapter was that adult controls elicited eye movements indicative of remembering face-scene associations when no instructions were provided to memorise the pairings at learning. Although both young and older adults elicited preferential looking during identical-perspective, this preferential looking was more prolonged in the younger adults. This could indicate an effect of ageing on memory for the face-scene pairs (if older adults are switching between the faces on-screen at test as they are less confident in their memory for the face-scene pairing) or may reflect significant declines in sustained visual attention observed in healthy ageing (Zanto & Gazzaley, 2014). Nonetheless, these results mean that valid comparisons can be made between preverbal infants, older children and adult task performance and inferences can be made regarding how the looking behaviour of different age groups may correspond to underlying hippocampal-dependent memory processes.

Examining eye movement behaviour during the uninstructed eye-tracking task in children aged ≤4 years, all age groups with the exception of 3-year-olds elicited preferential looking towards the correct face during identical-perspective trials. Interestingly, when this looking behaviour occurred post-stimulus onset was highly variable across age groups, suggesting that eye movement behaviour veridical of memory for face-scene associations does not appear to increase in a progressive linear manner with age. These age differences in the location of this preferential looking across test trial time bins may suggest that different cognitive processes are underpinning performance at diverse ages.

Previous literature has shown that hippocampal-dependent binding processes increase progressively throughout infancy and into early childhood (Ghetti, 2017; see section 1.2.1.4).

Substantial increases in the ability to form associations between items and their spatial contexts are observed from the second year of life (Ribordy et al., 2013) with more complex binding of item-spatial relations emerging from 3.5 years (Ribordy et al., 2015; 2017). Equally, animal and human post-mortem studies alongside neuroimaging experiments have demonstrated that the hippocampal formation undergoes protracted development from birth into adolescence, with different pathways of connectivity reaching adult-like levels of maturity at different ages (Jábes & Nelson, 2015; see section 1.2.1.1). The entorhino-hippocampal circuits (particularly connectivity between the CA1 subfield and entorhinal cortex) reaches adult-like levels of maturity by around 2-years-old. The dentate gyrus and CA3 subfields, which are crucial components of the more complex trisynaptic pathway, begin to reach a level of functional maturity which is able to support more complex memories of events by around 3.5 years (Lavenex & Banta Lavenex, 2013). Considering this literature, perhaps differences in the functional maturation of hippocampal circuitry, and thus the proficiency of binding processes available to that individual, could be resulting in the distinctions in looking behaviour we observe across age groups.

In line with this proposal, previous authors have distinguished between diverse forms of binding available to young children, dependent on age and hippocampal maturation (Edgin et al., 2014). Unitized representations of events refers to the blending together of the separate features of a display (e.g. the face and the scene) to create a single memory representation and thus not flexibly associating the features with each other. In contrast, configural representations refers to the ability to remember the features of an event separately but also form associations between the distinct features of an event. Unitized binding is argued to be supported by the perirhinal cortex along with neocortical structures, while configural binding relies on the hippocampus (Diana et al., 2007; Gomez & Edgin, 2016). Edgin et al. postulate that children under 4-years-old are more likely to engage in unitary binding of objects and contextual features (although evidence of configural binding has been indicated from 18-months-old dependent on the task parameters), while increases in the ability to configurally bind object-context events increases from 4 years until approximately 10-14 years (Edgin et al., 2014). Therefore, age-related differences in preferential viewing of the test face could be explained by distinctions in the type of binding processes that are used when encoding face-scene stimuli between age groups.

In faces and places task, participants are required to correctly locate the face previously paired with the test scene in the presence of two equally familiar faces. Thus, the appearance of the face-scene pair at test is different from its original presentation at learning, due to two other faces also being present. It may be that young children are not processing the scene as a spatial context but simply bind the face-scene pair in a unitized manner. This could therefore be leading to poorer memory (and thus less preferential looking directed towards the correct face) when the face-scene display at test is not perceptually identical to the display presented at study (i.e. as two additional faces are also present). At 4-years-old, we see a longer peak of preferential looking compared to younger children. Therefore, perhaps the performance observed in 4-year-olds is reflective of the ability to bind items and contexts configurally, through the development of the trisynaptic circuitry within the hippocampal formation which is argued to emerge at approximately this age.

Regarding the absence of eye movements indicative of remembering face-scene pairs in the 3-year-olds, this result was unanticipated. Children aged 3 years have been shown to recall previously learnt item-spatial associations and do not significantly differ in their performance from 4-year-olds in these studies (e.g. Hayne & Imuta, 2011). Yet, here 3-year-olds fail to elicit preferential looking towards the correct face while younger children and 4-year-olds do. Perhaps this result can be explained by the structural and functional changes in the hippocampal formation argued to occur around this age. Synaptic pruning in the hippocampal subfields around this age may trigger a change in the processing underpinning the form of hippocampal-dependent binding used to approach the task, with 3-year-olds perhaps switching to using the more sophisticated albeit immature trisynaptic pathway for memory processes. Neuroimaging evidence is needed to support this proposal and to further understand these age-related differences in the eye movement expression of hippocampal memory.

Alternatively, differences in the timing of preferential looking behaviour directed to the test face may be reflective of the development of other cognitive processes outside of memory development but which may directly impact on memory processes. For instance, the ability to sustain attention may play an important role in performance on the faces and places task. The ability to direct attention to a specific stimulus and maintain it for an unbroken period of time, termed alertness, increases across the first year of life and continues to develop well into the

third year of life (Colombo, 2001; Posner et al., 2014). Alertness that is maintained over a longer time period is thereafter referred to as sustained attention (Colombo, 2001). Evidence suggests the ability to sustain attention emerges during primary school with improvements observed incrementally from ages 5-10 years, with only minor improvements observed with increasing age after this period (Betts et al., 2006). Therefore, the distinct differences across age groups in the timing of their preferential looking during the test trials could reflect fluctuating attention as a result of age-related differences in the ability to sustain attention during the task, in addition to age-dependent mnemonic ability.

A prominent finding in this chapter is that clear differences are observed when performance is disaggregated between identical-perspective and shifted-perspective trials during both uninstructed explicit recall and implicit eye movement behaviour. Firstly, during explicit recall, both older adults and patients perform significantly better in their retrieval of face-scene pairs during identical-perspective trials compared to shifted-perspective trials. Critically, this pattern of results is not observed in young adults. Therefore, ageing and damage to the hippocampus appears to particularly impact on the ability to remember associations between scenes and faces when scene view has been shifted between learning and test.

Furthermore, children aged 5-8 years demonstrated the ability to explicitly recall face-scene pairs which did not significantly differ from the performance of both younger and older adults. Recall of pairs on shifted-perspective trials did not significantly differ from performance on identical-perspective trials in all age groups, similar to performance observed in younger adults. 8-years-old marked the age that recall of face-scene pairs was significantly greater than that of patients with selective hippocampal damage, both with and without P01 included in the analysis. However, these results should be interpreted with caution due to low sample sizes used in these comparisons. Overall, the current study has demonstrated that children aged 5-8 years are capable of adult-like memory recall for face-scene associations, even when the scene perspective is shifted at test.

Examining looking behaviour during the eye-tracking task, both younger and older adults elicited eye movements indicative of remembering face-scene associations when the scene

view had been shifted during shifted-perspective trials. However, no child groups apart from 4-year-olds elicited eye movements indicative of remembering face previously paired with test scene when scene perspective was shifted. These findings suggest that again 4 years appears to mark a critical period in memory development whereby changing scene view does not eradicate the ability to identify a face previously paired with that scene.

When scene viewing behaviour was examined during shifted-perspective test trials, 7.5-month-olds elicited a looking bias to the novel scene area compared to equivalent unchanged scene regions in identical-perspective trials which was not observed in adult groups. 1-year-olds and 3-year-olds also demonstrated significantly greater viewing of the novel scene region during shifted-perspective trials compared to identical-perspective trials. However, these results failed to remain significant following Bonferroni correction and when this is visually compared to the region containing the novel content in shifted perspective test scenes (approximately 37% of the scene), the proportion of looking time in these groups largely falls under this threshold. These results suggest that all age groups, with the exception of 7.5-month-olds, appear to view the shifted scenes as relatively the same scenes as those shown at learning (due to a lack of novelty looking bias elicited to the new scene content on shifted trials). As the novel shifted region was highly salient to the 7.5-month-olds, this indicates that the lack of looking behaviour directed to the correct face during shifted-perspective trials cannot be dismissed in terms of failure to remember the scene between study and test. Equally, all groups, including 7.5-month-olds, devoted the majority of their looking time to the faces during shifted-perspective test trials. The novel region did not detract attention away from the faces and so cannot explain why children aged under 4 year's failure to show preferential looking towards the correct face at any time point.

Moreover, debrief questioning revealed that 50% of young adults did not notice the shift in scene perspective between learning and test. Preferential looking towards the correct face previously paired with a scene or explicit recall of face-scene pairings was not significantly different between young adults who did notice the shift and those who did not. Therefore, awareness of the change in scene view did not influence young adults' performance.

Considering this collection of findings as a whole, it appears that shifting the scene view between learning and test disrupts memory for associations between a face and the previously presented version of that scene in patients with hippocampal damage and children aged under 4 years. Although older adults' recall of shifted-perspective pairs is significantly poorer than their memory for pairs where scene view remains identical between learning and test, the scene viewing behaviour of both younger adults and older adults during eye-tracking suggests that adult controls are naturally processing this change in scene perspective.

An explanation for these findings may be routed in the boundary extension phenomenon, as the absence of looking behaviour directed towards the novel scene region during shifted-perspective trials is reminiscent of the classic boundary extension observation whereby participants fail to report a change between close-up and wider angle scenes (see section 5.1). For instance, in Intraub & Richardson (1989), participants first viewed a series of single scenes before completing a recognition test where they decided if the test scene is the same or different from the previously presented scene. When participants were shown a close-up version of the scene at test, participants rated the scene as being very different. This is consistent with the phenomenon of boundary extension as the close-up image is very different from their memory for the presented scene which contains extended boundaries; therefore exaggerating differences between the presentation and test scenes. When a wider angle version of the presented scene is displayed at test, the boundary extension effect is not as strong. This is due to the fact that although the wider angle version is different from the presented scene, memory for the original scene contains extended boundaries and therefore participants naturally remember viewing more of the scene than was originally presented. Thus, the difference between participants' memory for the presented scene and the wider angle test scene is smaller. Previous literature has demonstrated the presence of this phenomenon in infants as young as 3-months-old (Quinn & Intraub, 2007), Considering this literature, boundary extension should prevent all groups from looking towards the novel region during shifted-perspective trials as if they have already extrapolated beyond the borders of the scene shown at study, then the scene presented at test should not be grossly different from their existing representation of the study scene. As children aged ≥9-months-old, young and older adults did not elicit a looking bias towards the shifted region at test, these findings fit with this proposal.

However, we would anticipate that 7.5-month-olds would commit the boundary extension error and extrapolate beyond the borders of a presented scene at learning. This should therefore result in the infants not eliciting a significant looking bias towards the novel region, as if they had already processed the scene as wider than it actually is then the new shifted perspective version should not be a huge adjustment to their pre-formed mental representation of the original scene. On the contrary, 7.5-month-olds do elicit a looking bias towards the novel region, inconsistent with the assumptions of boundary extension. However, the results of Quinn & Intraub (2007) have not been replicated again in the literature. Attempts were made in this thesis to obtain a measure of boundary extension across all age groups (see appendix F). However, data collected from these tasks was found to be unreliable and thus it was not included in this thesis.

As successful recall of face-scene associations during shifted-perspective trials may require participants to extrapolate beyond the borders of a previously studied scene in conjunction with memory retrieval of the face-scene associations, one could infer that the poorer performance observed in patients with selective hippocampal damage and older adults (who are argued to experience reduced hippocampal volume and activity as a function of ageing) may be underpinned by decreased ability to construct continuous scenes in the mind's eye. This greater impairment in memory when scene view-point is shifted resonates with scene construction theory (Hassabis & Maguire, 2007; Mullally & Maguire, 2013), in that difficulties in the ability to extend representations of scenes in the mind may be impacting upon task performance in patients with hippocampal damage, and to a lesser extent in older adults who may have reduced hippocampal integrity.

However, as all child groups over the age of 7.5-months-old do not elicit preferential viewing of the novel scene region, this suggests that age-related differences in their ability to remember face-scene pairings may not be fully accounted for by differences in scene construction abilities. Therefore, it may be that age-related differences in the disruption caused by shifting scene perspective may be more likely reflective of the functional development of hippocampal circuitry across childhood and the corresponding emergence of more complex binding processes. If children under 4 years are encoding face-scene pairs in a more unitized manner (as discussed previously in this section), changing the scene perspective may mean that the test scene is now regarded as novel and thus this may lead to the failure to

retrieve the face that was previously paired with this scene, i.e. if the scene is no longer regarded as relevant to the previously encoded memory representation of the original scene and face. This may then result in memory retrieval failure of the previous pairing between the face and this scene.

A further explanation for the memory disruption caused by shifting scene perspective in children <4 years, older adults and the patients may be related to a specific process underpinned by the hippocampus termed pattern completion. This process refers to the retrieval of encoded memories when presented with partial cues (Norman & O'Reilly, 2003). Pattern completion has been found to rely upon the CA3 subfield of the hippocampal formation (see section 1.1.4.1). Importantly, selective bilateral atrophy to the CA3 subfield has been reported in patients with VGKCC_LE (Miller et al., 2017), which may explain why the VGKCC_LE patients demonstrate more profound memory deficits for pairs during shifted-perspective trials relative to identical-perspective trials. If patients are unable to engage in adequate pattern completion when presented with a partial component of a previously presented cue (i.e. the original version of the scene), this may explain why they exhibit greater deficits on shifted-perspective trials compared to trials where the complete cue is presented again at test (i.e. identical-perspective trials). However, compromised pattern completion cannot explain why the patients also have impaired performance on identical-perspective trials relative to controls, as the scene remains the same between learning and test (i.e. a partial scene is not presented at test).

While volume loss has been documented in the dentate gyrus and CA1 subfield with increasing ageing, CA3 subfield volume appears be spared in normal ageing (Wisse et al., 2014). Equally, a body of evidence largely based on rodent studies has suggested that changes in CA3 function with increasing ageing may mean that older adults are more likely to engage pattern completion processes (Yassa & Stark, 2011). CA3 place cells in young rodent brains have been found to rapidly alter their representations when placed in a similar environment, whereas CA3 place cells in ageing rodent brains retain their original place cell fields in spite of changes made to the environment (Wilson et al., 2006). In humans, reductions in dentate gyrus volume have been observed (Wisse et al., 2014), with this region being found to support pattern separation (Bakker et al., 2008), i.e. the process by which distinct representations are assigned to specific events by transforming similar memories into highly dissimilar and non-

overlapping patterns of activation (Norman, 2010). Older adults have been found to be more likely to engage pattern completion over pattern separation processes during a mnemonic similarity task (Yassa et al., 2011). In a continuous recognition task, participants viewed identical, similar (i.e. lures) and novel items and indicate whether each item was either "new", "old" or "similar". Older adults were significantly more likely to declare similar items as "old" than younger adults, thus signifying a propensity to engage in pattern completion as opposed to pattern separation. This collection of findings has led some authors to argue older adults have an increased tendency to engage in pattern completion (Yassa & Stark, 2011). Therefore, it seems less likely that diminished pattern completion abilities could explain why older adults performed worse in their recall for face-scene pairs during shifted-perspective relative to identical-perspective trials. Although the CA3 subfield does not support pattern completion in isolation and preserved structure does not necessarily mean that the function of this subfield and its neural connectivity remain intact.

Regarding the performance of children during shifted-perspective trials, the CA3 subfield and the trisynaptic circuitry in which this subfield is part of does not appear adult-like in structural maturity until approximately 4-years-old in humans (Fortman et al., 2001), with authors proposing that functions underpinned by this more sophisticated hippocampal circuitry, like pattern completion do not emerge until this point (Jábes & Nelson, 2015). As the neural substrates supporting pattern completion are not sufficiently developed by ≤3 years, these age groups should be unable to engage in pattern completion processes which could result in their absence of eye-movement behaviour indicative of remembering face-scene associations when scene perspective has been shifted at test. In contrast, 4-year-olds who possess an adequately mature trisynaptic circuitry should be able to engage in sufficient pattern completion to retrieve the face-scene association at test when presented with a partial cue i.e. the shifted version of the original scene. Moreover, as children aged ≥5 years demonstrate adult-like memory performance for shifted-perspective pairs during explicit recall, these results are congruent with current knowledge regarding the age that pattern completion processes may be present.

Additional analyses were also conducted (section 5.3.3) to examine the effect of instructions on memory performance within our adult groups. When instructed to memorise the face-scene pairs at learning, both younger and older adults elicit preferential looking towards the correct

face at test for almost the full 5000 ms, regardless of trial type. The onset of this looking bias is slightly later in older adults relative to young adults, which concurs with current knowledge that healthy ageing typically results in slower visual search performance (Madden, 2007). Equally, an effect of ageing and hippocampal damage is observed during explicit verbal recall of previously learnt pairs. Young adults remembered significantly more pairs than older adults and the patients, with older adults also recalling significantly more pairs than the patients. Therefore, we still observe poorer performance with healthy ageing and hippocampal damage that was documented previously during uninstructed explicit recall.

However, two findings were of particular interest. Firstly, the introduction of instructions eradicated the difference in recall between identical-perspective and shifted-perspective trials within-groups. Performance did not significantly differ between identical-perspective and shifted-perspective pairs within both older adults and patients. Secondly, when comparing uninstructed and instructed recall, we observe no evidence of practice effects as participants' progress through the tasks. However, the patients do not demonstrate a boost in recall performance with the introduction of instructions; an effect that is present within both young and older adults. Taken together, these findings suggest that while the use of instructions may have facilitated memory in the patients in terms of improving memory for shifted-perspective trial pairings, they did not benefit from the introduction of instructions to the same degree as healthy controls.

An explanation for these findings may be related to the interaction between the hippocampus and prefrontal cortex (PFC) during memory processing. The PFC has been documented to play an important role in long term memory consolidation (Eichenbaum, 2017). Once incoming information has been processed by the hippocampus, it is projected back to the neocortex, including the PFC (Squire et al., 2004; Wang & Morris, 2010). Equally, the PFC is argued to serve episodic memory by performing controlled strategies like top-down processing, which in turn decrease or augment memory for a particular event (Blumfeld & Ranganath, 2007). Recruitment of the PFC in adults has been shown during 'selection processes' i.e. directing attention towards goal-relevant information or inhibiting attention to irrelevant information (Bunge et al., 2001; Koechlin et al., 2003; Dosenbach et al., 2008). Therefore, in order to engage in successful memory consolidation and interpret incoming information in a controlled goal-relevant manner, intact functional circuitry must exist

between the hippocampus and PFC. Applying this notion, poorer recall performance when instructions have been provided to memorise the pairs at learning in the patients may reflect inadequate processing in the hippocampus, diminished hippocampal-neocortical interaction to engage in robust strategic memory processes or both. Further work is needed to support this proposal.

A limitation of this study was that eye-tracking data was not obtained for patients, due to low sample size and the unreliability of the portable eye-tracker data. While performance on the explicit memory tests provided valuable insight into memory for face-scene pairs in the patients, future research should endeavour to measure eye movement behaviour during our modified faces and places task in a larger cohort of patients and when access to a more robust eye-tracking device is available. This would allow investigation into the eye movement behaviour of patients when scene view-point is altered during shifted-perspective trials and consequently provide further insight into the mechanism that underpins the patient's more profound deficit in remembering pairs when the scene perspective has shifted relative to when the perspective remains the same between learning and test.

Although P01's performance on the explicit memory test was concurrent with other patients in that they demonstrated better memory for identical-perspective pairs than shifted-perspective pairs, overall this patient elicited retention of the face-scene pairs. This finding was unanticipated in light of P01 demonstrating episodic memory deficits in an earlier investigation (see appendix A). However, P01 obtained a 'definitely abnormal' score for childhood autobiographical memory and a 'borderline' score for recent autobiographical memory recollection when the Autobiographical Memory Interview (AMI; (Kopelman, Wilson & Baddeley, 1989) was administered, whereas all other patients obtained scores of 'acceptable' and definitely abnormal', respectively. In contrast with the rest of the patient cohort and previous research, P01 presents with a very atypical temporal gradient of amnesia. Selective hippocampal damage typically results in largely unaffected early premorbid episodic memories and severe anterograde episodic memory impairment (Zola-Morgan et al., 1986; Rempel-Clower, et al., 1996; Butler et al., 2014). Furthermore, a T2 weighted MRI scan performed showed no obvious hippocampal enhancement at illness onset (a significant predictor of later hippocampal lesions once inflammation in the brain has been treated).

Although left hippocampal atrophy was confirmed at the time P01 was first tested. Further neuropsychological evaluation is warranted to understand P01's task performance.

Due to testing venues, eye tracking data was not obtained in participants aged 5-8 years. Future research that obtains this data could provide invaluable insight into whether these age groups elicit eye movements veridical of memory for face-scene pairs during shifted-perspective trials. This data would provide the opportunity to determine whether this eye movement behaviour matches that of young adults and at what age this looking behaviour emerges. Similarly, obtaining performance on the explicit memory test in 4-year-olds would shed light on whether their eye movement indicative of remembering face-scene pairs during shifted-perspective trials is also concurrent with their verbal recall. These endeavours could provide exciting insights into how hippocampal-dependent memory and scene processing abilities develop in early childhood.

As outlined in chapter 4, earlier acquisition of independent locomotion (IL) in the first year of life was linked to significantly better memory for previously modelled actions by 9-months-old, compared to age-matched infants who acquire this developmental milestone later. Previously, authors have proposed that attaining greater experience of different contexts, including spatial environments, may provide scaffolding for increases in memory for events and the contexts that they occur in (Rovee-Collier & Cuevas, 2009). Another interesting direction for future research is therefore to examine how the attainment of IL may be influencing memory for face-scene associations, through increasing an infant's knowledge base regarding the relations between events and spatial contexts. This investigation was conducted in chapter 6.

6. Chapter 6. Moving towards Memory II: Does independent locomotion facilitate memory for face-scene associations?

Chapter 6 Summary

The ability to bind face-scene pairings and retain these associations has been demonstrated in infants as young as 7.5-months-old in this thesis (chapter 5) and from 9-months-old in previous literature (Richmond & Nelson, 2009). Infants also typically develop independent locomotion between the ages of 7.5-9 months old (Benson, 1993). The earlier acquisition of this developmental milestone has been associated with more flexible memory retrieval for a modelled action (Herbert et al., 2007) and significantly greater memory retrieval for a sequence of actions by 9-months-old (chapter 4), with some authors proposing that attainment of this developmental milestone (and the greater experience of the world that accompanies this) may be influencing memory development in early infancy (Rovee-Collier & Cuevas, 2009). In this chapter, eye movement behaviour indicative of remembering face-scene pairs was compared between 7.5-month-olds who had attained independent locomotion (IL group) and their non-locomotive peers (NIL group) on the faces and places eye-tracking task employed in chapter 5 (phase 1). Note this data was previously presented not grouped by locomotion status in chapter 5. Performance was assessed in a follow-up study (phase 2) when aged 9-months-old in a sub cohort of these infants; infants were grouped by those who had previously attained independent locomotion (IL-IL group) and those who attained independent locomotion after participating in the first phase of the study (NIL-IL). Infants who had acquired IL at 7.5-months-old (and thus had greater locomotive experience by 9-months-old) demonstrated eye-movements veridical of remembering previously presented face-scene pairs. In contrast, infants who were non-locomotive (NIL) at 7.5-months-old and had only recently acquired IL when aged 9-months (NIL-IL) failed to elicit eye-movements indicative of remembering the face-scene pairs. These findings tentatively hint that the acquisition of independent locomotion may be providing some mnemonic benefits in early infancy, specifically in the ability to retrieve face-scene associations.

6.1 *Introduction*

As outlined in chapter 4 section 4.1, the attainment of independent locomotion (IL) has been associated with various cognitive benefits including increases in spatial memory (Campos et al., 2000; Anderson et al., 2013). Regarding the mechanism in which IL may be providing these cognitive benefits, previous research has suggested that these changes occur due to the greater visual input acquired through moving oneself through their environment (Iverson, 2010; Kretch et al., 2014) and increase in knowledge base regarding their world around them (Rovee-Collier & Cuevas, 2009).

Alongside age-related differences in hippocampal memory processes in humans, previous research has documented how experiencing an event within a variety of different contexts in infancy results in greater memory retrieval for such events compared to when exposure to an event only occurs in one context (see section 1.3.3). By being able to navigate through environments at will, one is able to gain more experience in a variety of different spatial contexts. Herbert et al. (2007) tentatively associated the acquisition of crawling in 9-month-olds infants with more flexible memory retrieval for a target action when the environment was changed between learning and test, suggesting that attainment of this developmental milestone (and the greater experience of spatial contexts that accompanies this) may be influencing memory development in early infancy (see section 4.1 for a more detailed account of this study). In chapter 4, this thesis also reported significantly greater reproduction of previously modelled actions in infants who had achieved IL at an earlier age compared to their peers who achieved this developmental milestone later in their first year. Together, these findings suggest that IL may be enhancing basic memory for associations in early infancy.

In terms of how IL may be augmenting memory flexibility, relational theory (Eichenbaum & Cohen, 2001) may offer an explanation for this. Relational theory proposes that the hippocampus is crucially involved in forming associations between spontaneously occurring elements within an event and inserting these into existing relational memory networks (see section 1.1.3.4). As we rarely encounter the exact identical perceptual situation, we need to be able to flexibly apply our stored memory representations to novel albeit related situations, termed representational flexibility (Eichenbaum, 1997). IL may provide infants with experience in a variety of different contexts, through the ability to move oneself around their environment at will, and so these associations between different cues and events may be

entered into their relational memory network (Rovee-Collier & Cuevas, 2009). As this network grows with the more experience an infant gains, this body of associations becomes increasingly interconnected and as a result permits more flexible memory retrieval.

Relating this collection of findings to the current study, we hypothesised that IL may provide a memory advantage compared to age-matched non-locomotive peers through extending the relational memory network available to infants who have achieved IL. In the faces and places task previously employed in chapter 5, participants first study face-scene pairs before being presented with this pairing again along with two other equally familiar faces that were presented with different scenes at study. Therefore, participants must be able to retrieve the memory for the face-scene association when the test condition is similar albeit slightly different due to the additional presentation of the other faces, i.e. engage in representational flexibility. As previous research has demonstrated more flexible memory retrieval in 9-month-olds who had achieved IL (Herbert et al., 2007), we hypothesised that infants who have achieved IL in the current study may show better recall for face-scene associations during the faces and places task (indicated by significantly greater preferential viewing elicited to the correct face at test).

Faces and places task eye-tracking data for 7.5-month-old infants previously presented in chapter 5 was re-analysed with participants separated into two groups; those who had achieved independent locomotion (IL) and those who had not attained this milestone (NIL). Task performance was examined again aged 9-months-old in a subset of this cohort. Performance was compared between infants who took part in both phases of the experiment, to assess whether any increases in memory performance between ages are seen with acquisition of IL and if infants who have been self-locomotive for longer (IL-IL group) have a mnemonic advantage over their peers who acquired this milestone later (NIL-IL group). Due to the postulated increase in knowledge and experience that accompanies IL, it was hypothesised that infants who have achieved IL will show a greater proportion of preferential looking towards the face previously paired with the scene at test compared to non-locomotive infants; thus demonstrating better memory for face-scene associations. Taking into considerations the results of chapter 5 which demonstrated that children only elicited eye movements indicative of memory for face-scene associations during shifted-perspective trials when aged 4-years-old (see section 5.3.2.3), it was hypothesised that group differences would

only be present during identical-perspective trials and that neither group should demonstrate preferential viewing of the correct face at test during shifted-perspective trials.

6.2 *Methods*

6.2.1 Participants

Data for 7.5-month-olds (n=60) previously presented in chapter 5 was re-analysed grouped by locomotion status (IL; NIL). Locomotion status was established in the same manner as outlined in section 4.2.1. Data collected at 7.5-month-old therefore formed phase 1 of this study. Infants who had successfully contributed data in phase 1 were invited back to participate in phase 2 when aged approximately 9-months-old (+/- 2 weeks). 36 infants in total had completed the faces and places task at both phases of the study (an additional 8 infants who had not acquired IL by the time testing took place at follow-up provided eye-tracking data; however were not included in the analysis due to group size being too small for accurate group comparisons and statistical analysis). See table 6.1 for group descriptive statistics.

Table 6.1 Descriptive statistics for participants that contributed data to phase 1 and phase 2.

Phase 1 Participants (total n=60)		
Group	Gender	Mean age (*SD*)
IL (n=35)	24 F 11 M	7.80 (*.233*)
NIL (n=25)	15 F 10 M	7.85 (*.270*)
Phase 2 (Follow-up) Participants (total n=36)		
Group	Gender	Mean age (*SD*)
IL-IL (n=24)	16 F 8 M	9.41 (*.336*)
NIL-IL (n=12)	7 F 5 M	9.72 (*.419*)

Note. Mean age in months, SD= standard deviation, IL= independent locomotion acquired group, NIL = group that had not acquired independent locomotion, IL-IL= infants who had acquired independent locomotion in phase 1 when tested again at phase 2, NIL-IL = infants who acquired independent locomotion between phase 1 and attending at phase 2.

6.2.2 Stimuli and Apparatus

We utilised the same 'Faces and Places' task and apparatus outlined in chapter 5 sections 5.2.2 and 5.2.3 for both phases of the study.

6.2.3 Procedure

The exact procedure outlined in section 5.2.4 was used.

6.2.4 Statistical Analyses

The exact analysis outlined in section 5.2.5 was employed.

6.3 *Results*

6.3.1 Phase 1

6.3.1.1 Data Inclusion

Infants contributed test data for 44% of trials (mean= 3.5/8 trials watched, SD= 1.946). When separated by group, there was no significant difference in the number of trials included between IL (mean= 3.7/8 trials watched, SD= 1.856) and NIL infants (mean= 3/8 trials watched, SD= 2.041; U= 332.5, z= -1.595, p= .111, r= -.21).

6.3.1.2 Attention during Learning

Looking time during study trials was above 65% in both groups, in terms of attending to scenes only (IL= 74%; NIL= 74%) and attending to face-scene pairs (IL= 65%; NIL= 70%). No significant differences were observed between groups in their looking time devoted to face-scene pairs during identical-perspective trials (NIL mean= 3660 ms; IL mean= 3588 ms; U= 298.0, z= -1.584, p= .113, r= -.21) and shifted-perspective trials (NIL mean= 3451.30 ms; IL mean= 3166.50 ms; U= 225.0, z= -.753, p= .203, r= -.11).

6.3.1.3 Preferential Viewing of the Correct Face

Functional data analysis was performed within-groups to examine whether the proportion of looking time devoted to the correct face at test significantly differed depending on lag for each of the trial types (identical-perspective, shifted-perspective). No significant differences

in looking time were observed between lag types during identical-perspective trials; this was the case within both locomotion groups. Whilst IL did not show a difference in looking time between lag types during shifted-perspective trials, NIL infant's elicited greater proportion of viewing during time bins spanning 1000-2250 ms within lag 1 compared to lag 2 versions of shifted-perspective trials. Therefore, lag types were collapsed for identical-perspective trials during subsequent analyses while shifted-perspective trial performance was analysed separately by lag type.

Identical-Perspective Trials

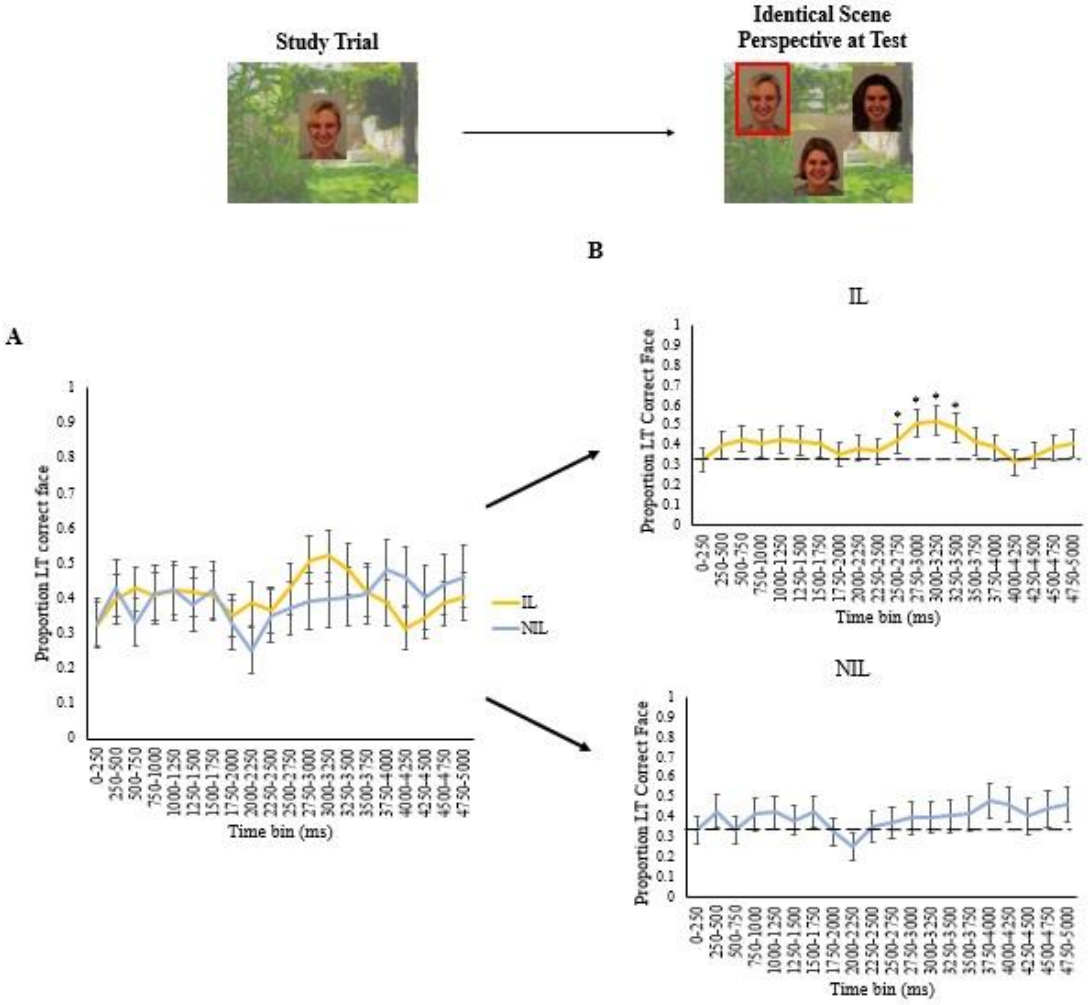

Figure 6.1 Mean proportion of looking time devoted to correct face during identical-perspective trials within-groups (IL; NIL), presented in 250ms epochs.

Note. Asterisks depict time bins where proportion of looking time significantly exceeds chance (.33) within the two groups. Error bars indicate SEM. Dashed line depicts chance proportion of looking time.

We observe different patterns of looking behaviour across groups (figure 7.1). IL Infants elicited preferential looking to the correct face that significantly exceeded chance during time

bins spanning 2500-3500 ms. Within the NIL group, we did not observe preferential viewing of the correct face at any time bin. Hence, the IL infant group demonstrated preferential looking for the correct face, indicative of remembering previously viewed face-scene pairs during identical-perspective trials. This eye-movement behaviour was not present in their non-locomotive (NIL) peers.

Shifted-Perspective Trials

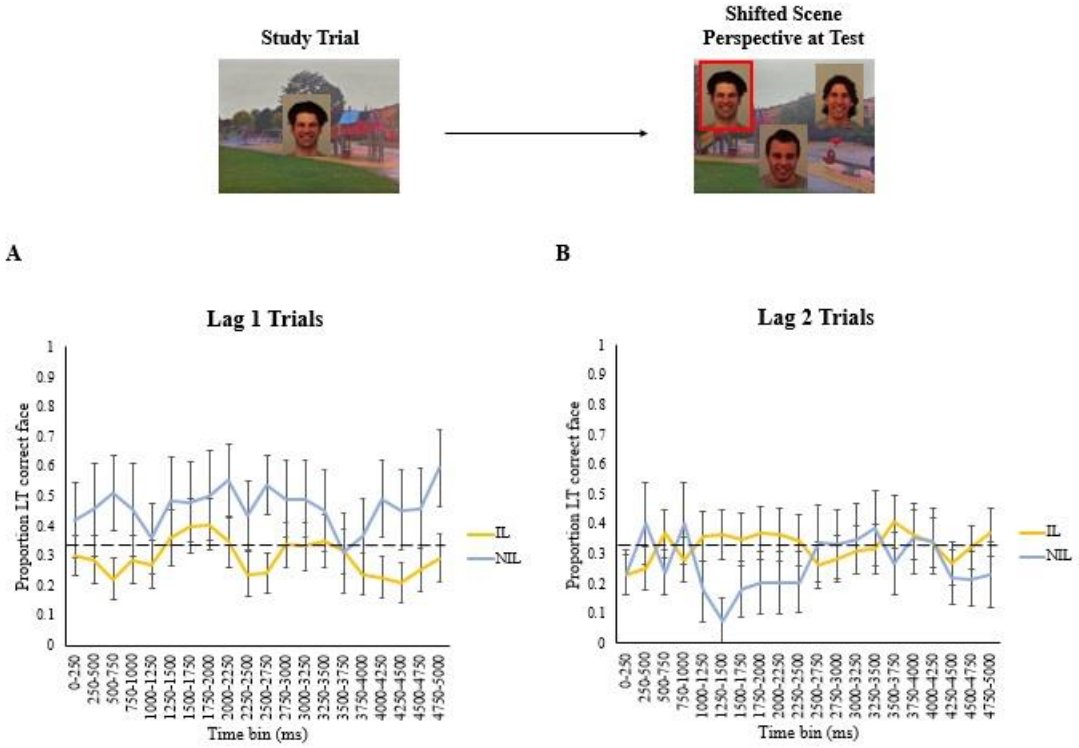

Figure 6.2 Mean proportion of looking time devoted to correct face during shifted-perspective trials when **A)** test trials are presented at lag 1 and **B)** test trials are presented at lag 2, within groups (IL; NIL).

Note. Error bars indicate SEM. Dashed line shows chance proportion of looking time (.33).

For lag 1 shifted-perspective trials, neither NIL infants nor IL infants elicited preferential looking of the correct face that significantly exceeded chance during any time bin (figure 6.2). This was also observed when examining looking behaviour during lag 2 shifted-perspective trials. Thus, both groups failed to show evidence of memory for face-scene pairs when scene perspective was shifted between study and test.

6.3.1.4 Scene Viewing Behaviour

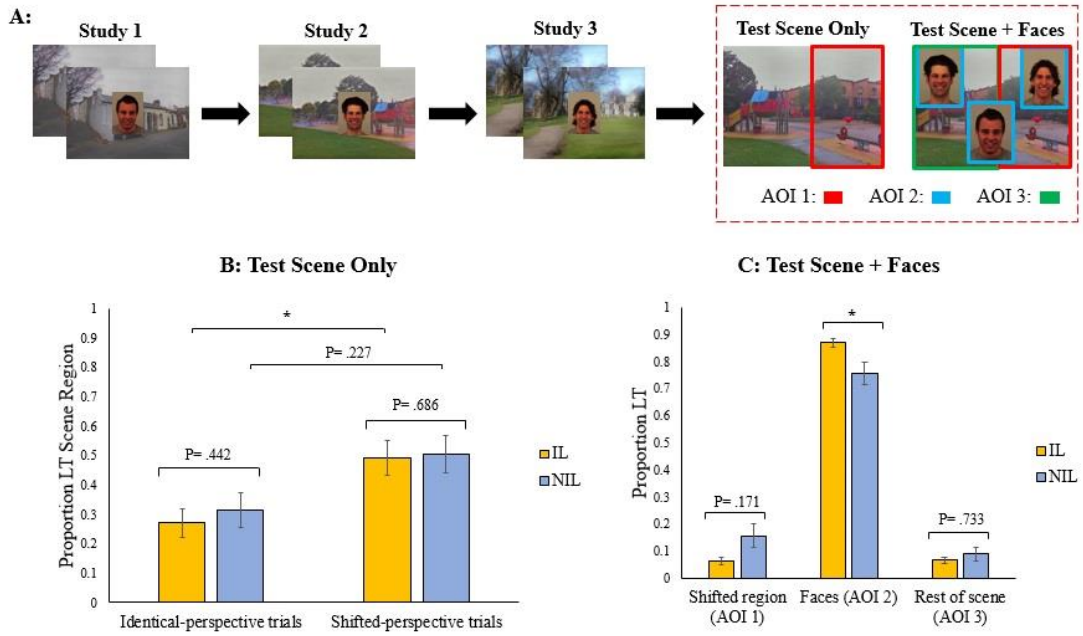

Figure 6.3 Between-group comparisons in scene viewing behaviour during presentation of test scenes in phase 1.

A: Areas of interest (AOIs) used to calculate the proportion of looking time devoted to AOI 1) the novel region (equivalent scene region on identical-perspective trials where no shift in scene view has occurred), AOI 2) the faces and AOI 3) the rest of the scene content during test trials **B:** Mean proportion of looking time (LT) devoted to the novel region during shifted-perspective trials and to the equivalent region during identical-perspective trials, when the test scene is presented alone. **C:** Mean proportion of looking time devoted to different AOI regions when faces superimposed over test scene during shifted-perspective trials. Asterisks mark group differences significant at * p<.05. Error bars indicate the standard error of the mean.

We explored whether the infants' looking behaviour differed between the identical-perspective and the shifted-perspective test scenes; specifically, in whether infants elicited significantly greater viewing of the novel region during shifted-perspective trials compared to the equivalent unchanged region during identical-perspective trials (see Fig 6.3B). If infants looked significantly more at this scene region during shifted-perspective trials, this is indicative of the infants remembering the previously presented scene and realising that this manipulated region is novel. Indeed, infants in the IL group elicited significantly greater viewing of the novel region in the shifted-perspective trials relative to the equivalent region in the identical-perspective trials (Z = -2.519, p =.012, r= -.45). Although this pattern of looking behaviour appears to be present within the NIL group, a significant difference was not observed (z= -1.207, p= .227, r= -.28).

However, when groups are compared in their looking time devoted to the scene region, no significant differences were observed between groups in their looking time devoted to the novel region in the shifted-perspective trials (U = 268.0, z = -.405, p= .686, r= -.06) and to the equivalent unchanged region during identical-perspective trials (U = 348.5, z = -.769, p= .442, r= -.10). Overall, IL and NIL infants are eliciting very similar looking behaviour whilst viewing the test scenes shortly before the faces appear and both groups appear to recognise that the scenes presented at test during shifted-perspective trials consist of scenes previously presented at learning.

To rule out the possibility that differences in performance within groups may arise as infants are unable to associate the faces and shifted-perspective test scenes due to the novel region biasing their attention at test (and so reducing their viewing of the faces), we also examined the proportion of looking time devoted to the three AOIs presented on-screen during shifted-perspective test trials (figure 6.3C). Infants regardless of locomotion status devote a great proportion of their looking time to the facial stimuli. No significant differences were observed between groups regarding the proportion of viewing devoted to the shifted region of the test scene (U = 221.0, z = -1.369, p=.171, r=.19) nor the part of the scene that has remained unchanged between encoding and test (U = 271.0, z = -.342, p=.733, r=.05). However, infants within the NIL group elicited significantly less looking time to the facial regions (U = 188.0, z = -2.022, p=.043, r=.29) compared to the IL group. Therefore, this suggests that the shift in scene perspective appears to be detracting attention away from the faces at tests within the NIL group only.

6.3.2 Phase 2 (Follow-Up)

6.3.2.1 Data Inclusion

Infants contributed test data for 53.5% of trials (Mean= 4.28/8 trials watched, SD= 1.891). When separated by group, there was no significant difference in the number of trials included between NIL-IL (Mean= 4.25/8 trials watched, SD= 2.006) and IL-IL infants (Mean= 4.23/8 trials watched, SD= 1.950; U= 130.5, z= -.055, p= .956, r= -.01).

6.3.2.2 Attention during Learning

Looking time during study trials was above 65% in both groups, in terms of attending to scenes only (IL-IL= 73.4%; NIL-IL= 69.9%) and attending to face-scene pairs (IL-IL= 62.3%; NIL-IL= 65.4%). No significant differences were observed between groups in their looking proportion of time devoted to face-scene pairs during identical-perspective trials (NIL-IL mean= .64; IL-IL mean= .67; U= 115.0, z= -.604, p= .546, r= -.10) and shifted-perspective trials (NIL-IL mean= .67; IL-IL mean = .57; U= 99.0, z= -1.012, p= .311, r= -.17).

6.3.2.3 Preferential Viewing of the Correct Face

Again, functional data analysis was performed within-groups to examine whether the proportion of looking time devoted to the correct face at test significantly differed depending on lag for each of the trial types (identical-perspective, shifted-perspective). From this analysis, no significant differences in looking time were observed between lag type in both identical-perspective and shifted-perspective trials. This was the case within both locomotion groups. Therefore, lag types were collapsed for all subsequent analyses.

Identical-perspective trials

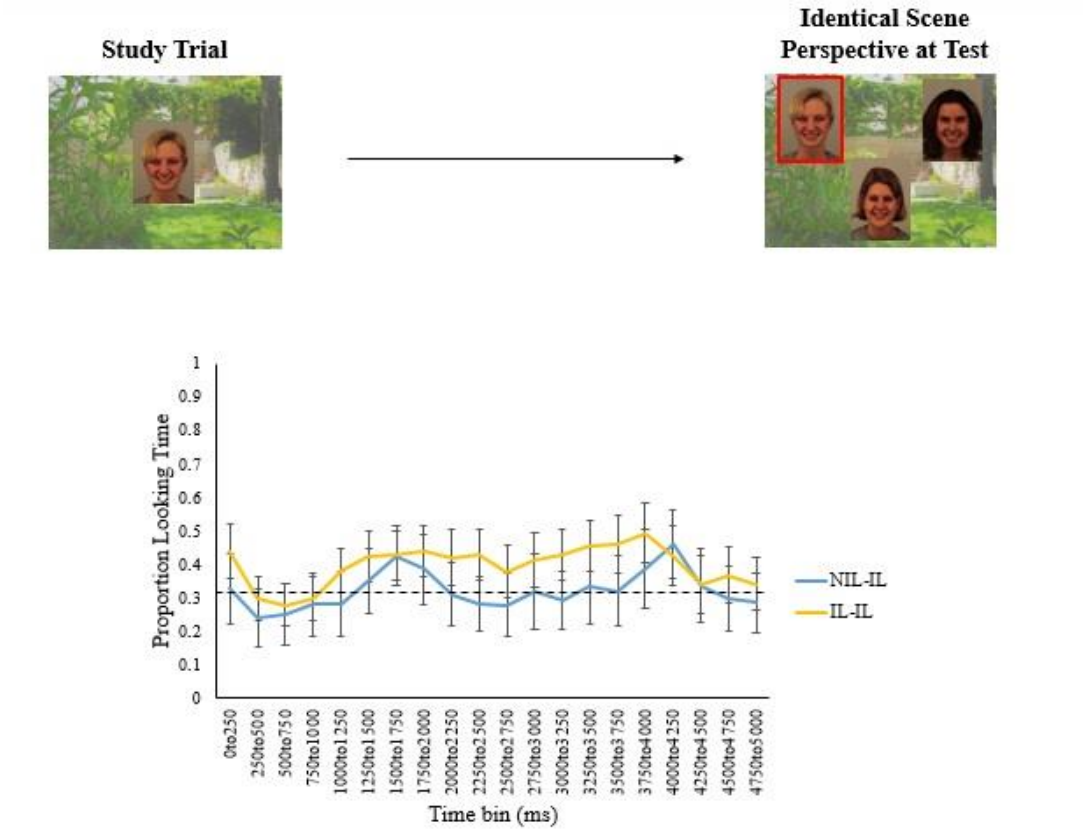

Figure 6.4 Mean proportion of looking time devoted to correct face during identical-perspective trials between-groups (IL-IL; NIL-IL), presented in 250ms epochs.

Note. Error bars indicate SEM. Dashed lines depict chance proportion of looking time.

When examining preferential looking devoted to the correct face during identical-perspective trials, proportion of looking time did not significantly exceed chance in either group. Infants regardless of locomotion group did not elicit preferential looking towards the test face and thus did not show evidence of memory for the face-scene pairs when the scene perspective remained the same at test.

Shifted-perspective trials

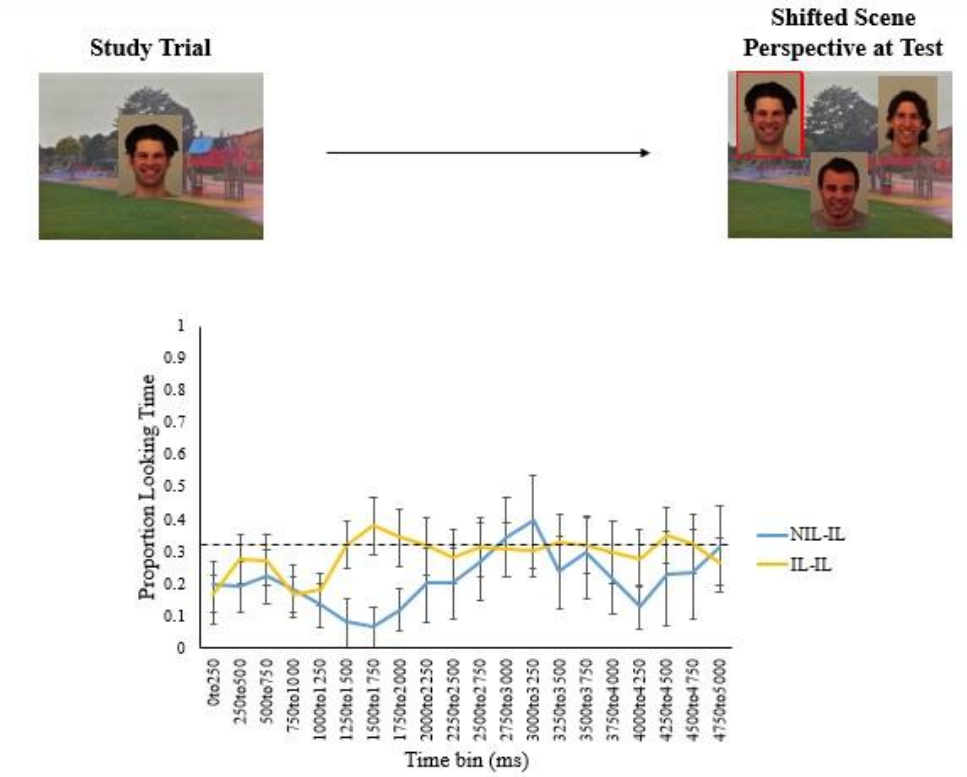

Figure 6.5 Mean proportion of looking time devoted to correct face during shifted-perspective trials within-groups (IL-IL; NIL-IL), presented in 250ms epochs.

Note. Error bars indicate SEM. Dashed lines depict chance proportion of looking time (.33).

When examining preferential looking devoted to the correct face during shifted-perspective trials, proportion of looking time did not significantly exceed chance in either group. Infants regardless of locomotion group did not elicit preferential looking towards the test face and thus did not show evidence of memory for the face-scene pairs when the scene perspective is shifted at test.

6.3.2.4 Scene Viewing Behaviour

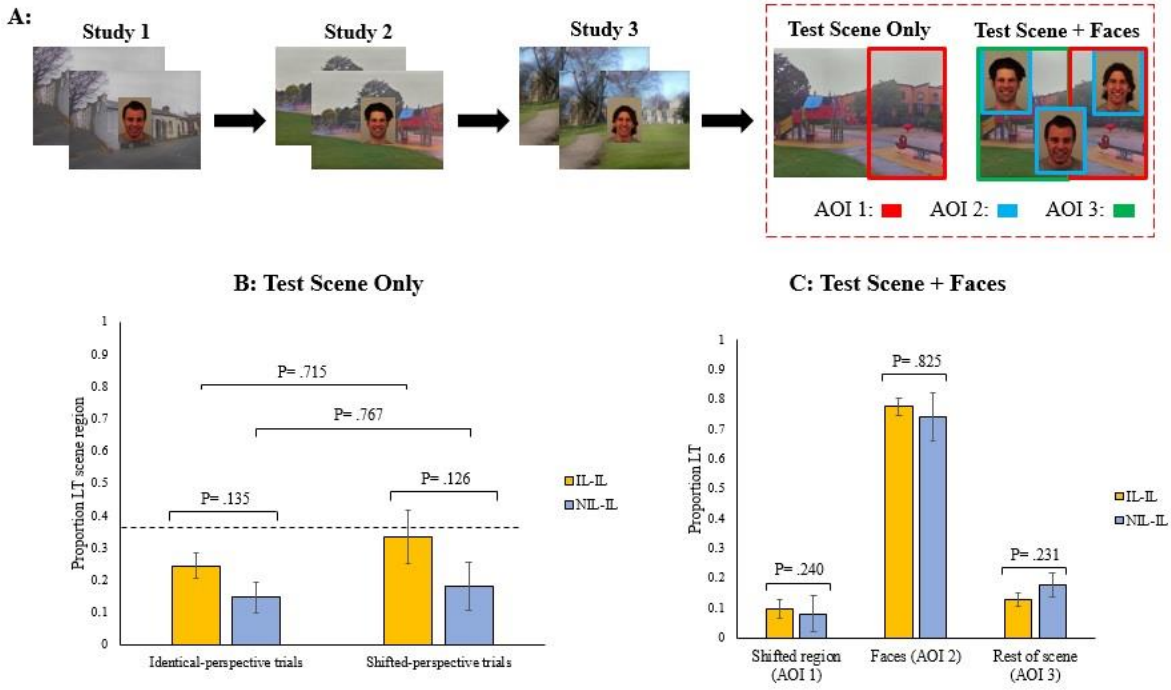

Figure 6.6 Between-group comparisons in scene viewing behaviour during presentation of test scenes in phase 2.

A: Areas of interest (AOIs) used to calculate the proportion of looking time devoted to AOI 1) the novel region (equivalent scene region on identical-perspective trials where no shift in scene view has occurred), AOI 2) the faces and AOI 3) the rest of the scene content during test trials **B:** Mean proportion of looking time (LT) devoted to the novel region during shifted-perspective trials and to the equivalent region during identical-perspective trials, when the test scene is presented alone. **C:** Mean proportion of looking time devoted to different AOI regions when faces superimposed over test scene during shifted-perspective trials. Error bars indicate the standard error of the mean.

When viewing the test scene alone (figure 6.6B), no significant differences were observed between groups in both their looking time devoted to the novel scene region during shifted-perspective trials (U= 85.0, z= -1.532, p= .126, r= -.26) and devoted to the equivalent unchanged region during identical-perspective trials (U= 86.0, -1.495, p= .135, r= -.26). Equally within-groups, there were no significant differences observed between looking time devoted to this region (IL-IL: z= -.356, p= .715, r= -06; NIL-IL: z= -.296, p= .767, r= -.05).

When examining whether group differences exist in looking time devoted to the different AOIs when the faces are presented with the scene at test (figure 6.6C), no significant differences were observed between groups regarding the proportion of viewing devoted to the facial stimuli (U = 120.5, z = -.221, p=.825, r= -.04), the shifted region of the test scene (U =

96.0, z = -1.174, p=.240, r= -.20) or the rest of the test scene (U = 94, z= -1.198, p=.231, r= -.21). It can be observed that regardless of locomotion status group, infant looking time was predominantly elicited to faces during the presentation of the faces and test scene at test.

6.4 *Discussion*

This chapter aimed to develop current understanding of how independent locomotion (IL) may influence the developmental trajectory of hippocampal-dependent associative memory processes in early infancy. In phase 1, 7.5-month-old infants who had achieved IL elicited preferential looking indicative of remembering the face previously paired with the test scene during identical perspective trials. However at phase 2 when aged 9-months-old, a sub cohort of these infants (IL-IL group) failed to elicit preferential looking towards to the correct face. Visibly it can be noted that there are peaks of preferential looking within the IL-IL group during identical-perspective trials (figure 6.5) however this does not significantly exceed chance. This may be due to insufficient power as a result of small sample sizes used. In contrast, infants who had not achieved IL when aged 7.5-months-old (NIL group) and infants who had only recently attained this milestone when aged 9-months-old (NIL-IL group) did not elicit preferential looking towards the face that had been previously paired with the test scene at any point. Taken together, these findings suggest that the acquisition of IL at an earlier age may be resulting in greater memory for previously presented face-scene pairs.

As the faces and places task requires infants to retrieve memory for a face-scene association to a later situation where the association occurs again but in the presence of two equally familiar faces, infants are required to flexibly apply their memory of the pairing in order to elicit preferential looking towards the face previously paired with the test scene relative to the two other simultaneously presented faces. As only infants who have acquired IL by 7.5-months-old elicited preferential looking towards the correct face at test, this suggests that the earlier acquisition of independent locomotion may be enabling these infants to flexibly apply their memory for the face-scene pairings at test. These results therefore appear to resonate with relational theory (Eichenbaum & Cohen, 2001), in that better memory for face-scene associations is observed within the group who have possessed IL for the longest amount of time as they are able to flexibly apply their memory for associations.

Regarding evidence for remembering the face-scene pairs during shifted-perspective trials, both 7.5-month-olds and 9-month-olds regardless of locomotion status do not display looking behaviour indicative of remembering face-scene associations when scene view is shifted between learning and test. This finding was anticipated due to the results of chapter 5 which demonstrated that preferential looking at the correct face at test does not emerge until 4-years-old (section 5.3.2.3). As noted in section 5.4, the absence of eye movement behaviour indicative of remembering the face-scene perspective when scene perspective has been shifted at test may reflect the inability to engage in pattern completion at both 7.5- and 9-months-old, i.e. to retrieve the face-scene association from the partial version of that scene presented at test.

When comparing locomotion groups in their looking behaviour devoted to the test scenes during shifted-perspective trials, we observed significant differences in viewing behaviour between groups. At 7.5-months-old, both groups elicited a looking bias towards the novel region of the test scene during shifted-perspective trials compared to the equivalent unchanged scene areas during identical-perspective trials (although this was only a significant difference in the IL group). These results suggest that 7.5-month-old infants regardless of locomotion status are remembering the previously shown scene as they are recognising that the shifted region is novel. As previously outlined in section 5.4, these findings are incongruent with predictions based on the boundary extension effect (Intraub & Richardson, 1989). If 7.5-month-olds were constructing an internal representation of a given scene that extends beyond the image they had in front of them during the study phase of the task, we would expect that 7.5-month-olds would not elicit a significant looking bias towards the novel shifted region at test, as if they had already processed the scene as wider than it actually is then the new shifted perspective version should not be a huge adjustment to their pre-formed mental representation of the original scene. On the contrary, 7.5-month-olds do elicit a looking bias towards the novel region, inconsistent with the assumptions of boundary extension.

When the faces appear on-screen over the test scene during shifted-perspective trials, NIL infants look significantly less at the faces compared to IL infants. NIL infants looked more at the shifted scene region even when the faces appear on-screen. This suggests that the change to the scene perspective at test is diverting the NIL infant's attention away from the faces and

therefore may be influencing their memory recall failure for face-scene pairs. However, IL infants do not display this looking behaviour whereby the shifted scene area is distracting their attention from the faces at test but still fail to elicit preferential looking towards the face that was previously paired with the test scene. Therefore, the notion that poor performance in the NIL group is resultant of the shifted scene region detracting their attention away from the faces cannot be a comprehensive explanation.

When looking behaviour is examined at phase 2, 9-month-old infants regardless of locomotion status do not elicit the looking bias towards the novel region during shifted-perspective trials and look at the faces for the majority of time when they appear at test. These results are congruent with boundary extension (Intraub & Richardson, 1989), in that as both groups are not eliciting preferential looking towards the novel region on shifted trials, this may suggest that they are less perceptive of this change. This may reflect the fact that if they are engaging in boundary extension and thus processing the original scene in their mind as more zoomed out than it actually is, the difference between their representation of the original scene and the new shifted scene will be less salient. As both groups are engaging in scene construction processes at 9-months-old and 7.5-month-old infants who had acquired IL did not show evidence of eliciting the boundary extension error despite demonstrating evidence of memory for the face-scene pairs in their looking behaviour, this may suggest that locomotion group differences observed in looking behaviour veridical of memory for face-scene pairs may more likely reflect the development of hippocampal binding memory processes rather than being accounted for by the maturation of hippocampal scene construction.

Due to the difficulties associated with eye-tracking young infants, small sample sizes were used. However, sample sizes were comparable with those used in previous eye-tracking literature, e.g. n=28 6-month-olds and n=25 12-month-olds provided sufficient test data in Richmond & Power (2014); n=34 9-month-olds provided sufficient test data in Richmond & Nelson (2009). Low sample sizes used in the follow phase was due to subject attrition between the study phases and that while some infants had successfully produced adequate eye-tracking data at phase 1, they failed to do so at phase 2. Future work should be mindful of using adequate sample sizes when examining infant eye-tracking data, to ensure sufficient statistical power and reduce noise attributed to high variance within data.

In summary, attainment of independent locomotion has been linked to a cascade of developmental changes, including increased social signalling behaviours (Campos et al., 2000), spatial search memory (Anderson et al., 2013) and importantly enhanced memory flexibility (Herbert et al., 2007). The results of chapter 6 suggest that the acquisition of independent locomotion earlier in the first post-natal year may offer mnemonic benefits in terms of greater memory retrieval for face-scene relations relative to age-matched infants who develop this ability later. These findings, coupled with the observation in chapter 4 that infants who have acquired IL earlier in their first year demonstrate significantly more previously modelled actions by 9-months-old compared to peers who attained this milestone later, suggest that the development of independent locomotion appears to correspond with an increase in rudimentary hippocampal associative memory processes. Interestingly, adult-like place cells develop suddenly in the CA1 region of the hippocampal formation at around 2.5 weeks of age in rodents (Langston et al., 2010; Wills et al., 2010), which also corresponds to when rat pups begin weaning and exploring their environment independently (Thiels et al., 1990; Gerrish & Alberts, 1996). Thus, the onset of independent locomotion in rodents appears to parallel when place cells within the rodent hippocampus begin to encode associative memories. Overall, the results of this chapter tentatively suggest that the acquisition of independent locomotion in early infancy may also parallel increases in memory for face-scene events. The potential link between independent locomotion onset and associative memory development is discussed in more detail in chapter 7 section 7.4.

7. Chapter 7. General Discussion

7.1 *Overview*

This thesis aimed to track performance on two previously used infant memory paradigms across the life span, employing tasks which can be used with both pre-verbal infants and adults, and aimed to shed light as to whether these paradigms do appear to be reliant on hippocampal processing. Performance during a deferred imitation task, which examined memory for a three-step action sequence, was assessed across children aged 7.5-months-old to 8-years-old and compared relative to the performance of young and older adult controls and patients with selective hippocampal damage (chapters 2 and 3). Memory for face-scene associations was then examined across all age groups using the faces and places task, with eye movement data obtained in children aged ≤4 years and adult controls (chapter 5). Comparing age groups across the life span using tasks that were not reliant on instructions allowed us to 1) infer whether these tasks are supported by hippocampal memory processes (as indicated by impaired performance in patients) and 2) characterise the developmental trajectory of task performance across early to middle childhood and how this fares with healthy ageing.

An important modification to the faces and places task previously used in Hannula et al. (2007) provided the opportunity to examine memory for face-scene pairings when additional processing of visual scenes was required. Memory for face-scene associations was assessed when scene viewing perspective either remained the same or was shifted slightly between learning and test (chapter 5). We examined whether participants could tolerate the change in scene perspective, i.e. recognise that it is the same place albeit the view of the scene has shifted slightly, to retrieve the previously formed association between that scene and a face.

Lastly, this thesis aimed to not just explore age-related differences in memory performance but assessed whether attaining independent locomotion (IL) in early infancy provides mnemonic benefits compared to peers who develop this ability later in the first year. Performance was compared between infants who had achieved IL and age-matched non-locomotive peers (NIL) at 7.5-months-old. A sub group of these infants returned to participate when aged 9-months-old and performance was compared between infants who had acquired IL by 7.5 months of age compared to age-matched peers who only recently acquired this milestone. Performance was compared between locomotion groups on the deferred imitation task, when the puppet and testing room either remained the same or were different between learning and test (chapter 4). This manipulation provided the opportunity to explore whether

more flexible memory retrieval, indicated by the ability to retrieve memory for the modelled actions when novel but relevant cues are present, is observed in infants who achieved IL earlier in their first year. Finally, performance on the faces and places task was examined between locomotion groups to establish whether attainment of this developmental milestone may be facilitating memory for face-scene associations (chapter 6).

In this concluding chapter, I begin by collectively considering the findings of the experimental chapters and relate these results to extant neuroanatomical knowledge and theoretical perspectives concerning episodic memory development. I also discuss limitations of this work and additional factors that may be influencing memory performance which fall outside of the remit of the hippocampus, before finally reflecting on whether employing a life span approach to study the developmental trajectory of episodic memory processes is a valid endeavour.

7.2 *Are infant memory paradigms dependent on the hippocampus?*

A major aim of this thesis was to establish whether typical infant memory paradigms previously used in the developmental literature appear to measure hippocampal memory processes. Without access to functional neuroimaging, this thesis was limited in its ability to confirm that task performance was underpinned by the hippocampus. However, inferences could be made regarding the recruitment of the hippocampus during each task, by comparing the performance of patients with selective hippocampal damage to that of healthy controls.

In chapter 2, evidence demonstrated that the infant deferred imitation task may successfully index hippocampal memory processing. There was a trend for patients to elicit significantly less actions than older adults, with young adults spontaneously reproducing significantly more correct actions than patients. Patients did not significantly differ in their performance from naïve age-matched controls that had not seen the action sequence modelled previously. The ability to significantly outperform age-matched peers who have not seen the action sequences being demonstrated is typically used in the infant literature as a means of inferring memory retention. Applying the amnesic filter (see section 1.3.2), these findings suggest that the patients demonstrated insufficient memory retention for actions previously modelled.

An important caveat to be considered is that, although visually mean temporal ordering performance is as one would expect i.e. the highest performance achieved by young adults, followed by older adults and then the patients, spontaneous reproduction of temporal ordering performance does not significantly differ between the patients and controls. However, it may be that spontaneous recall for temporal order information of the sequence event is not accurately capturing temporal order memory in adults. See section 7.5.3 for further discussion and consideration of task performance when instructions are used.

Employing the faces and places task, evidence for task reliance on the hippocampus was also observed. Patients verbally recalled significantly less face-scene pairs than both young and older adults. A prominent distinction in the performance of the patients was also observed when comparing memory for face-scene pairs when scene perspective remained the same between study and test (identical-perspective trials) and memory for face-scene pairs when scene perspective was shifted between study and test (shifted-perspective trials). Patients demonstrated poorer recall for face-scene pairs during shifted-perspective trials compared to identical-perspective trials, with this distinction in performance not observed in young adults.

Equally, the results of this thesis suggest that performance on both tasks appears to be sensitive to age-related memory decline. This would be consistent with previous literature which shows that reductions in hippocampal structure and function are observed in healthy ageing (Pudas et al., 2013). During the deferred imitation task, older adults reproduced significantly fewer actions compared to young adults and did not significantly differ from the patients in their reproduction of actions and correct temporal ordering of those actions. However it is noted that older adult mean performance on these measures is visibly higher and trends are observed. During the faces and places task, young adults recalled significantly more face-pairs than older adults. Older adults also demonstrated poorer recall for face-scene pairs during shifted-perspective trials compared to identical-perspective trials; this distinction in performance is not observed in young adults. Therefore, both ageing and damage to the hippocampus appears to particularly impact on the ability to remember associations between scenes and faces when scene view has been shifted between learning and test.

Considering patient performance on both the deferred imitation task and the faces and places task, patients appear to be impaired relative to controls. From these results, it appears that the hippocampus is needed for performance on both tasks. Two notable observations can be made regarding patient performance. Firstly, patients appear less able to retrieve associations between events, i.e. action events during the deferred imitation task and between the faces and scenes during the faces and places task. Secondly, patients elicit poorer memory for shifted-perspective face-scene associations relative to identical-perspective face-scene associations. Therefore, greater memory deficits are observed in the task condition that requires patients to engage in additional processing of the scenes in combination with remembering the face-scene associations. These observations can be related to two accounts of hippocampal function as a way of considering how the hippocampus may underpin performance on these paradigms.

7.2.1 Hippocampal binding processes

Considering relational theory (Cohen & Eichenbaum, 1993), the integrity of the hippocampus is required to successfully bind together the separate elements of an experienced episode (see section 1.1.3.4). As outlined above, patients are less able to sufficiently recall a sequence of actions or the association between simultaneously presented faces and scenes relative to controls. Thus, perhaps failure to bind together the action events and the face-scene pairings may underpin patients' poorer recall for these events.

Furthermore, the associative-deficit hypothesis (Naveh-Benjamin, 2000) postulates that poorer episodic memory observed in old age results from deficits in binding together and retaining the single elements of an experienced episode. Subsequent research has demonstrated that associative memory for items and their contexts declines with healthy ageing (Bastin & Van der Linden, 2005; Plancher et al., 2008; Cheke, 2016). Decreased ability to remember item-context associations may be reflective of CA1 subfield volume loss with ageing (Mueller & Weiner, 2009), with this hippocampal region documented to play a key role in forming associations between items and spatial contexts (Suthana et al., 2009). Therefore, poorer memory for face-scene pairings (i.e. item-spatial associations) in older adults relative to younger adults may reflect less robust binding processes.

However, both patients and older adults demonstrate poorer memory for shifted-perspective pairs, where scene view is shifted between learning and test, compared to identical-perspective pairs. Therefore, less robust hippocampal binding processes may not solely account for this distinction in memory recall within patients and older adults.

7.2.2 Scene construction abilities

A further explanation for poorer memory recall of face-scene pairs observed within the patients may lie in scene construction theory (SCT; Hassabis & Maguire, 2007). As outlined in section 1.1.3.5, the ability to construct continuous scenes in the mind's eye is supported by the hippocampus in adult controls (Hassabis et al., 2007), with this ability compromised in patients with selective hippocampal damage (Mullally et al., 2012a). SCT proposes that performance on any task which requires an internal representation of a scene to be formed should be substantially impaired in individuals with bilateral hippocampal lesions (Maguire & Mullally, 2013). Therefore, as patients overall perform significantly worse on memory for face-scene associations relative to controls, this may arise due to the task requiring participants to create mnemonic associations involving visual scenes.

Furthermore, reduced ability to engage in scene construction within the patients may also explain why they experience more profound memory recall difficulties during shifted-perspective trials relative to identical perspective trials. As outlined in section 5.1, boundary extension (BE; Intraub & Richardson, 1989) denotes the phenomenon whereby we construct an internal representation of a scene that extends beyond the image we have in front of us. This process is argued to occur as an adaptive process to enable the perceptual experience of a continuous world around us, due to our understanding that scenes continue beyond the borders of our available visual field. The BE error refers to a specific memory error whereby we remember seeing more of a scene than was previously viewed and so are more likely to experience a physically identical version of the original scene as more close-up but a wider angle version of such scene as more similar or identical to the original scene (Intraub, 2007). As BE requires the individual to construct internal representations of scenes, it is argued to be a marker of scene construction processing. If successful recall of face-scene associations during shifted-perspective trials involves participants first extrapolating beyond the borders of a previously studied scene in conjunction with binding of the face-scene associations, one could infer that the poorer performance observed in patients with selective hippocampal

damage may be underpinned by decreased ability to construct continuous scenes in the mind's eye and thus greater memory disruption when scene view is shifted as they have not extrapolated beyond the borders of the original scene.

In comparison, young adults did not differ in their recall of identical-perspective and shifted-perspective pairs. If young adults with intact hippocampi have already extrapolated beyond the borders of the scene shown at study, then the scene presented at test should not be grossly different from their existing representation of the study scene. The finding that younger adults do not elicit preferential looking towards the novel shifted region of the shifted-perspective test scenes and that 50% of this group did not notice the shift in perspective when asked suggests that young adults are extrapolating beyond the borders of the scene at study (thus engaging in boundary extension) and this may then allow them to flexibly apply their memory of the face-scene pair when scene perspective is shifted at test.

Although older adults also demonstrated poorer recall for face-scene pairs during shifted-perspective trials relative to identical-perspective trials, eye-tracking behaviour elicited during shifted-perspective trials implies that older adults did engage in scene construction processes. Older adults demonstrated preferentially viewing of the correct face at test and also did not elicit a looking bias towards the novel shifted region during shifted-perspective test trials. Even though task performance was not compared between older adults who noticed the shift and those that did not, due to low sample size, it can be acknowledged that 40% of older adults did not notice the shift. From these results, one could infer that older adults may be engaging in BE and thus performing scene construction processes. Considering SCT argues that any task involving internal representations of scenes is reliant on intact hippocampal functioning, it could be the case that scene construction processes in older adults are not as robust as those of younger adults due to the documented reductions in hippocampal structure and function with normal ageing (Pudas et al., 2013).

Overall, irrespective of the exact process underlying the impairment in memory for face-scene pairs and memory for the action sequence in the patient cohort, all of the potential processes outlined above are subserved by the hippocampus. Therefore, this thesis can infer that both

the deferred imitation task and faces and places task appear to be measuring hippocampal-dependent processes.

7.2.3 Limitations and Considerations

A limitation of this thesis is that a small sample size was obtained for the patient group. Therefore, these results need to be interpreted with caution as group sizes are unequal when making between-group comparisons. However, one must consider that VGKCC_LE is a rare disorder. Previous studies that have recruited this patient group are overwhelmingly single case design or typically only feature 3-10 patients (Radja & Cavanna, 2013). To the author's knowledge, the largest number of patients with VGKCC_LE included in a study has been n=19 (Butler et al., 2014). However, the data of Butler et al. was collected over a number of years, with different neuropsychological assessments used dependent on the timing of data collection. Although future research examining memory performance in patients with selective hippocampal damage with VGKCC_LE should attempt to include larger sample sizes, this may be a difficult endeavour. Another factor to be considered is that VGKCC_LE is most common in adults over 55 years (Radja & Cavanna, 2013). Therefore, impaired task performance in the patient cohort could potentially be increased by hippocampal functional decline arising from normal ageing too.

Moreover, as outlined in chapter 5, an unanticipated finding was that patient P01 demonstrated different (and greater) performance compared to the remaining patient cohort on the uninstructed explicit memory test of the faces and places task. P01 also presented with a very atypical profile in terms of the temporal gradient of their amnesia compared to the rest of the patient cohort (see appendix A) and previously reported cases of VGKCC_LE (Butler et al., 2014). Further evaluation should be conducted to determine the nature of P01's task performance and memory deficits.

A further limitation is that eye-tracking data was not obtained for the patients due to the unreliability of the portable eye-tracker data. Performance on the explicit memory tests provided valuable insight into memory retrieval of the face-scene pairs within the patient cohort and implied that this task is dependent on hippocampal memory processes for successful recall of the pairings. However, the explicit task was reliant on verbal recall and

therefore comparisons between implicit memory for the face-scene pairs obtained via eye-tracking could not be made between the patients and other groups. Previous research by Hannula et al. (2007) demonstrated that patients with selective hippocampal damage failed to elicit eye movements veridical of remembering face-scene pairs relative to controls, thus implying that looking behaviour was indicative of implicit hippocampal memory retrieval. Future research should attempt to measure eye movement behaviour during the modified faces and places task in a larger cohort of patients and when access to a more robust eye-tracking device is available. This would allow investigation into the eye movement behaviour of patients when scene view-point is altered during shifted-perspective trials and consequently provide further insight into the mechanism that underpins the patients' more profound deficit in remembering pairs when the scene perspective has shifted relative to when the perspective is identical between learning and test.

7.3 *Tracking task performance across the life span*

The second aim of this thesis was to establish the developmental trajectory of task performance across the life span and particularly how memory for associative elements within an experienced event develop across childhood and become adult-like. Performance on each task employed in this thesis is discussed, considering how performance at distinct ages may be explained by extant accounts of hippocampal function.

7.3.1 Age-related development of memory for action sequences

In chapter 2, 7.5-month-old infants imitated significantly more previously shown actions relative to naïve age-matched peers, thus concurring with previous literature indicating that infants aged between 6-9 months can demonstrate memory retrieval for previously modelled actions (Collie & Hayne, 1999; Meltzoff, 1988). However, 7.5-month-olds' performance did not significantly differ from that of patients and lacked the proficiency of healthy adults. Prior research has advocated that as 1) 6-9-month-old infants can outperform naïve age-matched peers on infant deferred imitation tasks and 2) adults with hippocampal damage are impaired relative to controls on adult deferred imitation tasks, this means that these young infants are demonstrating hippocampal-dependent memory (McDonough et al., 1995). While our results replicated both of these previous findings when the same methodology was used to permit direct comparisons between infants and patients, this comparison also revealed that 7.5-month-old infants are performing no different from patients with compromised hippocampi.

When task performance is examined across childhood in chapter 3, both spontaneous and instructed recall for actions and the correct temporal order of those actions was found to emerge at 4-years-old. At this age, performance did not significantly differ from young adults. From 4-years-old, memory for actions and the temporal order of those actions remained relatively constant between 4-8 years and did not significantly differ from young adults. Intriguing, subtle differences in the developmental trajectory for action memory and temporal order memory were observed (see figure 7.1). While both types of memory became adult-like by 4-years-old and remained relatively stable from this age onwards, memory for actions increased more incrementally with age from approximately 2-years-old whereas temporal order memory emerged more sharply around 4-years-old with another increase in performance observed at 8-years-old. When instructed to reproduce the action sequence, both memory for actions and memory for temporal order reflected adult-like performance by 4-5 years.

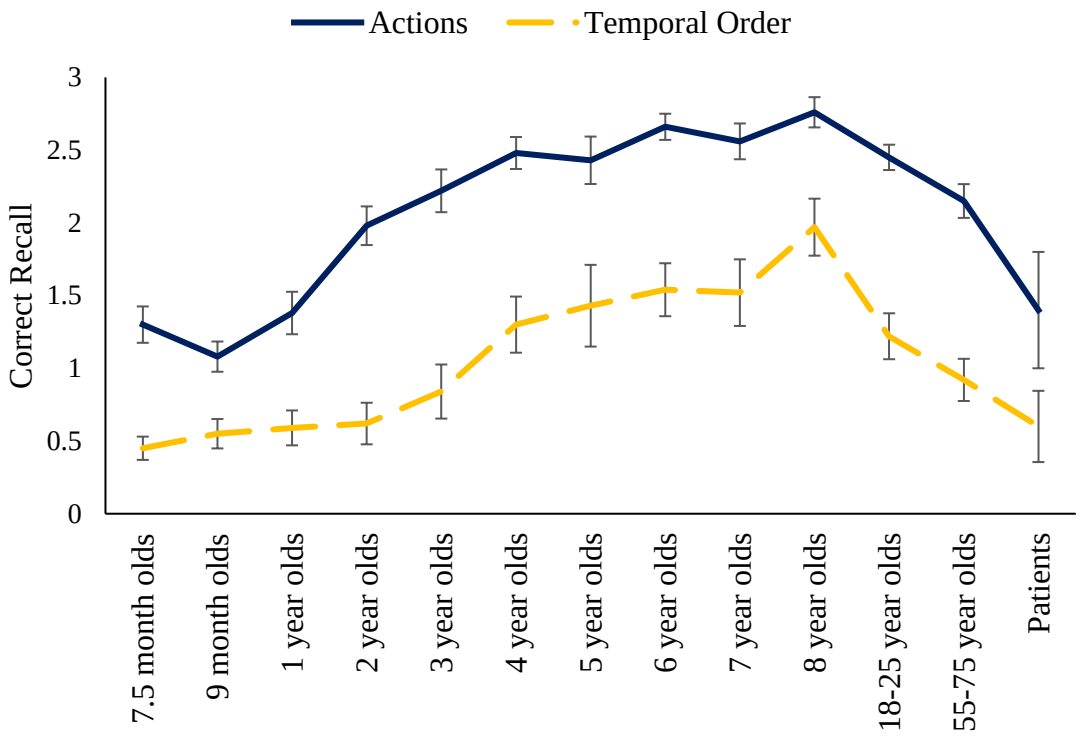

Figure 7.1 Illustration of differences in spontaneous reproduction of actions (solid line) and temporal order information (dashed line) across all experimental age groups.

Note error bars show standard error of mean. Taken from Chapter 3 section 3.3.2.

Overall, this collection of results is consistent with previous literature regarding the developmental trajectory of which memory for actions (or '*what*' memory) and memory for temporal order (or '*when*' memory) are postulated to emerge. At 2 years of age, children began to demonstrate significantly more correct actions than younger age groups; concurrent with previous research which has shown older infants within their second year of life demonstrate significantly more previously modelled actions than younger infants (Barr et al., 1996; Herbert & Hayne, 2000a).

The observation that children under the age of 2 years demonstrate poor temporal order recall is in agreement with previous research that has shown children younger than 20-months-old perform at chance on memory for temporal order of arbitrarily-paired actions (Wenner & Bauer, 1999). Studies employing different methodologies have also documented memory for the temporal context of associations emerges at 4 years (Hayne & Imuta, 2011; Cuevas et al., 2015) and continues to develop into middle childhood and beyond (Scarf et al., 2017). Thus, using the same task across all age groups, these results agree with these previous findings in that approximately 4-years-old marks the emergence of more adult-like temporal order memory. Additionally, the developmental trajectory for memory for temporal order information is delayed relative to memory for action information.

The results regarding the development of memory for an action sequence are also consistent with neuromaturational perspectives of episodic memory development (Jábes & Nelson, 2015; Gomèz & Edgin, 2016), which argue that the emergence of more complex hippocampal-memory processes, such as the ability to bind and retrieve specific context-rich content of episodic events, occurs due to the development of the trisynaptic circuitry within the hippocampal formation. As described in chapter 1 section 1.1.1.1, the monosynaptic pathway within the hippocampal formation that consists of the entorhinal cortex and the CA1 subfield is argued to undergo major structural changes between the ages of 0-24 months in humans, with evidence acquired from human infant post-mortem data (Insausti et al., 2010) and non-human primates (Lavenex and Banta Lavenex, 2013). The dentate gyrus (DG) and CA3 subfield, which form key sections of the trisynaptic pathway, follow a more prolonged developmental trajectory, only reaching adult-like levels of synaptic pruning by 4-5 years in humans (Bauer, 2007) and continuing to change both structurally and functionally into adolescence (Daugherty et al., 2017).

The subtle distinctions in the development of memory for actions relative to memory for temporal order may be reflective of the maturation of different hippocampal circuitry. The increase in memory for action information at 2-years-old may arise due to the maturation of the monosynaptic pathway and emergence of trisynaptic connectivity at around this age. Temporal order memory may then emerge later when a greater degree of maturation of the trisynaptic circuit has occurred around 4-years-old. Temporal order memory has also been intrinsically linked to the prefrontal cortex (Barker et al., 2017); thus, the development of this neural region and its functional connectivity with the hippocampus should influence the emergence of temporal order memory also. This is discussed in section 7.5.5.1 below. Overall, differences in the development of episodic memory processes observed during the deferred imitation task are congruent with previous theoretical perspectives linking the emergence of different building blocks of episodic memory with neuroanatomical development of the hippocampal formation (see figure 7.2; Jábes & Nelson, 2015).

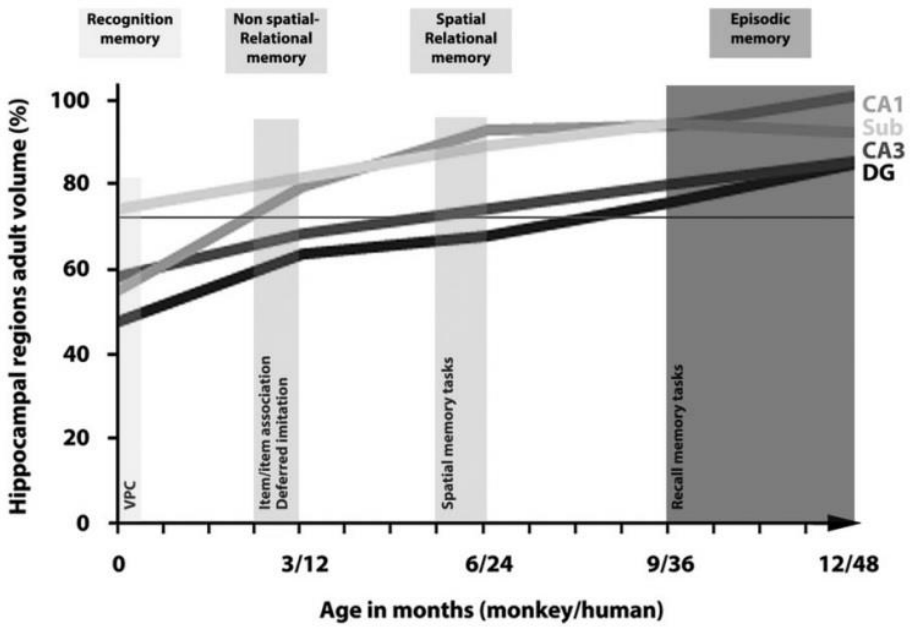

Figure 7.2 Visual representation of the parallel development of the hippocampal regions in monkeys and the emergence of different memory functions in humans.

Note one year in monkeys corresponds to 4 years in humans (Fortman et al., 2001). Taken from Jábes & Nelson (2015). Previously presented in chapter 1 section 1.3.3.

7.3.2 Age-related development of memory for face-scene associations

Chapter 5 demonstrated that all groups aged between 7.5-month-old to 4-years-old, with the exception of 3-year-olds, demonstrated eye movements veridical of remembering face-scene

pairs when scene view remained identical between study and test. However, the time course and consistency of this eye movement behaviour varied between age groups and did increase with age to reflect eye movement behaviour of young adults. Thus, these results suggest that looking behaviour indicative of remembering face-scene pairings does not follow a linear trajectory, in line with previous applications of the faces and places task in the literature (Koski et al., 2013; Richmond & Power, 2014; Liu, 2015). Changes in task performance with increasing age in childhood may reflect differences in cognitive processing underpinning memory performance at distinct ages.

Interestingly, it is again at 4-years-old that children first demonstrated evidence of looking behaviour indicative of remembering the face-scene pairs when scene perspective was shifted between study and test; children ≤3 years did not elicit this pattern of preferential looking. All age groups with the exception of 7.5-month-olds appear to view the shifted scenes as relatively the same as the original scenes shown at learning (due to a lack of novelty looking bias elicited to the new scene content on shifted trials). 7.5-month-old infants demonstrated significantly greater viewing of the novel region during shifted-perspective trials compared to the equivalent unchanged region during identical-perspective trials. As outlined above in section 7.2, shifting scene perspective between learning and test had a detrimental effect on memory for previously presented face-scene pairs in older adults and to a more significant extent in patients with selective hippocampal damage. In contrast, shifting scene perspective between learning and test did not impact on recall for face-pairs in young adults and children aged 5-8 years.

As outlined in chapter 5 (section 5.4) several theories of hippocampal function could potentially account for age-related differences in memory for face-scene pairs during the faces and places task. These results are interpreted in light of three prominent accounts of hippocampal function below.

7.3.2.1 Age-related differences in binding processes

Differences in the type of binding processes employed during the faces and places task may explain distinctions in looking behaviour between age groups. As outlined in section 7.3.1, the monosynaptic pathway reaches adult-like levels of maturity by around 2-years-old, while

the dentate gyrus and CA3 subfields which are central parts of the trisynaptic pathway begin to reach a level of functional maturity which is able to support more complex memories of events by around 3.5 years (Lavenex & Banta Lavenex, 2013). Children under 4-years-old are argued to engage in more unitary binding of objects and contextual features, with unitary processing argued to be supported by the perirhinal cortex and neocortical areas. In contrast, configural binding (i.e. processing discrete elements of an event separately but also forming associations between these elements) is argued to increase from 4 years into adolescence, with this type of binding argued to be supported by the hippocampus (Edgin et al., 2014; see section 5.4). The early emergence of the monosynaptic pathway is postulated to permit basic associative memory processes (Jabès & Nelson, 2015); therefore, rudimentary configural binding processes may be present from 2-years-old (Gomez & Edgin, 2016).

As outlined in section 5.4, participants are required to correctly locate the face previously paired with the test scene in the presence of two equally familiar faces. Thus, the appearance of the face-scene pair at test is not visually identical to its original presentation at learning. Age-related differences in the availability of the more complex trisynaptic circuitry in early childhood may mean that binding processes are subserved by different neural circuitry depending on the age of the participant. If younger children are processing the face-scene display in a unitized way, memory for the pairing (and thus preferential viewing of the correct face) may be disrupted when the face-scene display at test is not perceptually identical to the display presented at study (i.e. with two additional faces present). Weaker binding abilities may result in some evidence of memory of the face-scene pairings, as indicated by the presence of preferential viewing from 7.5-months-old, but this memory retrieval may not be as robust as that of older children. The longer peak of preferential looking observed in 4-year-olds compared to younger children may be reflective of the emergence of functional trisynaptic circuitry around this age and may signify the performance of 4-year-olds is beginning to reflect more adult-like configural binding.

Moreover, shifting the scene perspective is a more drastic change to the face-scene display if bound in a unitized manner. If children under 4 years are encoding face-scene pairs in a more unitized manner, changing the scene perspective may mean that the test scene is now regarded as novel and thus this may lead to the failure to retrieve the face that was previously paired

with this scene, i.e. if the scene is no longer regarded as relevant to the previously encoded memory representation of the original scene and face.

Furthermore, we do not know whether young children are regarding the scenes *as* scenes or whether they are binding the face stimuli with a low level feature of the scene, e.g. the colour of an object within a scene. Although we do know that children cannot be using spatial frequency, luminance or contrast as low level features to bind with the face, as these were controlled for by applying the SHINE toolbox filter to all scene stimuli (see chapter 5 section 5.2.2.1). If younger children are binding the faces to low level features of the scenes, this could mean that the portion of the scene that contained the low level feature may not be present when the scene perspective is shifted during shifted-perspective trials. This could then lead to memory retrieval failure as one of the elements within their memory representation is absent. Overall, age-related differences in preferential viewing of the test face may be related to distinctions in the type of binding processes that are used when encoding face-scene stimuli between age groups.

7.3.2.2 Shifted-perspective scenes and scene construction abilities

As discussed in chapter 5 section 5.4, the absence of looking directed to the novel region during shifted-perspective trials reflects the classic boundary extension observation whereby participants fail to report a change between close-up and wider angle scenes as their pre-existing representation of the original scene contains more content due to extrapolating beyond the borders of the scene (Intraub & Richardson, 1989). Therefore, the shifted test scene should not be radically different from their memory of the original scene and so they should not elicit biased viewing of the novel scene region. 7.5-month-olds do elicit a looking bias towards the novel region, inconsistent with the assumptions of boundary extension and with previous literature that has documented the presence of this phenomenon in infants as young as 3-months-old (Quinn & Intraub, 2007). Nonetheless, as all age groups over the age of 7.5-months-old do not elicit preferential viewing of the novel scene region, this suggests that age-related differences in their ability to remember face-scene pairings may not be fully explained by differences in scene construction abilities.

7.3.2.3 Shifted-perspective scenes and pattern completion

An alternative explanation for the emergence of eye movements indicative of remembering shifted-perspective face-scene pairs at 4-years-old could be related to the proposed increases in functional maturation within the trisynaptic circuitry around this age. The ability to retrieve memory representations from partial cues, i.e. pattern completion, is supported by the CA3 subfield of the hippocampus, with this subfield not appearing structurally mature until approximately 4-years-old (Fortman et al., 2001) and possessing a prolonged developmental trajectory for functional maturity (Jábes et al., 2011).

As the neural substrates supporting pattern completion are not sufficiently developed by ≤3 years, these age groups should be unable to engage in pattern completion processes which could result in their absence of eye-movement behaviour indicative of remembering face-scene associations when scene perspective has been shifted at test. In contrast, 4-year-olds who possess an adequately mature trisynaptic circuitry may be able to engage in sufficient pattern completion to retrieve the face-scene association at test when presented with a partial cue i.e. the shifted version of the original scene. This proposal is supported by explicit memory performance in children aged 5-8 years; recall of pairs on shifted-perspective trials did not significantly differ from performance on identical-perspective trials in all age groups, similar to performance observed in younger adults. If 4-years-old marks the age where the trisynaptic circuitry in the hippocampus is adequately mature to support pattern completion, this would mean that children aged ≥5 years may be able to sufficiently engage in pattern completion processes during recall of shifted-perspective trials, i.e. by retrieving memory for the face previously paired with that scene from the partial cue available (the shifted version of the original scene). Equally, a lack of sufficient functioning in the CA3 subfield, and thus inadequate pattern completion abilities, could also explain the poorer memory performance observed during shifted-perspective trials relative to identical-perspective trials within the patient group.

7.3.3 Recognition memory

The hippocampus is argued to support recollection-based recognition, i.e. actively recollecting previous stimuli and their specific contexts upon encountering them again (Aggleton & Brown, 1999). In contrast, familiarity-based recognition, i.e. the sense of familiarity upon encountering a stimulus that was previously presented in the absence of specific contextual

information, is argued to be supported by rhinal areas particularly the perirhinal cortex (Bowles et al., 2007). This distinction between the hippocampus' role in recognition memory is referred to as dual process theory (Aggleton et al. 2005) and is vehemently debated in the literature (e.g. Wixted & Squire, 2004). To check that the patients could remember being shown the demonstration video containing the action sequence and to acquire additional information regarding how hippocampal recall processes may be developing, recognition memory was also examined in older children and adult groups. Recognition of actions modelled previously was examined in all groups (see chapter 3 section 3.3.3.4) and recognition for events occurring during demonstration was examined in adult groups (see chapter 2 section 2.3.4.3).

As all child age groups viewed the live demonstration of the action sequence, as opposed to the demonstration video used to present the action sequence to adults, this meant that recognition for single events was not measured in children. The decision to not use the demonstration video with the child groups was based on the phenomenon referred to 'video deficit', whereby very young children learn less from television/video clips than equivalent live experiences (Anderson & Pempek, 2005). Employing deferred imitation paradigms, infants aged 12-15 months shown a video version of an action sequence elicit significantly poorer reproduction of the modelled actions compared to age-matched infants who learnt the actions via live demonstration (Barr & Hayne, 1999). Hayne et al. (2003) also observed that this video deficit effect is still present in children aged 30-months-old (i.e. 2.5 years). In order to accurately compare deferred imitation performance across all child groups in this thesis, the decision was made to model the target action sequence via live demonstration. A demonstration video was used to present the action sequence within the adult groups as there were concerns that live demonstration without directing participants to the fact they had to learn the sequence may have been patronising or made adults feel uncomfortable. When live demonstration was used with an extra group of adults to rule this out as a memory confound (see appendix B), no significant differences were observed between adults who viewed the video or live demonstration.

In chapter 2, patients were able to successfully recognise whether single, visually distinct events had occurred previously in the demonstration video but were impaired relative to controls when they were required to determine whether visually-similar target and lure actions

had been previously presented. In chapter 3, 3-year-olds demonstrated recognition memory for single actions that did not significantly differ from the performance of patients and identified significantly more novel (i.e. false) actions as being previously modelled compared to all other age groups. In contrast, children aged 4 years and over did not significantly differ from young adults. Notably, the correct and false actions presented during the recognition test were very similar and possessed a great degree of feature overlap.

Applying the principles of dual-process theory, it could be inferred that perhaps the patients and 3-year-olds are unable to rely on familiarity-based recognition when judging whether actions had been demonstrated previously (a process argued to be supported outside of the hippocampal formation; Aggleton & Brown, 1999), due to the actions shown being highly similar. When forced to rely on recollection-based recognition subserved by the hippocampus, this could therefore result in poor recognition accuracy (and thus high false alarm rates) in the patients with damaged hippocampi and in 3-year-olds with immature hippocampal processes.

Higher rates of false alarms when forced to engage in recollection-based recognition as opposed to reliance on familiarity-based recognition could be attributed to the inability to discriminate between correct and novel actions that are visually-similar, i.e. ineffective pattern separation. As previously outlined, pattern separation appears to be supported by the DG and CA3 subfield within the hippocampal formation (Bakker et al., 2008; Lacy et al., 2011). While there are a dearth of studies that examine the development of pattern separation processes across childhood, Ngo et al. (2018) found that 4-year-olds frequently reported lure items as having being previously viewed when novel lures that were visually similar to previously presented items during a recognition test. This study reported that the ability to correctly discriminate between old items and visually similarly lures increased between 4-6 years. Relating this study to my findings, it could be inferred that high false alarm rates in 3-year-olds may reflect ineffective pattern separation abilities due to immature hippocampal circuitry within the DG and CA3 subfields at this age. Equally, hippocampal damage in the patients (particularly considering CA3 subfield atrophy has been documented in patients with VGKCC_LE) may be preventing this group from engaging in pattern separation processes to adequately distinguish between correct actions and highly similar novel actions.

Secondly, the high rates of false recognition in patients and 3-year-olds may be a result of using gist-based memory retrieval. Gist-based false recognition refers to the incorrect recognition of lure items that are perceptually similar to previously encountered items, as a result of failure to retrieve the specific details of an event but just the 'gist' of what occurred during the event (Brainerd & Reyna, 1998). In contrast, verbatim-based retrieval, e.g. the specific details of an event, is more demanding on memory, deteriorates at a faster rate than gist-based retrieval and is more prone to forgetting than gist memory. If the patients are unable to rely on familiarity-based recognition (due to item similarity) and also have impairments in their recollection-mediated recognition due to their hippocampal injury, they may be forced to rely on gist-based retrieval, resulting in their high rate of falsely recognised actions. Previous research in children aged 6- and 9-years-old found that presenting lures that were highly semantically similar to previously presented targets resulted in gist memories of targets being cued as opposed to verbatim memories (Reyna & Kiernan, 1994). Therefore, false recognition in the 3-year-olds may reflect reliance on gist-based memories for the correct actions, due to faster deterioration of verbatim memories and as high similarity between target and novel actions meant that gist-based memory for correct actions presented was cued.

Furthermore, this thesis measured recognition confidence during both action and event recognition in the adult groups, as confidence ratings have been commonly applied to indicate whether familiarity-based recognition is being used as opposed to recollection-based recognition (Yonelinas, 2002). Research argues that low confidence ratings are reflective of weak familiarity-based recognition but high confidence recognition responses could be indicative of either strong familiarity-based recognition or recollection-based recognition (Migo et al., 2012).

All groups, including the patients, provided confidence ratings that fell within the ranges of '*fairly confident*' to '*quite confident*' for both action and event recognition responses (which are middle-high range responses on the confidence Likert scale) and there were no significant differences in confidence ratings between the patients and adult controls. As the patient's confidence ratings were in the higher end of the response scale, this would suggest that patients are either employing recollection-based recognition or strong familiarity-based recognition for their responses. However, as discussed above, the novel actions in the

recognition test were visually similar to the correct actions and so this would imply that recollection-based recognition must be relied upon to remember the specific actions previously modelled. The patient's high false alarm rate indicates that the patients are impaired at performing recollection-based recognition. Therefore, it is surprising that patient confidence ratings are high, even for their responses to the false actions for which they had very poor memory accuracy as indicated by a high false alarm rate.

As noted previously, making conclusions regarding the basis of recognition memory using confidence ratings should be tentatively employed, because relying on subjective reports may be problematic in terms of accuracy and subject self-awareness. 'High confidence errors' are found to occur when the ability to match subjective confidence with memory accuracy is miscalibrated (Shing et al., 2009). If recollection is compromised in patients with hippocampal damage, it may be difficult for them to adequately gauge the accuracy of their memories when recollection is required. Thus, patients may have a skewed reference point if they do not experience true recollection-based memory processes.

A potential limitation of this thesis is that confidence ratings were not obtained for children completing the action recognition test, as this could have shed light further on whether 3-year-olds were using recollection- and opposed to familiarity-based recognition. However, the decision to omit the confidence rating scale from the children's recognition task was 1) to avoid responses being confounded by language ability (as confidence ratings in younger children may be dependent on whether they understand language related to introspection and that they are being asked to introspect on their performance) and 2) there is conflicting evidence for the existence of poor calibration between performance accuracy and confidence ratings in young children. For instance, Pressley et al. (1987) demonstrated that when children aged 6-11 years were asked to rate their confidence in their ability to select the picture that best matched the target word out of a choice of 4 pictures, children aged 6-8 years provided high confidence ratings for both correct and incorrect responses and were less accurate in judging the correctness of their responses compared to 9-11-year-olds. In contrast, other studies have reported that children as young as 3-5 years can provide high confidence ratings that are congruent with correct memory performance (Lyons & Ghetti, 2013; Destan et al., 2014)

However, there is still evidence that increasing the presence of lure questions at recognition test results in children aged 8- and 10-years-old showing over-confidence for incorrect responses (Roebers, 2002). In this thesis, the task involved making memory judgments when highly similar lure items were present (i.e. novel actions were visually similar to previously modelled correct actions during the recognition task). Therefore, using confidence ratings to evaluate recollection- vs. familiarity-based recognition in children aged 3-8 years would have contaminated by the fact that confidence ratings provided by younger children may not be congruent with the memory processes they are argued to reflect.

7.3.4 Section Summary

Overall, we observed age-related increases in these forms of hippocampal-dependent memory. A common observation across both tasks is that 4 years appears to mark a critical age whereby children begin to demonstrate more adult-like hippocampal-dependent memory, with recall for temporal order of actions and action recognition reflecting adult-like performance at this age and the emergence of the ability to recollect face-scene pairs when scene perspective is shifted by 4 years. However, there is also evidence to suggest that individual experience may play a fundamental role in memory development (see chapter 1 section 1.3.3). Ecological accounts of memory development propose that the acquisition of diverse experiences in early life, including the acquisition of developmental milestones may be related to increases in mnemonic abilities in early childhood (Rovee-Collier & Cuevas, 2009). Indeed, the findings of this thesis suggest that the acquisition of independent locomotion (IL) may be providing mnemonic benefits to young infants (outlined subsequently in section 7.4).

7.4 *The acquisition of independent locomotion (IL) and memory development*

In this thesis, performance was examined on a deferred imitation task (chapter 4) and the faces and places task (chapter 6) between infants who acquired IL at an earlier age and age-matched counterparts who developed this milestone later in their first year. During the deferred imitation, significant differences were not observed between locomotion groups when aged 7.5-months, both in action reproduction and correct temporal ordering. However in the subgroup assessed later when 9-months-old, infants who had attained IL at an earlier age (IL-IL) reproduced significantly more actions than infants who had only recently acquired this

developmental milestone (NIL-IL). When performance is assessed during the faces and places task, infants who had acquired IL at 7.5-months-old (and thus had greater locomotive experience by 9-months-old) demonstrated eye-movements veridical of remembering previously presented face-scene pairs. In contrast, infants who were non-locomotive (NIL) at 7.5-months-old and who had only recently acquired IL when aged 9-months (NIL-IL) failed to elicit eye-movements indicative of remembering the face-scene pairs. Overall, these findings tentatively hint that the acquisition of independent locomotion may be providing some mnemonic benefits in early infancy.

As discussed in chapter 4 section 4.4 and chapter 6 section 6.4, a hypothesis as to how the earlier acquisition of independent locomotion may be providing memory advantages may lie in the ideologies of relational memory theory (Eichenbaum & Cohen, 2001). Relational theorists proposed that the hippocampus forms associations between spontaneously occurring elements within an event and inserts these into existing relational memory networks (see chapter 1 section 1.1.3.4). As we rarely encounter the identical perceptual situation twice, we need to be able to flexibly apply our stored memory representations to novel albeit related situations, termed representational flexibility (Eichenbaum, 1997). Independent locomotion may provide infants with experience in a variety of different contexts, through the ability to move oneself around their environment at will, and so these associations between different cues and events may be entered into their relational memory network. As this network develops with the more experience an infant attains, this system of associations becomes increasingly interconnected and as a result permits more flexible memory retrieval. This hypothesis is compatible with previous research which has demonstrated that increasing experience in different contexts at learning allows infants to elicit greater memory retrieval for previously seen actions than assumed possible for their age (see chapter 1 section 1.3.3). Relating this hypothesis to the results of this thesis, it could be that greater memory flexibility with a larger attainment of locomotion experience is allowing infants to form more robust associations between actions presented within an action sequence and between face-scene pairings within the faces and places task. If acquisition of independent locomotion is allowing infants to gain more knowledge about the world, this may mean that they have a greater number of relational representations to insert new knowledge into.

Spatial context is a key component of episodic memory (Tulving, 1972) as all events that we experience take place within some form of environment or spatial location. When an infant first begins to move independently, they are able to enhance their knowledge of spatial relations in a variety of different contexts and learn how to transport themselves from one place to another. Thus it is not surprising that research suggests an association between experience with self-produced locomotion and performance on spatial search tasks, typically applying the A-not-B paradigm (Campos et al., 2000). Piaget (1954) originally documented that infants under 9 months of age consistently search for a hidden object in location 'A' after object retrieval has previously been repeated at this location, even when they observe the object being moved to location 'B', termed the 'A-not-B-error'. Studies which have compared the performance of 7.5-9.5 month old infants that are either crawling, non-crawling or non-crawling with experience using a walker, have demonstrated that the more crawling experience an infant has, the better their performance on the A-not-B task (Horobin & Acredolo, 1986; Kermoian & Campos, 1988). Greater knowledge of spatial contexts could be providing mnemonic scaffolding to allow infants who attain IL earlier to remember pairings between faces and spatial contexts, i.e. scenes. This view is consistent with literature which argues that spatial context acts as a foundation on which to encode episodic memories (Maguire & Mullally, 2013) and that the presence of a spatial context scaffold results in richer and more vivid memories for events compared to instances where memories for events are encoded in the presence of minimal spatial context information (Robin, Wynn & Moscovitch, 2016).

The proposal that the onset of independent locomotion may be linked to increases in memory for associations between items and spatial contexts are supported in non-human animal studies that document the emergence of hippocampal-dependent place learning. In rodents, adult-like place cells develop suddenly in the CA1 region of the hippocampal formation at around 2.5 weeks of age (Langston et al., 2010; Wills et al., 2010), which also corresponds to when rat pups begin weaning and exploring their environment independently (Thiels et al., 1990; Gerrish & Alberts, 1996). As outlined previously in section 1.1.3.3, place cells and grid cells support the mental representation of previously visited environments which individuals can then use as a basis for memory and navigation, with place cells eliciting firing patterns isolated to single locations while grid cells elicit numerous firing fields in a grid-like array representing the entire environment available to the individual. As noted by previous studies (Langston et al., 2010; Wills et al., 2010), these adult-like place cells that develop abruptly

around post-natal day 16 (P16) before the emergence of adult-like grid cell firing and at the age that rat pups first show evidence of exploratory behaviour if removed from the boundaries of their nest by the experimenter.

Along with the onset of spontaneous independent locomotion, allocentric spatial abilities become functional at around P21 (Tan et al., 2017), with the maturation of these abilities extending into the second month of life in rats (Scott et al., 2011). In Muessig et al. (2016), electrophysiological recordings were obtained in rats at P16 when engaging in spatial exploration in novel environments and environments sharing common cues with the spatial environment in which they had been previously exposed to. In the absence of adult-like grid cells, the hippocampus fired during processing novel environments and showed reactivation of previous firing patterns when placed in a familiar environment or a novel environment that shared a large degree of visual and sensory features with a familiar environment. Therefore, these results suggest that the rodent hippocampus begins to encode and retrieve associative memories when rats first engage in spatial exploration and when they do not possess functional mature grid cells. Hence, the onset of independent locomotion in rodents may facilitate the encoding and retrieval of spatial memory representations.

These findings, coupled with human infant studies indicating an increase in allocentric spatial learning that appears to be associated with the acquisition of independent locomotion (Anderson et al., 2013), correspond with a theory proposed by Nadel & Moscovitch (1984). These authors suggest that the development of allocentric spatial memory facilitates the advancement of episodic memory functions in infancy. Lavenex & Banta Lavenex (2013) echo this sentiment and argue that the acquisition of path integration- obtained through self-generated movement- and basic allocentric spatial memory is obtained in human children in a hierarchical manner that reflects underlying maturation of hippocampal circuitry (see figure 7.5). If the onset of independent locomotion is linked with increases in spatial memory abilities, perhaps this key developmental milestone (and the spatial knowledge that accompanies this) is providing the first building blocks for the later emergence of more complex associative learning.

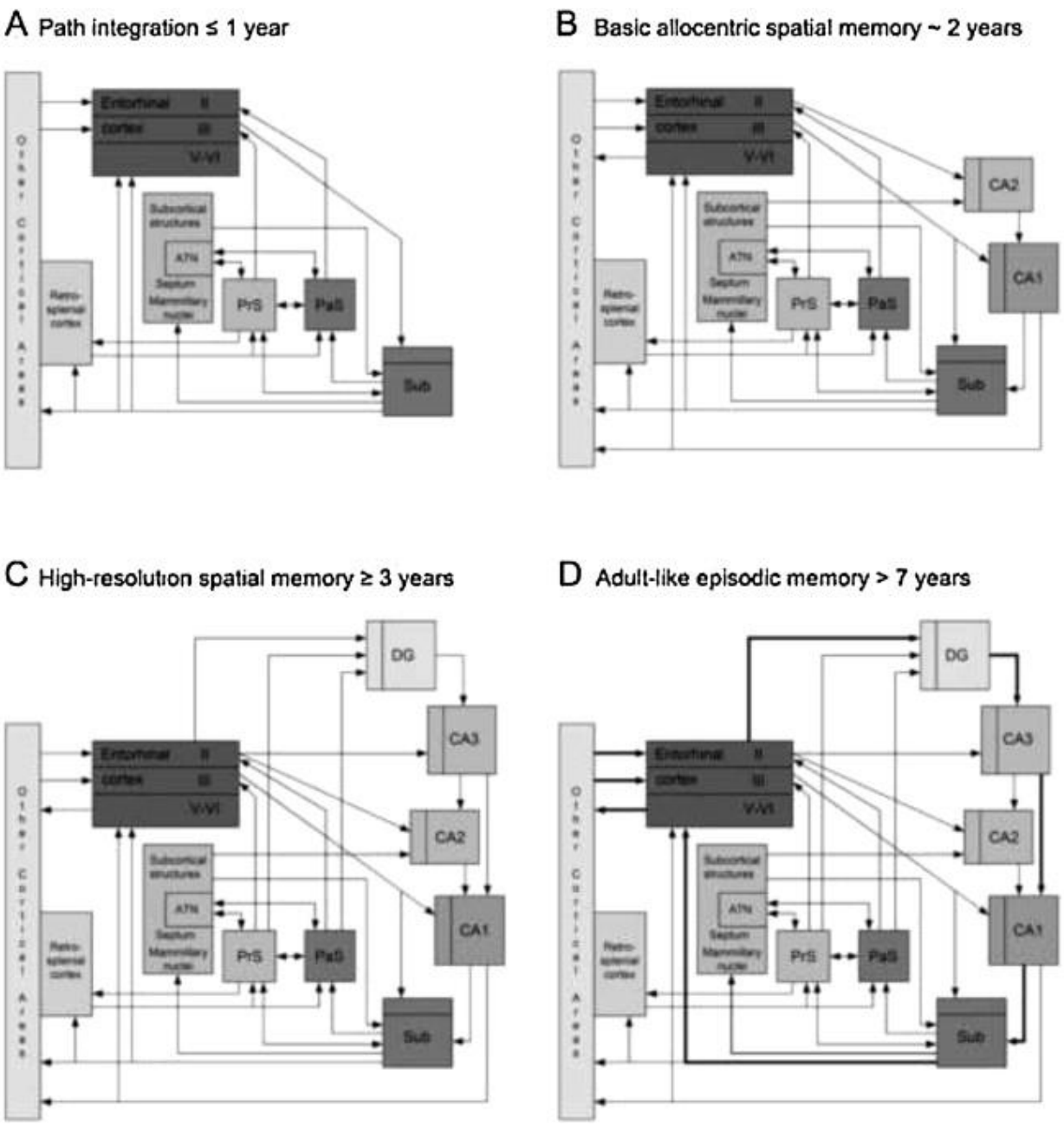

Figure 7.3 Model of the postnatal maturation of the primate hippocampal formation and how this may correspond to the gradual emergence of hippocampal-dependent functions in human children. Taken from Lavenex & Banta Lavenex (2013).

A= Maturation of the subiculum, presubiculum and parasubiculum may support path integration abilities before 1 year of age in children.

B= Maturation of hippocampal circuits involving the direct projections from the superficial layers of the entorhinal cortex to CA1 may result in the emergence of basic allocentric spatial memory abilities at 2 years of age in children.

C= Prolonged maturation of the dentate gyrus and CA3 subfields may underpin the emergence of high-resolution allocentric spatial memory after 3 years of age in children.

D= More complete maturation of hippocampal circuitry may support episodic memory abilities after 7 years of age in children.

Note ATN= anterior thalamic nuclei; DG= dentate gyrus; Sub= subiculum; PrS= presubiculum; PaS= parasubiculum; II, III, V–VI= layers of the entorhinal cortex.

Therefore, one could hypothesise that the experience gained from exploring ones environment following the onset of independent locomotion could be facilitating rudimentary hippocampal-dependent memory processes, resulting in the memory advantages observed in groups that have achieved this developmental milestone earlier within this thesis. The acquisition of this ability may increase an infant's knowledge base and thus provide cognitive scaffolding to enable more flexible memory retrieval processes as an infant learns more about the world around them.

7.5 *Is tracking task performance across the life span a valid approach?*

Generally, the results of this thesis suggest that there are age-related increases in memory for action sequences and face-scene pairs when using tasks that appear to rely on the hippocampus. However, conducting this research has highlighted important caveats that should be considered when employing the same tasks to track memory across the life span.

7.5.1 Potential age-related differences in the neural correlates of performance

Firstly, various accounts of hippocampal function could be used to explain the findings of this thesis. For instance, as highlighted in section 7.5, differences between age groups in looking behaviour indicative of remembering face-scene pairs during shifted-perspective trials could reflect age-related differences in pattern completion ability, relational binding processes and/or the ability to engage in scene construction. The two tasks employed in this thesis are also very different in their demands, e.g. the deferred imitation task involves temporal ordering memory which is not probed in the faces and places task. Reflecting on the recent findings of Dalton et al. (2018), who observed that distinct processing circuits within the hippocampus are recruited depending on task requirements (see chapter 1 section 1.1.5.1), it may be that age-related differences across the tasks used in this thesis reflect differences in the circuitry underpinning task performance according to task demands as well as considering the age of the participant.

Another important consideration when reviewing task performance across the life span is whether older children and adults are approaching the tasks in the same way as infants and younger children, i.e. are the same neural structures and cognitive inputs underpinning

performance on each task. Similar performance across different age groups (e.g. a similar number of actions recalled in the deferred imitation task between 4-year-olds and young adults) does not necessarily mean that the same cognitive processes are underpinning these outcomes. Episodic memory development appears to follow a prolonged and complex developmental course which seems to align with the protracted maturation of hippocampal circuitry underlying this cognitive faculty, with hippocampal subfields (and the functions they support) reaching maturity at different ages (Jabes & Nelson, 2015). Therefore, we should not make assumptions that similar performance across different ages is underpinned by the same neural areas.

A restriction of this thesis is that although we can infer that performance on the deferred imitation task is hippocampal dependent (deduced from patients with selective hippocampal damage performing poorly on this task relative to healthy adults), we do not have direct functional neuroimaging evidence that performance in child participants is underpinned by hippocampal processing. In the absence of access to neuroimaging techniques in this thesis, inferences were instead made regarding hippocampal involvement by determining at what age children show adult-like performance that exceeds that of the patients. Neuroimaging would provide invaluable insight into the structural and functional maturation of the hippocampal formation and interconnecting cortical regions. A handful of studies have innovatively examined developmental changes in hippocampal structure and function and how these correspond to episodic memory processes in middle childhood (e.g. Ghetti et al., 2010; DeMaster & Ghetti, 2013; Lee et al., 2014; Daugherty et al., 2017). However, these procedures have been largely restricted to paediatric populations aged over 8 years. This is due to the practical difficulties in performing brain scanning with very young children.

Future research should attempt to directly examine the neural correlates of behavioural performance on memory tasks in early childhood and also contrast neural patterns of activation between children and adults, both with or without hippocampal damage. This knowledge is needed to comprehensively confirm task reliance on the hippocampus during typical infant memory paradigms and to determine whether parallel performance observed between infants aged 7.5-months-old and patients with hippocampal damage in chapter 2 is due to residual functioning remaining in the patient group that corresponds to rudimentary hippocampal functioning in the infant brain or whether performance in both groups is

subserved by neural substrates outside of the hippocampal formation. Equally, functional neuroimaging employed during task performance would also shed light on whether similar behavioural performance elicited between children and adults is underpinned by the same neural activity.

7.5.2 Cross-sectional versus longitudinal approaches

In this thesis, memory was assessed across the life span in a cross-sectional manner, purely due to time constraints. The only exception was that task performance was tracked across a two month period in the locomotion study (chapters 4 and 6). Longitudinal studies which focus on select age groups and follow-up these children over time are able to track individual performance and patterns of behaviour over critical periods of development. However, longitudinal approaches are not always feasible. In this thesis, data collection from 7.5-months-old to 8-years-old provided a wealth of information about task performance from early infancy to middle childhood which would not have been achievable within the time constraints of this thesis if conducted in a longitudinal manner. Furthermore, repeating testing on an annual or semi-annual basis would have introduced the issue of practice effects, which could have confounded any potential age-related increases in memory.

A factor to be considered is that segmenting age groups by year (i.e. 1-year-olds, 2-year-olds, 3-year-olds, etc.) meant that we could not explore differences at ages that fall between age brackets. For instance, as children assigned to the age bracket '3-year-olds' could be +/- 4 months of their 3rd birthday, this meant that children in this age group could be aged 32-40 months. Previous literature has argued that more complex '*what-where*' memory has been found to emerge at around 42-months-old (i.e. 3.5 years; Ribordy et al., 2015). Therefore, as more complex memory abilities appear to emerge at around 3.5 years, it may be the case that although we see temporal order memory during spontaneous recall in the 4-year-olds that does not significantly differ from young adults, this could potentially be emerging just prior to this age (as the 4-year-old age bracket spans children aged 44-52 months). This could also be the case when contrasting performance between the 1-year-old and 2-year-old age groups. The 1-year-old group contains infants aged up to 14 months while the 2-year-old group contains infants aged from 20-28 months. Previous literature has documented that 18-month-olds demonstrate significantly better memory for previously modelled actions compared to 12-month-olds and performance at 18 months did not significantly differ from that of 24-

month-olds (Barr et al., 1996). Therefore, there is the potential that the increase in action reproduction observed within the 2-year-old group may emerge slightly earlier at 18-months-old. Future studies should be mindful when dividing participants into age brackets, to ensure performance is being assessed at key points in development.

Future research could also assess task performance across late childhood into early adolescence, as memory was not assessed within these age groups in this thesis. Varying measures of episodic memory have demonstrated age-related increases in memory between the ages of 10-15 years (Shing et al., 2008; Ghetti, 2017), with neuroimaging data revealing distinct structural and functional changes in the hippocampus (Gogtay et al., 2006; Daugherty et al., 2017) and other key neural regions within the core memory network (Giedd, 2004; Sowell et al., 2004) that extend into late adolescence. Therefore, investigating task performance from 8-years-old to young adulthood would allow the developmental trajectory of memory for action sequences and face-scene associations to be evaluated while these key behavioural and neuroanatomical changes are occurring. It would also be of interest to investigate task performance from young adulthood to old age, as decline in memory proficiency has been noted to occur from 20-30 years of age onward (Salthouse, 2003; 2009).

7.5.3 Suitability of using tasks without explicit instructions across the life span

It is important to consider the amount of language demands required during tasks when attempting to track performance across the life span. As highlighted in section 1.3.1, tasks used with older children and adults typically rely on instructions. Thus, comparisons between language proficient groups and pre-verbal infants are not suitable as instructions may provide older groups with an unfair memory advantage (see section 7.5.5.3 below for further discussion on the impact of language on memory development). This thesis aimed to utilise paradigms that did not rely instructions for successful performance, in order to permit valid comparisons across all age groups. However, as noted in chapter 3, we observed significant differences in performance during the deferred imitation task dependent on whether instructions were provided within older children and adult groups, which may question whether the use of tasks without explicit instructions are accurately capturing mnemonic abilities in older participants.

During the deferred imitation task, we observed that young adults did not significantly differ from the patients in their memory for the temporal ordering of actions when recall was assessed spontaneously, i.e. without being directly instructed to perform the actions in the correct order. Temporal ordering ability during spontaneous reproduction of the action sequence does not reach ceiling within any age group, including older children and young adults. When instructed to reproduce the actions in the correct temporal order, young adult performance significantly increases and exceeds that of both older adults and patients. Significant increases in temporal order recall are also observed in children aged ≥6 years when instructions are provided. Verbally probing memory for the order of the actions also increased recall of temporal order information in children aged 4-years-old, thus, suggesting that perhaps not emphasizing the need to reproduce the actions in the correct order may be resulting in their lower temporal ordering score obtained prior to verbal assessment of order. Overall, these results suggest that spontaneous reproduction of an action sequence in infant paradigms may not accurately capture temporal order memory in older children and adults. Perhaps certain infant paradigms are too simplistic for use with older children and adults and thus may underestimate performance in these groups. While avoiding the use of instructions may mean that comparisons can be made from pre-verbal infants to adults, one must consider that an absence of instructions may mean that tasks are not suitably measuring their target construct in older age groups.

7.5.4 The impact of experience of memory

As outlined in section 1.1.3, a large body of literature has demonstrated that increasing an infant's experience with different contextual information facilitates more flexible memory retrieval (Rovee-Collier & Cuevas, 2009). This thesis also tentatively suggests that the acquisition of independent locomotion at an earlier age in the first year of life provides infants with mnemonic benefits that are not observed in age-matched peers who attain this developmental milestone slightly later (see section 7.4). While these results have implications for how experience may play a role in memory development in addition to neural maturation of hippocampal circuitry, these findings also highlight how individual differences in experience may play a role in performance. Therefore, when authors are employing a life span approach, the impact of attaining different developmental milestones (and individual differences in acquiring these) should be considered.

7.5.5 Age-related differences in cognitive input outside of the hippocampus

While this thesis aimed to establish age-related changes in episodic memory processes across the life-span, using a task that is supported by the hippocampus; it is not assuming that any changes in memory with age are solely dependent on the maturation of this neural structure. The hippocampus does not support memory in isolation (Spreng et al., 2009) and so the development of interconnecting cortical regions (and the cognitive functions they underpin) must be considered, particularly those which belong to the network consistently recruited during episodic memory processing. Equally, the development of cognitive abilities that are required to support task performance outside of providing mnemonic functions should also be considered, e.g. attention, metacognitive strategies and visual perception. I discuss below factors that may have particular relevance to the findings of this thesis.

7.5.5.1 Pre frontal cortex development and episodic memory

Amongst the identified structures in the episodic memory network, the prefrontal cortex (PFC) has been shown to play a dominant role in long-term memory consolidation (Eichenbaum, 2017; Kitamura et al., 2017). The PFC is argued to serve episodic memory by performing controlled strategies like top-down processing, which in turn decrease or augment memory for a particular event (Blumfeld & Ranganath, 2007). Recruitment of the PFC in adults has been shown during metacognitive strategies like rehearsal (Rowe et al., 2000; Wagner et al., 2001; Narayanan et al., 2005) and 'selection processes' i.e. directing attention towards goal-relevant information or inhibiting attention to irrelevant information (Bunge et al., 2001; Dosenbach et al., 2008).

Neuroimaging data indicate that the PFC follows a protracted maturational course that appears to continue into adolescence (Giedd, 2004). Studies have demonstrated that there are no structural differences observed between participants aged 5-30-years-old in the fornix (which connects the hippocampus to brain regions like the basal forebrain and mammillary bodies; Amaral & Insausti, 1990). In contrast, white matter tract connectivity within the uncinate fasciculus (connecting the anterior hippocampus to the lateral and orbitofrontal PFC) follows a protracted developmental course that continues into adulthood (Lebel et al., 2008; Lebel & Beaulieu, 2011). Gray matter volume in the dorsolateral prefrontal cortex is one of the last regions to reach maturity (Gogtay et al., 2004) and PFC cortical thickness changes are observed across childhood into adolescence (Sowell et al., 2004) and reach adult-like levels in the early twenties (Giedd, 2004).

The structural and functional maturation of the PFC, along with increases in white matter connectivity between this region and the hippocampus, is argued to be an impetus for episodic memory development (Ghetti & Bunge, 2012). Specifically, age-related improvements in episodic memory are postulated to arise from acquiring strategic processes mediated by the PFC (Shing et al., 2008; 2010; DeMaster & Ghetti, 2013). Age-related increases in functional connectivity between the left medial temporal lobe and left PFC are observed between the ages of 11-19 years when encoding outdoor visual scenes (Menon et al., 2005).

The ability to engage in controlled processes has been observed from 3-4-years-old. Balcomb & Gerkin (2008) reported that 3.5-year-olds were more likely to skip memory trials that they subsequently answered incorrectly relative to those they later answered correctly when required to answer all questions in a forced-choice memory task. Other studies have found that strategic memory processes emerge slightly later around 4 years. Hembacher & Ghetti (2014) conducted a study where children aged 3-5 years first encoded items before completing a forced-choice memory task. Participants also provided confidence ratings for each of their responses and were then allowed to decide whether or not to exclude or select answers to be evaluated for a possible reward if found to be correct. Only 4- and 5-year-olds reported lower confidence for items they had provided incorrect responses for compared to correct responses and also excluded their weakest memories from the evaluation, resulting in their more accurate memories being judged for a potential reward. From 4 years children appear able to introspect on their memory accuracy and begin to monitor their own mental state.

The results of this thesis may be related to prefrontal cortex development in two ways. Firstly, more adult-like memory for the action sequence and face-scene associations from 4-years-old may be underpinned by the development of prefrontal cortex controlled processes. If older children are able to engage in control processes and process information in a strategic manner, this may enable them to elicit superior memory for events and their spatiotemporal context (temporal context being the temporal ordering of the actions in the deferred imitation task and spatial context relating to scenes during the faces and places task). Furthermore, adult-like temporal order memory observed from 4 years onwards may be reflective of prefrontal cortex development due to the role this neural region plays in temporal order memory (Barker et al., 2017; see chapter 3 section 3.4).

7.5.5.2 Oculomotor Control and Attention

It is acknowledged that age-related differences in oculomotor control and visual attention may have impacted upon task performance during the faces and places task, principally when using looking behaviour as an implicit measure of memory during the eye-tracking task. As discussed in section 5.4, children aged from 7.5-months-old to 4-years-old (with the exception of 3-year-olds) elicited preferential looking towards the correct face during identical-perspective trials. However, the timing of this looking behaviour differed between groups in terms of where the looking bias fell within the test trial epoch and how prolonged a given fixation was. Potential age-related differences in the ability to fixate on the correct face at test and maintain attention towards this stimuli in the presence of additional stimuli may have resulted in younger participants approaching the tasks differently compared to older children and adults.

Firstly, group differences in the duration of fixations elicited to the correct face at test may be related to the development of visual fixation, i.e. the ability to retain a static visual stimulus in the fovea and resist making inappropriate eye movements (Krauzlis, 2012). This process is crucial in order to maintain focused attention (discussed subsequently in this section). The ability to engage in visual fixation emerges early in the first post-natal year, with infants demonstrating relatively stable fixations prior to 6-months-old (Scerif et al., 2005), consistent with the development of the visual system in the brain and accompanying increases in visual acuity at this age (Chandna, 1991). However, the stability and control over fixations increases through childhood and into adolescence (Luna et al., 2008). For instance, several studies have shown from the ages of 4-15 years, the duration of visual fixations increases with age whereas the amount of intruding saccades (i.e. rapid eye movements between fixations) decreases (Ygge et al., 2005; Aring et al., 2007).

Another form of oculomotor control which could influence fixation duration and therefore impact on task performance during the faces and places task, is the development of both reflexive and voluntary saccades. As stated above, saccades are rapid eye movements between fixation points and play an important role in visual perception by bringing selected retinal images to the fovea (i.e. the region of the eye that permits the greatest visual acuity) and working collaboratively with smooth pursuit movements to maintain fixation directed to the selected image (Krauzlis, 2012). Reflexive saccades refer to involuntary or automatic eye

movements in response to visual stimuli while voluntary saccades consist of eye movements that are controlled and not stimulus-driven (Luna et al., 2008). The development of these two forms of saccades appear to follow different trajectories; reflexive saccades appear to be relatively mature at birth while voluntary eye movements develop gradually across infancy into toddlerhood (Scerif et al., 2005a), increasing across middle childhood and into adolescence (Paus et al., 1990; Munoz et al., 1998; Fukushima et al., 2000).

Age-related increases in the ability to exert saccadic control could be linked to the protracted maturation of the prefrontal cortex (Luna et al., 2008), as this neural region has been implicated in controlled strategies like top-down processing of incoming visual stimuli (as outlined in section 7.5.5.1) and has been identified as one of the regions within a widespread network of brain areas that appears to support voluntary saccades (Gaymard et al., 1998; Munoz & Everling, 2004). Despite participants not being instructed to memories the face-scene pairs during the faces and places eye-tracking task, there is the possibility that eye movement behaviour during the task could be reflective of both reflex or voluntary saccades activity if the participant had worked out that one of the previously presented face-scene pairs would be shown alongside two equally familiar faces at test. Both reflexive and voluntary saccades would allow the individual to locate and fixate upon the correct face. However, the application of voluntary saccades would be more likely to maintain the fixation on the correct face for a more prolonged duration, as if the participant had actively located the correct face from memory then this may inhibit them from eliciting reflexive saccades to the other incorrect faces on-screen which would result in the fixation being interrupted and thus briefer in duration. This could explain why more prolonged periods of preferential looking elicited to the correct face are observed in 4-year-olds and adults, as the greater prefrontal cortex maturation could be allowing these groups to exert greater levels of saccadic control.

Furthermore, the ability to sustain attention may play a crucial role in performance during the faces and places eye-tracking task. Alertness refers to the ability to direct attention to a specific stimulus and maintain this attentional focus for an unbroken period of time, with this ability increasing during the first year life and continuing to develop into the third postnatal year (Colombo, 2001; Posner et al., 2014). Sustained attention refers to alertness that is maintained over a longer time period (Colombo, 2001), with research indicating that sustained attention emerges during primary school with improvements observed incrementally from

ages 5-10 years and only minor improvements observed after this period (Betts et al., 2006). Differences across age groups in the timing of their preferential looking during the faces and places eye-tracking task could reflect fluctuating attention as a result of age-related differences in the ability to sustain attention to the stimuli on-screen. However, while fluctuating attention may explain age-related differences in the onset and duration of preferential looking during identical-perspective trials, this explanation cannot account for the absence of preferential looking elicited in the shifted-perspective trials in children aged under 4 years.

7.5.5.3 Language Development

The results of this thesis, coupled with the vast body of literature outlined in chapter 1 section 1.2.2, demonstrate that preverbal infants and young children are capable of notable memory feats prior to possessing mature receptive and productive language and thus being able to verbally declare their memories. However, previous research has indicated that the development of language may provide scaffolding to facilitate episodic memory processes (Nelson & Fivush, 2004).

Prior to 18-months-old, infants make seldom, if any, references to past personal experiences (Fivush et al., 1997). A substantial increase is then observed from 18-months-old to 2.5 years in children's' ability to refer to past events, however this is largely in the context of locating an absent object or in response to questioning and engagement in conversation with adults (Fivush et al., 1997). Typically, from 2.5-3 years, children begin to engage in brief albeit fragmented conversations about past events which are frequently self-initiated as opposed to adult initiated. From 3.5 years, children are able to provide a relatively coherent narrative about a past event and have begun to include spatiotemporal contextual details in their accounts, e.g. specifying where events took place and using temporal markers such as "yesterday", "now" and "today" (Fivush et al., 1997). Narratives of past personal experiences then appear to increase in detail and coherency of structure as children grow older.

Authors have advocated that this gradual increase in language abilities observed across early childhood may be facilitating recall for episodic events in several ways. Nelson and colleagues proposed that recall of autobiographical memories (comprised of both semantic and episodic memory related to an experienced event that is personally relevant) emerges

gradually across preschool years, with the development of both rudimentary memory abilities and language amongst other factors contributing to this process (Nelson & Fivush, 2004). This theory, referred to as the social cultural developmental theory of autobiographical memory, argues that infants possess a basic memory system for events that is later supplemented by an explicit memory system from preschool age onwards. These authors suggest that the acquisition of language plays a crucial role in the development of memory for past events by 1) allowing children to engage in conversations with others about past events which permits the rehearsal and structuring of previously encoded and future memories and 2) by providing an organisational framework to insert memories into (Nelson & Fivush, 2004).

By attaining greater receptive and productive language, young children can be reminded of events verbally without the need to re-experience the specific context and details of an event. This can occur through self-reminding or via engaging in conversations about the past with others, thus, providing them with greater opportunity to re-experience and rehearse past events. In contrast, pre-verbal infants are dependent on re-encountering physical or perceptual cues that were present during the encoding of an event in order to engage in memory retrieval (Fivush et al., 1997).

Furthermore, narration provided by adults may provide scaffolding to enhance memory recall for events in young children. A specific form of adult narration has been found to result in individual differences across children in their recall for past events. Fivush (2007; 2013) conducted a series of studies which demonstrated that individual differences in maternal reminiscence style, i.e. how often mothers engage in conversations about the past with their children and in what level of detail, has implications for children's autobiographical memory. Fivush and colleagues observed that mothers who engaged in highly elaborate reminiscing, whereby they outlined past events in a highly detailed manner and frequently engaged in conversations about the past with their children (referred to as 'high elaborator' mothers), tended to have children who later produce more structurally coherent and comprehensive narratives compared to children with 'low elaborator' mothers (Fivush & Fromhoff, 1988; Reese et al., 1993; Bauer & Burch, 2004). In contrast, 'low elaborator' mothers tend to ask their children fewer questions about the past, only pointed out isolated details of events and generally engaged in less conversations about past events with their children (Fivush, 2007). The authors postulated that adults are providing the linguistic scaffold that supports children

to organise their experiences, both as events occur and retrospectively, and that this framework then enables children to represent and verbally recall past events in a detailed and coherent manner (Nelson & Fivush, 2004).

The acquisition of language is also argued to support more comprehensive recall of past events, through language providing a timeline for which memories can be inserted into and thus more easily recalled in a temporally-structured manner (Nelson & Fivush, 2004). In a study by Pathman et al., 2013, temporal information related to past autobiographical events was examined in children aged 4, 6 and 8-years-old. Prior to taking part, parents recorded unique events which their children had been involved in across a four month period. Children were then tested on their memory for these events, specifically in making judgments regarding how recent these events had taken place and to estimate the timing of two separate events using conventional time-scales consisting of time of day, day of week, month of year and the season. Additionally, children provided justifications for their time-scale judgments. The study observed that 6- and 8-year-olds could accurately determine the order of the two events which was not seen in 4-year-olds. The ability to place past personal events on the varying time-scales was found to improve significantly with age. Critically, children who made correct time-scale judgments (e.g. correctly identified what time of day, week, month or season an event had taken place) provided more meaningful justifications for their judgments (e.g. the unique event had occurred at a time when the child was usually taking part in a routine event). Moreover, 4-year-olds did not offer as many justifications for their temporal judgments compared to the older children. This association between accuracy in making time-scale judgments and the ability to provide meaningful justifications for those judgments implies that children may be able to reconstruct past personal events in a more temporally constructed manner if greater meaning is attached to those events (Pathman et al., 2013). Critically, these justifications are language-based.

Considering these findings, differences in productive language and the ability to understand verbal instructions may be confounds to memory performance when comparing younger versus older children/adults. Firstly, the experimenter did not verbally narrate during the demonstration of the deferred imitation task presented in chapters 2-4 and thus did not provide linguistic scaffolding for the action sequence. However, the acquisition of language abilities in older children have meant that these children were better able to encode and

retrieve the sequence event compared to younger children, through being able to self-generate an accompanying narrative to the experienced event and their previous experience in structuring past events in a coherent and temporally-organised manner.

Moreover, the deferred imitation task employed in this thesis tested memory for arbitrarily-related events, as this is argued to more accurately measure hippocampal-dependent memory processes through the reproduction of later actions in the sequence not being dependent on preceding actions being performed first, compared to enabling actions which may inflate memory for the action sequence (see chapter 1 section 1.2.1.4). However, arbitrarily paired actions do not follow a conventional timeline and thus younger children's performance may be reduced by not having this timeline structure to make sense of the events occurring within the action sequence. Considering the findings of Pathman et al. (2013), the action sequence used in the deferred imitation task in this thesis also may not have been meaningful, i.e. the actions performed on the puppet do not tell a story. Therefore, performance may also be lowered in younger children who do not have sufficient productive language to produce their own narrative in the absence of obvious narrative links between the action events.

Furthermore, as children aged under 3.5 years are typically limited in their ability to use temporal indicators in their recall of past events (Fivush et al., 1997), this begs the question as to whether young children have a concept of temporal order prior to the acquisition of temporal language. As noted in chapter 3 section 3.3.2, spontaneous temporal ordering ability during the deferred imitation task is poor prior to the age of 4 years, thus perhaps providing evidence for the inability to recall temporal order memory when unable to verbally articulate temporal order. However, although only 56% of 3-year-olds compared to 84% of 4-year-olds passed the temporal language task (see appendix C), we noted no within-group differences in the performance of 3- and 4-year-olds during their reproduction of the action sequence when comparisons were made between children who passed a temporal ordering task (thus indicating an understanding of temporal language terms like "first" and "next") and children who failed this task. Therefore, perhaps memory for temporal information surrounding events may exist, albeit in a rudimentary form, prior to the acquisition of temporal order language. As discussed in chapter 3 section 3.4, future research that applies more accurate measures of temporal ordering ability that can be used across the life span may shed light on this issue.

It is noted that temporal ordering performance in the 4-year-olds when instructed to perform the action sequence was significantly poorer than young adults. However, when the experimenter followed up elicitation of the action sequence by probing temporal order memory in more detail, 4-year-olds demonstrated better temporal order memory that did not significantly from young adults (see chapter 3 section 3.3.3.1). Therefore, not emphasizing the need to reproduce the actions in the correct order at initial instructed reproduction may be resulting in their lower temporal ordering score obtained prior to more in-depth assessment of order. This may be related to language ability at 4 years, as by only recently acquiring the capacity to use temporal order language and greater experience in engaging in conversations with others about past events, they may be less proficient in representing experienced events in a temporally coherent manner. Equally, through the experimenter providing elaborative reminiscence questioning, e.g. by specifically asking the child what was 'first', 'next' and 'last', this may have allowed these children to retrieve their memories in a more structured manner and thus resulted in better recollection of temporal order information related to the actions.

7.5.6 Section Summary

Reflecting on the points raised in this section, researchers should not be discouraged from employing a life span approach to track task performance across the life span. However, when employing this approach, researchers should be aware of the challenges that it poses and the degree of consideration that must be undertaken when comparing task performance across a wide range of ages. Critically, researchers need to acknowledge that performance at different ages may not be underpinned by the same processes and neural regions. Efforts should be made to utilise tasks that are not reliant on instructions. However, the removal of instructions should not reduce the accuracy at which the task is measuring its target construct. A holistic approach should be taking when interpreting age-related differences in task performance, specifically in considering the maturation of a variety of cognitive functions that could be influencing performance (and their neural correlates). These are important issues which need to be considered in future research, in order to further our understanding of how disparate memory processes may be subserved by specific neural regions and to accurately track the development of these brain areas and the cognitive functions that they underpin. Bridging the gap between adult memory and developmental research is of paramount importance to gain a full understanding of how hippocampal-dependent memory processes rise and fall across the human life span.

7.6 *Concluding Comments*

In summary, this thesis has found evidence that:

- Typical infant memory paradigms do appear to measure hippocampal-dependent memory processes; although further work is needed that uses functional neuroimaging to concretely confirm the neural correlates of these tasks.
- Using the deferred imitation task as an implicit measures of temporal order memory (assessed in this thesis via spontaneous reproduction of the action sequence) may not accurately measure this construct in older participants.
- Cross-sectional tracking of task performance across childhood and in young and older adults suggests that memory for action sequences follow developmental trajectories that appear to be concordant with extant knowledge regarding the development of the hippocampal formation and the cognitive processes that distinct hippocampal regions underpin. Again, functional neuroimaging is needed to confirm that performance in children is supported by the same neural activity as that of adults.
- Memory for face-scene associations may be reliant on the development of other hippocampal processes besides mnemonic functions, such as scene construction.
- The acquisition of independent locomotion in early infancy may be providing mnemonic benefits in terms of spatial experience and knowledge to scaffold rudimentary hippocampal memories. Therefore, it is likely that the development of both hippocampal episodic memory and hippocampal spatial processing are fundamentally intertwined.

By tracking the ontogeny and subsequent decline in hippocampal-dependent memory across the life span using the same task across age groups, I hope to have increased interest in the importance of using tasks that accurately index hippocampal memory and that can be validly applied to all ages. Modifying these paradigms for use with functional neuroimaging may provide exciting insights into hippocampal-dependent memory development and would bring us closer to determining how the developmental trajectories of distinct hippocampal processes may be interlinked to produce multifaceted episodic memories that we experience in adulthood.

8. References

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9. Appendix A

Patient Cohort Information- taken from supplementary material from Lad et al. (in prep)

Supplementary Material

Patient Summaries

Patient 1 was a retired engineer who graduated from the University of Cambridge. He was fit and well with no past medical or psychiatric history. He presented in 2012 with a progressive syndrome of anterograde and retrograde amnesia over months. This culminated with a generalised tonic-clonic seizure for which he was admitted to hospital locally and transferred to our centre. A T2 weighted MRI Brain scan showed no obvious hippocampal enhancement. He was treated with steroids, plasma exchange and anti-epileptic medication for an empirical diagnosis of auto-immune limbic encephalitis. His lumbar puncture showed no abnormality and he was positive for VGKCC-LE based on serum measurements. He underwent serial Addenbrookes Cognitive Examinations – Revised Version (ACE-R) over two years. This improved from 87/100 (memory 20/26) to 96/100 (memory 25/26) in one year. At the time of testing, he did not volunteer any difficulties with his memory however, he could not remember incidents to around 2 years prior to admission. He was living independently and leading an active lifestyle.

Patient 2 is a software developer with a post-graduate diploma degree. He had a past medical history of central core myopathy, from which he suffered no symptoms. He presented in 2014 with a progressive syndrome of anterograde and retrograde amnesia. He had two generalised tonic-clonic seizures which led to hospital admission. There were no motor neurological signs on examination and he had normal blood tests, apart from a low sodium level of 120mmol/L, and normal cerebrospinal fluid. A T2 weighted MRI Brain shown left hippocampal enhancement and subsequent atrophy a year later. He was treated empirically with intravenous steroids, plasma exchange and anti-epileptic medication and improved within months. His serial ACE-R scores improved from 72/100 (memory 8/26) to 99/100 (memory 26/26) within two months. He returned to work taken up a managerial role. He currently lives independently with his family.

Patient 3 was a retired shop-assistant kitchen lady in a school who left school at the age of 15. She was fit and well with no past medical history. She developed progressive global amnesia in 2012 and jerky movements of her right arm which were consistent with faciobrachial dystonic seizures. She had had no generalised seizures. A T2 weighted MRI Brain scan showed left hippocampal enhancement. She had normal blood tests and a lumbar puncture revealed no abnormality in her cerebrospinal fluid. Her VGKCC-LE antibody results were strongly positive and so she was started on plasma exchange, steroids and anti-epileptic drugs. She recovered after a few months and continues to live independently. Her initial ACE-R was 77/100 (memory 13/26).

Patient 4 was a house-wife and carer for her husband who had suffered from a stroke. She had no past medical history but her symptoms began in 2008 with progressive ‘confusion’ and altered behaviour. A predominant aspect of this was anterograde and retrograde amnesia. This

progressed over a month and she also developed left-sided faciobrachial dystonic seizures and a low sodium. An MRI Brain showed left hippocampal enhancement on FLAIR sequences and her antibody was positive for VGKCC. He had no abnormality in her cerebrospinal fluid. She was initiated on intravenous immunoglobulin, oral steroids and methotrexate and improved over many months. She is asymptomatic currently and lives independently with her husband. She states that she may have 'forgotten' important incidents around the time of her illness. Her ACE-R improved from 78/100 to 93/100 within 5 months.

Patient 5 was a retired organ-tuner, mechanic and police worker with a past medical history of asthma and meningitis as a child (no neurological sequelae). He presented to our department via clinic with up to 20 episodes per day of 'electric-shock-like' sensations throughout his body. Over a few months this culminated in him developing a generalised tonic-clonic seizure. An MRI Brain conducted at the time showed no abnormality in T2 and FLAIR sequences. His also complained of memory difficulties at the time but these were not characterised in detail at the time. This gentleman had positive antibodies for VGKCC-LE and was started on intravenous and oral steroids for a year. He was also on anti-epileptic drugs. Although he had an improvement in his memory after treatment he has not recovered fully. At work, he noticed that he would frequently forget where he had placed his tools and that he may have become slightly more tearful than before with subjectively low mood. However, he lives independently with his wife.

Patient 6 is a businessman with a past medical history of nephrotic syndrome with has been treated with immunosuppression since 2009. He did a diploma are leaving school and has been in business throughout his life. He presented in 2012 with frequent sensations of 'déjà vu'. He was admitted locally and treated for focal seizures. He was a description of altered behaviour but this was not characterised further at the time. His MRI Brain at the time showed bilateral increases in signal in both hippocampi on T2 FLAIR sequences, which was more marked on the left. A lumbar puncture at the time showed no abnormality in cerebrospinal fluid but his serum antibodies were positive for VGKCC. He was treated with intravenous then oral steroids and improved substantially. Since leaving hospital, he continues to work and has had no mishaps in his activities of daily living.

Patient 7 was a mechanic who was usually fit and well without any medical conditions. He presented in 2010 with worsening anterograde amnesia over months and 'strange sensations' throughout his body, especially in his stomach, which were consistent with focal seizures. At that time, he was assessed by neuropsychology services and showed impairments in delayed verbal and visual memory tests. He was treated with anti-epileptic medication with minimal improvement. An MRI Brain revealed high T2 signal in the right hippocampal region and antibodies confirmed his a diagnosis of autoimmune limbic encephalitis. He was treated with steroids and continued anti-epileptic therapy to good effect. Further scans excluded an underlying malignancy and since then he has been well and is living independently. He continues to be under follow-up for focal seizures and only suffers from day-to-day forgetfulness. He has not had any accidents that are related to memory issues.

Clinical Neuropsychological Assessments on Patients

Methods

As part of their routine neuropsychological evaluation patients performed cognitive tests to assess general intelligence (IQ), executive function, visuospatial ability, and memory (retrograde and anterograde memory). Current wellbeing was also assessed.

General Intelligence. An estimate of pre-morbid IQ was generated using the Weschler Test of Adult Reading (WTAR) (Wechsler, 2001). An index-based, seven subtest, short form of the Weschler Adult Intelligence Scale III (WAIS-III) was administered to estimate current IQ (Crawford *et al.*, 2008). The seven subtests were as follows: Vocabulary, Similarities, Block Design, Matrix Reasoning, Arithmetic, Digit Span, and Digit Symbol - Coding. Scores were computed from an executive program which produced index scores, confidence intervals and the reliability and abnormality of the differences between index scores.

Executive Function: Executive function was assessed using the Delis-Kaplan Executive Function System (DKEFS): Verbal Fluency Test, Colour-Word Interference Test, and the Trail Making Test (Delis, Kramer, Kaplan, & Holdnack, 2004), and the Hayling and Brixton tests (Burgess & Shallice, 1997; (Bielak, Mansueti, Strauss, & Dixon, 2006)): the Hayling Sentence Completion Test and the Brixton Spatial Anticipation Test.. A DKEFS index was calculated as a composite score of executive function (Crawford, Garthwaite, Sutherland, & Borland, 2011). The Hayling-Brixton scores were converted to their IQ equivalents according to the manual.

Visuospatial Ability: Visuospatial ability was assessed using two tests from the Visual Object and Space Perception test (VOSP); the Cube Analysis test and the Object Decision test (E. K. J. Warrington, M., 1991).

Retrograde Memory: The nature and extent of the patients' retrograde memory deficits were characterised using the Autobiographical Memory Interview (AMI) (Kopelman, Wilson, & Baddeley, 1989). The AMI control means and standard deviations were obtained from the manual and were used in statistical analysis.

Anterograde memory: Anterograde memory was assessed using the British-normed BIRT Memory and Information Processing Battery (BMIPB; Coughlan, Oddy and Crawford, 2007; Story Recall (immediate and delayed), Figure Recall (copy, immediate and delayed recall) and List Learning ()), the Warrington Recognition Memory Test (E. K. Warrington, 1984); Words and Faces), and the Doors and People Test (Baddeley, 1994). The BMIPB was administered as there are British norms available. These tasks share a number of similarities with more commonly used measures of memory; i.e. Story Recall is analogous with the Wechsler Memory Scale Logical Memory subtest, Figure Recall is analogous to the Rey Complex Figure Test (Rey, 1941), and List Learning (List A x5 (max); List B; List A) is roughly analogous to the Rey Auditory and Verbal Learning Task (Cohen, 1996).

Results

General Intelligence: Patients had a mean pre-morbid score on the WTAR of 40.4 (StDev: 4.5, Range: 36-49). This translates to a predicted IQ of 110 (StDev=8.5). All patients completed the WAIS-III (short-form) with a mean IQ score of 108 (StDev: 12). There were no significant differences between pre-morbid and WAIS-III IQ scores (t=-1.549, P=0.172). Both of these measures were correlated (r=0.756, P=0.049). Patients scored on the 57th percentile for verbal comprehension, 87th for perceptual organisation, 68th for working memory and 39th for processing speed.

Executive Function: Mean scaled scores for letter and category fluency were 12.5 (81st percentile, StDev=4.4) and 9.1 (42nd percentile, StDev=4.6), respectively. There were no differences in the scaled scores for letter and category fluency (t=1.922, P=0.103) Mean DKEFS index scores were in the 68th percentile (StDev: 32). The Hayling Sentence Completion test and Brixton Spatial Anticipation test gave mean scores of 5.4 (StDev: 1) and 6 (StDev: 1.2) respectively, which translates to equivalent percentiles of 25-50 for both.

Visuospatial Ability: Patients showed no deficit in visual perception during Cube Analysis and Object Decision from the VOSP battery. Group level performances for Object Perception and Cube Analysis were of the 70th and 80th percentile respectively.

Memory: Patients performed poorly in the BMIPB Verbal Immediate (7th percentile, StDev=6) and Delayed Recall (16th percentile, StDev=13). Patients were in the 25th (StDev=22) and 46th (StDev=30) percentile for Immediate and Delayed Visual Recall respectively. Patients performed in the 24th percentile (StDev=35) for List A Learning over 5 trials. This result was skewed by 1 patient using a mneumonic technique for remember the words in the list. Without this patient the mean percentile was 10 (StDev=6). They performed in the 8th percentile (StDev=4) for the interfering List B over 1 trial only. Patients performed in the 50-75th percentile in the Warrington Recognition Test for Words and in the 10th percentile for Faces. Patients had a mean score of 21 out of 30 in the Graded Naming test of semantic memory which translates to a ‘high average’ IQ range. The AMI showed no deficits in the Personal Semantic Schedule in Childhood, Early Adulthood and Recent life when compared to control data from the manual (Supplementary Table 1 & Figure 1). The Autobiographical Incident Schedule showed significant deficits in Early Adulthood (p=0.001) and Recent Life (0.006).

S*upplementary Table* **Autobiographical Memory Interview**						
	Personal Semantic Schedule			**Autobiographical incident schedule**		
Patient Number	**Childhood**	**Young adult**	**Recent**	**Childhood**	**Young adult**	**Recent**
1	**Definitely Abnormal	Borderline	Borderline	*Probably Abnormal	**Definitely Abnormal	Borderline
2	Acceptable	Borderline	Borderline	Acceptable	Borderline	**Definitely Abnormal
3	Acceptable	Acceptable	Acceptable	*Probably Abnormal	**Definitely Abnormal	**Definitely Abnormal
4	Acceptable	Acceptable	Acceptable	Acceptable	**Definitely Abnormal	**Definitely Abnormal
5	Acceptable	Acceptable	Acceptable	Acceptable	*Probably Abnormal	**Definitely Abnormal
6	Acceptable	Acceptable	Acceptable	Borderline	Borderline	**Definitely Abnormal
7	Acceptable	Borderline	**Definitely Abnormal	**Definitely Abnormal	**Definitely Abnormal	**Definitely Abnormal

This table shows the Autobiographical Memory Interview scores for each patient for Personal Semantic information and Autobiographical Incident information. Asterisks indicate abnormal domains where patients have deficits.

10. Appendix B

Live vs. Video Demonstration in Adults

As a means of verifying that differences observed between child and adult participants in their memory performance were not attributed to using different methods to administer the demonstration, two additional groups of adults were tested using the live modelling of the action sequence at demonstration.

Additional Participants

Twenty young adults (16 males, 4 females) with a mean age of 19.9 years (SD= 1.2, age range = 18-23 years) were recruited. A further nine older adults (5 males, 4 females) with a mean age of 63.5 years (SD= 5.1, age range = 57-74 years) also took part in the study. Participants were recruited from Newcastle University Institute of Neuroscience participant database and Newcastle University School of Psychology Undergraduate research participation scheme. Participants were compensated with payment or course credits for Undergraduate Psychology students. All participants provided informed consent and ethical approval was granted from Faculty of Medical Sciences Ethics Committee at Newcastle University.

Procedure

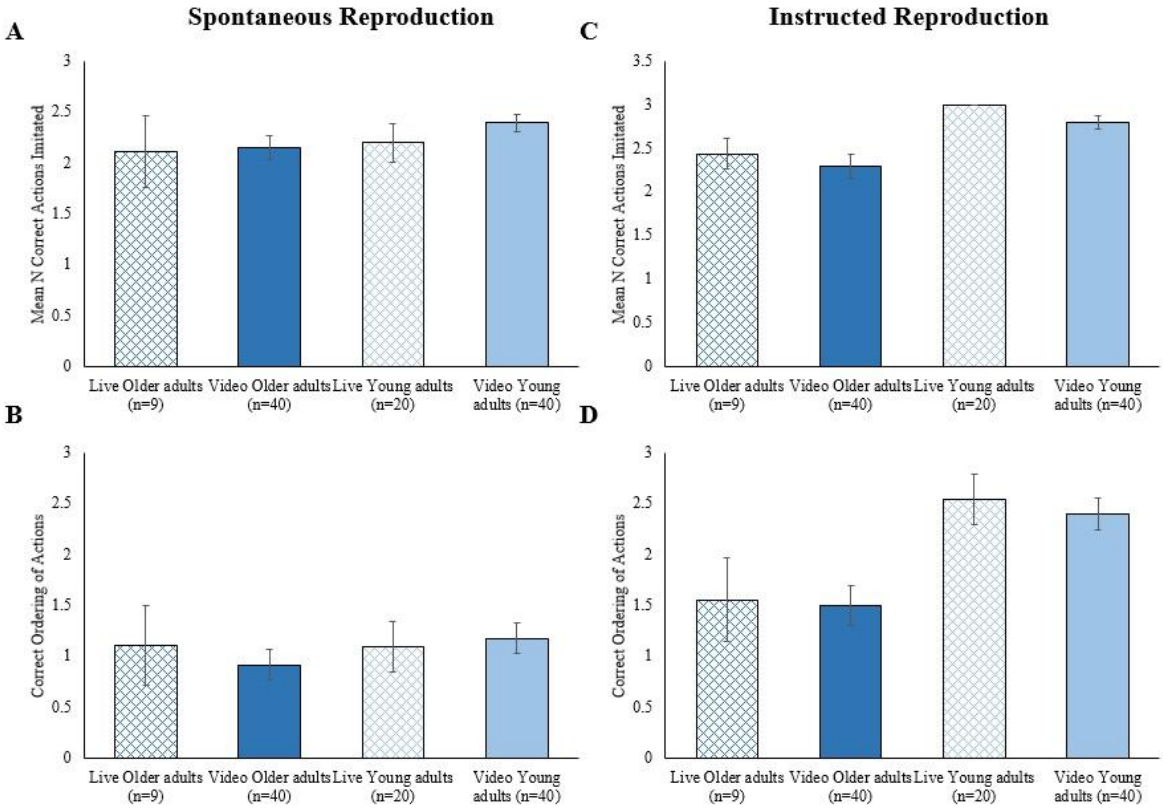
The procedure was identical to that used with children aged 3-8 years outlined in Chapter 3 section 3.2.3 with the exception of more adult-appropriate phrasing used immediately before the experimenter modelled the action sequence on the puppet during live demonstration. The experimenter was seated in front of the participant with the puppet on her hand and stated *"Something that we do with the babies when they visit the lab is play with puppets"*. The experimenter then performed the action sequence in the exact same manner as outlined in chapter 2 section 2.2.3, ensuring that silence was maintained during the demonstration. Following the retention interval, spontaneous and instructed recall was assessed in the same manner outlined in chapter 2 section 2.2.3.

Statistical Analyses

Videos were coded and scored in the exact manner outlined in chapter 2 section 2.2.4. Between-group comparisons were made in terms of whether the mode of demonstration (live

or video) significantly impacted on task performance within both age groups (young adults and older adults). The four dependent variables which were examined were spontaneous recall of 1) correct actions and 2) correct temporal ordering of actions, and instructed recall for 3) correct actions and 4) correct temporal ordering of actions. As data was not normally distributed, between-group comparisons were made using Mann-Whitney U tests. Bonferroni correction was used to account for multiple statistical comparisons.

Results



Supplementary Figure. Comparisons in spontaneous reproduction performance (**A:** mean number of correctly imitated actions; **B** temporal ordering of actions) and instructed reproduction performance (**C:** mean number of correctly imitated actions; **D** temporal ordering of actions) between groups. *Note.* Error bars depict standard error of mean.

Group comparisons were made between participants who viewed the live demonstration of the action sequence and participants who viewed the video demonstration within each age group (young adults; older adults). No significant differences in performance were observed, with the exception that young adults who watched the live demonstration performed significantly more actions than young adults who watched the video demonstration during instructed reproduction only, (U = 330.0, z= -1.972, p=.049, r= -.25). However, when Bonferroni correction was applied to account for multiple comparisons (alpha level of

0.00625 adopted), this difference ceases to remain significant. Also note, when making these comparisons that there is large variance in sample size between groups. Overall, we can infer that the mode of demonstration does not impact on adult performance in either age group. We can also deduce that differences observed between child and adult participants in terms of their memory performance are not related to differences in the mode of presentation used to demonstrate the action sequence.

11. Appendix C

Temporal Order Language Task

This task was created to examine whether difficulties in understanding language related to temporal order, e.g. 'first', may have impacted upon the performance of younger child participant groups when specifically asked to reproduce the action sequence previously demonstrated in the correct order within the instructed reproduction component of the deferred imitation task.

Stimuli and Procedure

Images of a popular children's cartoon character engaging in three different actions (dancing, playing on a swing and feeding a duck) were obtained from the internet. These images were then assembled into a line to form a sequence of activities (see figure below).

Supplementary Figure. The sequence of activities that the character is engaging in during the temporal order language task.

The sequence of activities was then used as a way of measuring participant's understanding of temporal language, such as '*first*', '*next*' and '*last*', which were iterated when assessing memory for temporal order information during instructed reproduction in the deferred imitation task. The task was performed typically at the start of the testing session, prior to the child engaging in the deferred imitation task.

The experimenter placed the picture sequence in front of the child and explained that the images "*showed Bing* (the character) *doing lots of things during his day. During his day, he went to the park and did some dancing (experimenter pointed at image 1), then he played on the swings (experimenter pointed at image 2) and then he fed the ducks (experimenter points at image 3)".* The picture sequence then remained in front of the child (so that memory load

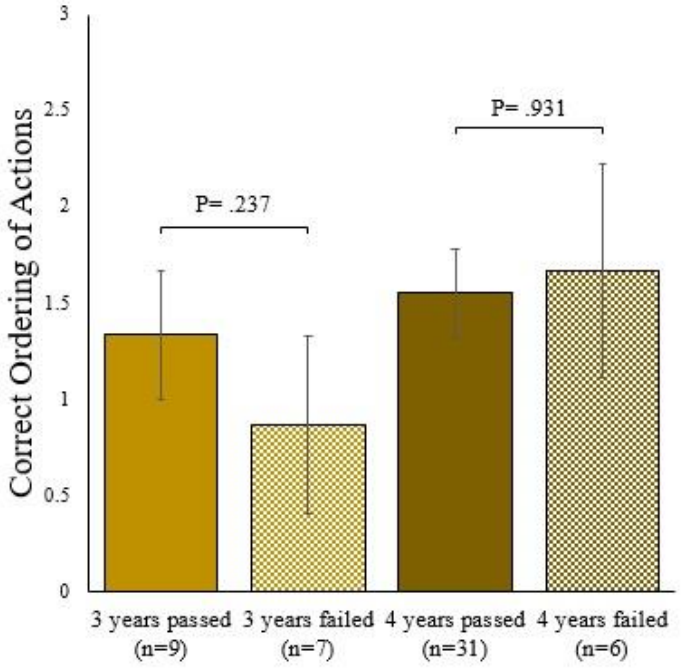
was not present) and the experimenter asked the child *"Can you tell me what Bing did first? What did he do next? And then what did he do last?"* The experimenter recorded the participants verbal or gestural response (i.e. pointing) for each question.

Statistical Analyses

The response to each of the three temporal questions (first, next, last) was coded as a score of 1 (correct) or 0 (incorrect). Therefore, each participant could receive a maximum score of 3. Participants were then coded as 1) children who had reported the activities in the correct order (and so passed the temporal language task) and 2) children who did not report the activities in the correct order (and so failed the temporal language task). Instructed reproduction performance data outlined above in experiment 2 was then re-analysed in 3- and 4-year-old children, to determine whether differences in performance existed between children who showed understanding of temporal language and children who did not within each of the two age groups. Mann-Whitney U tests were employed to make between-subject comparisons due to the data not following normal distribution.

Results

Data was obtained for 16/25 3-year-olds and 37/42 4-year-olds who had completed the instructed reproduction test in experiment 2. Within each group, 56% of 3-year-olds and 84% of 4-year-olds passed the temporal language task.



Supplementary Figure. Temporal ordering performance during the instructed recall test within each age group (3 years; 4 years) when separated into children who passed and failed the temporal language task. *Note*. Error bars depict standard error of the mean.

Although mean temporal ordering score was visibly poorer in 3-year-old children who failed the temporal language task compared to their peers who passed the task, no significant differences in performance within this age group were observed (U= 21.0, z= -1.183, p=.237, r= -.29). Equally, within the 4-year-old group, no significant differences in temporal ordering were observed between children who passed and children who failed the temporal language task (U= 91.0, z= -.086, p=.931, r= -.01). It is also acknowledged when making these comparisons that there are substantial differences in sample size between groups.

12. Appendix D

Parent Questionnaires Administered

Screening Questionnaire

Questionnaire for Parents

The purpose of this questionnaire is to enable the researchers to ascertain whether your child is suitable to participate in this particular study of infant memory. Each study that we conduct asks a unique set of very specific questions. Therefore, we are only able to test infants who meet a specific set of criteria. If your child is not eligible to participate in this particular study, it does not mean that they would not be ineligible for future studies. If this is the case, and you would like us to keep your child's details on file for future studies, please indicate this by ticking the appropriate box at the end of the questionnaire. We thank you in advance for taking the time to fill out this questionnaire and for considering participating in our research.

Please note that all information collected is for research purposes only, and will be securely stored in the Institute of Neuroscience, Newcastle University. If you have any queries about this or regarding any of the questions listed below, please do not hesitate to contact Alexandra Houston or Dr Mullally.

Contact Details: E-mail: sinead.mullally@ncl.ac.uk a.l.houston@ncl.ac.uk

Please answer the following questions

Name of Parent:

_____

Parent Contact Details:

_____

_____

__

_____

__

Name of Child:

_____

Gender of Child: ☐ Male ☐ Female

Child Date of Birth: _____

Gestational Age at Birth (in weeks):_____

1. Has your child suffered any significant medical issues (e.g. birth complications)?

☐ Yes ☐ No

If yes, has your child spend time in a Special Care Baby Unit (SCBU)?

☐ Yes ☐ No

2. Do you know what your child's Apgar score was five minutes post-birth?

☐ Yes ☐ No

If yes, please specify:

_____

3. Can your child crawl? (We define 'crawling' as the ability to continuously transverse at least one meter on their arms and/or knees)

☐ Yes ☐ No

If yes, at what age did they begin to crawl?

_____

4. Does your child engage in any of these other motor behaviours?

☐ Rolling (rolling from their tummy onto their back, or from their back onto their tummy)

☐ Rolling significant distances (for instance, rolling across the room)

☐ Slithering on their stomach (again across significant distances)

☐ Bottom shuffling (we define this scooting around on their bottom using a hand behind and a foot to propel themselves)

☐ Cruising (walking whilst holding on to furniture)

☐ Walking

5. Thinking of all these activities (e.g. crawling, rolling, slithering, bottom shuffling), how often does your child explore their environment on a daily basis?

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

6. With regards to your baby's speech and language use, has your child engaged in any of these behaviours?

Smiles and laughs in response to you smiling and laughing

☐ Not yet ☐ Occasionally ☐ Frequently

Turns their body/head to the sources of sounds e.g. towards someone speaking

☐ Not yet ☐ Occasionally ☐ Frequently

Indicates what he/she wants through gestures e.g. reaching to be picked up or pointing

☐ Not yet ☐ Occasionally ☐ Frequently

Can make vowel-like sounds e.g. "Ooh" and "Aah"

☐ Not yet ☐ Occasionally ☐ Frequently

Babbles or repeats sounds e.g. bababa or duhduh

☐ Not yet ☐ Occasionally ☐ Frequently

Responds to commands like "No" e.g. stopping behaviour or looking at you

☐ Not yet ☐ Occasionally ☐ Frequently

7. Can your child use sign language?

☐ Yes ☐ No

If yes, how often do they use it to communicate with you/others?

☐ Rarely ☐ Occasionally ☐ Frequently

8. Would you like to receive further information about this study prior to completing these questions?

☐ Yes ☐ No

If yes, how would you like to be contacted? _____

9. If we are unable to include your child in this particular study, would you like us to keep your details on file and contact you if we are running further studies in the future?

☐ Yes ☐ No

If yes, how would you like to be contacted? _____

Thank you for taking the time to complete this questionnaire.

Please send this back either via email to Alex Houston: a.l.houston@ncl.ac.uk or by post to the following address:

Alexandra Houston, Institute of Neuroscience, Henry Wellcome Building,
Faculty of Medical Sciences, Newcastle University, Framlington Place, NE2 4HH.

Family Demographics Questionnaire

Family Questionnaire

The purpose of this questionnaire is to enable the researchers to ascertain any demographic or health factors that may influence the results of our study. **This information will be used for research purposes only**. We thank you in advance for taking the time to fill out this questionnaire and for considering participating in our research.

Please note that all information collected will be securely stored in the Institute of Neuroscience, Newcastle University. If you have any queries about this or regarding any of the questions listed below, please do not hesitate to contact Dr Mullally (sinead.mullally@ncl.ac.uk; 0191 208 3869).

If you do not wish to answer any of the following questions, or if they are not relevant, please leave them blank.

MATERNAL DETAILS

Q1: Current age?

Under 21	21-25	26-30	30-35	35-40	40-45	45+
☐	☐	☐	☐	☐	☐	☐

Q2: Current/most recent occupation?

_____
_____
_____

Q3: Highest educational level attained:

High school	College/Sixth form	Undergraduate degree	Postgraduate degree	Other
☐	☐	☐	☐	☐

If ticked 'Other' please specify:

_____

Q4: Any significant current or past medical problems?

Yes ☐ No ☐ Prefer not to say ☐

If yes, please outline briefly any problems (including when they occurred) if you are happy to do so:

_____
_____
_____
_____

PATERNAL DETAILS

Q5: Current age?

Under 21 ☐ 21-25 ☐ 26-30 ☐ 30-35 ☐ 35-40 ☐ 40-45 ☐ 45+ ☐

Q6: Current/most recent occupation?

_____
_____
_____

Q7: Highest educational level attained:

High school ☐ College/Sixth form ☐ Undergraduate degree ☐ Postgraduate degree ☐ Other ☐

If ticked 'Other' please specify:
_____

Q8: Any significant current or past medical problems?

Yes ☐ No ☐ Prefer not to say ☐

If yes, please outline briefly any problems (including when they occurred) if you are happy to do so:

_____
_____
_____
_____

******

Q9: Does your child have any siblings?

Yes ☐ No ☐

If yes, please specify how many and the ages of these children:

_____
_____
_____

If yes, do any of your child's siblings have any significant medical/developmental difficulties?

_____
_____
_____
_____
_____

Debrief Questionnaire

The purpose of this questionnaire is to enable the researchers to obtain information about your child's level of independent locomotion (e.g. crawling) and a clearer idea about how much they explore their environment. The questions towards the end of the questionnaire are related to whether your child will have visited any of the places/areas that have been selected as pictures in the computer task. This is to avoid any ambiguity in our results because if your child has seen/visited one of these places before, he/she may be more likely to look at that scene for longer.

If you have any queries about this or regarding any of the questions listed below, please do not hesitate to contact Alexandra Houston.

Contact Details: E-mail: a.l.houston@ncl.ac.uk

1. As of today, would you say that your child can crawl? ☐ Yes ☐ No

2. Thinking back over <u>the last few days</u>, how often does your child explore their environment on a daily basis?

(This includes all independent types of locomotion e.g. crawling, walking, bottom shuffling (scooting around on their bottom using a hand behind and a foot to propel themselves, slithering on their stomach, cruising (walking whilst holding furniture) and rolling across the room).

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

3. Again thinking back over <u>the last few days</u>, how much time on a daily basis does your child typically spend....

a) in your/other's arms

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

b) on the floor (e.g. on a play mat…etc.)

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

c) in a sling

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

d) in a pram

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

e) in a car seat and in a car

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

f) in a highchair

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

g) in a bouncer

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

h) other (please specify: ……..)

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

4. If/when your child is in a pram, are they typically facing forwards (i.e. looking out at the world) or backwards (i.e. looking at you):

☐ Facing forwards ☐ Facing backwards

4. If/when your child is in a sling, are they typically facing forwards (i.e. looking out at the world) or backwards (i.e. looking at you):

☐ Facing forwards ☐ Facing backwards

Please can you provide the estimated age (in months and weeks) that your child achieved the following developmental milestones.

(If your child has not yet achieved a particular milestone, please put a slash (/) through the answer space for that milestone).

a) First rolled? _____

b) First sat up independently? _____

c) First bottom shuffled?_____

d) First crawled? _____

e) First stood independently? _____

f) First cruised? _____

g) First walked independently? _____

5. Has your child been to any of the following places/areas before?

a) Heaton Park ☐ Yes ☐ No

b) Tynemouth Beach ☐ Yes ☐ No

c) Chillingham Road shops ☐ Yes ☐ No

d) Jesmond Dene ☐ Yes ☐ No

e) Beach (generally) ☐ Yes ☐ No

f) Park (generally) ☐ Yes ☐ No

6. Did you recognise any of the places in the pictures? ☐ Yes ☐ No

If Yes, can you elaborate?
_____

_____
_____

_____
_____

7. Do you think your child would have recognised any of the places in the pictures? ☐ Yes ☐ No

If Yes, can you elaborate?
_____

_____
_____

_____
_____

8. Does your child play with puppets/puzzle boards on a regular basis?

☐ Yes ☐ No

If yes, what kind of puppet(s) has your child seen? (e.g. bears, popular characters)

_____
__

_____
__

9. Do the puppets/boards that we showed your child today look familiar?

Participant Code: _____

☐ Yes ☐ No

10. Do you have any other comments about the tasks that we showed your child today?

_____
_____

_____
_____

_____
_____

_____
_____

_____
_____

_____
_____

Locomotion Study Follow-up Phase Questionnaire

****TO BE COMPLETED 6 WEEKS AFTER COMPLETION OF THE STUDY****

The purpose of this questionnaire is to enable the researchers to obtain whether there has been any change in your child's level of independent locomotion (e.g. crawling) and spatial exploration over the past 6 weeks.

If you have any queries about this or regarding any of the questions listed below, please do not hesitate to contact Alexandra Houston

Contact Details: E-mail: a.l.houston@ncl.ac.uk

Child Date of Birth:_____

1. As of today, would you say that your child can crawl? ☐ Yes ☐ No

2. Thinking back over the last few days, how often does your child explore their environment on a daily basis?

(This includes all independent types of locomotion e.g. crawling, walking, bottom shuffling (scooting around on their bottom using a hand behind and a foot to propel themselves, slithering on their stomach, cruising (walking whilst holding furniture) and rolling across the room).

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

3. Again thinking back over the last few days, how much time on a daily basis does your child typically spend....

a) in your/other's arms

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

b) on the floor (e.g. on a play mat…etc.)

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

c) in a sling

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

d) in a pram

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

e) in a car seat and in a car

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

f) in a highchair

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

g) in a bouncer

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

h) other (please specify: ……..)

☐ Under 1 hour ☐ 1-3 hours ☐ 3-5 hours ☐ 6 hours +

4. If/when your child is in a pram, are they typically facing forwards (i.e. looking out at the world) or backwards (i.e. looking at you):

☐ Facing forwards ☐ Facing backwards

4. If/when your child is in a sling, are they typically facing forwards (i.e. looking out at the world) or backwards (i.e. looking at you):

☐ Facing forwards ☐ Facing backwards

Please can you provide the estimated age (in months & weeks) that your child achieved the following developmental milestones.

(If your child has not yet achieved a particular milestone, please put a slash (/) through the answer space for that milestone).

a) First rolled? _____

b) First sat up independently? _____

c) First bottom shuffled?_____

d) First crawled? _____

e) First stood independently? _____

f) First cruised? _____

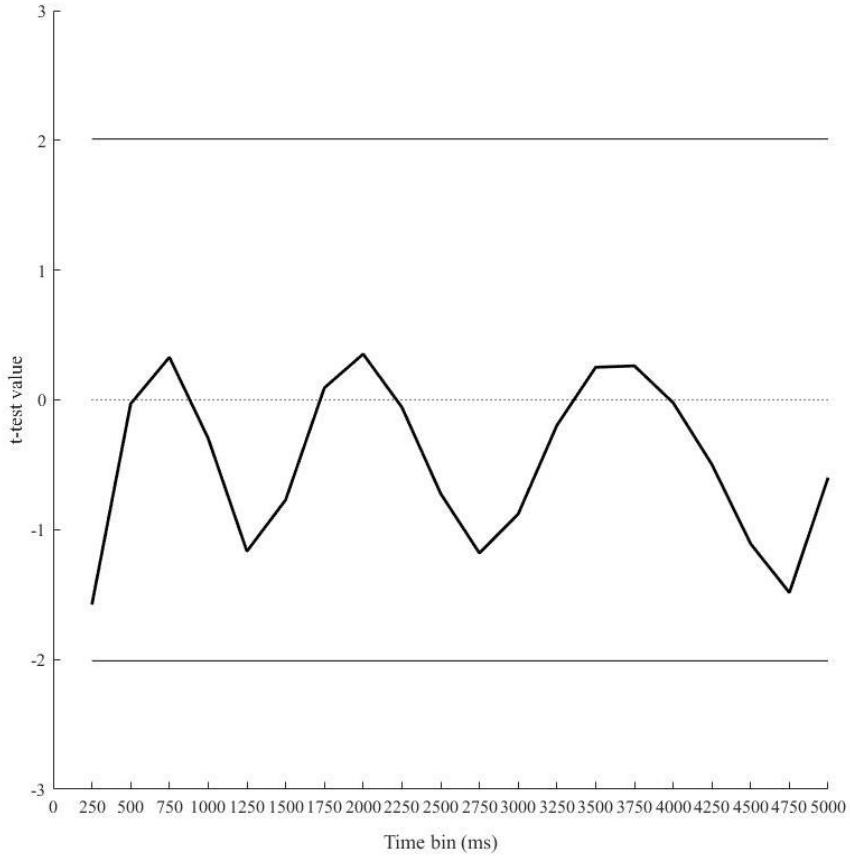
g) First walked independently?_____

Thank you for taking the time to complete these questions & for being part of our research!

13. Appendix E

Functional Analysis Example

Functional data analysis (FDA; Ramsay & Silverman, 1997) was highly applicable to the eye-tracking data, as looking time is a function of time bins. Once time-bin data was converted into functional data, the higher and lower critical values were calculated around a reference value from the functional data. One-sampled or independent sample t-tests were then computed in MATLAB based on this functional data; time bins whose t-values were greater than this critical value (or less than when making two-tailed comparisons) were considered significant. See example below.

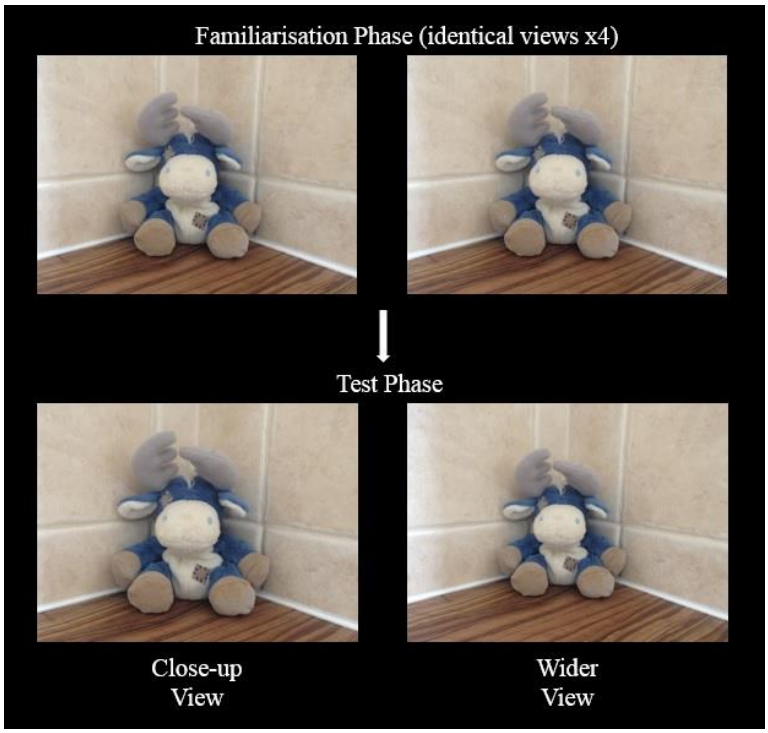


Supplementary Figure. Example of functional data analysis to assess whether infants' viewing of the correct face across time bins significantly exceeded chance (.33) during shifted-perspective trials. The curve represents the value of the t-statistic as a function of time bin (ms). The solid horizontal lines represent the two-tailed critical values for the t distribution. *Note.* No time bins were found to exceed the higher critical value and therefore infants did not elicit preferential viewing of the correct face at any time bin during shifted-perspective trials.

14. Appendix F

Boundary Extension Task

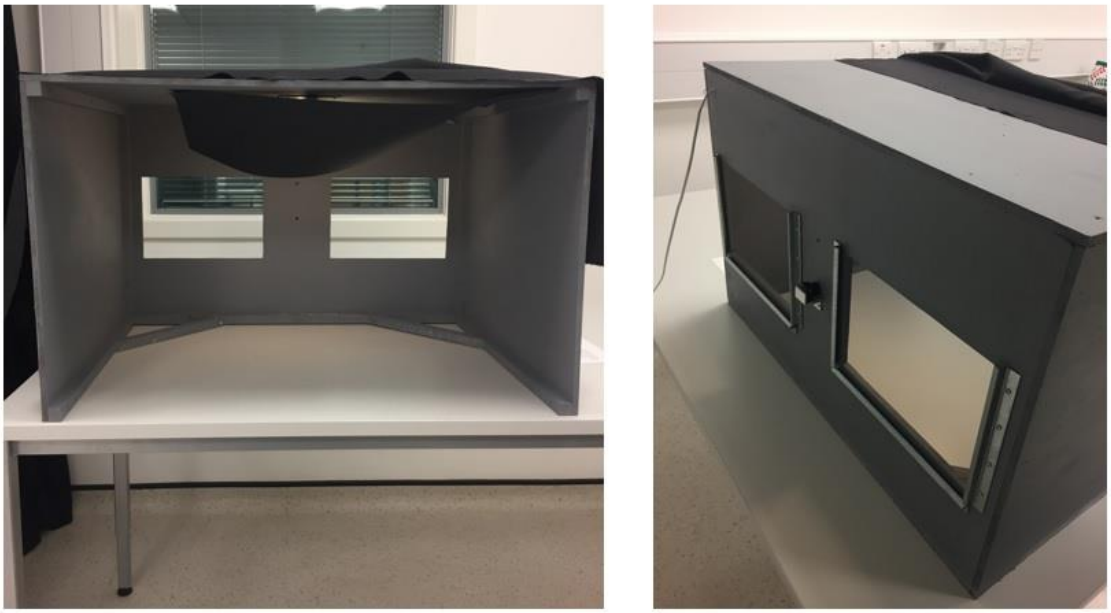
To address the proposal that scene construction abilities may be impacting upon performance during the faces and places task (see section 5.4), attempts were made to obtain a measure of boundary extension (as an index of scene construction abilities). Firstly, a computerised version of the boundary extension task used in Quinn & Intraub was created whereby participants were first presented with a pair of identical images which depicted a child-friendly object (e.g. a toy) against a background (e.g. on a kitchen countertop). The pair of images were presented four times to familiarise the participant with the stimuli (familiarisation phase) before being presented with a close-up version of the original image and a wider angle (zoomed out) version of the original image at test (see figure below). Eye-tracking behaviour was measured during the task with comparisons made between looking behaviour duration directed to the close-up image versus the wider angle image. Preferential looking directed to the close-up image would indicate the boundary extension error was being made, as lower levels of fixations devoted to the wider image would suggest children are regarding this image as more similar to the original image presented at familiarisation. Unfortunately, including a third task in the study protocol was too much for infant groups and inclusion of the boundary extension task greatly reduced the amount of eye-tracking data obtained during the faces and places task (due to infants becoming more restless when faced with sitting in the car seat for longer, etc., during eye-tracking).



Supplementary Figure. Procedure for the Boundary Extension Task attempted in this thesis.

A further attempt was made to replicate the procedure of Quinn & Intraub (2007), whereby a looking box was created to perform a non-computerised version of the task outlined in the previous paragraph (see figure below). Here the experimenter loaded the images into two panels of the box and used to stopwatch to monitor presentation times. The child was seated on their parent's knee (or in the car seat if possible) and viewed the images by facing into the box. Each trial was signified with a light within the box being turned on so that the inside of the box was illuminated for the child to see the images. Viewing behaviour of participants was recorded by a pinhole camera drilled into the back of the looking box between the two image slots (see figure below). During piloting of this task, it became apparent that it was extremely difficult to replicate Quinn & Intraub's procedure. For instance, in Quinn & Intraub, the experimenters checked the child was attending to the images via a peephole in the back of the apparatus and recorded attention directed to each image through this hole using two Accusplit electronic stop watches (one of which was held in each hand). Even with my modification of using a peephole camera to record visual attention during the task and scoring this after, the data was very unreliable and it was difficult to check during the task that the infant was paying attention to the stimuli. Therefore, this task was discontinued.

A B



Supplementary Figure. Looking box apparatus used to deliver the boundary extension task.

A) Front view of apparatus.

B) Back view of apparatus, with peephole camera in place.