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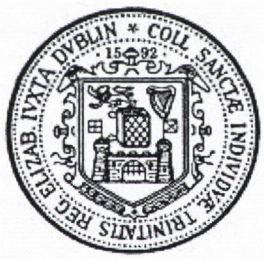
Neurocognitive Changes in Associative- and Working Memory with Aging

Joanne Feeney



A thesis submitted for the degree of Doctor of Philosophy

University of Dublin, Trinity College

2010

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Summary

This thesis sought to determine the nature of associative- and working memory decline during adulthood, and to try and elucidate some of the factors which contribute to this age-related mnemonic decline.

In the first study we examined associative- and working memory decline in group of healthy individuals aged 18-64 years. We found that significant impairments in both associative memory and working memory function emerged in the 5th decade of life. Controlling for IQ and education, there remained a significant age-related deficit.

A subgroup of these participants also donated saliva samples for analysis of the stress hormone cortisol, and the relationship between memory performance and cortisol levels was explored in a second study. Regression analyses showed a significant effect of the interaction between older participants (aged 40+) and higher cortisol levels, on associative- and working memory performance; that is, higher levels of the stress hormone were more strongly inversely related to memory performance in the older group than the younger group.

The third study compared associative- and working memory performance in the 40's group with the 20's group, this time using emotional stimuli. The aim of this study was to investigate whether altering stimulus valence could modulate memory performance differently in the middle-aged group compared with the younger group. The study also explored emotion processing in these two age groups via an emotional Face Judgment task. It was found that working memory task accuracy was greater in the 20's group than the 40's group only when angry faces were viewed. All participants exhibited increased accuracy and quicker reaction times when judging happy faces as opposed to neutral or angry faces. There was also a relationship between cortisol levels and Face Judgment task performance, such that higher cortisol levels at test resulted in faster reaction times to emotional faces, and in a greater tendency to falsely categorise faces as emotional.

The final study examined whether there was a relationship between regional brain volume (focusing on the prefrontal cortex and medial temporal lobe in particular) and associative memory performance in a group of individuals in their 20's versus a group in their 40's. The group in their 40's were found to exhibit a significant reduction in grey matter volume in many regions, when compared with the 20's group. Grey matter volume in the

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Firstly, I would like to thank my supervisor Prof. Shane O'Mara for all his support and guidance, and for always knowing what to say to stop me from worrying – at least for a short while! I would also like to thank Peter Gaffney in the Adelaide and Meath Hospital, Tallaght, for analysing the saliva samples for me, and for always being so accommodating. My sincere thanks also go to Gillian Cooke and Sinéad Mullally for all their help and support, both from a personal and professional point of view. I also formally acknowledge their contribution to the work presented in this thesis, along with the contribution of Lynn Ormond. I would also like to extend my gratitude to Cathal Walsh, Joshua Balsters and Simon Dunne for the help and advice they gave me.

I am very lucky to be part of a great lab group – thanks to Kim, Wen, Johannes, Charlotte, Andrea, Vincent, Marian, Rosalind, Colleen, Deborah and Ehsan for making it such a fun working environment. I was also very fortunate to start the PhD programme with 6 other great people – Kim, Joe, Kevin, Julie-Ann, Dana and Stephen. We have remained friends throughout and I hope we will still keep in touch no matter what parts of the world we all end up in. Special thanks go to Kim for looking out for me these past 4 years – you have been a really good friend. Thanks to Emma for our mutual support sessions on via gmail. I think we helped keep one another sane (or crazy, depending on your point of view!).

To my parents - thank you so much for all your love and unwavering support over the years. You have both been instrumental in giving me the strength to persevere with this at times when I was having doubts.

Finally, thanks to Hugh for being a constant in my life during the ups and downs of this PhD. Thank you, not only for putting up with my being stressed and neurotic for the last 6 months (or possibly 4 years!), but for being so patient and understanding.

Abbreviations

ACTH – Adrenocorticopic Hormone

AD – Alzheimer's Disease

ADH – Associative Deficit Hypothesis

AUCg – Area Under the Curve with respect to ground

AVP – Arginine Vasopressin

BLA – Basolateral Nucleus of the Amygdala

cAMP – cyclic Adenosine Monophosphate

CAR – Cortisol Awakening Response

CBG – Corticosteroid Binding Globulin

CBV – Cerebral Blood Volume

CRH – Corticotrophin-Releasing Hormone

DEX/CRH – Dexamethasone-suppressed Corticotrophin-Releasing Hormone

DLPFC – Dorsolateral Prefrontal Cortex

fMRI – functional Magnetic Resonance Imaging

GC – Glucocorticoid

GG – Greenhouse Geisser

GRs – Glucocorticoid Receptors

HADS – Hospital Anxiety and Depression Scale

HC – Hippocampal Complex

HPA – Hypothalamic-Pituitary-Adrenal

ISI – Inter-Stimulus Interval

KDEF – Karolinska Directed Emotional Faces

LTD – Long-Term Depression

LTM – Long-Term Memory

LTP – Long-Term Potentiation

MCI – Mild Cognitive Impairment

MMSE – Mini Mental State Exam

MRI – Magnetic Resonance Imaging

MRs – Mineralocorticoid Receptors

MTL – Medial Temporal Lobe

MTS – Match-to-Sample

NART – National Adult Reading Test

OFC – Orbitofrontal Cortex

PFC – Prefrontal Cortex

PHG – Parahippocampal Gyrus

POFA – Pictures of Facial Affect

PTSD – Post-Traumatic Stress Disorder

PVN – Paraventricular Nucleus

ROCs – Receiver Operating Characteristics

STAI – State-Trait Anxiety Inventory

TIV – Total Intra-cranial Volume

TSST – Trier Social Stress Test

VBM – Voxel-Based Morphometry

VLPFC – Ventrolateral Prefrontal Cortex

WAIS-R – Wechsler Adult Intelligence Scale – Revised

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Chapter 1

General Introduction

1.1 Summary

This literature review discusses the concept of memory, with a focus on episodic and working memory, and their neuroanatomical bases. The reader is introduced to glucocorticoids and to cortisol in particular, with an emphasis on its regulation and effects on the brain and memory. The interaction between emotion, memory and glucocorticoids is also discussed briefly. Finally, the presented studies are outlined.

1.2 Progress in modern memory research

Over the last century our understanding of memory has evolved and expanded rapidly, from the previously held view of memory as a unitary concept, to a now increasingly complex picture, typified by many hierarchical subdivisions and overlapping yet functionally discrete brain networks.

Arguably, one of the most important events in modern memory research was the publication in 1949 of Hebb's postulates on the neurophysiologic changes that are necessary for the formation and persistence of memories (Hebb, 1949). These hypotheses were further supported and extended by the seminal experiments of Bliss and Lomo (1973) which provided evidence of long-term potentiation (LTP) in the rabbit hippocampus, a finding which continues the be a basis for much of the physiological study of learning and memory today.

Hebb's theories marked the beginning of a division of memory into short-term memory (STM) and long-term memory (LTM) which is still upheld by most researchers today. This school of thought was strengthened and developed through the 1960's and 1970's with the emergence of behavioural (Peterson & Peterson, 1959) and neuropsychological (Milner, 1966; Shallice & Warrington, 1970) evidence for a distinction between STM and LTM. Early dual component models of memory, such as the Atkinson and Shriffrin model (Atkinson & Shriffrin, 1968), proposed that short-term memory acts as a gateway to long-term memory storage (processing in short-term memory leading to long-term storage) . More complex models started to emerge in the 1970's and research progress during this time led to a division of the singular concept of long-term memory into several sub-categories, and also the emergence of a new concept termed "working memory" in an effort to compensate for the failings of the existing short-term memory model. This fractionation of the fundamental process of memory, with subsequent revisions, has formed the basis for current memory research.

1.3 Declarative memory

An accepted classification of long-term memory is one of a basic division into declarative (explicit) and non-declarative (implicit) processes (Squire, 1992). Declarative memory is generally taken to mean the conscious recollection of facts and events, traditionally assessed by tests of recall and recognition. Non-declarative or implicit memory refers to non-conscious memory abilities, including procedural memory, priming, simple classical conditioning and non-associative learning (Squire & Zola-Morgan, 1991; see Figure 1.1).

Tulving first conceived of declarative memory as having two major subcategories: episodic and semantic memory (Tulving, 1972). This original dichotomy has been well supported by studies of amnesic patients who present with intact remote memory but an impaired ability to learn new facts (Baddeley & Wilson, 1986; Manns et al., 2003). The original proposition was that semantic memory concerned memory for facts and knowledge about the world, whereas episodic memory was the ability to remember experienced events in one's past (Tulving, 1972). Episodic memory relies on contextual/associative processing, whereas declarative memory that is not episodic in nature does not rely on context (Cohen, Poldrack & Eichenbaum, 1997). Tulving's emphasis was originally on the recollective experience, incorporating the concepts of autonoesis and mental time travel (Tulving, 1983). Therefore, he asserted that a distinction should be made in an experimental setting between 'remembering' and 'knowing', the former representing overt recollection and the latter, a mere feeling of familiarity. Only recollection is associated with the retrieval of an item's context, whereas familiarity represents the ability to judge the previous occurrence of an item without retrieving the context in which that item was encountered (Mandler, 1980).

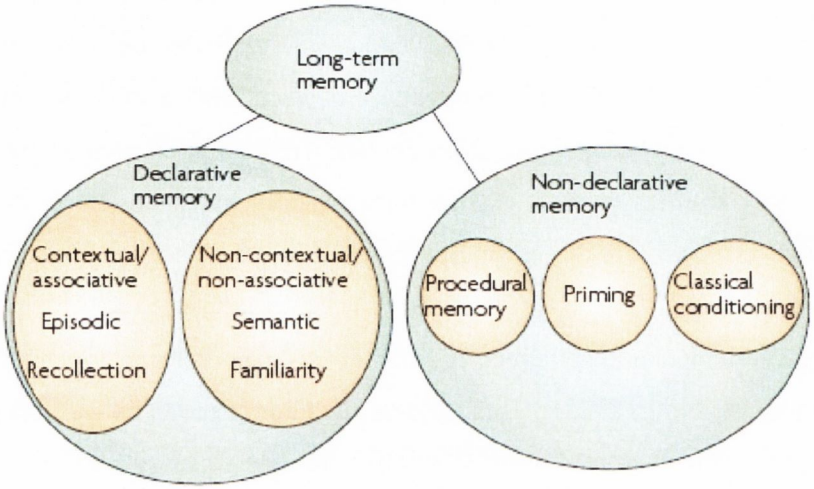

Figure 1. 1: The division of Long-term memory. Adapted from Bird & Burgess, 2008.

A neuroanatomical distinction between declarative and non-declarative memory was properly established with the demonstration of profound and selective declarative memory impairment in the now famous patient H.M after a medial temporal lobe resection (Milner 1966; Scoville & Milner, 1957).

1.4 The Medial Temporal Lobe (MTL)

The medial temporal lobe has, for several decades, been posited to be crucial for declarative memory storage and retrieval (Squire, 1992). Evidence to support this assertion came first from the study of H.M. and of other similar cases of MTL resection, and has since been strengthened by studies in humans and animals alike, using a variety of methods including lesioning, electrophysiology and neuroimaging (for reviews see Bachevalier & Vargha-Khadem, 2005; Buckley, 2005; Schacter & Wagner, 1999; Suzuki & Eichenbaum, 2000). Much of the focus of research has been on the hippocampus (CA1, CA2, CA3, and CA4 fields, the dentate gyrus and the subicular complex), and the adjacent entorhinal, perirhinal and parahippocampal cortices (Squire & Zola-Morgan, 1991; see Figure 1.2). These adjacent structures can be collectively referred to as the parahippocampal region (Eichenbaum, Yonelinas, & Ranganath, 2007). Studies of brain damaged patients, as well as monkeys, have demonstrated the importance of the

parahippocampal region in addition to the hippocampal formation in declarative memory (Corking, 1997; Mishkin, 1978; Zola-Morgan & Squire, 1985).

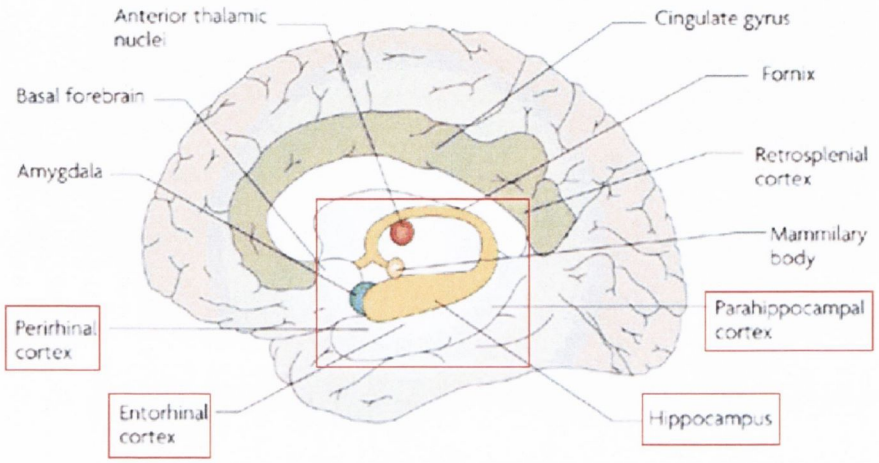

Figure 1.2: The hippocampus and its associated neocortical areas (highlighted in red). Adapted from Bird & Burgess, 2008.

Connectivity within the medial temporal lobe has been described in terms of a hierarchy of increasing amounts of sensory convergence (Lavenex & Amaral, 2000; Suzuki & Eichenbaum, 2000). The perirhinal and parahippocampal cortices receive sensory input from unimodal areas (visual, olfactory, auditory and somatosensory) and polymodal association areas (in the prefrontal cortex, parietal, and temporal lobes). The entorhinal cortex receives most input from perirhinal and parahippocampal cortices and, in turn, provides the main cortical input to the hippocampal formation, via dentate gyrus, CA1 region, and subiculum (Squire, Stark, & Clark, 2004; Suzuki et al., 2000). The perirhinal and parahippocampal cortices also project (albeit with weaker input) to the CA1 and subicular areas within the hippocampal formation (Suzuki & Amaral, 2004, Suzuki et al., 2000). While other areas of the MTL have bi-directional projections, information flows in a feed-forward circuit in the hippocampus proper. Information received from the entorhinal cortex is projected to the dentate gyrus, then to the CA3 field, the CA1 field and finally, the subiculum. A key feature of the anatomy of the MTL is the reciprocity of the connections between its constituent areas. All areas, except for those within the hippocampal formation itself, have strong back, as well as forward, serial and parallel projections (see Figure 1.3). This interconnectivity implies that the MTL structures have

similar access to information and so, to a certain extent, alludes to the possibility that these structures may encode, store, or process memory in similar ways.

Conversely, it has been proposed that the difference in the amount and source of the cortical projections to each of the MTL areas signifies a functional distinction between them (Suzy et al., 2000). While both of these assertions have support, it is still unclear whether there exists an element of functional redundancy within the MTL for certain types of memory.

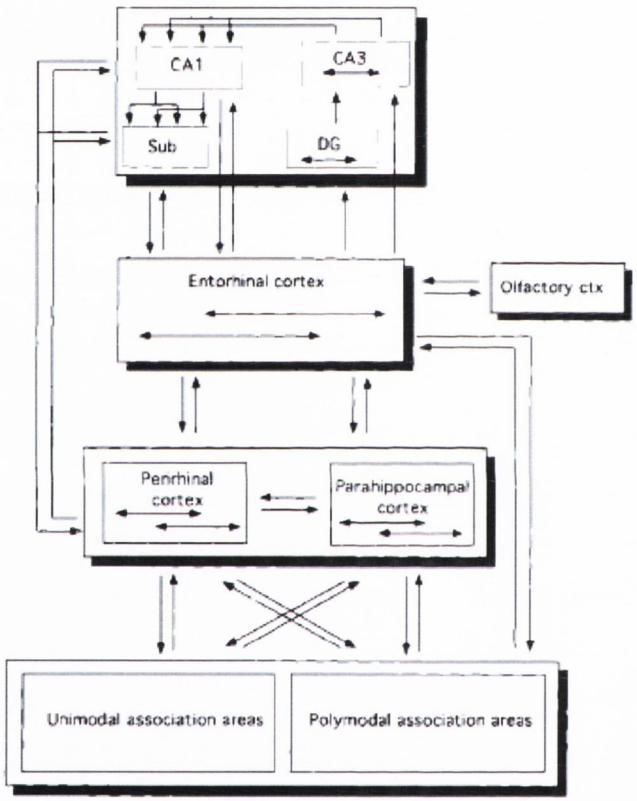

Figure 1.3: Network of projections between the cortex and MTL structures (Lavenex & Amaral, 2000).

1.5 *Recognition memory, associative memory, and their neuroanatomical bases*

1.5.1 Recognition memory

Of some debate in the literature is the question of whether the ability to recognise previously learned material comprises two separable components- recollection and familiarity- and whether or not they are supported by distinct neuroanatomical regions. The process of identifying a stimulus as having been previously encountered could be said to reflect either recollection or simply a feeling of familiarity (Mandler, 1980). In accordance with Tulving's theory only the phenomenon of recollection represents episodic memory and thus the distinction between "remembering" and "knowing" is crucial in determining whether a memory is truly episodic in nature (Tulving, 1985). There is some evidence for a anatomical distinction between these two processes, suggesting that recollection is dependent on the hippocampus to a greater extent than the adjacent cortical structures, and that the converse is true for familiarity (Eichenbaum, Yonelinas, & Ranganath, 2007; Sauvage et al., 2008; Yonelinas et al., 2005). There is also evidence from rodent literature that object recognition memory tasks depend on the hippocampus to a lesser extent than spatial memory tasks (Broadbent et al., 2004; Duva et al., 1997; Gaskin et al, 2003). However, there is contradictory evidence to suggest that recollection and familiarity are equally dependent on the hippocampus (Manns et al., 2003; Wais, Squire, & Wixted, 2010). Furthermore, large hippocampal lesions still impair recognition task performance (Clark et al., 2002; Gould et al., 2002). These results raise the possibility that the hippocampus and adjacent cortex contribute differently to recognition memory, but that input from both structures is necessary for intact task performance (Squire et al., 2004).

1.5.2 Associative memory

Learning novel associations is fundamental to episodic memory. The ability to link and later retrieve bound units of information is central to the experience of recollection, which has been defined as the "recovery of qualitative associations prompted by a critical cue" (Eichenbaum et al., 2007). Early studies of MTL amnesics suggested that an inability to easily form associations between previously unrelated stimuli was a hallmark of declarative memory impairment in this group (see Squire, 1992). Neuroimaging studies have shown that the hippocampus is differently involved in the retrieval of episodic, contextual details relative to non-recollective memory (Brown & Aggleton, 2001; Yonelinas, 2001). This has now been extended to encoding. Recent research provides evidence that the hippocampus is crucial to the ability to associate items in memory and is

also selectively activated during the recollection of these associations (Chua et al., 2007; Davachi & Wagner, 2002; Kirwan & Stark, 2004; Prince et al., 2005). The importance of a distinction between the encoding of single items and the encoding of associated item pairs has become evident in more recent memory research. Associative memory seems to rely on the hippocampus to a greater extent than item memory (Cohn, McAndrews, & Moscovitch, 2009; Davachi, 2006; Konkel et al., 2008).

One theory is that the hippocampus is necessary for recollecting associations, whereas the parahippocampal region can support single item memory (Brown et al., 2001; Chua et al., 2007; Davachi et al., 2002; Eichenbaum, 1994, Yonelinas et al., 2002) and recency judgments (Brown et al., 2001). However, other neuropsychological studies do not support this hypothesis (Stark et al., 2002, Stark & Squire, 2003), finding instead that patients with damage limited to the hippocampus are equally impaired on memory for items and associations. Furthermore, some studies implicate MTL structures, other than the hippocampus, as supporting associative, and not merely item based, processing. There is evidence for the involvement of the parahippocampal gyrus in both the encoding (Jackson & Schacter, 2004; Kirwan et al., 2004, Pihlajamaki et al., 2003) and the retrieval (Eldridge et al., 2005; Fenker et al., 2005, Kirwan et al., 2004) of associations. There is also evidence from the animal literature to support the involvement of the parahippocampal region in memory for novel associations. Examples from rat and monkey literature (Bunsey & Eichenbaum, 1993; Murray et al., 1993) show that associative learning is impaired by lesioning the perirhinal cortex in these animals. In addition, there is some evidence that memory for certain types of associations can remain intact in amnesic patients when damage is restricted to the hippocampus (Mayes et al., 2004; Vargha-Khadem et al., 1997, but see Holdstock et al., 2005), suggesting that parahippocampal areas can perhaps compensate in these situations. Thus, the literature presents plenty of contradictions. The view that a straightforward anatomical distinction exists between the structures underpinning item versus associative memory, and recollection versus familiarity, is constantly being challenged. As the ability to encode and retrieve novel associations has been posited to be crucial for normal episodic memory functioning, associative memory has mostly been viewed as being entirely recollective in nature. Thus studies have presumed it to reflect episodic recall ("remembering") rather than a familiarity judgment ("knowing"). A recent study by Haskins and colleagues (2008), however, implicates the perirhinal cortex in associative familiarity-based recognition. The results of the Haskins study suggest that novel associations can be

encoded in a unitary manner, and that the perirhinal cortex can support familiarity-based recognition of these novel (word) pairings. Thus the possibility exists that recognition may be based on familiarity when associations are encoded as a unit (Graf & Schacter, 1989), and that regions outside the hippocampus are able to support associative recognition when associations are encoded in this unitised manner (Haskins et al., 2008; Quamme et al., 2007). There is also evidence from the animal literature to suggest that recognition of associations based on familiarity strength can compensate for the impairment in recollection following hippocampal damage (Sauvage et al., 2008).

Prefrontal brain regions are also necessary for intact associative processing (Dimitrov et al., 1999; Petrides, 1997; Tanabe & Sadato, 2009). This has been attributed to the importance of the frontal lobes in strategy utilisation (Gershberg & Shimamura, 1995) and in cognitive control in the face of irrelevant or competing memory associations (Petrides, 1997). Thus, the existence of an anatomical distinction between associative and single-item encoding has important ramifications for any assertion that they involve different cognitive processes, and particularly so in light of the view held by some researchers that impaired associative memory underlies impaired episodic memory functioning (Naveh-Benjamin, 2000).

1.6 Working memory: theories and processes

The term "working memory" generally refers to the maintenance and manipulation of information for use in the performance of a cognitive task (Baddeley & Hitch, 1974, Daneman & Carpenter, 1980). However, there is some conflict among researchers as to what exactly constitutes working memory as distinct from short-term memory, and there is also debate over whether working memory represents a unitary contruct or is composed of several complementary systems.

Baddeley and Hitch (1974) proposed a model of "working memory" which they maintained would encompass some functions hitherto attributed to short-term memory and also account for some of the previously unexplained observations. They originally described a tripartite model of working memory that consisted of a central executive, phonological loop and visuospatial sketchpad (Baddeley et al., 1974). The central executive was responsible for the manipulation of information and controlled the two subordinate systems, which stored phonological and visual/spatial information respectively. Later, a fourth element, the episodic buffer was added to the model

(Baddeley, 2000) in an effort to explain the seeming need in working memory for some sort of back-up memory store. This latter system is proposed to function in a temporary storage and integrative capacity, receiving information from LTM as well as from the phonological loop and the visuospatial sketchpad (see Figure 1.4).

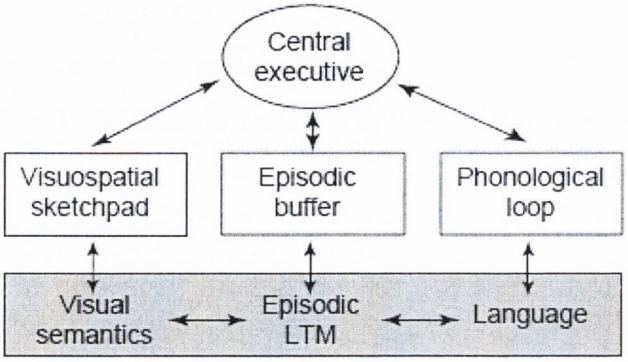

Figure 1.4: A multi-component working memory model. The shaded areas represent systems which accumulate long-term knowledge, whereas the sketchpad, buffer and loop systems are "fluid capacities" gated by the central executive, and involved in attention and temporary storage (Baddeley, 2000).

The most recent version of this theoretical model holds that the central executive oversees the other components of the system and provides attentional control in working memory as well as in other facets of cognition. It is important in divided attention and task switching, and also in the manipulation of information. The phonological loop and visuospatial sketchpad are responsible for holding information in separate stores. The episodic buffer serves to connect working memory to LTM, integrating the information into "complex multimodel representations" (Repovs & Baddeley, 2006).

An alternative embedded-processes view of working memory has been suggested by Cowan (1999). This model holds that working memory is the result of a hierarchical arrangement of cognitive faculties: long-term memory; the subset of long-term memory that is currently activated; and the subset of this activated memory that is the focus of attention and awareness. Central to this model is the interplay between memory and attention. The focus of attention is partly controlled by a central executive system, and partly involuntarily by the attentional orienting system (Wood & Cowan, 1995). The activation of memory is time-limited, with activation fading in between 10 and 20s unless reactivated (Cowan et al., 1994; 1997).

A common feature of both these models is a reliance of some sort of central executive system, influenced by attention, which is necessary for the control of working memory. While short-term memory and working memory are undoubtedly related constructs which most likely rely on the same storage systems, working memory also requires a central executive to maintain activation of task-relevant information, and to prevent interference from distractors (Engle et al., 1999).

1.7 Working memory and the Prefrontal Cortex (PFC)

It is well established that the prefrontal cortex is a critical region of the brain for working memory function. Early studies in macaques demonstrated that neuronal firing in the lateral prefrontal cortex was necessary for maintaining information across short delays (Funahashi et al. 1989; Fuster & Alexander 1971; Kubota & Niki 1971). Similarly, delayed-response task performance was found to be impaired by lesioning the dorsolateral prefrontal cortex in macaques (Funahashi, Bruce, & Goldman-Rakic, 1993; Miller & Orbach, 1972). In more recent years there has been an explosion of neuroimaging studies investigating the neural correlates of working memory (for reviews see Collette & Van der Linden, 2002; Curtis & D'Esposito, 2003; Smith & Jonides, 1998; Wager & Smith, 2003). Many of these studies have also implicated the prefrontal cortex in executive control processes required for the maintenance and manipulation of information in working memory. These include attention switching (D'Esposito et al., 1995), and the temporal ordering of information (Cohen et al., 1997). Some studies argue for a functional distinction between different regions of the PFC, with the ventrolateral area (VLPFC) involved in receiving information from association areas and organizing it, and the dorsolateral region (DLPFC) responsible for the monitoring and manipulation of information (Owen et al., 1998; 1999; see Figure 1.5). Both VLPFC and DLPFC activation have been reported in neuroimaging studies of working memory maintenance (Cohen et al., 1997; D'Esposito et al., 1999; Postle & D'Esposito, 1999; Ranganath et al., 2004; Ranganath, Johnson, & D'Esposito, 2003). The results of the Postle and D'Esposito study suggest that greater activation in the DLPFC only occurs during manipulation and is unchanged by working memory load, thus while both VLPCF and DLPFC activation occurs during active maintenance, the DLPFC activation reflects manipulation processes and not storage of material per se (D'Esposito et al., 2000; Postle et al., 1999).

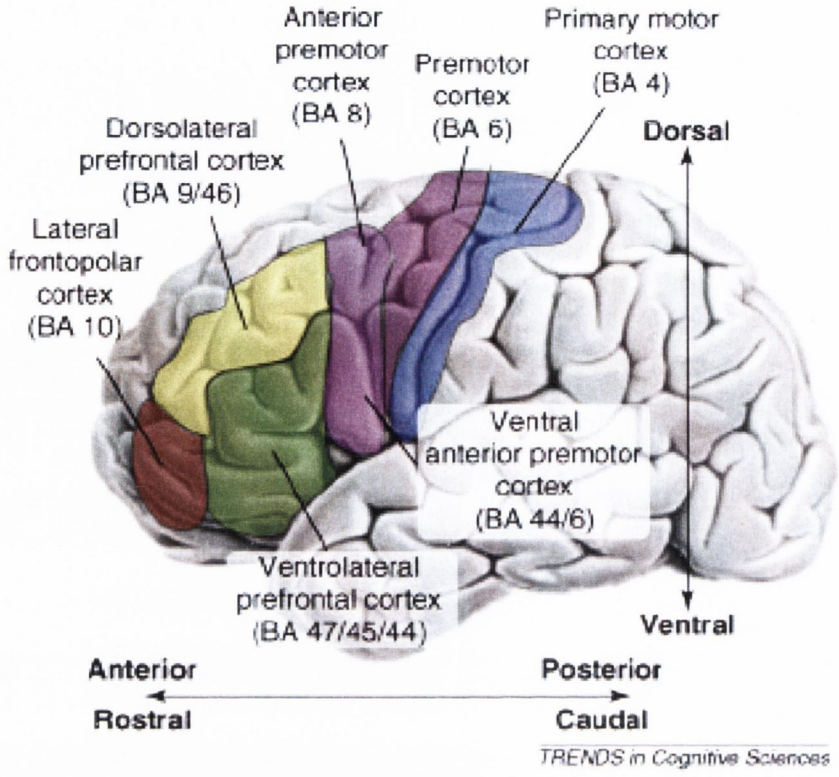

Figure 1.5: A schematic of the anatomical organization of the frontal lobes, showing the DLPFC and VLPFC (Badre, 2008).

A general role for the prefrontal cortex seems to be in top-down cognitive control. This includes attention-dependent modulation of neural activity (Bushman & Miller, 2007; Gazzaley et al., 2007) as well as the inhibition of task irrelevant activity, preventing interference in working memory and facilitating the temporal flow of information (Constantinidis, Williams, & Goldman-Rakic, 2002; Thompson-Schill et al., 2002). Miller and Cohen (2001) have described a function of the prefrontal cortex as "the active maintenance of patterns of activity that represent goals and the means to achieve them". The role of the PFC in long-term memory is discussed further below. One school of thought is that a functional distinction exists between the dorsolateral and ventrolateral PFC in the context of both working memory and long-term memory. According to this theory the DLPFC is primarily involved in monitoring and manipulation of information within working memory, and the VLPFC facilitates basic decision processes about stimuli held in short- and long-term memory (Petrides, 1994, 1996).

1.8 Connectivity of the prefrontal cortex

The prefrontal cortex exhibits many reciprocal connections with other cortical and sub-cortical areas, as well as having a high degree of intrinsic connectivity. The dorsolateral PFC has dense anatomic connections with motor and sensory areas and with the limbic system, many of which are strongly reciprocal (Petrides, 2005). The orbital and medial PFC are closely associated with the hippocampus and parahippocampal cortex, as well as with the amygdala (Amaral & Price, 1984; Barbas & De Olmos, 1990; Goldman-Rakic et al., 1984). Morris et al. (1999) have demonstrated projections from the mid-dorsolateral PFC to the retrosplenial cortex and posterior presubiculum, and have proposed that this link to the posterior hippocampal region could account for the interaction of this region with the PFC on certain types of working memory task (Petrides & Milner, 1982). Dorsolateral PFC also projects reciprocally to the parietal cortex, and co-activation of these two areas is frequently observed during performance of working memory or executive function tasks (see Smith et al., 1998; Wager et al., 2003 for reviews). The ventrolateral PFC also receives projections from the visual, auditory and somatosensory cortices. Mid-ventrolateral PFC (Brodmann's areas 47/12 and 45) is strongly connected to the perirhinal and parahippocampal cortices and to the superior temporal gyrus (Petrides & Pandya, 2002). The connectivity of mid-ventrolateral PFC to posterior association areas renders it ideally placed to influence these areas when mnemonic information must be retrieved, and indeed it seems to play an important role not only in the active verbal memory retrieval (Kostopoulos & Petrides, 2008; Petrides, 2002), but also in long-term memory encoding (see section 1.8.1).

1.9 The MTL and PFC both contribute to working memory and episodic memory

Contrary to an old school of thought that long-term memory and working memory processes are underpinned by different anatomical regions and functional circuits, more recent evidence suggests that the MTL and PFC both contribute to long-term and working memory processes. Thus the prior concept of different types of memory being 'housed' in different subcortical or cortical regions is no longer a valid one. Instead an integrative view is perhaps more appropriate, whereby connectivity between, and co-activation of different regions is necessary for optimal mnemonic task performance.

1.9.1 The role of the MTL in working memory

Recent evidence suggests that the medial temporal lobe may be essential for the active maintenance of information during working memory or short-term memory tasks. Ranganath and D'Esposito (2001) demonstrated that the MTL was necessary for maintenance of information across a delay of 7 seconds during a working memory task for faces. They also demonstrated that right anterior hippocampal activation was greater during working memory maintenance of novel rather than familiar faces, indicating that this structure is also activated during novelty detection in working memory. Consistent also with the role of the MTL in associative memory, there is evidence that working memory for associations is impaired in medial temporal lobe patients (Axmacher et al., 2007; Olson et al., 2006). Recent data suggest that the MTL is activated whenever multiple items or conjunctions of item features are being maintained in working memory, and that working memory for multiple items is dependent on top-down control of activity in higher cortical areas by the MTL (Axmacher et al., 2008).

1.9.2 The role of the PFC in episodic memory encoding and retrieval

As well as displaying impaired executive functioning, patients with frontal lobe damage often show deficits in episodic memory tasks such as those testing source or temporal order memory, and memory for associations (Dimitrov et al., 1999; Schacter, Harbluk, & McLachlan, 1984; Shimamura, Janowsky, & Squire, 1990). Top-down modulation of executive processes by the prefrontal cortex seems to play a role in long-term memory retrieval as well as in working memory (Tomita et al., 1999). Some evidence suggests the PFC activity is necessary for recollection but not familiarity (Schacter et al., 1984), however neuroimaging evidence has demonstrated certain prefrontal regions which are active during familiarity-based judgments but not recollection (Henson et al., 1999; Yonelinas et al., 2005). Consistent with the functional differentiation of PFC regions proposed by Petrides (1994, 1996) the VLPFC is thought to facilitate the encoding (Fletcher et al.,1998a; Henson et al., 1999; Wagner et al., 1998) as well as retrieval (Dobbins et al., 2002; Cabeza et al., 2002; Fletcher et al., 1998b; Raye et al., 1999; Wagner et al., 1998) of episodic memories. There is evidence too of hemispheric lateralization, whereby the left PFC is activated during episodic memory encoding with the right PFC specialized for retrieval (Nyberg, Cabeza & Tulving, 1996; Tulving et al., 1994). It appears that the DLPFC has a role to play in the organization of material for encoding (Fletcher et al., 1998a) and in monitoring processes during episodic retrieval (Fletcher et al., 1998b). A distinction has also been made between medial and lateral prefrontal areas.

The former, in particular the orbitofrontal cortex, is thought to facilitate reward-based processing and the appraisal of emotion, whereas the lateral areas appear to function more in the cognitive control of memory encoding and retrieval (Fletcher & Henson, 2001; Kringelbach & Rolls, 2004).

Blumenfeld & Ranganath (2007) proposed a further functional distinction between the dorsolateral PFC and the ventrolateral PFC within the framework of episodic memory encoding. They posited that the VLPFC functions in the selection of goal-relevant information and inhibition of task-irrelevant information and that the DLPFC supports the use of organizational strategies when they are required to facilitate LTM encoding (such as in associative encoding). Many neuroimaging studies have demonstrated VLPFC activity for items that are subsequently remembered versus those which are forgotten (see Blumenfeld et al., 2007 for a review), and both VLPFC and DLPFC activity have been related to successful memory for associations (Sommer et al., 2005; Sperling et al., 2003; Staresina & Davachi, 2006; Summerfield et al., 2006). There is also evidence that DLPFC activity during the re-ordering of items in working memory promotes LTM encoding. These findings would seem to support the theory that the DLPFC is activated when information to be encoded needs to be organized in some way (Blumenfeld & Ranganath, 2006).

The nature of the interaction between the PFC and MTL during episodic memory encoding and retrieval is coming under increasing investigation in neuroimaging research (see Figure 1.6 for proposed connectivity). Several studies have identified brain regions in which activity during encoding predicts subsequent remembering for words and source judgments. These include prefrontal regions and parahippocampal and fusiform gyri (Cansino et al., 2002; Henson et al., 1999; Wagner et al., 1998). There is also evidence for hemispheric lateralization during encoding, with left hemisphere regions being predominantly activated during verbal memory encoding and retrieval, and right hemisphere regions being activated when stimuli are non-verbal in nature (Kelley et al., 1998, Wagner et al. 1998). Further research in the areas of functional and effective connectivity during memory encoding and retrieval should help to illuminate which neuroanatomical regions function in a cooperative manner during different types of mnemonic processing.

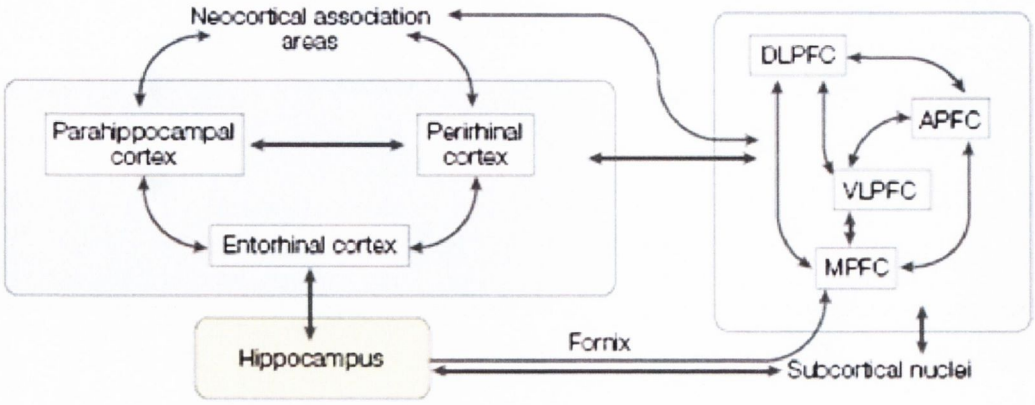

Figure 1.6: Connectivity between the MTL and PFC. DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; APFC = anterior prefrontal cortex; MPFC = medial prefrontal cortex. Adapted from Simons & Spiers, 2003.

1.10 Age-related mnemonic decline

The fact that our memory declines with age is a universally accepted phenomenon. However, far from exhibiting uniform decline, it appears that all cognitive faculties do not show the same age-related depreciation. There is much evidence to suggest that certain functions are relatively resistant to the effects of aging. Knowledge or facts about the world, often categorized as semantic memory, is relatively spared in aging (e.g. Light, 1991; Beier & Ackerman, 2001; Wingfield & Stine-Morrow, 2000), with some evidence to suggest that old adults can, in fact, outperform younger adults on tests of semantic memory (Verhaeghen, 2003) and priming (Laver & Burke, 1993). Skill acquisition also remains intact into old age (Brown, Robertson & Press, 2009), and it seems that there are no age affects on skill performance, provided the skill is kept in practice (e.g. Krampe & Ericsson, 1996).

These findings are in stark contrast with studies of the effect of aging on episodic memory and working memory, which have typically found a pronounced age-related impairment in these cognitive abilities (e.g. Nilsson et al., 1997; Park et al., 2002; Salthouse & Babcock, 1991). However, there is a certain amount of variability, between the types of tasks employed, in the degree of age-related impairment exhibited. The failure of episodic memory is a hallmark of the onset of dementia; however, certain types of episodic memory tasks have been shown to be markedly impaired in 'normal' aging also. Free- and cued-recall tend to be more impaired in aging than recognition memory (Craik & McDowd, 1987). Memory for associations is typically more affected than memory for item

information (e.g. Castel & Craik, 2003), and source and temporal order judgments also show increased vulnerability to age-deficits (Cabeza et al., 2000). Working memory also declines with age (Dobbs & Rule, 1989; Park et al., 2002) and this has often been attributed to the failure of older adults to actively inhibit competing information or that which is no longer relevant, rendering them more susceptible to interference effects (Hasher & Zacks, 1988). Inter-task variability also exists within the rubric of working memory, however, perhaps due to the varying extent to which different tasks tax cognitive control/executive functions (Smith & Jonides, 1999).

From a cognitive neuroscience perspective, researchers have increasingly looked to the frontal and medial temporal lobes to try and explain the memory impairments exhibited in aging. There is good evidence that the prefrontal cortex has an important role to play when it comes to memory decline in aging. Both structural and functional neuroimaging studies have linked changes in PFC structure and/or functional recruitment with age-related memory decline (e.g. Cabeza, 2001; Persson et al., 2006; Stebbins et al., 2002; Tisserand et al., 2004). The significance of age-related changes in the MTL for memory performance in aging is less clear-cut. Studies aimed at exploring the association between the MTL and memory impairments in 'normal' aging have typically yielded mixed results (see Cabeza, 2001 and Van Petten, 2004 for reviews).

The nature of episodic- and working memory change in aging, and their relationship to cognitive neuroscience, will be further discussed in Chapters 3 and 6, respectively. To date, however, research on age-related decline of these mnemonic functions has typically focused in greater detail on the changes that take place in old-age, leaving memory function in middle-age considerably less explored. Uncertainty still hangs over the typical age of onset and nature of certain types of memory impairment, which must be addressed if we are to further our understanding of cognitive aging.

1.11 Glucorticoids: production, mode of action, and effect on the brain

1.11.1 Cortisol

Cortisol (corticosterone in rats) is an endogenous hormone essential for the maintenance of several body functions. It belongs to a class of steroid hormones called glucocorticoids involved in immune, anti-inflammatory, metabolic and stress responses in the body. Cortisol is synthesized from cholesterol in the adrenal cortex. About 90% of cortisol in the blood is bound to corticosteroid binding globulin (CBG) and albumin. The remainder of

the hormone circulates freely in the bloodstream binding to receptors (Aron & Tyrell, 1994). Cortisol is one of the end-products of activation of the hypothalamic-pituitary-adrenal (HPA) axis. When a stimulus is perceived as being stressful the paraventricular nucleus of the hypothalamus (PVN) in the brain releases two neuropeptides, corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP), which, through a cascade of events involving the production of adrenocorticotropic hormone (ACTH) from the pituitary gland, ultimately stimulates the release of cortisol from the cortex of the adrenal glands. Cortisol itself acts via a negative feedback mechanism on the pituitary gland and the hypothalamus, in an effort to switch off further production of the hormone. Cortisol and adrenaline (released from the adrenal medulla via the sympathetic nervous system) in tandem mount the body's stress response. Adrenaline is responsible for the more immediate physiological adaptations to stress, such as increased heart rate and vasodilation. Cortisol exerts effects which serve to aid the body in coping with stress, and which also facilitate recovery after stress (Sapolsky, Romero, & Munck, 2000). During the initial stress response it brings about physiological changes such as the mobilisation energy stores and stimulation of inflammatory and immune mediators. In addition to this, corticosteroids also exert more long-term adaptive and maladaptive effects, particularly on cognition.

Broadly speaking, corticosteroid actions can be divided into four types: permissive, suppressive, stimulating, and preparative (Sapolsky et al., 2000). Permissive actions are those which are exerted in the seconds and minutes after perception of the stressor, and stem from circulating levels of corticosteroids already present before the onset of stress. Suppressive actions manifest from about an hour after the stress response and serve to inhibit or dampen the effects of the initial stress response to prevent them from overshooting. Stimulating actions also occur around this time and act to enhance/preserve initial stress responses, and thus compete with the suppressive actions of the hormones. Finally, preparative actions are not involved in the immediate stress response, but instead modify the response of the organism to a subsequent stressor. In these ways, the release of cortisol (corticosterone in rats) can be both beneficial and detrimental to the future well being of the organism.

1.11.2 Non-genomic glucocorticoid effects

While there is a substantial literature on the genomic mechanisms of action of glucocorticoids, less is known about the supposed faster-acting non-genomic effects. The

genomic effects of corticosteroids are thought to typically manifest from about an hour after the stressor (Sapolsky et al., 2000), whereas the hormones secreted during the first wave of the stress response, that act in the order of minutes, are thought to be non-genomic in nature. These so-called non-genomic effects include activation of second messenger systems, modulation of other neurotransmitter systems through membrane bound receptors, and alteration of neuronal excitability. However, relatively little is known as to the direct consequences of non-genomic steroid action and there is ambiguity concerning which glucocorticoid actions can be classified as genomic and non-genomic in nature (Haller, Mikics, & Makara, 2008; McEwen, 1994).

1.11.3 Glucocorticoid receptors

Certain areas of the brain such as the hippocampus, prefrontal cortex and the amygala are rich in glucocorticoid receptors (Herman et al., 2005). These receptors can be divided into two types: mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). These subtypes exhibit a ten-fold difference in affinity for the hormone (Arriza et al., 1988; Reul & de Kloet, 1986). MRs bind cortisol with high affinity and maintain receptor activation between bursts of hormone secretion (de Kloet, Joels, & Holsboer, 2005). In contrast, GRs have a relatively low affinity for cortisol, and are associated with circadian and stress-induced increased in hormone release (Reul et al., 1985; Young, Abelson, & Lightman, 2004). GRs are widely distributed throughout the brain while MRs have a more limited distribution, but both receptor subtypes have been found in the hippocampus (Arriza et al., 1988; Reul et al., 1985) and also in the amygdala (Arriza et al., 1988; Fuxe et al., 1985), and prefrontal cortex (Fuxe et al., 1985; Patel et al., 2000).

The different characteristics of these receptor subtypes has led to the hypothesis that GRs are important in mediating glucocorticoid feedback following stress and are responsive to circadian fluctuations in hormone levels, whereas MRs serve to regulate basal HPA axis tone (Arriza et al., 1988; De Kloet et al., 1998; see Figure 1.7). With specific regard to the stress response, MRs are postulated to be involved in the appraisal and onset of the response, whereas GRs are thought to terminate stress reactions and facilitate recovery (De Kloet et al., 2005).

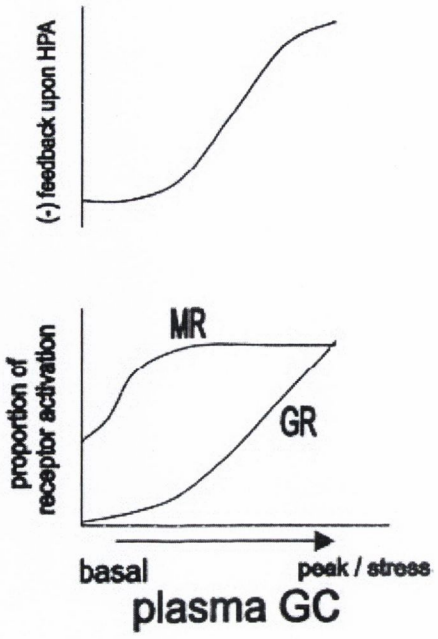

Figure 1.7: Proportionate occupation of MRs and GRs with increasing levels of circulating glucocorticoids, and relative feedback upon the HPA axis (Hibberd, Yau, & Seckl, 2000).

1.11.4 The role of sub-cortical and cortical areas in glucocorticoid regulation

Due to its abundance of GRs and MRs, and its role in memory processes, the hippocampus has been the most studied structure in relation to both feedback inhibition of the HPA axis and the effects of stress and glucocorticoids on cognitive function.

Many studies have linked the hippocampus with HPA axis function (see Jacobson & Sapolsky, 1991; Sapolsky, Krey, & McEwen, 1986). Removal or lesioning of the hippocampus leads to an increase in corticosterone release (see Jankord & Herman, 2008; Sapolsky et al., 1984). These effects appear to be most pronounced following stress-induced glucocorticoid secretion (Herman et al., 2005). Furthermore, stimulation of the hippocampus decreases glucocorticoid secretion in humans (Dunn & Orr, 1984; Rubin, Mandell, & Crandall, 1966), suggesting that the hippocampus has an inhibitory effect on HPA axis function. It is likely that the hippocampal regulation of the HPA axis may be particular to the nature of the stressor involved (Herman et al., 2005, Mueller et al., 2004). In addition, this effect may be region specific. Several studies have highlighted the importance of the ventral subiculum-CA1 pathway in inhibition of stress-induced corticosterone release (Herman et al., 1995; O'Mara, 2005), and lesioning of the CA3 area causes stress-induced hypersecretion of corticosterone in rats (Roozendaal et al., 2001).

However, large neurotoxic lesions of the entire hippocampus appear to cause no change to corticosterone levels at rest or under stress (Tuvnes et al., 2003).

In humans, hippocampal volume has been inversely correlated with the cortisol response to a psychosocial stress task in the MRI scanner (Pruessner et al., 2005), as well as with cortisol levels after administration of hydrocortisone (Tessner et al., 2007). Moreover, high glucocorticoid levels, both acutely and chronically, have been associated with hippocampal dysfunction in humans, a finding which will be discussed in greater detail in the next section.

Notwithstanding the above findings, the role of the hippocampus in HPA axis regulation is far from clear cut and more complex models of HPA axis regulation are now being explored, involving several higher brain structures such as the prefrontal cortex as well as the amygdala.

It is now known that the PVN receives direct input from several brain structures which are thought to be involved in reflexive activation of the HPA axis. These structures include the nucleus of solitary tract, raphe nucleus, subfornical organ, and other hypothalamic regions (Herman et al., 2003). In addition to the hippocampus, limbic areas such as the amygdala, prefrontal cortex, as well as the septum and midline thalamus project to the PVN indirectly via intermediary neurons (Herman et al., 2003).

The medial PFC is rich in GR receptors (Fuxe et al., 1985) and is also thought to be involved in stressor-specific HPA axis inhibition (Jankord et al., 2008; Lupien & Lepage, 2001). However, recent research indicates that the role of the PFC in HPA axis regulation is complex as well as region specific (Herman et al., 2005). In humans, activity in the orbitofrontal cortex and anterior cingulate cortex during performance of a stressful task has been inversely related to the magnitude of the stress response (Pruessner et al., 2007). It has been suggested that the role of the PFC may be in stress appraisal, monitoring, and in maintaining a state of hyperarousal and vigilance in response to a stressor (Dedovic et al., 2009).

In the rodent literature, the amygdala has been shown to have an important role in the regulation of stress-induced GC secretion, promoting activation of the axis in response to a stressor (Herman, 2005; Jankord et al., 2008). This is consistent with its well known role

in fear processing and threat detection (Armony & LeDoux, 1997; LaBar et al., 1998; LeDoux et al., 1983). The amygdala, which boasts both GC receptor subtypes, serves to activate the HPA axis in order to generate a stress response necessary to deal with the challenge (Lupien et al., 2009). Furthermore, chronic stress in rodents has been associated with dendritic hypertrophy in the basolateral amygdala (Mitra et al., 2005).

The proposed interaction between sub-cortical/cortical regions and the hypothalamus in controlling HPA axis activity is outlined in Figure 1.8.

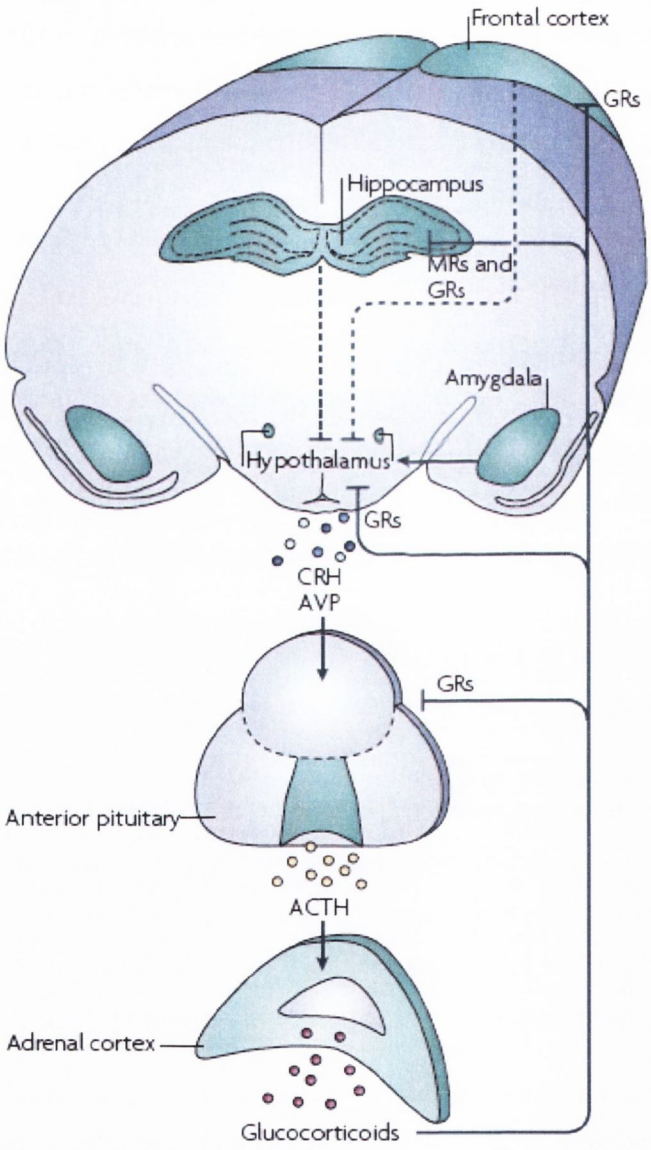

Figure 1.8: The stress system. A schematic showing the influence of key brain areas on HPA axis activity, and feedback effects of circulating glucocorticoids on these areas. ACTH = adrenocorticotropic hormone, CRH = corticotrophin releasing hormone, AVP = arginine vasopressin, GRs = glucocorticoid receptors, MRs = mineralocorticoid receptors (Lupien et al., 2009).

1.12 Glucocorticoids and memory

1.12.1 Acute effects: evidence for an inverted U-shaped relationship

An inverted U-shaped relationship between stress and cognition in animals was first proposed as far back as 1908 by Yerkes and Dodson. They demonstrated that intermediate stress levels had a beneficial effect on learning in mice over no stress or high stress, the latter of which was found to be deleterious (Yerkes & Dodson, 1908). This set of experiments gave rise to the so-called Yerkes-Dodson law, which has garnered considerable support from both the animal and the human literature. According to this law, both high levels and very low levels of glucocorticoids are detrimental to cognitive function, with moderate levels of the hormone being optimum for learning and memory. In support of this, low concentrations of exogenous glucocorticoids and mild stress facilitate spatial memory and passive avoidance learning in rats and chicks (Sandi et al., 1997; Sandi & Rose, 1994, 1997). In contrast, high stress or glucocorticoid levels have been shown to impair spatial memory in rodents (Conrad et al., 1997; De Quervain, 1998; Diamond et al., 1996). Moreover, studies in adrenalectomized rats have demonstrated impaired performance in a spatial water-maze task (Oitzl & De Kloet, 1992), providing further evidence the basal glucocorticoid secretion is necessary for cognitive performance.

It has been hypothesised that the GR/MR receptor occupation ratio may be the key to explaining the deleterious/beneficial effects of varying levels of stress and glucocorticoids on cognition (Conrad et al., 1999). When MRs are predominantly activated, both excitatory and inhibitory information is maintained at a stable level. When cortisol levels are markedly increased, and more GRs are additionally activated, CA1 hippocampal output is reduced (De Kloet, 1998). Diamond and colleagues (1992) demonstrated that a bi-phasic effect of GCs on hippocampal LTP was mediated by differential receptor occupation, with MR occupation leading to an increase in LTP and GR activation causing a decrease in LTP. Moreover, Pavlides and collaborators have shown that GR activation induces LTD in the dentate gyrus, providing evidence for the suppressive effects of high levels of GCs on hippocampal plasticity (Pavlides et al., 1995). These results may support an initially beneficial (predominantly MR occupation) but later deleterious (high concomitant GR occupation) effect of these hormones on cognition.

In the human literature, both detrimental and beneficial effects of glucocorticoids on memory have been reported. Acute or repeated administration of glucocorticoids in humans has been shown to result in declarative memory and working memory impairments

(De Quervain et al., 2000, 2003; Kirschbaum et al., 1996; Lupien et al., 1999; Newcomer et al., 1994; Newcomer et al., 1999; Young et al., 1999). An elegant study carried out by Lupien and colleagues provides support for an inverted U-shaped relationship between glucocorticoids and cognitive performance in human. They decreased endogenous cortisol levels by metyrapone administration and then subsequently restored them to baseline levels with subsequent hydrocortisone treatment, testing declarative memory at both time points. It was found that the depletion of endogenous glucocorticoids resulted in an impairment of declarative memory. This effect was reversed by returning circulating glucocorticoid levels to baseline, whereupon there was then no difference in cognitive performance between the treatment and placebo groups (Lupien et al., 2002).

Social stress paradigms also provide evidence that stress hormones can have a negative effect on memory, paralleling the pharmacology literature. Individuals who have a high cortisol response to social stress paradigms such as the Trier Social Stress Test (TSST) display poorer subsequent episodic memory and working memory performance (Kirschbaum et al., 1996; Kuhlmann, Piel, & Wolf, 2005; Schoofs et al., 2008; Wolf et al., 2001). The majority of these studies have examined the effects of cortisol on memory retrieval. There is also evidence to suggest that glucocorticoid effects on memory consolidation can conversely result in superior task performance.

Andreano and Cahill (2006) demonstrated an increase in memory performance in males (but not females) in response to subjecting participants to cold pressor stress immediately prior to a learning paradigm. Social stress paradigms have also been shown to enhance memory consolidation as high cortisol responders to the TSST have been shown to display better immediate free recall in comparison to low cortisol responders (Nater et al., 2007). Pharmacological manipulation can also enhance memory consolidation. Lupien and colleagues (2002) showed that acute hydrocortisone treatment resulted in quicker recognition of correct word-stem pairs in a cohort of young males. Importantly, in the latter two studies, the drug administration and cognitive testing were carried out at the time of day when endogenous cortisol levels are low (approaching the circadian trough).

While these results may indeed support the hypothesis that glucocorticoids have opposing effects on memory consolidation and retrieval, they could equally be interpreted as simply upholding the inverted U-shaped relationship between memory and glucocorticoids. If only mild increases in cortisol levels were achieved during the circadian trough, they could

result in an improvement in memory performance. An increase in cortisol in the morning, however, when levels are naturally high, could cross a threshold to the detriment of cognitive function. The literature on steroid hormone receptor pharmacology would seem to provide a reasonable pharmacological basis for this assertion. Furthermore, some researchers have argued that glucocorticoids only enhance memory consolidation when the material to be remembered is emotionally arousing. This will be discussed further in section 1.12.4.

No single model of the acute effects of GCs on memory has been universally accepted and findings are constantly emerging which seem to be at odds with the extant literature. Many factors should be taken into account when interpreting the equivocal results of studies in this area. The concentration of circulating glucocorticoids achieved under the various experimental conditions may indeed be important in determining the observed effects. In animal studies, there is a certain degree of subjectivity as to what constitutes high stress and what constitutes a mildly stressful behavioural paradigm. Furthermore, corticosterone levels have rarely been tested in these animals. Studies of the cognitive effects of glucocorticoid administration in humans are not directly comparable with those employing stress paradigms, as the cortisol levels induced by pharmacological treatment would likely be substantially higher than any increase resulting from a social stressor. Factors such as the circadian fluctuation in cortisol levels may also go some way to explaining contradictory results in human studies, as studies are only now beginning to control for the diurnal variation in cortisol levels.

1.12.2 Chronic effects of glucocorticoids on memory

Thus far, in this introduction, we have mainly focused on the acute effects of glucocorticoid administration and/or stress on memory. There is also a modest literature concerning the effects of chronic glucocorticoid administration or chronically high endogenous cortisol levels. The most naturalistic model of the longer-term effects of high cortisol levels on the brain is Cushing's disease. This is an unfortunate condition whereby individuals display abnormally high circulating levels of cortisol, most commonly due to a pituitary tumour causing hypersecretion of adrenocorticopic hormone (ACTH). Cushing's disease patients display impaired memory and hippocampal atrophy which appears to be ameliorated with treatment (Grillon et al., 2004; Starkman et al., 1992, 1999).

Chronic treatment with synthetic glucocorticoids such as hydrocortisone and prednisone has been shown to adversely affect memory and mood, with episodic memory seeming more susceptible than implicit or short-term memory measures (Brown et al., 2004, 2008; Brunner et al., 2005; Keenan et al., 1996). Furthermore, individuals receiving chronic glucocorticoid therapy display smaller hippocampal and amgydala volumes, when compared with matched controls (Brown et al., 2004, 2008). In recent years, the effect chronic elevation of cortisol levels on cognition in humans has also gained interest as a possible marker for 'unsuccessful' aging and predisposition to dementia. This will be discussed further in Chapter 4.

1.13 Emotion and memory

1.13.1 The concept of emotional capture

Emotional stimuli attract attention. Simple visual search paradigms demonstrate this nicely, showing that the time to detect a target stimulus among many distractors is shorter if the stimulus is emotionally salient, for example, a positive or negative face or a fear-inducing picture (Hahn et al., 2006; Ohman et al., 2000). The enhancing effect of emotion on attention can also be seen with dot probe tasks whereby participants are required to respond to the appearance of a dot on a particular side of the screen. Participants are fastest to respond when the dot appears on the same side as an emotional stimulus (face, picture), and slowest when the dot appears on the opposite side to an emotional stimulus (Armony, 2002). It appears that perception of emotional stimuli can occur even in the absence of conscious awareness - that these emotional stimuli can be processed even without attracting focal attention. Backward masking paradigms have demonstrated that brief presentation of an emotional stimulus prior to a second 'masking stimulus' induces a galvanic skin response indicating an autonomic response to the stimulus without the participant having consciously perceived it (Esteves et al., 1994). Consistent with its proposed role in the processing of emotional/socially relevant and threat stimuli, damage to the amygdala has been demonstrated to impair the recognition of different facial expressions of emotion (see Cristinzio, Sander, & Vuilleumier, 2007 for a review). Activation of the amygdala has also been demonstrated in response to masked emotional stimuli but not to masked neutral stimuli, indicating that this structure also plays a role in the pre-conscious detection and/or processing of emotional stimuli (Morris, Ohman, & Dolan, 1998; Whalen et al., 1998).

1.13.2 The influence of emotion on episodic memory

It is well established that emotion can enhance memory. Perhaps among the most well documented examples of this is the phenomenon of flashbulb memory - enhanced memory for autobiographical events that are emotionally arousing or traumatic in some way, such as the assassination of President Kennedy, or the terrorist attacks of 9/11. These anecdotal accounts have been well supported and extended to include a beneficial effect of emotion on episodic memory under experimental conditions also. These effects are particularly pronounced for recall, and include a variety of stimuli, such as pictures, stories and words (Dolan, 2002; Hamann, 2001). There is also evidence that these effects become more marked when recall is tested after a delay, rather than immediately (LaBar & Phelps, 1998).

1.13.3 The role of the amygdala and other brain regions

Much of the focus of research into the interaction between emotion and memory has been on the role of the amygdala. Increased activation of the amygdala during memory encoding has been shown to be predictive of better memory for emotionally arousing pictures (Canli et al., 2000). This effect appears to be true for both positive and negative stimuli, and at delayed, more so than immediate recall (Dolan et al., 2000; Hamann, 1999). Furthermore, patients with amygdala damage do not show enhanced recall of emotional stimuli (Adolphs, Cahill, & Schul, 1997). Amygdala activity was correlated with activity in the hippocampus in a study by Hamann and colleagues (1999), supporting the notion that functional connectivity between the amygdala and hippocampus enhances explicit memory (see Figure 1.9). Activation of the medial temporal lobe has been associated with memory for fearful faces (Fischer et al., 2007). Furthermore, firing of individual neurons in the amygdala and hippocampus during encoding and subsequent recognition of emotional faces has also been demonstrated (Fried et al., 1997). Nevertheless, there is evidence from the neuropsychology literature that the amygdala can enhance explicit memory for emotional material in the absence of complete hippocampal involvement. Amnesic individuals with damage to the hippocampus but not the amygdala display impaired overall explicit memory, but still demonstrate emotional enhancement of residual explicit memory function, indicating that the amygdala can still modulate whatever hippocampal function remains (Hamann et al., 1997a, 1997b). Some researchers argue that arousal, not valence per se, is the key to the emotional enhancement of explicit memory processes (Cahill & McGaugh, 1998). Canli and colleagues (2000), for example,

found that enhanced memory for pleasant and aversive pictures only occurred for those pictures that were given the highest arousal rating.

The amygdala, it seems, can also modulate memory when the emotional tag is merely an associated context. Studies investigating memory for neutral items that were learned paired with an emotional context have demonstrated amygdalar and orbitofrontal cortex (OFC) involvement in the retrieval of those items, relative to those items learned in the absence of emotional context (Maratos et al., 2001; Somerville et al., 2006). Activity in areas associated with explicit memory retrieval, such as the hippocampus and prefrontal cortex, was also shown to be enhanced when items were paired with an emotional context. This led the authors to suggest that both a general enhancement of activity associated with explicit memory retrieval, and specific activation of areas associated with emotional processing, occur during the retrieval of information with an emotional context (Maratos et al., 2001).

There is increasing evidence that the prefrontal cortex is important in the response to, and regulation of, emotion (Dolcos, LaBar & Cabeza, 2004; Ochsner & Gross, 2005). The OFC is known to play a role in emotion recognition and in social emotional responses (Adolphs, 2002; Roelofs et al., 2009). A recent study by Satterwaite and colleagues (2009) demonstrated greater activation of the left amygdala and OFC in response to faces that had previously been viewed with a threatening facial expression as opposed to a neutral expression. Tsukiura and Cabeza (2008) also found that activity in the hippocampus and orbitofrontal cortex showed a stronger association with encoding of happy rather than neutral face-name pairs. These results indicate that the OFC in addition to the amygdala, plays a role in memory for emotional facial expressions.

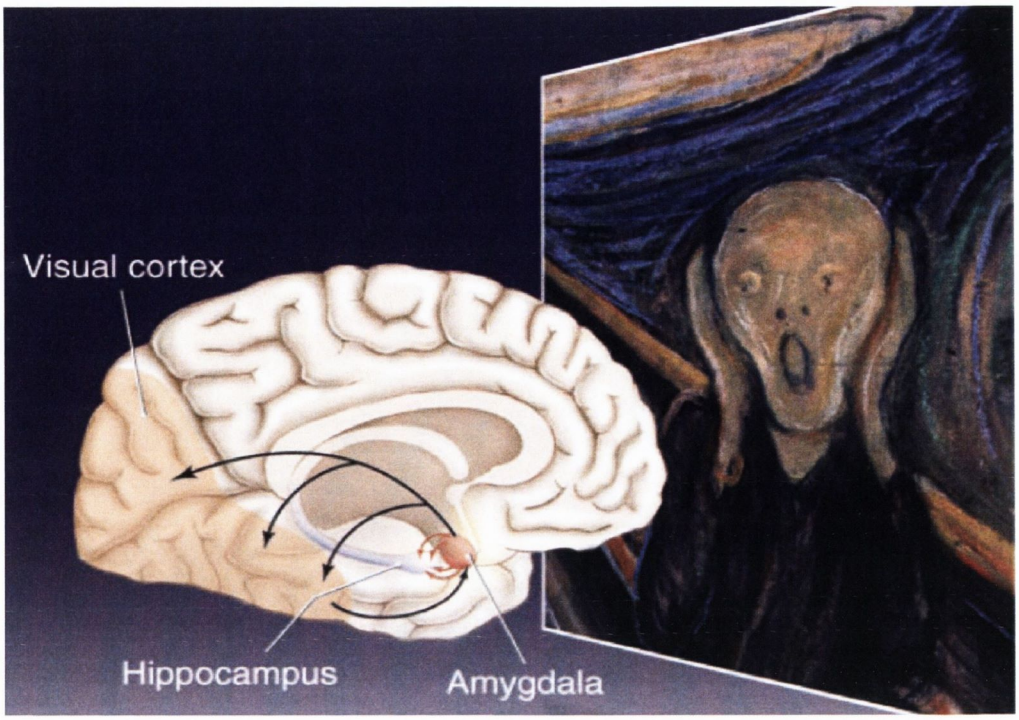

Figure 1.9: Emotion-perception-memory circuit in the brain. The amygdala registers an emotional stimulus and modulates the function of the visual cortex (perception) and the hippocampus (memory), accordingly (Dolan, 2002).

1.13.4 The effect of glucocorticoids on emotional modulation of memory

There is recently evidence that cortisol elevations can have more pronounced effects on consolidation and retrieval of emotionally salient stimuli over neutral stimuli. A study carried out by Abercrombie and colleagues (2006) found a relationship between cortisol levels during stress, negative affect, and memory for emotionally salient material. In this study, men were exposed to a public speaking task after viewing neutral and emotional stimuli. Higher cortisol output during the task and higher ratings of negative effect by participants were found to predict better subsequent recall, particularly for emotional material. Acute administration of glucocorticoids has also been shown to modulate memory for emotional material. High dose hydrocortisone (40mg) administration was shown to increase processing of angry faces during a spatial working memory task (Putman, Hermans & Van Honk, 2007). Acute hydrocortisone administration before exposure to neutral and arousing pictures facilitated memory for the arousing pictures one week later (Buchanan & Lovallo, 2001).

The same authors also demonstrated a negative relationship between cortisol levels and retrieval of arousing pictures (Buchanan & Tranel, 2008). Participants were subject to a social stress paradigm, following which, retrieval of previously learned arousing and non-

arousing pictures was tested. They found that a high cortisol response to the stressor led to impaired retrieval of both arousing and non-arousing pictures. Participants who exhibited no significant cortisol response to the stressor, showed better retrieval of arousing pictures over neutral stimuli. These results suggest that cortisol elevations preferentially alter memory for emotional stimuli, and that a similar encoding– retrieval distinction exists, whereby higher levels of cortisol are beneficial during the encoding/consolidation phase, but maladaptive at the retrieval stage of memory. It must also be noted that these investigations involved elevating cortisol significantly above baseline, and thus no conclusions can be drawn as to the relationship between cortisol and processing of emotional/socially relevant stimuli, when levels are not artificially elevated.

Putman, Van Honk and colleagues, however, explored the association between baseline levels of salivary cortisol and memory preference for emotional faces over neutral faces in a spatial memory task in women. They found that higher cortisol levels were related to better long term memory for emotional faces (happy and fearful; Putman et al., 2004). Interestingly, however, an earlier study from this group demonstrated an inverse relationship between cortisol levels and immediate recall of the location of emotional faces (in this case, happy and angry).

There has been some debate recently in the literature as to the effect of emotion on memory for items themselves versus memory for neutral contextual features associated with those items. It seems that emotion may enhance item memory at the expense of associated neutral information, and the possibility exists that high levels of glucocorticoids may further exacerbate this, promoting better item but impaired associative memory (Mather, 2007).

A probable neurochemical basis for the interaction between glucocorticoids, emotion processing and memory has been elucidated via the use of rodent models. Infusions of a glucocorticoid receptor antagonist into the basolateral nucleus of the amygdala (BLA) have been shown to attenuate the facilitatory effects of chronic corticosterone treatment on contextual fear conditioning in rats (Conrad et al., 2001). It also appears that the effect of glucocorticoids on the amygdala in memory processing may be sensitive to noradrenergic input. Roozendaal and colleagues demonstrated that systemic administration of a noradrenergic receptor antagonist can block the corticosterone-induced impairment in contextual memory retrieval in rats (Roozendaal et al., 2004). In humans, a recent study

has shown that the impairing effects of cortisol on the retrieval of emotional words can be blocked by the β- receptor antagonist propranolol, however, administration of propranolol alone has no effect on retrieval of emotional or neutral words (De Quervain et al., 2007). It appears that corticotrophin-releasing-hormone (CRH) and glucocorticoid systems interact within the BLA to influence ß-adrenoceptor-cAMP effects on consolidation (Roozendaal, Schelling, & McGaugh, 2008).

1.13.5 Emotion and working memory

There is a considerable literature on the relationship between emotion, episodic and spatial memory and the biological mechanisms that may be responsible, as reviewed above. To date, however, there has been very little research carried out into the relationship between working memory and emotion. Mood modulation has been shown to alter working memory processes (Gray, 2001), and several studies have demonstrated that anxiety can impair working memory (Derakshan & Eysenck, 1998; Shackman et al., 2006). A study by Kensinger and Corkin (2003) found slower reaction times in response to fearful faces than neutral faces in an n-back task, suggesting that emotional salience can negatively affect processing speed during working memory task . Interestingly, however, no such effect was found during a working memory task using verbal stimuli. Thus this effect may not be robust across all types of stimuli, and perhaps is only evident with stimuli such as emotional faces, which elicit robust activation of the amygdala even at brief presentation intervals (Morris et al., 1998). Perstein, Elbert and Stenger (2002) conducted an elegant study examining prefrontal cortex activation during working memory and target detection tasks involving pleasant, neutral and unpleasant pictures. They found that DLPFC activity during the working memory paradigm was greatest for pleasant pictures and was decreased for unpleasant stimuli when compared with neutral. Similarly, performance accuracy mirrored the fMRI results, with accuracy being greatest in response to pleasant stimuli, and poorest for negative stimuli. All stimuli were tested to make sure that they were emotionally arousing prior to the working memory task, thus the results suggest that emotional valence may be more important than arousal in modulating working memory performance. These results are also supported by the findings of a study by Dolcos, LaBar and Cabeza (2004). Participants rated positive, neutral and negative pictures while in the fMRI scanner, and it was found that DLPFC activity correlated with positive ratings while VLPFC activity was associated with negatively-rated pictures.

1.14 The current studies

It is clear that the medial temporal lobe and the prefrontal cortex have an important role to play in memory. This has been further highlighted by studies of memory dysfunction in both healthy aged individuals and in those suffering from dementia, which have shown evidence of a relationship between structural changes in these regions and memory impairment (e.g. Tisserand et al., 2004). Moreover, it seems that some types of memory are more susceptible to age-related decline than others. Episodic memory and working memory seem to be particularly vulnerable to age-related impairments. However, within the framework of episodic memory and working memory, it appears that there is considerable variation between tasks in the degree of age-related impairment that typically manifests. The exact nature of this variability and the reasons for it, have yet to be fully elucidated. Understanding when significant age-related impairments first manifest and the types of memory that are first affected has important implications for the study of brain and behavioural changes in aging.

It is likely that there are several factors that may negatively influence memory in aging. One biological candidate is an elevation in levels of the stress hormone cortisol due to an alteration of HPA axis function. As high cortisol levels have been shown to have a marked effect on memory, and are often a consequence of chronic or acute stress, the role of this hormone in age-related memory decline must be thoroughly investigated.

Emotional salience has been shown to render material more memorable. Therefore, the relationship between emotion and memory in age-related cognitive dysfunction merits investigation. However, most studies focusing on this relationship have contrasted only elderly individuals with young adults, leaving emotional regulation in mid-life relatively unexplored.

With the above considerations in mind, we aim to focus on the changes that may occur in episodic and working memory during adulthood before 'old-age'. To this end, we will investigate memory performance in young and middle-aged adults. In addition, we will explore the relationship of cortisol levels to task performance in these groups, as a possible factor which could affect age-related memory decline. We will then investigate emotional memory in young adulthood and middle-age, and how the use of emotional stimuli might alter task performance. Finally, we will investigate possible structural correlates of age-

related memory decline, in the hope of furthering our knowledge of the biological basis of cognitive aging.

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Chapter 2

Methods

2.1 Summary

This chapter outlines how the current studies were conducted, from the recruitment of participants to the design and execution of the cognitive, behavioural and biological measures employed.

2.2 Introduction

Each of the four experimental chapters in this thesis consists of a number of experimental cognitive tasks in combination with neuropsychological tests, questionnaires, and salivary cortisol measurements. The cognitive tasks were primarily aimed at exploring long-term memory and working memory function. In Chapter 6 performance on one of these tasks (Face-Name Pairs) was further investigated in relation to structural magnetic resonance imaging (MRI) data obtained from participants during task performance. The neuropsychological tests and questionnaires can be further subdivided into control (National Adult Reading Test) and affective measures. The latter include self-rating scales designed to reflect mood state, experience of stress, and aspects of personality. These scales were examined in relation to cognitive task performance and/or were used to assess the effect of a particular intervention (i.e. undergoing an MRI scan) on psychological well-being. Salivary cortisol measurements were aimed at assessing basal hormone levels as well as the HPA axis response to a potentially stressful intervention such as MRI. The relationship between cortisol levels, cognitive task performance, and other psychological indices was explored.

This methods section details each of the cognitive tasks, neuropsychological measures, cortisol measurement, and MRI preprocessing and analysis. Information specific to a particular study (regarding participants, order of presentation of the tasks, or the further specifics of a particular analysis) is largely reserved for the relevant experimental chapter.

All cognitive tasks were programmed using E-Prime 1.2 stimulus presentation package (Psychology Software Tools, Pittsburgh, PA) software. Tasks were presented on a Dell personal computer (details and screen dimensions) or a Dell Latitude laptop (dimensions). Participants were positioned roughly 60 cm from the screen. Responses were recorded via the keyboard or a Cedrus RB-420 response pad (see Figure 2.4).

2.3 Participants

Participants were drawn from the college (Trinity College Dublin) and local communities. They were recruited by means of advertisement within the college and outside the college via posters and word of mouth. All participants were aged between 18 and 64 (though specific age ranges varied for each study). All participants had normal or corrected-to-normal vision. Exclusion criteria varied slightly between studies but included a history of neuropsychiatric or neurological disorder, head trauma, endocrine disorder, and any medication thought to impact cognitive or endocrine function. Participants received cash payment (in accordance with Trinity College School of Psychology guidelines), or course credit (applicable only to Psychology Junior and Senior Freshmen), for their participation. Written, informed consent was obtained from every participant in accordance with Trinity College Ethics Committee guidelines. Participants were given an information leaflet for each study which also set out their rights under the Freedom of Information Act and data protection guidelines.

2.4 Working memory tasks

2.4.1 *N*-Back task (0-Back, 1-Back and 2-Back): Numbers

2.4.1.1 Design

The *N*-Back paradigm was the primary task used in this thesis to assess working memory function. This task has been widely used to study working memory, particularly in functional neuroimaging (e.g. Cohen et al., 1997). It has been also used to explore focal attention, and how information is processed and exchanged between memory and focal attention when attentional capacity is exceeded (Mc Elree, 2001). Participants must judge whether the current item on screen matches the *n*th item, in a serially presented list of items. It places considerable demands on executive function, as participants have to constantly update their mental set. There is evidence to suggest that only one item can be maintained in focal attention at a time (Garavan, 1998; McElree, 2001). As the task load increases (e.g. moving from a 1-Back task to the 2-Back task), working memory is taxed to a greater extent, as participants are forced to try and maintain items that are outside their focus of attention, and so active retrieval from working memory is required.

This *N*-Back task requires participants to respond to digits presented one at a time on screen, by pressing the digit that appeared *n* trials previous. Participants performed three levels of this task (0-, 1- and 2-Back) with task difficulty increasing as the *n* increased.

The 0-Back task serves as a sensorimotor baseline. Percentage accuracy scores were recorded by the E-prime programme.

2.4.1.2 *Materials and stimuli*

The stimuli for this task (Meyer-Lindenberg et al., 2001) consisted of grey coloured diamond shapes with a black outline (dimensions: 16.9 cm long, 16.9 cm wide). Each diamond was presented centrally on screen and contained the digits "1" (1.2 cm x 0.7 cm (height x base width); located in the top corner); "2" (1.2 cm x 0.7 cm; located in the left corner); "3" (1.2 cm x 0.8 cm; located in the right corner); "4" (1.2 cm x 0.3 cm; located in the bottom corner) or contained no numerical information (i.e. a blank diamond; see Figure 2.1).

Responses were recorded via a Cedrus RB-530 response pad using four buttons which corresponded in both number and positioning, to the numbers on screen (see Figure 2.4).

2.4.1.3 *Procedure*

Participants viewed diamond shaped stimuli consecutively for 1800 ms per stimulus. Between each stimulus there was a blank screen which lasted for 200 ms. Stimuli were presented in a random sequence for the 0-Back task, and in a pseudorandom sequence for the 1-Back and 2-Back tasks. In the case of these two latter tasks every nine digits were followed by either one (1-Back) or two (2-Back) blank diamonds.

O-Back (Sensorimotor Control)

Participants viewed numerical stimuli (45 stimuli presentations in total). They were instructed to press the button on the response pad that corresponded to the number currently on screen (see Figure 2.1). There were no blank diamonds.

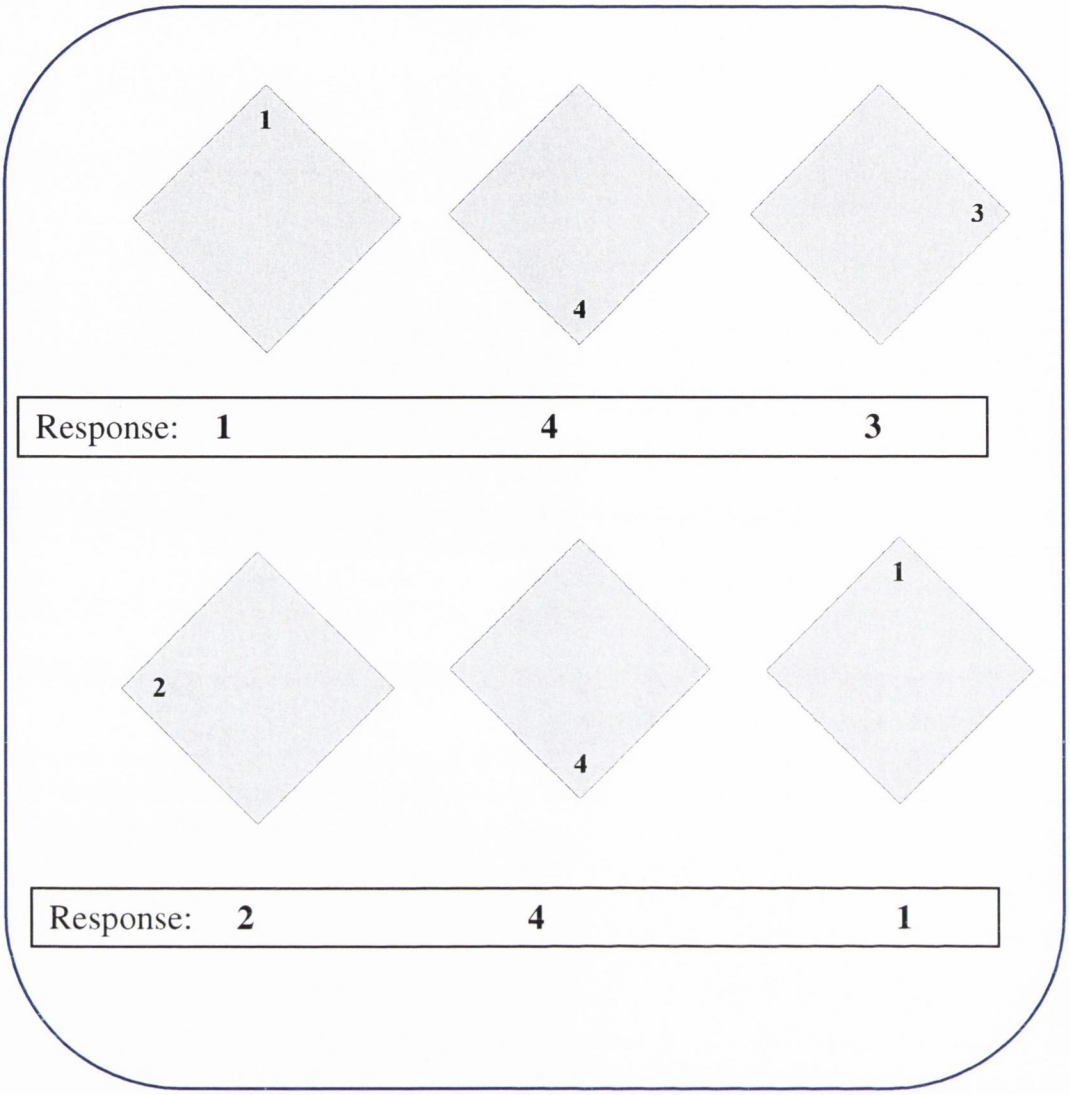

Figure 2.1: 0-Back task. Participants were required to press the number corresponding to the number in the diamond currently on screen. Each number was presented for 1800 ms (ISI = 200ms)

1-Back

Participants viewed 9 consecutive numerical stimuli presentations followed by 1 blank stimulus. As they viewed the sequence of stimuli, they were required to press the button that corresponded to the number presented one trial previously (see Figure 2.2). This required participants to store the current and previous number and to update these two numbers with each presentation. When the blank stimulus was presented, participants used the same strategy, thus pressing the button corresponding to the number viewed one trial previously. Furthermore, the blank stimulus served to initiate a new number sequence and so no response was required for the first number of the new sequence.

Each 10 stimuli (9 numerical, 1 blank) constituted a block. Participants were given two practice blocks before commencing the experimental blocks. Following the practice blocks, and once the experimenter was happy that the task requirements were understood, the experimental blocks began (5 blocks in total).

2-Back

Participants viewed 9 consecutive numerical stimuli followed by 2 blank stimuli. For this task they were instructed to press the button corresponding to the number presented two trials previously (see Figure 2.3). This meant that participants had to store the current and previous two numbers in working memory, and update them accordingly. When the blank stimuli were presented, participants continued to press the button corresponding to the number two trials previously. Again, as with the 1-Back task, the blank diamonds preceded a new number sequence, therefore no response was required for the following two numerical stimuli.

Each 11 stimuli (9 numerical, 2 blank) constituted a block. As with the 1-Back task, participants were given two practice blocks before commencing the experimental blocks. Again, responses made during the practice blocks were not recorded by the computer, and participants did not commence the experimental blocks (4 in total) until the experimenter was satisfied that they understood the task requirements.

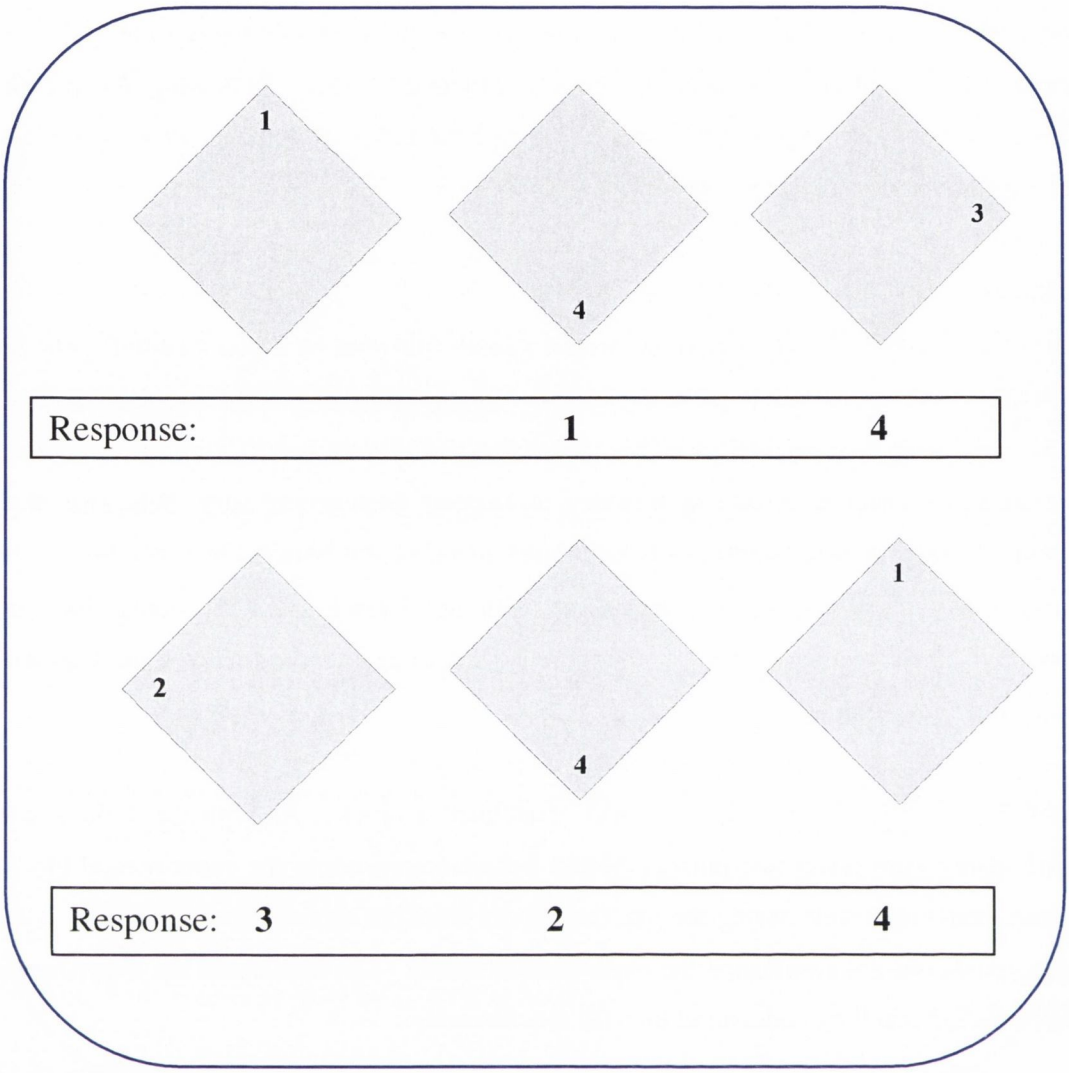

Figure 2.2: 1-Back task. Participants were required to press the number presented one diamond previously. Each number was presented for 1800 ms (ISI = 200ms).

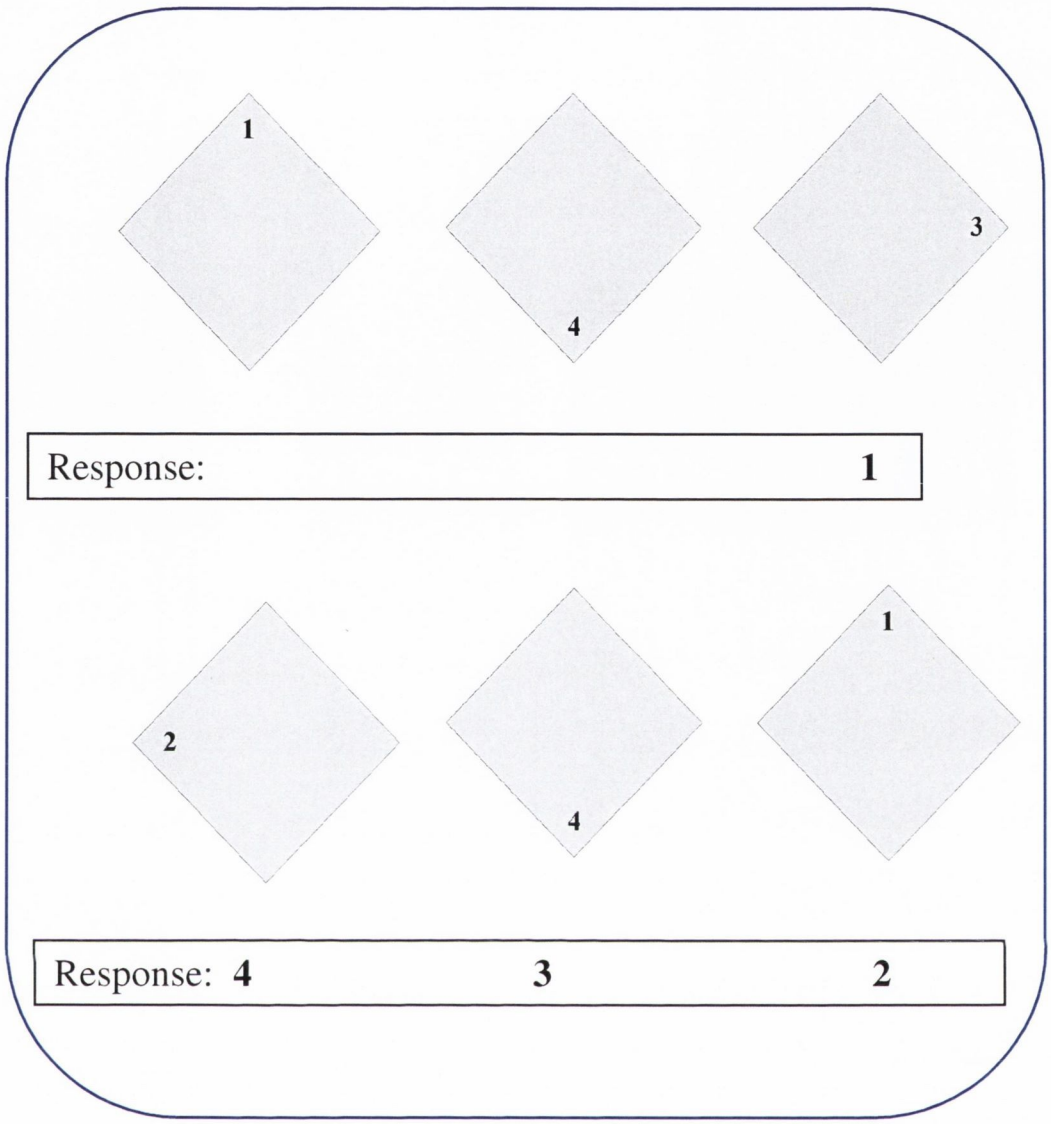

Figure 2.3: 2-Back task. Participants were required to press the number corresponding to the number two diamonds previous. Each number was presented for 1800 ms (ISI = 200ms).

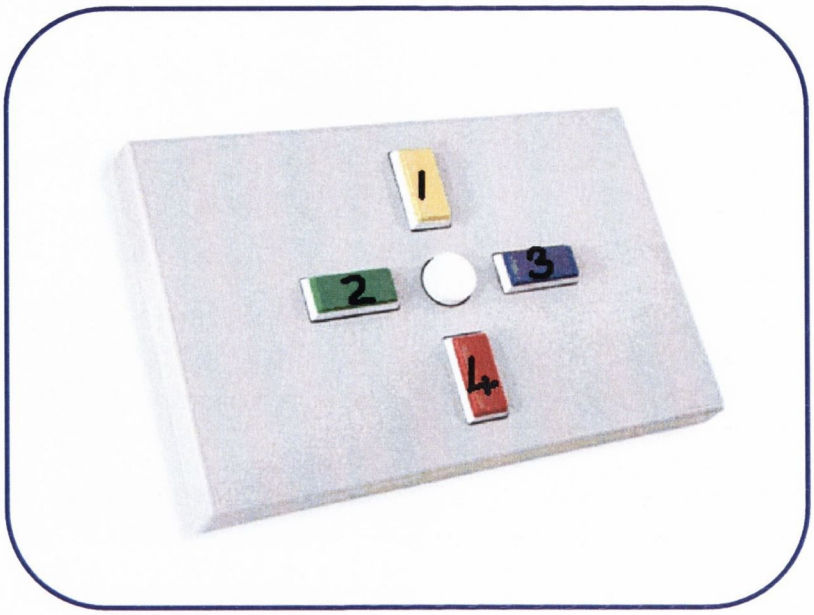

Figure 2.4: Cedrus RB-530 response pad.

2.4.2 *N*-Back task (0-Back, 1-Back and 2-Back): Emotional Faces

2.4.2.1 Design

This task was a form of *N*-Back task using faces (Kensinger et al., 2003). As with the *N*-back task using numbers, there were three levels to this task: 0-Back, 1-Back and 2-Back. 0-Back served as a sensorimotor control task. Percentage accuracy scores and reaction times were recorded by E-prime.

2.4.2.2 Materials and stimuli

The faces used were taken from the Karolinska Directed Emotional Faces (KDEF; Lundqvist, Flykt, & Ohman, 1998) stimulus set. Hair and other distinguishing features were removed, and each face was presented in black and white, centred against a black background on screen (see Figure 2.5). Four faces, two female and two male, were chosen for the tasks. In addition to these four faces, inverted versions of faces were used. These inverted faces appeared similar to photographic negatives and were also centred against a black background.

As in the case of the Face-Name Pairs task outlined in section 2.5.2, there were three versions of this task. The first group were given a task with faces that displayed a happy expression, the second group were given faces with an angry expression, and the third

group viewed neutral faces. Thus, each participant viewed faces with the same expression (happy, angry or neutral) throughout the task.

2.4.2.3 Procedure

Participants viewed each face for 1800 ms. Between each stimulus there was a black screen which lasted for 200 ms (ISI). For each condition participants were instructed as to the rule that they had to follow, and were required to press the spacebar in response to target faces as dictated by the condition (0, 1, or 2-Back). Before each condition, 0, 1 or 2-Back, participants were given a practice block that consisted of twelve trials or stimuli. Participants were told that this was to enable them familiarise themselves with the task, and that their responses were not being recorded. Once the experimenter was satisfied that participants understood the task requirements, the task proper was started. For the 0-back condition this consisted of forty-eight trials. Each trial consisted of either a normal or inverted face. For the 1-Back and 2-Back conditions, there were fifty-four trials, but again comprising four blocks. Each block consisted of twelve normal faces followed by an inverted face repeated. Stimuli were presented in pseudo random order.

0-Back

For this condition the four faces were alternated with inverted faces in a pseudorandom order. Participants were instructed that they need only respond to the inverted faces, so that any time they saw an inverted face, they should press the spacebar on the keyboard, as quickly as possible (see Figure 2.5 upper panel). The inverted faces comprised 33% of all trials, so that 33% of all trials required a response.

1-Back

For the 1-Back condition participants were now instructed to respond by pressing the spacebar when they saw a normal face (i.e. not inverted) that had been presented in the previous trial, i.e. when they saw the same face twice or three times in a row (see Figure 2.5 lower panel). They were told that for all other trials they need not respond. The four normal faces were alternated for twelve trials. At the end of every block of twelve trials, two inverted faces were presented. This was the same inverted face repeated, and these two trials served to mark the end of one block and the beginning of the next block. Participants were advised that these inverted faces (unlike in the 0-Back condition) merely served as a break between blocks in this condition, and that they need not respond to them.

On 33% of trials the same face was repeated in a row, therefore 33% of trials required a response.

2-Back

For the 2-Back condition, participants were instructed to press the spacebar when they saw a face that had been presented two trials previously (see Figure 2.6). They were told that for all other trials they need not respond. Once again four normal faces were alternated for twelve trials, at the end of which an inverted face was again presented twice, marking the end of that block and the beginning of the next. The same inverted face was used for the 1-Back and 2-Back conditions. Participants were reminded not to respond to the inverted faces in this condition. As in the 1-Back condition, 33% of trials required a response.

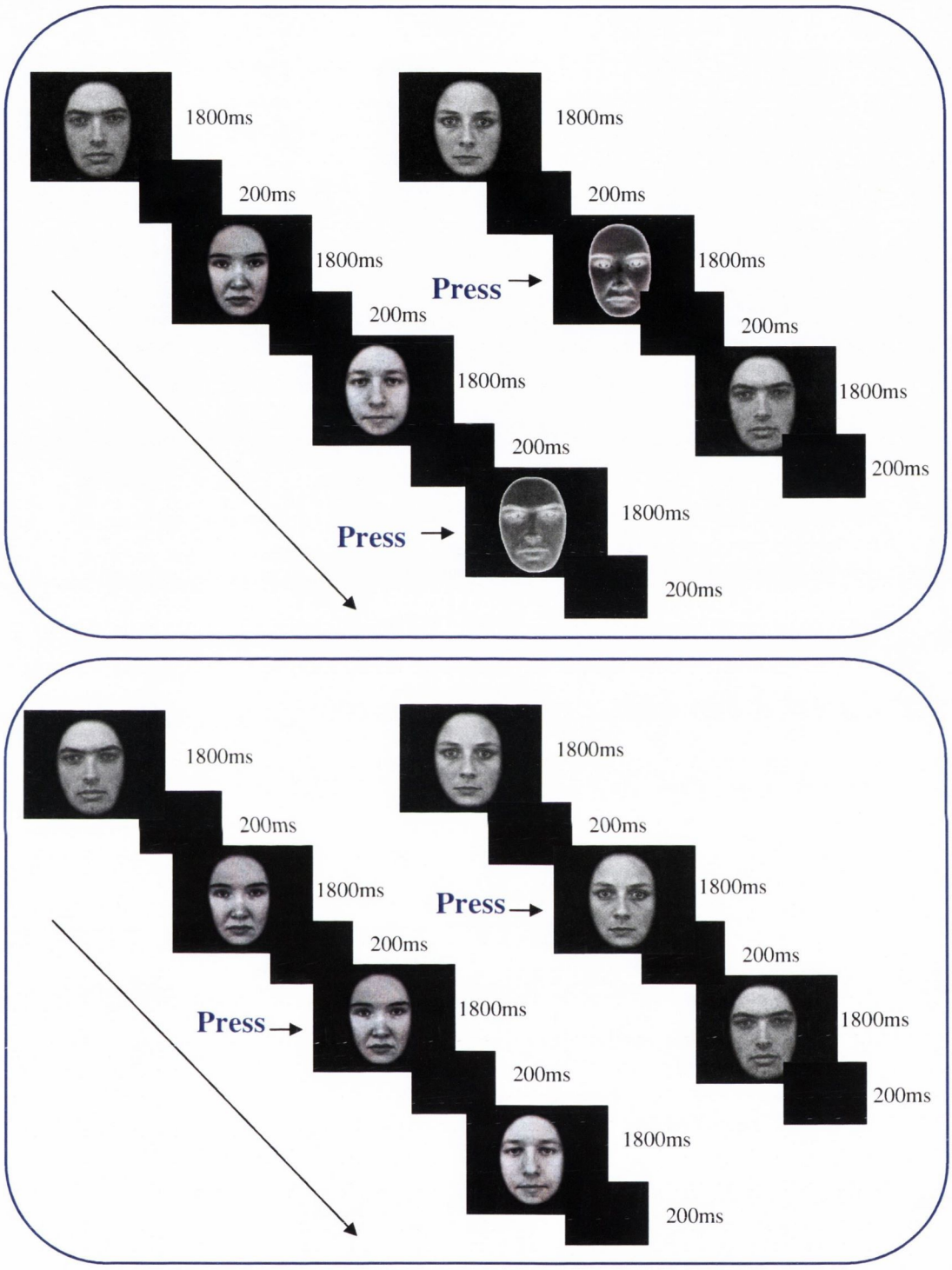

Figure 2.5: (Upper Panel) 0-Back task - Emotional Faces. Participants were required to press the spacebar in response to the presentation of an inverted face. (Lower Panel) 1-Back task. Participants were required to press the spacebar when a face appeared that had been presented one trial previously. Each face was presented for 1800 ms (ISI = 200ms).

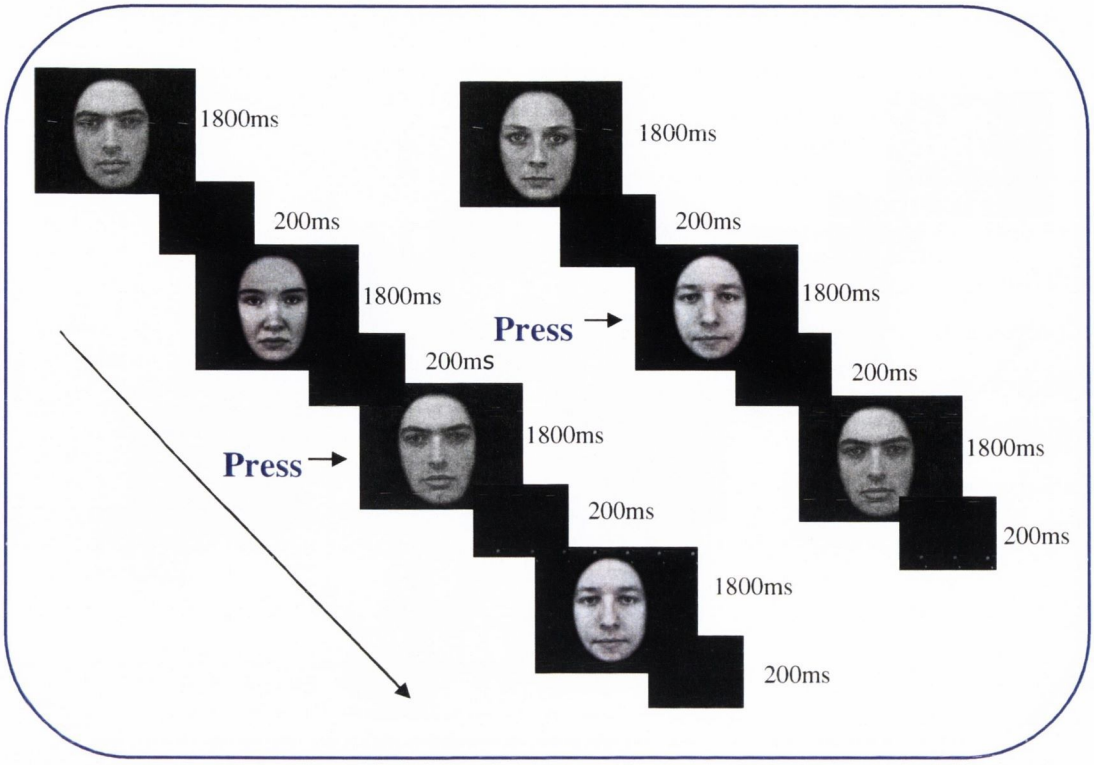

Figure 2.6: 2-Back task - Emotional Faces. Participants were required to press the spacebar in response to a face that had been presented two trials previously. Each stimulus was presented for 1800 ms (ISI = 200 ms).

NOTE: Neutral faces are used in the above example schematics. The tasks also ran in an identical fashion with angry faces and happy faces.

2.4.4 Match-to-Sample task

2.4.4.1 Design

This task (Ranganath et al., 2005) comprised a working memory maintenance task and a delayed recognition task. Ranganath and colleagues propose that activity in the prefrontal cortex and hippocampus during early working memory maintenance contributes to successful long-term memory, as assessed by the delayed recognition task.

The stimuli comprised drawings of novel objects. In the working memory task participants were shown a cue object followed by a target object, the judgment being whether the target matched the cue object or not. The delayed recognition task took place some twenty minutes later and comprised the presentation of objects, some of which were used in the working memory task, and some of which were foils. For this task participants were instructed to indicate whether each object was seen in the earlier task or not. Percentage

accuracy scores were recorded by E-Prime for the working memory task, and by the experimenter for the delayed recognition task (see section 2.3.3.3b).

2.4.4.2 *Materials and Stimuli*

Stimuli used consisted of black line drawings of three-dimensional novel objects centred against a white background, on a computer screen (Williams & Tarr, 1997). Participants used the keyboard to respond during the working memory task. During the delayed recognition task participants responded by circling answers on a sheet of paper.

2.4.4.3 *Procedure*

Working Memory task

During this task participants were presented with a drawing of a novel object (cue) followed by a second object (target). There was a countdown of 3 s (ISI=0.5 seconds) before the presentation of the cue object. The cue object was presented on screen for 1 second, followed by a variable delay period of 7, 9, 11, or 13 seconds, during which participants viewed a fixation square. After the delay the target object appeared and remained on screen until the participant made a response (see Figure 2.7). For each pair of objects participants were instructed that they should press '1' on the keyboard if the second object was identical to the first and '2' if the second object did not match the first. Participants were given a short practice task during which the delay period was fixed at 1 second. Once the experimenter was satisfied that the participant understood the task requirements, the actual task was started. Twenty pairs (cue and target) of objects were presented during the task.

Delayed Recognition task

Participants viewed thirty-five line drawings of objects on screen, one at a time. They were instructed to identify whether or not they had seen the object during the earlier task by circling "yes" or "no" to each on a response sheet. Participants were instructed to press the spacebar once they had made a decision, to view the next object. Twenty-five of the stimuli viewed had been part of the earlier task (either in the training or main task), with ten new stimuli. The number of hits (objects correctly identified as having been previously seen), foils (objects correctly identified as being new), misses (objects previously seen but identified as being new), and false positives (new objects identified as having been previously seen) were recorded. Percentage accuracy scores were calculated using the following formula: [(Hits – False Positives) /25*100].

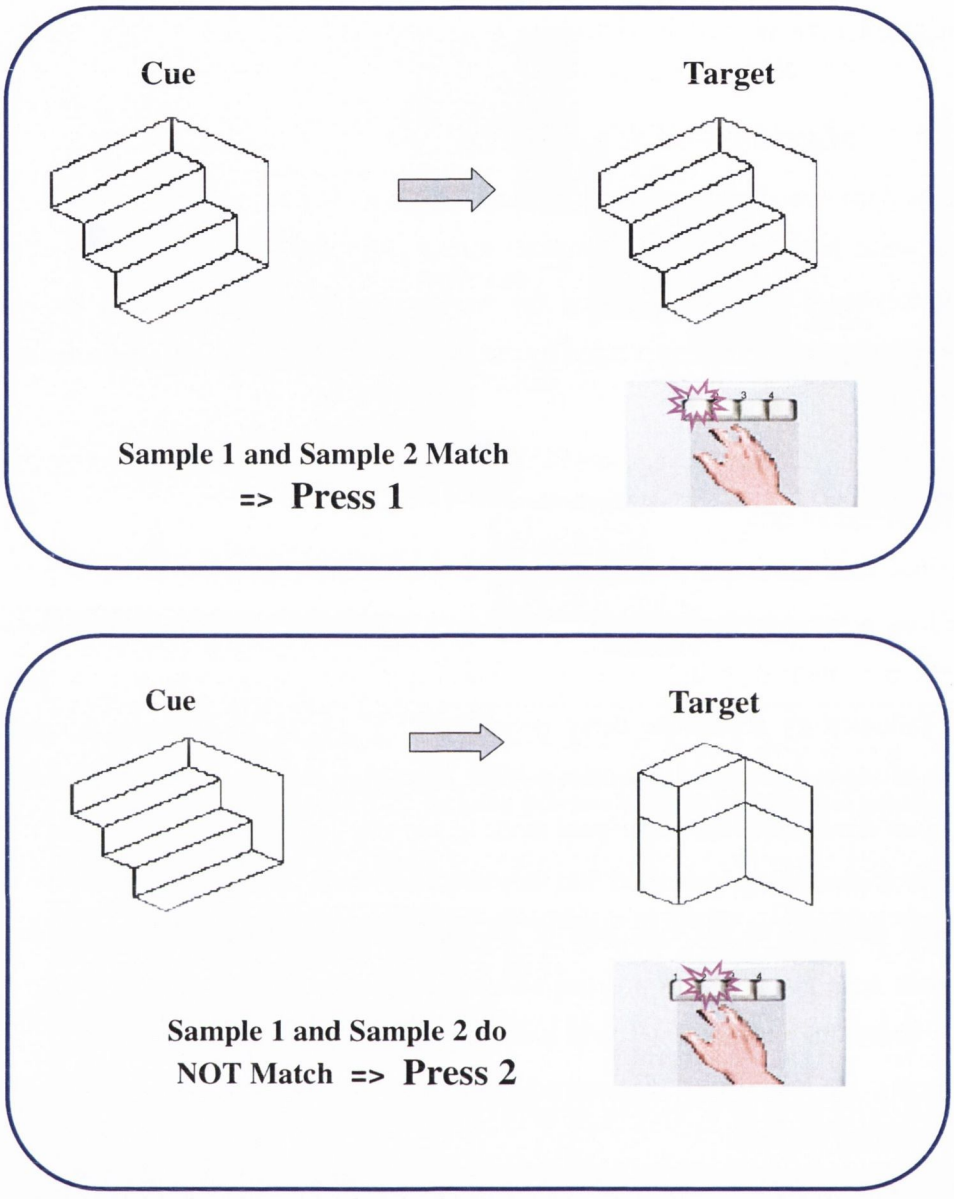

Figure 2.7: Match-to-Sample Task. (Upper Panel): When the cue matched the target stimulus the participants had to press '1' on the keyboard. (Lower Panel): When the cue did not match the target stimulus participants were required to press '2' on the keyboard.

2.5 Associative memory tasks

2.5.1 Face-Name Pairs task

2.5.1.1 Design

The Face-Name Pairs task was the key paradigm used in these studies to assess associative memory function. This task is thought to be among the most ecologically valid measures of associative memory, and performance on this task has been shown to be impaired in patients with mild cognitive impairment (e.g. Petrella et al., 1996). Thus this task is ideal for studying how associative memory ability changes with normal aging. Evidence from the functional neuroimaging literature strongly suggests that performance success relies on activation of the anterior hippocampus (Chua et al., 2007; Sperling et al., 2003; Zeineh et al., 2003).

The task design used was based on that of Zeineh and colleagues (2003). It consisted of 4 blocks of encoding, each block being followed by an immediate recall task. A brief distraction task separated each encoding block from the subsequent recall task. The sequence of encoding –distraction- recall was thus repeated a total of four times, with the same face-name pairs being presented at each repetition. In addition, delayed recall and recognition tasks followed approximately fifteen minutes later.

2.5.1.2 Materials and stimuli

Eight female faces (selected from a college yearbook in black and white with hair removed) were presented on a black background, to the left of a central bisecting line. In the encoding phase the name corresponding to each face was presented to the right of this line (see Figure2.8) upper panel). During the recall phase the names were replaced with the prompt "Name?" (see Figure 2.8 lower panel). All names selected were English names, had two syllables each, and were matched for frequency.

2.5.1.3 Procedure

Face-Name Encoding

Participants viewed 8 face-name pairs, presented serially at a rate of one every 3.5 seconds (ISI= 500 milliseconds). Participants were instructed to study each face-name pair and to try and memorize the name corresponding to each face. The presentation order was consistent across each of the encoding blocks.

Distraction task

The distraction task (Zeineh et al., 2003) consisted of a fixation cross within a circle and required participants to press a central white button on the Cedrus RB-530 response pad every time the cross changed to a solid black circle (see Figure 2.9). This occurred intermittently every 2-5 seconds, and in each case the solid black circle remained on screen for 500 milliseconds before reverting back to the cross. The aim of this task was to prevent participants from actively rehearsing the pairings from the encoding phase.

Face-Name Immediate Recall

Participants viewed the same 8 faces, presented in a random order, with the prompt "Name?" appearing to the right of each face (see Figure 2.8 lower panel). Each face was presented for 3.5 seconds (ISI = 500 milliseconds), during which participants were required to recall and verbalise the names corresponding to each of the eight faces. The experimenter recorded correct and incorrect responses (non-responses were also recorded as incorrect).

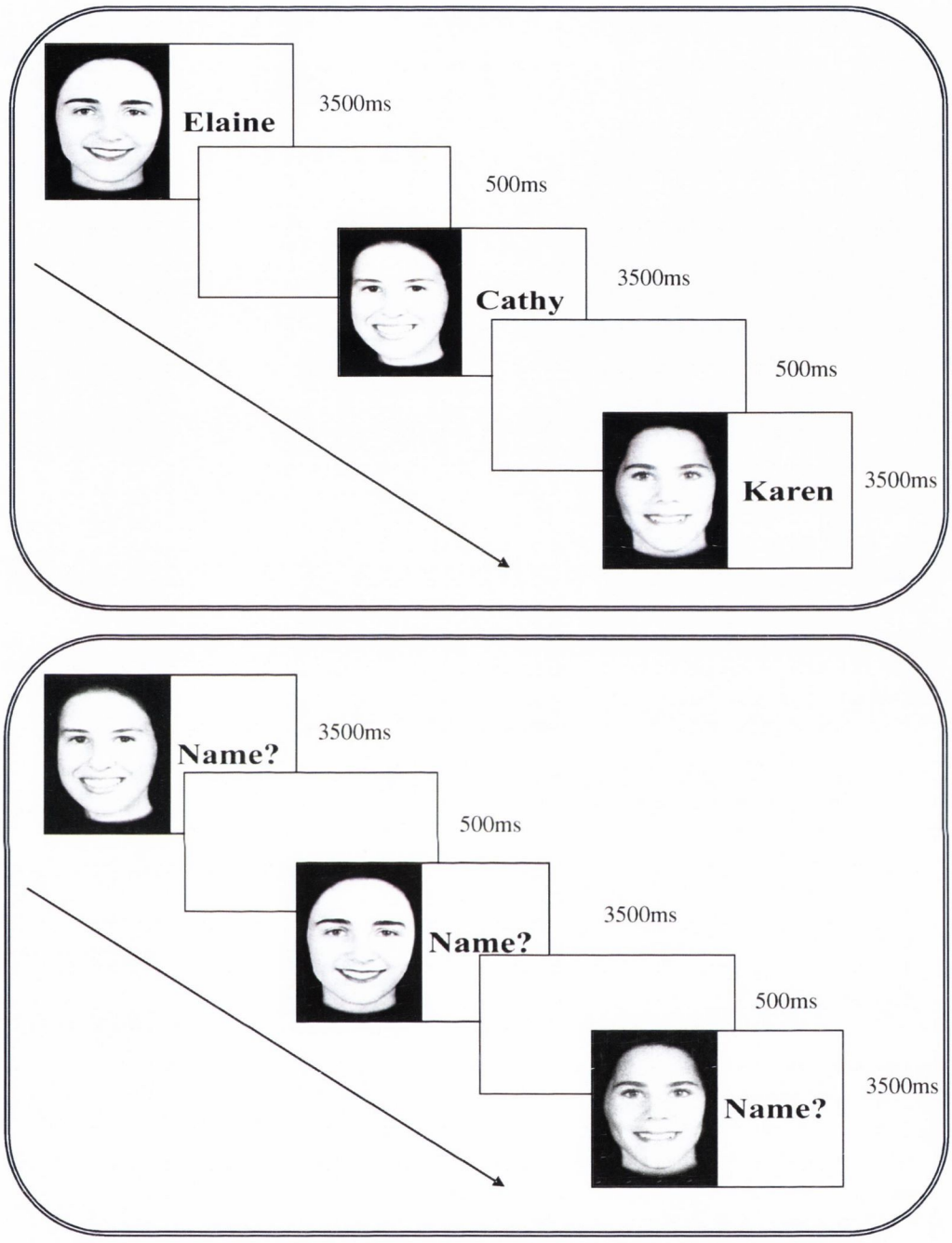

Figure 2.8: Face-Name Pairs Encoding and Recall. (Upper Panel): Participants viewed each face-name pair for 3.5 seconds (ISI = 0.5s). (Lower Panel): Participants were presented with each of the eight previously viewed faces (in random order). They were required to vocally recall the name corresponding to each face. Each face was viewed for 3.5 seconds (ISI = 0.5 s).

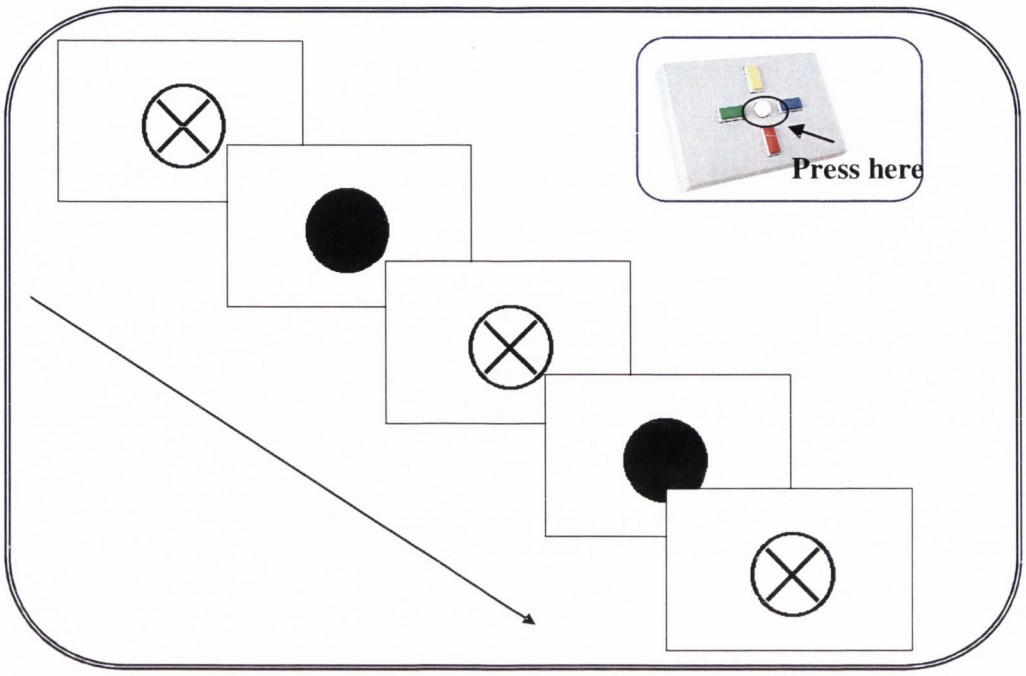

Figure 2.9: Distraction Task. (Main Panel): Participants focused on the fixation cross and pressed a button every time it changed to a solid black circle. (Inset): Cedrus RB-530 response pad. Participants pressed the white circular button every time the circle and cross-changed to a solid black circle.

Delayed Face-Name Recall

The delayed recall phase of the task took place approximately 15 minutes after the main task. Participants viewed the same eight faces again, without the names, and were required to vocally recall them. The experimenter recorded correct and incorrect responses.

Face Recognition

Following the delayed recall, participants were presented with sixteen faces, appearing one at a time on screen. They were instructed, for each face, to indicate whether or not it had been part of the earlier task by circling "yes" or "no" on a response sheet. Participants were instructed to press the spacebar to move through the faces. All the faces that had appeared in the earlier task, plus eight foils, were present. Responses were scored as per section 2.4.4.3.

Name Recall

Next, participants were asked to try and recall completely from memory (i.e. free-recall), the names used in the task. The experimenter noted correct and incorrect responses, and percentage accuracy scores were calculated as above.

Name Recognition

Following the name recall, participants were presented with sixteen names (eight from the original task and eight foils) listed on the response sheet. They were instructed to read all the names and identify the ones from the earlier task. Responses were recorded and scored as per the Face Recognition task above.

2.5.2 Emotional Face-Name Pairs task

2.5.2.1 Design

This task was a modification of the Face-Name Pairs task described in section 2.4.1. 1. It was identical in design and execution. Briefly, the task consisted of an encoding phase and a recall phase with a distraction task in between. The sequence of encoding –distraction-recall was repeated a total of four times, with the same face-name pairs presented at each repetition.

A delayed associative recall task as well as name recall, and face and name recognition tasks followed approximately 20 minutes later.

2.5.2.2 Materials and stimuli

The stimuli used in this experiment were taken from two sets of faces used in emotion research: Pictures of Facial Affect (POFA; Ekman and Friesen, 1975); and the Karolinska Directed Emotional Faces (KDEF; Lundqvist, et al., 1998). Faces chosen from these sets were happy, neutral, or angry in expression. Faces were modified using Photoshop software to remove their hair and any other distinguishing features (e.g. moles or birth marks), and all photos were presented in black and white. There were 8 faces presented per task, 4 male and 4 female. The presentation of the faces was identical to that of the Face-Name Pairs task used in Chapter 3 (see section 2.5.1.).

There were three versions of this task and participants were randomised to one of three groups. Group 1 were given a Face-Name Pairs task using faces that were all happy in expression. Group 2 had to complete the task with the same individuals, but this time each had an angry facial expression. Group 3 were given a task with the same individuals

posing with a neutral or expressionless face. Thus the actual faces used in each task were identical; it was solely the expression of emotion that varied between the three versions of the task (see Figure 2.10).

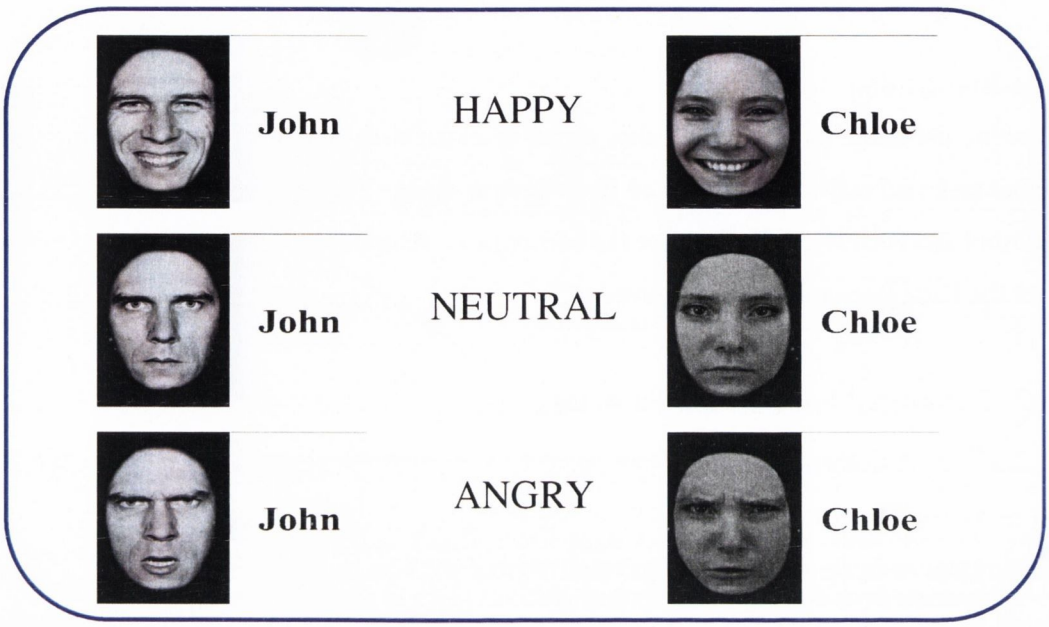

Figure 2.10: Emotional Face-Name Pairs. Examples of the three types of face stimuli used. The faces used in each version of a task differed only in the emotion being portrayed. Participants performed task with either all angry faces, neutral faces, or happy faces.

2.5.2.3 Procedure

The procedure for this task was identical to that of the Face-Name Pairs task described in section 2.5.1.

2.5.3 Picture-Word Association task

2.5.3.1 Design

This task is a modified version of the task used by Eldridge and colleagues (2005). Participants were required to try and learn a set of pictures paired with unrelated words, and to then retrieve the words when presented with the pictures. Furthermore they were required to later identify pairings which had appeared in the earlier task. The task as a whole had four separate components: an encoding phase, a distraction task, an immediate cued recall phase, and a delayed recognition task (occurring some twenty minutes after the immediate recall phase).

2.5.3.2 Materials and stimuli

The stimuli for this task were taken from a standardized set of pictures (Snodgrass & Vanderwart, 1980). Stimuli consisted of twenty images of items or animals and twenty nouns unrelated to the pictures. During the encoding phase of the task each picture was paired with a word and presented on a computer screen (see Figure 2.11 upper panel). Half of the picture-word pairings showed the picture on the right half of the screen with the word on the right, with the other half showing the reverse. In the immediate recall phase of the task the pictures were positioned centrally on screen (see Figure 2.11 lower panel). Participant responses were vocalised for the free recall task, and made using the keyboard for the delayed recognition task.

2.5.3.3 Procedure

Picture-Word Encoding

Participants viewed 20 picture-word pairs which appeared consecutively onscreen. Each stimulus pair was presented serially for 3.5 seconds followed by a blank screen (ISI) for 0.5 seconds. The order of presentation of the pairs was the same for all participants. Participants were told that they were going to be viewing picture-word pairs and were given the instruction to try and memorise as much detail about the pairs as possible, as their memory of them would be later tested.

Distraction task

Described previously, see section 2.5.1.3.

Immediate Recall

Participants viewed the 20 pictures from the previous picture-word pairings in the same order as in the original pairs. Each picture remained onscreen for 3.5 seconds with and ISI of 0.5 seconds. Participants were instructed to try and remember the word that was paired each picture and to verbalise their response. The experimenter recorded correct and incorrect responses (a non-response was also recorded as incorrect).

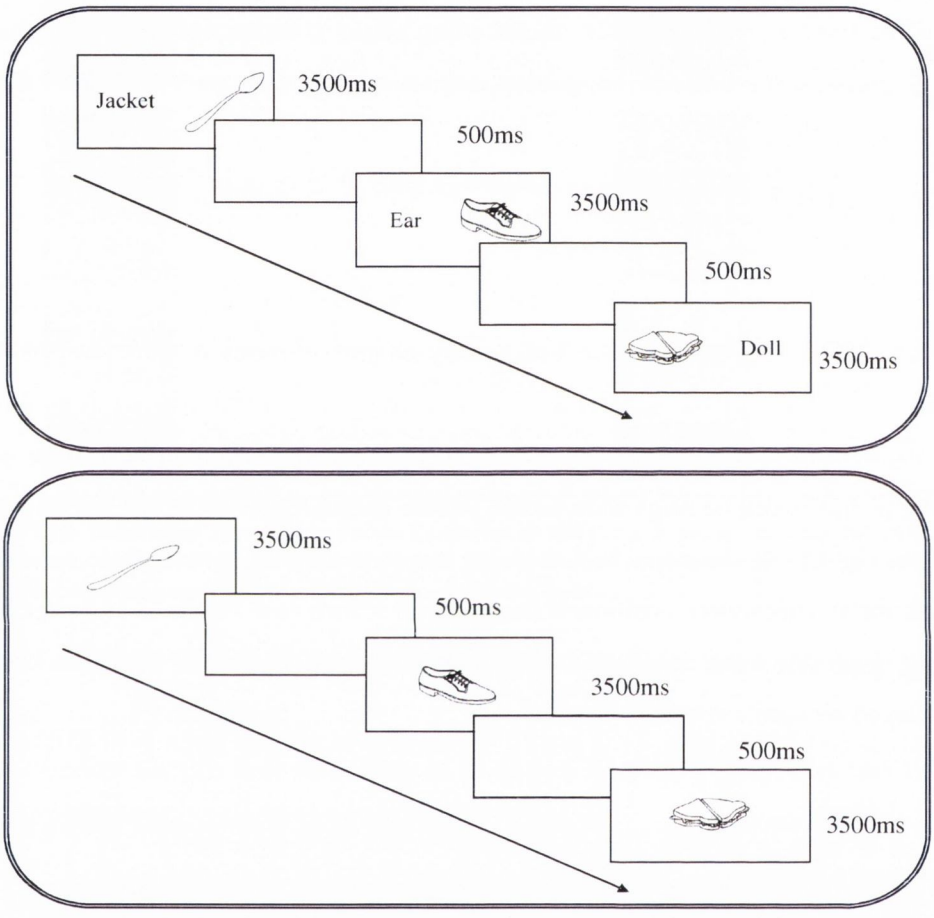

Figure 2.11: Picture-Word Encoding and Immediate Recall. (Upper Panel): Participants viewed each picture-word pair for 3.5 s (ISI = 0.5s). (Lower Panel): Participants were presented with each of the previously pictures in their original order. Each picture was viewed for 3.5 s (ISI = 0.5s). They were required to vocally recall the corresponding word for each picture.

Delayed Recognition task

The delayed recognition component of this task took place approximately twenty minutes after the encoding and immediate recall phases. Participants were presented with the same twenty pictures as before. The pictures were once again paired with the words from earlier, but were presented in three different formats: as originally seen in the encoding phase; in reverse order (e.g. if the picture was positioned to the left of the word it was now

on the right); and recombined (the picture was paired with a different word; see Figure 2.12). Participants were instructed to decide whether each picture-word pair was identical to or different from its previous presentation. Participants were informed of the two ways in which the pairs could differ. For each stimulus pair presented on screen, participants were required to indicate "same" or "different" by pressing either of two keys on the keyboard. Each stimulus pair remained on screen until the participant made a response.

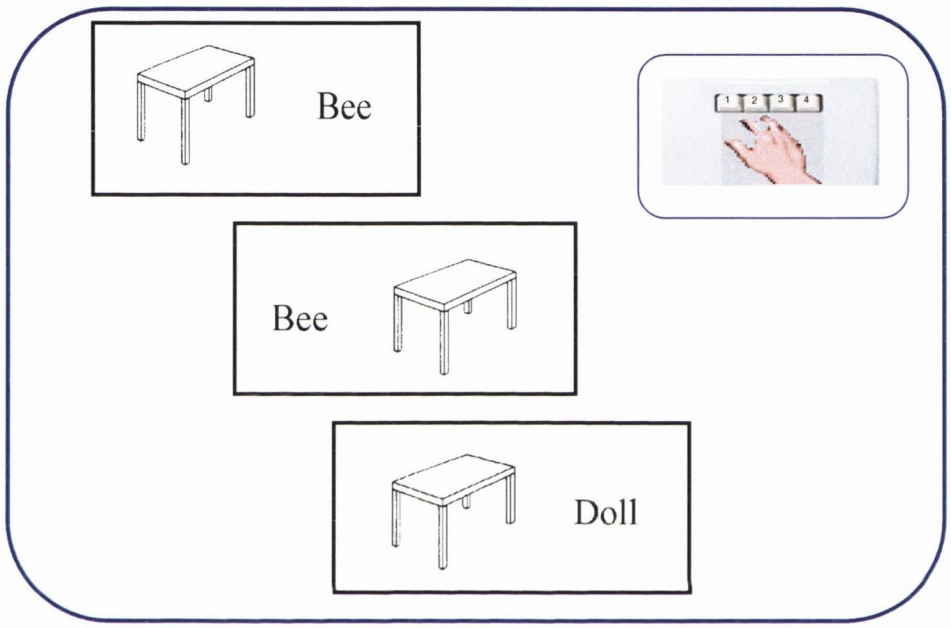

Figure 2.12: Picture-Word Task Delayed Recall Stimuli. (Upper panel): An example of a picture-word pair as presented during the encoding task. (Middle panel): The same picture-word pairing reversed. (Lower panel): The picture recombined with a different word. (Inset): Participants pressed '1' if the pairing was the same as in the encoding task, and '2' if the pairing differed from the previous viewing in any way.

2.6 Face Judgment task

2.6.1 Design

This task was based on similar tasks used by Keightley and colleagues (2006) and by Roelefs et al. (2009). Participants were required to make simple emotion judgements about faces serially presented to them. The faces were happy, neutral, or angry in expression. Participants first performed a practice task which served to enable them to learn associations between the three conditions and specific buttons on the response box. They then performed the emotion judgment task.

2.6.2 Materials and stimuli

Forty-eight faces were selected from two sets of affective face stimuli: Pictures of Facial Affect (POFA; Ekman et al, 1976); and the Karolinska Directed Emotional Faces (KDEF; Lundqvist et al., 1998). Sixteen happy, sixteen neutral, and sixteen angry faces were chosen. Both males and females were used. All photographs were converted to greyscale, and hair and any other distinguishing features were removed. Stimuli were presented in the centre of the screen against a black background. For the practice task the words "Happy", "Neutral" and "Angry" were presented in Times New Roman font, in white, centred against a black background (see Figure 2.13 middle panel). Participants responded using the three buttons (yellow, white and blue) on the Cedrus RB-530 response box (see Figure 2.13 lower panel).

2.6.3 Procedure

Practice task

Participants viewed twenty-four trials with the words appearing on screen one at a time. On eight trials the word "Happy" was presented, on another eight trials "Neutral" was presented, and on a further eight "Angry" was presented. Participants were instructed that they should press three different buttons on the response box in response to the three different words. Each word remained on screen until the participant made a response (ISI = 500 milliseconds), and then the next word would appear (see Figure 2.13 middle panel). Participants were told that speed of response was important and that they should respond as quickly as possible to each face while trying to make as few mistakes as possible.

Emotion Judgment task

Participants viewed two blocks of twenty-four faces each. The presentation of faces was randomised within and between blocks, though eight happy, eight neutral, and eight angry faces were always presented in each block. Participants were instructed that for each face they should indicate using the response box (using the same buttons as in the practice task) whether they thought the face was happy, neutral, or angry in facial expression. Each face remained on screen until the participant made a response (ISI = 500 milliseconds; see Figure 2.13 upper panel). Again, participants were reminded that the speed of response was important. There was a pause between blocks (5 seconds), following which there was a countdown (2 seconds) before the second block of faces began.

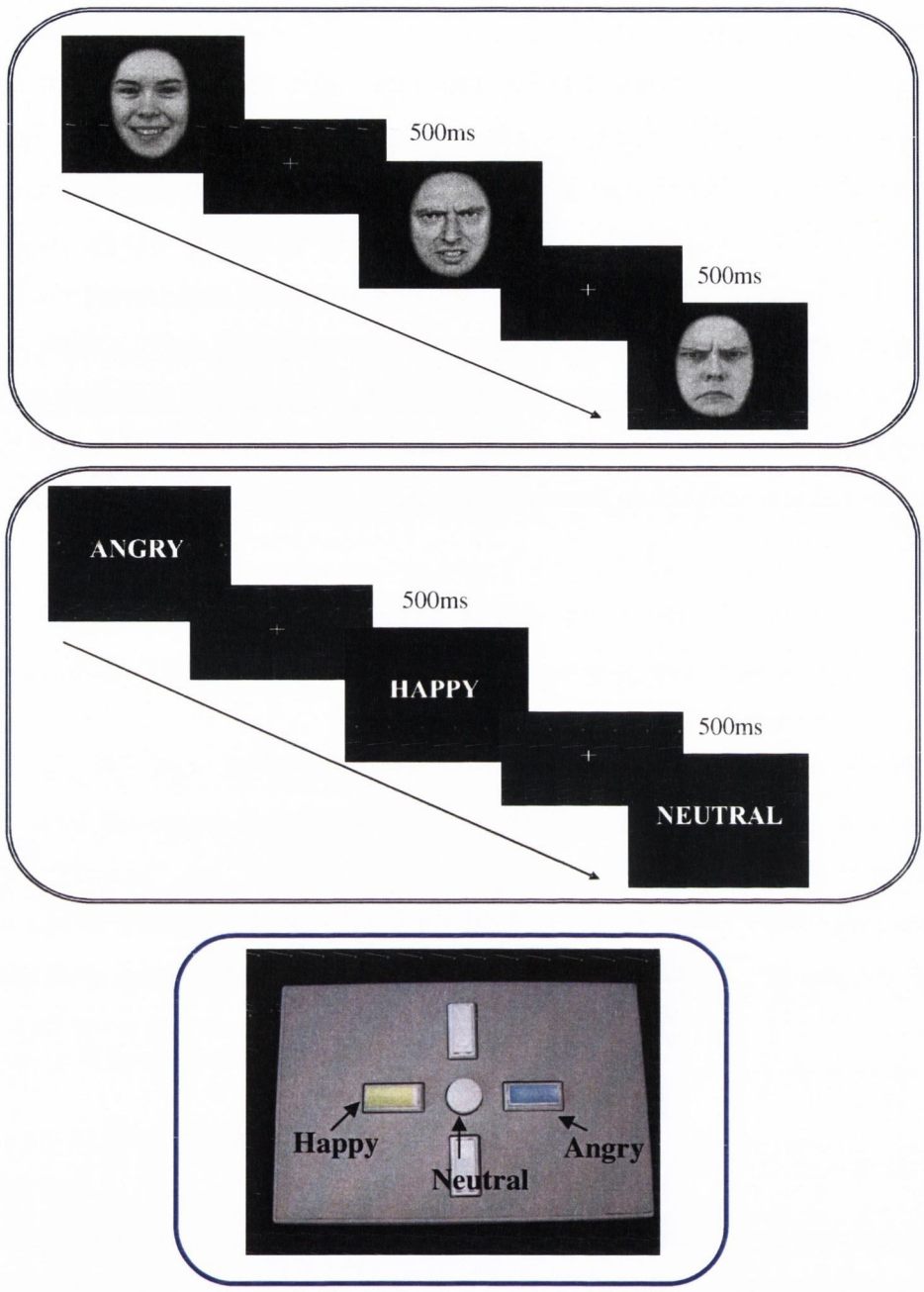

Figure 2.13: Emotion Judgment and Practice Tasks. (Upper panel): Participants were presented with consecutive faces (happy, neutral and angry; ISI = 500 ms), and were required to judge the emotion being portrayed by pressing the corresponding button on the response box. (Middle panel): During the practice task participants were presented with alternating words ('Happy', 'Neutral', and 'Angry'; ISI = 500 ms), and were required to press the corresponding buttons on the response box. (Lower panel): Participants were instructed to press the left button for happy faces (or the word 'Happy'), the middle button for neutral faces (or the word 'Neutral'), and the right button for angry faces (or the word 'Angry').

2.7 Affective self-rating scales

2.7.1 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) is self report questionnaire designed to assess anxiety and depression. HADS consists of seven items which reflect depression (2,4,6,8,10,12,14) and seven items for anxiety (1,3,5,7,9,11,13). Examples of questions include: "Do you take as much interest in things as you used to? Do you feel cheerful? Do you worry a lot?" Somatic symptoms of anxiety and depression have been excluded. Participants are instructed to read each item carefully and circle the response that comes closest to how they have been feeling in the last week. Each item is answered on a four point (0-3) response category. Possible scores therefore range from 0 to 21 for anxiety and 0 to 21 for depression. A score of 0-7 for either subscale could be regarded as being normal, 8-10 mild, 11-14 moderate and 15-21 severe disorder (Zigmond et al., 1983).

The HADS was originally designed as a screening tool in a hospital setting, but has since been shown to be a useful tool in assessing anxiety and depression in non-clinical populations also (Bjelland, et al., 2002).

2.7.2 State-Trait Anxiety Inventory (STAI)

The STAI (Spielberger, et al., 1983) has been used extensively in research and in clinical practice. It consists of two self-report scales for measuring state and trait anxiety. Trait anxiety (T-Anxiety) refers to "differences between people in the tendency to perceive stressful situations as dangerous or threatening and to respond to such situations with elevations in the intensity of their state anxiety". State anxiety (S-Anxiety) is a transient phenomenon, dictated by a particular circumstance or situation. The S-Anxiety scale consists of 20 questions that probe how participants are feeling "right now". The T-Anxiety scale aims to assess how people generally feel.

On the S-Anxiety scale each statement is rated on a scale of 1 to 4, with 1 = "not at all", 2 = "somewhat", 3 = "moderately so" and 4 = "very much so". Participants are instructed to indicate to what degree they feel each statement applies to them at this moment ("I feel calm"). The T-Anxiety scale responses are a modification of those used in the S-Anxiety scale. On this scale 1 = "almost never", 2 = "sometimes", 3 = "often", and 4 = "almost always". Participants are instructed to indicate to what degree they feel each statement

applies to them in general ("I feel nervous and restless"). Each scale consists of ten negative and ten positive items, with reverse scoring operating for the latter. Total scores on each scale can vary between 20 and 80.

2.8 National Adult Reading Test- 2nd Edition (NART)

The National Adult Reading Test (NART) was developed by Nelson and Willison and was designed as a measure of premorbid intelligence. It consists of a list of 50 words printed in order of increasing difficulty (Nelson, 1982; Nelson & Willison, 1991). These words are not pronounced phonetically and so prior exposure to the word is necessary for accurate pronunciation. It is based on the premise that participants should be able to accurately pronounce words in their vocabulary, and therefore should make errors on unfamiliar words only (Nelson et al., 1991). Participants were instructed to read aloud each of the fifty words in order. The experimenter used the NART answer sheet (which had the words written phonetically) to record any errors made. The total number of errors made was subtracted from the maximum score (i.e. 50 minus errors made) to produce an error score. From this score the Wecshler Adult Intelligence Scale – Revised (WAIS-R) Full scale, Verbal and Performance IQs can be predicted. Error scores were transformed into predicted WAIS-R full scale IQ scores.

2.9 Salivary Cortisol Measurement

Salivary cortisol measurements are indicative of plasma free cortisol concentrations in normal and pathological situations (Laudat et al., 1988). Samples were collected by using a Salivette® device (manufactured by Sarstedt, Numbrecht, Germany). This consisted of a suspended insert within an outer tube, both plastic (see Figure 2.14). The suspended insert contained a cotton swab for participants to chew on, and a small hole at the bottom of the insert to allow for saliva to collect in the outer tube upon centrifugation. Participants were instructed to remove the swab from the inner tube and chew on it for approximately 2 minutes, or until they felt that the swab was saturated with saliva (de Weerth, et al., 2003). They then replaced the swab back in the inner tube and placed the plastic cap on the device.

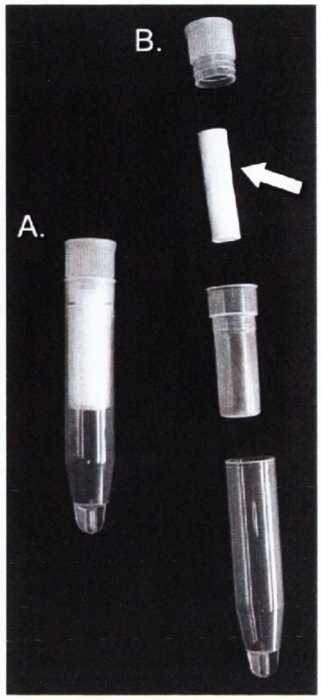

Figure 2.14: Salivette Sampling Device. (A): The assembled Salivette device. (B): The device split into its subcomponents. Participants were instructed to chew the cotton roll and place it back into the inner tube which then fitted into the outer tube. Image courtesy of www.tidsskriftet.no.

After collection, Salivettes were then centrifuged for 2 minutes at 1000g to separate off the saliva into the outer tube. The inner tube containing the used swab was then disposed of and the outer tube containing the centrifuged supernatant was stored. Centrifuged samples were stored according to the guidelines set out by Roche diagnostics for Elecsys® Cortisol in saliva Immunoassay (either at 2-8°C for up to 5 days, or a -20°C for up to 3 months before analysis).

Samples were analysed by the Elecsys® Cortisol in saliva Immunoassay method (Roche Diagnostics, Manheim, Germany) in the Adelaide and Meath Hospital, incorporating the National Children's Hospital, Tallaght (AMNCH). This assay makes use of a competition test principle using a polyclonal antibody specific for cortisol. Sensitivity was 0.500 nmol/L or 0.018µg/dL. All values were reported as concentrations in nmol/L.

2.10 Magnetic Resonance Imaging (MRI)

2.10.1 MRI data acquisition

Scanning was conducted using a Philips Intera Achieva 3.0 Tesla MR system (Best, The Netherlands). Stimuli were displayed on a panel positioned outside the scanner, behind the participants' head. A mirror was mounted on the head coil directly in the participants' line of vision, and this reflected the visual display. A parallel Sensitivity Encoding (SENSE) approach (Pruessmann et al., 1999) with a reduction factor of 2 was used. A high-resolution T1-weighted MP-RAGE (magnetization-prepared rapid gradient echo) anatomical sequence was acquired for each participant (180 oblique-axial slices, field of view 230 mm, slice thickness 0.9 mm, voxel size 0.9 x 0.9 x 0.9, total duration 5.43 minutes).

2.10.2 Voxel-Based Morphometry (VBM) protocol

Data preprocessing

Voxel-Based Morphometry (VBM; Ashburner & Friston, 2000) analyses were carried out using SPM 5 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK), on a MATLAB platform (Math Works, Natick, Massachusetts, USA). SPM5 uses a unified segmentation approach to VBM (Ashburner & Friston, 2005). There were three basic preprocessing steps that were implemented: spatial normalisation; tissue segmentation and spatial smoothing. During the spatial normalisation step all MR images are normalised to a standard stereotactic space. The neuroanatomical templates used for this registration step in SPM5 are the ICBM probalistic atlases (International Consortium for Brain Mapping; http://www.loni.ucla.edu/ICBM/ICBMTissueProb.html). These atlases were derived from 452 T_1 weighted MR scans, classified into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). A combination of linear affine and non-linear transformations were made during normalization to the tissue-specific templates, and the spatially normalized images were partitioned into GM, WM and CSF using the ICBM priors in Montreal Neurological Institute (MNI) space and according to Bayesian rules. The unified segmentation method (Ashburner & Friston, 2005) combines the above steps into a single generative model, whereby both image registration and the classification of voxels into tissue types are combined, along with a bias correction for intensity inhomogeneity. This leads to improved segmentation (Ashburner & Friston, 2005). Optimized VBM uses an additional modulation step in order to compensate for expansion and contraction of certain brain areas which is inevitable during non-linear warping, in order for images to 'fit'

properly to the template. This modulation step involves the multiplication of the voxel values by Jacobian parameters derived from the spatial normalization step. Modulation allows for subsequent analysis of regional differences in absolute grey matter volume (Good et al., 2001), of interest in our study; whereas the analysis of un-modulated images allows for the investigation of regional differences in the distribution of grey matter (Keller et al., 2008).

The final preprocessing step carried out was the spatial smoothing step. The normalised, segmented and modulated grey matter partitions were spatially smoothed with a 12 mm FWHM (full-width half-maximum) isotropic Gaussian kernel. This smoothing step attempts to compensate for the variability in gyral anatomy and it also renders the data more normally distributed (Worsley et al., 1996).

Analyses

Voxel-wise statistical analyses based on Gaussian field theory (Friston et al., 1995) were carried out using the general linear model (GLM). In all analyses the total intracranial volume (TIV) was entered as a global covariate (Good et al., 2001) and all analyses followed the ANCOVA model. TIV was calculated by extracting GM, WM and CSF volumes for each subject and summing them, to give a total intracranial volume measure for each participant (Buckner et al., 2004). The reason for the inclusion of the TIV measure was in order to control for regional volume differences resulting from individual variability in head size. Between-group comparisons were made using *t*-tests, and multiple regression analyses were carried out to examine the relationship between regional volumes and behavioural measures. The resulting set of voxel values for the contrast of interest made up the statistical parametric map of the *t* statistic (SPM{t}). The initial height threshold was at $p < .001$, and voxels that survived adjustment for multiple comparisons via the False Discovery Rate (FDR $p < .05$) correction were subsequently reported. Where a priori regions of interest were concerned, any significant local maxima were identified and a small volume correction applied in SPM to the volume of interest. Significant voxels were then reported at $p < .05$ corrected level. Regions corresponding to the 3-dimensional MNI coordinates were identified using the WFU PickAtlas tool (Maldjian et al., 2003). Statistical colour maps were displayed on an averaged canonical image, and 3-D surface renderings were created using the xjView tool (Cui and Li, Human Neuroimaging Lab, Baylor College of Medicine).

Chapter 3

Associative- and working memory decline across the lifespan

3.1 Summary

This chapter investigates the changes in associative memory and working memory performance that take place across the lifespan, in a cohort of healthy adults aged 18-64. It aims to establish the trajectory of decline of specific mnemonic functions and to ascertain the influence of global factors such as education and IQ on task performance.

3.2 Introduction

3.2.1 The trajectory of memory decline – a lifespan perspective

It is clear that memory is impaired in aging, but the majority of research has thus far focused on comparisons between an aged group (typically over 60 yrs) and a young group (typically under 30 yrs), with less research attempting to chronicle age-related changes in memory across the lifespan. Furthermore, the body of extant research into lifespan memory changes has yielded some contradictory findings concerning the gradient of the age-related decline in different mnemonic functions, and to what extent other factors can alter the trajectory of this decline.

Existing studies of lifespan memory changes have generally taken either a cross-sectional or a longitudinal approach. Data from these studies, along with studies from which both cross-sectional and longitudinal estimates of age-related change can be derived, have led to somewhat conflicting results. The results from cross-sectional studies generally point toward a relatively steady linear decline beginning in the 20s-30s for episodic memory and working memory, with short-term and semantic memory showing a lesser decline (Nilsson et al., 1997; Park et al., 2002; Salthouse, 2009). Longitudinal data, however, paint a somewhat different picture, with some researchers maintaining that a significant age-related decline in memory doesn't manifest until approximately age 60 (Nilsson, 2009; Ronnlund et al., 2005; Ronnlund, Lovden & Nilsson, 2008; Schaie, Willis, & Caskie, 2004). To what extent methodological factors, such as cohort variation in cross-sectional data and practice effects and selective attrition in longitudinal studies, can account for the discrepancy between results is currently a matter of some debate (Nilsson et al., 2009; Ronnlund et al., 2005, 2008; Salthouse, 2009).

3.2.2 Episodic memory deficits

Episodic memory has traditionally shown the most pronounced decline with age. It would appear, however, that the same rate of decline does not hold true for all facets of episodic memory. Thus, the individual tasks utilised under this umbrella term are of some importance. Recognition memory seems to show smaller age-related performance decrements than tests of recall (Craik & McDowd, 1987; Nyberg et al., 2003). A proposed explanation for this is that older adults have a greater difficulty engaging in self-initiated processing, compared with younger adults (Craik, 1983). That is, they require more environmental support in order to perform at the same level as younger adults. Thus, they

perform better on recognition and cued-recall tasks than on free-recall measures, which have a greater processing requirement (Craik et al., 1987).

A related theory is that recall tasks rely on conscious recollection, whereas recognition memory can be supported by a mere feeling of familiarity (Rugg & Yonelinas, 2003). This dual-process theory of memory in aging (Jacoby, 1991) is one theory put forward to explain findings of marked age deficits on some tasks but relative age invariance on other tasks. According to the theory, tasks which rely heavily on recollection should be impaired in aging, whereas those which can be adequately supported by familiarity are relatively spared. While it is well established that recollection is impaired in older adults, familiarity seems to be less affected by aging (see Yonelinas, 2002 for a review). There is, however, some uncertainty in this regard, possibly owing to the variance in the techniques used in the experimental setting to try and discern familiarity from recollection. Age-related impairments have been found on tasks where 'Remember/Know' judgments and Receiver Operating Characteristics (ROCs) are used, but recognition memory seems to be less affected in aging studies where process dissociation procedures are employed (Light et al., 2000; Prull et al., 2006).

3.2.3 Associative memory deficits in aging

A common complaint among older individuals is that they cannot remember the name of a particular person when they meet them, or that they cannot put a face to a given name (Cohen & Faulkner, 1984; Scanlan & Johnston, 1997). This type of episodic memory relies on the ability to make associations, or bind units of information together to form coherent contextual representations (Rhodes, Castel, & Jacoby, 2008). Binding features is an integral part of everyday functioning, and is used to integrate distinct features of any stimulus (e.g. colour, size, sound). These features are represented in so-called 'feature maps' in the brain, whereby information about aspects of the same stimulus must be linked or bound in order for that stimulus to be successfully encoded and retrieved (Kersten et al., 2008). There is evidence that the ability to make successful associations between items in memory is reliant on the hippocampus and the prefrontal cortex (Eichenbaum, 2000; Dimitrov et al., 1999; Sperling et al., 2003; Squire, 1992; Staresina et al., 2008; Zeineh et al., 2003), structures that are particularly vulnerable to age-related change (Raz, 2000). Moreover, this specific impairment has been posited by some to underpin episodic memory deficits in aging.

3.2.3.1 The Associative Deficit Hypothesis (ADH)

The associative deficit hypothesis (ADH; Naveh-Benjamin, 2000) holds that memory for associations is disproportionately affected in aging, with memory for single units or items being less impaired. According to this theory, it is this associative deficit which is one of the main factors in poorer episodic memory in the aged. A related theory, proposed by Chalfonte and Johnson (1996), is that older adults have a feature binding deficit which results in a difficulty integrating contextual features. There is considerable evidence to support these hypotheses. In the Chalfonte and Johnson study, item object recognition was intact in older adults, but memory for object-colour and object-location associations was impaired in the older group while intact in young adults. Naveh-Benjamin and colleagues have conducted an elegant set of studies demonstrating that older adults are particularly impaired on memory tests that require associations to be made. This includes both inter-item (such as word-word pairs) and intra-item (such as word-font pairs) associations (Naveh-Benjamin, 2000), and extends to other types of stimuli including pictures (Naveh-Benjamin et al., 2003) and face-name associations (Naveh-Benjamin et al., 2004). Recognition memory for associations was also shown to be impaired in older adults in comparison to young adults in a study using face-face and face-location pairs (Bastin & Van der Linden, 2006).

A consistent finding of these studies is that, while older adults are often impaired on tests of item memory compared with young, they are considerably more impaired on tests of associative memory. Although most studies of associative memory have utilised recognition memory tests, there is also some evidence that cued-recall is most impaired in older adults compared with young, with less impairment on free-recall tasks, and recognition memory being the most intact (Naveh-Benjamin et al., 2003). The authors suggest that this pattern of performance deficits arises from the reliance of cued-recall tasks purely on associative processes – the specific weakness of older individuals- with free-recall relying only indirectly on successful binding and retrieval of information, and also on other self-initiated processes (Naveh-Benjamin et al., 2000). Thus there is a distinction between the ADH and Craik's hypothesis of poorer self-initiated processing in older adults (Craik, 1983). While the former predicts that cued-recall would be more impaired than free-recall in older adults (due to its reliance on associative processing), the latter theory predicts the converse, as cued-recall offers more environmental support than free-recall.

There is no doubt that strategy plays some part in associative encoding. This is supported by the finding that older adults show greater deficits in task performance when encoding is intentional rather than incidental (Naveh-Benjamin, 2000), and that when older adults are given strategies for forming associations between items, the age-related impairment is ameliorated somewhat (Jones et al., 2006; Naveh-Benjamin, Brav, & Levy, 2007). It would appear, however, that strategic ability cannot entirely account for the associative memory deficit in older adults, as their associative memory performance shows little improvement with practice in utilising strategic techniques (Shing et al., 2008). There is also evidence that dividing attention does not produce a greater impairment in memory for associations than memory for items alone (Kilb & Naveh-Benjamin, 2007; Naveh-Benjamin, Guez & Schulman, 2004), indicating that the associative memory deficit exhibited by older individuals is not fully mediated by reduced attentional resources.

3.2.4 Working memory deficits

Working memory impairments in aging have been relatively well documented. Previous studies have indicated that performance on working memory tasks declines from early adulthood on (Dobbs & Rule, 1989; Gilinsky & Judd, 1994; Morris, Craik & Gick, 1990; Park et al., 2002; Salthouse & Babcock, 1991). This rate of decline may vary, however, depending on the task or tasks that are used. Short-term or primary memory tasks, which typically require the straightforward storage and retrieval of material only, appear to be only slightly affected by aging (Craik & Jennings, 1992). A the other end of the spectrum, complex working memory tasks which rely on the constant updating or manipulation of information in addition to storage, seem to be affected to a greater extent by the aging process (Craik et al., 1992). Thus, researchers are endeavouring to distinguish sub-types of working memory in terms of the cognitive processes engaged (e.g. maintenance only versus maintenance/manipulation of information).

One theory put forward is that reduced speed of processing capabilities in older individuals could account for age-related decline on working memory tasks generally (Salthouse et al., 1991). There is also the notion of reduced "attentional resources" in aging (Craik & Byrd, 1982; Morris, Gick, & Craik, 1988). A related, but perhaps more specific deficit, is that older adults exhibit decreased inhibitory efficiency, that is, a reduced ability to inhibit task or goal irrelevant information, which impacts negatively on working memory task performance (Hasher & Zacks, 1988). A well documented example of decreased

inhibitory efficiency is the poor performance of older adults on tasks such as the Stroop task (Dulaney & Rogers, 1994; Spieler, Balota, & Faust, 1996). In support of these theories, there is evidence of impaired 'top-down' suppression of cortical activity associated with task-irrelevant stimuli in older adults during a working memory task (Gazzaley et al., 2005). Furthermore, this inability to suppress irrelevant stimuli was correlated with impaired working memory performance. Vogel and colleagues recently showed, in an event-related potential study, that participants who could remember more items from a serial array were able to suppress irrelevant stimuli more effectively (Vogel, McCollough, & Machizawa, 2005). Whether age-related deficits in working memory reflect a decline of executive processes generally, or more specific components of executive control, is not fully clear. The results of the Vogel et al. (2005) study, however, seem to suggest that the ability to perform well at high working memory loads and the ability to suppress goal-irrelevant information may be intrinsically linked, thus facilitating optimum working memory performance.

Studies have also investigated the relationship between working memory and the focus of attention. McElree (2001) maintains that only one item can be held in the focus of attention at a time. Thus, at memory loads greater than N = 1, it is necessary to transfer information back and forth between memory and focal attention. There is evidence that the extra demand this places on cognitive processing leads to greater performance deficits in older individuals compared with young. Using an N-Back working memory paradigm, Verhaeghen and Basak (2005) showed that older adults exhibited a larger 'switch-cost in accuracy' moving from the 1-Back to the 2-Back condition than younger adults. The authors suggest that the act of focus switching may lead to age-related deficits in working memory performance.

3.2.5 Cognitive deficits in aging – inevitability and uniformity

A common question posed, in an increasingly health-conscious 21st century society, is "what can I do to improve my memory?". The "use it or lose it" school of thought has lead to an explosion of interest among the general population in ways to keep cognitively fit. This has been paralleled in the cognitive aging literature by substantial evidence that middle-aged and elderly adults can improve their performance on certain cognitive tasks as a result of various training techniques (for a review see Lustig et al., 2009).

A related area under increasing investigation is the idea of a 'cognitive reserve' (Stern, 2002). This theory was formulated in an attempt to explain the, often wide, variation in cognitive abilities among older individuals. In attempting to explain this phenomenon of seeming cognitive robustness, researchers have formulated two types of reserve, which could be having a compensatory effect in aging. The notion of a passive reserve relates the preservation of cognitive ability to physical attributes, such as increased brain size or stronger neural networks (Stern, 2002). This may result in an increased capacity to withstand brain aging up to a certain threshold, after which deficits start to appear (Staff et al., 2004). The active reserve refers to the ability to engage in functional compensation - the use of other cognitive strategies or recruitment of other neurocognitive networks – in order to ameliorate task performance (Stern, 2002).

A key aspect to this hypothesis is that high education, high pre-morbid intelligence and good health contribute substantially to the cognitive reserve, acting as a buffer against the effects of aging and disease (Satz, 1993). Education and pre-morbid intelligence have been positively related to cognition, especially where attention and executive functions are concerned (Gomez-Perez & Otrosky-Solis, 2006), and varying education levels have been proposed to account for discrepancies between cross-sectional and longitudinal studies of memory decline (Ronnlund et al., 2005). While many studies have found a strong positive relationship between education and/or pre-morbid intelligence and cognitive performance, the findings with respect to a relationship between education/IQ, structural brain changes, and cognitive ability, have been somewhat mixed. Some studies have found a strong relationship between the three, and others have maintained that brain volume is unrelated to education or intelligence and cognitive performance (see Christensen et al., 2007). Research is thus increasingly looking also to active compensatory mechanisms to explain the cognitive reserve. There is evidence that older adults may recruit different functional networks in the brain to younger individuals, in an attempt to maximise their performance (Stern et al., 2005). Neuroimaging research has also shown that high performing older adults show preserved or increased activation of prefrontal areas compared with poor performing older adults or with young adults (Cabeza, 2001, 2002; Rosen et al., 2002).

These findings have led some researchers to hypothesize that reduced frontal lobe function may underlie the decline in episodic and working memory documented in aging (Tisserand & Jolles, 2003; West, 1996). This hypothesis is in line with the view that prefrontal-dependent executive processes are vital to complex working memory and episodic memory

tasks (Blumenfeld & Ranganath, 2007; Miller & Cohen, 2001). In support of this view, common prefrontal activations have been associated with episodic memory and working memory tasks (Braver et al., 2001; Cabeza et al., 2002; Nyberg et al., 2003; Tanabe & Sadato, 2009), and increasing task load in both episodic memory and working memory produces overlapping prefrontal activations (Marklund et al., 2007). It is plausible that the trajectory of episodic and working memory decline may thus be influenced by the extent to which the tasks engage executive processes or necessitate a high level of cognitive control; with more demanding tasks such as associative memory paradigms and high-load working memory tasks showing an earlier onset of age-related decline.

3.2.6 Aims of the current study in the context of the literature

While associative memory function in aging has been somewhat well explored, this exploration has been largely confined to contrasting an aged group (typically over 60 years of age) with a younger age group (typically under 30 years). There is a need to investigate changes in associative memory performance across the lifespan, particularly in relation to the associative deficit hypothesis theory of cognitive aging and the notion that associative memory tasks place a higher demand on executive processes than single-item recall and recognition tasks. There has also been an over-reliance on recognition memory measures to assess associative memory encoding and retrieval. Naveh-Benjamin and colleagues have, in the main, used measures of forced-choice recognition to assess both item and associative memory particularly for face-name associations (Naveh- Benjamin, 2004), with few measures of cued- and free-recall being utilised except where verbal memory tasks are concerned (Naveh-Benjamin, 2000). Given the apparent vulnerability of recall measures to the effects of aging, and the ambiguity over the degree to which recollection or familiarity underlies recognition memory (Yonelinas, 2002), it is important to assess associative memory encoding with measures of cued- and free-recall in order to be able to make meaningful inferences about any impairment exhibited by older adults.

We chose to investigate performance on associative and working memory tasks across the lifespan from young adulthood to late middle-age/early old-age (18-64 years), consistent with evidence for the involvement of the MTL and PFC in associative- and working memory, and the vulnerability of these regions to age-related change (Raz, 2000). With respect to associative memory, both recall and recognition memory measures are included in the current study, in order to discern the rate of decline of these two aspects of memory. We will also include working memory tasks that differ slightly in the processes engaged

(maintenance only versus maintenance/manipulation) to deduce whether age-related decline varies between these two types of working memory task. Close attention will be paid to the effect of education and pre-morbid intelligence on task performance.

3.2.7 Hypotheses

1. The primary hypothesis is that there should be a pronounced negative effect of age on associative memory and working memory across the lifespan.
2. A second hypothesis is that measures of associative memory should show greater age-related impairment than measures of item memory.
3. A third hypothesis is that age-related deficits on a working memory maintenance and manipulation task (N-Back task) will be greater than on a task which requires the maintenance of information only (Match-to-Sample task).
4. A fourth hypothesis is that education and pre-morbid intelligence should be significantly and positively related to performance on both episodic and working memory tasks.

3.3 Methods

3.3.1 Participants

3.3.1.1 Primary study

A total of 177 participants aged 18 to 64 years of age took part in the study. They were recruited via college e-mail and online noticeboard, recruitment posters, and advertisement in a local newspaper. All participants were fluent English speakers and had normal or corrected-to-normal vision. Exclusion criteria were a history of stroke, heart disease, head trauma, psychiatric or neurological illness, current use of psychoactive medication, and pregnancy. The study was approved by the School of Psychology Ethics Committee, Trinity College Dublin. Participants were compensated for their time and travel expenses in accordance with School of Psychology guidelines. Psychology undergraduate students who participated were offered research credits as an alternative to monetary compensation. Written, informed consent was obtained from each participant prior to the commencement of the study (see Appendix). The 18-29 group consisted of 49 participants (18 male; mean age = 24.18, SD = 3.38, range = 18-29). The 30's group consisted of 39 participants (14 male; mean age = 34.20, SD = 2.89, range = 30-39). The 40's group consisted of 46 participants (15 male; mean age = 44.43, SD = 2.84, range = 40-49). The 50-64 group consisted of 42 participants (16 male; mean age = 55.45, SD = 3.94, range = 50-64).

3.3.1.2 Education-matched subgroup

A total of 44 individuals, matched for years spent in formal education across the four age groups, were included in a second analysis. These individuals were taken from the parent group. Eligibility for inclusion in this subgroup analysis was determined by education matching. The education range was 13-20 years and was thus identical for each age group. The 18-29 group consisted of 11 participants (7 male; mean age = 23.45, SD = 3.80, range = 19-29). The 30's group consisted of 11 participants (4 male; mean age = 34.91, SD = .99, range = 30-39). The 40's group consisted of 11 participants (2 male; mean age = 44.27, SD = .79, range = 40-49). The 50 -64 group consisted of 11 participants (5 male; mean age = 57.54, SD = 1.34, range = 52-64).

3.3.2 Cognitive testing battery

A battery of cognitive tests lasting approximately 1 hour was performed by each individual in the study. Each participant was tested alone, with only the experimenter present in the room. Participants completed a range of tasks presented on a computer screen, for which they were positioned roughly 20 cm away from the screen. In addition, they also completed several pen and paper questionnaires. The tasks were chosen to probe associative long-term memory function and working memory function. Estimates of premorbid intelligence, anxiety and depression levels were also taken. The test battery is outlined below.

3.3.2.1 Control Measures

An estimate of premorbid intelligence was obtained using the National Adult Reading Test (Nelson, 1982; described in Chapter 2, section 2.6). This gave a predicted IQ score, and its effect on task performance was examined in subsequent analyses. Self-reported mood and well-being was recorded using the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983; described in Chapter 2, section 2.5.1).

3.3.2.2 Associative memory tasks

Face-Name Pairs Learning and Recall task

This task was as described in Chapter 2, section 2.4.1. Briefly, it consisted of 4 encoding blocks each with a subsequent recall test. The delayed component of the task took place some 15 minutes later. This consisted of a delayed face-name recall test, a free name recall test, and face and name recognition tests (see section 2.4.1.3).

Performance on the task was assessed using the following indices:

1. The number of face-name pairs successfully recalled following each encoding block (blocks 1, 2, 3, 4).
2. Face-Name Total Recall – the total number of face-name pairs successfully recalled during the above encoding and immediate recall trials.
3. Improvement Score – the improvement in the number of face-name pairs successfully recalled from the 1st recall trial to the 4th recall trial (block 4 – block 1) was computed and expressed as a percentage of the maximum possible improvement that each individual could make from block 1 to block 4. The maximum possible improvement that could be made was calculated by subtracting

the number of pairs successfully recalled at block 1, from the total number of face-name pairs in each block (8).

4. Delayed Face-Name Recall – the number of face-name pairs successfully recalled after a 15 minute delay.
5. Name Recall – the number of names successfully (and freely) recalled after the delay period.
6. Face Recognition Accuracy- the ability to accurately discriminate between previously seen and novel faces after the delay period. This was calculated by (number of Hits – number of False Positives)/ total number of previously seen faces. The raw numbers of hits, false positives, foils and misses were also examined.
7. Name Recognition Accuracy – the ability to accurately discriminate between previously seen and novel names after the delay period (calculated as above).

Picture-Word task

This task was described in Chapter 2, section 2.4.2. Briefly, it consisted of picture-word associative learning followed by an immediate recall task (note there was only one learning and recall block for this task). This was followed by a delayed associative recognition task, which took place some 15 minutes later.

Performance on this task was assessed on the basis of two indices:

1. Immediate Recall – the number of picture-word pairs correctly recalled after initial encoding.
2. Delayed Recognition – the number of intact pairings (i.e. not altered in any way from the original presentation) correctly identified after the delay period.

3.3.2.3 Working memory tasks

N-Back Task

This task was described in some detail in Chapter 2, section 2.3.1. There were 3 levels to this task 0-, 1- and 2-Back, performed in that order. The 0-Back task served as a sensorimotor control, whereas the 1-Back and 2-Back tasks were designed to tax working memory to increasing degrees.

Performance on the task was assessed by:

1. 0-Back Accuracy – the percentage of trials in the 0-Back condition for which the correct response was made (this included withholding a response when this was necessary).
2. 1-Back Accuracy – the same as above, but for the 1-Back condition.
3. 2-Back Accuracy – the same as above, but for the 2-Back condition.
4. Switch-Cost in Accuracy between 1- and 2-Back – 1-Back accuracy minus 2-Back accuracy.

Match-to-Sample Task

This task was described in some detail in Chapter 2, section 2.3.3. Briefly, it consisted of an initial working memory maintenance task, followed by a delayed recognition task after a delay period of approximately 15 minutes.

Performance on the Match-to-Sample task was assessed by:

1. Working Memory Task Accuracy – the percentage of trials for which the correct response was given (participants were asked to press either '1' or '2' on the keyboard indicating whether or not the target object matched the cue object, see section 2.3.3.3a).
2. Delayed Recognition Accuracy – calculated from the following equation (number of Hits – number of False Positives)/ total number of objects previously seen). The raw number of hits, false positives, foils and misses were also examined, as well as the relationship between hits and false positives.

3.3.3 Statistical Analyses

Analyses were carried out using SPSS (version 16) for PC. Data was expressed as mean ± standard error (SE) unless otherwise stated. The critical α value was set at .05. All statistical tests were two-tailed. Analysis of Variance (ANOVA) was the main statistical test utilised. Where performance was repeated across identical trials, a mixed between-within-subjects ANOVA (Tabachnick and Fidell, 2009) was used to compare performance across repeated trials and between groups. Main effects and interactions were reported and, where relevant, post-hoc analysis was carried out. Where sphericity could not be assumed, Greenhouse-Geisser values were reported. This is denoted in the results section by G.G. written in parentheses after the relevant statistic. Where a significant interaction was identified, one-way ANOVAs were conducted to examine between-group differences

at each level of the dependent variable. The effect of predicted IQ on task performance was explored by firstly examining main effects and interactions in a custom model univariate ANCOVA with the dependent variable in question, and then by running the full factorial univariate ANCOVA. Where predicted IQ was found to be a covariate, between age group effects were subsequently reported with predicted IQ held constant (thus removing variance in the dependent variable attributable to the covariate). Pairwise comparisons with adjusted means were then carried out where appropriate (using a Bonferroni correction). Preliminary checks were made prior to conducting all analyses to ensure the underlying data complied with assumptions of normality, homogeneity of variances, homogeneity of regression slopes and reliable measurement of the covariate, where applicable. Where parametric assumptions were violated, non-parametric tests were employed. Once again a Bonferroni correction was applied, when multiple comparisons were made, to control for the inflated risk of making a Type I error. A chi-squared test was used to explore the association between categorical variables, such as gender and age group.

3.4 Results

3.4.1 Education, predicted IQ, HADS anxiety and depression scores

There was no association between gender and age group, indicating that the proportions of males and females were the same across all age groups, $X^2(3) = 0.22$, $p > .10$. There was no between group difference in predicted IQ scores, $F(3, 171) = 0.27$, $p > .10$, and there were also no differences in Hospital Anxiety and Depression scale scores between the groups ($Fs < 1$, $ps > .10$; see Table 3.1).

Between group differences in years spent in formal education were explored using non-parametric analysis owing to the fact that the Levene's test for homogeneity of variance was violated. The results of the Kruskal-Wallis test showed that education was significantly different between the age groups $H(3) = 32.72$, $p < .001$. Subsequent post-hoc analysis was conducted using Mann-Whitney tests to determine where the between groups difference(s) lay. A Bonferroni correction was applied so that all effects were reported at the .0083 level of significance. There was a significant difference in education between the 18-29 and 30's group ($U = 527.5$, $r = -.31$) and between the 18-29 and 50-64 groups ($U = 582.5$, $r = -.37$). Significant differences were also found between the 30's and 40's groups ($U = 364$, $r = -.44$), and between the 30's and 50-64 groups ($U = 237.5$, $r = -.58$).

Age Group	**18-29 yrs (n=49)**	**30-39 yrs (n=38)**	**40-49 yrs (n=47)**	**50-64 yrs (n=43)**
Gender (M : F)	18:31	14:24	15:32	16:28
Education (yrs)	17.42 (± 0.33)	19.29 (± 0.46)	16.46 (± 0.55)	15.11 (± 0.51)
Predicted IQ	117.16 (± 0.84)	117.40 (± 1.09)	116.23 (± 1.10)	117.36 (± 1.20)
HADS Anxiety	6.57 (± 0.57)	6.05 (± 0.50)	5.98 (± 0.44)	6.41 (± 0.41)
HADS Depression	2.59 (± 0.31)	3.08 (± 0.41)	3.23 (± 0.41)	2.64 (± 0.28)

Table 3.1: Education, predicted IQ, anxiety and depression scores for each age group. Values reported as means (± SEM).

NOTE: Given the widely published relationship between IQ and cognitive task performance, predicted IQ was included as a covariate in the between group analysis of

task performance. Where predicted IQ was found to be a significant covariate, adjusted means are reported.

3.4.2 Face-Name Pairs task

3.4.2.1 Face-Name Learning and Recall

Face-Name recall across the four encoding blocks was examined using repeated measures ANOVA (see Figure 3.1). There was a significant main effect of block, $F(2.86, 497.65) = 203.25$, $p < .001$ (G.G.). There was also a significant main effect of age group, $F(3, 174) = 31.370$, $p < .001$. Furthermore there was a significant interaction between block and age group, $F(8.58, 497.65) = 9.27$, $p < .001$ (G.G.). Subsequent post-hoc analysis found that the 18-29 group accurately recalled significantly more face-name pairs than those in the 40's group ($p < .001$), and than the 50-64 group ($p < .001$). Those in their 30's also recalled significantly more correct pairs than those in their 40's ($p < .001$), and than those in the 50-64 group ($p < .001$). Those in their 40's also performed significantly better than the 50-64 group, though this difference was not as pronounced ($p < .05$).

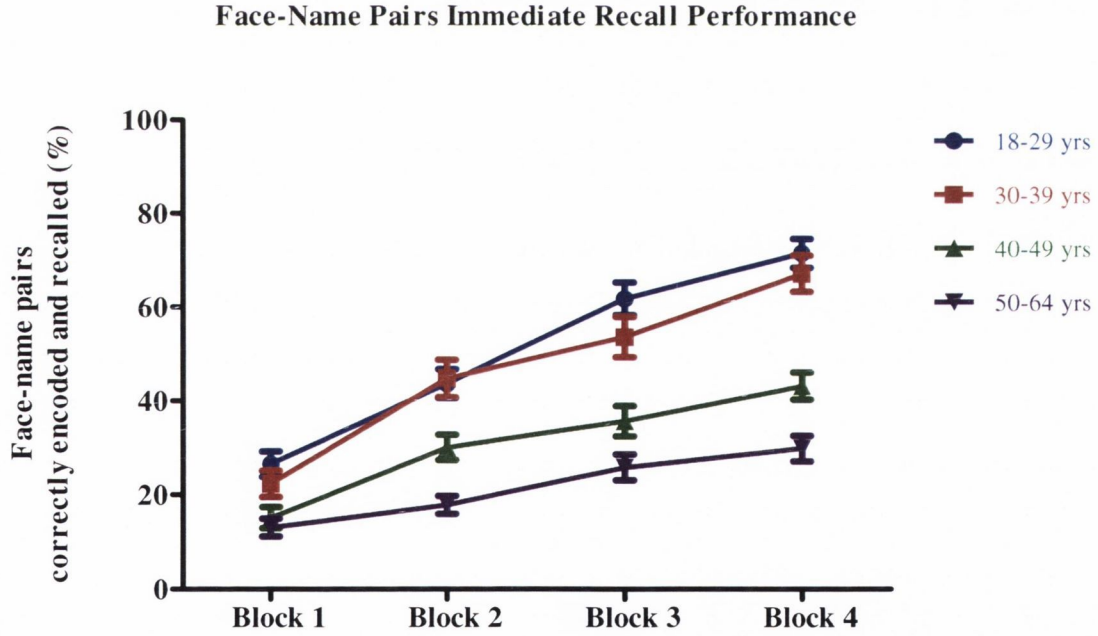

Figure 3.1: Graph showing the trajectory of Face-Name Pairs recall performance across the 4 encoding blocks as a function of age group.

Total Recall score

Predicted IQ was significantly positively related to the total score (all four blocks summed) $F(1, 170) = 40.49$, $p < .001$. There remained a statistically significant effect of age group on total score after controlling for the effect of IQ, $F(3, 170) = 37.75$, $p < .001$, partial $\eta^2 = .40$ (see Table 3.2).

In order to identify at which points the groups differed (controlling for the effect of predicted IQ), a series of one-way ANOVAs were carried out at each block between the age groups (see Figure 3.2).

Block 1

Predicted IQ was significantly positively related to performance at block 1 $F(1, 170) = 14.82$, $p < .001$. After controlling for the effect of IQ there remained an overall difference between the age groups in the number of face-name pairs correctly recalled at block 1 $F(3,170) = 7.79$, $p < .001$, partial $\eta^2 = .12$. Pairwise comparisons, using marginal means, revealed that the 18-29 year olds recalled significantly more pairs than those in their 40's ($p < .01$), and than those in the 50-64 age group ($p < .001$). The 30's group also recalled significantly more pairs than those in the 50-64 group ($p < .05$).

Block 2

Predicted IQ was significantly positively related to performance at block 2, $F(1,170) = 24.61$, $p < .001$. After controlling for IQ there remained an overall difference in the number of face-name pairs correctly recalled at block 2, $F(3,170) = 21.02$, $p < .001$, partial $\eta^2 = .27$. The 18-29 year olds recalled significantly more pairs than those in their 40's ($p < .01$) and than the 50-64 year olds ($p < .001$). The 30's group also recalled significantly more pairs than those in their 40's ($p < .01$) and than those aged 50-64 ($p < .001$). The 40's group also performed significantly better than those aged 50-64 ($p < 0.01$).

Block 3

Predicted IQ was significantly positively related to task performance at block 3, $F(1, 170) = 37.46$, $p < .001$. After controlling for the effect of IQ, there remained a significant effect of age group on performance, $F(3, 170) = 28.08$, $p < .001$, partial $\eta^2 = .33$. The 18-29 year olds performed significantly better than the 40's and 50-64 groups ($p < .001$ for both comparisons). Those in their 30's significantly outperformed both the 40's ($p < .01$) and 50-64 groups ($p < .001$).

Block 4

Predicted IQ was significantly positively related to task performance at block 4, $F(1, 170) = 25.27$, $p < .001$. After controlling for the effect of IQ, there remained a statistically significant effect of age group on performance, $F(3, 170) = 43.95$, $p < .001$, partial $\eta^2 = .44$. The 18-29 year olds recalled more pairs than those in their 40's and than those aged 50-64 ($p < .001$ for both comparisons). Those in their 30's performed better than those in the 40's and 50-64 groups ($p < .001$ for both comparisons). Those in their 40's also performed better than those aged 50-64 ($p < .01$).

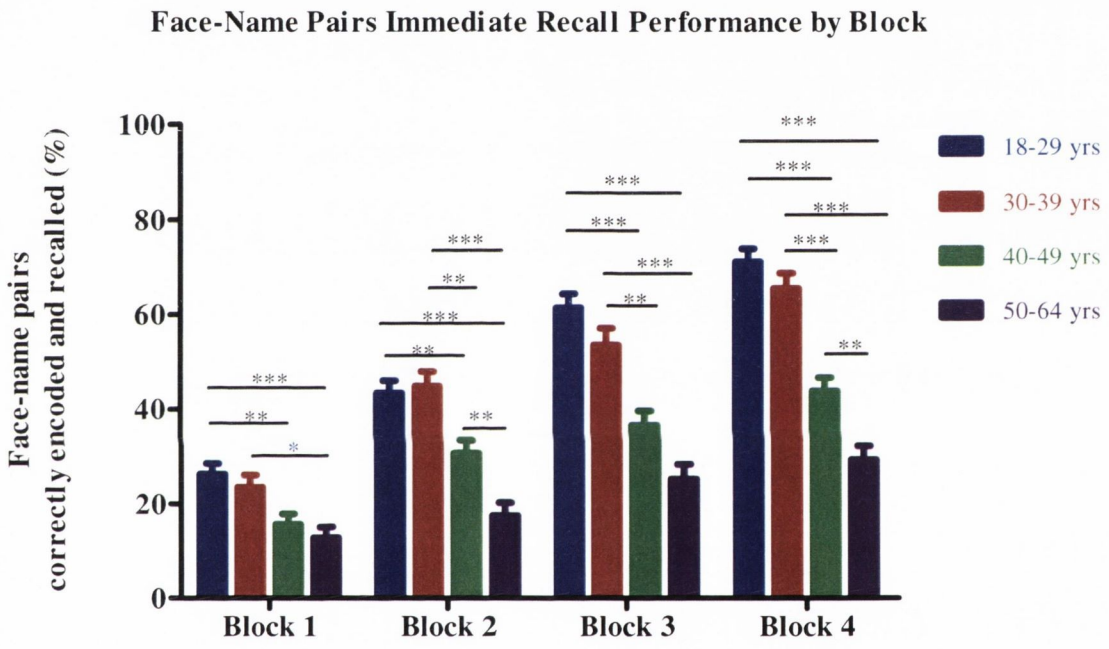

Figure 3.2: The percentage of face-name pairs successfully encoded and recalled for each age group at each encoding block, controlling for the effect of IQ.

Age Group	18-29 yrs	30-39 yrs	40-49 yrs	50-64 yrs
Total Recall Score	50.67 (± 2.10)	46.21 (± 2.48)	31.78 (± 2.15)	21.16 (± 2.21)

Table 3.2: Face-Name Pairs total recall score after adjusting for the effect of IQ. Values reported as means (± SEM).

The relationship between age and Face-Name Pairs total recall is also displayed below (see Figure 3.3).

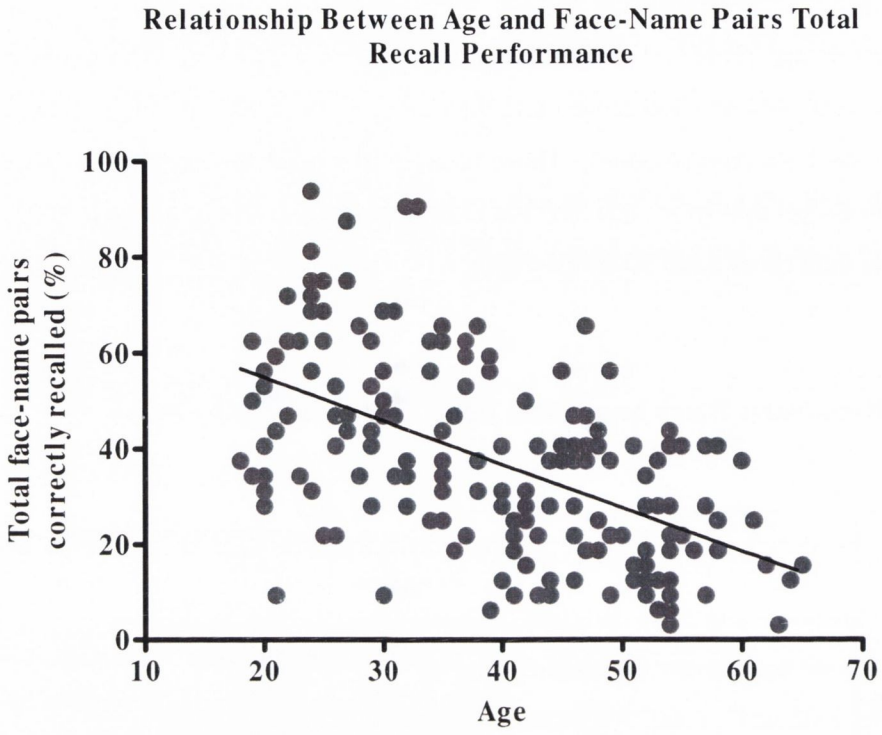

Figure 3.3: The relationship between age and Face-Name Pairs total recall performance.

Improvement score

The degree of improvement between block 1 and block 4, in the number of face-name pairs participants could correctly recall, was calculated. This was taken to be an index of participants' ability to learn the correct pairings with repeated exposure. It was expressed as a percentage of each individual's capacity for improvement from block 1 to block 4 (8 – score at block 1). Predicted IQ was positively related to improvement score, $F(1, 170) = 9.67$, $p < .01$. Controlling for the effect of IQ, there remained a significant between-group difference on this index of learning $F(3, 170) = 31.88$, $p < .001$, partial $\eta^2 = .36$. Subsequent Bonferroni pairwise comparisons revealed that the 18-29 year olds exhibited a significantly greater ability to learn the correct pairings with repeated exposure than those in their 40's and than those aged 50-64 ($p < .001$ for both comparisons). The 30's group also exhibited a greater ability to learn than those in the 40's and than those aged 50-64 ($p < .001$ for both comparisons). There was no significant difference between degree of improvement of those in their 40's and those aged 50-64 ($p > .05$; see Figure 3.4).

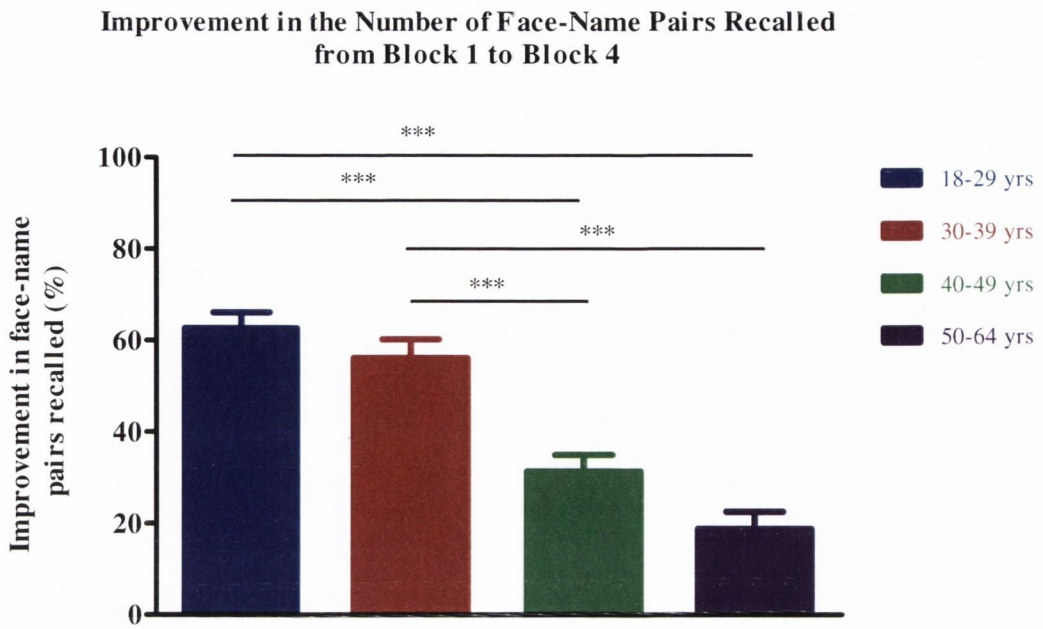

Figure 3.4: The improvement in Face-Name Pairs immediate recall performance for each age group from block 1 of encoding to block 4 of encoding, expressed at a percentage of the total recall capacity for each individual.

3.4.2.2 Delayed Recall

Face-Name Delayed Recall

Predicted IQ was positively related to performance on the delayed recall trial, $F(1, 170) = 33.30$, $p < .001$. After controlling for the effect of IQ, there remained a significant effect of age group, $F(3, 170) = 46.63$, $p < .001$, partial $\eta^2 = .45$. Pairwise comparisons revealed that the 18-29 year olds recalled significantly more pairs than those in their 40's and than those in the 50-64 group ($p < .001$ for both comparisons). The 30's group also performed significantly better than those in their 40's and 50-64 group ($p < .001$ for both comparisons). Those in their 40's also recalled significantly more pairs than those aged 50-64 ($p < .05$; see Figure 3.5).

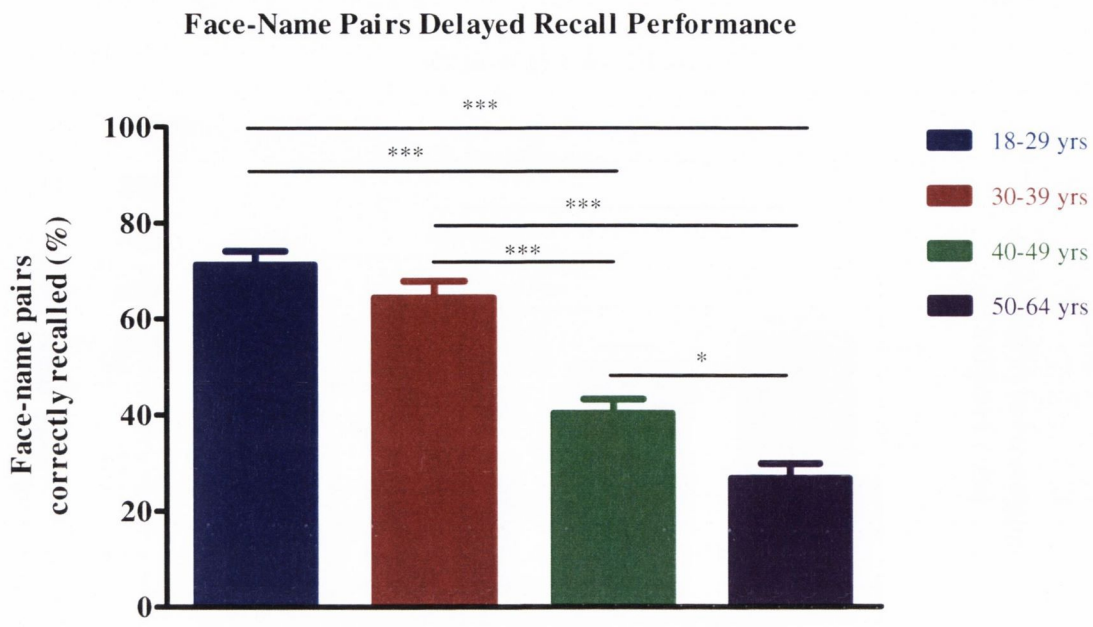

Figure 3.5: The percentage of Face-Name Pairs successfully recalled by each age group on the delayed recall trial (controlling for the effect of IQ).

Name Recall

Following the delayed recall trial, participants were then asked to engage in a free recall of the names from the task. Predicted IQ was once again found to be positively related to the number of names recalled, $F(1, 153) = 8.92$, $p < .01$. After controlling for the effect of IQ, there remained a significant difference between the age groups in the number of names successfully recalled, $F(3, 153) = 8.46$, $p < .001$, partial $\eta^2 = .14$. Pairwise comparisons with IQ adjusted means showed that the 18-29 year olds recalled significantly more names than the 50-64 year olds ($p < .001$), and the 30's also recalled significantly more names than the 50-64 group ($p < .001$; see Figure 3.6).

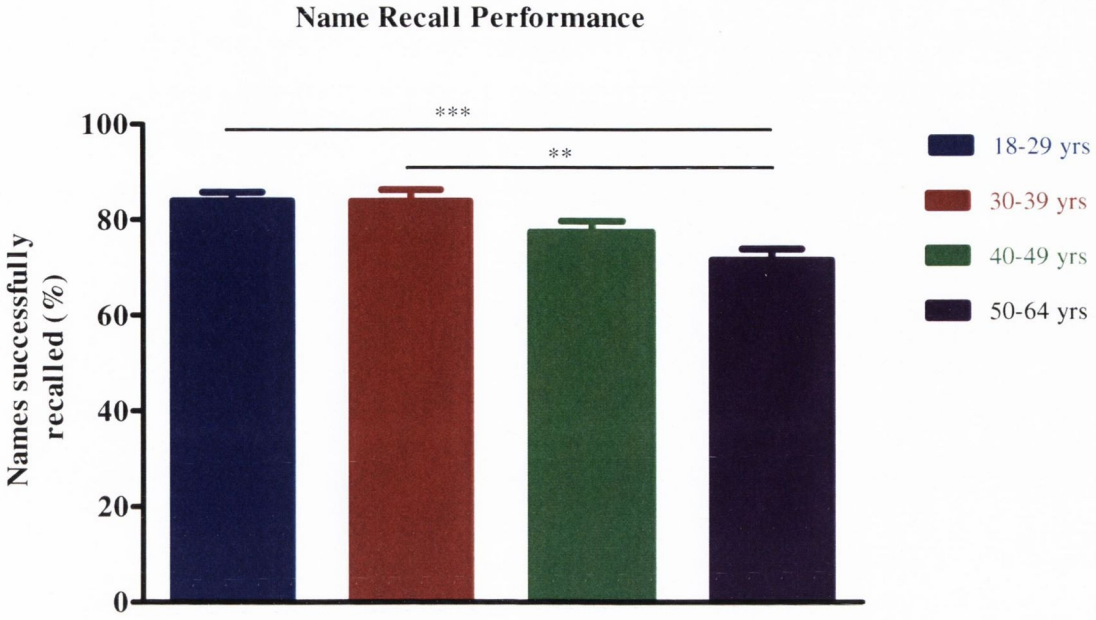

Figure 3.6: The percentage of names successfully recalled by each age group at delayed testing (controlling for the effect of IQ).

Face Recognition

Participants were then required to successfully identify the 8 previously seen faces out of a total of 16 faces (8 foils). There was a significant relationship between predicted IQ and recognition performance, $F(1, 169) = 9.13$, $p < .01$. After controlling for IQ, there remained a significant difference between the age groups in recognition accuracy $F(3, 169) = 7.46$, $p < .001$, partial $\eta^2 = .12$. The 18-29 year olds performed significantly better than the 40's ($p < .05$) and than the 50-64 year olds ($p < .001$). The 30's also performed significantly better than the 50-64 group ($p < .01$; see Figure 3.7).

Predicted IQ was positively related to the number of foils (previously unseen faces) correctly identified, $F(1, 169) = 7.10$, $p < .01$. After controlling for the effect of IQ, there were no significant differences between the age groups in the number of foils correctly identified, $F(3, 169) = 2.39$, $p > .05$. There was a negative relationship between predicted IQ and the number of misses (previously seen faces that the participant failed to recognise), $F(1, 169) = 5.47$, $p < .05$. After controlling for the effect of IQ, there was also a significant effect of age group on the number of misses, $F(3, 169) = 6.60$, $p < .001$, partial $\eta^2 = .10$. The 18-29 group and the 30's group both had significantly fewer misses than the 50-64 group ($p < .01$ for both comparisons). IQ was positively related to the number of hits (previously seen faces that were recognised), $F(1, 169) = 6.07$, $p < .05$.

There was a significant effect of age group on the number of hits after controlling for IQ, $F(3, 169) = 6.73$, $p < .001$, partial $\eta^2 = .11$. Both the 18-29 group and the 30's group had significantly more hits than the 50-64 group ($p < .01$ for both comparisons). Predicted IQ was negatively related to the number of false positives committed (previously unseen faces that were falsely recognised), $F(1, 169) = 6.25$, $p < .05$. After controlling for the effect of IQ, there was only a marginally significant effect of age on the number of false positives, $F(3, 169) = 2.26$, $p = .052$.

Name Recognition

Participants were then asked to identify the 8 names from the task out of a total of 16 names (8 foils). Predicted IQ was positively related to name recognition accuracy, $F(1, 115) = 5.59$, $p < .05$. After controlling for the effect of IQ there was a significant effect of age group on name recognition accuracy, $F(3, 115) = 5.11$, $p < .01$, partial $\eta^2 = .12$. Pairwise comparisons revealed that the 18-29 group performed significantly better than the 50-64 group ($p < .01$). Furthermore the 40's group performed significantly better than the 50-64 group ($p < .05$; see Figure 3.7).

Neither age group nor predicted IQ had a significant effect on the number of foils correctly identified, $F(3, 117) = 2.10$, $p > .10$, and $F(1, 115) = 2.92$, $p > .05$ respectively. IQ was negatively related to the number of misses, $F(3, 115) = 4.57$, $p < .05$. After controlling for predicted IQ, there was a significant effect of age group on the number of misses, $F(3, 115) = 3.60$, $p < .05$, partial $\eta^2 = .09$. The 18-29 year olds had significantly fewer misses than the 50-64 group ($p < .05$). Predicted IQ was positively related to the number of name recognition hits, $F(1, 115) = 4.51$, $p < .05$. After controlling for predicted IQ, there was a significant effect of age group on the number of hits, $F(3, 115) = 4.06$, $p < .01$, partial $\eta^2 = .10$. The 18-29 group had significantly more hits than the 50-64 group ($p < .01$). There was no relationship between predicted IQ and the number of false positives committed, $F(1, 115) = 2.60$, $p > .10$, nor was there a significant effect of age on the number of false positives committed $F(3, 117) = 2.04$, $p > .10$.

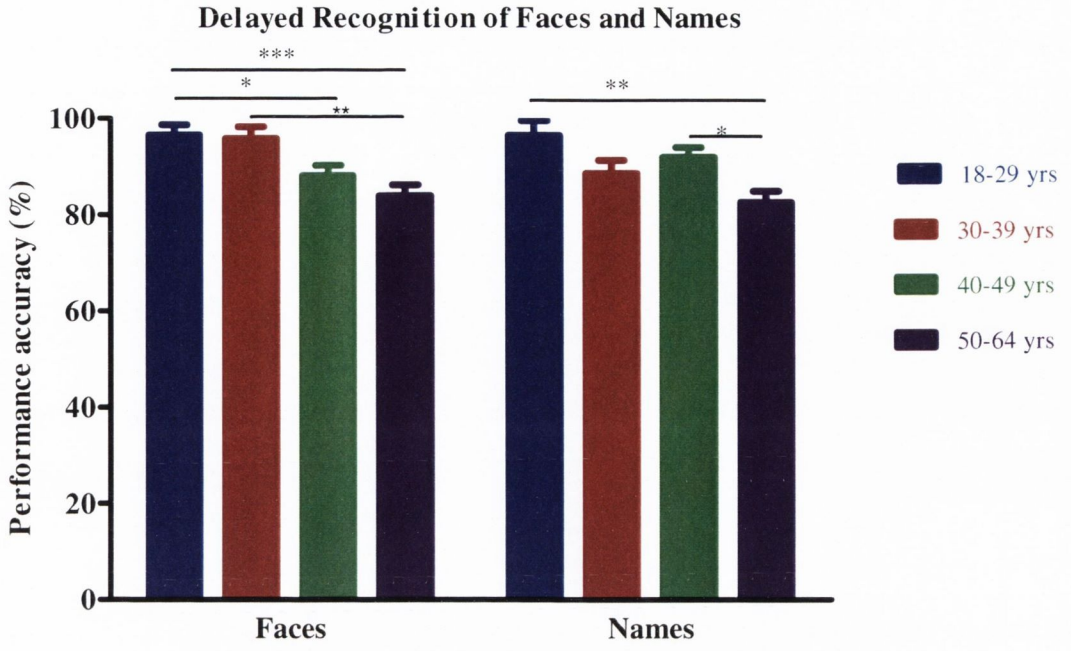

Figure 3.7: Percentage face and name recognition accuracy scores for each age group (controlling for the effect of IQ).

3.4.3 Picture-Word task

3.4.3.1 Immediate Recall

Predicted IQ was positively related to the number of picture-word pairs successfully recalled, $F(1, 151) = 20.99$, $p < .001$. After controlling for predicted IQ, there was a significant difference between the age groups in the number of picture-word pairs successfully recalled $F(3, 151) = 16.76$, $p < .001$, partial $\eta^2 = .25$. Pairwise comparisons with adjusted means revealed that 18-29 year olds recalled significantly more pairs than those in their 40's, and than those in the 50-64 group ($p < .001$ for both comparisons). Those in their 30's also recalled significantly more pairs than those in the 50-64 group ($p < .01$; see Figure 3.8).

3.4.3.2 Delayed Recognition

Predicted IQ was positively related to the number of picture-word pairs that participants recognised as being identical to those they viewed during the encoding task, $F(1, 158) = 34.65$, $p < .001$. After controlling for the effect of predicted IQ, there was a significant difference between the age groups, $F(3, 158) = 7.74$, $p < .001$, partial $\eta^2 = .13$. The 18-29 year olds performed significantly better than those in their 40's, and than those in the 50-64 group ($p < .01$ for both comparisons). The 30's group also performed significantly

better than those in their 40's and than those in the 50-64 group ($p < .05$ for both comparisons; see Figure 3.8).

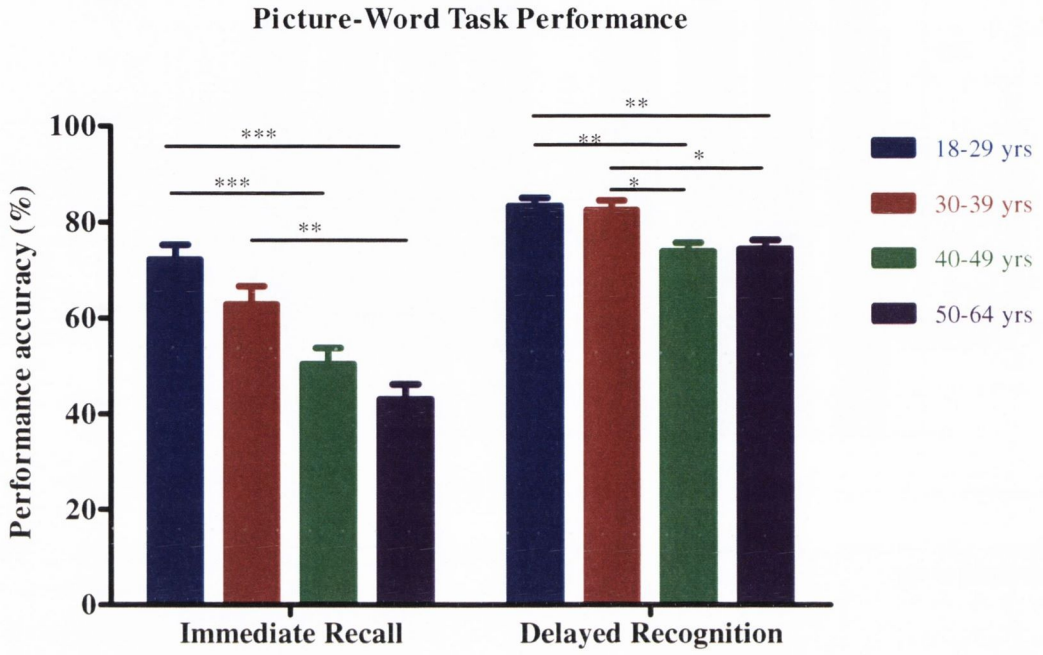

Figure 3.8: Performance of each group on the immediate recall and delayed recognition trials of the Picture-Word task (controlling for the effect of IQ).

3.4.4 N-Back task

3.4.4.1 0-Back

Predicted IQ was not found to be related to performance on the 0-Back task, $F(1, 156) = .26$, $p > .10$. Furthermore, there was no effect of age group on accuracy on the 0-Back, $F(3, 160) = .71$, $p > .10$ (see Figure 3.9).

3.4.4.2 1-Back

Predicted IQ was found to be positively related to performance on the 1-Back task, $F(1, 156) = 10.88$, $p < .001$. After controlling for the effect of IQ on performance, there was a significant effect of age group on 1-Back accuracy, $F(3, 156) = 18.84$, $p < .001$, partial $\eta^2 = .27$. Bonferroni pairwise comparisons with IQ adjusted means revealed that the 18-29 year olds were significantly more accurate than both the 40's and the 50-64 age groups ($p < .001$ for both comparisons). Furthermore the 30's were also significantly more accurate than the 40's ($p < .01$) and 50-64 groups ($p < .001$; see Figure 3.9).

3.4.4.3 2-Back

Predicted IQ was found to be positively related to performance on the 2-Back task, $F(1, 156) = 21.38$, $p < .001$. Controlling for the effect of IQ, there was a significant effect of age group on 2-Back accuracy, $F(3, 156) = 26.37$, $p < .001$, partial $\eta^2 = .34$. Bonferroni pairwise comparisons revealed that the 18-29 group were significantly more accurate than the 40's group and than the 50-64 groups ($p < .001$ for both comparisons). The 30's group were also significantly more accurate than the 40's and the 50-64 groups ($p < .001$ for both comparisons; see Figure 3.9).

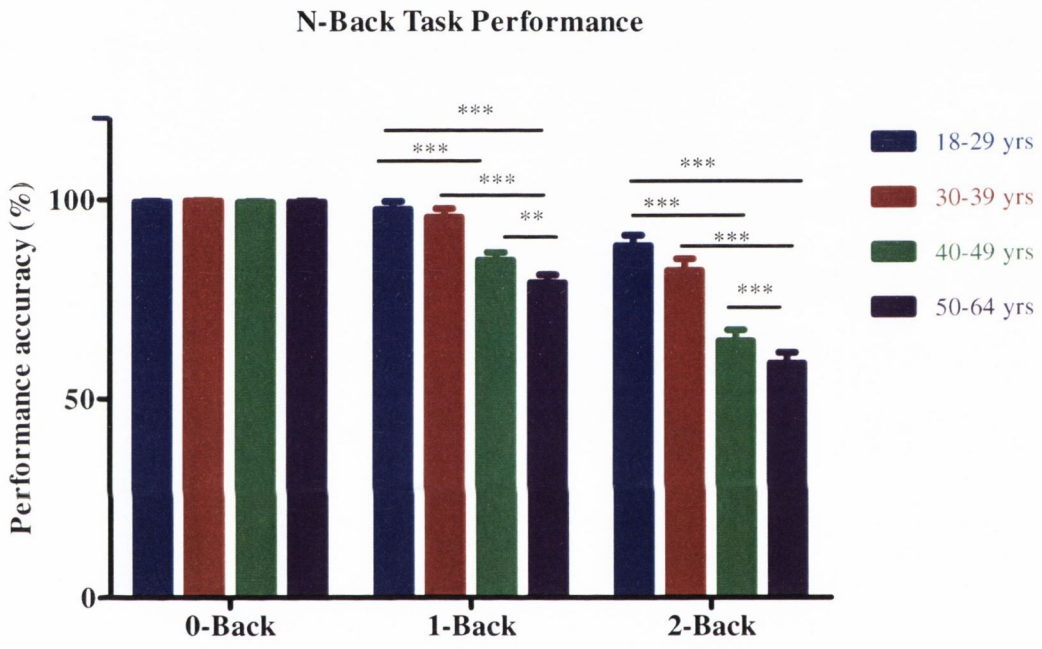

Figure 3.9: Performance accuracy of each age group at each level of the N-Back task (IQ adjusted for the 1-Back and 2-Back conditions).

3.4.4.3 Switch-cost in Accuracy

The mean "switch-cost" in accuracy (accuracy in the 2-back condition minus accuracy in the 1-back condition) was also computed. Predicted IQ was negatively associated with the switch-cost in accuracy, meaning that higher predicted IQ scores were associated with a smaller switch-cost in accuracy, $F(1, 156) = 5.21$, $p < .05$. Controlling for the effect of IQ, there remained a statistically significant effect of age group on switch-cost accuracy, $F(3, 156) = 4.79$, $p < .01$, partial $\eta^2 = .08$. Bonferroni pairwise comparisons revealed that both the 40's and 50-64 group demonstrated a significantly greater switch-cost in accuracy than those aged 18-29 yrs ($p < .05$ for both comparisons; see Figure 3.10).

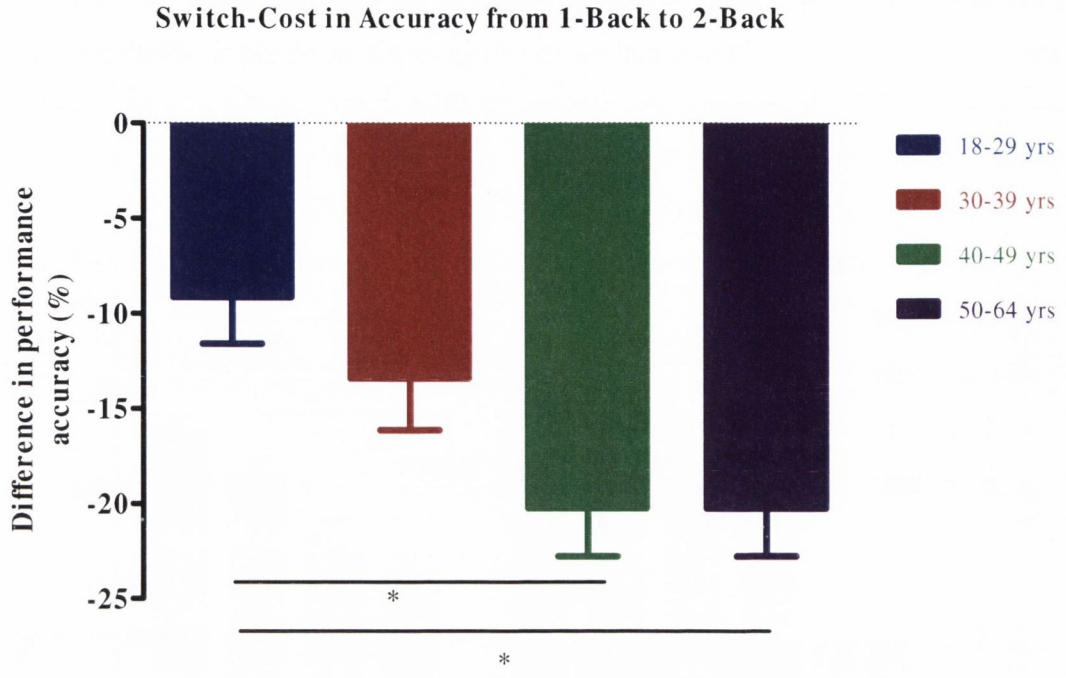

Figure 3.10: The switch-cost in accuracy from the 1-Back to 2-Back condition for each age group.

The relationships between age and 1-Back accuracy, and age and 2-Back accuracy are also displayed overleaf (see Figure 3.11).

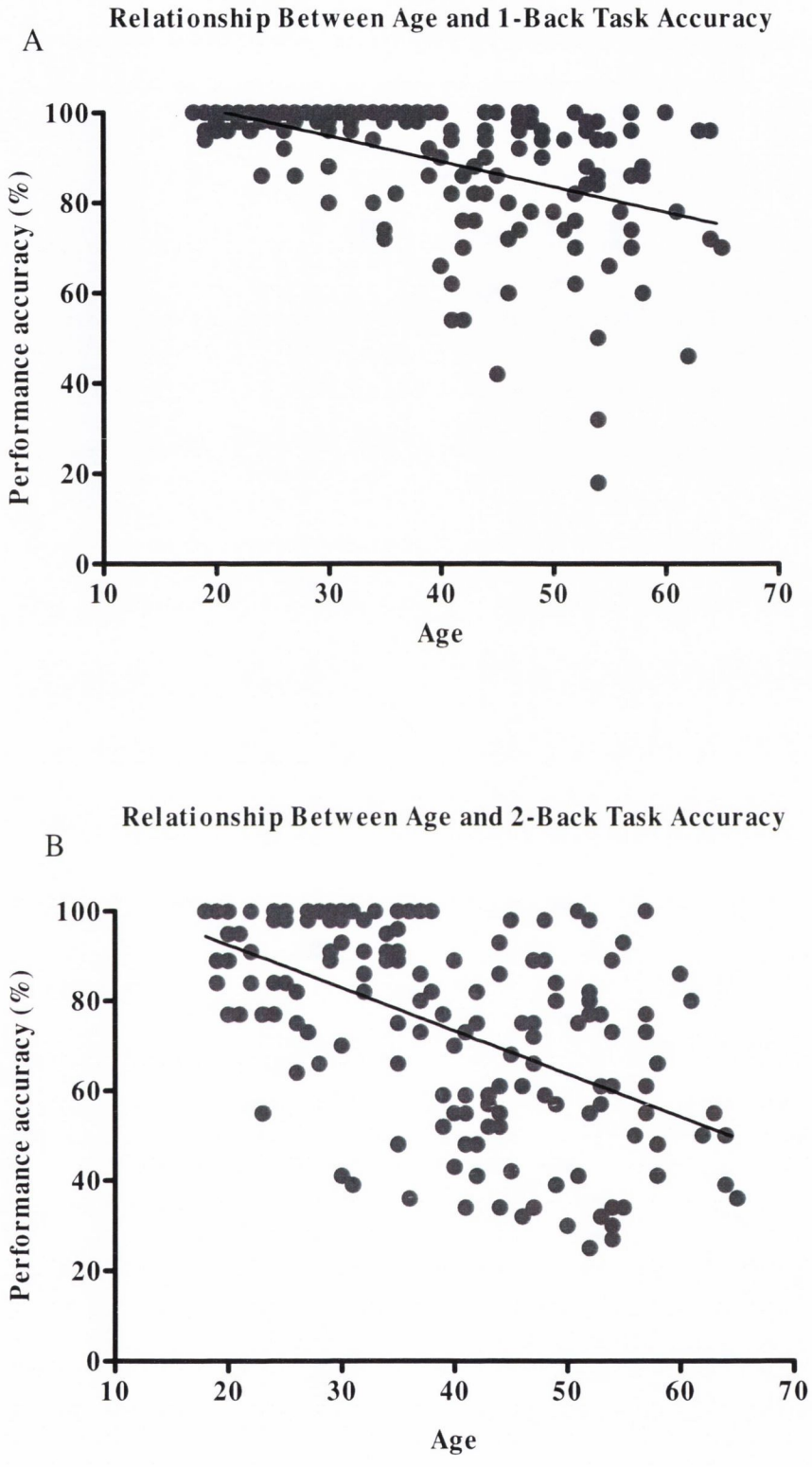

Figure 3.11: The relationship between age and performance accuracy on the (A) 1-Back task, and (B) 2-Back task.

3.4.5 The relationship between Face-Name Pairs and N-Back performance

The relationship between performance on the Face-Name Pairs task and 2-Back condition of the N-Back task was explored graphically (see Figure 3.12 and Table 3.3). A chi-squared test showed that the distribution differed significantly from that expected by chance, $X^2(1) = 112$, $p < .001$.

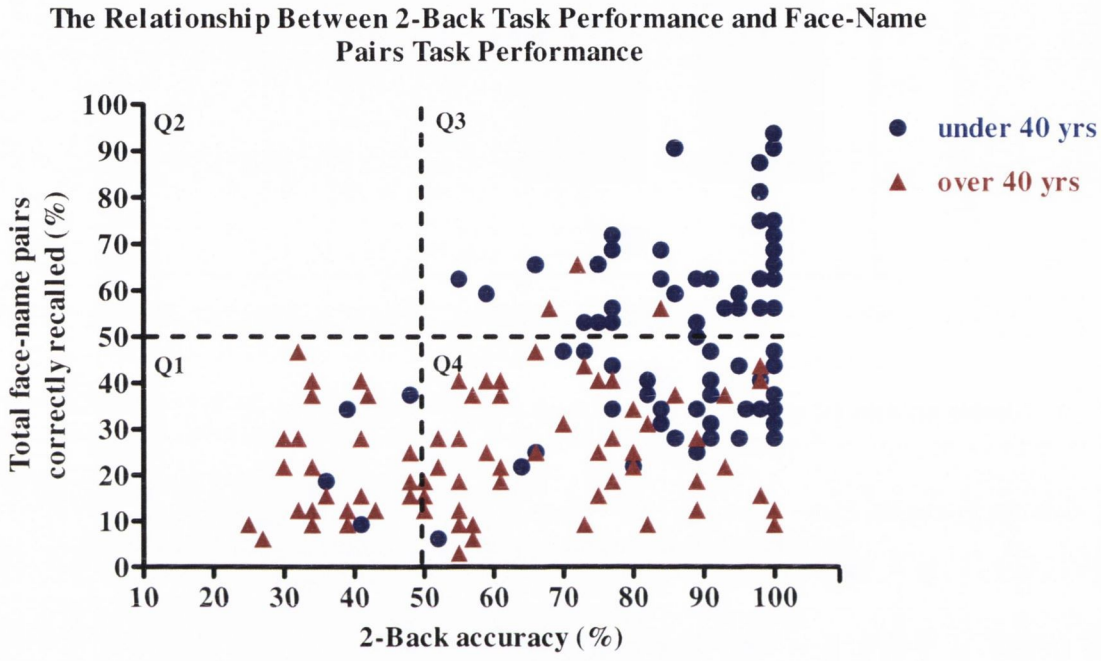

Figure 3.12: The relationship between 2-Back accuracy and Face-Name performance showing the numbers of participants performing at greater and less than 50 % accuracy on both tasks.

	< 50 % accuracy Face-Name Pairs task		> 50% accuracy Face-Name Pairs task	
< 50% accuracy N-Back task	*Q1* Under 40 N = 4	Over 40 N = 25	*Q2* Under 40 N = 0	Over 40 N = 0
	Total = 29		**Total = 0**	
> 50% accuracy N-Back task	*Q4* Under 40 N = 40	Over 40 N = 55	*Q3* Under 40 N = 42	Over 40 N = 3
	Total = 95		**Total = 45**	

Table 3.3: The number of participants falling into the different quadrants for 2-Back and Face-Name performance.

3.4.6 Match-to-Sample task

3.4.6.1 Working memory maintenance task

Predicted IQ was not related to performance on the working memory maintenance task, $F(1, 163) = .88$, $p > .10$. There was also no effect of age group on performance on the working memory maintenance task, $F(3, 167) = .58$, $p > .10$ (see Table 3.4).

3.4.6.2 Delayed recognition task

There was no effect of predicted IQ on participants' overall ability to accurately discriminate between objects they had seen or not seen in the earlier working memory task, $F(1, 166) = 1.55$, $p > .10$. There was also no effect of age group on recognition accuracy scores, $F(3, 170) = 1.18$, $p > .10$ (see Table 3.4). However, when the number of hits, foils, misses and false positives that were made were examined individually, significant differences between the age groups emerged (see Figure 3.13). There was a significant difference between the groups in the number of foils correctly identified, $F(3, 170) = 7.54$, $p < .001$. Post-hoc analysis revealed that the 18-29 year olds identified significantly more foils than the 40's group ($p < .001$) and than the 50-64 group ($p < .01$). There was also a significant between-group difference in the number of false positives committed, $F(3, 170) = 8.26$, $p < .001$. The 18-29 group committed significantly less false positives than the 40's group ($p < .001$), and than those in the 50-64 group ($p < .01$).

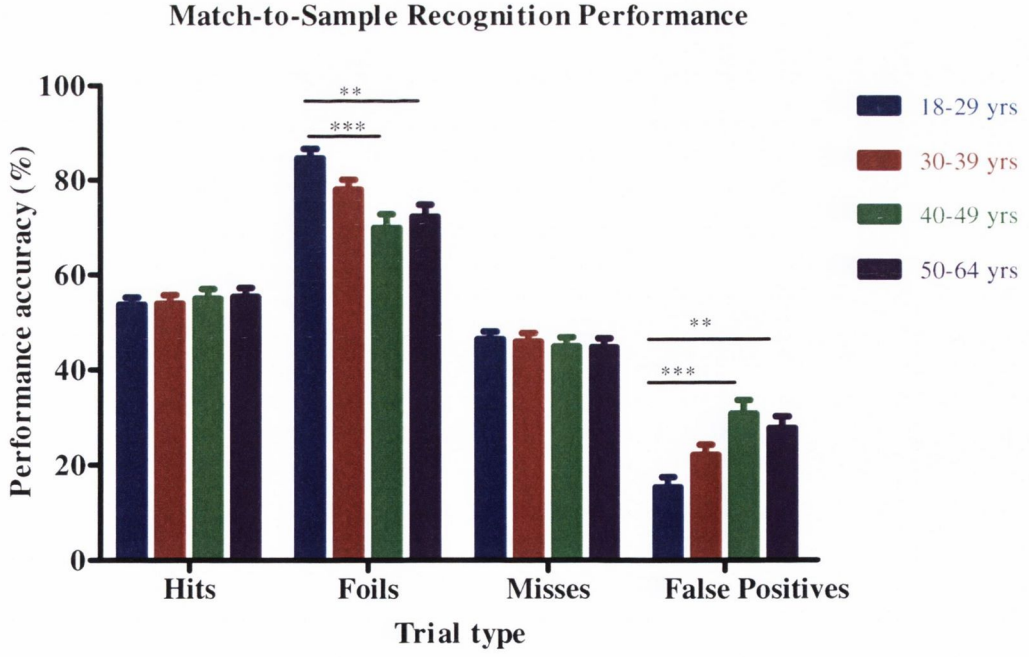

Figure 3.13: Match-to-Sample Recognition memory performance, as a function of trial type and age group.

Age Group	18-29 yrs	30-39 yrs	40-49 yrs	50-64 yrs
Working Memory	92.34 (± 1.25)	91.58 (± 1.49)	87.78 (± 1.49)	91.12 (± 1.50)
Recognition Accuracy	46.54 (± 1.85)	45.59 (± 2.08)	42.08 (± 2.23)	44.51 (± 1.66)

Table 3.4: Mean Match-to-Sample task performance for each age group (± SEM).

A regression line was fitted to the relationship between the number of false positives and the number of hits for each age group on the Match-to-Sample recognition task (see Figure 3.14 and Table 3.5). The gradient is steep for the 50-64 group, indicating that as the number of hits made increased, so too did the number of false positives. The regression line representing the 20's group, however, has an almost non-existent gradient, indicating that an increase in the number of hits made did not lead to a concomitant increase in the number of false positives.

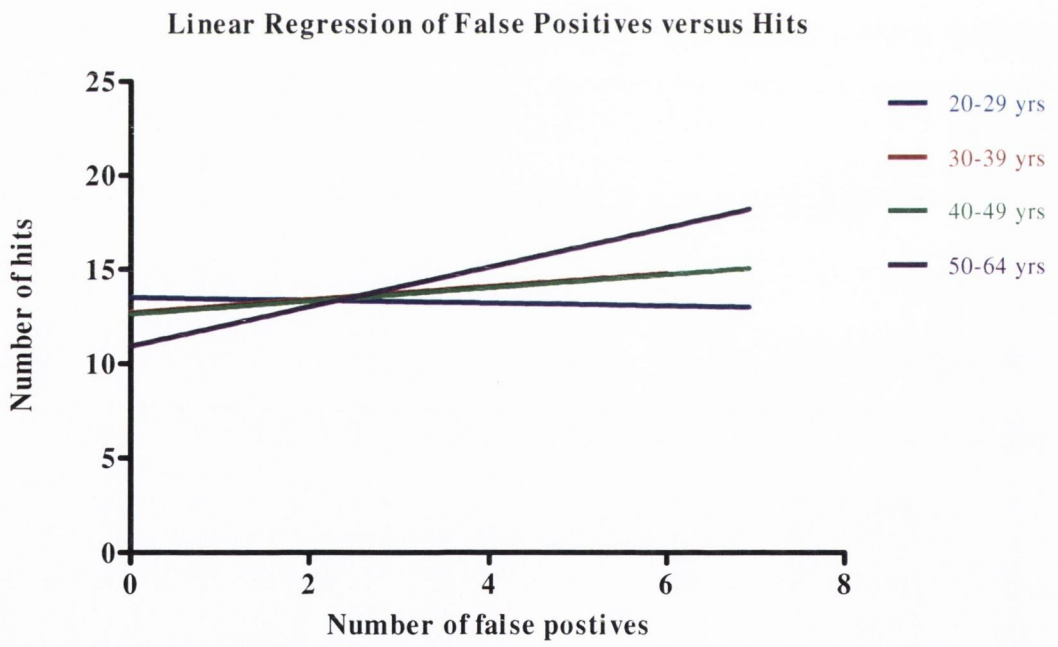

Figure 3.14: Linear regression line showing the relationship between the number of false positives and the number of hits for each age group on the Match-to-Sample Recognition task.

Age Group	18-29 yrs	30-39 yrs	40-49 yrs	50-64 yrs
Slope	-0.071 (± 0.27)	0.35 (± 0.33)	0.35 (± 0.26)	1.05 (± 0.25)

Table 3.5: Slope of the regression line depicting the relationship between the number of false positives and the number of hits on the Match-to-Sample recognition task (± SEM).

3.4.7 Education-matched subgroup

As there were between age group differences in education in the overall sample, the same analyses were conducted on a subgroup of participants matched for education levels.

There were no significant differences between the age groups in predicted IQ scores, $F(3,39) = 2.55$, $p > .05$. Nor were their differences in HADS anxiety, $F(3,40) = 0.48$, $p > .10$, or HADS depression scores, $F(3,40) = 0.41$, $p > .10$ (see Table 3.6).

Age Group	18-29 yrs (N=11)	30-39 yrs (N=11)	40-49 yrs (N=11)	50-64 yrs (N=11)
Predicted IQ	118.64 (± 1.62)	114.10 (± 2.38)	118.54 (± 1.35)	120.09 (± 0.94)
HADS Anxiety	6.45 (± 0.70)	6.65 (± 0.45)	5.54 (± 0 87)	6.73 (± 1.02)
HADS Depression	2.73 (± 0 57)	2.54 (± 0.72)	2.45 (± 0 43)	3.36 (± 0.73)

Table 3.6: Predicted IQ, anxiety and depression scores for the education-matched subgroup of participants.

Face-Name Pairs

Total Recall score

There was a positive effect of IQ on performance, $F(1,38) = 6.58$, $p < .05$. Controlling for IQ, there was a significant effect of age group, $F(3,38) = 5.37$, $p < .01$, partial $\eta^2 = .30$. The 18-29 year olds recalled significantly more pairs than the 50-64 year olds ($p < .01$).

Improvement score

There was a significant effect of age group on participants' improvement in performance from block 1 to block 4, $F(3,39) = 10.43$, $p < .001$. The 18-29 group showed significantly greater improvement across blocks than the 40's group ($p < .05$) and than the 50-64 group ($p < .001$). The 30's also showed greater improvement than the 40's ($p < .05$) and than the 50-64 group ($p < .001$).

Delayed Recall

There was a significant effect of age group on delayed recall performance, $F(3,40) = 4.38$, $p < .01$. The 18-29 year olds recalled significantly more pairs than the 50-64 year olds ($p < .05$). The 30's also recalled significantly more pairs than the 50-64 year olds ($p < .05$).

Name Recall

There was no significant difference between the age groups on name recall performance, $F(3,34) = .82$, $p > .10$.

NOTE: Name recognition performance was not analysed due to the fact that a large number of the participants in the education-matched subgroup were tested prior to this recognition measure having been added to the test battery. The stringency of matching on a variable such as education made it impossible to choose cases to include.

Face Recognition

There was a significant effect of age group on face recognition accuracy, $F(3,35) = 3.97$, $p < .05$. The 18-29 group were significantly more accurate than the 50-64 group ($p < .05$).

Picture-Word task

There was no effect of age group on immediate recall, $F(3,33) = 1.58$, $p > .10$.

There was a significant effect of IQ on delayed recognition accuracy, $F(1,36) = 9.13$, $p < .01$. After controlling for the effect of IQ, there was no effect of age group, $F(3,36) = 1.91$, $p > .10$.

N-Back task

0-Back

There was no significant effect of age group on 0-Back performance, $F(3,39) = 0.67$, $p > .10$.

1-Back

As there were unequal variances between the groups, the Kruskal-Wallis test was used to test for an effect of age group on mean rank scores on the 1-Back task. Age group was found to have a significant effect, $H(3) = 24.41$, $p < .001$. Mann-Whitney tests with Bonferroni correction were used to determine which groups differed significantly. Four comparisons were carried out and thus all effects are reported at a .0125 level of significance. The 18-29 year olds performed significantly better than both the 40's group ($p < .01$) and the 50-64 group ($p < .001$). The 30's group also performed significantly better than the 50-64 year olds ($p < .001$).

2-Back

There was a significant effect of age group on 2-Back performance, $F(3,39) = 9.27$, $p < .001$. The 18-29 group was significantly more accurate than both the 40's group ($p < .01$) and the 50-64 group ($p < .001$). The 30's group also performed significantly better than the 50-64 year olds ($p < .05$).

Match-to-Sample task

There was no effect of age group on performance on either the working memory task, $F(3,40) = 0.50$, $p > .10$, or on delayed recognition accuracy, $F(3,34) = 0.17$, $p > .10$. Furthermore, there was no difference between the age groups in the number of hits, foils, misses or false positives made.

3.5 Discussion

In this chapter, associative memory and working memory function were examined in a lifespan cohort (18-64 years). Pre-morbid IQ and education were also examined. In addition, other affective measures to assess anxiety and depression were included to ensure that age groups were matched for such criteria.

The main findings are as follows:

1. Impairments in associative memory performance, relative to the young adult group, were found to emerge in the 40's.
2. Impairments in N-Back working memory performance, relative to the young adult group, were found to emerge in the 40's. No significant age-related impairment was detected on the Match-to-Sample task working memory maintenance task.
3. Pre-morbid IQ was found to be a significant covariate on both associative memory measures and on the N-Back working memory task. When performance was examined in an education-matched sub-cohort, the same trends were evident.

3.5.1 The current findings and associative memory across the lifespan

Our primary hypothesis stated that we would expect to find a pronounced effect of age on associative memory across the lifespan. This hypothesis was supported, and the decade in which significant performance impairments emerge was found to be the 40's.

The first and primary task employed to assess associative memory, was the Face-Name Pairs task. Several indices of performance on this task were examined: successful encoding on blocks 1-4; the improvement in performance across these blocks; total recall score; delayed associative recall performance; delayed name recall performance; and delayed name and face recognition performance.

Those in their 40's and 50's were significantly impaired at learning the correct face-name pairs when compared with the 20's and 30's groups. This was evident from their recall performance after the learning blocks, as well as their improvement in performance from block 1 to block 4. This pattern of results was also upheld at the delayed recall trial some 20 minutes following initial encoding and recall. On a free-recall task of names, only the 50-64 group were impaired in comparison to the 20's and 30's. Face recognition and name recognition were then examined. The 50-64 group were again significantly impaired in

comparison to the 20's and 30's; however, the 40's group were also impaired when compared with the 20's. Name recognition results showed significant impairments emerging in the 50-64 group, though this was only in comparison to the 20's and 40's groups, as the 30's group performed at a level below that of the 40's, though not significantly so.

The second task used to assess associative memory was the Picture-Word task. There were two components to this task: an immediate cued-recall task; and a delayed associative recognition task. Significant impairments on the immediate recall task emerged in the 40's (though the 30's group performed significantly better than the 50-64 group only). At the delayed recognition trial, a dichotomy was more evident, with performance in the 20's and 30's virtually identical, and the 40's and 50-64 groups significantly impaired, and to the same degree.

To our knowledge this is the first study that has specifically explored associative memory changes across the lifespan with a cohort that included those aged from young adulthood right up to the mid 60's. Moreover, a great strength of this study is that it included measures of cued-recall, free-recall, item recognition and associative recognition. Thus, it allowed differentiation between associative- and item memory, and between measures which require considerable self-initiated processing versus those which offer more environment support (Craik, 1983). The findings from the current study support those of previous studies, that there is an age-related decline in associative memory. A study by Yesavage and Rose (1984) examining face-name pairs learning in a young, a middle-aged and an elderly group, found that associative memory was poorest in the elderly group, best in the young group, with the middle-aged group performing at an intermediate level. Our results, however, go one step further in pinpointing the emergence of a specific associative memory deficit in the 40's.

The results support our second hypothesis - that associative memory is more impaired by aging than item memory. A great deal of research on the effects of aging on associative memory performance has been conducted by Naveh-Benjamin and colleagues, comparing young and old age groups, and using a variety of associative memory tasks and memory measures (Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2003, 2004, 2007). A key aspect to their associative-deficit hypothesis is that memory measures which rely heavily on associative learning (such as cued-recall and associative recognition) should be the

most affected in aging, with free-recall and item recognition showing less vulnerability. This is provided that the information is novel and that items within a pair are not already associated in some way, prior to the task (Naveh-Benjamin, 2000). Support for this hypothesis has come from the finding that cued-recall of word pairs is most affected by aging, followed by free-recall of words, with word recognition being the most intact (Naveh-Benjamin, 2000). Associative- compared to item recognition was also tested using face-name pairs (Naveh-Benjamin et al., 2004). Again, it was found that the biggest age differences were on the associative memory measures, compared with the item memory measures. As our study contains all of the above mentioned types of memory measure, it is ideally placed to fully test this theory. Our findings, in the main, support the a priori hypothesis. The most pronounced age-related deficits were seen on cued-recall of face-name pairs and on cued-recall and associative recognition of picture-word pairs. Free-recall of names and name recognition appeared to be the least impaired by aging.

Impairments in face recognition also emerged in the 40's in this study. The reason why face recognition should be more vulnerable than name recognition to age-related deficits is not clear. It is also noteworthy, however, that although an impairment in face recognition was evident in the same decade as the associative memory impairments in this task, the overall effect size, after controlling for IQ, was much lower than that found on the tests of an associative memory impairment (η^2 = .17 versus η^2 = > .4). Additionally, the Naveh-Benjamin et al. (2004) study also observed an age-related impairment in face recognition. However, the age-related associative memory deficit was shown to remain in a sub-group of participants matched on item memory performance. Thus, the authors demonstrated that the associative memory deficit was not due to any impairment in face memory. It is also important to note, that in the present study, name recognition deficits did emerge, although only in the 50-64 group. This result, along with the finding that name recall was also impaired in the 50-64 group, is consistent with reports of a specific deficit among older adults in memory for proper names (Evrard, 2002; James, 2006). Our name recognition results should be interpreted with caution, however, in light of the finding of better performance in the 40's group than the 30's (albeit not significantly so).

The results of the present study indicate that associative memory deficits emerge in the 40's, with impairments evident at both immediate and delayed recall, and on associative recognition. Age effects on memory for faces and names individually are less pronounced, and may show a later onset of decline.

3.5.2 The current findings and working memory across the lifespan

It was hypothesized that the Match-to-Sample task, which involves the maintenance of information only, would be less affected by age-related decline across the lifespan than the N-Back task, which necessitates the manipulation as well as maintenance of information. This was found to be the case.

The indices of performance on the N-Back task were: 0-, 1- and 2-Back accuracy, and the switch-cost in accuracy from 1- to 2-Back. Both the 40's and 50-64 groups were significantly impaired at both the 1- and 2-Back levels, in comparison to the 20's and 30's groups. Furthermore, both the 40's and 50's groups displayed a significantly greater switch-cost in accuracy going from 1- to 2-Back, than those in their 20's. Thus, significant impairments on this task could be seen to first emerge in the 40's.

The second working memory task utilised was a Match-to-Sample (MTS) task. Two main performance measures on this task were examined: working memory maintenance accuracy, and delayed object recognition accuracy. There was no effect of age group on working memory maintenance accuracy in our sample. There was also no main effect of age group on delayed object recognition accuracy. However, when the number of hits, foils, false positives and misses were analysed separately, both the 40's and 50-64 groups committed significantly more false positives than the 20's group.

Decrements in performance with age on the N-Back working memory paradigm have been previously reported (Dobbs et al., 1989; Nyberg et al., 2009; Mattay et al., 2006; Van Gerven et al., 2009; Vaughan et al., 2008; Verhaeghen et al., 2005), though only one of these studies has explored changes in performance across the lifespan (Dobbs et al., 1989). The Dobbs and Rule study found significant deficits emerging in the 60's on performance at the 1- and 2-Back levels (which they termed Lag 1 and Lag 2). It is notable, however, that their youngest age group was 30-39 years. Other studies have contrasted N-Back performance in young individuals versus old. These studies have found a significant age-related impairment at the 2-Back level, with generally no impairment in performance found in the older group at the 1-Back level (Mattay et al., 2006; Verhaeghen et al., 2005; but see Nyberg et al., 2009). The results of the current study support the findings of previous studies with regard to performance at the 2-Back level, and show that the same pattern of age-related impairment can also be detected at the 1-Back level. Importantly, the current findings suggest that age-deficits on the N-Back task emerge earlier than

previously described, in the 40's. There are, however, differences between our study and several of the other studies in the type of N-Back paradigm used. The studies which found no effect of age on 1-Back performance typically required participants to respond only when they saw an item that had been presented *n* items previously. The current study, however, required participants to constantly update their memory and continuously respond to the stimuli on screen, choosing 1 of 4 buttons for each response, which is undoubtedly more demanding. While Mattay and colleagues (2006) used a task more or less identical to that used in the current study, the small size of their sample (N = 22) must be taken into account. An additional strength of our study is that we reported results after the variance attributed to IQ was removed, which may account for differences between our results and the findings of other studies. As was shown by graphing age against performance on both the 1-Back and 2-Back tasks (see Figure 3.11), there is considerable variability in performance, particularly in the older age groups, which is possibly, at least in part, explained by differences in pre-morbid IQ and education.

The findings of the current study support the contention that older individuals have a greater difficulty in switching between items held within and outside the focus of attention. We found that the 40's and 50's groups exhibited a significantly greater switch-cost in accuracy moving from 1- to 2-Back levels, than those in their 20's. Van Gerven and colleagues (2007) also reported a significant deficit, evident by middle-age, in switching between items in focal attention and those held in working memory, and Verhaeghen and colleagues have proposed that age differences in N-Back task accuracy at higher working memory loads are primarily due to the switch-cost between the 1- and 2-Back levels (Verhaeghen et al., 2005).

Despite the obvious impairments in N-Back performance observed to emerge in the 40's in our study, no age-related performance deficits were found on the MTS working memory maintenance task. It is possible that ceiling effects in part contributed to the lack of an age effect on this task. A second related, but perhaps more theory-driven explanation, is that this task did not sufficiently tax mental processes vulnerable to age-related change. The working memory maintenance task required the storage of a cue object in memory for between 7 and 13 seconds before a second object was presented and a decision as to whether the second matched the first was made. Thus, participants only ever had to hold one object in memory, which was then effectively 'dumped' before the next object had to be stored, and they had the luxury of a large window of time in which to respond. This is

in contrast to the N-Back task, which required participants to continuously press buttons (1 every 2 seconds), constantly update their mental representations, and hold more items online. Therefore, the Match-to-Sample task could be described as a primary memory task, for which adult age differences are small, relative to memory tasks more reliant on executive processes, on which large age differences have been found (Craik & Jennings, 1992; Smith & Jonides, 1999).

No age differences were found on the delayed MTS recognition task, which may reflect the lack of an age effect on the working memory maintenance task, or may be a product of a floor effect (no group attained an accuracy score of above 50 per cent). However, it is interesting to note, that those in the 40's and 50-64 age groups committed significantly more false positives than those in their 20's. This result is in line with the finding that older adults exhibit elevated false alarm rates when compared with young adults, which may be attributable to reduced recollection combined with an over-reliance on familiarity (Duarte, Graham, & Henson, 2008).

3.5.3 The relationship of IQ and education to task performance and evidence in support of a cognitive reserve

The issue of the relationship between pre-morbid IQ and education, and cognitive decline, was addressed in the current study. While significant differences in education between the age groups prohibited the inclusion of education as a covariate in subsequent analysis, predicted IQ was examined in relation to performance on all task measures. IQ was found to be positively related to all memory measures, except for MTS task performance. In addition, the strongest relationships that emerged were between IQ and the associative memory measures, and performance on the 1- and 2-Back tasks. As education could not be included as a covariate, we took an education-matched subgroup of participants and, again, explored the effect of age group on memory. The results from this small subgroup largely corroborated the findings from the main sample, with impairments emerging in the 40's on the Face-Name Pairs task and the N-Back task. The only task that did not exhibit the expected pattern of results was the Picture-Word task, on which no age differences were found. This could be related to the fact that, in the overall sample, the size of the age effect was smaller on this task than on the Face-Name Pairs and N-Back tasks to begin with, and so the effect was lost when group sizes were substantially reduced. Another possibility is that education is highly correlated with Picture-Word task performance, and thus age effects disappeared with education matching. That education matching should

completely remove the age-related impairment on the Picture-Word task and not affect the Face-Name Pairs task, however, seems somewhat unlikely, as both tasks require the use of similar cognitive strategies, and engage similar cognitive processes.

With respect to the idea of a cognitive reserve, and what might underpin such a phenomenon, it is evident from the findings of the current study that while IQ (and likely education also) are certainly strongly related to associative- and working memory performance, they cannot offer much protection against age-related decline on these tasks. Of interest also, are the graphs of age plotted against Face-Name Pairs performance and against 1-Back and 2-Back performance. These raw scatterplots give an idea of the spread of scores on these tasks, without taking into account predicted IQ or education. Face-Name Pairs task performance shows a decline with age and the variance is roughly similar within each age group, or even gets slightly smaller with age. The N-Back task, however, shows a different pattern. Variability increases markedly with age, particularly on the 1-Back task, and there are individuals who, even approaching age 60, can perform at near 100% accuracy. These observations support the idea that working memory ability can be preserved in some older individuals to allow them to perform at a level equal to that of an 18 year old. It is a plausible suggestion that IQ/education accounts for some of this variability. It is also likely that the Face-Name Pairs task is more reliant on the hippocampus/parahippocampal region than the N-Back task, given the proposed importance of these areas in performance on the former task (e.g. Sperling et al., 2003; Zeineh et al., 2003). Thus, the Face-Name Pairs task may be more vulnerable to an age-related decline in MTL structure/functional recruitment than the N-Back task.

When participants' performance on both the Face-Name Pairs task and N-Back task together was examined, it was found that no one who performed at greater than 50% accuracy on the Face-Name Pairs task achieved less than 50% accuracy on the N-Back task. 95 participants, however, did exhibit the reverse pattern. This is an interesting finding which would suggest that mnemonic processes which underpin performance on the N-Back task are also necessary for Face-Name Pairs task performance. However, further investigation is needed into the exact nature of the association between the two tasks.

There is also evidence from the neuroimaging literature that brain structural changes can account for some of the variability in cognitive performance, with some studies reporting larger grey matter density in regions such as the PFC and MTL in high performing older

adults (Rodrigue and Raz, 2004; Tisserand et al., 2004). In addition, several studies also report a tendency of high performing older adults to show different patterns of functional recruitment of brain areas than low performing older adults and young adults (Cabeza, 2002; Reuter-Lorenz, 2002; Rosen, 2002). This may be a possible attempt to compensate for the structural decline of certain brain regions, facilitating better task performance.

3.5.4 Limitations of the current study and future directions

While the wide age range included is a strength of the current study, it didn't include people over the age of 64 years. The reason for this was partly design - we wanted to investigate the changes in memory that occur across the decades of adult life before the onset of old age - and in part for logistical reasons. It could be interesting to extend the upper limit of the age range of the current study, to examine performance on the same tasks in elderly individuals.

There was no specific measure of attention included in this study (other than the 0-Back task). Some researchers have proposed that attention deficits in aging can account for cognitive decline (Craik & Byrd, 1982). The inclusion of a specific measure of attention would perhaps be beneficial in order to separate out task variance that is due to any attention deficit, and to ascertain the degree to which age deficits in attention are separable from age deficits on other executive processes underlying successful memory performance. However, it is interesting to note that Gomez-Perez and Otrosky-Solis recently reported that attention and memory have different trajectories of development and decline, and that while factors relating to memory are most sensitive to age-related decline, factors related to attention are more sensitive to education (Gomez-Perez et al., 2006).

This study also did not address the theory that general cognitive slowing, or a decline in speed of processing abilities with age, can account for memory decline (Salthouse, 1996). While speed of processing could affect performance on complex working memory tasks such as the N-Back task, it is difficult to see how it could account for a decline in performance on tasks with lengthy repeated encoding trials, as well as self-paced associative recognition and recall tasks.

There has recently been an explosion of interest in using neuroimaging to investigate brain changes in aging. There is evidence that certain structures, such as the PFC and MTL undergo marked age-related atrophy (Raz et al., 2005), leading researchers to question how

structural decline relates to function and adaptability in aging. It follows then, that a logical adjunct to the current study would be to investigate how brain changes that may occur early on in the aging process are related to performance on these age-sensitive memory measures, particularly in light of our finding of the emergence of significant memory impairments as early as the 5th decade of life.

It is probable, however, that age-related changes in cognitive function are multi-factorial, and are not solely influenced by specific task requirements or differences in IQ or education levels alone. Increasingly, research is taking other variables into account. Ronnlund and Nilsson (2008), for example, found that nutrition and sibship size can account for a significant amount of cohort variation in age-related memory decline.

An area that has gained considerable interest is the effect of stress on memory performance with age, as prolonged elevation of stress hormones has been associated with unhealthy aging and dementia (Lupien et al., 2009). The examination of neuroendocrine parameters and their relationship to memory across the lifespan would therefore help to further illuminate factors which delineate age-related cognitive change.

Chapter 4

The relationship between cortisol and memory function in young adulthood and middle-age

4.1 Summary

This chapter investigates the relationship between cortisol levels and associative- and working memory performance in a lifespan cohort, focusing on the comparison of young adults with middle-aged adults who exhibit associative- and working memory impairments.

4.2 Introduction

4.2.1 Basal cortisol levels and aging

There is growing evidence for a link between stress and deterioration in cognition with age. Studies in both rodents and humans have linked the prolonged elevation of cortisol levels to structural and functional changes in the hippocampal formation in aging. In aged rats, corticosterone levels correlate with poor performance on spatial memory tasks, hippocampal degeneration, volume loss, and disruption of electrophysiological function (Landfield, Baskin, & Pitler, 1981; Mc Ewen, 2000; Squire, 1992). There is evidence from the Cushing's disease literature, that hypercortisolaemia in humans correlates with reduced hippocampal volume and poor memory (Grillon et al., 2004; Starkman, 1992, 2003). In addition, basal cortisol levels have been found to be higher in Alzheimer's Disease (AD) patients than in healthy controls (Giubilei et al., 2001), and have been associated with poorer cognitive performance (Davis et al., 1986; Greenwald et al., 1986), and hippocampal atrophy in this group (De Leon et al., 1988).

It is important to note that an assumption of causality cannot be made in these studies. It is possible that hippocampal degeneration could cause hypothalamic-pituitary-adrenal (HPA) axis dysregulation, leading to higher cortisol levels, and not the other way around. A likely explanation has been put forward by Sapolsky and colleagues in the form of the 'Glucocorticoid Cascade Hypothesis' (Sapolsky et al., 1986). This hypothesis outlines a feedforward mechanism to explain the relationship between glucocorticoid levels and hippocampal dysfunction. Neurodegeneration in the aged hippocampus leads to an inability to adequately terminate the stress response. This produces a prolonged elevation of glucocorticoid levels which, in turn, causes further neurodegeneration.

4.2.2 Longitudinal and cross-sectional studies of aging

Recently, assessment of neuroendocrine markers has been incorporated into longitudinal and cross-sectional studies of memory changes in aging. Studies have indicated that approximately 30% of older animals and humans exhibit significant increases in glucocorticoids during aging (Lupien et al., 2005), and that this may be detectable from middle age (Hibberd et al., 2000). This is likely the result of HPA axis hyperactivity, as there is evidence of raised levels of corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) in the paraventricular nucleus of aged human adults (Calza et al., 1997).

A number of studies have investigated cortisol patterns in older individuals over time in relation to cognitive function, with the aim of determining the extent to which higher cortisol levels might be related to cognitive decline. The Douglas Hospital Longitudinal Study of Normal and Pathological Aging began in 1988 to chronicle age-related changes in memory with respect to cortisol levels (Lupien et al., 1994). Participants aged 60-87 years (at baseline) gave cortisol samples over a 24-hour period once yearly, and underwent physical and cognitive assessments. Based on the data gathered to date, the investigators found evidence for 3 subgroups of individuals with respect to cortisol levels: a group with high levels that were increasing year by year; a group with moderate levels that were increasing year by year; and a group with moderate levels that were decreasing year by year. It was found that the high/increasing group had significantly impaired declarative memory function and selective attention, compared to the other two sub-groups. Furthermore, the former group had a significantly smaller (14%) hippocampal volume than those in the moderate/decreasing group (Lupien et al., 1998). In another longitudinal study, Seeman and colleagues (1997) found a significant negative relationship between the change in night-time cortisol levels over a 2.5 year period and declarative memory performance. Furthermore, cross-sectional analyses carried out at baseline and at follow-up revealed a negative association between cortisol levels and delayed paragraph recall. Interestingly, these associations were only found in women. No significant relationship between cortisol and memory performance was found amongst male participants. Li et al. (2006) also found that high and increasing evening cortisol levels over a 3 year period predicted verbal memory decline in a group of elderly individuals, and a negative relationship was also found between cortisol levels and memory performance at both baseline and follow-up. Contrary to these results, however, Kalmijn et al. (1998) found no relationship between morning serum cortisol levels and Mini Mental State Exam (MMSE) scores at a follow up 1.9 years later, although higher cortisol levels at baseline did correlate with initial performance on the tasks.

In a purely cross-sectional design involving almost one thousand older adults between 50 and 70 years, Lee and colleagues (2004) found that higher cortisol levels during a once-off cognitive testing session were associated with poorer performance in 6 cognitive domains, including executive function, verbal memory and learning and visual memory. They sampled cortisol levels among participants at 4 times during the testing session and created 7 cortisol metrics from these samples, out of which pre-test levels, mean cortisol and the area under the curve (AUC) were found to be inversely associated with cognitive

performance. Cortisol levels during testing have also been inversely related to verbal associative memory performance in an elderly population (Wright et al., 2005).

The majority of the extant literature has focused on the relationship between cortisol, aging and hippocampal functioning, assessed cognitively by hippocampal-dependent memory measures, namely declarative memory recall. There are comparatively fewer longitudinal or cross-sectional studies which have examined the association between cortisol and frontal lobe functioning in aging. This is somewhat surprising given the large concentration of glucocorticoid receptors in the prefrontal cortex (Patel et al., 2000), and the evidence from the pharmacology literature that exogenous cortisol can impair working memory performance (see section 1.12.1).

With respect to aging, high levels of glucocorticoids can lead to enhanced elevation of glutamate post-stress in both the hippocampus and prefrontal cortex of aged rats compared with young rats (Lowy, Wittenberg, & Yamamoto, 1995). Furthermore, using a novel *in vitro* post-mortem tracing method on human brain slices, Dai et al. (2004) found a stimulating effect of low concentrations of glucocorticoids on axonal transport in prefrontal cortex neurons, with high concentrations having a detrimental effect. In both the Lee et al. (2004) study and the Li et al. (2006) study, higher cortisol levels at test were related to poorer performance on tasks of executive function (Trail-Making test and Stroop task), though in the latter study they were not predictive of a longitudinal decline in these abilities. Thus, there is the suggestion that the glucocorticoid cascade hypothesis (Sapolsky, 1986), which relates prolonged glucocorticoid exposure to impaired hippocampal functioning, could also apply to the prefrontal cortex (Lupien et al., 2009).

4.2.3 The relationship between cortisol and cognitive challenge in aging

There is some evidence to suggest that cognitive testing can act as a mild psychosocial stressor. Lee and colleagues found that subjective measures of distress increased in elderly individuals from pre-testing to post-testing during a cognitive testing session, indicating that the cognitive testing was a slight stressor in this aged group (Lee et al., 2004). However, this did not translate into an increase in cortisol levels across the testing session. The study carried out by Wright et al. (2005) investigated the relationship between cognitive function and salivary cortisol at testing in individuals aged 60 to 80 years. They found a significant cortisol response to cognitive testing, which was negatively related to task performance and positively related to subjective ratings of task difficulty and distress.

The possibility also exists, however, that associations between cortisol measures at testing and memory performance may not imply a simple unidirectional mode of causality (whereby higher basal cortisol levels lead to worse cognitive performance) but might, in some circumstances, be reflective of increased cortisol levels in some individuals resulting from perceived task difficulty.

There is some evidence to suggest that, while older adults who produce higher cortisol levels in response to cognitively challenging situations exhibit poorer performance on cognitive tasks, the opposite may be true for younger individuals. Kukolja and collaborators investigated cortisol responses to a functional imaging paradigm and their relationship to task performance amongst young (< 30 years) and older (> 52 years) adults. They found that a higher cortisol response to undergoing fMRI was associated with poorer memory for items and their spatial location in the older group, but was associated with better task performance in the younger group. Moreover, cortisol was positively correlated with increased prefrontal activation during memory encoding in the younger individuals, and was negatively related to hippocampal and prefrontal activation during retrieval in the older group (Kukolja et al., 2008). Important also in this study is the finding that there was no difference in mean cortisol levels between the young and old group either pre- or post-testing.

This latter study raises the possibility that the relationship between cortisol levels and performance during cognitive challenge may be different in young and older individuals. The majority of the recent research into the relationship between cortisol and memory in young individuals has focused on pharmacological manipulation, or on the use of physiological or pronounced psychological stressors. Very little, if any, research has examined cortisol patterns in healthy young individuals relative to cognitive performance. It is important that such research be conducted if we are to fully understand the complexity of the relationship between cortisol and cognitive function, especially with regard to the aging process.

The results of Chapter 3 showed significant associative memory and working memory impairments emerging from the 40's on. What exactly is contributing to this sudden dip in performance in middle-age is not clear. There is a considerable literature on the effect of high cortisol levels on memory in old age, but to our knowledge no one has yet explored

the relationship between cortisol levels and memory in a middle-aged sample with our age range.

Taking the above considerations into account, we sought to examine the relationship between cortisol levels and memory performance in a young group (20's and 30's), who display little age-related change in performance, and a middle-aged group (40-64 years), who exhibit significant impairments when compared with the younger group.

4.2.4 Hypotheses

1. The primary hypothesis is that there is a difference in the relationship between basal cortisol levels and associative and working memory performance in young and middle-aged individuals, with a stronger negative association between cortisol levels and task performance emerging in the over 40's group compared with the younger group.
2. A secondary hypothesis is that middle-aged individuals will exhibit an increase in cortisol during the testing session due to mild psychosocial stress, which may affect their performance.

4.3 Methods

4.3.1 Participants

83 participants from the lifespan study (Chapter 3) were included in this additional study. Exclusion criteria were thus the same as for the previous study; however, there were some additional criteria which rendered participants ineligible for participation in this particular study. These were: a history of endocrine disorder (e.g. thyroid dysfunction or diabetes); and current use of glucocorticoid (steroid) medication. The study was approved by the School of Psychology Ethics Committee, Trinity College Dublin. Participants were compensated for their time and travel expenses in accordance with School of Psychology guidelines (undergraduate psychology students were eligible to receive research credits). Written, informed consent was obtained from each participant prior to the commencement of the study.

The mean age of the participant group as a whole was 40.45 yrs with a standard deviation of 13.05 yrs. The age range was 19-64 yrs. This group did not differ significantly from that of the larger study in years spent in education, predicted IQ, anxiety or depression scores (see Table 4.1 in the results section).

The results of the lifespan study demonstrated an age-related impairment in task performance, which began to manifest in the 40's decade within our sample for many of the tasks employed. This was especially true in the case of the Face-Name Pairs task and the N-Back task, where there was a clear division in terms of performance between those in their 20's and 30's, and those in the 40's and 50-64 age groups. For the main part of the analysis in this chapter, the sample as a whole was split into two age groups based on these findings: an 18-39 group; and a 40-64 group. The 18-39 group consisted of 41 participants (9 male; mean age = 29.19, SD = 6.82, range = 19-39). The 40-64 group consisted of 42 participants (13 male; mean age = 41.45, SD = 6.68, range = 41-64).

4.3.2 Salivary cortisol sampling

In order to assess cortisol levels, participants donated 3 saliva samples over the course of the testing session, from which the concentration of cortisol in the body was determined. Samples were collected by means of a Salivette sampling device (Starstedt, Numbrecht, Germany), and were analysed by the Elecsys Cortisol in Immunoassay method, in the Adelaide and Meath Hospital, Tallaght (see Chapter 2, section 2.7 for a full description of the methods).

The area under the curve with respect to ground (AUCg) for the 3 cortisol samples in total was computed according to the formula set out by Pruessner and colleagues (2003):

$$AUC_G = \sum_{i=1}^{n-1} \frac{(m_{(i-1)} + m_i) \cdot t_i}{2}$$

With t_i denoting the individual time distance between measurements, m_i the individual measurement, and n the total number of measures. The AUCg thus represents the total cortisol output over a period of time. This metric was used in subsequent regression analyses.

4.3.3 Procedure

4.3.3.1 General

All participants were tested in the afternoon. This was to control for the diurnal fluctuation in cortisol levels. Participants were instructed to fast for an hour before the testing session, to avoid any interaction between glucose release and cortisol (Kirschbaum et al., 1997). This extended to the intake of all drinks (except for water). Participants were also asked not to smoke during this time owing to the acute effects of nicotine on cortisol levels (Mello, 2009).

4.3.3.2 Cognitive testing battery

The tasks and questionnaires used were identical to those used in Chapter 3 (see section 3.2.2). In addition to these measures, participants also completed the state form (S-Anxiety) of the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983). This is a self-report mood questionnaire, and was described in detail in Chapter 2, section 2.5.2. Participants were administered this questionnaire before starting the battery of tasks, and again immediately upon finishing them, in order to assess their levels of anxiety at both time points.

Task Order

Three saliva samples were taken over the course of the testing session: Time 1 (immediately prior to starting the cognitive battery); Time 2 (approximately mid-way through the session); Time 3 (immediately after the session). The order of tasks and sampling is outlined in Table 4.1.

Order	Task/Measure	Time (approx.)
1.	Information leaflet and consent form	0 mins
2.	Cortisol Time 1	3 mins
3.	S-Anxiety (Before)	5 mins
4.	Face-Name Pairs Learning and Recall	7 mins
5.	Match-to-Sample Working Memory	17 mins
6.	Picture-Word Pairs Learning and Recall	24 mins
7.	National Adult Reading Test (NART)	27 mins
8.	Hospital Anxiety and Depression Scale (HADS)	29 mins
9.	Cortisol Time 2	31 mins
10.	Face-Name Pairs Delayed Recall and Recognition tasks	33 mins
11.	Match-to-Sample Delayed Recognition	40 mins
12.	Picture-Word Pairs Delayed Recognition	47 mins
13.	N-Back Task (0-, 1-, and 2-Back conditions)	49 mins
14.	S-Anxiety (After)	59 mins
15.	Cortisol Time 3	61 mins

Table 4.1: Running order of test battery.

4.3.4 Statistical Analyses

All analyses were carried out using SPSS (version 16) for PC. Data are expressed as mean ± SEM unless otherwise stated. The critical α level was .05. ANOVA and multiple regression analysis were the primary statistical tools used. Paired sample *t*-tests were used to explore differences across repeated measures (e.g. cortisol levels), during the analysis of the group as a whole. Where performance was repeated across identical trials and there was also a between group factor, a mixed-between-within group ANOVA was used to compare performance across repeated trials and between groups. Main effects and interactions were reported, and where relevant, post-hoc analysis was carried out. Where a significant interaction was identified, one-way ANOVAs were conducted to examine between-group differences at each level of the dependent variable. Where a significant within group effect was found, but no significant main effect of group and no significant interaction, paired sample *t*-tests were used to explore the differences across the repeated measure for each group individually. Where sphericity could not be assumed, Greenhouse-Geisser corrected values were reported (G.G.).

For the multiple regression analyses, the variables of interest were entered into the model using the forced entry mode of model building. The use of a 'dummy' or 'indicator' variable was employed to explore the effect of age group on the relationship between various task performance measures, and cortisol levels. Preliminary checks were carried out to ensure that no assumptions were violated prior to running the analysis. These included: no perfect multicollinearity; homoscedasticity; independent errors; and normal distribution of the residuals. These assumptions were checked by inspecting residual plots, the Durbin-Watson test for independent errors, examining the correlation matrix and the variance inflation factor (VIF). Any outliers (mean ± 2 SDs) that were having undue influence on the model were removed.

4.4 Results

4.4.1 Participant education, predicted IQ, HADS anxiety and depression scores

Participant education, predicted IQ, anxiety and depression scores are displayed below (Table 4.2). Scores for this subgroup did not differ significantly from that of the parent group.

Education	Predicted IQ	HADS Anxiety	HADS Depression
16.33 (± 0.34)	115.73 (± 0.73)	6.83 (± 0.37)	3.05 (± 0.26)

Table 4.2: Mean education, predicted IQ, anxiety and depression scores (± SEM).

4.4.2 The effect of gender and oral contraceptive use on cortisol levels

In order to investigate whether gender had a significant effect on cortisol levels, a mixed between-within-subjects ANOVA with sample time as the within subject factor and gender as the between subject factor was conducted. This revealed no main effect of sample time, $F(1.69, 124.90) = 0.55$, $p > .10$ (G.G.) or gender, $F(1, 74) = 2.03$, $p > .10$ on cortisol levels. Furthermore, there was no significant interaction between gender and sample time, $F(1.69, 124.90) = 1.39$, $p > .10$ (G.G.). Participants were then further divided into males, females taking oral contraceptives, and females not taking oral contraceptives. Once again there was no main effect of sample time, $F(1.51, 95.43) = 0.86$, $p > .10$ (G.G.) or participant group $F(2, 63) = 0.65$, $p > .10$ on cortisol levels. Furthermore there was no interaction between participant group and sample time, $F(3.03, 95.43) = 0.44$, $p > .10$ (G.G.; see Table 4.3). Thus for subsequent analyses the data were collapsed across gender and oral contraceptive use.

Cortisol (nmol/L)	Time 1	Time 2	Time 3
Males (N= 21)	8.21 (± 0.73)	9.57 (± 1.0)	8.95 (± 0.58)
Females (N = 59)	7.67 (± 0.43)	7.59 (± 0.51)	7.39 (± 0.55)
Oral contraceptives (N = 20)	7.35 (± 0.70)	6.90 (± 0.75)	6.50 (± 0.68)
No oral contraceptives (N =32)	8.21 (± 0.62)	8.39 (± 0.79)	7.69 (± 0.72)

Table 4.3: Mean cortisol levels (± SEM) at each of the three sample time points, broken down by gender and oral contraceptive use.

4.4.3 Change in cortisol levels across the testing session

As one of our a priori hypotheses was that stress due to cognitive testing might lead to an increase in cortisol levels across the testing session, a repeated measures ANOVA was carried out to determine whether there was a difference between cortisol levels across the three time points. The main ANOVA was followed up with Bonferroni pairwise comparisons. There was no significant effect of sampling time on cortisol levels, $F(1.68, 125.86) = 0.69$, $p > .10$ (G.G.). The pairwise comparisons of the difference between the sample time points yielded p values of $> .10$ (see Figure 4.1).

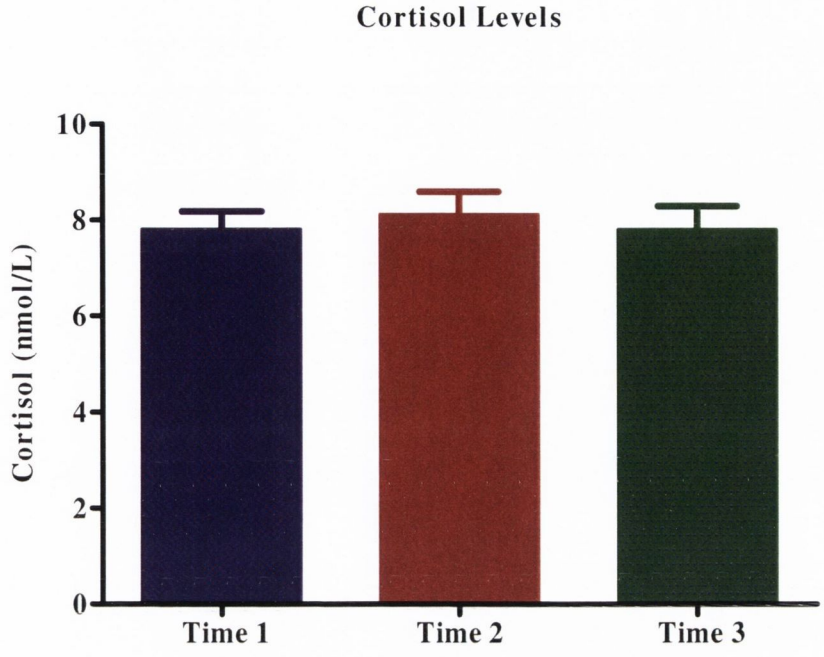

Figure 4.1: Cortisol levels for the group as a whole, at each of the three sample time points.

4.4.4 The effect of age group on cortisol levels

Given the effects of age group on task performance that were observed in Chapter 3, we sought to examine the interaction between cortisol levels and cognitive performance in each of two categories: 18-39 year olds (n = 41); 40-64 year olds (n = 42).

The effect of age group on cortisol levels was analysed using a mixed between-within-subjects ANOVA. Cortisol values were log transformed to correct for inhomogeneity of variance (see Table 4.4). There was no significant main effect of time $F(1.63, 117.52) = 2.46$, $p > .10$ (G.G.). There was no significant interaction between age group and time, $F(1.63, 126.37) = 1.85$, $p > .10$ (G.G.). There was, however, a significant main effect of age group, $F(1, 72) = 6.48$, $p < .05$, with the 40-64 year olds displaying higher cortisol levels than the 18-39 year olds (see Table 4.4).

Log Cortisol (nmol/L)	Time 1	Time 2	Time 3
18-39 yrs	0.82 (± 0.03)	0.78 (± 0.03)	0.77 (± 0.03)
40-64 yrs	0.89 (± 0.03)	0.93 (± 0.04)	0.91(± 0.04)

Table 4.4: Mean cortisol levels (log transformed) at each of the three sampling times.

AUCg

The area under the curve with respect to ground (AUCg) was calculated for each age group in turn (Pruessner et al., 2003). This can be taken to represent the total cortisol output over a period of time (in this case the duration of the testing session). There was a significant difference in total cortisol output between the age groups, $t(72) = -2.56$, $p < .05$. The 40-64 group had a significantly larger AUCg than the 18-39 group (see Figure 4.2).

Area Under the Curve with Respect to Ground (AUCg) for Cortisol

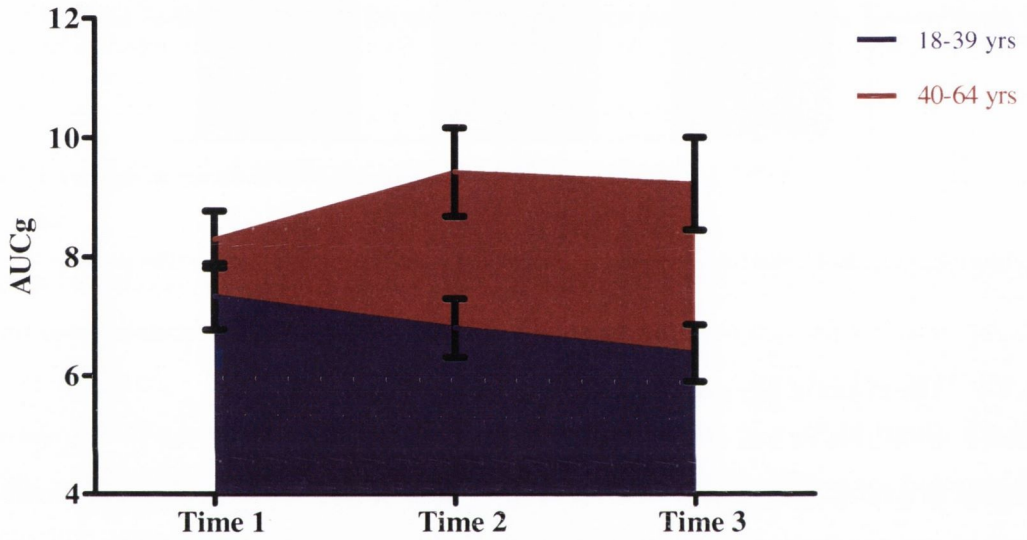

Figure 4.2: Cortisol output at each of the three sampling points during the test session for each age group, displayed as the area under the curve with respect to ground (AUCg).

4.4.5 The relationship between age group and state anxiety pre- and post-testing.

A repeated-measures ANOVA was carried out to examine the difference in anxiety between the age groups, pre- and post-testing. There was a significant main effect of time, $F(1, 78) = 5.31$, $p < .05$, but no significant main effect of age group, $F(1, 78) = 2.76$, $p > .10$, and no significant interaction between time and age group, $F(1, 78) = 0.33$, $p > .10$ (see Table 4.5). In light of a significant main effect of time on anxiety scores, paired sample *t*-tests were then carried out to determine where this difference lay (see Figure 4.3).

18-39 yrs

Pre-testing anxiety scores (mean = 31.18, SE = 1.48) did not differ significantly from post-testing scores (mean = 32.79, SE = 1.18) in this group, $t(37) = -1.06$, $p > .10$.

40-64 yrs

Post-testing anxiety scores (mean = 30.98, SE = 1.13) were significantly higher than pre-testing scores (mean = 28.31, SE = 0.97) in this group, $t(41) = -2.39$, $p < .05$.

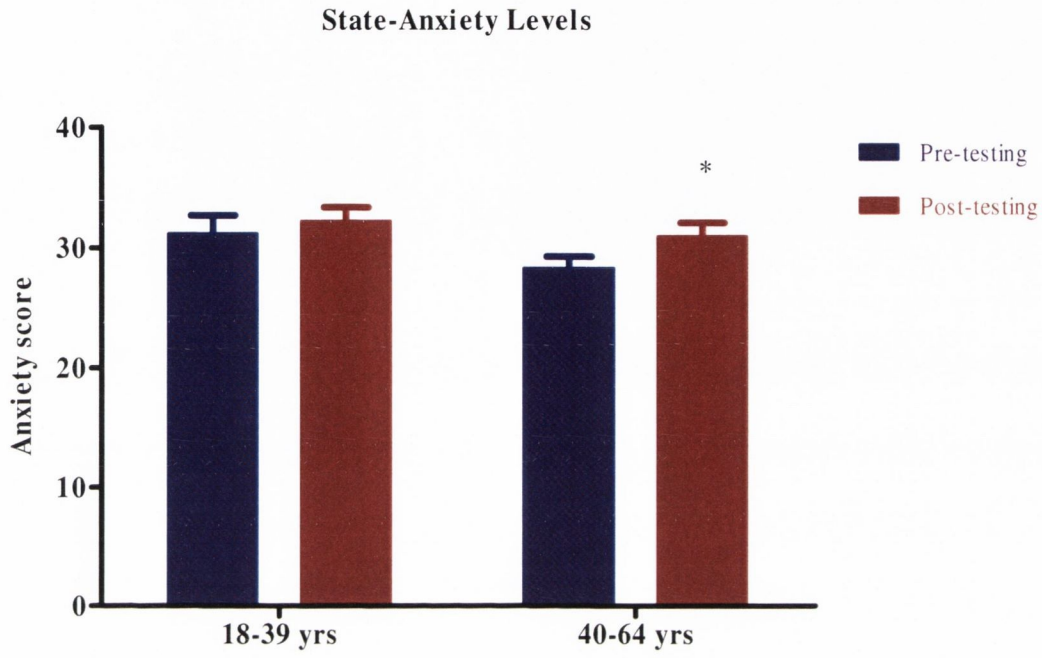

Figure 4.3: State-Anxiety scores for each age group pre- and post-testing session.

4.4.6 The ability of cortisol levels, age group and predicted IQ to predict cognitive task performance

A series of multiple regression analyses were conducted in order to determine whether cortisol levels, along with age group and predicted IQ scores, could account for a significant amount of variation in performance on the various cognitive tasks. An indicator variable $Y_0 O_1$ was included in the analysis, whereby '0' was assigned to participants in the 18-39 group, and '1' was assigned to participants in the 40-64 group. Total cortisol output (AUCg) was also included in the analysis, as was predicted IQ. Furthermore an interactive term, $Y_0 O_1$ X AUCg was added to the regression model. This was in order to assess any possible effect of the interaction between cortisol levels and age group on performance, separate to any main effect that cortisol might have. The regression equation was derived as follows:

$$Y = \beta_0 + \beta_1 * Y_0O_1 + \beta_2 * \text{Predicted IQ} + \beta_3 * \text{AUCg} + \beta_4 * Y_0O_1 \text{ X AUCg} + \varepsilon$$

Where

Y is the outcome variable

ε is the error term

NOTE: The use of the indicator variable meant that for the 18-39 age group variables one and four were equal to zero.

The total amount of variance in the outcome variable that can be explained the model (R^2), as well as the importance of the individuals predictors in turn (standardized β values, t and associated p values), are reported below in Table 4.5.

Y	R^2	Predictors	Std. β	*t*	*p*
Face-Name Total Score	0.62	Y_0O_1	- 0.673	- 2.016	.048*
		Predicted IQ	0.443	5.837	.000***
		AUCg	- 0.237	- 2.089	.744
		Y_0O_1 X AUCg	- 0.120	- 0.328	.041*
Face-Name Improvement Score	0.62	Y_0O_1	- 0.732	- 2.108	.033*
		Predicted IQ	0.025	0.334	.740
		AUCg	- 0.119	- 1.081	.283
		Y_0O_1 X AUCg	- 0.013	- 0.035	.972
Face-Name Delayed Recall	0.66	Y_0O_1	- 0.590	- 1.866	.066
		Predicted IQ	0.333	4.685	.000***
		AUCg	- 0.065	- 0.621	.537
		Y_0O_1 X AUCg	- 0.129	- 0.377	.707
Name Recall Accuracy	0.24	Y_0O_1	0.161	0.341	.734
		Predicted IQ	0.319	2.956	.004**
		AUCg	0.011	0.171	.944
		Y_0O_1 X AUCg	- 0.536	- 1.041	.302

Y	R^2	Predictors	Std. β	*t*	*p*
Face Recognition Accuracy	0.28	Y_0O_1	- 0.954	- 2.084	.041*
		Predicted IQ	0.360	3.540	.001**
		AUCg	- 0.042	- 0.278	.782
		Y_0O_1 X AUCg	0.631	1.269	.201
Name Recognition Accuracy	0.31	Y_0O_1	0.078	0.171	.864
		Predicted IQ	0.357	3.156	.001**
		AUCg	- 0.209	- 1.394	.168
		Y_0O_1 X AUCg	- 0.361	- 0.732	.467
Picture-Word Immediate Recall	0.66	Y_0O_1	- 0.579	- 1.742	.087
		Predicted IQ	0.667	8.549	.000***
		AUCg	- 0.215	- 1.918	.060
		Y_0O_1 X AUCg	0.232	0.644	.522
Picture-Word Delayed Recognition	0.30	Y_0O_1	- 0.299	- 0.651	.517
		Predicted IQ	0.534	5.294	.000***
		AUCg	0.010	0.066	.947
		Y_0O_1 X AUCg	0.213	0.430	.668
1-Back Accuracy	0.35	Y_0O_1	- 0.968	- 2.102	.040*
		Predicted IQ	0.386	3.169	.001**
		AUCg	0.196	1.324	.191
		Y_0O_1 X AUCg	0.680	1.385	.172
2-Back Accuracy	0.43	Y_0O_1	0.363	0.857	.395
		Predicted IQ	0.353	3.720	.000***
		AUCg	0.146	1.060	.293
		Y_0O_1 X AUCg	- 0.954	-2.094	.040*
Match-to-Sample Recognition Accuracy	0.10	Y_0O_1	0.650	1.266	.210
		Predicted IQ	0.144	0.998	.322
		AUCg	0.390	2.326	.023*
		Y_0O_1 X AUCg	- 0.935	- 1.679	.098

Table 4.5: Multiple regression analysis the relationship between age group, cortisol levels and predicted IQ on task performance for the group as a whole.

4.4.7 Further exploration of the relationship between cortisol and task performance in each age group individually

Where a significant or near significant effect of the indicator variable $Y_0 O_1$ or AUCg was found, and/or a significant effect of the interactive term $Y_0 O_1$ X AUCg, the outcome variable in question was retained for further analysis. This involved conducting separate multiple regression analyses for each age group. This was carried out in order to examine the relationship of cortisol levels to performance for each age group separately, with the intention of ascertaining whether there was a fundamental difference between the age groups in the nature of this relationship. Predicted IQ was also retained as a covariate. The regression equation was as follows:

$$Y = \beta_0 + \beta_1 * \text{Predicted IQ} + \beta_2 * \text{AUCg} + \varepsilon$$

Where

Y is the outcome variable

ε is the error term

The total amount of variance in the outcome variable that can be explained the model (R^2), as well as the importance of the individuals predictors in turn (standardized β values, t and associated p values), are reported below in Table 4.6.

NOTE: Results for Match-to-Sample Recognition Accuracy in the 40-64 yrs group and Face Recognition accuracy in the 20-39 group are not displayed as less than 1% of the variance in task performance could be explained by the regression model.

Y	Age Group	R^2	Predictors	Std. β	*t*	*p*
Face-Name Total	**18-39 yrs**	0.40	Predicted IQ AUCg	0.608 - 0.205	4.599 - 1.551	.000*** .130
	40-64 yrs	0.31	Predicted IQ AUCg	0.531 - 0.200	3.621 - 1.363	.001*** .182

Y	Age Group	R^2	Predictors	Std. β	*t*	*p*
Face-Name Improvement Score	**18-39 yrs**	0.04	Predicted IQ	0.062	0.357	.724
			AUCg	- 0.195	- 1.125	.269
	40-64 yrs	0.14	Predicted IQ	0.056	0.341	.735
			AUCg	- 0.374	- 2.278	.030*
Face-Name Delayed Recall	**18-39 yrs**	0.18	Predicted IQ	0.381	2.412	.021*
			AUCg	- 0.100	- 0.636	.529
	40-64 yrs	0.33	Predicted IQ	0.537	3.662	.001**
			AUCg	- 0.223	- 1.518	.139
Face Recognition Accuracy	**40-64 yrs**	0.28	Predicted IQ	0.498	3.368	.002
			AUCg	0.171	1.156	.256
Picture-Word Immediate Recall	**18-39 yrs**	0.17	Predicted IQ	0.402	2.570	.015*
			AUCg	- 0.075	- 0.479	.635
	40-64 yrs	0.22	Predicted IQ	0.455	2.948	.006**
			AUCg	- 0.101	- 0.653	.518
1-Back Accuracy	**18-39 yrs**	0.24	Predicted IQ	0.438	2.702	.011*
			AUCg	0.200	1.233	.228
	40-64 yrs	0.02	Predicted IQ	0.134	0.742	.464
			AUCg	0.002	0.012	.991
2-Back Accuracy	**18-39 yrs**	0.22	Predicted IQ	0.395	2.488	.018*
			AUCg	0.231	1.456	.155
	40 -64 yrs	0.26	Predicted IQ	0.426	2.709	.011*
			AUCg	- 0.266	- 1.691	.101
Match-to-Sample Recognition Accuracy	**18-39 yrs**	0.38	Predicted IQ	0.058	0.429	.671
			AUCg	0.615	4.564	.000***

Table 4.6: Multiple regression analyses of the effect of cortisol and predicted IQ on task performance in young and middle-aged participants separately.

Graphs of the relationship between cortisol and task performance, contrasting the 18-39 group with the 40-64 group, are displayed below (see Figures 4.4, 4.5, 4.6, 4.7, 4.8 and 4.9).

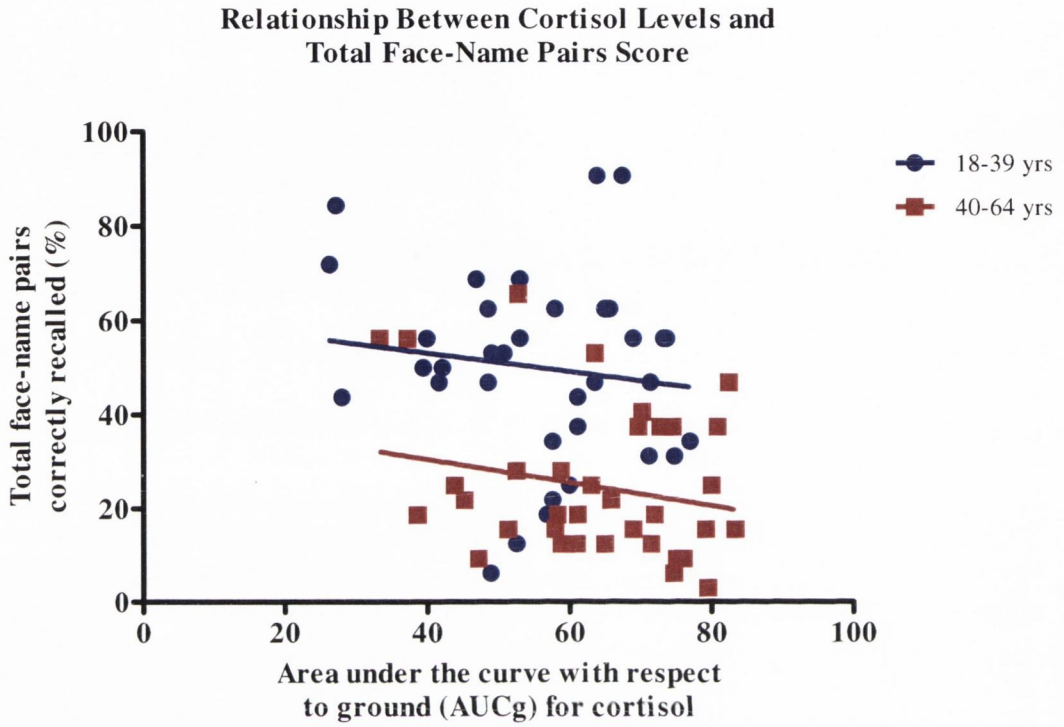

Figure 4.4: The relationship between cortisol levels (expressed as AUCg) and Face-Name Pairs task performance, for each age group.

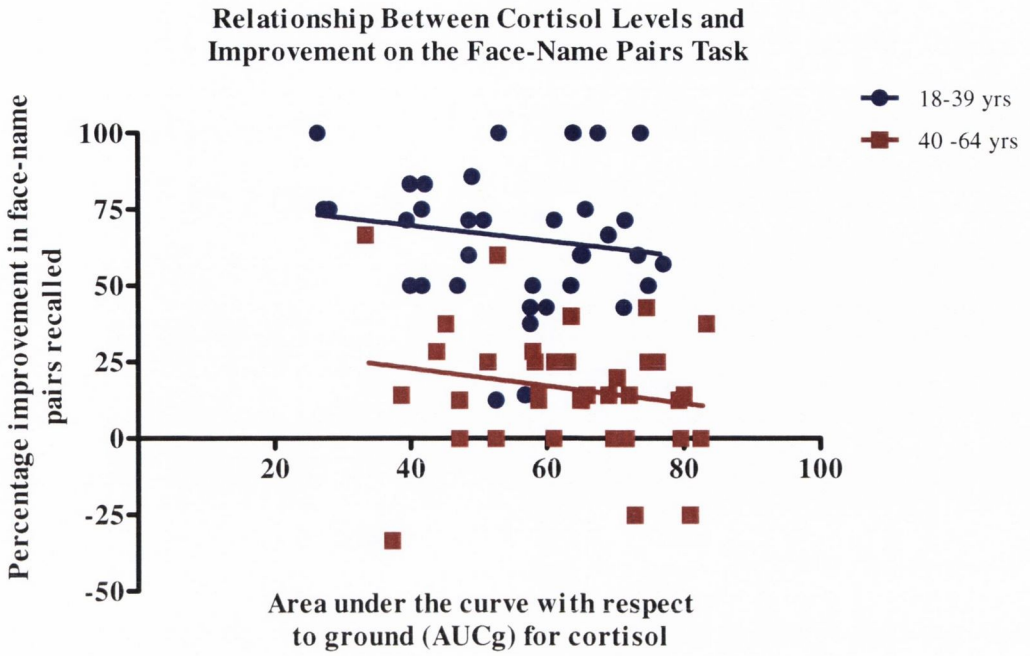

Figure 4.5: The relationship between cortisol levels (expressed as AUCg) and the percentage improvement in the face-name pairs successfully recalled from Block 1 to Block 4 for each age group.

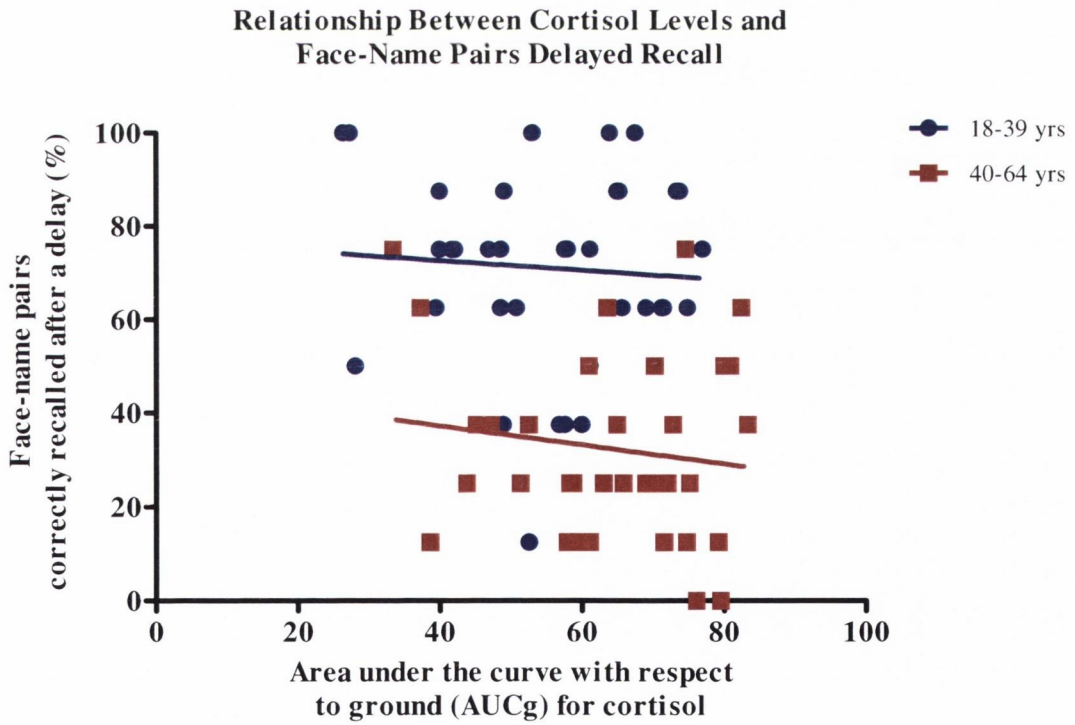

Figure 4.6: The relationship between cortisol levels (expressed as AUCg) and the percentage of face-name pairs successfully recalled after a delay.

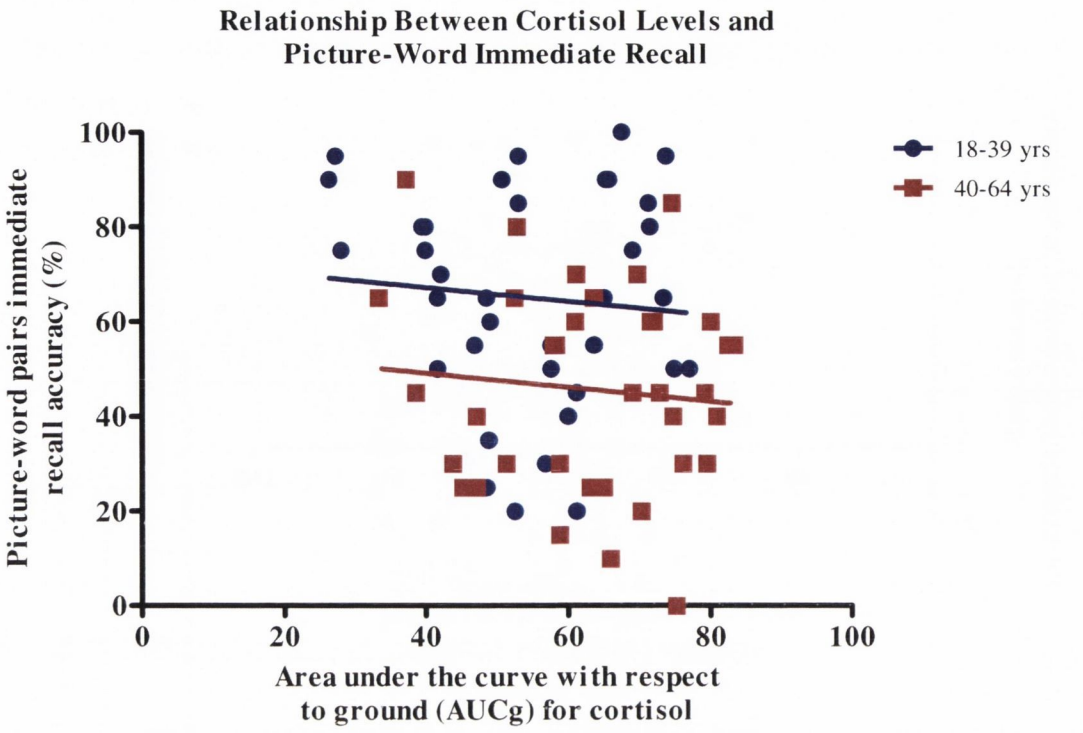

Figure 4.7: The relationship between cortisol levels (expressed as AUCg) and percentage accuracy on the Picture-Word Immediate Recall task for each age group.

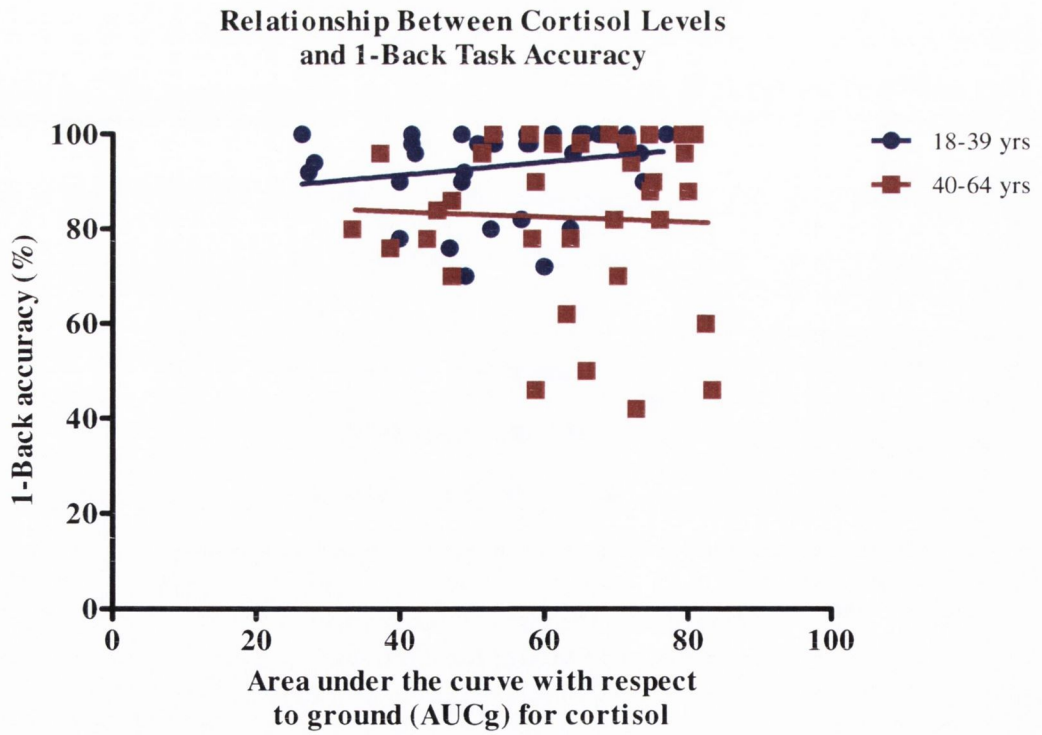

Figure 4.8: The relationship between cortisol levels (expressed as AUCg) and percentage accuracy on the 1-Back task for each age group.

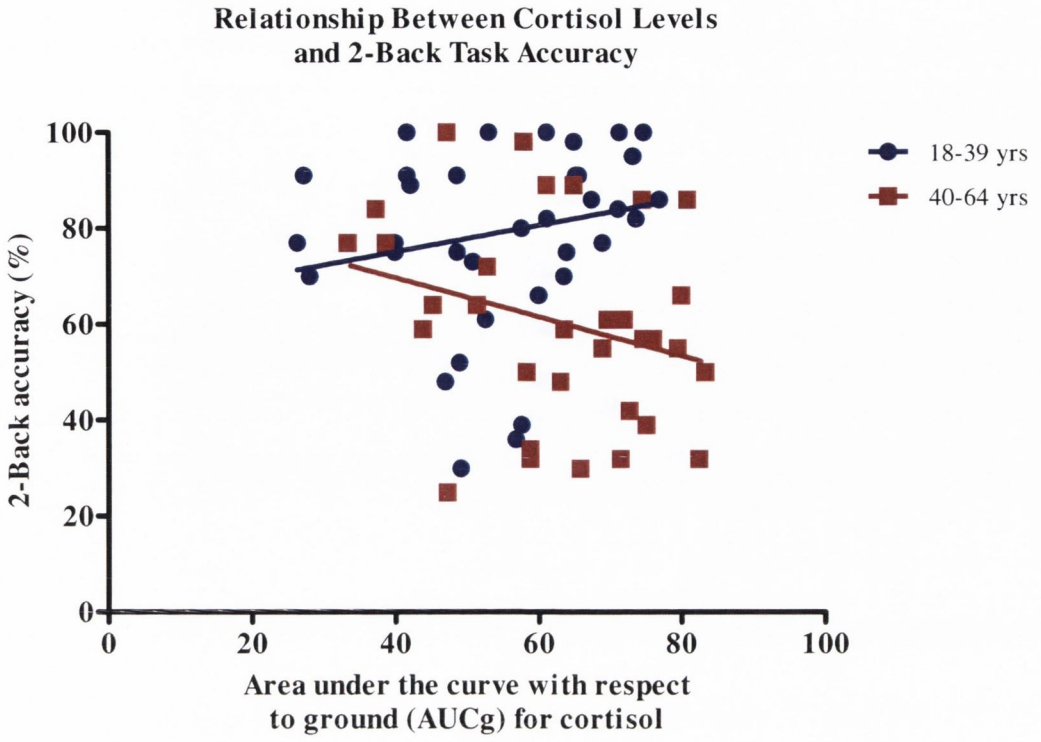

Figure 4.9: The relationship between cortisol levels (expressed as AUCg) and percentage accuracy on the 2-Back task for each age group.

4.5 Discussion

In this chapter, associative memory and working memory performance were examined in relation to cortisol levels in a subgroup of participants who took part in the large lifespan study (N = 83). Participants were divided into two separate age groups based on a clear division in task performance, which emerged from the lifespan study between those in the 20's and 30's, and those in the 40's and 50-64 age groups. Cortisol levels over the test session were examined and a series of multiple regression analyses were carried out to ascertain whether or not cortisol levels could contribute significantly to a predictive model of task performance, accounting also for IQ levels.

The main findings are as follows:

1. Cortisol levels did not increase significantly across the testing session in either group.
2. There was evidence of a negative relationship between total cortisol output over the testing session, and performance on the Face-Name Pairs task and on the 2-Back task in the middle-aged group.
3. Higher cortisol levels were found to be positively associated with Match-to-Sample recognition accuracy in the younger group only.

4.5.1 The effect of psychological testing on cortisol levels

The hypothesis that mild stress due to psychological testing might cause an increase in cortisol levels during the testing session in the middle-aged group was not supported, as there was no significant change in cortisol levels across the three sample time points in either group. While there was no significant difference in the change in cortisol levels over time between the two age groups, the younger age group exhibited slightly decreasing cortisol levels across the testing session, whereas the older group did show a very slight increase. It is also interesting to note that there was a significant increase in self-reported anxiety levels from pre- to post-testing in the older age group, but not in the young group. It could be argued, however, that this effect is confounded by the fact that the younger group had higher anxiety levels at pre-test than the older group. As the change in cortisol levels across the testing session and between the groups was not significant, we cannot conclude cognitive testing was having a measurable effect on the stress levels of either participant group.

Wright and colleagues (2005) found that during cognitive testing in a group of participants aged 65 to 85 years, salivary cortisol levels increased significantly, and that this increase was inversely related to cognitive performance. The results of the current study do not mimic those of the Wright et al. study in this respect. It must be noted, however, that the cohort sampled in this latter study was older than in the current study, and thus it is reasonable to think that cognitive testing may have been a greater stressor in this older age group. The sample size in that study was also larger (N = 139) than in the current study, allowing for a greater chance of detecting an effect. Lee and colleagues (2004) also found a small but significant increase in cortisol levels over the testing session in their considerably larger sample (N = 967) of 50 to 70 year olds. It is notable, however, that this increase was only found to be related to hand-eye coordination, and not to any of the other cognitive domains tested.

Taking the three cortisol samples together (in the creation of the AUCg metric), it was found that total cortisol output was higher in the middle-aged group than in the younger group. Thus, the possibility exists that anticipation of the cognitive testing session elevated cortisol levels both before and during testing in this group. It is also possible however, that this between group difference reflects a natural increase in cortisol levels with age (Yen & Laughlin, 1998).

4.5.2 The relationship between cortisol, age and memory performance

4.5.2.1 Whole-group analyses

Regression analyses were conducted, first on the sample as a whole, including an indicator variable in the model, the value of which was '0' for young participants and '1' for older participants. The results of these analyses showed an inverse relationship between the interaction of age and cortisol levels, and total Face-Name Pairs learning and recall. Thus, over and above any effect of age on performance, the combination of older age and higher cortisol levels was significantly associated with poorer task performance. The same interaction was also found to be a significant predictor of performance on the 2-Back working memory task, so that a combination of older age and higher cortisol levels was significantly associated with poorer accuracy on the 2-Back task. An inverse relationship between cortisol levels and performance on the Picture-Word Pairs immediate recall task neared significance in the group as a whole. Cortisol was also found to be a significant predictor of performance on the Match-to-Sample delayed recognition task, but in this case, the relationship was positive. It seems that this effect is driven by the younger age

group, as a negative association between the age group by cortisol interactive term, and performance, neared significance. Cortisol levels were not found to be predictive of performance on any of the other task variables for the group as a whole.

That an effect of the interaction between age and cortisol on performance emerged on the Face-Name Pairs task and the 2-Back working memory task is interesting, especially given that in the lifespan study the 40-64 year olds were found to be the most impaired on these tasks. While the majority of studies have investigated declarative memory performance in relation to cortisol, there is evidence also of an inverse relationship between acute cortisol elevations and working memory performance (Lupien, Gillin, & Hauger, 1999; Young et al., 1999), with performance on the N-Back task specifically shown to be affected by social stress-induced elevations of cortisol (Qin et al., 2009; Schoofs et al., 2008). To our knowledge no longitudinal or cross-sectional studies of aging have examined the relationship between cortisol and performance on working memory tasks such as the N-Back task. However, both the Li et al. (2006) and Lee et al. (2004) have reported negative associations between high cortisol levels in aging and performance on the Trail-Making Test, which also probes executive functioning.

It is our understanding that, as yet, no one has examined the effect of cortisol elevations or stress on Face-Name Pairs task performance specifically. As hippocampal-associated memory measures, including paired-associates learning (Wright et al., 2005) have been shown to be susceptible to cortisol-induced impairments with age, our results extend the current literature to show a relationship between age, cortisol and performance on an ecologically valid test of associative memory. This result is further supported by the finding of an effect of cortisol on Picture-Word associative recall that approached significance.

4.5.2.2 Analyses of each age group separately

When regression analyses were conducted on the two age groups separately, no significant effect of cortisol on Face-Name Pairs total score or 2-Back accuracy could be observed. However, cortisol was found to be negatively associated with the degree of improvement across Face-Name Pairs learning blocks made by the 40- 64 group. No relationship existed between cortisol and improvement scores in the younger group. Thus, it seems that the higher the cortisol levels in this middle-aged group, the smaller the degree of improvement

in recall scores with repeated exposure, again suggesting that higher cortisol levels may interfere with the ability to successfully encode the Face-Name Pairs in this group.

The finding of a significant positive relationship between Match-to-Sample recognition accuracy is interesting as there were no age-related performance decrements found on this task in Chapter 3, though individuals in the 40+ age group did commit more false positives than their younger counterparts. The suggestion that the positive effect of cortisol on performance in the whole group was driven by the younger participants was largely confirmed when regression analyses were carried out for each age group separately. The regression model for the 40-64 group was discarded as it was found to explain less than 1% of the variance in performance for this group. The positive effect of cortisol on performance in the younger group, however, was found to be highly significant. As accuracy levels on this task overall were low, it is possible that higher cortisol levels were beneficial in the younger participants, when faced with the high difficulty of the task. This is somewhat supported by the aforementioned evidence that higher cortisol levels resulting from cognitive challenge may be beneficial in younger participants (Kukolja et al., 2008).

A second possibility is that higher cortisol levels in the younger group conferred an encoding benefit during the initial Match-to-Sample task. This relationship may have been masked by a ceiling effect on the initial working memory maintenance task in both groups, but may have become evident at delayed recognition, when the task was substantially more difficult, and also more episodic in nature. Both the findings of the Kukolja study and more general reports in the literature of cortisol enhancing encoding/consolidation of material (e.g. Abercombie et al., 2003; Buchanan et al., 2001), lend some support to this hypothesis.

4.5.3 Weaknesses and strengths of the regression analyses

The results from the regression analyses of each age group separately should be interpreted with caution. These separate regression analyses were conducted in order to determine whether there existed a different underlying relationship between cortisol and cognitive performance in the young group compared with the middle-aged group. This hypothesis was largely unsupported, as there were few marked differences between the groups. In dividing a sample in this way, sample size is halved and thus there is an inherent loss of power to detect an effect, especially when using a tool such as multiple regression analysis.

The whole group regression analyses probably offer the most useful insight into any relationship between cortisol, age group and task performance. The inclusion of the dummy variable for age, and the interaction term, in these analyses, allowed us to address the possibility that those with high cortisol levels in the middle-aged group exhibited significantly poorer task performance, further to any main effects of age group and cortisol levels on performance in the group as a whole. This was indeed found to be the case for Face-Name Pairs task performance and 2-Back task performance. These results add to the current literature by suggesting that an inverse relationship between cortisol and associative- and working memory performance might exist in a middle-aged sample.

Furthermore, when predicting performance on the associative memory measures, our regression model was able to account for over 60% of the variance in task performance in the sample. The percentage of variance explained was about 40% for the working memory tasks. These results suggest that the variance in associative memory performance in a lifespan cohort can be quite well explained by age, IQ and cortisol levels. Multiple regression analysis is also a useful tool in that it allows us to show the effect of one particular predictor variable on the outcome variable, when the other predictors are held constant. Thus our results show that any significant effect of an interaction between cortisol and age on task performance is independent of predicted IQ levels.

On a cautionary note, our interpretation of the associations found between cortisol, memory performance and age group, is clouded somewhat by the finding that the middle-aged group had slightly higher cortisol levels overall, compared with the young age group. Thus the possibility exists that the alleged interactions could reflect a relationship between cortisol and performance simply when hormone levels are higher as opposed to lower, and may not be related specifically to age group.

4.5.4 Outstanding methodological issues and future directions

As already mentioned, our small sample size was a limitation in both detecting effects and in interpreting them when found. Unfortunately it was not logistically possible to examine cortisol levels in the entire sample from the lifespan study. It would be useful, therefore, to increase the current sample size in order to increase the possibility of detecting further effects that may be present but that were missed in this sample.

Recently, neuroendocrine research has shown that changes in the cortisol awakening response (CAR) and the diurnal cortisol rhythm, along with an altered response to HPA axis challenge (assessed using the DEX/CRH test) are associated with cognitive dysfunction in later life (Kalmijn et al., 1998; Wolf et al., 2005). Furthermore, altered diurnal patterns of cortisol secretion have also been found in AD patients (Giubilei et al., 2001). An interesting follow-on from this study would thus be to investigate the relationship between performance on the same tasks and diurnal cortisol patterns or CAR in a similar sample. This would also help to determine whether the results from the current study reflect an association between basal cortisol levels and memory performance, or between memory and cortisol levels modulated by cognitive testing stress or other immeasurable stressors that were present on the particular testing day in question. While measures of state anxiety were included in our study, it would be useful in future studies to include questionnaires probing exposure to recent stressors and life stress in general. This would enable us to discern the impact of inter-individual differences such as these on the relationship between cortisol and cognition in this model of aging.

A considerable effort was made in this study to control for factors which might unduly influence cortisol levels. Accordingly, all participants were testing in the afternoon to control for the effect of circadian fluctuations on cortisol levels. Oral contraceptive use/ hormone replacement therapy was also taken in account. In addition, participants were asked to refrain from eating, drinking anything except water, or smoking for the hour before the testing session, so as to minimise any acute elevations in cortisol levels due to these variables. However, we did not discriminate between smokers and non-smokers in this study. This might be a consideration in any future studies, as there is evidence that smokers have higher daily cortisol levels than non-smokers (Steptoe & Ussher, 2006).

Chapter 5

The processing of emotional stimuli in aging: effect on memory performance and association with cortisol levels

5.1 Summary

This chapter explores how the use of faces conveying different expressions of emotion can affect associative- and working memory in young adulthood and middle-age. It also examines the basic response to emotional faces via a simple emotion judgment task. Finally, the possible influence of cortisol levels on emotion-processing is investigated.

5.2 Introduction

5.2.1 Emotion-cognition interactions in aging

There is evidence that as people age, they focus more and more on their internal emotional state and that their memories are increasingly driven by their own feelings (Mather 2004). This often results in enhanced memory for semantic information but a reduction in memory for contextual details (Mather, Johnson & De Leonardis, 1999). Studies have also shown that compared with young adults, older adults are more likely to selectively process emotional information in their environment than neutral information. Carstensen and Turk-Charles (1994) tested paragraph recall in a group of participants who ranged in age from 20 to 83 years. Though the paragraph contained approximately equal amounts of neutral and emotional information, the amount of emotional information that was recalled at later testing increased proportionately with age. There is also evidence that source memory can be improved in older adults by attaching emotional significance to the information to be remembered (Rahhal, May, & Hasher, 2002). One theory which has been put forward to explain these findings is the socioemotional selectivity theory.

5.2.2 Socioemotional Selectivity Theory

The socioemotional selectivity theory (Carstensen, Isaacowitz, & Charles, 1999) is a lifespan theory that is based on time-relevant appraisal and goal setting. The focus of the theory is on the motivational consequences of the perception of time in relation to age. According to the theory, when time is perceived as being lengthy or open-ended, the primary motivation for individuals is the pursuance of information. This typically occurs in youth, where the motivation is to gather as much information as possible, experience new things, form relationships. However, as people age and they perceive time to be increasingly limited, their motivational bias is shifted to the achievement and maintenance of emotional satisfaction. In relation to the mechanisms of cognitive change with age, the theory holds that motivational changes also merit investigation in addition to more measurable physiological changes, as they may help to give a more rounded view of the mechanisms underlying age-related cognitive change.

Two main postulates have arisen out of this theory with respect to cognition and aging: 1) older adults should allocate greater attentional resources to emotion-laden information, particularly that which is positive in nature, and engage in selective processing of this information; and 2) older adults should invest more time and resources in emotional regulation, and thus regulation should become more automatic for older than for younger

people (Carstensen et al., 1999). Evidence to support the first prediction has already been outlined above. In addition, there is also support for the latter prediction. Older adults report that they focus more on regulating their emotions and rate their success in doing so as being better than younger adults (Gross et al., 1997; Lawton et al., 1992). Furthermore, when participants' moods were sampled repeatedly over the course of a week, it was found that negative emotions were inclined to persist much longer in younger individuals than in older individuals (Carstensen et al., 2000).

5.2.3 Positivity effects in aging - attention and memory

Attention

Consistent with the socioemotional selectivity theory, there is evidence that older adults bias their attention toward positive, rather than neutral and negative information. A study using the dot probe task in younger and older adults found that compared with younger adults, older adults were slowest to respond when the dot was placed beside negative faces compared with neutral, and quickest to respond when the dot was beside positive faces compared with neutral (Mather & Carstensen, 2003). Response to emotional pictures was also investigated in an fMRI study. Young and older participants underwent scanning while viewing positive, neutral or negative pictures. Both younger and older adults showed greater amygdala activation while viewing emotional rather than neutral pictures, but for older adults activity was greater when viewing positive than negative pictures, whereas no such relationship was found in younger adults (Mather et al., 2004). A recent study found that viewing negative rather than positive images activated the VLPFC to a greater extent in younger individuals, while the opposite was true for older individuals (Leclerc & Kensinger, 2008).

There is some evidence, however, that older adults are not attentionally biased toward positive rather than negative stimuli. In a visual search paradigm, both older and younger adults were fastest to detect emotional faces in an array of neutral faces when the emotion displayed was anger, rather than sadness or happiness (Mather & Knight, 2006). The results of the above studies suggest that older adults may attend to, but not actively process, negative information. Instead, they may down-regulate it. Interestingly, younger adults show reduced amygdala activation in response to negative pictures, when explicitly instructed to down-regulate negative emotion (Ochsner et al., 2004).

Memory

There is also evidence that older adults have better memory for positive stimuli. Charles, Mather and Carstensen (2003) explored memory for positive, negative and neutral images in young, middle-aged, and older adults. Participants viewed the images, and then both recall and recognition were tested following a distractor task. They found that while all groups recalled significantly more positive and negative images than neutral, the middle-aged and older participants recalled significantly more positive images than negative, with no effect of valence on the younger group on this recall task. In the recognition memory task, however, younger participants recalled significantly more negative images than positive or neutral, with no valence-specific effects emerging in middle-aged or older adults (Charles et al., 2003).

A recent study by Kensinger (2008) of young and older adults tested participants' memory for positive, neutral, and negative emotionally arousing and non-arousing words. They found that while the young group remembered significantly more negative words compared with positive or neutral, the older adults remembered significantly more positive words, compared to negative and neutral. However, in a study carried out by Leigland, Schulz and Janowsky, (2004) both younger and older adults showed a positive bias when recalling previously studied words, albeit the bias was more marked in the older group. These effects were only evident at delayed and not at immediate recall.

While the majority of studies to date have examined the interaction between aging, emotion and episodic memory, there is evidence that aging can affect working memory for emotional stimuli. Using a delayed-response maintenance task, Mikels and colleagues (2005) showed that while working memory for purely visual information was impaired in older adults compared with a young group, working memory for emotional information using this task was unimpaired. Furthermore, an age by valence interaction emerged, with older adults exhibiting superior performance on positive relative to negative emotion trials, and younger adults showing the converse. It may be the case that working memory for emotionally salient stimuli maybe somewhat more resistant to age-related decline than working memory for neutral information. However, it is noteworthy that the latter study used emotive pictures (for example, a pit-bull terrier, a snake) and instructed participants to think about the intensity of the emotion elicited in them by each photograph. It would be interesting (and indeed the authors themselves raise this point) to see if these findings could be extended to working memory paradigm, whereby the participants are not required

to experience the emotion themselves, but rather merely view stimuli that have some emotional significance or relevance for social functioning, such as facial expressions of emotion. A study by Kensinger and Corkin (2003) employed an N-Back paradigm using neutral and negative faces, to investigate working memory performance in healthy young adults. They found no effect of emotion on task accuracy but a slight effect of reaction time, whereby participants took longer to respond when faces were negative compared with neutral in expression, suggesting that emotional salience may interfere with working memory performance.

5.2.4 Emotional face processing in aging

Faces provide strong socioemotional information. Facial expressions are typically universally understood and often supersede verbal communication (Ekman, 1993). The ability to perceive other people's mood is essential to optimum social functioning and is related to adequate social adjustment (Engelberg & Sjoberg, 2004). There is evidence that negative faces capture attention more rapidly than neutral or positive faces (Fox et al., 2000). However, there is also evidence that negative expressions can interfere with task performance when processing of other facial features is required, perhaps because they pull attentional focus (Eastwood, Smilek, & Merikle, 2003). Happy faces, on the other hand, seem to be remembered more often than neutral or negative faces (D'Argembeau et al., 2003; Shimamura, Ross, & Bennett, 2006). Happy expressions are also more easily identified than other facial expressions (Kaufmann & Schweinberger, 2004; Leppanen & Hietanen, 2004).

Some researchers have proposed that a preference for happy expressions reflects reward-based processing. A recent study by Tsukiura and Cabeza showed that memory for face-name associations was better when faces were happy rather than neutral in expression. Futhermore, activation of the OFC and hippocampus, and functional connectivity between the two areas, was stronger during successful encoding of happy face-name pairs than of neutral (Tsukiura et al., 2008). There are several aspects to this study, however, that must be noted. Firstly, recall was tested by presenting the names and asking participants to respond by pressing a key to indicate whether the name: 1) corresponded to a happy expression; 2) corresponded to a neutral expression; 3) was a new name; or 4) corresponded to a face for which the expression could not be recalled. Due to the nature of the recall task and the fact that participants were required to try and learn 240 face-name pairs each presented only once for a duration of 2.5 seconds, it is highly likely that these

results reflect enhanced recall of happy facial expressions, rather than that happy expressions conferred a memory benefit for those particular faces over neutral ones. There is also evidence that the influence of facial expression on memory is actually more pronounced when attention is not specifically drawn to the processing of the facial expression, such that expression is allowed to modulate memory in an automatic, and in some cases perhaps, unconscious way (D'Argembeau & Van der Linden, 2007).

The social/emotional relevance of faces makes them a good tool with which to investigate memory changes in aging, particularly with reference to the sociemotional selectivity theory. A number of studies have explored the difference between young and older adults in their memory for emotional faces. There is some evidence that recognition memory for negative faces is impaired in older individuals compared with young (Leigland et al., 2004; Mather et al., 2003). However, there is also evidence older adults are impaired in recognising a particular facial expression as being negative to begin with (Orgeta & Phillips, 2008; Ruffman et al., 2008), which would make for a difficulty in interpreting any seeming effect of facial expression on memory. Keightley and colleagues (2006) conducted a study to investigate age-related differences in social and emotional processing. They found no differences between younger and older adults on self-reference tasks, identifying emotional words, or in theory of mind. In line with other findings, older adults exhibited impairments in recognising specific facial expressions of sadness, compared with younger adults. When asked to judge emotional valence there were no differences in accuracy between young and older individuals, however, older adults were significantly slower in responding to negative faces than younger adults. Overall accuracy for both groups was highest when viewing positive and negative faces rather than neutral. In addition, both young and older adults were quickest to identify positive facial expressions overall. However, younger adults were slower to identify neutral faces compared with positive, than negative faces compared with positive, whereas older adults were equally slowed by neutral and negative faces, compared with positive. The authors suggest that younger adults may be slowed by task difficulty (judging neutral faces), but that older adults may be slowed by both task difficulty (neutral faces) and emotion (negative faces; Keightley et al., 2006).

Older adults may recruit different areas of the brain than younger individuals when performing tasks with emotional faces. Successful emotional face processing has been thought to involve the amygdala, as well as other medial temporal lobe areas and the

prefrontal and orbitofrontal cortices (Adolphs et al., 1994, Damasio, 1997; Sergerie, Lepage, & Armony, 2005; Tsukiura et al., 2008). Less research, however, had been devoted to examining age differences in activation for emotional faces. Gunning-Dixon and colleagues conducted an fMRI study during which older and younger adults viewed faces portraying a variety of facial expressions, including neutral. Participants engaged in alternating blocks of emotion discrimination and age discrimination tasks. It was found that while younger adults activated visual, frontal and limbic regions during the emotion discrimination task, older adults activated frontal, parietal and temporal regions. Crucially, when activation patterns for the emotion discrimination task were compared with those from the age discrimination task, it was found that younger adults activated the amydgala and limbic-temporal regions, whereas older adults activated left frontal regions (Gunning-Dixon et al., 2003). A recent study by Fischer, Nyberg & Backman (2010) found that young adults recruited the amygdala and hippocampus to a greater extent than older individuals during the successful encoding of fearful faces, whereas older individuals showed greater activity in superior frontal gyrus and insular cortex. As increased recruitment of frontal areas with age has been reported in the cognitive aging literature (e.g. Cabeza, 2002), the above results may indicate that this finding may extend to emotion processing also.

5.2.5 Negative findings with respect to the changes in emotional memory with age

Though there is undoubtedly support for a change in emotional memory with age, it must also be noted that some individual studies have produced negative findings in this regard (Comblain, 2004; D'Argmembeau & Van der Linden, 2004; Kensinger et al., 2002). Furthermore, a recent meta-analysis conducted by Murphy and Isaacowitz (2008) of age differences in the preference for emotional information in memory and attention, found few age differences overall. The only differences which emerged between the age groups were in the effect of emotional salience on recognition memory and negativity preferences in recognition memory, for which younger adults exhibited significantly larger effect sizes. No age differences emerged on attention or memory recall tasks, or on tests of a positivity preference. As the authors themselves suggest, there may be differences arising from the use of different measures (attention, recognition, recall) which reduces the likelihood of detecting robust effects in a meta-analysis of different task and stimulus types. Thus overall age differences may be subtle, and very much dependent on the specifics of the individuals tasks employed.

5.2.6 Aims of the current study in the context of the literature

A relatively consistent element in the design of the studies reviewed in this introduction is that stimuli were interleaved, that is, participants almost always viewed differently valenced stimuli within the same task. Given the evidence for attention orienting toward emotional stimuli over neutral stimuli, one could argue that any effect of emotion on subsequent memory could stem purely from the fact that emotional stimuli capture attention to a greater degree. Despite this, hardly any of the studies of memory have addressed this concern, relying purely on measures of recognition and recall after initial encoding. An exception to this is the Leigland et al. (2004) study, which found no effect of emotion when immediate recall was tested but an effect at delayed recall, which would suggest that consolidation or retrieval processes were in some way altered by emotional valence. There is a need to examine differences in task performance when all the stimuli are of one emotional valence and to compare the results to task performance using stimuli of a different valence. In this manner, any inherent bias in memory processing due to attentional orienting toward emotional stimuli in general, or toward either positive or negative stimuli specifically, should be eliminated. This should help to disentangle the effect of emotion on attention from an effect on memory.

A general finding in the cognitive aging literature is that there is very little research examining memory in middle-aged individuals. This is true also of changes in emotional memory with age, with most researchers preferring to contrast an older group (typically greater than 60 years of age) with a younger age group (typically under 30 years of age). It is important to investigate emotion processing in midlife also. There is evidence that middle-aged adults use optimism as a mood-regulating strategy to a greater extent than young adults (Chapman & Hayslip, 2006). Furthermore, as earlier reported, there is also evidence of a difference in emotional memory between middle-aged individuals and young individuals (Charles et al., 2003). These results point to the possible emergence of a positivity effect in midlife which merits further investigation.

There is a tendency for researchers to rely on recognition measures to make inferences about the effects of emotion on memory, with fewer studies testing memory by means of cued- or free-recall. There is also a need to focus to a greater extent on memory measures which require greater self-initiated processing, such as associative-recall. In addition, most of the current research has focused on the effect of emotion on episodic memory, with quite a gap existing in the literature with regard to emotion effects in working memory.

In light of the evidence that glucocorticoids can affect memory for emotional material (see Chapter 1, section 1.11) and our findings from Chapter 4 that cortisol may be differently related to cognitive performance in young and middle-aged individuals, it would be interesting to examine cortisol levels in relation to emotional memory performance in both age groups.

The present study aims to address these issues. The results of the lifespan study (Chapter 3) showed associative memory and working memory impairments emerging in the 40s. Young participants (aged in their 20s) will be compared with middle-aged participants (aged in their 40's) on similar tasks using happy, neutral and angry faces. Participants will be randomised into one of three groups so that they either perform the Face-Name Pairs and N-Back task with all happy faces, or all neutral faces, or all angry faces. In addition, their response to, and accuracy in identifying, happy, neutral and angry facial expressions will also be assessed by means of an emotion judgment task (similar to that used by Keightley et al., 2006).

In a second focus of the study, salivary cortisol will be sampled throughout the test session to investigate any interaction between age, emotion processing and cortisol levels.

5.2.7 Hypotheses

1. If older adults exhibit a positivity effect in memory, and if it is evident as early as middle-age, then age differences in associative memory and working memory performance should be smallest when happy faces are used and largest when angry faces are used.
2. In the Face Judgment task, participants should show increased accuracy and decreased response times when judging happy faces compared with angry or neutral faces. Older adults should be slowed to a greater extent than younger adults by angry faces, manifesting as increased reaction time when responding to angry faces compared with happy or neutral.
3. Cortisol levels should be differently related to memory and processing of emotional stimuli than of neutral stimuli.

5.3 Methods

5.3.1 Participants

74 participants took part in this study. Recruitment procedures and inclusion/exclusion criteria were identical to those outlined in Chapter 3 section 3.2.1 and Chapter 4 section 4.2.1. They were divided into two age groups; those in their 20's and those in their 40's. The 20's group consisted of 37 individuals (9 male; mean age = 24.45, SD = 2.75, range = 20-29). The 40's group consisted of 37 individuals (13 male; mean age = 45.00, SD = 2.75, range = 40-49). Within each age group, participants were further randomly assigned to one of three facial expression conditions: happy, neutral, or angry. This meant that in the case of the Face-Name Pairs task and the N-Back task, participants were given the task with all happy, all neutral or all angry faces, depending on which experimental condition they had been assigned to.

Note: In the case of the Face Judgment task, however, participants were not assigned to a facial expression condition, as facial expression was manipulated within the task.

This effectively created 6 separated experimental groups: 3 facial expression groups aged in their 20's; and 3 facial expression groups aged in their 40's.

The 20's group that viewed all happy faces consisted of 12 individuals (3 male; mean age = 24.42, SD = 0.73, range = 20-28). The 20's group that viewed neutral faces consisted of 13 individuals (4 male; mean age = 25.30, SD = 0.74, range = 20.29). The 20's group that viewed angry faces consisted of 12 individuals (2 male; mean age = 23.50, SD = 0.86, range = 20-28). The 40's group that viewed happy faces consisted of 13 individuals (4 male; mean age = 45.30, SD = 0.74, range = 41-49). The 40's group that viewed neutral faces consisted of 12 individuals (5 male, mean age = 45.41, SD = 0.80, range = 40-49). The 40's group that viewed angry faces consisted of 12 individuals (4 male, mean age = 44.25, SD = 0.83, range = 40-49).

5.3.2 Cognitive Testing

5.3.2.1 General Procedure

Testing took place in the afternoon to minimise diurnal fluctuations in cortisol levels. As per Chapter 4, section 4.3.2.1, participants were instructed to fast for the hour before the testing session and not to smoke.

5.3.2.2 Control Measures

An estimate of premorbid intelligence was obtained using the National Adult Reading Test (Nelson, 1982; described in Chapter 2 section 2.8). Self-reported mood and well being was recorded using the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983; described in Chapter 2 section 2.7.1). Participants also completed the trait form (T-Anxiety) of the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983). This is a self-report mood questionnaire, and was described in detail in Chapter 2 section 2.7.2.

5.3.2.3 Emotional Face-Name Pairs task

This task was described in Chapter 2 section 2.5.2.

5.3.2.4 N-Back Task (0-Back, 1-Back and 2-Back): Emotional Faces

This task was described in Chapter 2 section 2.4.2.

5.3.2.5 Face Judgment task

As described in Chapter 2, section 2.6.

5.3.3 Salivary Cortisol Sampling and Task Order

Three saliva samples were taken over the course of the testing session: Time 1 (immediately prior to starting the cognitive battery); Time 2 (over mid-way through the session); Time 3 (immediately after the session). From these three samples, the area under the curve with respect to ground (AUCg) for the session was calculated, using the formula stated in Chapter 4, section 4.2.2. This metric was then used for subsequent statistical analyses.

The order of tasks and sampling is outlined in Table 5.1.

Order	Task/Measure	Time (approx.)
1	Information leaflet and consent form	0 mins
2	Cortisol Time 1	3 mins
3	Face-Name Pairs Learning and Recall	5 mins
4	National Adult Reading Test (NART)	15 mins
5	Hospital Anxiety and Depression Scale (HADS)	17 mins
6	Trait Anxiety Inventory	20 mins
7	Face Judgment Task	25 mins
8	Cortisol Time 2	28 mins
9	Face-Name Pairs Delayed Recall and Recognition tasks	35 mins
10	N-Back Task (0-, 1-, and 2-Back conditions)	47 mins
11	Cortisol Time 3	50 mins

Table 5.1: Running order of test battery

5.3.4 Statistical Analyses

Analyses were carried out using SPSS (version 16) for PC. Data was expressed as mean ± standard error of the mean (SEM), unless otherwise stated. The critical α value was set at .05. All statistical tests were two-tailed. Two – way Analysis of Variance (ANOVA) was the main statistical test utilised. Main effects and interactions were reported, and where appropriate, post hoc tests and simple effects analyses were carried out. Where performance was repeated across identical trials, a mixed between-within-subjects ANOVA (Tabachnick and Fidell, 2009) was used to compare performance across repeated trials and between groups. Where sphericity could not be assumed, Greenhouse-Geisser values were reported. This is denoted in the results section by G.G. written in parentheses after the relevant statistic. Preliminary checks were made prior to conducting all analyses to ensure the underlying data complied with assumptions of normality, homogeneity of variances, homogeneity of regression slopes and reliable measurement of the covariate,

where applicable. Where parametric assumptions were violated and transformation of the data did nothing to rectify this, non-parametric tests were employed. Chi-squared analyses were used to explore the association between categorical variables. For the multiple regression analyses, the variables of interest were entered into the model using the forced entry mode of model building. The use of a 'dummy' or 'indicator' variable was employed to explore the effect of age group on the relationship between various task performance measures and cortisol levels. Preliminary checks were carried out to ensure that no assumptions were violated prior to running the analysis. These included: no perfect multicollinearity; homoscedasticity; independent errors; and normal distribution of the residuals. These assumptions were checked by inspecting residual plots, the Durbin-Watson test for independent errors, examining the correlation matrix and the variance inflation factor (VIF). Any outliers (mean ± 2 SDs) that were having undue influence on the model were removed.

5.4 Results

5.4.1 The effect of age group and facial expression on associative memory, working memory, and face judgment ability.

5.4.1.1 Education, predicted IQ, HADS anxiety and depression scores

Two-way ANOVAs were carried out to determine whether there were significant differences in any of the above control variables across both age group (20's versus 40's), and facial expression (happy, neutral, or angry).

Education

There was no significant main effect of either age group, $F(1, 68) = 3.57$, $p > .05$, or facial expression, $F(2, 68) = 1.426$, $p > .10$, on the number of years spent in formal education. Furthermore, there was no significant interaction between age group and facial expression, $F(2, 68) = 0.01$, $p > .10$.

Predicted IQ

There was no significant main effect of age group, $F(1, 68) = 0.19$, $p > .10$, or facial expression, $F(2, 68) = 1.53$, $p > .10$, on predicted IQ scores. There was no significant interaction between age group and facial expression, $F(2, 68) = 0.51$, $p > .10$.

HADS anxiety and depression scores

Neither anxiety nor depression scores differed significantly between age groups (anxiety; $F(1, 68) = 1.49$, $p > .10$, depression; $F(1,68) = 2.03$, $p > .10$), or facial expression (anxiety; $F(2, 68) = 0.71$, $p > .10$, depression; $F(2, 68) = 1.04$, $p > .10$). There were no significant interactions between the independent variables in the case of either dependent variable ($Fs < 1$, $ps > .10$).

Trait Anxiety

There was no main effect of age group, $F(1, 68) = 0.00$, $p > .10$, or facial expression, $F(2, 68) = 0.64$, $p > .10$, on trait anxiety scores. There was also no significant interaction between age group and facial expression, $F(2, 68) = 0.12$, $p > .10$.

Age Group	**20's**			**40's**		
Facial Expression	**Happy**	**Neutral**	**Angry**	**Happy**	**Neutral**	**Angry**
Education	17.25 (± 0.86)	18.46 (± 0.80)	17.58 (± 0.38)	15.92 (± 0.63)	17.33 (± 0.90)	16.33 (± 1.07)
Predicted IQ	113.28 (± 3.51)	111.83 (± 4.21)	108.50 (± 4.95)	118.75 (± 1.51)	118.66 (± 1.73)	103.25 (± 4.90)
HADS anxiety	7.08 (± 1.10)	7.15 (± 1.12)	6.25 (± 1.10)	5.23 (± 0.91)	7.15 (± 1.12)	5.42 (± 1.11)
HADS depression	2.83 (± 0.77)	3.15 (± 0.70)	1.67 (± 0.55)	3.46 (± 0.83)	3.15 (± 0.70)	3.17 (± 0.82)
Trait Anxiety	39.00 (± 2.53)	38.15 (± 3.08)	36.08 (± 2.04)	37.69 (± 1.92)	39.25 (± 2.18)	36.17 (± 2.72)

Table 5. 2: Education, predicted IQ, and scores on affective rating scales (values expressed as means ± SEM)

5.4.1.2 The distribution of gender across age group and facial expression

Owing to the small number of males in the sample, Chi-squared tests were carried out to determine whether the ratio of males to females was the same across a) age group, and b) facial expression (NOTE: log-linear analysis was not possible due to the fact that expected frequencies were less than 5 for half of the cells). The proportion of males to females was not found to differ statistically between the two age groups, X^2 (1) = 1.03, $p > .10$. Gender was also proportionately distributed across the three levels of facial expression, X^2 (2) = 0.76, $p > .10$.

5.4.1.3 The effect of age group and facial expression on Face-Name Pairs learning and recall

A repeated measures two-way ANOVA was carried out to determine the effect of age group and facial expression on Face-Name Pairs learning and immediate recall performance across the 4 blocks. There was a significant main effect of age group on Face-Name performance, $F(1, 66) = 4.90$, $p < .05$, with those in their 20's performing significantly better than those in their 40's. There was no significant main effect of facial expression, $F(2, 66) = 0.94$, $p > .10$, and no interaction between age group and facial

expression, $F(2, 66) = 0.18$, $p > .10$. There was no significant interaction between age group and Face-Name block, nor between facial expression and face-name block ($Fs < 2$, $ps > .10$). Finally, the triple interaction of block x age group x facial expression was not significant, $F(5.38, 180.36) = 0.19$, $p > .10$ (G.G.).

Total Score

A two-way ANCOVA was carried out to ascertain the effect of age group and facial expression on total learning and recall, with years spent in education as a covariate. Education was not found to have a significant effect on the total number of Face-Name Pairs that were successfully encoded and recalled, $F(1, 66) = 2.56$, $p > .10$. There was a significant effect of age group on total recall performance, $F(1, 66) = 5.03$, $p < .05$, partial $\eta^2 = 0.07$, with those in their 20's performing better than those in their 40's (see Table 5.3). There was no significant main effect of facial expression, $F(2, 66) = 0.85$, $p > .10$, and no significant interaction between age group and facial expression, $F(2, 66) = 0.19$, $p > .10$ (see Figures 5.1 – 5.4).

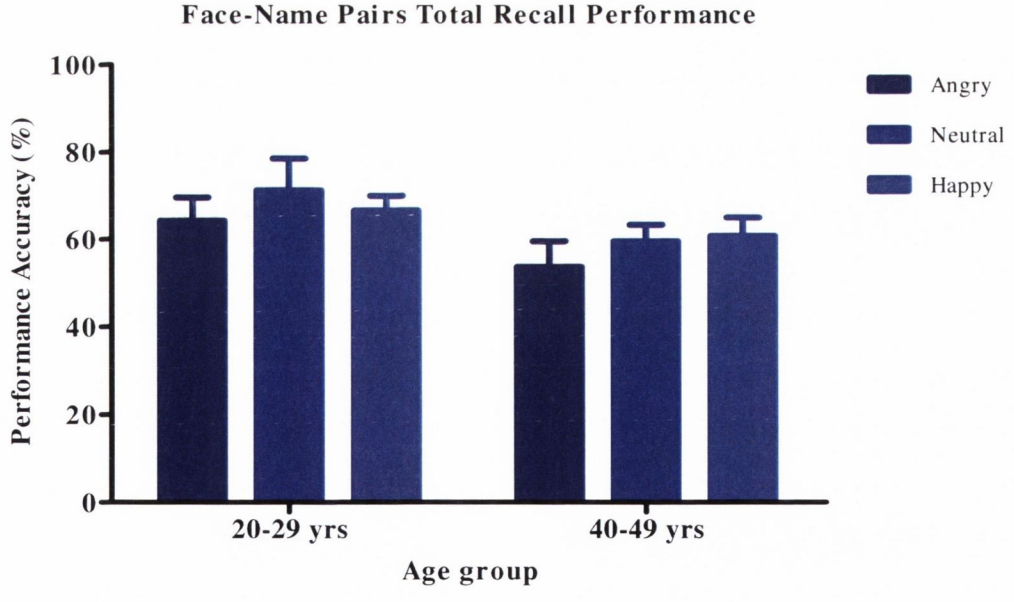

Figure 5.1: Face-Name Pairs total recall performance as a function of age group and the type of facial expression viewed.

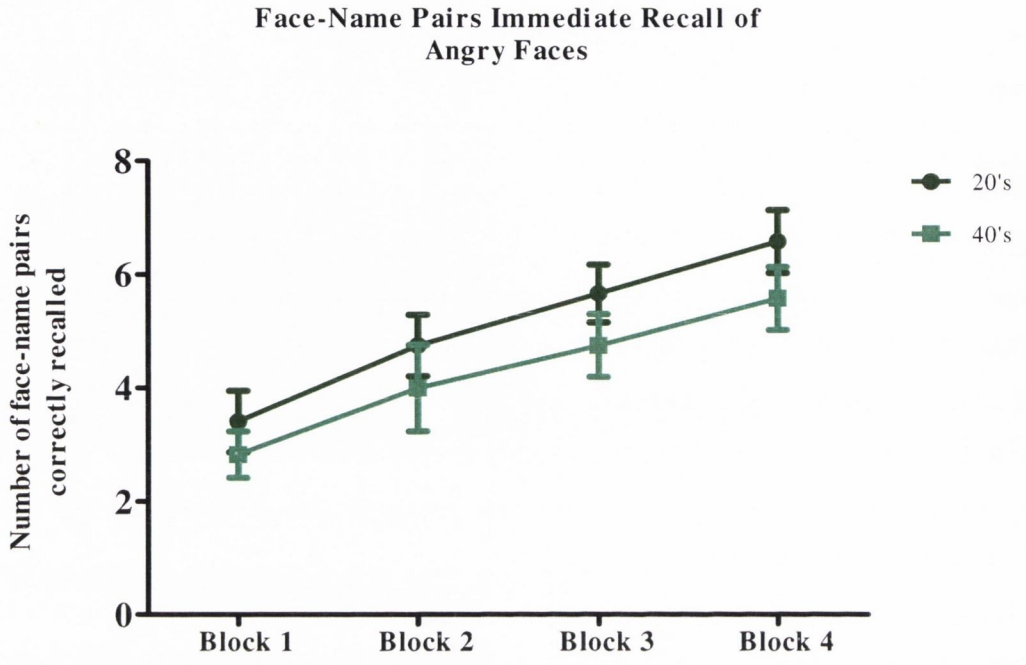

Figure 5.2: Face-Name Pairs task performance across blocks as a function of age group when faces were angry in expression.

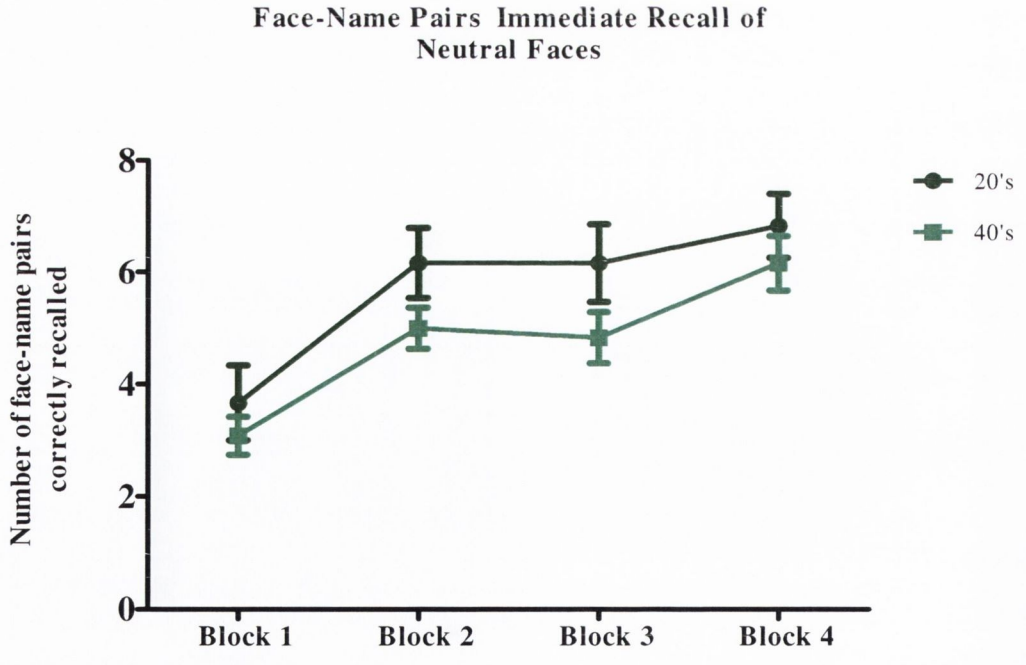

Figure 5.3: Face-Name Pairs task performance across blocks as a function of age group when faces were neutral in expression.

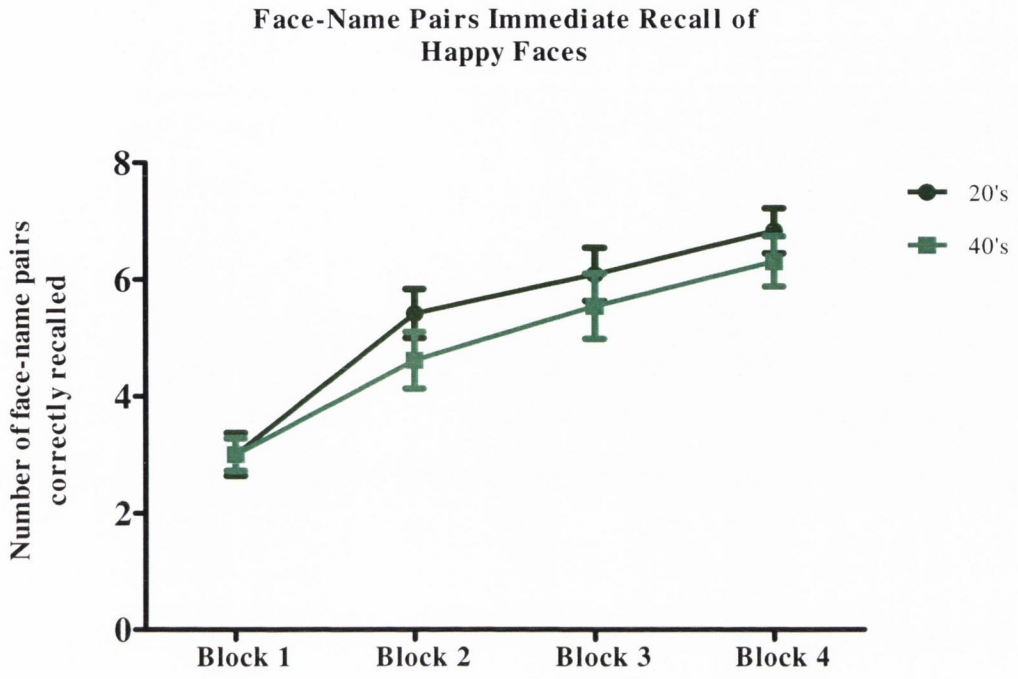

Figure 5.4: Face-Name Pairs performance across blocks as a function of age group when faces were happy in expression.

Improvement Score

There was no significant effect of education on the percentage of improvement in performance from block 1 to block 4, $F(1, 66)= 1.19$, $p > .10$. Once again, there was a significant main effect of age group, $F(1, 66) = 4.45$, $p < .05$, partial $\eta^2 = 0.06$, with the 20's group showing greater improvement across testing blocks, than the 40's group. There was no main effect of facial expression, $F(2, 66) = 0.45$, $p > .10$, and no interaction between age group and facial expression, $F(2, 66) = 0.21$, $p > .10$ (see Figure 5.5).

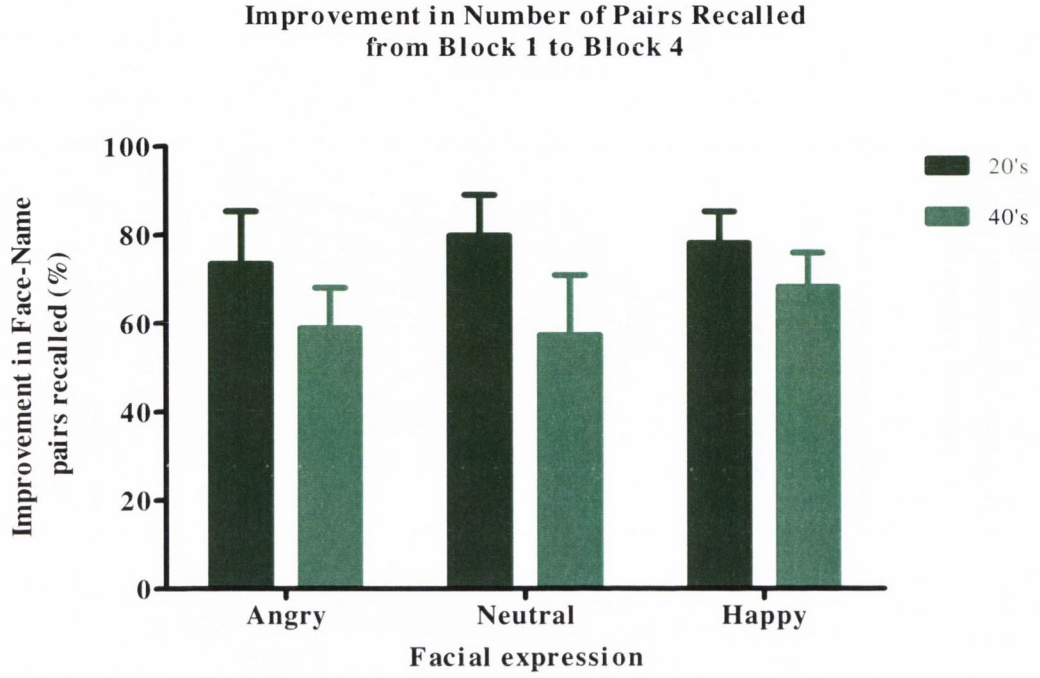

Figure 5.5: The improvement in Face-Name Pairs task performance across encoding blocks as a function of age group the type of facial expression viewed.

Delayed Recall

There was a positive relationship between education and delayed recall performance, $F(1, 66) = 5.42$, $p < .05$. After controlling for the effect of education on performance, there was no significant main effect of age group, $F(1, 66) = 1.15$, $p > .10$, or facial expression, $F(2, 66) = 1.79$, $p > .10$, on performance. Furthermore, there was no significant interaction between age group and facial expression, $F(2, 66) = 0.16$, $p > .10$ (see Table 5.3)

Name Recall

A two-way ANCOVA was carried out to determine the effect of age group and facial expression on name recall performance, controlling for education. There was a positive effect of education on name recall performance, $F(1, 66) = 6.75$, $p < .05$. After controlling for the effect of education on name recall performance, there was no significant effect of age group, $F(1, 66) = 1.08$, $p > .10$, nor a significant effect of facial expression, $F(2, 66) = 1.26$, $p > .10$. Finally, there was no significant interaction between age group and facial expression, $F(2, 66) = 0.34$, $p > .10$ (see Table 5.3).

Name Recognition Accuracy

Education was not significantly related to name recognition accuracy, $F(1, 66) = 0.71$, $p > .10$. There was no main effect of age group, $F(1, 66) = 0.19$, $p > .10$, or facial expression, $F(2, 66) = 1.29$, $p > .10$, on performance. Finally, there was no interaction between age group and facial expression, $F(2, 66) = 0.09$, $p > .10$ (see Table 5.3).

Face Recognition Accuracy

Education was not found to be significantly related to face recognition accuracy, $F(1, 66) = 0.47$, $p > .10$. There was no main effect of age group on performance, $F(1, 66) = 0.57$, $p > .10$. There was no main effect of facial expression, $F(2, 66) = 1.55$, $p > .10$, nor was there a significant interaction between age group and facial expression, $F(2, 66) = 2.17$, $p > .10$ (see Table 5.3).

Age Group	**20's**			**40's**		
Facial Expression	**Happy**	**Neutral**	**Angry**	**Happy**	**Neutral**	**Angry**
Face-Name Pairs Delayed Recall	7.42 (± 0.26)	6.83 (± 0.70)	6.42 (± 0.56)	6.46 (± 0.54)	6.50 (± 0.51)	5.50 (± 0.66)
Name Recall	94.79 (± 1.86)	92.71 (± 3.02)	92.71 (± 2.86)	92.31 (± 3.33)	87.50 (± 3.86)	83.33 (± 4.03)
Name Recognition	98.96 (± 1.24)	94.79 (± 3.04)	95.83 (± 1.78)	97.11 (± 2.07)	93.79 (± 2.41)	93.75 (± 3.60)
Face Recognition	98.96 (± 1.24)	94.79 (± 3.05)	88.54 (± 2.86)	93.27 (± 3.43)	98.96 (± 1.04)	94.79 (± 2.01)

Table 5.3: Performance on Face-Name Pairs delayed recall and recognition trials (values expressed as means ± SEM).

Trait Anxiety and face-name pairs task performance

It is interesting to note that the variable trait anxiety was differently related to task performance depending on the facial expression viewed. There was no correlation between trait anxiety scores and any of the task measures in the groups that viewed happy and neutral faces. However, in the group that viewed angry faces, there was a significant

negative correlation between trait anxiety and total Face-Name Pairs performance (r = -.429, $p < .05$) and between trait anxiety and delayed Face-Name Pairs recall (r = -.494, $p < .05$).

5.4.1.4 The effect of age group and facial expression on working memory performance using an N-Back task

0- Back Accuracy

Due to ceiling effects on this task, it was not possible to carry out an analysis of variance of the effect of age group and facial expression on accuracy. Instead, the distribution of errors was examined, first across age group, and then across facial expression, using a Chi-squared analysis (log-linear analysis was not possible because of a large number of cells with frequencies of under 5). This was in order to see whether the proportion of errors made was different for those in the 20's group compared with those in their 40's, and to see if the errors were related to the facial expression of the stimuli.

Firstly, there was no significant relationship between age group and errors, $X^2(1) = 0.29$, $p > .10$. There was also no significant relationship between emotion and errors, $X^2(2) = 1.77$, $p > .10$.

0-Back Reaction Time

Education was not found to be significantly related to reaction time in the 0-Back task, $F(1, 65) = 0.72$, $p > .10$. There was no main effect of age group on reaction time, $F(1, 65) = 1.27$, $p > .10$, nor was there a significant effect of facial expression, $F(1, 65) = 0.86$, $p > .10$. Furthermore, there was no significant interaction between age group and facial expression, $F(2, 65) = 1.09$, $p > .10$.

In order to make sure that there was no ***motoric or perceptual slowing*** in the older age group, we conducted an independent t test on the pooled 0-Back reaction time data for the 20's group and the 40's group. This revealed no significant difference between the age groups on reaction time in the 0-Back condition, $t(70) = -1.084$, $p > .10$. Thus there appears to be no motoric or perceptual slowing in the older age group with regard to performance on this task (see Table 5.4).

1-Back Accuracy

There was no significant effect of education on 1-Back task performance, $F(1, 67) = 0.25$, $p > .10$. Age group did not have a significant effect on task performance, $F(1, 67) = 0.61$, $p > .10$, nor was there a significant effect of facial expression on task accuracy, $F(2, 67) = 0.34$, $p > .10$. Finally, the interaction between age group and facial expression was not significant, $F(2, 67) = 1.57$, $p > .10$ (see Table 5.4)

Age Group	**20's**			**40's**		
Facial Expression	**Happy**	**Neutral**	**Angry**	**Happy**	**Neutral**	**Angry**
0-Back Accuracy (%)	99.50 (± 0.26)	99.38 (± 0.27)	99.83 (± 0.17)	99.07 (± 0.37)	100.00 (± 0.00)	99.16 (± 0.30)
0-Back Reaction Time (ms)	418.46 (± 13.60)	436.65 (± 19.11)	424.81 (± 16.32)	460.22 (± 19.89)	430.76 (± 30.45)	435.33 (± 17.20)
1-Back Accuracy (%)	99.50 (± 0.36)	98.54 (± 0.67)	99.50 (± 0.26)	98.92 (± 0.43)	99.17 (± 0.38)	98.25 (± 0.83)

Table 5.4: 0-Back accuracy, 0-Back reaction time and 1-Back accuracy (values expressed as means ± SEM).

1-Back Reaction Time

Education was not found to be significantly related to reaction time, $F(1, 67) = 0.26$, $p > .10$. There was no main effect of age group on reaction time, $F(1, 67) = 0.76$, $p > .10$. There was, however, a marginally significant effect of facial expression on reaction time in the 1-Back task, $F(2, 67) = 3.11$, $p = .05$, partial $\eta^2 = 0.08$. Bonferroni pairwise comparisons revealed that participants who viewed happy faces had significantly quicker reaction times than those who viewed faces that were neutral in expression. There was no significant interaction between age group and facial expression, $F(2, 67) = 0.15$, $p > 10$ (see Figure 5.6).

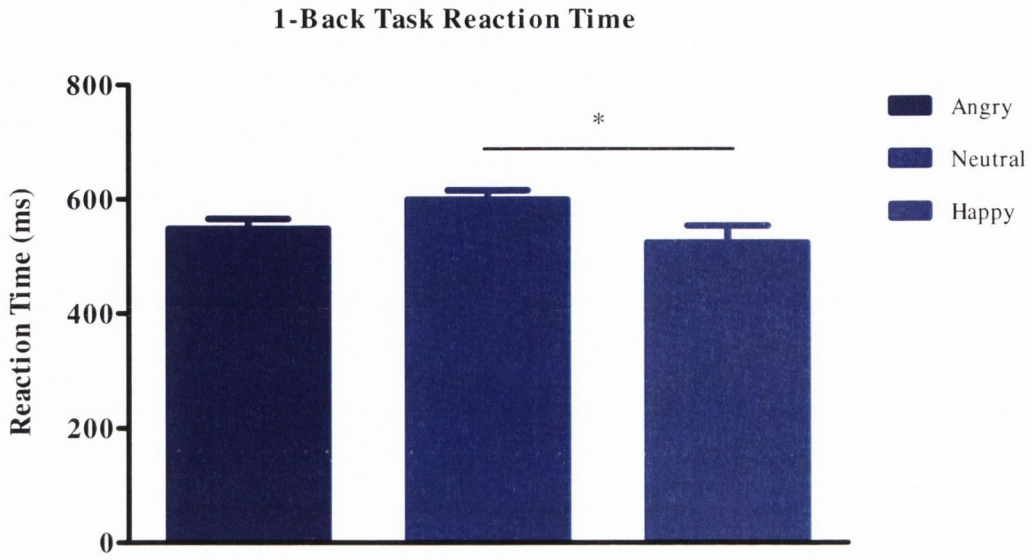

Figure 5.6: The effect of facial expression on 1-Back reaction time performance.

2-Back Accuracy

Education was not significantly related to accuracy on the 2-Back task, $F(1, 65) = 2.92$, $p > .05$. There was, however, a significant main effect of age group on performance accuracy, $F(1, 65) = 5.47$, $p < .05$, partial $\eta^2 = .06$, whereby the 20's group were significantly more accurate than the 40's group. There was no main effect of facial expression on performance accuracy, $F(2, 65) = 1.17$, $p > .10$, nor was there any interaction between age group and facial expression, $F(2, 65) = 0.85$, $p > .10$.

In order to explore the between group differences further, we examined participant accuracy on target and non-target trials. Target trials were essentially hits, whereby participants viewed a face that had been presented 2 trials previously and were thus required to make a response. Non-target trials were foils, meaning that the face had not been presented 2 faces previous and therefore participants were required not to respond.

2-Back: Target trial accuracy

There was a marginally significant positive relationship between education and target accuracy, $F(1, 65) = 3.74$, $p = .057$. After controlling for the effect of education, there was no significant effect of age group on target accuracy performance, $F(1, 65) = 2.24$, $p > .10$. There was no main effect of facial expression on performance accuracy, $F(2, 65) = 0.75$, p

> .10. Finally, the interaction between age group and facial expression was not significant, $F(2, 65) = 0.99$, $p > .10$ (see Figure 5.7).

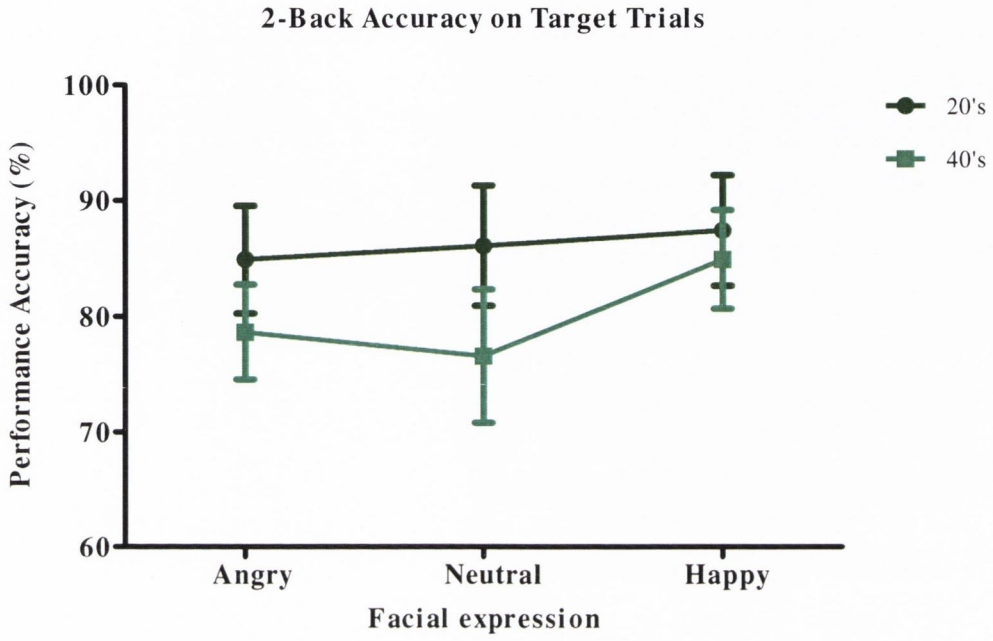

Figure 5.7: Performance accuracy on target trials in the 2-Back condition as a function of age group and the type of facial expression viewed.

2-Back: Non-target trial accuracy

Education was not significantly related to performance accuracy on non-target trials, $F(1, 65) = 0.12$, $p > .10$. There was, however, a main effect of age group on performance accuracy, $F(1, 65) = 4.97$, $p < .05$, as the 20's age group were significantly more accurate on the non-target trials than the 40's age group. Thus the older age group were more likely than the younger group to make a response, by pressing the spacebar, when to do so was incorrect.

There was no main effect of facial expression on non-target accuracy, $F(2, 65) = 0.81$, $p > .10$. There was, however, a significant interaction between age group and facial expression, $F(2, 65) = 3.59$, $p < .05$, partial $\eta^2 = .09$, thus the main effect of age group should be interpreted in light of this interaction (see Figure 5.8).

Simple effects analysis revealed that when participants viewed neutral faces, performance accuracy on non-target trials was lower in the 20's group (mean = 92.10, SD = 5.03) than

the 40's group (mean = 93.17, SD = 4.23), but not significantly so. When participants viewed happy faces, there was no significant difference between performance accuracy in the 20's group (mean = 95.32, SD = 3.62), and the 40's group (mean = 92.44, SD = 4.76). However, when participants performed the 2-Back task with angry faces, the 20's group (mean = 95.25, SD = 2.99) were significantly more accurate ($p < .01$) on non-target trials than the 40's group (mean = 89.29, SD = 6.20).

There were no significant differences on 2-Back performance between happy, neutral, or angry faces in the 20's age group ($p > .05$), or in the 40's group ($p > .10$).

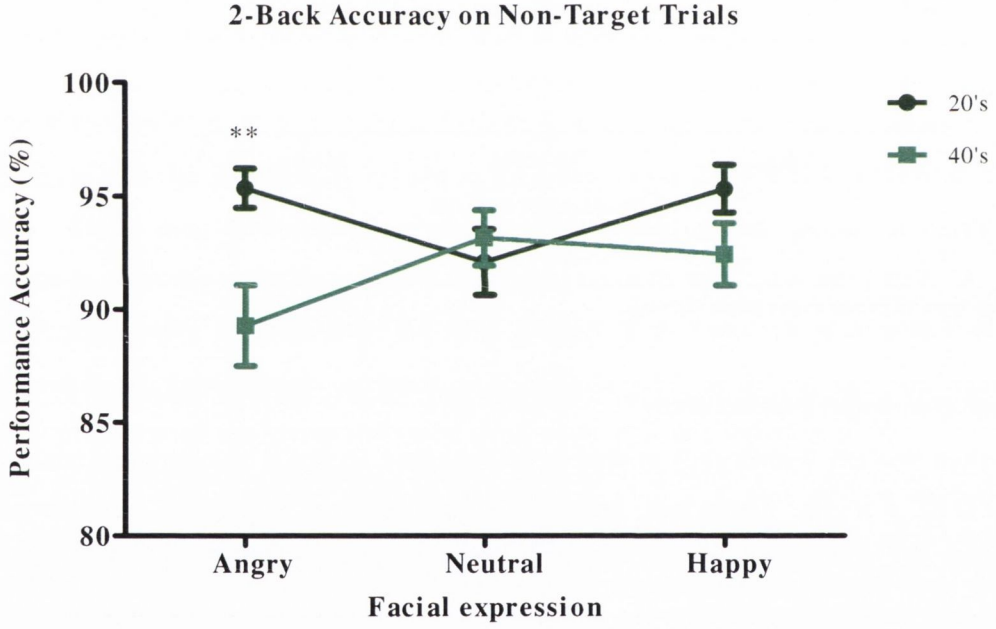

Figure 5.8: Performance accuracy on non-target trials in the 2-Back condition as a function of age group and the type of facial expression viewed.

2-Back Reaction Time

Education was not found to be significantly related to reaction time on the 2-Back task, $F(1, 65) = 2.27$, $p > .10$. There was a significant main effect of age group on reaction time, $F(1, 65) = 9.67$, $p < .01$, with the 20's group responding significantly quicker than the 40's group (see table 6.5). There was no significant main effect of facial expression, $F(2, 65) =$

0.35, $p > .10$, nor was there a significant interaction between age group and facial expression, $F(2, 65) = 0.02$, $p > .10$ (see Figure 5.9).

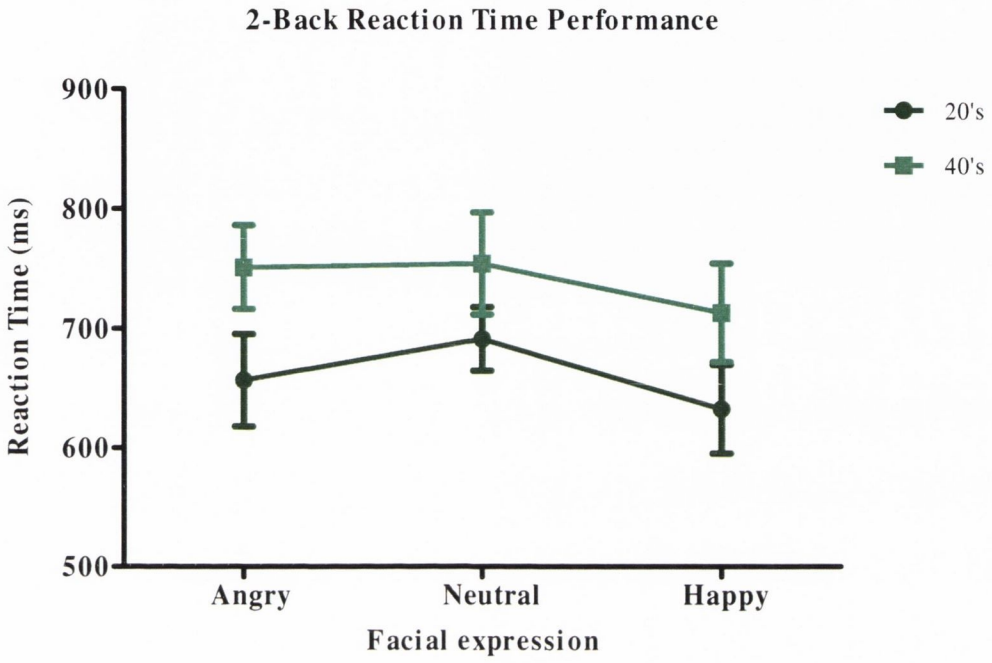

Figure 5.9: Reaction time performance in the 2-Back condition as a function of age group and the type of facial expression viewed.

5.4.1.5 The effect of age group and facial expression on Face Judgment task performance

Face Judgment accuracy

Owing to the discrete nature of the face judgment accuracy variable, the effect of facial expression on judgment accuracy was analysed with a non-parametric Friedman's test. There was a significant main effect of facial expression, X^2 (2) = 14.996, $p < .001$. Further investigation using the Wilcoxon signed ranks test (results were Bonferroni corrected for multiple comparisons so that the accepted threshold for significance was $p < .016$) found that accuracy in judging happy faces (mean rank = 2.32) was significantly higher than accuracy for neutral faces (mean rank = 1.91) and angry faces (mean rank = 1.72; $p < .001$ for both comparisons). Using the Mann-Whitney U test, it was found that there was no effect of age on judgment accuracy for any of the facial expression types ($ps > .10$).

Face Judgment reaction time

A one-way repeated-measures ANOVA was carried out to determine the effect of facial expression (within-subject variable) and age group (between-subject variable) on participant reaction times when they were able to correctly identify the emotion being expressed by a face. There was a significant main effect of facial expression on reaction time, $F(1.87, 130.42) = 29.24$, $p < .001$ (G.G.). Bonferroni pairwise comparisons revealed that reaction times were significantly shorter when participants correctly judged happy faces, than when they correctly judged neutral or angry faces ($p < .001$ for both comparisons). Furthermore, participants were significantly quicker to judge angry faces correctly than neutral faces ($p < .05$). There was no significant main effect of age group on reaction time, $F(1, 71) = 2.95$, $p > .05$, nor was there a significant interaction between facial expression and age group, $F(1.87, 130.42) = 0.81$, $p > .10$ (see Figure 5.10).

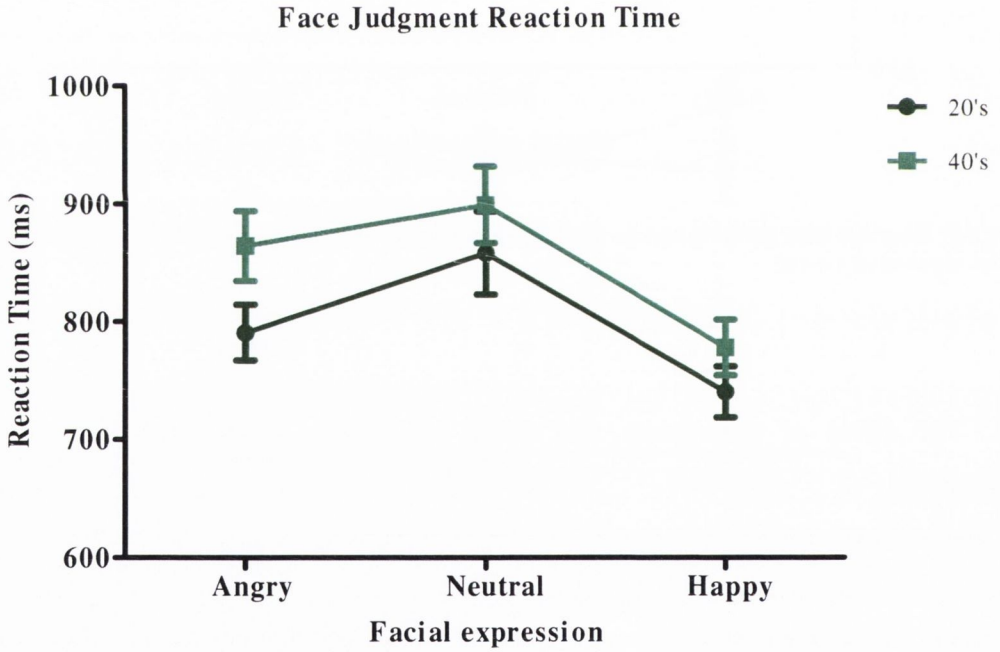

Figure 5.10: Reaction time performance on the Face Judgment task as a function of age group and the type of facial expression viewed.

Incorrect responses

The effect of facial expression and age group on the distribution of false positives was also investigated using non-parametric statistics owing to the discrete nature of the dependent variable. The Friedman's test revealed a significant effect of facial expression on the number of false positives committed, X^2 (2) = 18.750, $p < .001$. Follow-up Wilcoxon

signed ranks tests (with Bonferroni correction for multiple comparisons as above) found that the number of faces incorrectly judged to be neutral in expression (mean rank = 2.23) was significantly higher than the number of faces incorrectly judged to be happy in expression (mean rank = 1.68), $p < .001$. The number of faces incorrectly judged to be neutral was also significantly higher than the number incorrectly judged to be angry in expression (mean rank = 2.00), $p < .01$. Finally, the number of faces incorrectly judged as angry was greater than the number incorrectly judged to be happy, $p < .01$. The results of a Mann-Whitney U test revealed that there was no effect of age group on the number of false positives committed for any facial expression type, $ps > .10$.

5.4.1.6 The effect of gender on Face-Name Pairs learning and recall

Two-way ANCOVAs were carried out to examine the effect of gender and facial expression on Face-Name Pairs learning and recall performance (again with education as a covariate). This was in order to make sure that no differing effect of facial expression on task performance existed for males and females.

Total Score

There was no main effect of education on Face-Name Pairs total recall, $F(1, 66) = 3.75$, $p > .05$. There was also no main effect of facial expression, $F(2, 66) = 0.96$, $p > .10$. There was no main effect of gender on total Face-Name Pairs learning and recall, $F(1, 66) = 0.54$, $p > .10$, and no interaction between gender and facial expression, $F(2, 66) = 0.30$, $p > .10$.

Improvement Score

There was no main effect of education on the percentage of improvement made from block 1 to block 4, $F(1, 65) = 2.29$, $p > .10$. There was no main effect of facial expression, $F(2, 65) = 0.40$, $p > .10$. There was no main effect of gender on improvement score, $F(1, 65) = 0.05$, $p > .10$, and no significant interaction between gender and facial expression, $F(2, 65) = 0.01$, $p > .10$.

Delayed Recall

There was a significant main effect of education on delayed recall performance, $F(1, 66) = 6.58$, $p < .05$. Controlling for education, there was no main effect of facial expression on performance, $F(2, 66) = 1.84$, $p > .10$. Furthermore, there was no main effect of gender on delayed recall accuracy, $F(1, 66) = 1.28$, $p > .10$, and no significant interaction between gender and facial expression, $F(2, 66) = 0.63$, $p > .10$.

5.4.1.7 The effect of gender on N-Back task performance

Two-way ANCOVAs were carried out to examine the effect of gender and facial expression on N-Back task performance (again with education included as a covariate).

1-Back Accuracy

There was no main effect of education on 1-Back accuracy, $F(1, 67) = 0.87$, $p > .10$. There was also no main effect of facial expression on performance, $F(2, 67) = 0.95$, $p > .10$. Furthermore, there was no main effect of gender on 1-Back task accuracy, $F(1, 67) = 0.24$, $p > .10$, and no interaction between gender and facial expression, $F(2, 67) = 1.06$, $p > .10$.

1-Back Reaction Time

There was no main effect of education on performance, $F(1, 67) = 0.71$, $p > .10$, and no main effect of facial expression on performance, $F(2, 67) = 2.34$, $p > .10$. There was, however, a significant main effect of gender on reaction time on the 1-Back task, $F(1, 67) = 4.30$, $p < .05$, whereby the females (mean = 539.28, SD = 117.64) were quicker to respond correctly than the males (mean = 601.81, SD = 89.99), regardless of facial expression. There was no interaction between gender and facial expression, $F(2, 67) = 0.15$, $p > .10$.

2-Back Accuracy

There was a significant main effect of education, $F(1, 67) = 5.62$, $p < .05$. Controlling for this, there was no main effect of facial expression, $F(2, 67) = 0.62$, $p > .10$, and no significant main effect of gender, $F(1, 67) = 1.52$, $p > .10$,. Furthermore, there was no significant interaction between gender and facial expression on performance accuracy, $F(2, 67) = 0.91$, $p > .10$.

2-Back Reaction Time

There was no main effect of education on reaction time, $F(1, 66) = 0.07$, $p > .10$. There was also no main effect of facial expression, $F(2, 66) = 0.95$, $p > .10$. Furthermore, there was no main effect of gender on reaction time, $F(1, 66) = 0.68$, $p > .10$, nor was there a significant interaction between gender and facial expression on reaction time, $F(2, 66) = 0.38$, $p > .10$.

5.4.1.8 The effect of gender on Face Judgment task performance

Face Judgment Accuracy

There was a significant effect of gender on face judgment accuracy when happy faces were viewed, such that males (mean rank = 45.68) were more accurate than females (mean rank = 34.04), $U = 392$, $p < .05$; however, when a Bonferroni correction for multiple comparisons was applied this difference did not remain significant at the new threshold of $p < .016$.

Face Judgment Reaction Time

There was a significant main effect of facial expression on reaction times, $F(1.841, 130.737) = 28.44$, $p < .001$. (G.G.) Bonferroni pairwise comparisons revealed that participants were significantly faster in responding to happy faces than neutral or angry ($p < .001$ for both comparisons). Participants were also faster in responding to angry faces than neutral ($p < .05$). There was no main effect of gender, $F(1, 71) = 2.05$, $p > .10$, and no interaction between facial expression and gender, $F(1.841, 130.737) = 0.80$, $p > .10$ (G.G.).

False Positives

A Mann-Whitney U test revealed that there was no significant difference between males and females in the number of false positives committed ($ps > .10$).

5.4.2 The relationship between task performance and cortisol levels

5.4.2.1 The effect of gender and oral contraceptive use on cortisol levels

A one-way repeated measures ANOVA was carried out to investigate the effect of gender on cortisol levels. There was a significant main effect of sample time, $F(1.550, 108.527) = 4.95$, $p < .05$ (G.G.). There was no significant main effect of gender, $F(1, 70) = 5.11$, $p < .05$ on cortisol levels. Finally, there was no significant interaction between sample time and participant group, $F(1.550, 108.527) = 0.58$, $p > .10$ (G.G.).

A second repeated measures ANOVA was carried out to examine the effect of oral contraceptive use on cortisol levels in females. There was a significant main effect of sample time, $F(1.590, 74.774) = 0.48$, $p < .05$ (G.G.). There was no main effect of oral contraceptive use on cortisol levels, $F(2, 47) = 0.15$, $p > .10$. Finally, there was no significant interaction between oral contraceptive use and sample time, $F(3.182, 74.774) = 1.39$, $p > .10$ (G.G.; see Figure 5.11).

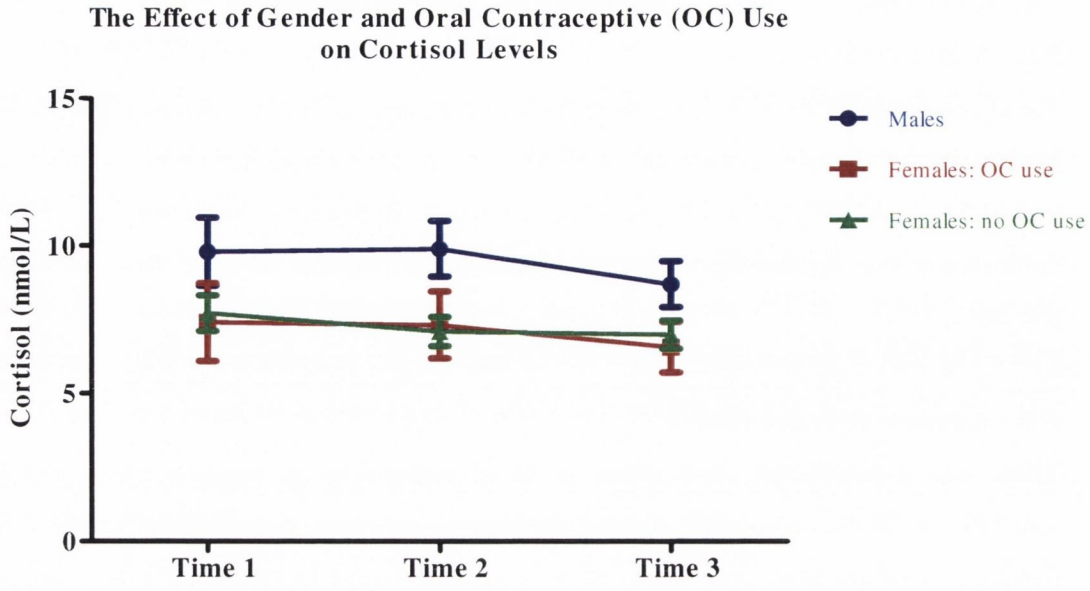

Figure 5.11: The effect of gender and oral contraceptive (OC) use on cortisol levels over the testing session.

5.4.2.2 The difference in cortisol levels between age- and facial expression-groups

The effect of age group and facial expression on cortisol levels was examined using a two-way ANOVA. The area under the curve with respect to ground (AUCg) was once again used as measure of total cortisol output over the testing session (the effect of age group and facial expression on individual cortisol measurements could not be examined due to significant heterogeneity of variance, however, means and standard errors are displayed in Table 5.5)

The two-way ANOVA revealed no main effect of age group, $F(1, 66) = 0.21$, $p > .10$, and no main effect of facial expression, $F(2, 66) = 2.06$, $p > .10$, on AUCg values. There was, however, a significant interaction between age group and facial expression, $F(2, 66) = 4.29$, $p < .05$ (see Figure 5.12).

Simple effects analysis revealed a significant difference in AUCg values in the 20's group, $F(2, 33) = 5.86$, $p < .01$. Tukey post-hoc tests showed that AUCg values were significantly higher in the group that viewed neutral faces compared with angry faces ($p < .01$), and with happy faces ($p < .05$). AUCg values did not differ significantly as a function of facial expression in the 40's group, $F(2, 33) = 0.44$, $p > .10$. The difference between the 20's and 40's across each facial expression condition was to be investigated using Mann-Whitney U tests, owing to a violation of the assumption of homogeneity of variance.

There was no significant difference in AUCg values between the 20's and 40's groups who viewed angry faces ($p > .10$), nor between the 20's and 40's who viewed happy faces ($p > .10$). There was, however, a significant difference between the 20's and 40's who viewed the neutral faces, with the 20's group having a significantly higher AUCg values than the 40's group, $U = 22.5$, $p < .01$ (see Figure 5.12).

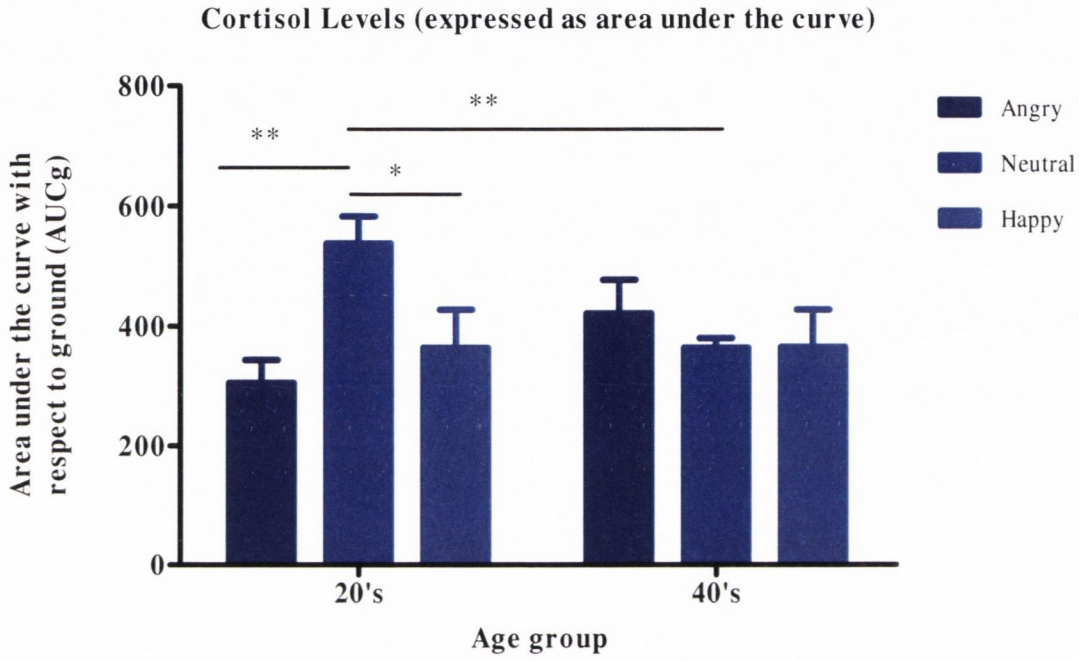

Figure 5.12: Cortisol levels (expressed as the area under the curve with respect to ground) for the testing session as a function of age group and facial expression viewed.

Age Group	**20's**			**40's**		
Facial Expression	**Happy**	**Neutral**	**Angry**	**Happy**	**Neutral**	**Angry**
Cortisol Time 1 (nmol/L)	7.33 (± 1.28)	10.5 (± 1.06)	6.36 (± 1.01)	6.67 (± 0.88)	7.83 (± 0.59)	7.27 (± 0.70)
Cortisol Time 2 (nmol/L)	7.50 (± 1.36)	11.00 (± 0.93)	6.00 (± 0.70)	6.45 (± 0.81)	7.16 (± 0.32)	7.54 (± 0.90)
Cortisol Time 3 (nmol/L)	7.83 (± 1.19)	9.77 (± 0.83)	5.75 (± 0.62)	6.61 (± 0.94)	7.00 (± 0.30)	8.58 (± 1.03)

Table 5.5: Cortisol levels for each of the testing groups (expressed as means ± SEM).

5.4.2.3 The relationship between cortisol (AUCg), age group, education and task performance

A series of multiple regression analyses were conducted in order to determine whether cortisol levels, along with age group and education, was a significant predictor of task performance. The regression model was similar to that used in Chapter 4. An indicator variable $Y_0 O_1$ was included in the analysis, whereby '0' was assigned to participants in their 20's, and '1' was assigned to participants in their 40's group. Total cortisol output (area under the curve with respect to ground, or AUCg) was also included in the analysis, as was education. Education was included as a covariate instead of predicted IQ as the former was positively correlated with performance on the Face-Name Pairs task and on the 2-Back task (*p*s < .05). Predicted IQ was not significantly correlated with any of these measures. The interactive term, $Y_0 O_1$ X AUCg was once again included in the regression model. This was in order to assess any possible effect of the interaction between cortisol levels and age group on performance, separate to any main effect that cortisol might have. The regression equation was derived as follows:

$$Y = \beta_0 + \beta_1 * Y_0 O_1 + \beta_2 * \text{Education} + \beta_3 * \text{AUCg} + \beta_4 * Y_0 O_1 \text{ X AUCg} + \varepsilon$$

Where

Y is the outcome variable

ε is the error term

Important note: A decision was taking not to include gender and trait anxiety in the regression model, as it was deemed that our relatively small sample size would not support the addition of further predictors to the model (Cohen, 1988; Maxwell, 2000). Furthermore, the focus of our analysis was to investigate the relationship between age group, cortisol levels and facial expression, on task performance.

In the case of the Face-Name Pairs task and the N-Back task, the relationship between cortisol and task performance was examined for each of the three types of face stimuli separately: Angry, Neutral, and Happy. Thus the possibility was explored that the relationship between cortisol and task performance could vary with the facial expression viewed by participants. The results are set out in Tables 5.6, 5.7, and 5.8 below.

A) The ability of cortisol, age group and education to predict performance on the Face-Name Pairs and N-Back tasks when *angry faces* were viewed

Y	R^2	Predictors	Std. β	*t*	*p*
Face-Name Total Score	0.37	Y_0O_1	- 1.137	- 2.245	.038*
		Education	0.314	1.569	.135
		AUCg	- 0.590	- 1.522	.146
		Y_0O_1 X AUCg	1.193	1.771	.095
Face-Name Improvement Score	0.26	Y_0O_1	- 0.605	- 1.142	.268
		Education	0.071	0.334	.742
		AUCg	- 0.333	- 0.821	.423
		Y_0O_1 X AUCg	0.319	0.450	.658
Face-Name Delayed Recall	0.28	Y_0O_1	- 0.347	- 0.666	.514
		Education	0.410	1.978	.063
		AUCg	0.096	0.241	.812
		Y_0O_1 X AUCg	0.143	0.205	.840
1-Back Accuracy		Y_0O_1	- 0.372	- 0.656	.521
		Education	- 0.267	- 1.178	.255
		AUCg	- 0.425	- 0.971	.345
		Y_0O_1 X AUCg	0.319	0.417	.682
1-Back Reaction Time	.07	Y_0O_1	- 0.215	- 0.362	.722
		Education	0.171	0.723	.479
		AUCg	- 0.345	- 0.761	.457
		Y_0O_1 X AUCg	0.604	0.762	.456
2-Back Accuracy	0.20	Y_0O_1	- 0.301	- 0.549	.590
		Education	- 0.141	- 0.646	.526
		AUCg	0.308	0.733	.473
		Y_0O_1 X AUCg	- 0.282	- 0.383	.706

Y	R^2	Predictors	Std. β	*t*	*p*
2-Back Targets	0.18	Y_0O_1	0.353	0.613	.548
		Education	- 0.275	- 1.222	.238
		AUCg	0.623	1.428	.171
		Y_0O_1 X AUCg	- 0.895	- 1.148	.267
2-Back Non-Targets	0.30	Y_0O_1	- 0.666	- 1.292	.213
		Education	- 0.142	- 0.691	.499
		AUCg	- 0.095	- 0.241	.813
		Y_0O_1 X AUCg	0.160	0.232	.819
2-Back Reaction Time	0.51	Y_0O_1	0.797	1.822	.086
		Education	0.549	3.071	.007**
		AUCg	0.361	1.064	.302
		Y_0O_1 X AUCg	- 0.398	- 0.680	.506

Table 5.6: Regression analyses of Face-Name Pairs and N-Back task performance when angry faces were viewed.

B) The ability of cortisol, age group and education to predict Face-Name Pairs and N-Back task performance when *neutral faces* were viewed

Y	R^2	Predictors	Std. β	*t*	*p*
Face-Name Total Score	0.48	Y_0O_1	1.300	1.406	.177
		Education	- 0.177	- 0.976	.342
		AUCg	0.564	2.418	.026*
		Y_0O_1 X AUCg	- 1.494	1.719	.103
Face-Name Improvement Score	0.16	Y_0O_1	1.258	1.058	.305
		Education	0.180	0.767	.453
		AUCg	0.369	1.243	.231
		Y_0O_1 X AUCg	- 1.299	- 1.097	.288
Face-Name Delayed Recall	0.23	Y_0O_1	1.656	1.474	.157
		Education	0.290	1.372	.186
		AUCg	0.579	2.065	.053
		Y_0O_1 X AUCg	- 1.350	- 1.279	.216
1-Back Accuracy	0.35	Y_0O_1	- 2.520	- 2.413	.027*
		Education	- 0.218	- 1.030	.317
		AUCg	- 0.692	- 2.625	.018*
		Y_0O_1 X AUCg	2.111	2.143	.047*
1-Back Reaction Time	0.20	Y_0O_1	0.987	0.876	.391
		Education	0.052	0.243	.810
		AUCg	- 0.294	- 1.079	.293
		Y_0O_1 X AUCg	- 0.891	- 0.836	.413
2-Back Accuracy	0.50	Y_0O_1	- 0.093	- 0.103	.919
		Education	0.734	4.243	.000***
		AUCg	0.739	1.713	.103
		Y_0O_1 X AUCg	0.450	0.531	.601

Y	R^2	Predictors	Std. β	*t*	*p*
2-Back Targets	0.34	Y_0O_1	0.492	0.477	.639
		Education	0.554	2.786	.012*
		AUCg	0.103	0.404	.691
		Y_0O_1 X AUCg	- 0.555	- 0.570	.575
2-Back Non-Targets	0.27	Y_0O_1	- 0.815	- 0.739	.469
		Education	0.217	1.048	.308
		AUCg	0.413	1.552	.137
		Y_0O_1 X AUCg	1.327	.271	.219
2-Back Reaction Time	0.39	Y_0O_1	2.584	2.433	.025*
		Education	- 0.011	- 0.059	.954
		AUCg	- 0.266	- 0.952	.353
		Y_0O_1 X AUCg	- 2.431	- 2.407	.026*

Table 5.7: Regression analyses of Face-Name Pairs and N-Back task performance when neutral faces were viewed.

C) The ability of cortisol, age group and education to predict Face-Name Pairs and N-Back task performance when *happy faces* were viewed

Y	R^2	Predictors	Std. β	*t*	*p*
Face-Name Total Score	0.17	Y_0O_1	- 0.024	- 0.053	.958
		Education	0.376	1.641	.117
		AUCg	0.033	0.105	.917
		Y_0O_1 X AUCg	- 0.107	- 0.218	.830
Face-Name Improvement Score	0.08	Y_0O_1	- 0.143	- 0.299	.768
		Education	0.196	0.814	.426
		AUCg	- 0.128	- 0.393	.699
		Y_0O_1 X AUCg	0.057	0.111	.913
Face-Name Delayed Recall	0.16	Y_0O_1	0.131	0.285	.779
		Predicted IQ	0.347	1.463	.161
		AUCg	0.028	0.088	.931
		Y_0O_1 X AUCg	- 0.289	- 0.584	.566
1-Back Accuracy	0.31	Y_0O_1	0.163	0.360	.723
		Education	0.310	1.314	.205
		AUCg	0.450	1.420	.170
		Y_0O_1 X AUCg	- 0.208	- 0.430	.673
1-Back Reaction Time	0.30	Y_0O_1	- 0.219	- 0.513	.614
		Education	- 0.153	- 0.686	.501
		AUCg	- 0.143	- 0.485	.633
		Y_0O_1 X AUCg	0.726	1.597	.128
2-Back Accuracy	0.44	Y_0O_1	0.475	1.193	.248
		Education	0.598	3.051	.007**
		AUCg	0.601	2.361	.030*
		Y_0O_1 X AUCg	0.799	- 1.867	.078

Y	R^2	Predictors	Std. β	*t*	*p*
2-Back Targets	0.32	Y_0O_1	0.871	2.069	.053
		Education	0.517	2.356	.030*
		AUCg	0.434	1.494	.152
		Y_0O_1 X AUCg	- 0.987	-2.203	.041*
2-Back Non-Targets	0.31	Y_0O_1	- 0.270	- 0.639	.531
		Education	0.246	0.116	.279
		AUCg	0.412	1.413	.175
		Y_0O_1 X AUCg	0.000	0.000	.999
2-Back Reaction Time	0.27	Y_0O_1	- 0.219	- 0.669	.512
		Education	- 0.195	- 0.860	.401
		AUCg	- 0.510	- 1.699	.107
		Y_0O_1 X AUCg	0.771	1.664	.113

Table 5.8: Regression analyses of Face-Name Pairs and N-Back task performance when happy faces were viewed.

The regression model was then applied to reaction time performance on the Face Judgment task. Education was omitted as a covariate as it was not correlated with Face Judgment task performance. All participants viewed angry, neutral and happy faces within the one task, thus the results of the regression analyses below refer to the whole sample for each of the different face stimuli (see Table 5.9). Linear regression could not be deemed to be a useful predictive model in the case of face judgment accuracy and the number of false positives committed, owing to their discrete nature. Thus, relationships between cortisol and these outcome variables were investigated with Kendall's tau-b correlation (Table 5.11).

Y	R^2	Predictors	Std. β	*t*	*p*
Face Judgment Reaction Time – Neutral Faces	0.07	Y_0O_1	- 0.166	- 0.574	.568
		AUCg	- 0.113	- 0.710	.480
		Y_0O_1 X AUCg	0.433	1.439	.155
Face Judgment Reaction Time – Angry Faces	0.15	Y_0O_1	- 0.281	- 1.028	.308
		AUCg	- 0.383	- 2.519	.014*
		Y_0O_1 X AUCg	0.587	2.056	.044*
Face Judgment Reaction time – Happy Faces	0.10	Y_0O_1	- 0.366	- 1.306	.196
		AUCg	- 0.337	- 2.205	.031*
		Y_0O_1 X AUCg	0.579	1.991	.052

Table 5.9: Whole group regression analyses of Face Judgment reaction time performance.

In order to explore the significant effect of the interaction between age group and AUCg on response times when angry and happy faces were viewed, we conducted linear regression analyses for each age group separately (see Table 5.10).

Y	Age Group	R^2	Predictors	Std. β	*t*	*p*
Reaction Time Happy Faces	20's	0.14	AUCg	- 0.375	- 2.367	.024*
	40's	0.01	AUCg	0.120	0.695	.492
Reaction Time Angry Faces	20's	0.10	AUCg	- 0.320	- 1.970	.057
	40's	0.01	AUCg	0.087	0.503	.618

Table 5.10: Linear regression analyses of the effect of cortisol levels on reaction times to angry and happy faces, for each group separately.

Variable	Correlation coefficient and *p* value
Accuracy for Happy Faces	$\tau_b = .030$ $p = .755$
Accuracy for Neutral Faces	$\tau_b = -.200$ $p = .026$
Accuracy for Angry Faces	$\tau_b = .034$ $p = .701$
False Positives - Happy Faces	$\tau_b = .256$ $p = .007$
False Positives - Neutral Faces	$\tau_b = .072$ $p = .416$
False Positives - Angry Faces	$\tau_b = .160$ $p = .090$

Table 5.11: Kendall Tau-b correlation coefficients (τ_b) and related *p* values showing the strength of the relationship between cortisol levels (calculated as the area under the curve with respect to ground) and task measures of accuracy and number of false positives committed for each facial expression type.

Plots displaying the strongest relationships that emerged from the regression and correlation analyses are shown below (Figures 5.13 to 5.16).

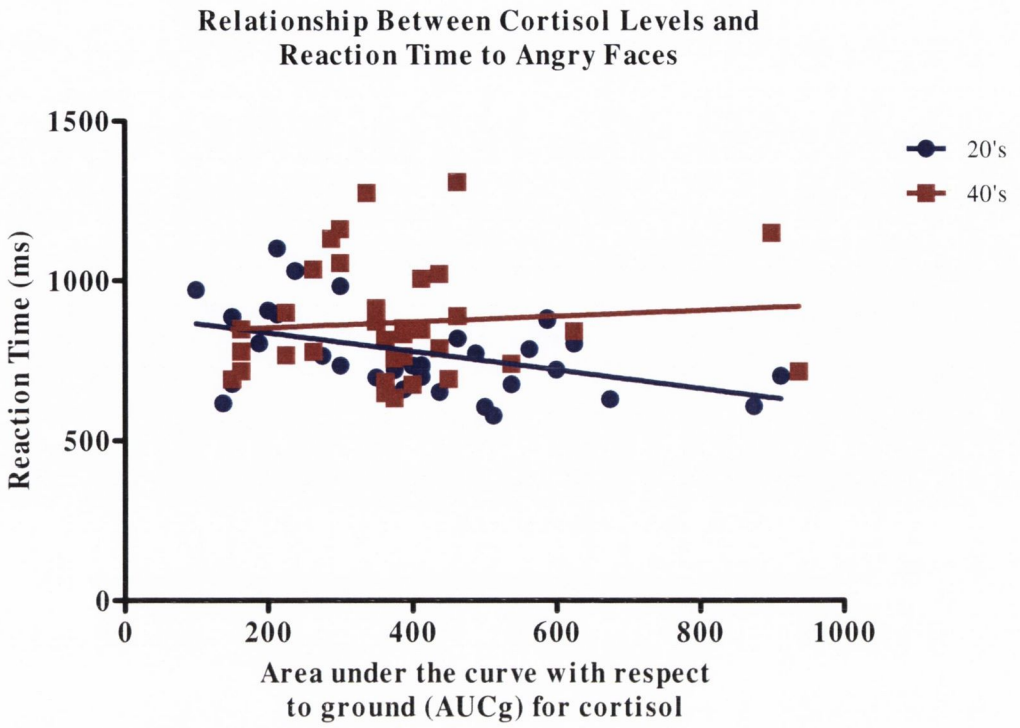

Figure 5.13: The relationship between cortisol levels (expressed as AUCg) and reaction time to correctly judge angry faces.

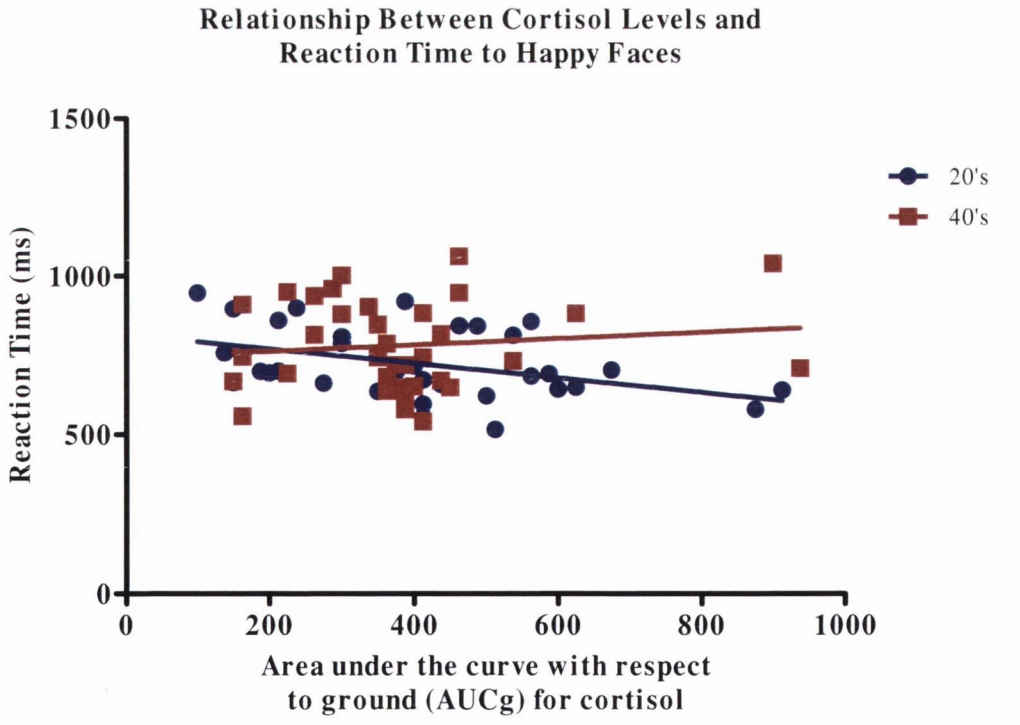

Figure 5.14: The relationship between cortisol levels (expressed as AUCg) and reaction time to correctly judge happy faces.

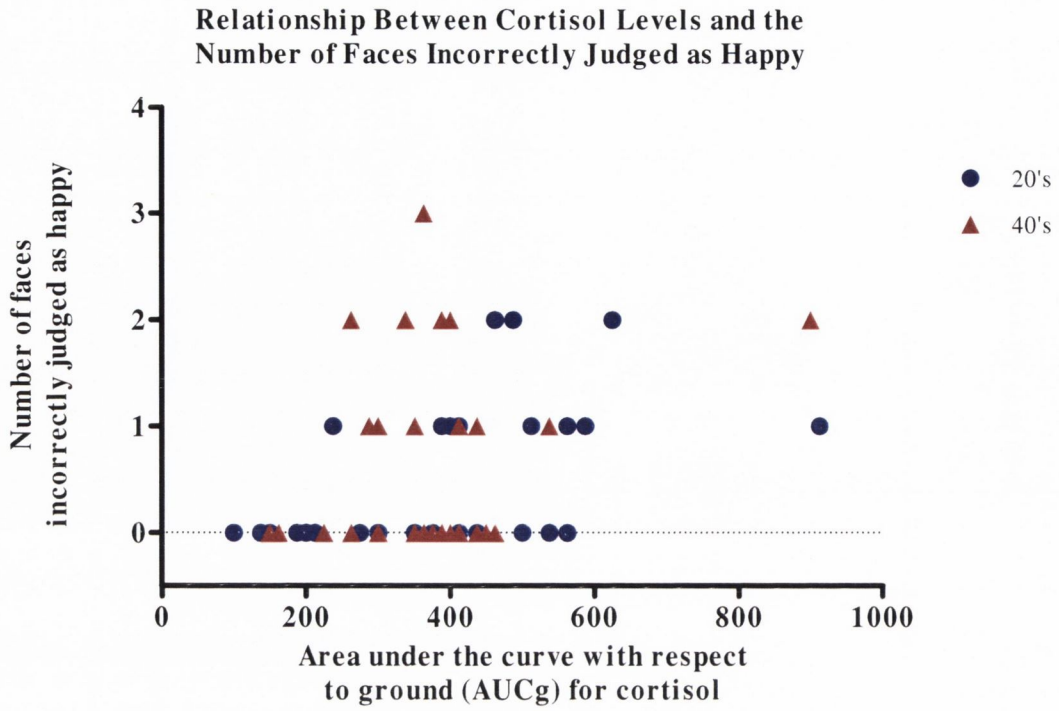

Figure 5.15: The relationship between cortisol levels (expressed as AUCg) and the number of faces incorrectly judged as being happy in expression.

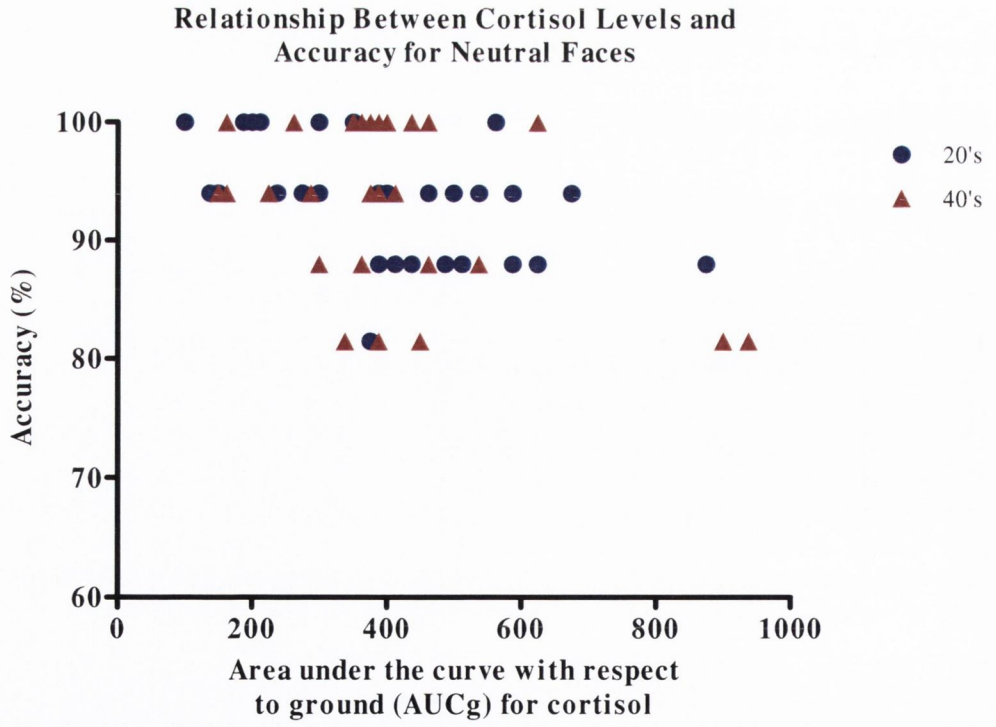

Figure 5.16: The relationship between cortisol levels (expressed as AUCg) and the percentage of faces that were accurately judged to be neutral in expression.

5.5 Discussion

In this study, the effects of using emotional stimuli on associative and working memory performance was assessed in a young and middle-aged group, using an associative- and working memory task. Participant accuracy and speed of response in judging emotional facial expressions was also investigated, using a face judgment task. Finally, the relationship between cortisol levels, task performance, and the emotion being portrayed by the faces, was explored.

The main findings are as follows:

1. There was no effect of facial expression on Face-Name Pairs associative memory performance; however, there was a main effect of age group on immediate Face-Name Pairs recall performance, with the 20's group performing significantly better than the 40's group.
2. There was a main effect of facial expression on reaction time in the 1-Back working memory task, with participants responding fastest to happy faces in comparison to neutral or angry faces. There was no main effect of age group on reaction time, and no effect of facial expression or age group on performance accuracy.
3. There was no main effect of facial expression or age group on 2-Back accuracy on target trials. There was, however, a main effect of age group on accuracy on non-target trials, and a significant interaction between facial expression and age group. The 20's group were significantly more accurate on non-target trials than the 40's group when angry faces were viewed.
4. There was no main effect of facial expression on 2-Back reaction time; however, there was a main effect of age group, with the 20's responding significantly quicker than the 40's. This effect appeared to be driven by a difference in reaction time when angry faces were viewed, although this difference did not reach statistical significance.
5. There was a main effect of facial expression on performance accuracy on the Face Judgment task. Participants were significantly more accurate when judging happy faces, than when judging neutral or angry faces. There was no main effect of age group on performance accuracy.
6. There was also a significant main effect of facial expression on reaction time in this task, with participants responding significantly faster to happy faces, than to neutral or angry faces. Participants were also quicker in judging angry faces correctly

compared with neutral faces. There was no main effect of age group on reaction time. Furthermore, significantly more faces were incorrectly judged as being neutral, than happy or angry in expression (false positives).

7. In the main, males and females were not found to differ in their performance on the tasks.
8. There was some evidence for a relationship between cortisol levels and performance on the face-name pairs and N-Back tasks when neutral faces and happy faces were viewed, but the fundamental nature of this relationship was not clear.
9. Cortisol levels were negatively correlated with accuracy in judging neutral faces and were also positively correlated with the number of faces incorrectly judged as being happy in expression. Furthermore, cortisol levels were inversely related to reaction time, when participants correctly judged happy and angry faces. The age group X AUCg interaction regression term was found to be significantly positively related to reaction time to judge happy and angry faces.

5.5.1 The effect of age group and emotion on Face-Name Pairs performance

The first hypothesis stated that any effect of age on associative memory performance should be smallest when faces were happy in expression and largest when faces were angry in expression, in accordance with the theory of a positivity effect in aging. This hypothesis was not supported as no significant effect of facial expression was evident, nor was there a significant interaction between age group and facial expression.

A strength of this task was that it probed the effect of emotional expression on memory without the confound of increased attentional orienting toward certain emotional faces over others. A further strength, and a difference between this study and the Tsukiura and Cabeza study (2008), is that the current design tested an effect of facial expression on subsequent memory for face-name associations, rather than memory for expression-name associations. The current design ensured that no obvious semantic linking between facial expression and name could enhance subsequent memory performance, as all facial expressions were of the same valence in each task. To our knowledge, the Tsukiura and Cabeza study is the only study that has explored the effect of varying facial expressions on memory for face-name pairs.

It is entirely possible that, in some of the other studies of the effect of emotion on episodic memory, the observed enhancement in memory for emotional stimuli was a result, at least in part, of increased attentional orienting toward the stimuli which conferred a subsequent memory benefit. The effect of the emotional capture of attention on memory has seldom been controlled for in these studies, as discussed in section 5.1.

The task design employed in the current study resulted in incidental, and for some participants perhaps, the unconscious encoding of emotion, whereas many of the other studies in this area have probed memory when participants have been encouraged to specifically attend to the emotional aspects of the stimuli. Perhaps asking participants to rate the intensity of the emotion being expressed by each face, as was done in the Tsukiura and Cabeza study, might have resulted in more focused processing of the emotion of the face, and therefore may have modulated subsequent memory. Against this theory, however, a study by D'Argembeau and Van der Linden (2007) found that the effect of emotion on memory for facial expressions was more pronounced under incidental than intentional processing of the emotional expression.

In previous chapters, the level of difficulty of the Face-Name Pairs task has been discussed, and the results have shown that older adults are impaired to a greater degree on associative memory tasks than on single item recall and recognition tasks. Thus, another possible explanation for the negative findings is that the level of task difficulty, particularly for the older participants, masked any effect of emotion on memory performance. It is noteworthy that the vast majority of positive findings with regard to the effect of emotion on memory have been on recall and recognition tasks involving single items only.

Recently, however, studies have emerged investigating the effect of emotion on binding processes, both within-object and between-object binding (for a review see Mather, 2007). There is evidence that a memory benefit for a central, emotional detail in a scene comes at a cost to memory for neutral background information, particularly for older adults (Kensinger, Gutchess, & Schacter, 2007; Kensinger, Piguet, & Krendl et al., 2005). It also seems that between-object binding may be unaffected by the emotion, or even suffer, if one of the objects is emotionally salient (Anderson & Shimamura, 2005; Mather, 2007; Mather & Nesmith, 2008). In a study conducted by Kensinger and Schacter (2006), source memory for emotional items was shown to be unaffected by emotion, whereas memory for

the individual items themselves was enhanced for emotional items compared with neutral. Moreover, amygdala activation during encoding predicted subsequent item memory, but not source memory, the latter of which was found to be predicted by the degree of hippocampal activation. Recent evidence suggests that when an emotional item is presented with neutral information in the background (for example in a scene), memory for that neutral information is impaired. However, when the paired neutral information is presented alongside the emotional information in the foreground (as in picture pairs), memory for that neutral information is unaffected by its emotional partner (Mather, Gorlick, & Nesmith, 2009).

In the context of the current study, there is little evidence that face-name pairs binding was impaired when emotional faces were viewed compared with neutral, but instead was unaltered, consistent with the predictions made by Mather and colleagues (2009). Nonetheless, evidence of an enhancement in face recognition memory for emotional faces over neutral might have been expected, which was not found in this study. It could be the case that the associative processing requirement of the encoding task allowed less time to be allocated to specific face processing, which resulted in no benefit in subsequent recognition memory for the faces. A further series of experiments would be required in order to test these differing hypotheses and predictions. In addition, this discussion highlights the need for more research aimed at teasing apart effects of emotion on attention, from those on memory, as well as further investigation into the effect of emotion on associative memory.

It is interesting nonetheless, that trait anxiety was inversely correlated with Face-Name Pairs performance when angry faces were viewed, but not when neutral or happy faces were viewed. Previous research has shown that highly anxious individuals have an attention bias for negative versus positive or neutral information (Telzer et al., 2008), and processing of negative stimuli in anxious individuals has been correlated with activity in the dorsomedial PFC (Cremers et al., 2010). It is possible that increased focus on the angry faces in highly trait-anxious participants resulted impaired binding of the face-name pairs.

5.5.2 The effect of age group and emotion on N-Back performance

The first hypothesis was largely supported by performance on the N-Back task. There was no effect of age group or facial expression on performance on the 0-Back control task, as

expected. There was also no effect of age group or facial expression on performance accuracy in the 1-Back condition. This finding is perhaps not surprising as there have been reports of no age differences on N-Back task performance accuracy at the 1-Back level when N numbers are small (Mattay et al., 2006). There was no main effect of age group on reaction time on the 1-Back task; however, there was a main effect of facial expression, whereby participants who viewed happy faces responded faster than participants who viewed neutral faces. Very few studies have examined the effect of emotion on working memory performance, and we are aware of only one that investigated the effect of modulating real facial expressions on performance on an N-Back task (Kensinger et al., 2003). Kensinger and Corkin found that reaction times were slightly slower in response to negative emotional faces compared with neutral. However, they did not include positive faces in their task, and furthermore only examined performance accuracy and reaction times in the 2-Back condition. It is clear that the 1-Back task used in the current study was of a very low level of difficulty, given the very high level of performance accuracy (over 90%) attained by both age groups on this task. It is thus possible that the 1-Back condition in the current study more accurately represents a measure of sustained attention rather than working memory. If this were indeed the case, then the quicker response times exhibited by participants to happy faces over neutral faces could be due to heightened attention to the stimuli in participants who viewed positive emotional facial expressions. There is plenty of evidence from the literature to suggest that on attention tasks, presenting emotional faces results in faster response times than presenting neutral faces (see Dolan, 2002 for a review).

There was no main effect of facial expression on performance accuracy in the 2-Back condition. There was, however, a main effect of age group, with the 40's group performing at a significantly lower level compared with the 20's group. When performance accuracy for target trials (trials that required a response) and non-target trials (trials that did not require a response) was analysed separately, no difference between the groups was evident on the target trials; however, the 40's group were significantly more likely to commit false positives (respond on the non-target trials) than the 20's group. Moreover, there was a significant interaction between age group and facial expression, with further analysis revealing that the 40's group were significantly impaired compared to the 20's group on non-target trials when angry faces were viewed.

There was a main effect of age group on reaction time in the 2-Back condition, with the 40's group being significantly slower to respond accurately than the 20's group. Though not quite reaching statistical significance, this effect appeared to be most pronounced when angry faces were viewed.

These results support the a priori hypothesis that age differences would be largest on the task when angry faces were viewed. There are several reports in the literature of older adults exhibiting poorer performance than younger individuals on memory tasks when stimuli are negative, rather than neutral or positive in valence (Charles et al., 2003; Mather et al., 2003; Mikels et al., 2005). These findings are consistent with the predictions made by the socioemotional selectivity theory that older adults are motivated to engage in emotional regulation to a greater extent than younger adults, which impinges on cognitive processing and leads to decreased memory performance for negative material (Charles et al., 2003). A different interpretation of our results could, however, also be taken in line with the findings of a study carried out by Eastwood, Smilek and Merickle, (2003). They showed that prolonged time spent looking at angry faces resulted in longer time to count specific facial features in these faces, compared with neutral or happy faces. The authors suggest that these results can be explained by the fact that negative faces capture attention more readily than positive and neutral faces, and that this attention capture interferes with the participant's ability to perform an ongoing task. However, it is noteworthy that only young undergraduate students were included in this study, as there is evidence that younger adults focus on negative material to a greater extent than older individuals (Kensinger, 2008).

5.5.3 The effect of age group and emotion on Face Judgment task performance

The second hypothesis was largely supported by the results of the Face Judgment task. There was no main effect of age group on performance accuracy; however, there was a main effect of facial expression. Participants were significantly more accurate in judging happy faces, than in judging neutral or angry faces. Furthermore, they exhibited decreased response latency when judging happy faces correctly compared with neutral or angry faces. These findings are supported by the literature. Several studies have shown that positive facial expressions are recognised faster than neutral or negative facial expressions (Esteves & Ohman, 1993; Keightley et al., 2006; Leppanen et al., 2004). There is also evidence that happy facial expressions are consistently recognised with high accuracy, regardless of the

emotional intensity of the expression (Hess, Blairy, & Kleck, 1997). The mechanisms underlying this advantage for happy faces are not entirely clear. However, Leppanen and Hietanen (2004) showed that shorter response latencies to categorise happy faces than neutral or sad faces were not due to any low-level perceptual/physical differences between the faces. When they tested participants' ability and response time to categorise simple line-drawings of up-turned, straight or down-turned mouths, they found no significant difference in ability to recognise up-turned versus down-turned mouths, indicating that the bias for happy faces is not due to facilitated processing of an up-turned mouth, the most well established indicator of the physical expression of happiness.

There have been reports in the literature that older adults are impaired in recognising some facial expressions of emotion compared with younger adults, particularly when those expressions are negative in valence (Ebner & Johnson, 2009; Orgeta et al., 2008). The current findings provide no evidence in support of this contention as there was no effect of age group on judgment accuracy. Our findings are in line with those of Keightley and colleagues (2006), who also demonstrated a recognition bias in both groups manifesting as both increased accuracy and decreased response time to categorise positive faces compared with negative and neutral. The Keightley et al. study did, however, show that older adults were significantly slower than younger participants in responding correctly to negative faces, in line with the socioemotional selectivity theory of aging. While our results showed no interaction between age group and facial expression with regard to reaction times, it is evident that from the Figure 5.12 that the difference in reaction times between the 20's and the 40's was greatest when angry faces were viewed. Perhaps had we contrasted performance of 20's group with that of a slightly older group (as in the Keightley et al. study), this difference might have been more marked.

There was no difference between the age groups in the percentage of faces that they incorrectly classed as being happy, angry and neutral in expression. There was, however, an effect of facial expression, with participants incorrectly categorising faces as being neutral in expression, more often than angry or happy. Furthermore, they misclassified faces as being angry more often than happy. That there would be an effect of facial expression on the distribution of false positives was expected, owing to the significant difference in response accuracy across the different levels of facial expression. The fact that the smallest number of incorrectly categorised faces were classed as happy lends further support to the contention that individuals have an inherent bias toward the

recognition of happy faces rather than neutral or negative faces. The relatively large number of faces that were incorrectly classed as being neutral, suggests that when participants made an error in judging happy and angry faces, they were more likely to misclassify the face as displaying no specific emotion, rather than displaying an emotion of opposing valence. Evidence suggests that neutral and negative faces are often more confused than neutral and happy faces (Johnston, Kasikitis, & Carr, 2001), thus the high number of incorrectly classified faces that were neutral, may stem primarily from low accuracy in judging angry faces, though this was not directly investigated in the current study.

5.5.4 The relationship between cortisol levels and task performance

The third hypothesis stated that cortisol levels should be differently related to the processing of emotional faces than neutral. This hypothesis was not supported by performance on the Face-Name Pairs or N-Back task, but was supported by performance on the Face Judgment task.

Cortisol levels during the test session were not found to predict performance on either the Face-Name Pairs task or the N-Back task when angry faces were viewed. When happy faces were viewed, cortisol levels were found to predict 2-Back accuracy. However, for the older age group, higher cortisol levels were significantly associated with lower performance on this task. When neutral faces were viewed, there was a positive association between cortisol levels and total Face-Name Pairs recall, but a negative association between cortisol and 1-Back accuracy. However, the interaction between age group and cortisol was significant, such that increased cortisol levels in the 40's group were associated with better performance on the 1-Back task.

Higher stress-induced cortisol levels during task performance have been found to predict better subsequent memory for emotional material (Abercrombie et al., 2006). The relationship between basal cortisol levels and memory performance for facial expressions of emotion, however, has been poorly investigated. Work by Putman, Van Honk and colleagues, has indicated that the relationship between basal cortisol levels and subsequent memory for emotional facial expressions may vary depending on the type of memory that is being probed. Their research has shown both a positive association between cortisol levels and long-term memory for emotional faces, and a negative relationship between cortisol levels and memory for the location of emotional faces (Putman et al., 2004; Van

Honk et al., 2003). These results suggest that perhaps higher cortisol levels affect a greater shift in processing toward emotional rather than neutral faces, which may benefit subsequent memory for those faces, but impair memory for neutral background information such as location. This interpretation also has support from studies showing that elevated cortisol levels during times of stress can impair memory for associations/context associated with a central emotional item or event (Nadel & Jacobs, 1998).

Our results with regard to the Face-Name Pairs and N-Back task seem to paint a conflicting picture and no clear inferences can be made from these results with regard to the relationship between basal cortisol levels and emotion processing. There are two likely contributing factors to this. Firstly, there were baseline differences in cortisol levels between age groups and facial expression groups, such that participants in their 20's who viewed neutral faces had significantly higher cortisol levels than those who viewed happy or angry faces in the 20's, and than those who viewed neutral faces in the 40's group. Thus, the relationship with age and emotion may have been confounded by differences in cortisol levels. Secondly, the small number of participants in each group meant that the regression analyses possibly suffered from a lack of power to detect any effect that was small to medium in size (Maxwell, 2000).

The results from the regression analyses of Face Judgment task performance are statistically more robust, owing to the fact that facial expression was a within group variable and thus the sample size for the analyses was close to 80. Furthermore, the difference in cortisol levels between facial expression subgroups now becomes irrelevant as groups were collapsed across facial expression for this task. The combination of the older age and higher cortisol levels was significantly positively related to response latency when angry faces were viewed, and non-significantly when happy faces were viewed. However, when each age group was examined separately, it appeared that this effect was driven by an inverse relationship between response latency and cortisol levels in the 20's group. To our knowledge, no other study has explored the association between cortisol levels and the recognition of emotional facial expressions in different age groups. Our results suggest that higher cortisol levels are associated with heightened attention to emotional stimuli, but not to neutral stimuli. This is also supported by the correlation results showing a negative relationship between accuracy for neutral faces and cortisol levels, such that higher cortisol levels corresponded with lower accuracy for neutral faces.

Cortisol levels were also positively correlated with the number of faces incorrectly judged as being happy in expression. This result could be expected, as higher cortisol was related to poorer accuracy in correctly judging neutral faces. Nevertheless, it is an interesting finding as the number of faces incorrectly classed as neutral was significantly higher than happy or angry faces. Thus, the relationship between cortisol and the tendency to falsely judge a face as being emotional does not seem to be related to a general tendency to commit false positives. The results of the current study suggest that higher cortisol levels result in heightened attention to emotional stimuli and a greater tendency to categorise neutral faces as being emotional. However, this relationship might differ slightly depending on the age group in question. Further research is needed to corroborate and extend these findings.

5.5.5 Limitations of the current study and future directions

A limitation of our study with respect to the effect of age group and facial expression on face-name pairs and N-Back task performance was the small sample size per group. The necessity for 6 experimental groups overall and the time involved in testing each participant singly, meant that it was not feasible to have a larger sample size. Future work should focus on adding to participant numbers so as to strengthen and add to the current findings. The fact that different participants viewed different facial expressions in the Face-Name Pairs and N-Back tasks meant that there is also between group variability to take into account. However, it was decided to design the tasks in this way in order eliminate the possibility of an attentional bias toward certain facial expressions over others within a task. Another possibility would have been to utilise a cross-over design, whereby participants completed the tasks with stimuli of a single valence, and then were subsequently brought back and repeated the experiment with stimuli of another valence, and so on. In this case however, there would be an inherent practice effect which would be difficult to control for.

Another feature of the current study was that we did not directly explore the effect of arousal on memory for emotional material. There is current debate in the literature as to whether arousal or valence contributes to a greater extent to enhanced memory for emotional material. Many studies have maintained that arousal is necessary to facilitate altered processing of emotional stimuli (Abercrombie et al., 2006; Cahill et al, 1998; Mather et al., 2008), and there is evidence for a neurochemical mechanism by which arousal-mediated glucocorticoid increases interact with the amygdala to influence memory

for emotionally arousing stimuli (Roozendaal & McGaugh, 1997). It is possible that had we chosen stimuli that were arousing to a greater extent, such as emotive pictures or taboo words, we may have observed a greater interaction between cortisol levels and memory performance. Nonetheless, there is support for the contention that valence can modulate memory and stimuli processing, in some cases to a greater degree than arousal, and that this might be particularly marked in aging (Kensinger, 2008). Furthermore, brain regions such as the amygdala and PFC that are purported to be involved in emotion appraisal and emotional memory, show valence-specific responses to stimuli (Leclerc et al., 2008; Nielen et al., 2009), which are different in young and older individuals (Mather et al., 2004). Future studies should address the issue of the effect of arousal versus the effect of valence on the processing of emotional stimuli, particularly to shed further light on the relationship between cortisol levels and emotional memory. A possible future study could investigate brain structure and activity in young and middle-aged participants when performing both memory and judgment tasks with emotional and neutral stimuli, to better elucidate any difference between these age groups in the effect of emotion on cognitive processing at a neuroanatomical level.

Chapter 6

Regional grey matter volume changes in aging and their association with memory performance and cortisol levels

6.1 Summary

This chapter examines the differences in regional grey matter volume between a group of young adults (aged in their 20's) and a group of middle-aged adults (aged in their 40's), using voxel-based morphometry (VBM). Furthermore, the association between grey matter volume and performance on an associative memory task in the MRI scanner is investigated. Finally, the relationship between cortisol levels during scanning and regional brain volume is explored.

6.2 Introduction

6.2.1 Structural brain changes in aging

Given the decline in cognitive function that takes place in old age, not only in dementia but also during 'healthy aging', researchers have increasingly looked toward neuroanatomical changes for an explanation. Cross-sectional studies of structural brain changes in older adults have produced considerably varied results. Taken together, studies have found volume loss in practically all regions of the brain. Fotenos and colleagues (2005) conducted a study examining brain volume in 370 adults aged 18-97. They found that a significant reduction in total brain volume was evident by age 30, with grey matter showing a faster rate of decline than white matter. Reductions in white matter integrity in aging have also been reported however, particularly in the more anterior regions of the brain (Head et al., 2004, Raz et al., 2005). Within the context of grey matter decline, many studies have found volume reductions in the prefrontal cortex, temporal neocortex and parietal cortex (Curiati et al., 2009; Raz et al., 1997; Raz et al., 2004; Resnick et al., 2007; Walhovd et al., 2009). The Walhovd et al. study examined structural brain changes across a total of 883 participants, aged from 18-93 years. They found widespread age-related volume decline, with the strongest changes evident in the cerebral cortex generally, as well as the in the putamen, pallidum and accumbens. Some cross-sectional studies, on the other hand, argue that frontal regions are the most susceptible to age-related volume change with temporal cortical regions showing more moderate decline and occipital and parietal regions exhibiting an even smaller volume decline with age (e.g. Raz, 2005; see Figure 6.1).

On the issue of grey matter decline in medial temporal lobe regions, the literature does not seem to have reached a consensus. Several cross-sectional studies have reported that MTL volume declines with age (Jernigan et al., 2001; Lupien et al., 2007; Raz et al., 2005) with other studies finding no evidence of an association between MTL volume and age (Good et al., 2001; Van Petten, 2004). Pronounced age-related volume decline of the cerebellar cortex has also been reported (Good et al., 2001; Raz et al., 2005; Walhovd et al., 2009; see Figure 6.1)

Longitudinal studies offer an advantage in the study of brain changes in aging, as they eliminate, to some extent, inter-individual variability that can make it difficult to detect effects in cross-sectional designs. Notwithstanding this characteristic, there is evidence from longitudinal data that there remains considerable inter-individual variability with respect to volume changes (Raz, 2005) in aging, as well as considerable between-study

variability. The Raz et al. study, which combined both a cross-sectional and longitudinal approach, found that longitudinal estimates of volume decline exceeded those of cross-sectional studies. The hippocampus and association cortices, prefrontal cortex, cerebellum and caudate showed increased shrinkage with age, with an accelerated rate of grey matter volume reduction reported from the 5th decade on in the hippocampus and cerebellum. Contrary to these results, Smith and colleagues (2007) examined longitudinal volume changes in an elderly cohort, and found the marked reductions in frontal, parietal and temporal lobe grey matter, but not in medial temporal lobe regions. The onset of volume decline of certain structures is still also a matter of debate. It is noteworthy that the majority of these longitudinal studies have focused on tracking the progression of regional volume reductions in old age, while several cross-sectional studies have included quite a wide age range (Good et al., 2001; Raz et al., 2005; Walhovd et al., 2009). Variation in the age groups included in these studies as well as differences in the design (cross-sectional versus longitudinal) mean that considerably more research is needed in order to try and shed light on the discrepant findings between studies.

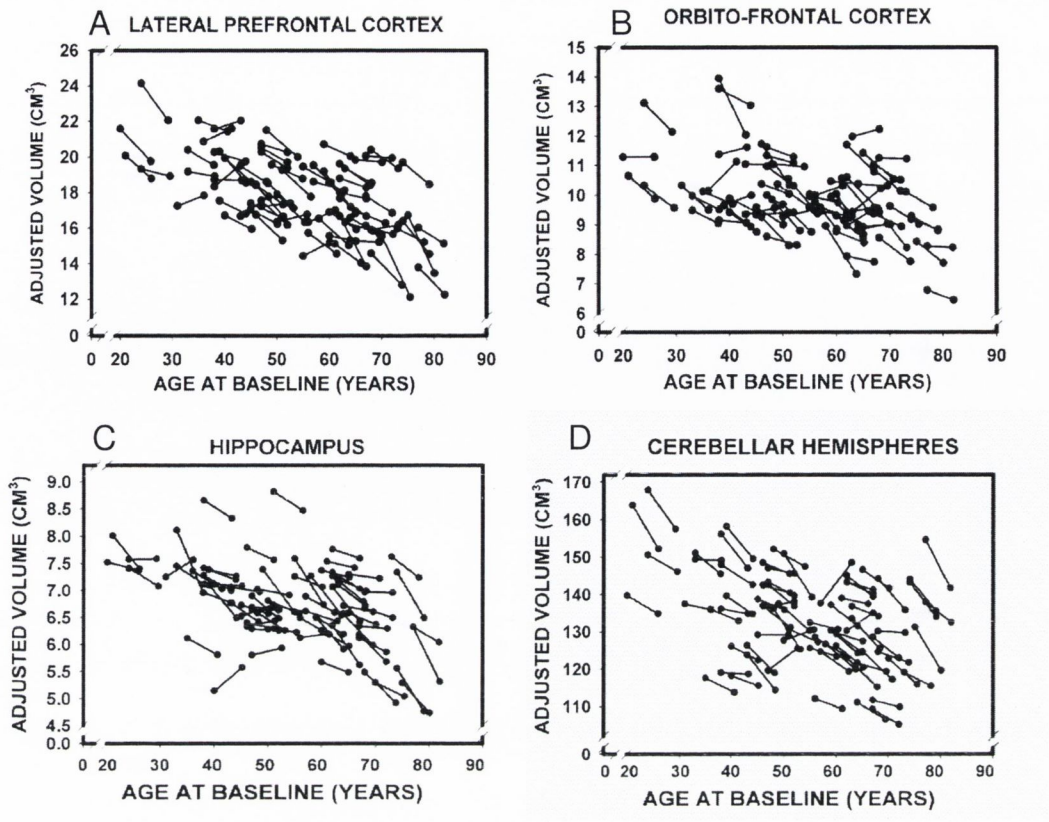

Figure 6.1: Graphs showing the relationship between age and the volume of hippocampus, cerebellum and prefrontal areas. (A = lateral prefrontal cortex; B = orbitofrontal cortex; C = hippocampus; D = cerebellum). Adapted from Raz et al., 2005.

Changes in MTL volume, PFC volume and relationship to memory

Some associations between volumetric changes in aging and cognitive ability have been reported. For instance, one longitudinal study found that older adults with declining sentence recall and face recognition performance over time exhibited a reduction in hippocampal volume compared with older adults whose task performance remained stable over time (Persson et al., 2006). In a cross-sectional design Rosen and colleagues (2003) showed a significant relationship between verbal memory performance and MTL volume in older adults; with the strongest associations found between entorhinal cortex volume and immediate word recall, and between hippocampal volume and delayed paragraph recall. Rodrigue and Raz (2004) found that shrinkage of the entorhinal cortex but not the hippocampus or PFC, over a 5 year period, was related to poorer verbal memory performance at follow-up. Although hippocampal and PFC volumes were also found to be negatively related to age at baseline and at follow-up, these volume differences were not found to be associated with memory performance once age was taken into account. A 3-

year study carried out by Tisserand and colleagues (2004) on an elderly cohort found that participants who exhibited significant cognitive decline between baseline and follow-up showed a significant reduction in grey matter density in prefrontal cortex, parietal cortex, and in the medial temporal lobe, in comparison to age-matched controls whose cognitive performance remained stable over the same time period. There is also evidence of a distinction where cortical grey matter volume and hippocampal grey matter volume are concerned, with one study finding that cortical volume predicted successful verbal recall at short delays, whereas hippocampal volume predicted recall after a number of weeks (Walhovd et al., 2004).

There have also been several negative findings with respect to an association between cognitive task performance and regional volumes (e.g. Gunning-Dixon & Raz, 2003; Tisserand et al., 2000). Gunning-Dixon and Raz found no relationship between prefrontal cortex volume and working memory performance in a group of older adults (50-81 years), though greater PFC volume and fewer white matter hyperintensities were associated with better performance on the Wisconsin Card Sort Task of executive function. Furthermore, in some cases, a negative relationship between brain volume and task performance has actually been reported (Van Petten et al., 2004; Salat et al., 2002). The latter study found that larger orbitofrontal cortex volumes predicted poorer working memory performance in a group of older adults ranging from 72 to 94 years of age. Haier and colleagues (2005) examined the relationship between memory task reaction times and volume changes in aging. Interestingly, they found a dichotomy where aging was concerned. In several frontal regions, including the prefrontal cortex, smaller volumes were associated with slower reactions times in middle-aged participants, but with faster reaction times in the elderly group. Thus, it may be the case that the relationship between cognitive task performance and volume is variable throughout the lifespan, and may be very region specific.

Buckner (2004) has suggested that separable processes of neuroanatomical change underlie the cognitive deficits in normal aging and dementia. He maintains that while medial temporal lobe pathology is a hallmark of AD and MCI, it is frontal-striatal change that is primarily responsible for the milder impairments in memory and cognitive function evident in normal aging. This view is consistent with reports of an association between changes in frontal grey matter and cognitive function (e.g. Tisserand et al., 2004), as well as evidence

from cross-sectional studies of lifespan changes that the PFC shows the most pronounced age-related change (Raz et al., 2005).

Buckner argues that cross-sectional and longitudinal studies of age-related change that show evidence of hippocampal shrinkage are possibly marred by the inadvertent inclusion of individuals who may be in the pre-clinical stages of dementia (Buckner, 2004). Support for this theory is provided by a recent study by Reitz and colleagues (2009). They examined the association between hippocampal and entorhinal cortex volumes, cerebral blood volumes (CBVs) and episodic memory in an elderly cohort comprising a mixture of healthy aged individuals and individuals with dementia. They found a strong association between hippocampal volume reduction and episodic recall, however, when individuals with Alzheimer's disease were omitted from the analysis, this association disappeared. Nevertheless, a strong association between reduced entorhinal cortex CBV and poorer memory performance remained.

The possibility that pre-clinical dementia could be a confounding factor in interpreting age-related structural brain change is a worthy caveat to the interpretation such studies, particularly in longitudinal studies that have not screened for the presence of pre-clinical dementia, and where the age range for inclusion is elderly (in the range of 60 to 90 years of age).

6.2.2 Hippocampal volume and the stress response in aging

Although an age-related decline in hippocampal volume has frequently been reported, less is known about the variability in hippocampal volume during aging. Lupien and colleagues (2007) carried out a study which aimed to shed light on this issue. Their primary goal was to determine whether aging was associated with increased variability in hippocampal volume. Interestingly, while the authors demonstrated a general age-related volumetric decline, they found no evidence that aging is associated with greater variability in hippocampal volumes. Instead, it appears that hippocampal volume is as variable in youth as it is in old age, with some individuals in their 20's having hippocampi that are as small as those in their 70's. The authors also pose the question of whether this inter-individual variability, which seems to be unrelated to age, could reflect the variation between individuals in their exposure to early-life stressors. A related question is whether small hippocampal volumes, in turn, render individuals more susceptible to stress-related pathologies and cognitive dysfunction in later life?

Studies in rodents have shown that increased prenatal and perinatal stress is associated with both inhibition of hippocampal neurogenesis and age-related hippocampal impairments (Lemaire et al., 2000; Meaney et al., 1988). Moreover, increased stress during adolescence in rodents alters hippoccampal morphology and increases subsequent sensitivity to stress in adult life (Isgor et al., 2004). In the human literature adults with a history of childhood sexual abuse display reduced hippocampal volumes when compared to those with no history of exposure to such stress in youth (Andersen & Teicher, 2008). In addition, there is evidence that childhood stress can impede the proper development of the prefrontal and anterior cingulate cortices (Cohen et al., 2006), suggesting that these structures, which continue to develop into adolescence, may also be vulnerable to the effects of early-life stress.

The psychopathology literature would seem to support the above hypotheses, as smaller hippocampal volumes and poorer performance on related memory measures have been associated with various stress-related pathologies such as PTSD and depression (Bremner et al., 1995; Frodl et al., 2006; Kaymak et al., 2009; Sheline et al., 1996). Furthermore, several studies have demonstrated an inverse relationship between hippocampal volume and cortisol levels in aging, with prolonged elevated cortisol levels being correlated with reduced hippocampal volume and memory impairments in elderly individuals (e.g. Lupien et al., 1998; see Chapter 4, section 4.2). Thus it seems likely that there is a close relationship between the volume of brain structures involved in the stress response, exposure to stressors, and cognitive decline in aging. The question of directionality however, remains an issue, as the dynamics of cause and effect are not yet clear. The age at which this relationship manifests is also an issue of uncertainty. Most research to date has focused on the relationship between cortisol, hippocampal volume and cognitive dysfunction in elderly individuals only, thus making it difficult to pinpoint at what point such a relationship might emerge.

6.2.3 Aims of the current study in the context of the literature

In Chapter 3 we showed the emergence of a pronounced deficit in associative memory in the 5th decade in our lifespan cohort. While pre-morbid IQ and education undoubtedly influence memory performance, it was noteworthy that a marked deficit in performance still remained after controlling for these factors. Thus, the question as to what can account for this pronounced decrement in performance at this relatively early stage in the aging process, is a pertinent one. There is considerable evidence that grey matter volume

declines in aging, and that certain regions may be more susceptible to this age-related decline, or show an accelerated rate of decline, compared with other regions (Raz et al., 2004, 2005). The relationship between this volume decline and memory, however, is less clear as studies probing this relationship have yielded mixed results. Furthermore, the majority of studies exploring the relationship between episodic memory and volume decline, in particular, have used relatively elderly cohorts and either tracked changes in elderly subjects longitudinally, or compared elderly individuals with young controls. The reason for this is likely that researchers feel that any association between memory performance and regional grey matter volumes should be more pronounced the further along in the aging process they probe. However, in some cases, this approach may be flawed or clouded by the risk of including individuals who are in the pre-clinical stages of dementia, if proper screening is not applied. There is a need to examine the relationship between memory performance and structural brain change earlier on in the normal aging process, especially with regard to the evidence from our lifespan study that healthy middle-aged adults exhibit significant impairments on certain types of memory task, when compared younger adults.

An inverse relationship between cortisol levels and cognitive performance in old age has been previously reported. In addition, some studies have found a negative relationship between cortisol levels and hippocampal volume (e.g. Lupien et al., 1998). While effects of stress on the integrity of the prefrontal cortex have been reported (Cohen et al., 2006; Kremen et al., 2010), to our knowledge no one has explicitly investigated the relationship between cortisol levels and prefrontal cortex volume in aging. The results presented in Chapter 4 also raise the possibility that higher cortisol levels could be negatively related to hippocampal and perhaps prefrontal volumes in aging, which in turn may be related to poorer memory performance.

A second question of interest is whether there is a relationship between the response to stress and regional brain volumes, particularly the hippocampus and prefrontal cortex, and whether this may affect cognitive performance in aging. MRI scanning may be a useful tool not only to examine brain changes in aging, but also as a mild stressor. Previous research as shown an association between an increase in cortisol levels during scanning and memory performance (Kukolja et al., 2008).

With the aim of attempting to address the above issues, the current study will use voxel-based morphometry (VBM) to assess regional grey matter volume changes in aging, and their association with associative memory performance and cortisol levels. We chose to examine middle-aged adults in their 40's, being the age group during which associative memory problems first seem to emerge, and included a young adult group in their 20's as a comparison. Participants will perform the Face-Name Pairs task while in the MRI scanner, in order to see whether this mildly stressful environment would affect cortisol levels and task performance.

6.2.4 Hypotheses

1. The 40's age group should exhibit smaller regional grey matter volumes than the 20's age group, particularly in frontal areas.
2. Hippocampal and prefrontal grey matter volumes will be positively related to associative memory performance in the 40's group.
3. Higher cortisol levels will be associated with poorer cognitive performance and smaller hippocampal volume; in particular, a greater cortisol response to MRI scanning should be associated with poorer task performance and smaller hippocampal volume.

6.3 Methods

6.3.1 Participants

A total of 46 participants aged 20 to 49 years took part in this study. They were recruited via college e-mail and online noticeboard, recruitment posters, and advertisement in local newspaper. All participants were fluent English speakers and had normal or corrected-to-normal vision. Exclusion criteria were: a history of stroke; heart disease; head trauma; left-handedness; psychiatric or neurological illness; current use of psychoactive medication; a history of endocrine disorder (e.g. thyroid dysfunction or diabetes); current use of glucocorticoid (steroid) medication and pregnancy. The study was approved by the School of Psychology Ethics Committee, Trinity College Dublin. Participants were compensated for their time and travel expenses in accordance with School of Psychology guidelines. Psychology undergraduate students who participated were offered research credits as an alternative to monetary compensation. Written, informed consent was obtained from each participant prior to the commencement of the study (see Appendix), and participants' attention was especially drawn to the contraindications to undergoing an MRI scan. Exclusion criteria specific to MRI scanning included: presence of metal implants; large tattoos; pregnancy. General practitioner (GP) details were obtained from each participant once a scanning appointment was made, and a letter was sent to each participants's GP notifying them of the impending scan in accordance with university policy (see Appendix).

Participants were divided into two age groups: 20-29 years and 40-49 years. The 20's group consisted of 21 participants (6 males; mean age = 24.75, SD = 2.99, range = 20-29). The 40's group consisted of 25 participants (8 males; mean age = 43.65, SD = 3.15, range = 40-49). A subgroup of these participants provided saliva samples for cortisol analysis pre- and post-scanning. The total number of participants included in the cortisol analyses was 36. The 20's group consisted of 20 participants (4 males; mean age = 24.80, SD = 2.98, range = 20-29), and the 40's group comprised 16 participants (4 males; mean age = 43.68, SD = 3.15, range = 40-49).

6.3.2 Pre-scanning measures

On arrival participants were brought to a briefing room. They were taken through the information leaflets and consent forms, and informed consent was obtained. Participants then filled in the checklist and were administered the state form of Spielberger's State-

Trait Anxiety Inventory (see Chapter 2, section 2.7.2). Participants then had the scanning procedure and tasks explained to them in full. They performed a Face-Name pairs training task (encoding phase, distraction task, and recall phase), which was identical in procedure to the actual tasks used in the MRI scanner (apart from the faces and names used). Participants practised writing their responses on an A4 pad and raising their pencil during the distraction task (see below, section 6.3.3.2). After task training was completed, participants gave a saliva sample (pre-scan cortisol) using the Salivette sampling device (see Chapter 2, section 2.9) and were brought down to the MRI scanner.

6.3.3 Procedure

6.3.3.1 General

The time of day at which participants underwent the MRI scanning and cognitive testing ranged from 9 am to 3 pm (see section 6.2.2). This was due to logistic difficulties in obtaining scanning slots at a particular time of day. To control for this fact, the time of testing was included as a nuisance covariate in regression analyses involving cortisol measures, where it was deemed to be an influencing factor in interpretation of the results.

Participants who donated saliva samples for cortisol analyses were instructed to fast for an hour before the testing session, to avoid any interaction between glucose release and cortisol (Kirschbaum et al., 1997). This extended to the intake of all drinks (except for water). Participants were also asked not to smoke during this time as owing to the acute effects of nicotine on cortisol levels (Mello, 2009).

All participants undergoing MRI scanning were instructed to remove any metal jewellery, belts, coins, or any other metal items from their person, before entering the inner room where the magnet was housed. Participants who wore glasses were offered prescription goggles to facilitate easier viewing of the stimuli when inside the scanner.

6.3.3.2 Face-Name Pairs task design and procedure

The cognitive task used was the Face-Name Pairs task (see Chapter 2, section 2.5.1) which was chosen to probe associative memory. Participants performed two Face-Name Pairs tasks in the scanner, Task 1 and Task 2. Both tasks were identical in procedure and length, the only difference between the two being the use of different faces and names for each.

The experiment was part of a larger study involving a functional neuroimaging component and thus there were several modifications made to the design and execution of the Face-Name Pairs task from that which was used in Chapters 3 and 4 to facilitate this. Participants performed five blocks of encoding and recall for each task. In addition, during the recall phase, participants were required to write their responses, as verbalising them would have led to considerable head movement. Participants were equipped with an A4 pad of paper and a pencil which they rested on their lower torso, and ensured that they could write comfortably and legibly on the paper whilst in the horizontal position, before entering the scanner. Participants were instructed to write down the name corresponding to each face during the recall phase of the task, one under another, and that if they did not know a name they should put either a question mark or a dash on the sheet. One of the experimenters sat beside the scanner during the scan. After each recall phase, they gently removed the A4 pad from where it was positioned, tore away the top sheet, and gently replaced it. This was to ensure that the participant had a blank A4 sheet of paper to write on for every block. The distraction task was also modified slightly from the version outlined in Chapter 2, section 2.5.1.3. Instead of pressing a button on a response box, participants were required to raise their hand (from the wrist only) every time the cross was replaced with a solid black circle. This was in order to keep their attention focused on this visual stimulus and prevent overt rehearsal of the face-name pairs.

6.3.3.3 Face-Name Encoding and Immediate Recall

Each task was divided into 3 runs: Runs 1 and 2 each contained 2 blocks of encoding and recall; run 3 contained 1 block of encoding and recall. Thus each task consisted of 5 blocks in total. The order of presentation of the tasks was counterbalanced between subjects, as was the order of presentation of the runs (although run 3 was always last as it was shorter). At the beginning of each run participants' viewed a countdown for 6 seconds. Each block started with instructions for 3 seconds (the instructions merely indicated the task phase, e.g. "Face-Name Encoding"). Each face-name pair was then presented for 4 seconds interspersed with a variable (jittered) interstimulus interval (ISI) of 2, 4, 6, or 8 s (end ISI was 1.5 seconds). During the ISI participants viewed a fixation cross which moved around the screen. They were under instruction to visually track the movement of this cross. Following the encoding phase, participants viewed instructions (3 seconds) for the distraction task which lasted 17 seconds. This was followed by the recall phase of the task, which began with instructions (3 seconds). Each face then appeared with

the prompt "NAME?" beside it for 4 seconds with a jitter of 2, 4, 6, or 8, seconds (end jitter 1.5 seconds). Each block lasted a total of 212 seconds.

The T_1 – weighted anatomical scan and clinical scan were obtained following performance of the Face-Name Pairs task. The T_1 – weighted images were subsequently used for MRI analysis using Voxel-Based Morphometry (VBM).

6.3.4 Post-scanning Measures

Immediately following the scan participants were brought back to the briefing room. They then donated another saliva sample for cortisol analysis (post-scan cortisol), and also completed the state form of the State-Trait Inventory once again. Participants were then debriefed and compensated for their time.

6.3.5 Data acquisition, preprocessing and statistical analyses

6.3.5.1 Behavioural data

All analyses were carried out using SPSS (version 16) for PC. Data are expressed as mean ± SE unless otherwise stated. The critical α level was .05. ANOVA and multiple regression analysis were the primary statistical tools used. Where sphericity could not be assumed, Greenhouse-Geisser corrected values were reported (G.G.). Where homogeneity of variance could not be assumed, Mann-Whitney U non-parametric tests were employed to test for between-group differences on the behavioural measures. Multiple regression analyses were carried out as detailed in Chapter 4, section 4.3.4.

6.3.5.2 MRI data

The preprocessing steps required for the VBM analysis of the MRI data, as well as the main analysis techniques and statistical thresholds are detailed in Chapter 2, section 2.10. The statistical tool used to examine between-group differences in regional grey matter volume was the *t*-test. A one-tailed test was chosen as the hypothesis was that the 20's would show larger volumes than the 40's group. Thus the 20s> 40's contrast was applied. However, the opposite contrast, 40s>20s, was also tested. Multiple regression analyses were then carried out in order to explore any association between task performance and grey matter volume, and between cortisol levels and brain volume. Where Face-Name Pairs task performance was the covariate of interest, age was also entered into the regression model as a nuisance covariate, along with TIV. This was in order to remove any variance in the model that was attributable to age. Where pre- scan cortisol levels was

the covariate of interest, the time of testing was entered into the analyses as a nuisance covariate in order to minimise variance due to the natural diurnal fluctuation in cortisol levels. Regression analyses were also run for each age group separately, so as to indicate the strength of any associations observed and whether the relationship between the variable of interest and regional grey matter volume differed depending on the age group in question. We hypothesised that we would see a positive relationship between regional brain volume and task performance, and a negative relationship between regional brain volume and cortisol levels; however, we also tested the opposing contrast in each case.

Exclusion of participants

3 participants in the 40's group (1 male and 2 females) had to be excluded from the MRI analysis due to improper segmentation and registration during the preprocessing stage. Thus the total number of participants available for VBM analysis was N = 43 (20s' N = 21, 6 males; 40's N = 22; 7 males).

6.4 Results

6.4.1 Education levels

There was no significant difference in education levels between the groups, $F(1,45) = 3.37$, $p > .05$ (see Table 6.1).

Age Group	20s	40s
Education	18.59 (± 0.55)	17.00 (± 0.66)

Table 6.1: Mean number of years spent in formal education (± SEM)

6.4.2 Time of testing

As there is considerable diurnal variation in cortisol levels, the time of day during which the cortisol sampling and MRI scanning took place was taken into account. A chi-squared analysis was first conducted in order to ascertain whether both levels of the variable Age Group (20s vs 40s) were equally distributed across both levels of the variable Time of Testing (before noon vs after noon). The analysis revealed no significant association between age group and the time of the testing session, $X^2(1) = 1.950$, $p > .10$ (see Table 6.2).

Age Group	20s	40s
Before noon	14	12
After noon	7	13

Table 6.2: Numbers of participants tested in the morning and afternoon

6.4.3 Effect of age group and time of testing on cortisol levels

Salivary cortisol was assessed immediately before MRI scanning and again just after scanning. The cortisol response was derived by subtracting the pre-scanning cortisol value from the post-scanning value, and was investigated as an indicator of stress during the scanning procedure (Kukolja et al., 2008).

Mean values for both age groups are displayed in the table below, and reflect concentration in nmol/L (see Table 6.3).

Age Group	**20s**	**40s**
Pre-scanning cortisol	7.00 (± 0.98)	8.50 (± 1.34)
Post-scanning cortisol	6.90 (± 0.79)	8.81 (± 1.09)
Cortisol response	- 0.63 (± 0.75)	0.29 (± 0.89)

Table 6.3: Mean salivary cortisol levels (± SEM) pre- and post-scanning, and the response to scanning.

A mixed within-between ANCOVA was conducted to examine the effect of age group on pre- and post-scanning cortisol levels, with time of testing as a covariate. There was no significant main effect of the time of testing on cortisol levels, $F(1,34) = 1.91$, $p > .10$, nor was there is significant within-group interaction between sample time (pre- or post scanning) and time of testing, $F(1, 34) = 3.37$, $p > .05$. There was no main effect of age group on cortisol levels, $F(1,34) = 0.50$, $p > .10$, nor was there a within-group interaction between age and sample time, $F(1, 34) = 0.36$, $p > .10$. Finally, there was no significant within-group effect of sample time on cortisol levels, $F(1, 34) = 3.05$, $p > .05$.

6.4.4 Task performance in the 20's and 40's

Face-Name Pairs Learning and Recall

Task 1

A repeated-measures ANOVA was carried out to explore between group differences in performance across the 5 encoding blocks. There was a significant main effect of task block on performance $F(3.352, 150.849) = 150.099$, $p < .001$ (G.G.). There was also a significant main effect of age group on performance, $F(1,43) = 9.386$, $p < .01$. There was no significant interaction between age group and block $F<1$, $p > .10$ (see Figure 6.2).

Task 2

A repeated-measures ANOVA was again carried out to explore performance across the 5 blocks. There was a main effect of block on performance, $F(3.001, 138.516) = 92.354$, $p < .001$ (G.G.). There was also a main effect of age group on performance, $F(1,44) = 8.954$, $p < .01$. There was no significant interaction between age group and block, $F < 1$, $p > .10$ (see Figure 6.3).

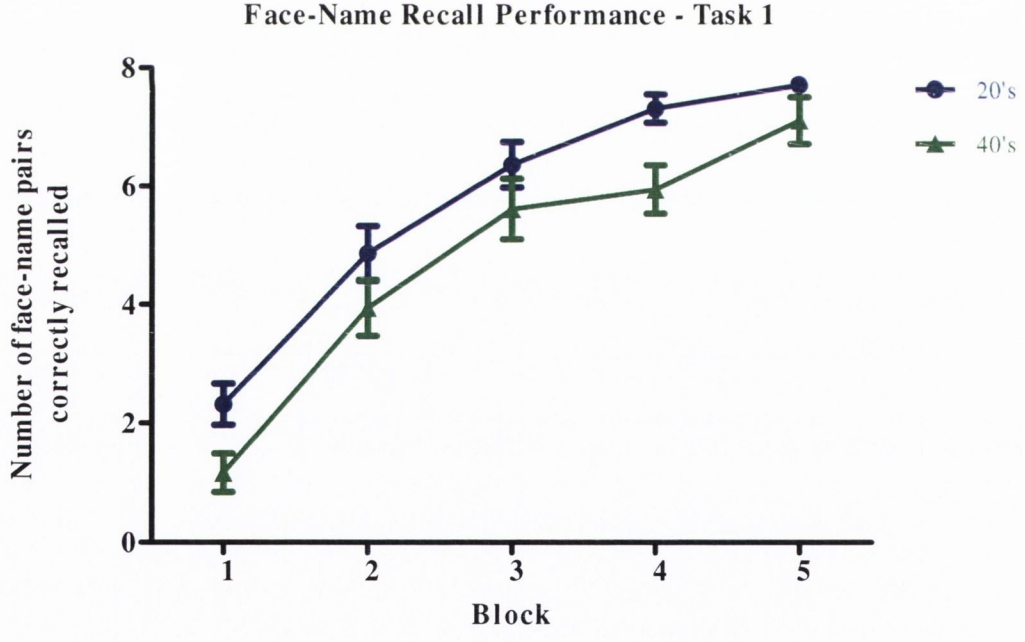

Figure 6.2: The number of face-name pairs successfully encoded and recalled at each block in Task 1 for each age group.

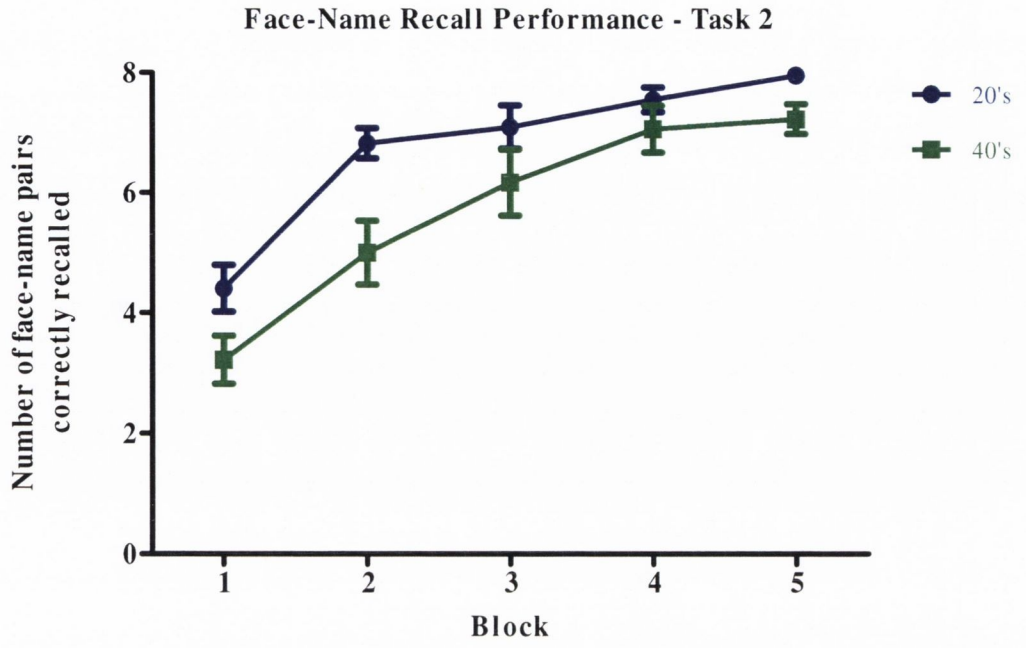

Figure 6.3: The number of face-name pairs successfully encoded and recalled at each block in Task 2 for each age group.

Total learning and immediate recall

Task 1

A one-way ANOVA was carried out to determine the effect of age group on total recall performance for Task 1. There was a significant difference in performance between the age groups, with the 20's group (mean = 29.55, SD = 5.19) performing better than the 40's group (mean = 23.92, SD = 5.55), $F(1,43) = 12.08$, $p < .01$.

Task 2

Owing to the violation of the assumption of homogeneity of variance between the groups on total recall performance in this task, a Mann-Whitney U non-parametric test was employed to test for a between-group difference. This revealed that the 20's group (mean rank = 30.74) performed significantly better than the 40's (mean rank = 18.56), U = 131.5, $p< .01$.

Total Score

Participants' total recall score on both tasks was summed to give an overall recall score for the two tasks. The Mann-Whitney U test revealed that the 20's group (mean rank = 30.45) had a significantly higher total recall score than the 40's group (mean rank = 16.46), U = 86.5, $p < .001$.

6.4.5 State anxiety pre- and post-scanning

A repeated measures ANOVA was carried out to determine whether the groups differed in their change in anxiety scores from before scanning to immediately after scanning. The analysis revealed no main effect of time, $F(1, 45) = 2.55$, $p > .10$, nor a main effect of age group, $F(1, 45) = 0.39$, $p > .10$. Finally, there was no significant interaction between age group and time, $F(1, 46) = 0.11$, $p > .10$ (see Table 6.4).

Age Group	**20's**	**40's**
State Anxiety Pre-testing	30 76 (± 1.85)	31.79 (± 2.06)
State Anxiety Post-testing	28.48 (± 1.16)	30.73 (± 1.74)

Table 6.4: State-anxiety scores pre- and post-scanning.

6.4.6 Association of cortisol levels with task performance

We firstly conducted a series of multiple regression analyses to determine whether the cortisol response to scanning was predictive of task performance. The indicator variable $Y_0 O_1$ was entered into the equation, along with the interactive term $Y_0 O_1$ X response. Furthermore, pre-scanning cortisol levels were also entered into the equation as a nuisance covariate. Thus the equation was derived as follows:

$$Y = \beta_0 + \beta_1 * Y_0 O_1 + \beta_2 * \text{Response} + \beta_3 * Y_0 O_1 \text{ X Response} + \beta_4 * \text{Pre-scan cortisol} + \varepsilon$$

Where

Y is the outcome variable

ε is the error term

The total amount of variance in the outcome variable that can be explained the model (R^2), as well as the importance of the individuals predictors in turn (standardized β values, t and associated p values), are reported below in Table 6.5.

Y	R^2	Predictor	Std. Beta	*t*	*p*
Task 1: Total Recall Score	0.55	Y_0O_1	- 0.535	- 3.854	< .001***
		Response	- 0.200	- 0.714	> .10
		Y_0O_1 X Response	- 0.021	- 0.083	> .10
		Pre-scan cortisol	- 0.473	- 2.704	< .01**
Task 2: Total Recall Score	0.45	Y_0O_1	- 0.349	- 2.349	< .05*
		Response	- 0.097	- 0.334	> .10
		Y_0O_1 X Response	- 0.142	- 0.537	> .10
		Pre-scan cortisol	- 0.113	- 0.712	> .10
Total Score	0.45	Y_0O_1	- 0.578	- 4.113	< .001***
		Response	- 0.132	- 0.259	> .05
		Y_0O_1 X Response	- 0.098	- 0.199	> .05
		Pre-scan cortisol	- 0.232	- 1.474	> .05

Table 6.5: Multiple regression analyses showing the association of the cortisol response with task performance.

Given that the cortisol response was not found to significantly predict task performance, but pre-scan cortisol levels were found to have predictive value, the regression analyses were run again. This time the terms containing the variable Response were omitted and an age group X pre-scan cortisol interactive term was added to the equation, to ascertain whether the combination of older age and higher pre-scan cortisol levels was predictive of worse Face-Name Pairs task performance. Time of day was also included as a nuisance covariate in order to control for the diurnal fluctuation in cortisol levels.

The regression equation was thus derived as follows:

$$Y = \beta_0 + \beta_1 * Y_0 O_1 + \beta_2 * \text{Pre-scan cortisol} + \beta_3 * Y_0 O_1 \text{ X Pre-scan} + \beta_4 * \text{Time of day} + \varepsilon$$

The total amount of variance in the outcome variable that can be explained the model (R^2), as well as the importance of the individuals predictors in turn (standardized β values, *t* and associated *p* values), are reported in Table 6.6.

Y	R^2	Predictor	Std. Beta	*t*	*p*
Task 1: Total Recall Score	0.46	Y_0O_1	0.594	1.277	> .10
		Pre-scan cortisol	0.249	1.082	> .10
		Y_0O_1 X Pre-scan	- 1.234	- 2.457	< .05*
		Time of day	- 0.118	- 0.621	> .10
Task 2: Total Recall Score	0.49	Y_0O_1	0.064	0.222	> .10
		Pre-scan cortisol	- 0.070	- 0.320	> .10
		Y_0O_1 X Pre-scan	- 0.690	- 2.071	< .05*
		Time of day	- 0.159	- 1.069	> .10
Total Score	0.51	Y_0O_1	- 0.164	- 0.482	> .10
		Pre-scan cortisol	- 0.109	- 0.452	> .10
		Y_0O_1 X Pre-scan	- 0.480	- 1.216	> .10
		Time of day	- 0.163	- 0.881	> .10

Table 6.6: Multiple regression analyses of the association between pre-scan cortisol levels and task performance

We then carried out the multiple regression analyses for each group separately (see Table 6.7) to further explore the interaction between age group and pre-scan cortisol levels.

Y	Age Group	R^2	Predictor	Std. Beta	*t*	*p*
Task 1: Total Recall Score	20s	0.24	Pre-scan cortisol	0.569	1.148	> .05
			Time of day	0.337	1.097	> .10
	40s	0.46	Pre-scan cortisol	- 0.655	- 3.258	< .01**
			Time of day	- 0.473	- 2.367	< .05*
Task 2: Total Recall Score	20s	0.16	Pre-scan cortisol	0.284	0.838	> .10
			Time of day	0.486	1.438	> .10
	40s	0.28	Pre-scan cortisol	- 0.521	- 2.368	< .05*
			Time of day	- 0.308	- 1.402	> .10
Total Score	20s	0.08	Pre-scan cortisol	0.301	0.703	> .10
			Time of day	0.035	0.090	> .10
	40s	0.30	Pre-scan cortisol	- 0.507	- 2.248	< .05*
			Time of day	- 0.452	- 2.094	> .05

Table 6.7: Multiple regression analyses of the association between pre-scan cortisol levels and task performance, split by age group.

6.4.7 Voxel-Based Morphometry Results

6.4.7.1 Between-group differences in regional grey matter volume

We first explored whether there were any differences in regional brain volume between the 40's group and the 20's group. A one-tailed *t*-test revealed that the 40's group had significantly smaller grey matter volume in several areas of the brain (NOTE: no significant voxels were found for the opposite contrast 40's > 20's). All supra-threshold voxels that survived the FDR ($p < .05$) correction for multiple comparisons are displayed below (Figure 6.4) and reported in Table 6.8.

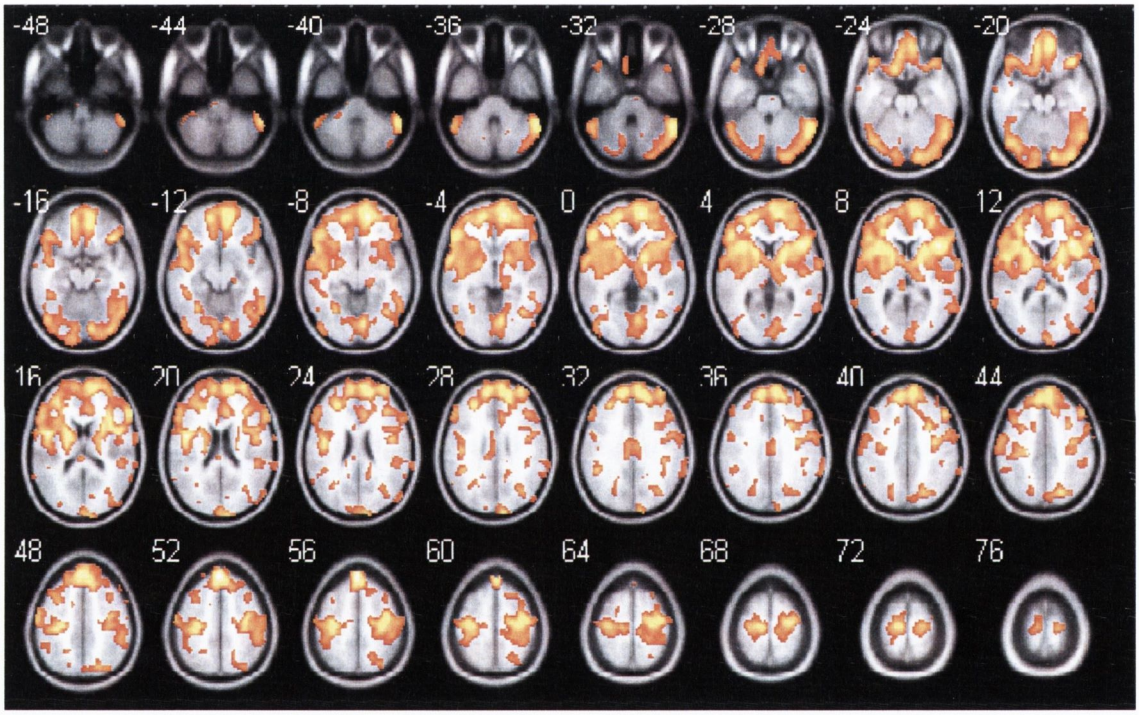

Figure 6.4: A slice-by-slice view of the brain regions that showed reduced grey matter volume in the 40's group compared with the 20's group.

cluster k	p (FWE-cor)	p (FDR-cor)	T	Z	p (unc)	x y z (mm)	Region
68452	0.000	0.000	8.67	6.61	0.000	-2 42 52	Left superior frontal gyrus (BA8)
	0.000	0.000	8.06	6.31	0.000	14 56 -4	Right medial frontal gyrus
	0.000	0.000	7.91	6.23	0.000	-46 0 18	Left inferior frontal gyrus (BA44)
102	0.398	0.001	4.35	3.95	0.000	-50 -60 -2	Left middle temporal gyrus
433	0.488	0.001	4.24	3.87	0.000	-30 -60 24	Left middle temporal gyrus
	0.703	0.001	4.00	3.68	0.000	-20 -70 42	Left precuneus
	0.867	0.002	3.78	3.50	0.000	-20 -54 34	Left precuneus
121	0.621	0.001	4.09	3.75	0.000	14 -52 26	Right cingulate gyrus
	0.977	0.003	3.50	3.27	0.001	16 -36 26	Right cingulate gyrus
106	0.671	0.001	4.03	3.71	0.000	-28 -86 10	Left middle occipital gyrus
160	0.735	0.001	3.96	3.65	0.000	-68 -52 10	Left superior temporal gyrus (BA22)
	0.995	0.003	3.34	3.14	0.001	-58 -58 24	Left superior temporal gyrus
64	0.749	0.001	3.94	3.63	0.000	-22 -52 48	Left precuneus
37	0.919	0.002	3.69	3.43	0.000	28 -82 -50	Right cerebellum
16	0.989	0.003	3.42	3.21	0.001	14 -62 -34	Right cerebellum
15	0.957	0.002	3.58	3.34	0.000	6 -18 -30	Right cingulate gyrus
4	0.993	0.003	3.37	3.16	0.001	-38 2 -30	Left middle temporal gyrus (BA21)
19	0.993	0.003	3.37	3.16	0.001	-56 -62 40	Right inferior parietal lobule (BA40)

Table 6.8: Regions displaying reduced grey matter volume in the 40's group compared with the 20's. FWE-cor = Family Wise Error corrected; FDR-cor = False Discovery Rate corrected; BA = Brodmann's area; x, y, z coordinates correspond to the values in MNI space.

6.4.7.2 The relationship between Face-Name Pairs performance and regional grey matter volume

We next explored whether there was any association between regional grey matter volume and participant performance on the Face-Name Pairs tasks when age was included as a covariate. Whole-brain multiple regression analysis revealed several suprathreshold clusters of voxels. However, no voxels survived the FDR correction for multiple comparisons. Regions of a priori interest (the hippocampus and parahippocampal gyrus, as well as the prefrontal cortex) were further examined by applying a small volume correction using local maxima of interest from the whole-brain SPM as the centre of a small volume (Maguire et al., 2000; Yamasue et al., 2003) and then setting significance levels at $p < .05$ corrected. This revealed a positive association between Face-Name pairs scores and grey matter volumes in Brodmann's area 11, encompassing the left medial frontal gyrus ($x = 6$, $y = 50$, $z = -18$; T score = 4.17), the right orbital gyrus ($x = -2$, $y = 20$, $z = -52$; T score = 4.08) and the middle frontal gyrus bilaterally (left: $x = -40$, $y = 42$, $z = -14$, T score = 4.84; right: $x = 44$, $y = 40$, $z = -14$, T score = 4.26; see Figure 6.5). Thus better performance on the Face-Name Pairs task was associated with larger prefrontal volumes in the group as a whole.

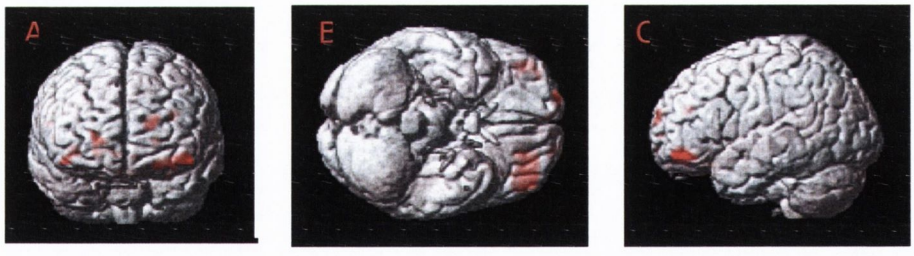

Figure 6.5: 3-D surface rendering of regions showing a significant positive association between grey matter volume and Face-Name Pairs task performance, in coronal (A), axial (B) and sagittal (C) views.

Separate group analysis

20's group

No voxels survived the correction for multiple comparisons at the whole-brain level. A small volume correction applied to local maxima of interest revealed only one cluster that survived the threshold ($p < .05$), located in the left middle frontal gyrus (BA11; coordinates $x = -40$, $y = 40$, $z = -16$ and $x = -40$, $y = 44$, $z = -15$; T scores = 4.11 and 4.04 respectively; see Figure 6.6).

Therefore, better Face-Name Pairs task performance was only associated with larger grey matter volume in the left middle frontal gyrus in this group.

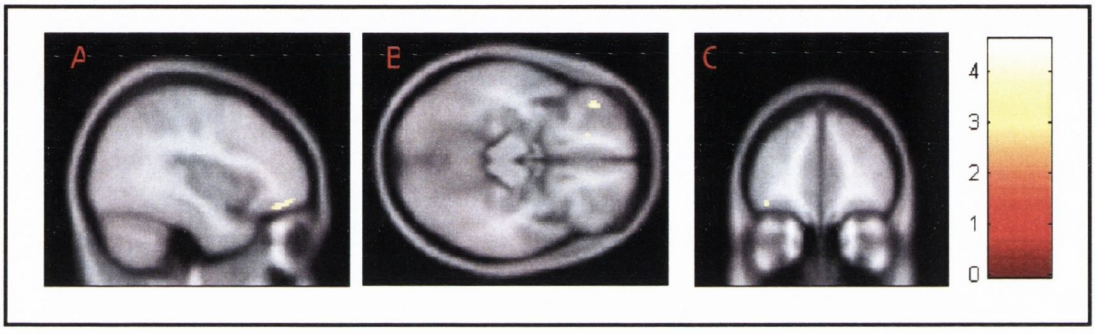

Figure 6.6: Colour maps displaying a significant positive association in the 20's group between task performance and middle frontal gyrus volume,(A = sagittal view, B = axial view, C = coronal view). The coloured bar displays T values.

40's group

Whole-brain analysis of the 40's group revealed many significant grey matter regions at the FDR ($p < .05$) corrected threshold, including left hippocampus, right parahippocampal gyrus, and prefrontal cortical areas bilaterally. Supra-threshold voxels surviving the correction were also identified in areas of the temporal, parietal and occipital cortices, as well as the cerebellum (see Figures 6.7 and 6.8).

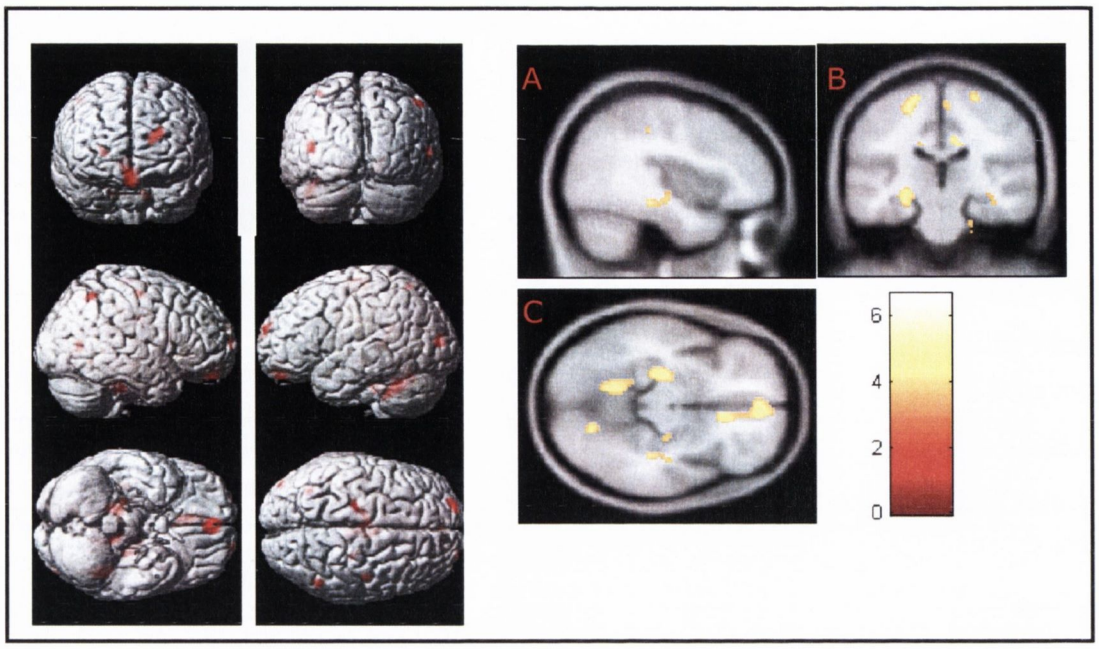

Figure 6.7: 3-D surface rendering and statistical colour maps showing regions in the 40's group (corrected for multiple comparisons) where task performance was positively related to grey matter volume. (A = sagittal view; B = coronal view; C = axial view). The coloured bar displays T values.

Thus better Face-Name Pairs task performance was significantly associated with larger grey matter volume in the brain regions outlined below (Table 6.9).

cluster k	p (FWE-cor)	p (FDR-cor)	T	Z	p (unc)	x y z (mm)	Region
78	0.085	0.050	6.63	4.66	0.000	64 -68 6	Right middle temporal gyrus (BA39)
911	0.240	0.050	5.91	4.35	0.000	10 30 -4	Right anterior cingulate
	0.557	0.050	5.22	4.02	0.000	4 50 -20	Right orbital gyrus (BA11)
160	0.310	0.050	5.72	4.26	0.000	12 -28 32	Right cingulate gyrus
	0.942	0.050	4.44	3.60	0.000	22 -34 40	Right cingulate gyrus
493	0.404	0.050	5.51	4.16	0.000	-44 -52 -32	Left cerebellum
131	0.474	0.050	5.37	4.10	0.000	-46 -92 12	Left middle occipital Gyrus (BA18)
128	0.480	0.050	5.36	4.09	0.000	54 -58 54	Right inferior parietal lobule (BA4)

cluster k	p (FWE-cor)	p (FDR-cor)	T	Z	p (unc)	x y z (mm)	Region
190	0.494	0.050	5.34	4.08	0.000	-24 64 24	Left superior frontal gyrus (BA10)
168	0.573	0.050	5.20	4.01	0.000	18 -74 0	Right lingual gyrus
	0.644	0.050	5.08	3.95	0.000	16 -72 -8	Right lingual gyrus
294	0.636	0.050	5.09	3.96	0.000	-14 -38 -36	Left cerebellum
	0.753	0.050	4.89	3.85	0.000	-14 -48 -32	Left cerebellum
	0.961	0.050	4.35	3.55	0.000	-8 -30 -30	Left cerebellum
158	0.744	0.050	4.90	3.86	0.000	-42 -38 6	Left superior temporal gyrus
	0.94	0.050	4.43	3.60	0.000	-42 -44 18	
260	0.810	0.050	4.78	3.79	0.000	-26 -22 -10	Left hippocampus
	0.941	0.050	4.44	3.60	0.000	-16 -18 -8	Substantia nigra
484	0.856	0.050	4.68	3.74	0.000	-14 -14 68	Left superior frontal gyrus (BA6)
	0.902	0.050	4.57	3.67	0.000	-8 -12 62	Left medial frontal gyrus (BA6)
	0.966	0.050	4.33	3.54	0.000	-24 -24 58	Left precentral Gyrus
326	0.884	0.050	4.61	3.70	0.000	-12 -54 -4	Left lingual Gyrus (BA19)
10	0.926	0.050	4.49	3.63	0.000	20 4 40	Right cingulate gyrus (BA24)
95	0.949	0.050	4.41	3.58	0.000	38 -30 -14	Right parahippocampal gyrus
65	0.962	0.050	4.35	3.55	0.000	46 -14 54	Right precentral Gyrus (BA4)
76	0.968	0.050	4.31	3.53	0.000	26 70 8	Right superior frontal gyrus
17	0.981	0.050	4.23	3.48	0.000	-46 -18 30	Left postcentral gyrus
40	0.981	0.050	4.22	3.47	0.000	46 -16 30	Right precentral gyrus
44	0.989	0.050	4.14	3.43	0.000	26 -24 66	Right precentral gyrus

Table 6.9: Grey matter regions showing a significant association with task performance in the 40's group. FWE-cor = Family Wise Error rate corrected; FDR-cor = False Discovery Rate corrected; BA = Brodmann's areas; x,y,z coordinates are in MNI space.

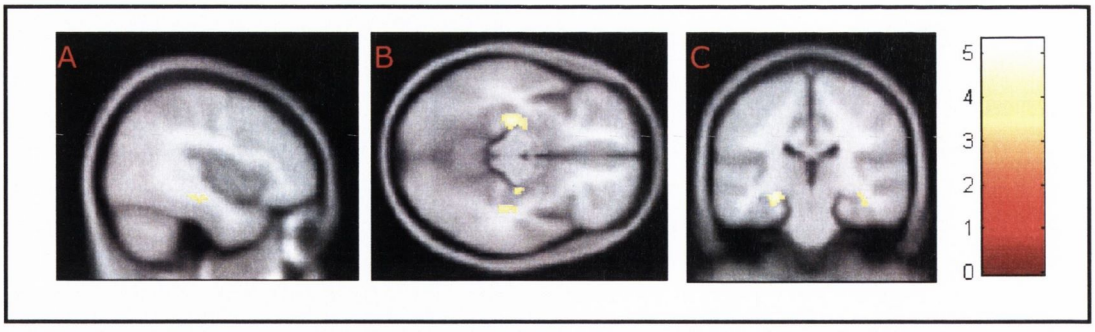

Figure 6.8: Statistical colour-maps showing a significant positive association between Face-Name Pairs task performance and the volume of the hippocampal complex bilaterally in the 40's group (A = sagittal view; B = axial view; C = coronal view). The coloured bar displays T values.

Scatter plots showing the relationship between hippocampal volume and task performance in the 40's group and 20's group are displayed overleaf (see Figures 6.9, 6.10, 6.11, and 6.12). The β weights from the multiple regression analyses were extracted for each individual and are plotted against the total Face-Name Pairs score.

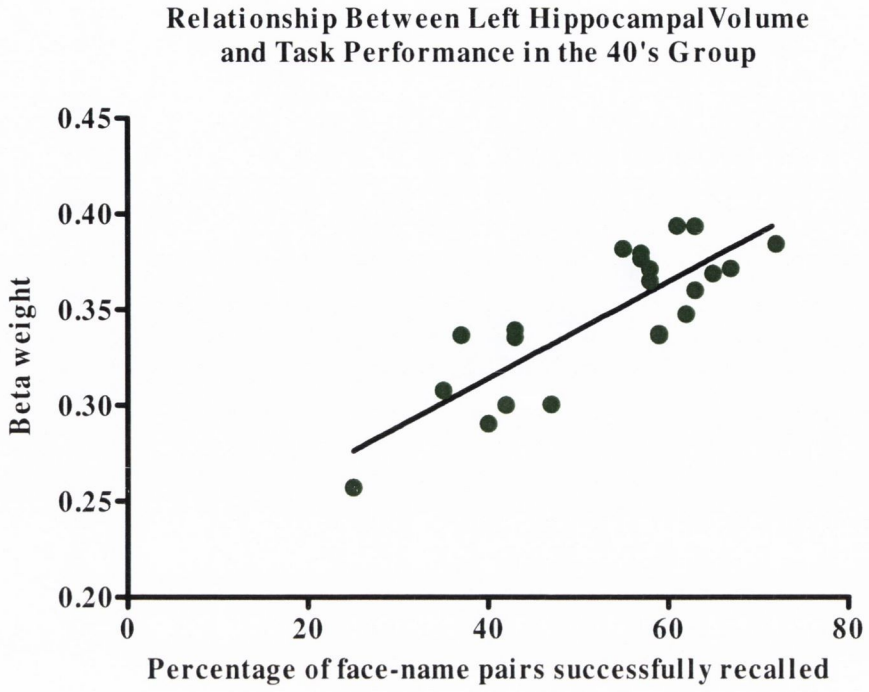

Figure 6.9: The relationship between left hippocampal volume (approximated by the size of the regression coefficient, or beta weight) and total Face-Name Pairs task performance in the 40's group.

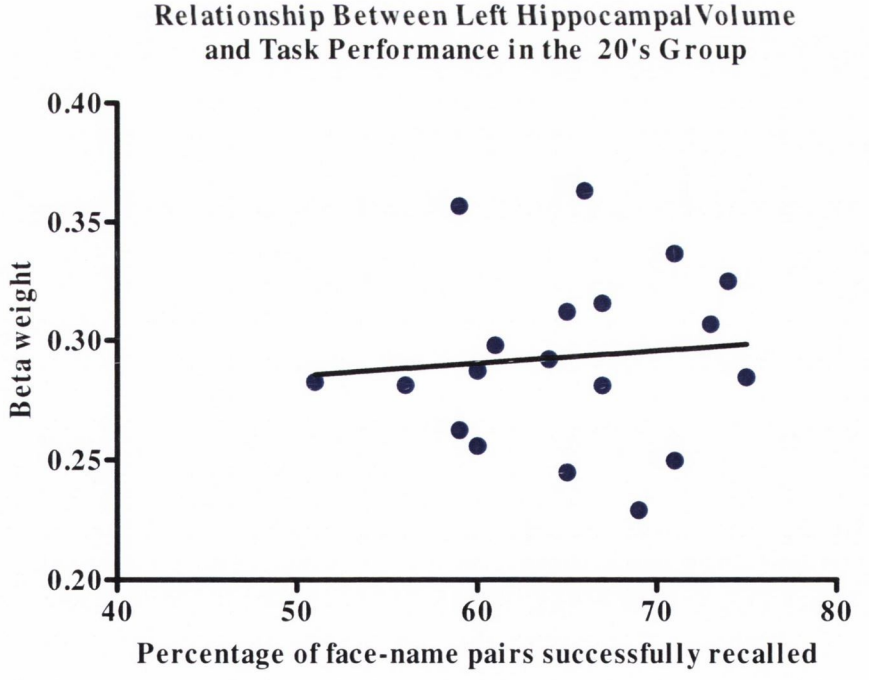

Fig 6.10: The relationship between left hippocampal volume (approximated by the size of the regression coefficient, or beta weight) and total Face-Name Pairs task performance in the 20's group.

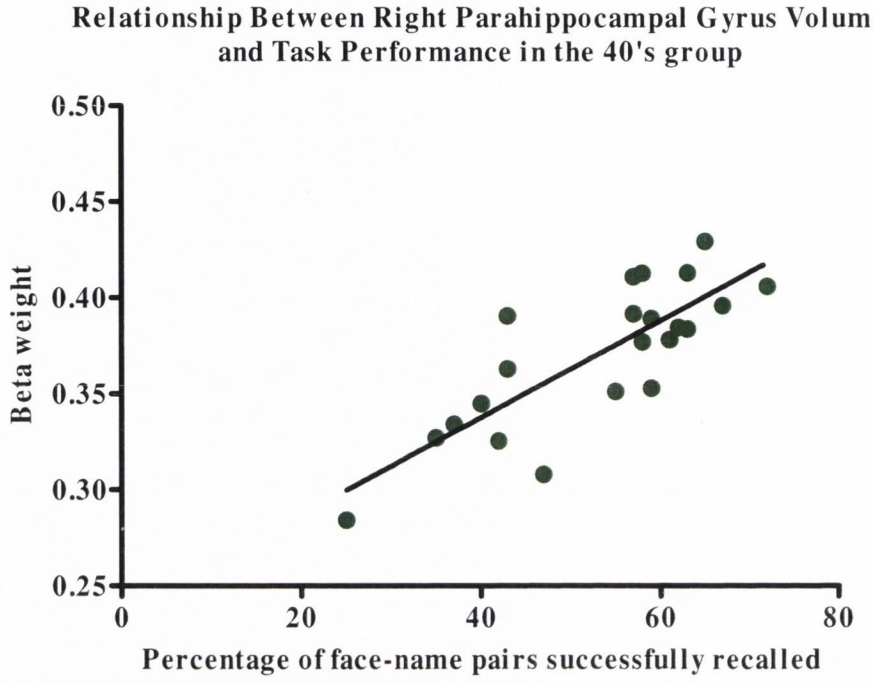

Figure 6.11: The relationship between right parahippocampal gyrus (PHG) volume (approximated by the size of the regression coefficient, or beta weight) and total Face-Name Pairs task performance in the 40's group.

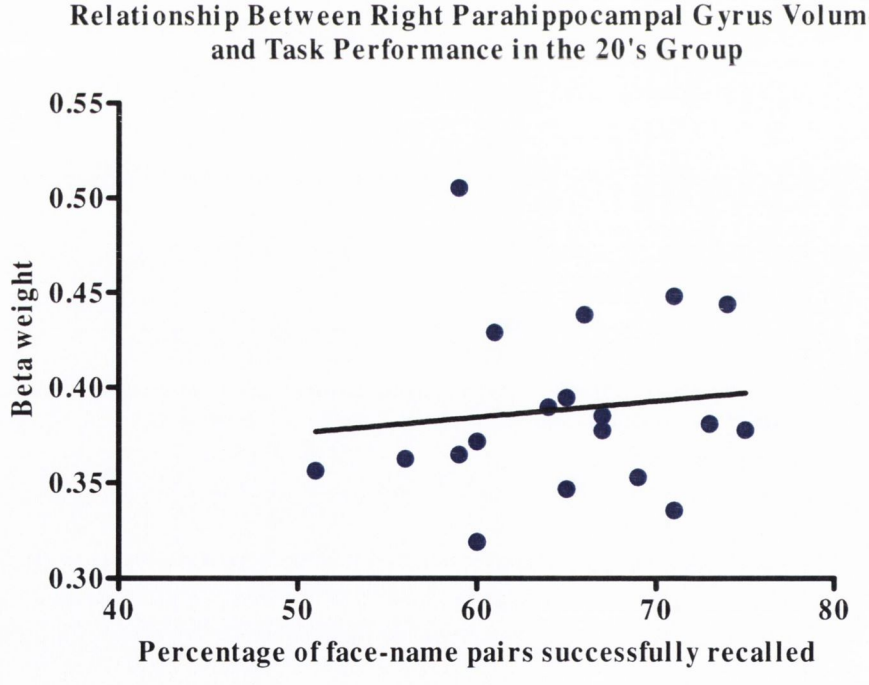

Figure 6.12: The relationship between right parahippocampal gyrus (PHG) volume (approximated by the size of the regression coefficient, or beta weight) and total Face-Name Pairs task performance in the 20's group.

6.4.7.3 The relationship between regional grey matter volume and cortisol levels

Regression analyses of the association between pre-scan cortisol levels and grey matter volume, with time of testing and TIV as nuisance covariates revealed no supra-threshold voxels. Equally, there was no association between post-scan cortisol levels and regional brain volume.

A multiple regression analysis entering cortisol response (post-scan minus pre-scan levels) as the covariate of interest revealed several clusters of voxels though none of these survived the correction for multiple comparisons. Analysis of local maxima in the MTL and PFC regions, however, revealed a significant negative association between an increase in cortisol levels during the MRI scan and regional grey matter volume in the left parahippocampal gyrus (x = -21, y = -20, z = -10, T score = 4.15, k = 43), and right medial frontal gyrus (BA11; x = 4, y = 52, z = -18; T score = 3.46, k = 15).

To ensure that the association between regional brain volumes and cortisol response was independent of task performance, we ran the regression analysis again including total Face-Name Pairs task score as a covariate of no interest.

While the right medial frontal gyrus no longer showed an association with cortisol response, the significant negative association between left parahippocampal gyrus volume and the cortisol response to scanning remained (x = -22, y = -20, z = -10, T score = 4.11, k = 18). In addition, supra-threshold voxels were also located in the right parahippocampal gyrus (x = 22, y = -18, z = -14; T score = 3.64, k = 7; see Figure 6.9). Thus a greater increase in cortisol levels during the MRI scan was significantly associated with smaller parahippocampal gyrus volumes bilaterally.

Investigation of each age group individually did not reveal supra-threshold voxels in any regions of interest.

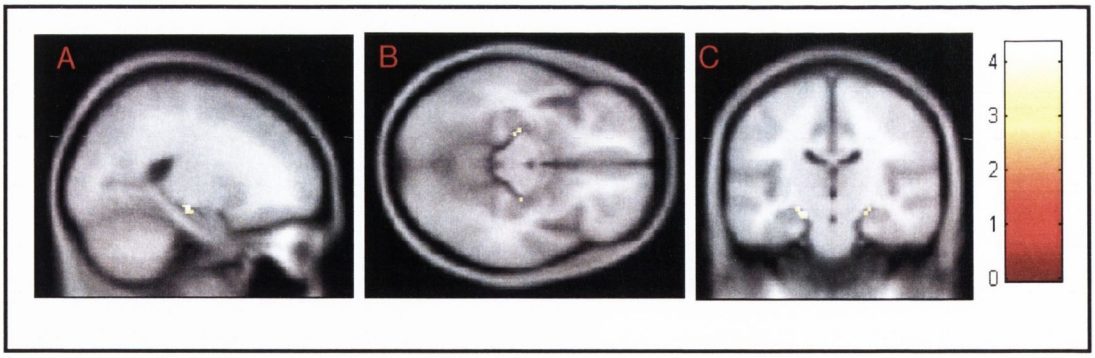

Figure 6.13: Statistical colour maps showing a significant negative association between grey matter volume in the parahippocampal gyrus bilaterally and the cortisol response to MRI scanning. (A = sagittal view; B = axial view; C = coronal view).

6.5 Discussion

This study investigated the grey matter volume changes that are evident in middle-age and how regional brain volumes may be related to associative memory task performance in this age group. A further aim of the study was to examine the relationship between cortisol levels during MRI scanning, memory performance in the scanner, and regional brain volume differences. To this end, we examined a middle-aged cohort (40's group) in which associative memory deficits have been previously shown to manifest, compared with a young adult group (20's).

The main findings are as follows:

1. The 40's group exhibited smaller regional grey matter volume in comparison to the 20's group in many areas. The most pronounced differences were evident in the region of the prefrontal cortex, encompassing the superior, medial and inferior frontal gyri. Differences were also found in areas of the parietal and temporal lobes as well as in the cerebellum. Notably, no significant volume differences were found in the medial temporal lobe.
2. The 40's group performed significantly worse than the 20's group on the Face-Name Pairs task. In the sample as a whole, better task performance was significantly associated with larger grey matter volume in frontal areas (the medial frontal and middle frontal gyrus and the orbital gyrus). When each age group was examined separately, many grey matter regions showed a significant positive relationship with task performance in the 40's group, including prefrontal cortex, hippocampus and parahippocampal gyrus. In contrast, only the middle frontal gyrus was significantly positively related to task performance in the 20's group.
3. There was a significant negative association between Face-Name Pairs task performance and cortisol levels immediately before scanning in the 40's group. However, no significant association was found between pre-scan cortisol levels and task performance in the 20's group and pre-scan cortisol levels were not significantly associated with regional grey matter volume in either group.
4. The change in cortisol levels during the MRI scan (cortisol response) was not found to be significantly associated with task performance. However, the magnitude of the cortisol response was found to be inversely related to grey matter volume in the medial frontal gyrus and in the left parahippocampal gyrus (PHG). Further analysis confirmed that the association between grey matter

volume in the left PHG and the cortisol response was independent of task performance, and an additional association between grey matter volume and cortisol response was found in the right parahippocampal gyrus.

6.5.1 The impact of aging on regional grey matter volume

The results of the VBM analysis comparing regional grey matter volume in the 20's group with those in the 40's group showed that the most pronounced volume differences appear to lie in the superior, medial and inferior frontal gyri. This evidence that grey matter volume is significantly reduced in these areas by middle-age is in line with previous cross-sectional and longitudinal findings that maintain that the prefrontal cortex is the most susceptible to age-related volume decline (Curiati et al., 2009; Raz et al., 2004, 2005; Resnick et al., 2007). Furthermore the between-group differences that were evident in other cortical areas in the parietal and temporal lobes in particular, are consistent with the view that the cerebral cortex in general shows more age-related volume decline than subcortical areas (Jernigan at al., 2001; Walhovd et al., 2005, 2009). Our results also showed significantly reduced grey matter volume in the cerebellum in the 40's group compared with the 20's. This too is consistent with prior reports that this structure is rather susceptible to age-related decline (Jernigan et al., 2001; Raz et al., 2005; Walhovd et al., 2005). The finding of a significant difference in grey matter volume in the occipital cortex in the current study is somewhat surprising, given that there is evidence that the visual cortex is relatively preserved in aging (Raz et al., 2005; Van Petten et al., 2004), though it has not typically been an area that has been the subject of much investigation.

The decline of hippocampal grey matter in aging is a matter of some debate, with considerable divergence among the results reported. We did not find any significant volume differences between the 20's and the 40's in medial temporal regions. A number of other studies which have attempted to chronicle changes in regional brain volume across the lifespan report that the hippocampus does not undergo marked age-related decline early on in the aging process, in comparison to cortical regions (Good et al., 2001; Smith et al., 2007; Van Petten, 2004). The Good et al. study is of particular interest as they investigated rates of acceleration of regional volume loss in relation to global grey matter decline, and found that medial temporal lobe regions showed relative preservation. Conversely, there is also support for the contention that hippocampal grey matter does undergo marked age-related decline (Jernigan et al., 2001; Lupien et al., 2007; Raz et al., 2004). Recently, several studies that have explored the nature of regional volume decline in aging have

reported that in contrast to regions like the frontal cortex that follow a roughly linear pattern of decline with age, the hippocampus exhibits a curvilinear decline (Fjell et al., 2005; Walhovd et al., 2005, 2009). This may help to explain discrepant findings, given that studies in this area typically draw inferences based on the use of considerably varied age groups and age ranges.

Given the finding from Chapter 5 that there are differences in the processing of emotional stimuli between the 20's and the 40's groups, it is also interesting to note that no difference in amygdala volume was found between the groups in the current analyses.

6.5.2 The relationship of associative memory performance to age and regional grey matter volume

The current study found that the 40's group performed significantly worse than the 20's group on the Face-Name Pairs task. This result was expected given the finding from the lifespan study that the 40's group were significantly impaired in their ability to successfully encode and recall face-name pairs, and serves to confirm our earlier findings in a different sample.

Our results showed a significant positive association between grey matter volume in the middle frontal, left medial frontal and right orbital gyri and performance on the Face-Name Pairs task. This finding has support from prior studies that have found a positive association between memory performance and prefrontal cortical grey matter volume, (Rodrigue and Raz, 2004; Tisserand et al., 2004; Van Petten et al., 2004; Walhovd et al., 2004). It is also in line with the increasing number of studies that are emerging indicating that prefrontal cortex has a crucial role to play in episodic memory function in both the organization of material for encoding and the subsequent retrieval of that information during recall (Blumenfeld & Ranganath, 2007; Braver et al., 2001; Eldridge et al., 2000; Stebbins et al., 2002), as well as specific evidence that the PFC has an important role to play in associative memory (Dimitrov et al., 1999; Shimamura et al., 1995).

The separate group analyses revealed an interesting variation in the relationship between task performance and regional grey matter volume between the age groups. While only one cluster in the middle frontal gyrus showed a positive association with memory performance in the 20's group, a number of regions showed a positive association with performance in the 40's group, including the left hippocampus, right parahippocampal

gyrus and several regions in the prefrontal cortex. This result is in keeping with previous findings of an association between medial temporal lobe grey matter volume and memory performance in aging (Lupien et al., 1998; Persson et al., 2006; Tisserand et al., 2004; Walhovd et al., 2004). Reports that the hippocampus exhibits an accelerated rate of decline only from the 5th decade on (Jernigan & Gamst, 2005; Raz et al., 2005) are interesting in the context of the current study, given that no association between this structure and memory performance was found in the 20's group. If hippocampal volume does start to decrease markedly only from middle-age on then it is plausible to think that an association between grey matter volume in this region and memory task performance might only emerge in middle-aged and elderly individuals. This view could also be interpreted in relation to reports of a curvilinear relationship between hippocampal volume decline and age if hippocampal volume were in fact to increase slightly between roughly the age of 20 and 40 and decline steadily thereafter, as is reported in the recent Walhovd et al. study (2009). Nevertheless, no between-group difference in MTL volume was detected, indicating that any possible volume difference that might exist between the 20's and the 40's in this area must be very subtle.

The association between hippocampal/parahippocampal volume and associative memory performance in the current study challenges the theory put forward by Buckner (2004) that the association of hippocampal volume decline with poorer memory performance in only a hallmark of pathological aging. Nevertheless, grey matter volume in prefrontal areas was strongly associated with associative memory performance in our study, confirming the importance of the region in influencing memory decline in aging. Furthermore, hippocampal shrinkage is considerably more pronounced in AD patients than in normal aging (Jack et al., 2000). It is possible that the type of episodic memory task used in our study shows a stronger relationship to hippocampal volume than other episodic memory tasks such as recognition paradigms or measures of verbal memory which are frequently used in other aging studies. Indeed, functional neuroimaging studies have shown that better associative memory performance is associated with greater hippocampal activation (Sperling et al., 2001, 2003; Zeineh et al., 2003).

It is noteworthy, however, that grey matter volume in a number of other regions outside the PFC and MTL was also positively related to Face-Name Pairs performance in the 40's group, and thus we cannot conclude that the former regions alone are the only contributors to memory performance this group. Several among these other structures seem at odds

with the literature on the neuroanatomy of memory, particularly regions of the motor cortex and somatosensory cortex. It is possible, however, that the demands of the memory task required the structural integrity of motor and somatosensory areas, as participants were required to write their responses on a pad positioned on their torso while lying horizontally in the MRI scanner, which one would presume requires good motor coordination and optimal functioning of the somatosensory cortex. Furthermore, the cerebellum may have a role to play in verbal memory processes, as it aids in articulatory rehearsal (Ravizza et al., 2006).

When drawing inferences between regional brain volume and performance it is important to bear in mind that larger volume may not always equate with better performance. There is some evidence that smaller hippocampal volume is associated with better memory in children, adolescents and young adults (Foster et al., 1999), although we did not find any significant negative association between regional grey matter volume and task performance in our sample. Another factor limiting the comparability of these studies is the issue of adjusting for total brain volume or head size. The inclusion of this covariate as well as the methods used to make the adjustment vary between studies and may significantly influence the results (Van Petten, 2004).

6.5.3 The relationship between cortisol levels, memory performance and grey matter volume

Cortisol levels assessed directly before the MRI scan were found to be inversely related to Face-Name Pairs task performance in the 40's group only. However, no significant association was found between the cortisol response to scanning and task performance. In contrast, pre-scan cortisol levels were not associated with regional grey matter volume; although the cortisol response to scanning was significantly negatively related to grey matter volume in the parahippocampal gyrus and medial frontal gyrus. The association between cortisol response and grey matter in the medial frontal gyrus disappeared however, when task performance was added as a covariate. These results suggest that while cortisol levels prior to scanning influenced memory performance in the 40's group to a significant degree, it was the increase in cortisol levels during the MRI scan that was associated with volume differences. Analysis of the association between the cortisol response and morphometry in each age group individually, revealed no supra-threshold voxels; thus we can only conclude that this inverse relationship exists for the sample as a

whole. Nevertheless it would be interesting to test this theory with a larger sample, in order to fully ascertain whether this association is dependent on the age-group in question. While no significant relationship was found between cortisol response and task performance, when task performance was included as a covariate of no interest in the regression analysis the significant association between cortisol and medial frontal grey matter volume disappeared. It is therefore reasonable to suggest that the relationship between this structure and the cortisol response to scanning was inflated by its relationship with task performance, although no significant association between cortisol response and task performance was detected in the regression analyses.

These results have relevance for the study of structural brain differences which may influence, or be influenced by, the stress response. Despite our negative finding with respect to an association between prefrontal volume and cortisol response covarying for task performance, it is notable that there is very recent evidence of a negative relationship between cortisol levels and prefrontal cortex thickness in large male sample (Kremen et al., 2010). Along with the abundance of glucocorticoid receptors in the PFC, this finding suggests that this brain region is certainly worthy of further investigation as a putative site of cortisol action.

As has been reviewed elsewhere in this thesis, there is strong evidence that the hippocampus plays a significant role in the stress response, and is in turn acutely susceptible to structural damage as a result of prolonged elevation of cortisol levels (see Chapter 1, section 1.11 and Chapter 4, section 4.2). The variability in hippocampal volume recently demonstrated throughout the adult lifespan from as young an age as age 20 (Lupien et al., 2007), suggests that certain phenotypic and or/genotypic factors must dictate hippocampal size to considerable degree. Exposure to high levels of stress early on in life is a candidate for such a phenotypic factor, which could result in hippocampal damage arising from dysregulation of the HPA axis. Evidence of smaller hippocampal volumes in psychopathology (e.g. Frodl et al., 2006) and in cognitive dysfunction in aging (e.g. Lupien et al., 1998) point toward a role for hippocampal integrity in maintaining healthy cognition and behavioural function. Equally, the evidence could be interpreted to mean that hippocampal damage is a result of some underlying, most-likely stress-related pathology. Or perhaps it is both a cause and a product of psychological ill-health. Further research is merited in this respect. Our results nevertheless add to the current literature by showing a relationship between the response to mild stress and the volume of the

parahippocampal gyrus in early and mid-adulthood. Whether this relationship affects cognitive function is not clear from the current study, but the findings do highlight that a relationship between medial temporal lobe regions and the stress response in humans in not only observable in old age. It may the case that within the range of normal function there is an observable relationship with the stress response that is merely indicative of inter-individual variability without ever becoming maladaptive. Or that the presence of some other latent variable is required to tip the balance. Our results also highlight the need for more studies to examine the effects of stress on not only the hippocampus, but also on its associated cortical regions. Given the importance of the parahippocampal gyrus in episodic memory, and the current findings, the possibility of interplay between this region, stress, and cognitive function should not be ignored.

6.5.4 Limitations of the current study and future directions

While VBM is a useful tool there are some recognised limitations to the technique which must be taken into account when interpreting the results of any VBM study. Between-subject normalisation is difficult due to differences in gyral anatomy, and the degree of accuracy of the normalisation step is also likely to vary somewhat between brain regions (Ridgway et al., 2008). The size of the smoothing kernel chosen can also significantly affect the results (Kubicki et al., 2002). The smoothing kernel chosen for this study was in line with other studies examining the cross-sectional affects of aging on regional grey matter volume (e.g. Good et al., 2001).

VBM also offers some advantages over manual volumetry. It allows the investigation of regional brain volume differences with out the need for an a priori determined region of interest. In the current study we conducted whole-brain analyses first and foremost, only applying a small volume correction to a region of interest if a supra-threshold voxels were discovered during the initial analysis. VBM is also fully automated, thus eliminating the variability of results obtained using manual volumetry due to differences in the way in which individual researchers define regions of interest anatomically prior to analysis.

There has been some debate in the literature as to whether gender is a considerable factor in age-related volume decline. Some studies have reported that males display a more pronounced age-related grey matter volume decline than females (Pruessner et al., 2001; Lupien et al., 2007) although larger studies have disputed this (Good et al., 2001; Raz et al., 2005). Nevertheless, the ratio of males to females was the same in both our age

groups, so this should not have significantly affected the interpretation of the results with respect to age-related regional volume decline.

Future studies should further explore the interplay between the inter-individual response to stress, cognitive function and regional brain volume in aging, extending the sample size and age-range included in the current study, in order to determine whether age-related differences in the nature of this relationship exist. With respect to the association between regional grey matter volume and memory performance found in this study in the 40's group in particular, it would also be interesting in future studies to extend the age range out at both ends. This would hopefully lead to further insight into the changes, particularly in hippocampal volume, which occur with age and how they are related to memory performance throughout the lifespan. Nonetheless, this study adds to the literature in showing that memory performance is differently related to regional brain volume in young adulthood and middle-age.

Recently there has been some evidence of a relationship between structure and function which may help to explain changes in cognitive function in aging (Persson et al., 2006; Rosen et al., 2005). Perhaps more combined structural/functional investigation in future studies would help shed light on the significance of regional brain volume differences for cognitive function and adaptability in aging.

Chapter 7

General Discussion and Conclusions

7.1 Summary

This chapter outlines the main findings of the current studies and raises further points for discussion with respect to each. The contribution to the literature of the studies, taken together, is discussed, and a model of how the various factors might affect age-related memory decline is offered. Finally, some additional limitations of the current studies and possible future directions are highlighted.

7.2 Outline of Results

This thesis explored the changes in associative- and working memory performance across the lifespan, focusing on the comparison of performance in young adulthood with performance in middle-age, during which performance deficits were found to first emerge. Furthermore, the current studies probed the relationship between cortisol levels and memory performance, as well as the modulatory effect of using emotionally salient stimuli on task performance, and how this relationship may vary with age. The main findings are listed below:

- Associative memory and working memory deficits in aging were found to emerge in the 40's for the Face-Name Pairs and N-Back tasks.
- A negative relationship between cortisol levels during testing and performance on the Face-Name Pairs and N-Back tasks was found to be significantly more pronounced in individuals over 40 compared with young adults.
- Working memory performance was shown to be modulated by facial expression, with the middle-aged group showing a specific impairment in N-Back task performance when angry faces were used.
- The accuracy in judging facial expressions of emotion varied as a function of stimulus valence with participants demonstrating higher accuracy and faster response times to happy faces, regardless of age. Furthermore, higher levels of cortisol at test were associated with faster response times when judging emotional faces, as well as the tendency to judge a neutral face as being emotional.
- Middle-aged adults were found to exhibit regional grey matter differences when compared with the 20's. They showed reduced grey matter volume in several areas of the cerebral cortex, most notably in the PFC.
- Better memory performance was associated with larger grey matter volume in several areas in the 40's group, including the PFC, hippocampus and parahippocampal gyrus. Only the middle frontal gyrus showed an association with performance in the younger group.
- The cortisol response to MRI scanning was inversely related to grey matter volume in the parahippocampal gyrus and hippocampus of participants.

7.3 The emergence of memory deficits in middle-age

Chapter 3 explored associative- and working memory performance in a cohort of healthy individuals aged 18-64 years of age.

Firstly, we found considerable support for an emergence of a specific associative memory deficit in the 5th decade of life. This was evidenced by performance on both the Face-Name Pairs task and on the Picture-Word Association task. Performance on the item recall and recognition components of the Face-Name Pairs task did not show the same marked drop in performance in the 40's, instead the pattern of decline appeared more graded and variable in nature. These results are thus in line with the view that forming associations or relationships between items in memory is an ability that is particularly susceptible to age-related impairments (e.g. Chalfonte and Johnson, 1996; Naveh-Benjamin, 2000).

Secondly, there was also evidence for a specific working memory impairment beginning in the 40's when the task demanded considerable effortful processing, most likely taxing executive functions that support the continuous updating and manipulation of items in a mental set. This was evidenced by significantly poorer performance on the N-Back task in the 40's and 50-64 groups compared with the 20's and 30's. Furthermore, the switch- cost in accuracy (accuracy in the 2-Back condition minus accuracy in the 1-Back condition), was also found to be significantly greater in the 40's and 50-64 groups when compared with the 20's. Given that the hypothesised limit for the number of items that can be held in the focus of attention is 1 (McElree, 2001), these results suggest that aging impairs the ability to efficiently switch between items held in focal attention and those held in working memory.

In line with our a priori hypothesis, greater age-related impairment was found on the N-Back task than on the Match-to-Sample task. No significant effect of age on performance was found on the latter task. This task could fall within the framework of a so-called 'primary memory' or short-term memory task, rather than a true working memory task per se, as it probes executive functioning to a minimal degree (Luo and Craik, 2008; Smith & Jonides, 1998). The literature on the susceptibility of primary memory tasks to age-related impairment suggests that such tasks exhibit little age-related change or at most show a late onset of decline (Nilsson, 2003). There is evidence that the MTS task relies on inferior temporal regions, medial temporal lobe regions, and the visual cortex (Mishkin, 1982; Mishkin & Murray, 1994). Neuroimaging studies have also suggested that the orbitofrontal

cortex plays and important role in this task; however, there is evidence to suggest that the DLPFC is only activated during this task when the memory load is significantly increased (Habeck et al., 2005). These findings further help to distinguish the cognitive processes involved in our MTS task from those involved in the N-Back task, the latter of which has been shown to produce robust activation of the DLPFC, consistent with the putative role of this region in the manipulation of information in memory (Braver et al., 2001; D'Esposito, et al., 2000; Postle et al., 1999). Thus it is likely that the MTS task did not engage the PFC, particularly the DLPFC, to the same extent as the N-Back task, though this cannot be confirmed by the current study.

The emergence of an impairment in associative memory performance, as well as an impairment in N-Back task performance in the 40's in our study, perhaps points to a general deficit in performance emerging relatively early on in the aging process on tasks which require optimum prefrontal cortex functioning. In addition to its role in working memory, the PFC has been shown to have a crucial role to play in the organisation of material for encoding in long-term memory (see Chapter 1, section 1.9.2), including memory for associations (Dimitrov et al., 1999; Shimamura et al., 1995). Perhaps then, it is PFC functioning that underlies the specific associative memory impairment which we observed to differentiate our 40's and 50's participants from our 20's and 30's, on both the Face-Name Pairs task and the Picture-Word task. This may also explain why, among older individuals, deficits appear to be more pronounced on measures of associative memory than on single-item recall and recognition tasks (Naveh-Benjamin et al., 2003), as changes in PFC structure and/or functional recruitment with age, may result in more pronounced deficits on the associative component of these tasks. In support of this, older individuals have been shown to exhibit less prefrontal activation than young individuals during the encoding of face-name pairs (Sperling et al., 2003).

7.4 The association of cortisol levels with poorer performance on associative- and working memory tasks

In Chapter 4 the relationship between levels of the stress hormone cortisol during the cognitive testing session, and performance on the various indices of memory was examined. An a priori hypothesis was that cortisol levels might significantly increase across the testing session in the over 40's group, due to performance stress. This hypothesis was not supported as there was no significant increase in cortisol levels across the testing session in either age group. Our second hypothesis was that cortisol levels

would be negatively associated with memory task performance, and that this relationship would be stronger in the older age group. This was partially supported by the results detailed in Chapter 4. Whole group regression analyses revealed that the interaction between age group and cortisol was a significant predictor of performance on the Face-Name Pairs task and the 2-Back task, such that the combination of the older age group and higher cortisol levels was associated with poorer task performance. When regression analyses were conducted for the age groups separately the same relationships were no longer evident, though a negative relationship between the improvement across encoding trials on the Face-Name Pairs task and cortisol levels was evident for the older group. A lack of power resulting from halving the sample size was likely an issue here, resulting in lower power to detect the same significant relationship between cortisol and several of the performance measures that we observed in the whole group analyses.

Another interesting finding to emerge from this study was that of a positive relationship between cortisol levels and Match-to-Sample recognition accuracy in the younger group only. This is particularly intriguing in light of the fact that there were no overall performance accuracy decrements with age evident on this task, and the task likely suffered from floor effects to some degree due to the high level of difficulty. Further investigation is thus required to try and elucidate a mechanistic basis for this result.

Previous studies have explored both the effect of pharmacological and social-stress based manipulation of cortisol levels in healthy young individuals, and the relationship between basal cortisol levels and memory performance in the elderly and in clinical populations. However, little research has investigated how the relationship between cortisol and memory may vary across the adult lifespan. Our results contribute to the literature by showing a greater negative effect of higher cortisol levels on task performance in middle-aged than young individuals. Furthermore, this effect emerged for the associative memory and N-Back tasks. These results thus tentatively suggest that higher cortisol levels may have a role to play in the decline of associative memory and working memory performance in middle-age that we observed in our lifespan study.

Social-stress induced elevations of cortisol have been associated with impairments in N-Back task performance (Schoofs et al., 2008). Also interesting with regard to the current studies, is the finding, by Domes and colleagues (2005), of a negative effect of oral hydrocortisone administration on verbal associative memory, but not on measures of

verbal and non-verbal item memory in healthy young participants. A negative relationship between exogenous cortisol and associative learning has also been reported in other studies with healthy individuals (e.g. Young et al., 1999). These findings suggest that associative memory may be more vulnerable to elevations in cortisol levels than single-item memory. In addition, there is evidence that post-traumatic syndrome (PTSD) sufferers – a condition in which abnormal cortisol regulation is a feature - show an accelerated rate of decline in associative memory performance with aging, which exists despite an improvement in symptom severity (Yehuda et al., 2006). This finding suggests that exposure to trauma and the ensuing dysregulation of the HPA axis may cause damage to the brain which leads to accelerated associative memory decline in aging. The neuroanatomical basis for this decline, however, is not implicit, and it is intriguing to note that these PTSD sufferers actually improved their performance over time on a measure of verbal long-term memory - the California Verbal Learning Test.

In the aforementioned Young et al. study, it was noted that cortisol administration in healthy subjects also led to impaired strategy use on a spatial working memory task. They proposed that high cortisol levels may adversely affect prefrontal cortex function, as both the hippocampus and PFC are rich in glucocorticoid receptors rendering them intrinsically vulnerable to the maladaptive effects of prolonged as well as acute elevations in cortisol levels (see Chapter 1, section 1.11).

Though the above studies describe pharmacological manipulations or changes in cortisol levels due to psychopathology - which undoubtedly are not representative of the variability of cortisol levels in the general population - they nevertheless provide insight into the vulnerability of certain mnemonic functions to high levels of the stress hormone. The current study adds to the general literature by showing an interaction between age and basal cortisol levels in predicting poorer associative- and working memory performance. There is evidence that higher basal cortisol levels are associated with poorer declarative memory in elderly individuals (Li et al., 2006; Lupien et al., 1998), and higher cortisol levels have been associated with smaller hippocampal volumes (Lupien et al., 1998). Our results suggest that this inverse relationship between cortisol levels and memory performance may be evident as early as mid-life, and may extend to PFC-associated tasks.

7.5 The modulatory effect of facial expression on memory task performance and on emotion judgment ability

Chapter 5 was concerned primarily with probing whether there is a change in the response to emotional stimuli in middle-age compared with young adulthood, and whether this can alter associative- and working memory performance. A second aim was to explore the association between cortisol levels at testing and task performance, when the stimuli differed in valence. We hypothesised that the proposed positivity effect in memory that has been described in the literature, frequently in more elderly cohorts, might by evident as early as middle-age (40-49 years in our study). Thus, we made the prediction that the negative effect of age on associative- and working memory task performance would be largest when angry stimuli were used. This prediction was not supported by performance on the Face-Name Pairs task, but was somewhat supported by performance on the N-Back task.

Although the expected effect of age group on Face-Name Pairs task performance was evident, there was no interaction between age group and facial expression, and performance within both age groups did not change significantly as a function of the facial expression used in the task. A possible explanation for this negative finding is that the associative nature of the task negated any effect of emotional expression on performance. There is evidence that binding processes are unaffected by emotion, particularly when equal emphasis is put on both elements of the to-be-remembered material (Mather et al., 2009).

The results of the N-Back task provide support for the hypothesis that emotional stimuli can affect memory performance differently in middle-aged than young adults. At high working memory loads, middle-aged adults were found to be significantly less accurate on non-target trials than the young adult group only when angry faces were used in the task. The greatest difference between the age groups in response time was also when angry faces were viewed. These results support the previous finding that older adults show better working memory performance when positive stimuli are used and worse performance in response to negative stimuli (e.g. Mikels et al., 2005).

The results of the Face Judgment task demonstrate that response accuracy as well as latency to correctly judge the emotion being portrayed by a face varies with the nature of the facial expression. Individuals, regardless of age, seem to be faster and more accurate

in judging happy faces than neutral or angry faces. This is a finding that also has support from other studies (Keightley et al., 2006; Leppanen and Hietanen, 2004). Furthermore, middle-aged adults appeared slowest in responding to angry faces when compared with the 20's group, though this difference was not large enough to yield a significant interaction between age group and facial expression overall. Thus, we can only conclude that there is some evidence of a bias away from the processing of negative stimuli that is evident in middle age, in line with the socioemotional selectivity theory.

A further aim of this study was to explore the relationship between cortisol levels and task performance. A hypothesis was that cortisol would be differently related to task performance when emotional stimuli were used compared with neutral. This can not be deemed to be supported by the results of the Face-Name Pairs and N-Back tasks as the relationship between cortisol, memory performance and age group, showed no easily comprehensible pattern. Once again, power may have been an issue here as the groups for the regression analyses were small, and baseline differences in cortisol between the groups may have confounded results also. The whole-group regression analyses of Face Judgment task performance, however, produced some interesting findings. Higher cortisol levels predicted both faster response times to emotional faces, and a greater tendency to falsely judge faces as being emotional in expression. A significant interaction with age group manifested in the reaction time to angry faces, where the combination of younger age and higher cortisol levels led to shorter response latencies to angry faces.

The socioemotional selectivity theory proposes that older adults exhibit a bias in attention and memory for positive stimuli, and that they allocate fewer processing resources to negative stimuli (Carstensen, 1993). While there is much support for this theory in the literature, more recent evidence suggests that this bias is not uniform in its operational capacity, and that there are circumstances when this age-related shift away from negative and toward positive stimuli in older age does not manifest. Studies have indicated that when older adults are allowed to process emotional information in an uncontrolled, non-goal directed manner, a positivity effect in aging appears (Mather & Carstensen, 2003). However, when participants are focused on performing a cognitive task, for which explicit instructions have been given, the positivity bias is eliminated (Mather and Knight, 2006). Our results could be interpreted in line with this view, as emotional valence did not have a global effect on Face-Name Pairs and N-Back task performance. Nevertheless, the notion that older adults selectively inhibit the processing of negative information as part of an

emotional regulation strategy is somewhat supported by our findings. Studies have shown that older adults are not impaired when it comes to unconscious threat detection (Mather and Knight, 2006), however, they may suffer when the task requires the conscious perception or active processing of the negative stimulus. Issacowitz and colleagues evaluated the length of time participants spent looking at emotional-neutral faces pairs. They found that older adults showed a preference in their gaze toward a happy face when it appeared in the pair, and tended to orient their attention away from an angry face when it appeared in the pair (Issacowitz et al., 2006). This may reflect a higher order cognitive control process which is geared toward inhibiting the processing of an incoming negative stimulus, perceived at a basic perceptual/sensory level. Research has suggested that emotional as well as non-emotional cognitive control requires the prefrontal cortex (Banich et al., 2009; Depue, Curran & Banich, 2007; Kompus et al., 2009). Interestingly, there is evidence that older adults are more successful at reducing interference from distractors during the performance of an emotional task than they are during a non-emotional task, while younger adults are more successful at inhibiting interference on a non-emotional task (Samenez-Larkin et al., 2009). These findings are consistent with the theory that older adults focus more on emotion-related goals and suggest that their mechanisms of cognitive control are more efficient when it comes to emotional regulation. Results from the N-Back task, which showed a higher error rate in the 40's group on non-target trials when angry faces were viewed, could be interpreted as having resulted from a lower level of processing of the features of the angry faces, and thus an impaired ability to detect whether it was that exact faces that was presented two trials previously. To date, research into the effect of emotional stimuli on memory and attention in aging has primarily focused on the comparison of an older adult group with a young adult group. There is evidence to suggest, however, that changes in emotion processing can occur as early as middle-age (Charles et al., 2003), and the current results suggest that this age group may merit further scrutiny.

The effect of cortisol on the processing of emotional faces in aging has not yet, to our knowledge, been explored. There are several studies, however, which have reported a relationship between cortisol levels and the processing of emotional faces in young adults. Van Honk and colleagues (1998) found that higher basal cortisol levels resulted in an attentional bias toward emotional faces, a finding which is also consistent with the heightened attention to emotional stimuli observed in psychopathological disorders (e.g. Ridout et al., 2003). Furthermore, exogenous administration of cortisol has been found to

enhance memory for emotional faces (Putman et al., 2004), in line with its putative interaction with noradrenergic signalling in the amygdala to enhance memory for emotional material (see Chapter 1, section 1.13.4). Our results demonstrate a heightened response to emotional stimuli in participants with higher cortisol levels, and a greater tendency to perceive neutral faces as being emotional in expression. There is also evidence for an interaction between cortisol and age in predicting the speed of response to emotional stimuli. It appears that this inverse association between cortisol levels and reaction time to emotional faces is largely driven by the younger age group.

7.6 Regional grey matter volume varies with age, memory performance and cortisol reactivity

In Chapter 6 we examined the differences in regional grey matter volume between a young adult group (20's) and a middle-aged group (40's). Furthermore, we explored the association between regional grey matter volume and performance on an associative memory task, as well as the cortisol response to scanning. We hypothesised that the 40's group would display smaller regional grey matter volume, particularly in the frontal cortex. This was found to be the case, and regional differences were also evident between the groups in other areas of the cerebral cortex such as the parietal and temporal lobes, as well as in the cerebellum. These results are supported by the literature which points to a steady deterioration in grey matter volume from the 20's on particularly in cerebral cortical areas (Walhovd et al., 2009), with the frontal lobes showing particular vulnerability to age-related decline (Raz et al., 2005). We also found a positive association between associative memory performance and PFC grey matter volume in our sample as a whole. This relationship was extended to several other regions, including the hippocampus and parahippocampal gyrus, when we examined the 40's group only. In contrast, only the relationship between PFC volume and memory performance remained in the 20's group, when examined separately.

Several studies have reported a relationship between regional grey matter volumes and memory decline in aging, though in general, results have been mixed, and for the most part only elderly participants have been tested (see Chapter 6, section 6.2.1). Our results contribute to the current literature by demonstrating that a positive relationship exists between several grey matter regions and memory performance in middle-age that does not manifest in young adulthood. Notably, the hippocampus and associated cortices are among these regions for which grey matter volume seems to influence memory

performance in the 40's, but not in the 20's. Areas of the PFC also show a stronger inverse relationship to memory performance in the 40's than in the 20's.

These results may offer some insight into the factors underlying age-related memory decline. Several studies have provided evidence to suggest that, unlike some cortical regions which exhibit linear decline with age, the hippocampus exhibits a curvilinear pattern of decline, with shrinkage occurring only from about mid-life on (Fjell et al., 2005; Walhovd et al., 2009). Thus perhaps it is in this latter half of adulthood that a relationship between memory and hippocampal integrity begins to emerge. Behavioural studies generally agree that older adults exhibit greater variability in memory performance than younger adults (see Morse, 1993 for a meta-analysis). As Lupien and colleagues (2007) have reported, however, hippocampal volume appears to be as variable in young adulthood as in middle-age or old age, which implies that the variability in memory performance exhibited by older adults is not a direct result of greater variation in hippocampal volumes in this age group. Nonetheless, it could be the case that the relative preservation of memory function that is displayed by some older individuals does bear a relationship to individual variability in hippocampal volume. If individual variability in hippocampal volume remains approximately constant throughout the lifespan, but hippocampal volume in general starts to decline from middle-age onward, then perhaps it is only from this time point on that subtle volume changes, along with an innate inter-individual variability in volume, start to have a bearing on memory performance. Individuals with smaller hippocampal volumes to begin with, may present with greater age-related cognitive dysfunction than those who started out at the larger end of the range.

It is likely that individuals with smaller hippocampi may have other biological factors which also influence this memory decline. Early life stressors (along with genotype) influence the development of brain structures such as the hippocampus and PFC and lead to altered HPA axis functioning and feedback (Lupien et al., 2009). Therefore, is possible that in some individuals, a combination of genetics and the exposure/maladaptive response to stress, could lead to significant atrophy of such structures in certain older adults but not in their-age-matched counterparts who do not share the same risk factors.

Our results provide some evidence to support this line of reasoning. We found a negative association between the cortisol response to MRI scanning and parahippocampal gyrus (PHG) volume. As many participants showed a decrease in cortisol levels from pre- to

post-scanning, this indicates that those who exhibited a small cortisol increase or perhaps whose levels remained constant during the scan, had a tendency toward smaller grey matter volume in the PHG. It is thus possible that a relationship between cortisol reactivity (even to mild stress) and PHG volume can be detected in a healthy adult sample. As the majority of studies have focused on the association between stress reactivity and the hippocampus specifically, our results point to the need to examine the associated cortices also.

There is evidence that the PFC, as well as MTL regions, regulates the HPA axis (Jankord & Herman, 2008). Furthermore, activity in prefrontal areas during performance on a stressful task has been inversely related to the magnitude of the stress response (Pruessner et al., 2008). Interestingly, we also found an inverse relationship between the cortisol response to scanning and grey matter volume in the middle frontal gyrus in the current study. However, this relationship was no longer significant when Face-Name Pairs task performance was taken into account. Nevertheless, the involvement of the PFC in the stress response and in the regulation of cortisol production merits continuing investigation.

7.7 Toward a greater understanding of memory decline in 'normal' aging

In the past, a failure of memory in old age was attributed to senile dementia. In recent years, however, researchers are beginning to tease apart processes which may underlie 'normal' aging from the pathological changes which take place in the development of Alzheimer's disease. It is hoped that the search for factors which influence cognitive decline in normal aging, and those which are present in dementia, will facilitate earlier detection and better management of age-related degenerative disease, as well as lead to a better understanding of the development and needs of an aging population.

Alzheimer's disease has been typically characterized, at a neuroanatomical level, by pronounced atrophy of the medial temporal lobe, a build up of Tau protein and amyloid plaques (Jack, 2000; Price et al., 2001). Moreover, this disease is coincident with an early, severe impairment in declarative memory function (Gold & Budson, 2008). Normal aging, on the other hand, shows no specific pathology, but instead is associated with a more widespread but less severe pattern of brain changes, as well as marked inter-individual variability in memory ability (Buckner, 2004). What then are the factors that impinge on this variability in age-related decline? This thesis was aimed at exploring some of the

possible influences on memory performance in aging, with particular focus on changes and patterns that may manifest early on in the aging process, by middle-age. It would be remiss of us, however, not to acknowledge the limitations of this thesis with respect to investigating age-related changes in memory performance. We cannot generalise to all types of memory and cognitive processes, as we focused mainly on only two types of tasks. Nevertheless, both associative memory and working memory tasks have been shown to be very susceptible to age-related performance impairments (e.g. Yeseavage & Rose, 1984; Dobbs & Rule 1989), possibly due to their reliance on prefrontal cortex functioning (e.g. Miller & Cohen, 2001). This thesis has shown that a significant impairment on these tasks emerges early on in the aging process and has explored just some of the possible factors contributing to this.

Raised basal cortisol levels, as a result of fetal or early-life programming of the HPA axis, or of exposure to acute or chronic stressors, may lead to increased cortisol levels in certain individuals by middle-age. This, in turn, may render them more vulnerable to further stressors, and to exhibiting greater memory impairment than their peers. There is evidence to suggest that the maladaptive effects of acute and/or chronic stress on brain structure and function may take some time to manifest (e.g. Andersen and Teicher, 2008; Yehuda et al., 2006). Our results suggest that the negative relationship between memory and higher basal cortisol levels may not be evident early on in adulthood, perhaps because altered HPA axis functioning in certain individuals hasn't yet raised cortisol levels sufficiently or because young adults show little variability in memory performance (Morse, 1993). By middle-age, however, a negative association may begin to manifest. It is noteworthy also, that we found an association between PHG volume and cortisol levels in participants during MRI scanning that was not explained by memory performance. This suggests that subtle structural differences may be present even before any effects on cognition are evident.

Also taken into consideration in this thesis was the effect that education and IQ can have on cognitive performance, given that successful aging has been associated with higher education levels. The results of the first study showed that while those factors are significantly positively related to memory performance, they do not protect against age-related decline. While we did not explore whether there was an association between education or IQ and cortisol levels, it should be noted that there is some evidence of an inverse relationship between education levels and the cortisol response to stress (Fiocco, Joober & Lupien, 2007). This complements other research which has indicated that

individuals from a lower socioeconomic background, and those with a low level of education, have a greater susceptibility to cognitive dysfunction later in life (Deeg et al., 2009; Habib, Nyberg & Nilsson, 2010; Leibovici et al., 1996).

It must also be noted that many other genetic, health and lifestyle factors almost certainly influence the trajectory of memory decline in aging. While it was not within the scope of this thesis to explore these factors directly, we excluded individuals with significant health issues that might affect cognitive performance, such as cardiovascular disease and thyroid dysfunction.

Of interest in the aging literature, is the emergence of evidence to suggest that although cognitive function in general declines with age, emotional well-being appears to improve or at the very least, remain constant. Considerable discussion has been given in Chapter 5 and in earlier in this chapter to the notion that motivational changes in aging may result in a change in cognitive processing facilitating the attainment of greater emotional satisfaction. Is there a relationship between emotional regulation in older adults and the decline in memory function? Few studies have attempted to answer this question, though there is some interesting evidence of a relationship between the two. For instance, better executive functioning has been shown to predict increased recall of positive stimuli relative to negative stimuli among older adults (Mather & Knight, 2005; Petrican, Moscovitch & Schimmack, 2008). Furthermore, as mentioned earlier, the lateral prefrontal cortex has been implicated in cognitive control processes when both non-emotional and emotional stimuli are used (Samenez-Larkin et al., 2009), though there is also evidence that the involvement of the prefrontal cortex in the cognitive control of emotion specifically, relates more to medial PFC regions (Kompus et al., 2009).. It seems likely that the PFC has an important role to play in emotion regulation as well as executive functioning, most likely via projections to subcortical areas such as the hippocampus and amygdala (Ochsner & Gross, 2005, Urry et al., 2006). Urry and colleagues (2006) investigated how the ability of older adults to regulate their emotions might be related to the degree of PFC and amygdala activation, as well as to HPA axis regulation. Interestingly, they found that reduced amygdala activation and increased PFC activation was evident when participants were instructed to actively inhibit feelings of negative affect. Furthermore, this pattern of activation was significantly associated with a steeper diurnal decline in cortisol levels, the latter of which is correlated with higher cognitive functioning (Fiocco et al., 2006).

Although executive functioning in general appears to decline with age, older adults may allocate more of their limited resources to the task of emotional regulation, rather than to the cognitive control of non-emotional processing (Mather & Knight, 2005). Nevertheless, a reduction in strategic processing ability generally, perhaps due to structural change in the PFC, is likely to reduce the capacity of older adults to engage in emotional regulation as efficiently. Urry and colleagues (2006) provide evidence that the ability to regulate feelings of negativity in aging is related to inhibition of subcortical areas by the PFC, and that this may be influenced by HPA axis function, such that better regulation of cortisol levels is associated with better PFC-mediated control of emotional experience.

Figure 7.1 outlines a possible model of the relationship between structural damage to the hippocampus and prefrontal cortex, raised cortisol levels and emotion regulation in aging; showing how the culmination of several factors might interact to negatively influence memory. Decreases in the structural integrity of age-sensitive brain regions such as the PFC and the hippocampal complex (HC), may cause a decline in memory performance with age. In addition, the trajectory of this decline may be influenced by HPA axis dysregulation (resulting from chronic or acute stress, or trauma very early on in life), leading to higher cortisol levels, which may accelerate the rate of memory loss. Furthermore, cortisol has feedback effects on the HC and PFC causing further impairment of structure/function, leading to further HPA axis dysregulation as well as increased memory problems. Below a certain threshold, a compromised PFC may no longer be able to engage in emotional regulation to the same extent as it otherwise would in other adults. An ensuing increase in the frequent or sustained experience of negative affect could contribute to the increase cortisol levels, leading to further volume decline and memory impairment.

It may be the case that this relationship only becomes important as age progresses, as young adults may be buffered from the effects of this maladaptive cycle by less age-related deterioration of brain regions, less drive to engage in emotion regulation and less allocation of cognitive resources to the maintenance of emotional well-being.

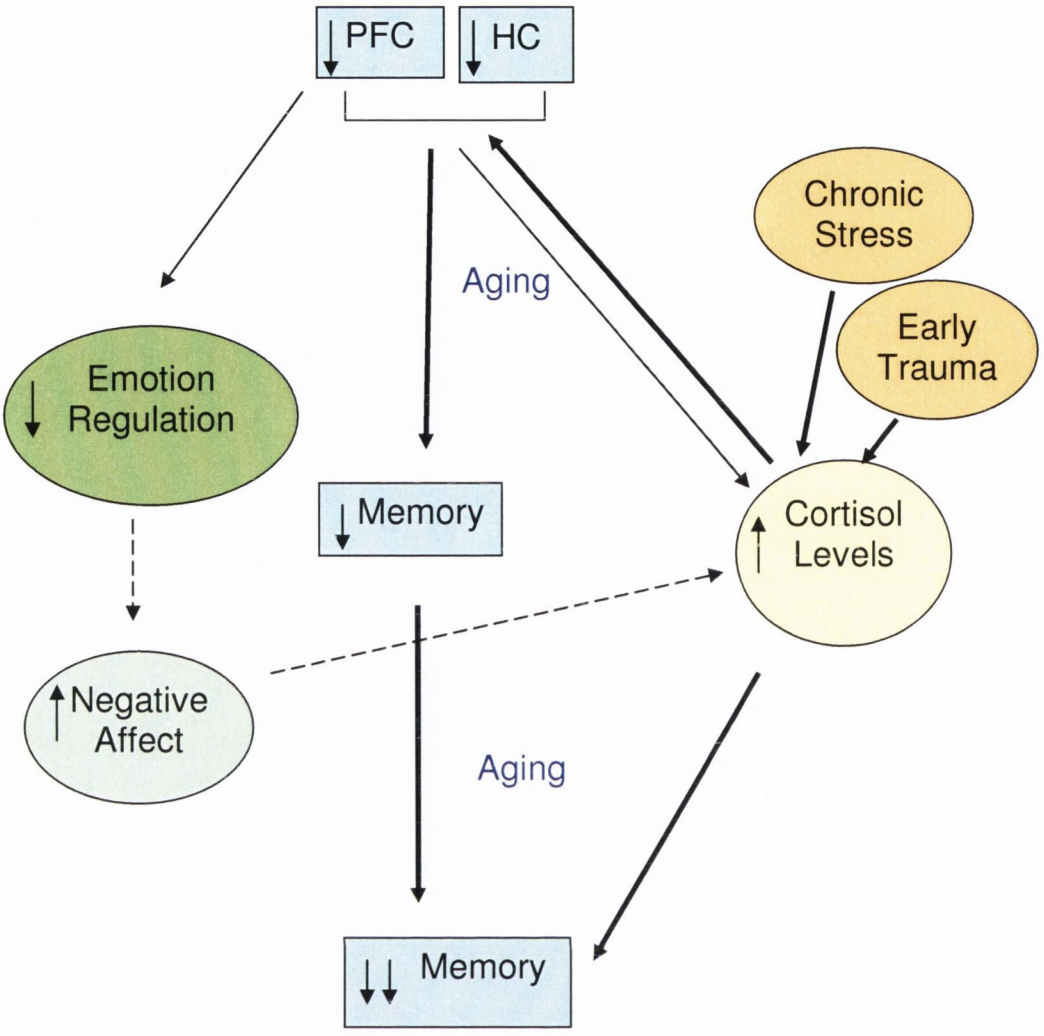

Figure 7.1: A proposed model of the relationship between structural decline, HPA axis regulation, and emotion regulation in age-related memory decline (HC = hippocampal complex; PFC = prefrontal cortex). Solid black lines indicate a strong causal relationship, thin black lines indicate a probable causal relationship, and dashed lines indicate a possible causal relationship.

7.8 Other limitations of the current studies and future directions

There are several other aspects and factors which much be mentioned in relation to the general applicability of these findings. We must acknowledge the intrinsic arbitrariness of dividing participants into age groups in order to facilitate comparisons. An individual aged 40 is in theory likely to be as similar to a 39 year- old as to a 41 year-old, and is probably more similar to a 39 year old than to a 49 year old, the latter with which they would have been placed based on the group divisions in this study. Nevertheless, age groups similar to ours are frequently used in cross-sectional studies of aging (e.g. Park et al., 2002; Van Gerven et al., 2007), and while caution and sense must be applied in interpreting the

results, especially with regard to cohort effects, there is no doubt that such approaches frequently yield valid findings.

With regard to our studies of cortisol levels, we did not take into account menstrual cycle phase in females, a factor which has previously been reported to alter the relationship between cortisol and long-term memory performance (Andreano, Arjomandi and Cahill, 2008). However, findings have been mixed, and a recent large and comprehensive study comprising 122 subjects tested at the beginning and end of a two-week period, found no relationship between cortisol levels and menstrual cycle phase (Liening et al., 2010). Thus any relationship, if it exists at all, is likely to be very weak.

It must also be noted that we did not have our participants rate the faces they viewed in the emotional face tasks. Thus we cannot deduce whether or not the participants found the facial expression portrayed by some faces easier to identify than others. Nonetheless, the faces chosen were from the Ekman Pictures of Facial Affect, and the Karolinska Directed Emotional Faces sets, the latter of which has previously been validated (Goeleven et al., 2008) and the former of which has been used extensively in prior emotion research, thus lending support to their use in the current studies.

Future directions

In recent years there have been an increasing number of studies that have employed functional neuroimaging techniques to investigate brain changes in aging. Researchers, however, are only beginning to use combined structural/functional neuroimaging techniques in order to try and elucidate the relationship between the shrinkage of regions such as the prefrontal cortex and hippocampus with age, and the changes in the functional recruitment of certain brain regions which seems to occur in aging (e.g. Persson et al., 2006). These structure/function investigations have been largely confined to examining elderly cohorts, or contrasting an elderly group with a young adult group. It would be interesting, in light of the current findings, to see whether a relationship exists between the volume of structures such as the hippocampus and prefrontal cortex, activation patterns during memory task performance, and cortisol levels in a middle-age. This may help further determine the functional significance of the structural changes evident at this stage, as well as the relationship to cortisol levels.

As events which take place early on in life may affect the development of certain brain regions, large longitudinal studies which follow individuals from birth, throughout childhood and adolescence, while logistically challenging, would be of benefit. These studies would offer insight into the individual differences and changes which make take place during the first half of life that could later influence the course of healthy aging.

7.9 Final thoughts

The present studies have shown that there are pronounced associative- and working memory changes which are evident by middle-age. These behavioural changes are also accompanied by evidence of grey matter volume changes, and an alteration in the relationship between regional brain volume and performance. Furthermore, it is likely that higher levels of the stress hormone, cortisol, render individuals more susceptible to these memory impairments, possibly through an interaction with structures such as the hippocampus and prefrontal cortex. Further research is needed to deduce the exact nature of such relationships and how they might combine with other factors to influence cognitive aging.

References

Abercrombie, H. C., Speck, N. S., & Monticelli, R. M. (2006). Endogenous cortisol elevations are related to memory facilitation only in individuals who are emotionally aroused. *Psychoneuroendocrinology, 31*(2), 187-196.

Adolphs, R. (2002). Neural systems for recognizing emotion. *Current Opinion in Neurobiology, 12*(2), 169-177.

Adolphs, R., Cahill, L., Schul, R., & Babinsky, R. (1997). Impaired declarative memory for emotional material following bilateral amygdala damage in humans. *Learning & Memory, 4*(3), 291-300.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the amygdala. *Nature, 372*(6507), 669-672.

Amaral, D. G., & Price, J. L. (1984). Amygdalo-corticol projections in the monkey (Macaca-Fascicularis). *Journal of Comparative Neurology, 230*(4), 465-496.

Andersen, S. L., & Teicher, M. H. (2008). Stress, sensitive periods and maturational events in adolescent depression. *Trends in Neurosciences, 31*(4), 183-191.

Anderson, L., & Shimamura, A. P. (2005). Influences of emotion on context memory while viewing film clips. *American Journal of Psychology, 118*(3), 323-337.

Andreano, J. M., Arjomandi, H., & Cahill, L. (2008). Menstrual cycle modulation of the relationship between cortisol and long-term memory. *Psychoneuroendocrinology, 33*(6), 874-882.

Andreano, J. M., & Cahill, L. (2006). Glucocorticoid release and memory consolidation in men and women. *Psychological Science, 17*(6), 466-470.

Armony, J. L., & Dolan, R. J. (2002). Modulation of spatial attention by fear-conditioned stimuli: an event-related fMRI study. *Neuropsychologia, 40*(7), 817-826.

Armony, J. L., & LeDoux, J. E. (1997). How the brain processes emotional information. *Psychobiology of Posttraumatic Stress Disorder, 821*, 259-270.

Aron, D., & Tyrell, J. (1994). Glucocorticoids and Adrenal Androgens. In F. Greesoan & J. Baxter (Eds.), *Basic and Clinical Endocrinology* (4th ed., pp. 307-346): Appleton and Lange, USA.

Arriza, J. L., Simerly, R. B., Swanson, L. W., & Evans, R. M. (1988). The neuronal mineralocorticoid receptor as a mediator of glucocorticoid response. *Neuron, 1*(9), 887-900.

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry - The methods. *Neuroimage, 11*(6), 805-821.

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *Neuroimage, 26*(3), 839-851.

Atkinson, R. C., & Shriffrin, R. M. (1968). Human memory: A proposed system and its control processes. In K. W. Spence & J. T. Spence (Eds.), *The psychology of learning and motivation: Advances in research and theory* (Vol. 2, pp. 89-195). New York: Academic Press.

Axmacher, N., Mormann, F., Fernandez, G., Cohen, M. X., Elger, C. E., & Fell, J. (2007). Sustained neural activity patterns during working memory in the human medial temporal lobe. *Journal of Neuroscience, 27*(29), 7807-7816.

Axmacher, N., Schmitz, D. P., Wagner, T., Elger, C. E., & Fell, J. (2008). Interactions between medial temporal lobe, prefrontal cortex, and inferior temporal regions during visual working memory: A combined intracranial EEG and functional magnetic resonance imaging study. *Journal of Neuroscience, 28*(29), 7304-7312.

Bachevalier, J., & Vargha-Khadem, F. (2005). The primate hippocampus: ontogeny, early insult and memory. *Current Opinion in Neurobiology, 15*(2), 168-174.

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends in Cognitive Sciences, 4*(11), 417-423.

Baddeley, A. D., & G.J.L., H. (1974). Working Memory. In B. G.A. (Ed.), *The psychology of learning and motivation:advances in research and theory* (Vol. 8, pp. 47-48). New York: Academic Press.

Baddeley, A. D., & Wilson, B. (1986). Amnesia, autobiographical memory and confabulation. In D. C. Rubin (Ed.), *Autobiographical Memory*. Cambridge: Cambridge University Press.

Badre, D. (2008). Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends in Cognitive Sciences, 12*(5), 193-200.

Barbas, H., & Deolmos, J. (1990). Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the Rhesus monkey. *Journal of Comparative Neurology, 300*(4), 549-571.

Bastin, C., & Van der Linden, M. (2006). The effects of aging on the recognition of different types of associations. *Experimental Aging Research, 32*(1), 61-77.

Beier, M. E., & Ackerman, P. L. (2001). Current-events knowledge in adults: an investigation of age, intelligence, and nonability determinants. *Psychol Aging, 16*(4), 615-628.

Bird, C. M., & Burgess, N. (2008). The hippocampus and memory: insights from spatial processing. *Nature Reviews Neuroscience, 9*(3), 182-194.

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res, 52*(2), 69-77.

Bliss, T. V., & Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol, 232*(2), 331-356.

Blumenfeld, R. S., & Ranganath, C. (2006). Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. *Journal of Neuroscience, 26*(3), 916-925.

Blumenfeld, R. S., & Ranganath, C. (2007). Prefrontal cortex and long-term memory encoding: An integrative review of findings from neuropsychology and neuroimaging. *Neuroscientist, 13*, 280-291.

Bookheimer, S. Y., Strojwas, M. H., Cohen, M. S., Saunders, A. M., Pericak-Vance, M. A., Mazziotta, J. C., et al. (2000). Patterns of brain activation in people at risk for Alzheimer's disease. *New England Journal of Medicine, 343*(7), 450-456.

Braver, T. S., Barch, D. M., Kelley, W. M., Buckner, R. L., Cohen, N. J., Miezin, F. M., et al. (2001). Direct comparison of prefrontal cortex regions engaged by working and long-term memory tasks. *Neuroimage, 14*(1), 48-59.

Bremner, J. D., Randall, P., Scott, T. M., Bronen, R. A., Seibyl, J. P., Southwick, S. M., et al. (1995). Mri-Based Measurement of Hippocampal Volume in Patients with Combat-Related Posttraumatic-Stress-Disorder. *American Journal of Psychiatry, 152*(7), 973-981.

Broadbent, N. J., Squire, L. R., & Clark, R. E. (2004). Spatial memory, recognition memory, and the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America, 101*(40), 14515-14520.

Brown, E. S., Woolston, D. J., Frol, A., Bobadilla, L., Khan, D. A., Hanczyc, M., et al. (2004). Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. *Biological Psychiatry, 55*(5), 538-545.

Brown, E. S., Woolston, D. J., & Frol, A. B. (2008). Amygdala volume in patients receiving chronic corticosteroid therapy. *Biological Psychiatry, 63*(7), 705-709.

Brown, M. W., & Aggleton, J. P. (2001). Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nature Reviews Neuroscience, 2*(1), 51-61.

Brown, R. M., Robertson, E. M., & Press, D. Z. (2009). Sequence skill acquisition and off-line learning in normal aging. *PLoS One, 4*(8), e6683.

Brunner, R., Schaefer, D., Hess, K., Parzer, P., Resch, F., & Schwab, S. (2005). Effect of corticosteroids on short-term and long-term memory. *Neurology, 64*(2), 335-337.

Buchanan, T. W., & Lovallo, W. R. (2001). Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology, 26*(3), 307-317.

Buchanan, T. W., & Tranel, D. (2008). Stress and emotional memory retrieval: Effects of sex and cortisol response. *Neurobiology of Learning and Memory, 89*(2), 134-141.

Buckley, M. J. (2005). The role of the perirhinal cortex and hippocampus in learning, memory, and perception. *Quarterly Journal of Experimental Psychology Section B-Comparative and Physiological Psychology, 58*(3-4), 246-268.

Buckner, R. L. (2004). Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron, 44*(1), 195-208.

Buckner, R. L., Head, D., Parker, J., Fotenos, A. F., Marcus, D., Morris, J. C., et al. (2004). A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *Neuroimage, 23*(2), 724-738.

Bunsey, M., & Eichenbaum, H. (1993). Critical role of the parahippocampal region for paired-associate learning in rats. *Behavioral Neuroscience, 107*(5), 740-747.

Buschman, T. J., & Miller, E. K. (2007). Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science, 315*(5820), 1860-1862.

Cabeza, R. (2001). Cognitive neuroscience of aging: Contributions of functional neuroimaging. *Scandinavian Journal of Psychology, 42*(3), 277-286.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging, 17*(1), 85-100.

Cahill, L., & McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neurosciences, 21*(7), 294-299.

Cahill, L., Prins, B., Weber, M., & McGaugh, J. L. (1994). Beta-Adrenergic Activation and Memory for Emotional Events. *Nature, 371*(6499), 702-704.

Calza, L., Pozza, M., Coraddu, F., Farci, G., & Giardino, L. (1997). Hormonal influences on brain ageing quality: focus on corticotropin releasing hormone-, vasopressin- and oxytocin-immunoreactive neurones in the human brain. *Journal of Neural Transmission, 104*(10), 1095-1100.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D. E., & Cahill, L. (2000). Event-related activation in the human amygdala associates with later memory for individual emotional experience. *Journal of Neuroscience, 20*(19).

Cansino, S., Maquet, P., Dolan, R. J., & Rugg, M. D. (2002). Brain activity underlying encoding and retrieval of source memory. *Cerebral Cortex, 12*(10), 1048-1056.

Carstensen, L. L., Isaacowitz, D. M., & Charles, S. T. (1999). Taking time seriously. A theory of socioemotional selectivity. *Am Psychol, 54*(3), 165-181.

Carstensen, L. L., Pasupathi, M., Mayr, U., & Nesselroade, J. R. (2000). Emotional experience in everyday life across the adult life span. *Journal of Personality and Social Psychology, 79*(4), 644-655.

Carstensen, L. L., & Turk-Charles, S. (1994). The salience of emotion across the adult lifespan. *Psychology and Aging, 9*(2), 259-264.

Chalfonte, B. L., & Johnson, M. K. (1996). Feature memory and binding in young and older adults. *Memory & Cognition, 24*(4), 403-416.

Chapman, B. P., & Hayslip, B. (2006). Emotional intelligence in young and middle adulthood: Cross-sectional analysis of latent structure and means. *Psychology and Aging, 21*(2), 411-418.

Charles, S. T., Mather, M., & Carstensen, L. L. (2003). Aging and emotional memory: the forgettable nature of negative images for older adults. *J Exp Psychol Gen, 132*(2), 310-324.

Christensen, H., Anstey, K. J., Parslow, R. A., Maller, J., Mackinnon, A., & Sachdev, P. (2007). The brain reserve hypothesis, brain atrophy and aging. *Gerontology, 53*(2), 82-95.

Chua, E. F., Schacter, D. L., Rand-Giovannetti, E., & Sperling, R. A. (2007). Evidence for a specific role of the anterior hippocampal region in successful associative encoding. *Hippocampus, 17*(11), 1071-1080.

Clark, R. E., Broadbent, N. J., Zola, S. M., & Squire, L. R. (2002). Anterograde amnesia and temporally graded retrograde amnesia for a nonspatial memory task after lesions of hippocampus and subiculum. *Journal of Neuroscience, 22*(11), 4663-4669.

Cohen, G., & Faulkner, D. (1984). Memory in old age - good in parts. *New Scientist, 104*(1425), 49-51.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences (2nd ed.).* Hillsdale, NJ: Erlbaum.

Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J., et al. (1997). Temporal dynamics of brain activation during a working memory task. *Nature, 386*(6625), 604-608.

Cohen, N. J., Poldrack, R. A., & Eichenbaum, H. (1997). Memory for items and memory for relations in the procedural/declarative memory framework. *Memory, 5*(1-2), 131-178.

Cohen, R. A., Grieve, S., Hoth, K. F., Paul, R. H., Sweet, L., & Tate, D. (2006). Early life stress and morphometry of the adult anterior cingulate cortex and cauclate nuclei (vol 59, pg 975, 2006). *Biological Psychiatry, 60*(9), 1023-1023.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *J Health Soc Behav, 24*(4), 385-396.

Cohn, M., McAndrews, M. P., & Moscovitch, M. (2009). Associative reinstatement: A novel approach to assessing associative memory in patients with unilateral temporal lobe excisions. *Neuropsychologia, 47*(13), 2989-2994.

Collette, F., & Van der Linden, M. (2002). Brain imaging of the central executive component of working memory. *Neuroscience and Biobehavioral Reviews, 26*(2), 105-125.

Comblain, C., D'Argembeau, A., Van der Linden, M., & Aldenhoff, L. (2004). The effect of ageing on the recollection of emotional and neutral pictures. *Memory, 12*(6), 673-684.

Conrad, C. D., Lupien, S. J., & McEwen, B. S. (1999). Support for a bimodal role for Type II adrenal steroid receptors in spatial memory. *Neurobiology of Learning and Memory, 72*(1), 39-46.

Conrad, C. D., Lupien, S. J., Thanasoulis, L. C., & McEwen, B. S. (1997). The effects of Type I and Type II corticosteroid receptor agonists on exploratory behavior and spatial memory in the Y-maze. *Brain Research, 759*(1), 76-83.

Conrad, C. D., Mauldin-Jourdain, M. L., & Hobbs, R. J. (2001). Metyrapone Reveals That Previous Chronic Stress Differentially Impairs Hippocampal-dependent Memory. *Stress, 4*(4), 305-318.

Constantinidis, C., Williams, G. V., & Goldman-Rakic, P. S. (2002). A role for inhibition in shaping the temporal flow of information in prefrontal cortex. *Nature Neuroscience, 5*(2), 175-180.

Cowan, N. (1994). Mechanisms of verbal short-term memory. *Current Directions in Psychological Science, 3*(6), 185-189.

Cowan, N. (1997). The development of working memory. In N. Cowan (Ed.), *The development of memory in childhood.* Hove, East Sussex, UK: Psychology Press.

Cowan, N. (1999). An Embedde-Processes Model of Working Memory. In M. A & S. P (Eds.), *Models of working memory: Mechanisms of active maintenance and executive control* (pp. 62-101). New York: Cambridge University Press.

Craik, F. I. M. (1983). On the transfer of information from temporary to permanent memory. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences, 302*(1110), 341-359.

Craik, F. I. M., & Byrd, M. (1982). Aging and cognitive deficits: The role of attentional resources. In F. I. M. Craik & S. E. Trehub (Eds.), *Aging and cognitive processes* (pp. 191-211). New York: Plenum.

Craik, F. I. M., & Jennings, J. M. (1992). Human Memory. In F. I. M. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition* (pp. 51-110). Hillsdale, N.J.: Erlbaum.

Craik, F. I. M., & McDowd, J. M. (1987). Age-differences in recall and recognition. *Journal of Experimental Psychology-Learning Memory and Cognition, 13*(3), 474-479.

Cremers, H. R., Demenescu, L. R., Aleman, A., Renken, R., van Tol, M.-J., van der Wee, N. J. A., et al. (2010). Neuroticism modulates amygdala-prefrontal connectivity in response to negative emotional facial expressions. *Neuroimage, 49*(1), 963-970.

Curiati, P. K., Tamashiro, J. H., Squarzoni, P., Duran, F. L. S., Santos, L. C., Wajngarten, M., et al. (2009). Brain Structural Variability due to Aging and Gender in Cognitively Healthy Elders: Results from the Sao Paulo Ageing and Health Study. *American Journal of Neuroradiology, 30*(10), 1850-1856.

Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences, 7*(9), 415-423.

Dai, J. P., Buijs, R., & Swaab, D. (2004). Glucocorticoid hormone (cortisol) affects axonal transport in human cortex neurons but shows resistance in Alzheimer's disease. *British Journal of Pharmacology, 143*(5), 606-610.

Damasio, A. R. (1997). Neuropsychology - Towards a neuropathology of emotion and mood. *Nature, 386*(6627), 769-770.

Daneman, M., & Carpenter, P. A. (1980). Individual-differences in working memory and reading. *Journal of Verbal Learning and Verbal Behavior, 19*(4), 450-466.

D'Argembeau, A., & Van der Linden, M. (2004). Identity but not expression memory for unfamiliar faces is affected by ageing. *Memory, 12*(5), 644-654.

D'Argembeau, A., & Van der Linden, M. (2007). Facial expressions of emotion influence memory for facial identity in an automatic way. *Emotion, 7*(3), 507-515.

D'Argembeau, A., Van der Linden, M., Comblain, C., & Etienne, A. M. (2003). The effects of happy and angry expressions on identity and expression memory for unfamiliar faces. [Article]. *Cognition & Emotion, 17*(4), 609-622.

Davachi, L. (2006). Item, context and relational episodic encoding in humans. *Current Opinion in Neurobiology, 16*(6), 693-700.

Davachi, L., & Wagner, A. D. (2002). Hippocampal contributions to episodic encoding: Insights from relational and item-based learning. *Journal of Neurophysiology, 88*(2), 982-990.

Davis, K. L., Davis, B. M., Greenwald, B. S., Mohs, R. C., Mathe, A. A., Johns, C. A., et al. (1986). Cortisol and Alzheimer's disease. 1.Basal studies. *American Journal of Psychiatry, 143*(3), 300-305.

Davis, M. (1980). A multidimensional approach to individual differences in empathy. *JSAS Catalog of Selected Documents in Psychology, 10*, 85.

Davis, M. (1983). Measuring Individual Differences in Empathy: Evidence for a Multidimensional Approach. *Journal of Personality and Social Psychology, 44*(1), 113-126.

de Kloet, E. R., Joels, M., & Holsboer, F. (2005). Stress and the brain: From adaptation to disease. *Nature Reviews Neuroscience, 6*(6), 463-475.

De Kloet, E. R., Vreugdenhil, E., Oitzl, M. S., & Joels, M. (1998). Brain corticosteroid receptor balance in health and disease. *Endocrine Reviews, 19*(3), 269-301.

De Leon, M. J., George, A. E., Miller, J., Kluger, A., Stylopoulos, L., Schwartz, L., et al. (1988). Longitudinal CT studies of normal aging and Alzheimer's disease AD. *Neurology, 38*(3 SUPPL. 1), 371.

De Quervain, D. J., Roozendaal, B., Nitsch, R. M., McGaugh, J. L., & Hock, C. (2000). Acute cortisone administration impairs retrieval of long-term declarative memory in humans. *Nat Neurosci, 3*(4), 313-314.

De Quervain, D. J. F., Aerni, A., & Roozendaal, B. (2007). Preventive effect of beta-adrenoceptor blockade on glucocorticoid-induced memory retrieval deficits. *American Journal of Psychiatry, 164*(6), 967-969.

De Quervain, D. J. F., Henke, K., Aerni, A., Treyer, V., McGaugh, J. L., Berthold, T., et al. (2003). Glucocorticoid-induced impairment of declarative memory retrieval is associated with reduced blood flow in the medial temporal lobe. *European Journal of Neuroscience, 17*(6), 1296-1302.

De Quervain, D. J. F., Roozendaal, B., & McGaugh, J. L. (1998). Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature, 394*(6695), 787-790.

De Weerth, C., Graat, G., Buitelaar, J. K., & Thijssen, J. H. (2003). Measurement of cortisol in small quantities of saliva. *Clin Chem, 49*(4), 658-660.

Dedovic, K., Duchesne, A., Andrews, J., Engert, V., & Pruessner, J. C. (2009). The brain and the stress axis: The neural correlates of cortisol regulation in response to stress. *Neuroimage, 47*(3), 864-871.

Deeg, D. J., Comijs, H. C., Thomese, G. C., & Visser, M. (2009). The Longitudinal Ageing Study Amsterdam: a survey of 17 years of research into changes in daily functioning. *Tijdschr Gerontol Geriatr, 40*(6), 217-227.

Depue, B. E., Curran, T., & Banich, M. T. (2007). Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. *Science, 317*(5835), 215-219.

Derakshan, N., & Eysenck, M. W. (1998). Working memory capacity in high trait-anxious and repressor groups. *Cognition & Emotion, 12*(5), 697-713.

D'Esposito, M., Detre, J. A., Shin, R. K., Alsop, D. C., Atlas, S. W., & Grossman, M. (1995). Functional magnetic resonance imaging of working-memory during a dual-task paradigm. [Meeting Abstract]. *Neurology, 45*(4), A264-A265.

D'Esposito, M., Postle, B. R., Ballard, D., & Lease, J. (1999). Maintenance versus manipulation of information held in working memory: An event-related fMRI study. *Brain and Cognition, 41*(1), 66-86.

D'Esposito, M., Postle, B. R., & Rypma, B. (2000). Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. *Experimental Brain Research, 133*(1), 3-11.

Diamond, D. M., Bennett, M. C., Fleshner, M., & Rose, G. M. (1992). Inverted-U relationship between the level of peripheral corticosterone and the magnitute of hippocampal primed burst potentiation. *Hippocampus, 2*(4), 421-430.

Diamond, D. M., Fleshner, M., Ingersoll, N., & Rose, G. M. (1996). Psychological stress impairs spatial working memory: Relevance to electrophysiological studies of hippocampal function. *Behavioral Neuroscience, 110*(4), 661-672.

Dimitrov, M., Granetz, J., Peterson, M., Hollnagel, C., Alexander, G., & Grafman, J. (1999). Associative learning impairments in patients with frontal lobe damage. *Brain and Cognition, 41*(2), 213-230.

Dobbins, I. G., Foley, H., Schacter, D. L., & Wagner, A. D. (2002). Executive control during episodic retrieval: Multiple prefrontal processes subserve source memory. *Neuron, 35*(5), 989-996.

Dobbs, A. R., & Rule, B. G. (1989). Adult-age differences in working memory. *Psychology and Aging, 4*(4), 500-503.

Dolan, R. J. (2002). Emotion, cognition, and behavior. *Science, 298*(5596), 1191-1194.

Dolan, R. S., Lane, R., Chua, P., & Fletcher, P. (2000). Dissociable temporal lobe activations during emotional episodic memory retrieval. *Neuroimage, 11*(3), 203-209.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2004). Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: an event-related fMRI study. *Neuroimage, 23*(1), 64-74.

Domes, G., Rothfischer, J., Reichwald, U., & Hautzinger, M. (2005). Inverted-U function between salivary cortisol and retrieval of verbal memory after hydrocortisone treatment. *Behavioral Neuroscience, 119*(2), 512-517.

Duarte, A., Graham, K. S., & Henson, R. N. (2008). Age-related changes in neural activity associated with familiarity, recollection and false recognition. *Neurobiology of Aging*.

Dulaney, C. L., & Rogers, W. A. (1994). Mechanisms underlying reduction in stroop interference with practice for young and old adults. *Journal of Experimental Psychology-Learning Memory and Cognition, 20*(2), 470-484.

Dunn, J. D., & Orr, S. E. (1984). Differential plasma-corticosterone responses to hippocampal stimulation. *Experimental Brain Research, 54*(1), 1-6.

Duva, C. A., Floresco, S. B., Wunderlich, G. R., Lao, T. L., Pinel, J. P. J., & Phillips, A. G. (1997). Disruption of spatial but not object-recognition memory by neurotoxic lesions of the dorsal hippocampus in rats. *Behavioral Neuroscience, 111*(6), 1184-1196.

Eastwood, J. D., Smilek, D., & Merikle, P. M. (2003). Negative facial expression captures attention and disrupts performance. *Perception & Psychophysics, 65*(3), 352-358.

Ebner, N. C., & Johnson, M. K. (2009). Young and Older Emotional Faces: Are There Age Group Differences in Expression Identification and Memory? *Emotion, 9*(3), 329-339.

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nature Reviews Neuroscience, 1*(1), 41-50.

Eichenbaum, H., Otto, T., & Cohen, N. J. (1994). Two functional components of the hipocampal memory system. [Review]. *Behavioral and Brain Sciences, 17*(3), 449-472.

Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annual Review of Neuroscience, 30*, 123-152.

Ekman, P. (1993). Facial expression and emotion. *American Psychologist, 48*(4), 384-392.

Ekman, P., & Friesen, V. (1976). *Pictures of Facial Affect*. Palo Alto, California: Consulting Psychologists Press.

Eldridge, L. L., Engel, S. A., Zeineh, M. M., Bookheimer, S. Y., & Knowlton, B. J. (2005). A dissociation of encoding and retrieval processes in the human hippocampus. *J Neurosci, 25*(13), 3280-3286.

Eldridge, L. L., Knowlton, B. T., Furmanski, C. S., Bookheimer, S. Y., & Engel, S. A. (2000). Remembering episodes: a selective role for the hippocampus during retrieval. *Nature Neuroscience, 3*(11), 1149-1152.

Elliott, R., & Dolan, R. J. (1999). Differential neural responses during performance of matching and nonmatching to sample tasks at two delay intervals. *Journal of Neuroscience, 19*(12), 5066-5073.

Engelberg, E., & Sjoberg, L. (2004). Emotional intelligence, affect intensity, and social adjustment. *Personality and Individual Differences, 37*(3), 533-542.

Engle, R. W., Tuholski, S. W., Laughlin, J. E., & Conway, A. R. A. (1999). Working memory, short-term memory, and general fluid intelligence: A latent-variable approach. *Journal of Experimental Psychology-General, 128*(3), 309-331.

Esteves, F., Parra, C., Dimberg, U., & Ohman, A. (1994). Nonconscious associative learning - Pavlovian conditioning of skin-conductance responses to masked fear-relevant facial stimuli. *Psychophysiology, 31*(4), 375-385.

Evrard, M. (2002). Ageing and lexical access to common and proper names in picture naming. *Brain and Language, 81*(1-3), 174-179.

Eysenck, M. W., & Calvo, M. G. (1992). Anxiety and Performance - the Processing Efficiency Theory. *Cognition & Emotion, 6*(6), 409-434.

Feldman, S., & Weidenfeld, J. (1993). The dorsal hippocampus modifies the negative feedback effect of glucocorticoids on the adrenocortical and media-eminence CRF-41 responses to photic stimulation. *Brain Research, 614*(1-2), 227-232.

Fiocco, A. J., Joober, R., & Lupien, S. J. (2007). Education modulates cortisol reactivity to the Trier Social Stress Test in middle-aged adults. *Psychoneuroendocrinology, 32*(8-10), 1158-1163.

Fiocco, A. J., Wan, N., Weekes, N., Pim, H., & Lupien, S. J. (2006). Diurnal cycle of salivary cortisol in older adult men and women with subjective complaints of memory deficits and/or depressive symptoms: relation to cognitive functioning. *Stress, 9*(3), 143-152.

Fjell, A. M., Walhovd, K. B., Reinvang, I., Lundervold, A., Dale, A. M., Quinn, B. T., et al. (2005). Age does not increase rate of forgetting over weeks - Neuro anatomical volumes and visual memory across the adult life-span. *Journal of the International Neuropsychological Society, 11*(1), 2-15.

Fletcher, P. C., & Henson, R. N. A. (2001). Frontal lobes and human memory - Insights from functional neuroimaging. *Brain, 124*, 849-881.

Fletcher, P. C., Shallice, T., & Dolan, R. J. (1998). The functional roles of prefrontal cortex in episodic memory - I. Encoding. *Brain, 121*, 1239-1248.

Fletcher, P. C., Shallice, T., Frith, C. D., Frackowiak, R. S. J., & Dolan, R. J. (1998). The functional roles of prefrontal cortex in episodic memory - II. Retrieval. *Brain, 121*, 1249-1256.

Foster, J. K., Meikle, A., Goodson, G., Mayes, A. R., Howard, M., Sunram, S. I., et al. (1999). The hippocampus and delayed recall: Bigger is not necessarily better? *Memory, 7*(5-6), 715-732.

Fotenos, A. F., Snyder, A. Z., Girton, L. E., Morris, J. C., & Buckner, R. L. (2005). Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. *Neurology, 64*(6), 1032-1039.

Fox, E., Lester, V., Russo, R., Bowles, R. J., Pichler, A., & Dutton, K. (2000). Facial expressions of emotion: Are angry faces detected more efficiently? *Cognition & Emotion, 14*(1), 61-92.

Fried, I., MacDonald, K. A., & Wilson, C. L. (1997). Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron, 18*(5), 753-765.

Friston, K. J., Holmes, A., Poline, J. B., Price, C. J., & Frith, C. D. (1996). Detecting activations in PET and fMRI: Levels of inference and power. *Neuroimage, 4*(3), 223-235.

Frodl, T., Schaub, A., Banac, S., Charypar, M., Jager, M., Kummler, P., et al. (2006). Reduced hippocampal volume correlates with executive dysfunctioning in major depression. *Journal of Psychiatry & Neuroscience, 31*(5), 316-323.

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1989). Mnemonic coding of visual space in the monkeys dorsolateral prefrontal cortex. *Journal of Neurophysiology, 61*(2), 331-349.

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1993). Dorsolateral prefrontal lesions and oculomotor delayed-response performance - evidence for mnemonic scotomas. *Journal of Neuroscience, 13*(4), 1479-1497.

Fuster, J. M., & Alexander, G. E. (1971). Neuron activity related to short-term memory. *Science, 173*(3997), 652-654.

Fuxe, K., Wikstrom, A. C., Okret, S., Agnati, L. F., Harfstrand, A., Yu, Z. Y., et al. (1985). Mapping of glucocorticoid receptor immunoreactive neurons in the rat telencephalon and diencephalon using a monoclonal-antibody against rat-liver glucocorticoid receptor. [Article]. *Endocrinology, 117*(5), 1803-1812.

Garavan, H. (1998). Serial attention within working memory. *Memory & Cognition, 26*(2), 263-276.

Gaskin, S., Tremblay, A., & Mumby, D. G. (2003). Retrograde and anterograde object recognition in rats with hippocampal lesions. *Hippocampus, 13*(8), 962-969.

Gazzaley, A., Cooney, J. W., Rissman, J., & D'Esposito, M. (2005). Top-down suppression deficit underlies working memory impairment in normal aging. *Nature Neuroscience, 8*(10), 1298-1300.

Gazzaley, A., Rissman, J., Cooney, J., Rutman, A., Seibert, T., Clapp, W., et al. (2007). Functional interactions between prefrontal and visual association cortex contribute to top-down modulation of visual processing. *Cerebral Cortex, 17*, I125-I135.

Gershberg, F. B., & Shimamura, A. P. (1995). Impaired use of organizational strategies in free-recall following frontal lobe damage. *Neuropsychologia, 33*(10), 1305-1333.

Gilinsky, A. S., & Judd, B. B. (1994). Working-memory bias anc reasoning across the life-span. *Psychology and Aging, 9*(3), 356-371.

Giubilei, F., Patacchioli, F. R., Antonini, G., Monti, M. S., Tisei, P., Bastianello, S., et al. (2001). Altered circadian cortisol secretion in Alzheimer's disease: Clinical and neuroradiological aspects. *Journal of Neuroscience Research, 66*(2), 262-265.

Goeleven, E., De Raedt, R., Leyman, L., & Verschuere, B. (2008). The Karolinska Directed Emotional Faces: A validation study. *Cognition & Emotion, 22*(6), 1094-1118.

Gold, C. A., & Budson, A. E. (2008). Memory loss in Alzheimer's disease: implications for development of therapeutics. *Expert Rev Neurother, 8*(12), 1879-1891.

Goldman-Rakic, P. S., Selemon, L. D., & Schwartz, M. L. (1984). Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal-formation and parahippocampal cortex in the Rhesus-monkey. *Neuroscience, 12*(3), 719-743.

Gomez-Perez, E., & Ostrosky-Solis, F. (2006). Attention and Memory Evaluation Across the Life Span: Heterogeneous Effects of Age and Education. *Journal of Clinical and Experimental Neuropsychology, 28*(4), 477-494.

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N. A., Friston, K. J., & Frackowiak, R. S. J. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage, 14*(1), 21-36.

Gould, T. J., Rowe, W. B., Heman, K. L., Mesches, M. H., Young, D. A., Rose, G. M., et al. (2002). Effects of hippocampal lesions on patterned motor learning in the rat. [Article]. *Brain Research Bulletin, 58*(6), 581-586.

Grady, C. L., McIntosh, A. R., Beig, S., Keightley, M. L., Burian, H., & Black, S. E. (2003). Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. *Journal of Neuroscience, 23*(3), 986-993.

Graf, P., & Schacter, D. L. (1989). Unitization and grouping mediate dissociations in memory for new associations. *Journal of Experimental Psychology-Learning Memory and Cognition, 15*(5), 930-940.

Gray, J. R. (2001). Emotional modulation of cognitive control: Approach-withdrawal states double-dissociate spatial from verbal two-back task performance. *Journal of Experimental Psychology-General, 130*(3), 436-452.

Greenwald, B. S., Mathe, A. A., Mohs, R. C., Levy, M. I., Johns, C. A., & Davis, K. L. (1986). Cortisol and Alzheimer's disease. 2. Dexamethasone suppression, dementia severity and affective symptoms. *American Journal of Psychiatry, 143*(4), 442-446.

Grillon, C., Smith, K., Haynos, A., & Nieman, L. K. (2004). Deficits in hippocampus-mediated Pavlovian conditioning in endogenous hypercortisolism. *Biological Psychiatry, 56*(11), 837-843.

Gross, J. J., Carstensen, L. L., Pasupathi, M., Tsai, J., Skorpen, C. G., & Hsu, A. Y. C. (1997). Emotion and aging: Experience, expression, and control. *Psychology and Aging, 12*(4), 590-599.

Gunning-Dixon, F. M., Gur, R. C., Perkins, A. C., Schroeder, L., Turner, T., Turetsky, B. I., et al. (2003). Age-related differences in brain activation during emotional face processing. *Neurobiology of Aging, 24*(2), 285-295.

Gunning-Dixon, F. M., & Raz, N. (2003). Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. *Neuropsychologia, 41*(14), 1929-1941.

Habeck, C., Rakitin, B. C., Moeller, J., Scarmeas, N., Zarahn, E., Brown, T., et al. (2005). An event-related fMRI study of the neural networks underlying the encoding, maintenance, and retrieval phase in a delayed-match-to-sample task. *Cognitive Brain Research, 23*(2-3), 207-220.

Habib, R., McIntosh, A. R., Wheeler, M. A., & Tulving, E. (2003). Memory encoding and hippocampally-based novelty/familiarity discrimination networks. *Neuropsychologia, 41*(3), 271-279.

Hahn, S., Carlson, C., Singer, S., & Gronlund, S. D. (2006). Aging and visual search: Automatic and controlled attentional bias to threat faces. *Acta Psychologica, 123*(3), 312-336.

Haier, R. J., Jung, R. E., Yeo, R. A., Head, K., & Alkire, M. T. (2005). Structural brain variation, age, and response time. *Cognitive Affective & Behavioral Neuroscience, 5*(2), 246-251.

Haller, J., Mikics, E., & Makara, G. B. (2008). The effects of non-genomic glucocorticoid mechanisms on bodily functions and the central neural system. A critical evaluation of findings. *Front Neuroendocrinol, 29*(2), 273-291.

Hamann, S. (2001). Cognitive and neural mechanisms of emotional memory. *Trends in Cognitive Sciences, 5*(9), 394-400.

Hamann, S. B., Cahill, L., McGaugh, J. L., & Squire, L. R. (1997). Intact enhancement of declarative memory for emotional material in amnesia. [Article]. *Learning & Memory, 4*(3), 301-309.

Hamann, S. B., Cahill, L., & Squire, L. R. (1997). Emotional perception and memory in amnesia. [Article]. *Neuropsychology, 11*(1), 104-113.

Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). A neuroimaging study of emotion and emotional memory. *Journal of Cognitive Neuroscience*, 19-19.

Hasher, L., & Zacks, R. T. (1988). Working memory, comprehension and aging: A review and a new view. In G. H. Bower (Ed.), *The psychology of learning and motivation: Advances in research and theory* (Vol. 22, pp. 193-225). San Diego, CA: Academic Press.

Haskins, A. L., Yonelinas, A. P., Quamme, J. R., & Ranganath, C. (2008). Perirhinal cortex supports encoding and familiarity-based recognition of novel associations. *Neuron, 59*(4), 554-560.

Hayes, S., Hirsch, C., & Mathews, A. (2008). Restriction of working memory capacity during worry. *Journal of Abnormal Psychology, 117*(3), 712-717.

Head, D., Buckner, R. L., Shimony, J. S., Williams, L. E., Akbudak, E., Conturo, T. E., et al. (2004). Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: Evidence from diffusion tensor imaging. *Cerebral Cortex, 14*(4), 410-423.

Hebb, D. O. (1949). *The organization of behavior.* New York: Wiley.

Henson, R. N. A., Rugg, M. D., Shallice, T., Josephs, O., & Dolan, R. J. (1999). Recollection and familiarity in recognition memory: An event-related functional magnetic resonance imaging study. *Journal of Neuroscience, 19*(10), 3962-3972.

Herman, J. P., Cullinan, W. E., Morano, M. I., Akil, H., & Watson, S. J. (1995). Contribution of the ventral subiculum to inhibitory regulation of the hypothalamic-pituitary-adrenal axis. *Journal of Neuroendocrinology, 7*(6), 475-482.

Herman, J. P., Figueiredo, H., Mueller, N. K., Ulrich-Lai, Y., Ostrander, M. M., Choi, D. C., et al. (2003). Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. *Frontiers in Neuroendocrinology, 24*(3), 151-180.

Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: Hypothalamo-pituitary-adrenocortical axis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 29*(8), 1201-1213.

Hess, U., Blairy, S., & Kleck, R. E. (1997). The intensity of emotional facial expressions and decoding accuracy. *Journal of Nonverbal Behavior, 21*(4), 241-257.

Hibberd, C., Yau, J. L. W., & Seckl, J. R. (2000). Glucocorticoids and the ageing hippocampus. *Journal of Anatomy, 197*, 553-562.

Holdstock, J. S., Mayes, A. R., Gong, Q. Y., Roberts, N., & Kapur, N. (2005). Item recognition is less impaired than recall and associative recognition in a patient with selective hippocampal damage. *Hippocampus, 15*(2), 203-215.

Isaacowitz, D. M., Wadlinger, H. A., Goren, D., & Wilson, H. R. (2006). Selective preference in visual fixation away from negative images in old age? An eye-tracking study (vol 21, pg 40, 2006). *Psychology and Aging, 21*(2), 221-221.

Isgor, C., Kabbaj, M., Akil, H., & Watson, S. J. (2004). Delayed effects of chronic variable stress during peripubertal-juvenile period on hippocampal morphology and on cognitive and stress axis functions in rats. *Hippocampus, 14*(5), 636-648.

Jack, C. R., Petersen, R. C., Xu, Y., O'Brien, P. C., Smith, G. E., Ivnik, R. J., et al. (2000). Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. *Neurology, 55*(4), 484-489.

Jackson, O., & Schacter, D. L. (2004). Encoding activity in anterior medial temporal lobe supports subsequent associative recognition. *Neuroimage, 21*(1), 456-462.

Jacobson, L., & Sapolsky, R. (1991). The role of the hippocampus in feedback-regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocrine Reviews, 12*(2), 118-134.

Jacoby, L. L. (1991). A process dissociation framework - separating automatic from intentional uses of memory. *Journal of Memory and Language, 30*(5), 513-541.

James, L. E. (2006). Specific effects of aging on proper name retrieval: Now you see them, now you don't. *Journals of Gerontology Series B-Psychological Sciences and Social Sciences, 61*(3), P180-P183.

Jankord, R., & Herman, J. P. (2008). Limbic Regulation of Hypothalamo-Pituitary-Adrenocortical Function during Acute and Chronic Stress. *Stress, Neurotransmitters, and Hormones: Neuroendocrine and Genetic Mechanisms, 1148*, 64-73.

Jernigan, T. L., Archibald, S. L., Fennema-Notestine, C., Gamst, A. C., Stout, J. C., Bonner, J., et al. (2001). Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiology of Aging, 22*(4), 581-594.

Jernigan, T. L., & Gamst, A. C. (2005). Changes in volume with age—consistency and interpretation of observed effects. *Neurobiology of Aging, 26*(9), 1271-1274.

Johnston, P. J., Katsikitis, M., & Carr, V. J. (2001). A generalised deficit can account for problems in facial emotion recognition in schizophrenia. *Biological Psychology, 58*(3), 203-227.

Kalmijn, S., Launer, L. J., Stolk, R. P., de Jong, F. H., Pols, H. A. P., Hofman, A., et al. (1998). A prospective study on cortisol, dehydroepiandrosterone sulfate, and cognitive function in the elderly. *Journal of Clinical Endocrinology & Metabolism, 83*(10), 3487-3492.

Kaufmann, J. M., & Schweinberger, S. R. (2004). Expression influences the recognition of familiar faces. *Perception, 33*(4), 399-408.

Kaymak, S. U., Demir, B., Senturk, S., Tatar, I., Aldur, M. M., & Ulug, B. (2009). Hippocampus, glucocorticoids and neurocognitive functions in patients with first-episode major depressive disorders. *European Archives of Psychiatry and Clinical Neuroscience*.

Keenan, P. A., Jacobson, M. W., Soleymani, R. M., Mayes, M. D., Stress, M. E., & Yaldoo, D. T. (1996). The effect on memory of chronic prednisone treatment in patients with systemic disease. *Neurology, 47*(6), 1396-1402.

Keightley, M. L., Winocur, G., Burianova, H., Hongwanishkul, D., & Grady, C. L. (2006). Age effects on social cognition: Faces tell a different story. *Psychology and Aging, 21*(3), 558-572.

Keller, S. S., & Roberts, N. (2008). Voxel-based morphometry of temporal lobe epilepsy: An introduction and review of the literature. *Epilepsia, 49*(5), 741-757.

Kelley, W. M., Miezin, F. M., McDermott, K. B., Buckner, R. L., Raichle, M. E., Cohen, N. J., et al. (1998). Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron, 20*(5), 927-936.

Kensinger, E. A. (2008). Age differences in memory for arousing and nonarousing emotional words. *J Gerontol B Psychol Sci Soc Sci, 63*(1), P13-18.

Kensinger, E. A., Brierley, B., Medford, N., Growdon, J. H., & Corkin, S. (2002). Effects of normal aging and Alzheimer's disease on emotional memory. *Emotion (Washington D C), 2*(2), 118-134.

Kensinger, E. A., & Corkin, S. (2003). Effect of negative emotional content on working memory and long-term memory. *Emotion, 3*(4), 378-393.

Kensinger, E. A., Gutchess, A. H., & Schacter, D. L. (2007). Effects of aging and encoding instructions on emotion-induced memory trade-offs. *Psychology and Aging, 22*(4), 781-795.

Kensinger, E. A., Piguet, O., Krendl, A. C., & Corkin, S. (2005). Memory for contextual details: Effects of emotion and aging. *Psychology and Aging, 20*(2), 241-250.

Kensinger, E. A., & Schacter, D. L. (2006). Amygdala activity is associated with the successful encoding of item, but not source, information for positive and negative stimuli. *Journal of Neuroscience, 26*(9), 2564-2570.

Kersten, A. W., Earles, J. L., Curtayne, E. S., & Lane, J. C. (2008). Adult age differences in binding actors and actions in memory for events. *Memory & Cognition, 36*(1), 119-131.

Kilb, A., & Naveh-Benjamin, M. (2007). Paying attention to binding: Further studies assessing the role of reduced attentional resources in the associative deficit of older adults. *Memory & Cognition, 35*(5), 1162-1174.

Kirschbaum, C., Bono, E. G., Rohleder, N., Gessner, C., Pirke, K. M., Salvador, A., et al. (1997). Effects of fasting and glucose load on free cortisol responses to stress and nicotine. *Journal of Clinical Endocrinology & Metabolism, 82*(4), 1101-1105.

Kirschbaum, C., Wolf, O. T., May, M., Wippich, W., & Hellhammer, D. H. (1996). Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sciences, 58*(17), 1475-1483.

Kirwan, C. B., & Stark, C. E. (2004). Medial temporal lobe activation during encoding and retrieval of novel face-name pairs. *Hippocampus, 14*(7), 919-930.

Konkel, A., Warren, D. E., Duff, M. C., Tranel, D. N., & Cohen, N. J. (2008). Hippocampal amnesia impairs all manner of relational memory. *Frontiers in Human Neuroscience, 2*.

Kostopoulos, P., & Petrides, M. (2002). Mid-ventrolateral prefrontal cortex: A region important for visual spatial and visual non-spatial retrieval mechanisms. *International Journal of Psychophysiology, 45*(1-2), 132-132.

Krampe, R. T., & Ericsson, K. A. (1996). Maintaining excellence: deliberate practice and elite performance in young and older pianists. *J Exp Psychol Gen, 125*(4), 331-359.

Kremen, W., O' Brien, R., Panizzon, M., Prom-Wormley, E., Eaves, L., Eisen, S., et al. (2010). Salivary cortisol and prefrontal cortical thickness in middle-aged men: A twin study. *Neuroimage*.

Kringelbach, M. L., & Rolls, E. T. (2004). The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Progress in Neurobiology, 72*(5), 341-372.

Kubicki, M., Shenton, M. E., Salisbury, D. F., Hirayasu, Y., & McCarley, R. W. (2002). Voxel-based morphometric analysis of gray matter in first episode schizophrenia. *Schizophrenia Research, 53*(3), 96-96.

Kubota, K., & Niki, H. (1971). Prefrontal cortical unit activity and delayed alternation performance in monkeys. *Journal of Neurophysiology, 34*(3), 337-&.

Kuhlmann, S., Piel, M., & Wolf, O. T. (2005). Impaired memory retrieval after psychosocial stress in healthy young men. *Journal of Neuroscience, 25*(11), 2977-2982.

Kukolja, J., Thiel, C., Wolf, O., & Fink, G. (2008). Increased cortisol levels in cognitively challenging situations are beneficial in young but not older subjects. *Psychopharmacology, 201*(2), 293-304.

LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E., & Phelps, E. A. (1998). Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron, 20*(5), 937-945.

LaBar, K. S., & Phelps, E. A. (1998). Arousal-mediated memory consolidation: Role of the medial temporal lobe in humans. *Psychological Science, 9*(6), 490-493.

Landfield, P. W., Baskin, R. K., & Pitler, T. A. (1981). Brain aging correlates - retardation by hormonal-pharmacological treatments. *Science, 214*(4520), 581-584.

Laudat, M. H., Cerdas, S., Fournier, C., Guiban, D., Guilhaume, B., & Luton, J. P. (1988). Salivary cortisol measurement: a practical approach to assess pituitary-adrenal function. *J Clin Endocrinol Metab, 66*(2), 343-348.

Lavenex, P., & Amaral, D. G. (2000). Hippocampal-neocortical interactions: a hierarchy of associativity. *Hippocampus, 10*(4), 420-430.

Laver, G. D., & Burke, D. M. (1993). Why do semantic priming effects increase in old age? A meta-analysis. *Psychol Aging, 8*(1), 34-43.

Lawton, M. P., Kleban, M. H., Rajagopal, D., & Dean, J. (1992). Dimensions of affective experience in 3 age groups *Psychology and Aging, 7*(2), 171-184.

Leclerc, C. M., & Kensinger, E. A. (2008). Age-related differences in medial prefrontal activation in response to emotional images. *Cognitive Affective & Behavioral Neuroscience, 8*(2), 153-164.

LeDoux, J. E., Thompson, M. E., Iadecola, C., Tucker, L. W., & Reis, D. J. (1983). Local cerebral blood-flow increases during auditory and emotional processing in the conscious rat. *Science, 221*(4610), 576-578.

Lee, B. K., Glass, T. A., McAtee, M. J., Wand, G. S., Bandeen-Roche, K., Bolla, K. I., et al. (2007). Associations of salivary cortisol with cognitive function in the Baltimore Memory Study. *Archives of General Psychiatry, 64*(7), 810-818.

Leibovici, D., Ritchie, K., Ledesert, B., & Touchon, J. (1996). Does education level determine the course of cognitive decline? *Age Ageing, 25*(5), 392-397.

Leigland, L. A., Schulz, L. E., & Janowsky, J. S. (2004). Age related changes in emotional memory. *Neurobiol Aging, 25*(8), 1117-1124.

Lemaire, V., Koehl, M., Le Moal, M., & Abrous, D. N. (2000). Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America, 97*(20), 11032-11037.

Leppanen, J. M., & Hietanen, J. K. (2004). Positive facial expressions are recognized faster than negative facial expressions, but why? *Psychological Research-Psychologische Forschung, 69*(1-2), 22-29.

Li, G., Cherrier, M. M., Tsuang, D. W., Petrie, E. C., Colasurdo, E. A., Craft, S., et al. (2006). Salivary cortisol and memory function in human aging. *Neurobiology of Aging, 27*(11), 1705-1714.

Liening, S. H., Stanton, S. J., Saini, E. K., & Schultheiss, O. C. Salivary testosterone, cortisol, and progesterone: two-week stability, interhormone correlations, and effects of time of day, menstrual cycle, and oral contraceptive use on steroid hormone levels. *Physiol Behav, 99*(1), 8-16.

Light, L. L., Prull, M. W., La Voie, D. J., & Healy, M. R. (2000). Dual-process theories of memory in old age. In T. J. Perfect & E. A. Maylor (Eds.), *Models of Cognitive Aging* (pp. 238-300). New York: Oxford University Press.

Lowy, M. T., Wittenberg, L., & Yamamoto, B. K. (1995). Effect of acute stress on hippocampal glutamate levels and spectrin. *Journal of Neurochemistry, 65*(1), 268-274.

Lundqvist, D., Flykt, A., & Ohman, A. (1998). The Karolinska Directed Emotional Faces - KDEF (CD-ROM). Department of Clinical Neuroscience, Psychology section: Karolinska Institute, Stockholm, Sweden.

Lupien, S., Lecours, A. R., Lussier, I., Schwartz, G., Nair, N. P. V., & Meaney, M. J. (1994). Basal cortisol-levels and cognitive deficits in human aging. *Journal of Neuroscience, 14*(5), 2893-2903.

Lupien, S. J., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Thakur, M., et al. (1998). Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience, 1*(1), 69-73.

Lupien, S. J., Evans, A., Lord, C., Miles, J., Pruessner, M., Pike, B., et al. (2007). Hippocampal volume is as variable in young as in older adults: Implications for the notion of hippocampal atrophy in humans. *Neuroimage, 34*(2), 479-485.

Lupien, S. J., Gaudreau, S., Tchiteya, B. M., Maheu, F., Sharma, S., Nair, N. P., et al. (1997). Stress-induced declarative memory impairment in healthy elderly subjects: relationship to cortisol reactivity. *J Clin Endocrinol Metab, 82*(7), 2070-2075.

Lupien, S. J., Gillin, C. J., & Hauger, R. L. (1999). Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: A dose-response study in humans. *Behavioral Neuroscience, 113*(3), 420-430.

Lupien, S. J., & Lepage, M. (2001). Stress, memory, and the hippocampus: can't live with it, can't live without it. *Behavioural Brain Research, 127*(1-2), 137-158.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience, 10*(6), 434-445.

Lupien, S. J., Schwartz, G., Ng, Y. K., Fiocco, A., Wan, N., Pruessner, J. C., et al. (2005). The Douglas Hospital Longitudinal Study of Normal and Pathological Aging: summary of findings. *J Psychiatry Neurosci, 30*(5), 328-334.

Lupien, S. J., Wilkinson, C. W., Briere, S., Menard, C., Kin, N., & Nair, N. P. V. (2002). The modulatory effects of corticosteroids on cognition: studies in young human populations. *Psychoneuroendocrinology, 27*(3), 401-416.

Lustig, C., Shah, P., Seidler, R., & Reuter-Lorenz, P. A. (2009). Aging, Training, and the Brain: A Review and Future Directions. *Neuropsychology Review, 19*(4, Sp. Iss. SI), 504-522.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage, 19*(3), 1233-1239.

Mandler, G. (1980). Recognizing - the judgment of previous occurrence. *Psychological Review, 87*(3), 252-271.

Manns, J. R., Hopkins, R. O., & Squire, L. R. (2003). Semantic memory and the human hippocampus. *Neuron, 38*(1), 127-133.

Maratos, E. J., Dolan, R. J., Morris, J. S., Henson, R. N. A., & Rugg, M. D. (2001). Neural activity associated with episodic memory for emotional context. *Neuropsychologia, 39*(9), 910-920.

Mather, M. (2007). Emotional Arousal and Memory Binding An Object-Based Framework. *Perspectives on Psychological Science, 2*(1), 33-52.

Mather, M., Canli, T., English, T., Whitfield, S., Wais, P., Ochsner, K., et al. (2004). Amygdala responses to emotionally valenced stimuli in older and younger adults. *Psychological Science, 15*(4), 259-263.

Mather, M., & Carstensen, L. L. (2003). Aging and attentional biases for emotional faces. *Psychol Sci, 14*(5), 409-415.

Mather, M., & Carstensen, L. L. (2005). Aging and motivated cognition: the positivity effect in attention and memory. *Trends Cogn Sci, 9*(10), 496-502.

Mather, M., Gorlick, M. A., & Nesmith, K. (2009). The limits of arousal's memory-impairing effects on nearby information. *American Journal of Psychology, 122*(3), 349-369.

Mather, M., Johnson, M. K., & De Leonardis, D. M. (1999). Stereotype reliance in source monitoring: Age differences and neuropsychological test correlates. *Cognitive Neuropsychology, 16*(3-5), 437-458.

Mather, M., & Knight, M. R. (2005). Goal-directed Memory: The role of cognitive control in older adults' emotional memory. *Psychology and Aging, 20(4),* 554-570.

Mather, M., & Knight, M. R. (2006). Angry faces get noticed quickly: Threat detection is not impaired among older adults. *Journals of Gerontology Series B-Psychological Sciences and Social Sciences, 61*(1), p54-p57.

Mather, M., & Nesmith, K. (2008). Arousal-enhanced location memory for pictures. *Journal of Memory and Language, 58*(2), 449-464.

Mather, P. G., Read, J. C., & Buhrman, R. A. (2006). Why memories may become more positive as people age. In B. Utttl, N. Ohta & A. L. Siegenthaler (Eds.), *Memory and Emotion: Interdisciplinary perspectives.* Blackwell publishing.

Mattay, V. S., Fera, F., Tessitore, A., Hariri, A. R., Berman, K. F., Das, S., et al. (2006). Neurophysiological correlates of age-related changes in working memory capacity. *Neuroscience Letters, 392*(1-2), 32-37.

Maxwell, S. E. (2000). Sample size and multiple regression analysis. *Psychological Methods, 5*(4), 434-458.

Mayes, A. R., Holdstock, J. S., Isaac, C. L., Montaldi, D., Grigor, J., Gummer, A., et al. (2004). Associative recognition in a patient with selective hippocampal lesions and relatively normal item recognition. *Hippocampus, 14*(6), 763-784.

McElree, B. (2001). Working memory and focal attention. *Journal of Experimental Psychology-Learning Memory and Cognition, 27*(3), 817-835.

McEwen, B. S. (1994). Steroid hormone actions on the brain: when is the genome involved? *Horm Behav, 28*(4), 396-405.

McEwen, B. S. (2000). Effects of adverse experiences for brain structure and function. *Biological Psychiatry, 48*(8), 721-731.

McIntosh, A. R., Nyberg, L., Bookstein, F. L., & Tulving, E. (1997). Differential functional connectivity of prefrontal and medial temporal cortices during episodic memory retrieval. *Human Brain Mapping, 5*(4), 323-327.

Meaney, M. J., Aitken, D. H., Vanberkel, C., Bhatnagar, S., & Sapolsky, R. M. (1988). Effect of neonatal handling on age-related impairments associated with the hippocampus *Science, 239*(4841), 766-768.

Mello. (2010). Hormones, nicotine and cocaine: Clinical studies. *Hormones and Behavior, In Press.*

Metcalfe, J., Jacobs, W. J., & Medin, D. L. (1998). Emotional memory: The effects of stress on 'cool' and 'hot' memory systems. In *The psychology of learning and motivation: Advances in research and theory, Vol. 38.* (pp. 187-222). San Diego, CA US: Academic Press.

Meyer-Lindenberg, A., Poline, J. B., Kohn, P. D., Holt, J. L., Egan, M. F., Weinberger, D. R., et al. (2001). Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. *Am J Psychiatry, 158*(11), 1809-1817.

Mikels, J. A., Larkin, G. R., Reuter-Lorenz, P. A., & Cartensen, L. L. (2005). Divergent trajectories in the aging mind: changes in working memory for affective versus visual information with age. *Psychol Aging, 20*(4), 542-553.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24*, 167-202.

Miller, M. H., & Orbach, J. (1972). Retention of spatial alternation following frontal lobe resections in stump-tailed macaques. *Neuropsychologia, 10*(3), 291-&.

Milner, B. (1966). Amnesia following operation on the temporal lobe. In C. W. M. Whitty & O. L. Zangwill (Eds.), *Amnesia*. London: Butterworth.

Mishkin, M. (1978). Memory in monkeys severely impaired by combined but not separate removal of amygdala and hippocampus. *Nature, 273*(5660), 297-298.

Mishkin, M. (1982). A memory system in the monkey. *Philosophical Transactions of the Royal Society B-Biological Sciences, 298*(1089), 85-95.

Mishkin, M., & Murray, E. A. (1994). Stimulus-Recognition. *Current Opinion in Neurobiology, 4*(2), 200-206.

Mitra, R., Jadhav, S., McEwen, B. S., Vyas, A., & Chattarji, S. (2005). Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. *Proceedings of the National Academy of Sciences of the United States of America, 102*(26), 9371-9376.

Morris, J. S., Ohman, A., & Dolan, R. J. (1998). Conscious and unconscious emotional learning in the human amygdala. *Nature, 393*(6684), 467-470.

Morris, R., Pandya, D. N., & Petrides, M. (1999). Fiber system linking the mid-dorsolateral frontal cortex with the retrosplenial/presubicular region in the rhesus monkey. *Journal of Comparative Neurology, 407*(2), 183-192.

Morris, R. G., Craik, F. I. M., & Gick, M. L. (1990). Age-differences in working memory tasks - the role fo secondary memory and the central executive system. *Quarterly Journal of Experimental Psychology Section a-Human Experimental Psychology, 42*(1), 67-86.

Morris, R. G., Gick, M. L., & Craik, F. I. M. (1988). Processing resources and age-differences in working memory. *Memory & Cognition, 16*(4), 362-366.

Morse, C. K. (1993). Does variability increase with age - an archival study of cognitive measures. *Psychology and Aging, 8*(2), 156-164.

Mueller, N. K., Dolgas, C. M., & Herman, J. P. (2004). Stressor-selective role of the ventral subiculum in regulation of neuroendocrine stress responses. *Endocrinology, 145*(8), 3763-3768.

Murphy, N. A., & Isaacowitz, D. M. (2008). Preferences for emotional information in older and younger adults: A meta-analysis of memory and attention tasks. *Psychology and Aging, 23*(2), 263-286.

Murray, E. A., Gaffan, D., & Mishkin, M. (1993). Neural substrates of visual stimulus association in Rhesus monkeys. *Journal of Neuroscience, 13*(10), 4549-4561.

Nadel, L., & Jacobs, W. J. (1998). Traumatic memory is special. *Current Directions in Psychological Science, 7*(5), 154-157.

Nater, U. M., Moor, C., Okere, U., Stallkamp, R., Martin, M., Ehlert, U., et al. (2007). Performance on a declarative memory task is better in high than low cortisol responders to psychosocial stress. *Psychoneuroendocrinology, 32*(6), 758-763.

Naveh-Benjamin, M. (2000). Adult age differences in memory performance: Tests of an associative deficit hypothesis. *Journal of Experimental Psychology-Learning Memory and Cognition, 26*(5), 1170-1187.

Naveh-Benjamin, M., Brav, T. K., & Levy, O. (2007). The associative memory deficit of older adults: The role of strategy utilization. *Psychology and Aging, 22*(1), 202-208.

Naveh-Benjamin, M., Guez, J., Kilb, A., & Reedy, S. (2004). The associative memory deficit of older adults: Further support using face-name associations. *Psychology and Aging, 19*(3), 541-546.

Naveh-Benjamin, M., Guez, J., & Shulman, S. (2004). Older adults' associative deficit in episodic memory: Assessing the role of decline in attentional resources. *Psychonomic Bulletin & Review, 11*(6), 1067-1073.

Naveh-Benjamin, M., Hussain, Z., Guez, J., & Bar-On, M. (2003). Adult age differences in episodic memory: Further support for an associative-deficit hypothesis. *Journal of Experimental Psychology-Learning Memory and Cognition, 29*(5), 826-837.

Nelson, H. (1982). *National Adult Reading Test (NART): test manual*: NFER-Nelson, Windsor, UK.

Nelson, H., & Willison, J. (1991). *The revised National Adult Reading Test (NART): Test Manual*: NFER-Nelson, Windsor, England.

Newcomer, J. W., Craft, S., Hershey, T., Askins, K., & Bardgett, M. E. (1994). Glucocorticoid-induced impairment in declarative memory performance in adult humans. *Journal of Neuroscience, 14*(4), 2047-2053.

Newcomer, J. W., Selke, G., Melson, A. K., Hershey, T., Craft, S., Richards, K., et al. (1999). Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Archives of General Psychiatry, 56*(6), 527-533.

Nielen, M. M. A., Heslenfeld, D. J., Heinen, K., Van Strien, J. W., Witter, M. P., Jonker, C., et al. (2009). Distinct brain systems underlie the processing of valence and arousal of affective pictures. *Brain and Cognition, 71*(3), 387-396.

Nilsson, L. G. (2003). Memory function in normal aging. *Acta Neurologica Scandinavica, 107*, 7-13.

Nilsson, L. G., Backman, L., Erngrund, K., Nyberg, L., Adolfsson, R., Bucht, G., et al. (1997). The Betula prospective cohort study: Memory, health and aging. *Aging Neuropsychology and Cognition, 4*(1), 1-32.

Nilsson, L. G., Sternang, O., Ronnlund, M., & Nyberg, L. (2009). Challenging the notion of an early-onset of cognitive decline. *Neurobiology of Aging, 30*(4), 521-524.

Nyberg, L., Cabeza, R., & Tulving, E. (1996). PET studies of encoding and retrieval: The HERA model. *Psychonomic Bulletin & Review, 3(2), 135-148.*

Nyberg, L., Dahlin, E., Stigsdotter Neely, A., Backman, L. (2009). Neural correlates of variable working memory load across adult age and skill: Dissociative patterns within the fronto-parietal network. *Scandanavian Journal of Psychology, 50(1), 41-6.*

Nyberg, L., Maitland, S. B., Ronnlund, M., Backman, L., Dixon, R. A., Wahlin, A., et al. (2003). Selective adult age differences in an age-invariant multifactor model of declarative memory. *Psychology and Aging, 18*(1), 149-160.

Nyberg, L., & Tulving, E. (1996). Classifying human long-term memory: Evidence from converging dissociations. *European Journal of Cognitive Psychology, 8*(2), 163-183.

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends Cogn Sci, 9*(5), 242-249.

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D. E., et al. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage, 23*(2), 483-499.

Ohman, A. (2005). The rote of the amygdala in human fear: Automatic detection of threat. *Psychoneuroendocrinology, 30*(10), 953-958.

Oitzl, M. S., & Dekloet, E. R. (1992). Selective corticosteroid antagonists modulate specific aspects of spatial orientation learning. *Behavioral Neuroscience, 106*(1), 62-71.

Olson, I. R., Moore, K. S., Stark, M., & Chatterjee, A. (2006). Visual working memory is impaired when the medial temporal lobe is damaged. *Journal of Cognitive Neuroscience, 18*(7), 1087-1097.

O'Mara, S. (2005). The subiculum: what it does, what it might do, and what neuroanatomy has yet to tell us. *Journal of Anatomy, 207*(3), 271-282.

Orgeta, V., & Phillips, L. H. (2008). Effects of age and emotional intensity on the recognition of facial emotion. *Experimental Aging Research, 34*(1), 63-79.

Owen, A. M., Herrod, N. J., Menon, D. K., Clark, J. C., Downey, S., Carpenter, T. A., et al. (1999). Redefining the functional organization of working memory processes within human lateral prefrontal cortex. *European Journal of Neuroscience, 11*(2), 567-574.

Owen, A. M., Stern, C. E., Look, R. B., Tracey, I., Rosen, B. R., & Petrides, M. (1998). Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. *Proceedings of the National Academy of Sciences of the United States of America, 95*(13), 7721-7726.

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., & Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychol Aging, 17*(2), 299-320.

Park, D. C., & Reuter-Lorenz, P. (2009). The Adaptive Brain: Aging and Neurocognitive Scaffolding. *Annual Review of Psychology, 60*, 173-196.

Patel, P. D., Lopez, J. F., Lyons, D. M., Burke, S., Wallace, M., & Schatzberg, A. F. (2000). Glucocorticoid and mineralocorticoid receptor mRNA expression in squirrel monkey brain. *Journal of Psychiatric Research, 34*(6), 383-392.

Pavlides, C., Watanabe, Y., Magarinos, A. M., & McEwen, B. S. (1995). Opposing roles of Type-I and Type-II adrenal-steroid receptors in hippocampal long-term potentiation. *Neuroscience, 68*(2), 387-394.

Perlstein, W. M., Elbert, T., & Stenger, V. A. (2002). Dissociation in human prefrontal cortex of affective influences on working memory-related activity. *Proceedings of the National Academy of Sciences of the United States of America, 99*(3), 1736-1741.

Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L. G., Ingvar, M., et al. (2006). Structure-function correlates of cognitive decline in aging. *Cerebral Cortex, 16*(7), 907-915.

Peterson, L. R., & Peterson, M. J. (1959). Short-term retention of individual verbal items. *J Exp Psychol, 58*, 193-198.

Petrella, J. R., Krishnan, S., Slavin, M. J., Tran, T. T. T., Murty, L., & Doraiswamy, P. M. (2006). Mild cognitive impairment: Evaluation with 4-T functional MR imaging. *Radiology, 240*(1), 177-186.

Petrican, R., Moscovitch, M., & Schimmack, U. (2008). Cognitive resources, valence, and memory retrieval of emotional events in older adults. *Psychol Aging, 23*(3), 585-594.

Petrides, M. (1994). Frontal lobes and behaviour. *Current Opinion in Neurobiology, 4*(2), 207-211.

Petrides, M. (1996). Specialized systems for the processing of mnemonic information within the primate frontal cortex. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences, 351*(1346), 1455-1461.

Petrides, M. (1997). Visuo-motor conditional associative learning after frontal and temporal lesions in the human brain. *Neuropsychologia, 35*(7), 989-997.

Petrides, M. (2002). The mid-ventrolateral prefrontal cortex and active mnemonic retrieval. *Neurobiology of Learning and Memory, 78*(3), 528-538.

Petrides, M. (2005). Lateral prefrontal cortex: architectonic and functional organization. *Philosophical Transactions of the Royal Society B-Biological Sciences, 360*(1456), 781-795.

Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal-lobe damage and temporal-lobe lesions in man. *Neuropsychologia, 20*(3), 249-&.

Petrides, M., & Pandya, D. N. (2002). Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. *European Journal of Neuroscience, 16*(2), 291-310.

Pihlajamaki, M., Tanila, H., Hanninen, T., Kononen, M., Mikkonen, M., Jalkanen, V., et al. (2003). Encoding of novel picture pairs activates the perirhinal cortex: An fMRI study. *Hippocampus, 13*(1), 67-80.

Postle, B. R., & D'Esposito, M. (1999). "What" - Then - "where" in visual working memory: An event-related, fMRI study. *Journal of Cognitive Neuroscience, 11*(6), 585-597.

Price, J. L., Davis, P. B., Morris, J. C., & White, D. L. (1991). The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. *Neurobiology of Aging, 12*(4), 295-312.

Prince, S. E., Daselaar, S. M., & Cabeza, R. (2005). Neural correlates of relational memory: Successful encoding and retrieval of semantic and perceptual associations. *Journal of Neuroscience, 25*(5), 1203-1210.

Pruessmann, K. P., Weiger, M., Scheidegger, M. B., & Boesiger, P. (1999). SENSE: Sensitivity encoding for fast MRI. *Magnetic Resonance in Medicine, 42*(5), 952-962.

Pruessner, J. C., Baldwin, M. W., Dedovic, K., Renwick, R., Mahani, N. K., Lord, C., et al. (2005). Self-esteem, locus of control, hippocampal volume, and cortisol regulation in young and old adulthood. *Neuroimage, 28*(4), 815-826.

Pruessner, J. C., Collins, D. L., Pruessner, M., & Evans, A. C. (2001). Age and gender predict volume decline in the anterior and posterior hippocampus in early adulthood. *Journal of Neuroscience, 21*(1), 194-200.

Pruessner, J. C., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., et al. (2008). Deactivation of the limbic system during acute psychosocial stress: Evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biological Psychiatry, 63*(2), 234-240.

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology, 28*(7), 916-931.

Prull, M. W., Dawes, L. L. C., Martin, A. M., Rosenberg, H. F., & Light, L. L. (2006). Recollection and familiarity in recognition memory: Adult age differences and neuropsychological test correlates. *Psychology and Aging, 21*(1), 107-118.

Putman, P., Hermans, E. J., & van Honk, J. (2007). Exogenous cortisol shifts a motivated bias from fear to anger in spatial working memory for facial expressions. *Psychoneuroendocrinology, 32*(1), 14-21.

Putman, P., van Honk, J., Kessels, R. P. C., Mulder, M., & Koppeschaar, H. P. F. (2004). Salivary cortisol and short and long-term memory for emotional faces in healthy young women. *Psychoneuroendocrinology, 29*(7), 953-960.

Qin, S. Z., Hermans, E. J., van Marle, H. J. F., Luo, J., & Fernandez, G. (2009). Acute Psychological Stress Reduces Working Memory-Related Activity in the Dorsolateral Prefrontal Cortex. *Biological Psychiatry, 66*(1), 25-32.

Quamme, J. R., Yonelinas, A. P., & Normani, K. A. (2007). Effect of unitization on associative recognition in amnesia. *Hippocampus, 17*(3), 192-200.

Rahhal, T. A., May, C. P., & Hasher, L. (2002). Truth and character: Sources that older adults can remember. *Psychological Science, 13*(2), 101-105.

Ranganath, C., Cohen, M. X., & Brozinsky, C. J. (2005). Working memory maintenance contributes to long-term memory formation: neural and behavioral evidence. *J Cogn Neurosci, 17*(7), 994-1010.

Ranganath, C., Cohen, M. X., Dam, C., & D'Esposito, M. (2004). Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval. *Journal of Neuroscience, 24*(16), 3917-3925.

Ranganath, C., & D'Esposito, M. (2001). Medial temporal lobe activity associated with active maintenance of novel information. *Neuron, 31*(5), 865-873.

Ranganath, C., Johnson, M. K., & D'Esposito, M. (2003). Prefrontal activity associated with working memory and episodic long-term memory. *Neuropsychologia, 41*(3), 378-389.

Ravizza, S. M., McCormick, C. A., Schlerf, J. E., Justus, T., Ivry, R. B., & Fiez, J. A. (2006). Cerebellar damage produces selective deficits in verbal working memory. *Brain, 129*, 306-320.

Raye, C. L., Nolde, S. F., Mitchell, K. J., D'Esposito, M., & Johnson, M. K. (1999). Activation of left prefrontal cortex during episodic memory tests: An fMRI study. *Journal of Cognitive Neuroscience*, 23-23.

Raz, N. (2000). Differential aging of the cerebral cortex: Implications for age-related differences in memory. *International Journal of Psychology, 35*(3-4), 183-184.

Raz, N. (2009). Decline and Compensation in Aging Brain and Cognition: Promises and Constraints. *Neuropsychology Review, 19*(4, Sp. Iss. SI), 411-414.

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., et al. (1997). Selective aging of the human cerebral cortex observed in vivo: Differential vulnerability of the prefrontal gray matter. *Cerebral Cortex, 7*(3), 268-282.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., et al. (2005). Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex, 15*(11), 1676-1689.

Raz, N., Rodrigue, K. M., Head, D., Kennedy, K. M., & Acker, J. D. (2004). Differential aging of the medial temporal lobe - A study of a five-year change. *Neurology, 62*(3), 433-438.

Reitz, C., Brickman, A. M., Brown, T. R., Manly, J., DeCarli, C., Small, S. A., et al. (2009). Linking Hippocampal Structure and Function to Memory Performance in an Aging Population. *Archives of Neurology, 66*(11), 1385-1392.

Repovs, G., & Baddeley, A. (2006). The multi-component model of working memory: Explorations in experimental cognitive psychology. *Neuroscience, 139*(1), 5-21.

Resnick, S. M., Lamar, M., & Driscoll, I. (2007). Vulnerability of the orbitofrontal cortex to age-associated structural and functional brain changes. *Linking Affect to Action: Critical Contributions of the Orbitofrontal Cortex, 1121*, 562-575.

Reul, J. M., & de Kloet, E. R. (1985). Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology, 117*(6), 2505-2511.

Reul, J. M., & de Kloet, E. R. (1986). Anatomical resolution of two types of corticosterone receptor sites in rat brain with in vitro autoradiography and computerized image analysis. *J Steroid Biochem, 24*(1), 269-272.

Rhodes, M. G., Castel, A. D., & Jacoby, L. L. (2008). Associative recognition of face pairs by younger and older adults: The role of familiarity-based processing. *Psychology and Aging, 23*(2), 239-249.

Ridgway, G. R., Henley, S. M. D., Rohrer, J. D., Scahill, R. I., Warren, J. D., & Fox, N. C. (2008). Ten simple rules for reporting voxel-based morphometry studies. *Neuroimage, 40*(4), 1429-1435.

Ridout, N., Astell, A. J., Reid, I. C., Glen, T., & O'Carroll, R. E. (2003). Memory bias for emotional facial expressions in major depression. *Cognition & Emotion, 17*(1), 101-122.

Rodrigue, K. M., & Raz, N. (2004). Shrinkage of the entorhinal cortex over five years predicts memory performance in healthy adults. *Journal of Neuroscience, 24*(4), 956-963.

Roelofs, K., Minelli, A., Mars, R. B., van Peer, J., & Toni, I. (2009). On the neural control of social emotional behavior. *Soc Cogn Affect Neurosci, 4*(1), 50-58.

Ronnlund, M., Nyberg, L., Backman, L., & Nilsson, L.G. (2005). Stability, growth, and decline in adult life span development of declarative memory: Cross-sectional and l,longitudinal data from a population-based study. *Psychology and Aging, 20(1), 3-18.*

Roozendaal, B., de Quervain, D. J. F., Schelling, G., & McGaugh, J. L. (2004). A systemically administered beta-adrenoceptor antagonist blocks corticosterone-induced impairment of contextual memory retrieval in rats. *Neurobiology of Learning and Memory, 81*(2), 150-154.

Roozendaal, B., & McGaugh, J. L. (1997). Glucocorticoid receptor agonist and antagonist administration into the basolateral but not central amygdala modulates memory storage. *Neurobiology of Learning and Memory, 67*(2), 176-179.

Roozendaal, B., Phillips, R. G., Power, A. E., Brooke, S. M., Sapolsky, R. M., & McGaugh, J. L. (2001). Memory retrieval impairment induced by hippocampal CA3 lesions is blocked by adrenocortical suppression. *Nature Neuroscience, 4*(12), 1169-1171.

Roozendaal, B., Schelling, G., & McGaugh, J. L. (2008). Corticotropin-releasing factor in the basolateral amygdala enhances memory consolidation via an interaction with the beta-adrenoceptor-cAMP pathway: Dependence on glucocorticoid receptor activation. *Journal of Neuroscience, 28*(26), 6642-6651.

Rosen, A. C., Gabrieli, J. D. E., Stoub, T., Prull, M. W., O'Hara, R., Yesavage, J., et al. (2005). Relating medial temporal lobe volume to frontal fMRI activation for memory encoding in older adults. *Cortex, 41*(4), 595-602.

Rosen, A. C., Prull, M. W., Gabrieli, J. D. E., Stoub, T., O'Hara, R., Friedman, L., et al. (2003). Differential associations between entorhinal and hippocampal volumes and memory performance in older adults. *Behavioral Neuroscience, 117*(6), 1150-1160.

Rosen, A. C., Prull, M. W., O'Hara, R., Race, E. A., Desmond, J. E., Glover, G. H., et al. (2002). Variable effects of aging on frontal lobe contributions to memory. *Neuroreport, 13*(18), 2425-2428.

Rubin, R. T., Mandell, A. J., & Crandall, P. H. (1966). Corticosteroid responses to limbic stimulation in man - localization of stimulus sites. *Science, 153*(3737), 767-&.

Ruffman, T., Henry, J. D., Livingstone, V., & Phillips, L. H. (2008). A meta-analytic review of emotion recognition and aging: Implications for neuropsychological models of aging. *Neuroscience and Biobehavioral Reviews, 32*(4), 863-881.

Rugg, M. D., & Yonelinas, A. P. (2003). Human recognition memory: a cognitive neuroscience perspective. *Trends in Cognitive Sciences, 7*(7), 313-319.

Rypma, B., & D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. *Nature Neuroscience, 3*(5), 509-515.

Salat, D. H., Kaye, J. A., & Janowsky, J. S. (2002). Greater orbital prefrontal volume selectively predicts worse working memory performance in older adults. *Cerebral Cortex, 12*(5), 494-505.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review, 103*(3), 403-428.

Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging, 30*(4), 507-514.

Salthouse, T. A., & Babcock, R. L. (1991). Decomposing adult age-differences in working-memory. *Developmental Psychology, 27*(5), 763-776.

Salvador, A. (2005). Coping with competitive situations in humans. *Neuroscience and Biobehavioral Reviews, 29*(1), 195-205.

Samanez-Larkin, G. R., Robertson, E. R., Mikels, J. A., Carstensen, L. L., & Gotlib, I. H. (2009). Selective Attention to Emotion in the Aging Brain. *Psychology and Aging, 24*(3), 519-529.

Sandi, C., Loscertales, M., & Guaza, C. (1997). Experience-dependent facilitating effect of corticosterone on spatial memory formation in the water maze. *European Journal of Neuroscience, 9*(4), 637-642.

Sandi, C., & Rose, S. P. R. (1994). Corticosterone enhances long-term retention in one-day-old chicks trained in a weak passive-avoidance learning-paradigm. *Brain Research, 647*(1), 106-112.

Sandi, C., & Rose, S. P. R. (1997). Training-dependent biphasic effects of corticosterone in memory formation for a passive avoidance task in chicks. *Psychopharmacology, 133*(2), 152-160.

Sapolsky, R. M., Krey, L. C., & McEwen, B. S. (1984). Glucocorticoid-sensitive hippocampal-neurons are involved in terminating the adrenocortical stress response. *Proceedings of the National Academy of Sciences of the United States of America-Biological Sciences, 81*(19), 6174-6177.

Sapolsky, R. M., Krey, L. C., & McEwen, B. S. (1986). The neuroendocrinology of stress and aging - the Glucocorticoid Cascade Hypothesis. *Endocrine Reviews, 7*(3), 284-301.

Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews, 21*(1), 55-89.

Satterthwaite, T. D., Wolf, D. H., Gur, R. C., Ruparel, K., Valdez, J. N., Gur, R. E., et al. (2009). Frontolimbic Responses to Emotional Face Memory: The Neural Correlates of First Impressions. *Human Brain Mapping, 30*(11), 3748-3758.

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology, 7*(3), 273-295.

Sauvage, M. M., Fortin, N. J., Owens, C. B., Yonelinas, A. P., & Eichenbaum, H. (2008). Recognition memory: opposite effects of hippocampal damage on recollection and familiarity. *Nature Neuroscience, 11*(1), 16-18.

Scanlan, L. C., & Johnston, R. A. (1997). I recognize your face, but I can't remember your name: A grown-up explanation? *Quarterly Journal of Experimental Psychology Section a-Human Experimental Psychology, 50*(1), 183-198.

Schacter, D. L., Harbluk, J. L., & McLachlan, D. R. (1984). Retrieval without recollection - an experimental analysis of source amnesia. *Journal of Verbal Learning and Verbal Behavior, 23*(5), 593-611.

Schacter, D. L., & Wagner, A. D. (1999). Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus, 9*(1), 7-24.

Schaie, K. W., Willis, S. L., & Caskie, G. I. L. (2004). The Seattle Longitudinal Study: Relationship between personality and cognition. *Aging Neuropsychology and Cognition, 11*(2-3), 304-324.

Schoofs, D., Preuss, D., & Wolf, O. T. (2008). Psychosocial stress induces working memory impairments in an n-back paradigm. *Psychoneuroendocrinology, 33*(5), 643-653.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry, 20*(1), 11-21.

Seeman, T. E., McEwen, B. S., Singer, B. H., Albert, M. S., & Rowe, J. W. (1997). Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. *Journal of Clinical Endocrinology & Metabolism, 82*(8), 2458-2465.

Sergerie, K., Lepage, M., & Armony, J. L. (2005). A face to remember: emotional expression modulates prefrontal activity during memory formation. *Neuroimage, 24*(2), 580-585.

Shackman, A. J., Sarinopoulos, I., Maxwell, J. S., Pizzagalli, D. A., Lavric, A., & Davidson, R. J. (2006). Anxiety selectively disrupts visuospatial working memory. *Emotion, 6*(1), 40-61.

Shallice, T., & Warrington, E. K. (1970). Independent functioning of verbal memory stores: a neuropsychological study. *Q J Exp Psychol, 22*(2), 261-273.

Sheline, Y. I., Wang, P. W., Gado, M. H., Csernansky, J. G., & Vannier, M. W. (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Sciences of the United States of America, 93*(9), 3908-3913.

Shimamura, A. P., Janowsky, J. S., & Squire, L. R. (1990). Memory for the temporal-order of events in patients with frontal-lobe lesions and amnesic patients. *Neuropsychologia, 28*(8), 803-813.

Shimamura, A. P., Ross, J. G., & Bennett, H. D. (2006). Memory for facial expressions: The power of a smile. *Psychonomic Bulletin & Review, 13*(2), 217-222.

Shing, Y. L., Werkle-Bergner, M., Li, S. C., & Lindenberger, U. (2008). Associative and strategic components of episodic memory: A lifespan dissociation. *International Journal of Psychology, 43*(3-4), 377-377.

Smith, C. D., Chebrolu, H., Wekstein, D. R., Schmitt, F. A., & Markesbery, W. R. (2007). Age and gender effects on human brain anatomy: A voxel-based morphometric study in healthy elderly. *Neurobiology of Aging, 28*(7), 1075-1087.

Smith, E. E., & Jonides, J. (1998). Neuroimaging analyses of human working memory. *Proceedings of the National Academy of Sciences of the United States of America, 95*(20), 12061-12068.

Snodgrass, J. G., & Vanderwart, M. (1980). A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *J Exp Psychol [Hum Learn], 6*(2), 174-215.

Somerville, L. H., Wig, G. S., Whalen, P. J., & Kelley, W. M. (2006). Dissociable medial temporal lobe contributions to social memory. *Journal of Cognitive Neuroscience, 18*(8), 1253-1265.

Sommer, T., Rose, M., Glascher, J., Wolbers, T., & Buchel, C. (2005). Dissociable contributions within the medial temporal lobe to encoding of object-location associations. *Learning & Memory, 12*(3), 343-351.

Sommer, T., Rose, M., Weiller, C., & Buchel, C. (2005). Contributions of occipital, parietal and parahippocampal cortex to encoding of object-location associations. *Neuropsychologia, 43*(5), 732-743.

Spencer, W. D., & Raz, N. (1995). Differential effects of aging on memory for content and context: A meta-analysis. *Psychology and Aging, 10*(4), 527-539.

Sperling, R., Chua, E., Cocchiarella, A., Rand-Giovannetti, E., Poldrack, R., Schacter, D. L., et al. (2003). Putting names to faces: successful encoding of associative memories activates the anterior hippocampal formation. *Neuroimage, 20*(2), 1400-1410.

Spielberger CD, Gorsuch RL, Lushene PR, Vagg PR, & AG, J. (1983). *Manual for the State-Trait Anxiety Inventory (Form Y)*: Consulting Psychologists Press, Inc.:Palo Alto.

Spieler, D. H., Balota, D. A., & Faust, M. E. (1996). Stroop performance in healthy younger and older adults and in individuals with dementia of the Alzheimer's type. *Journal of Experimental Psychology-Human Perception and Performance, 22*(2), 461-479.

Squire, L. R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol Rev, 99*(2), 195-231.

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The Medial Temporal Lobe. *Annual Review of Neuroscience, 27*, 279-306.

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253*(5026), 1380-1386.

Staff, R. T., Murray, A. D., Deary, I. J., & Whalley, L. J. (2004). What provides cerebral reserve? *Brain, 127*, 1191-1199.

Staresina, B. P., & Davachi, L. (2006). Differential encoding mechanisms for subsequent associative recognition and free recall. *Journal of Neuroscience, 26*(36), 9162-9172.

Staresina, B. P., & Davachi, L. (2008). Selective and shared contributions of the hippocampus and perirhinal cortex to episodic item and associative encoding. *Journal of Cognitive Neuroscience, 20*(8), 1478-1489.

Stark, C. E. L., Bayley, P. J., & Squire, L. R. (2002). Recognition memory for single items and for associations is similarly impaired following damage to the hippocampal region. *Learning & Memory, 9*(5), 238-242.

Stark, C. E. L., & Squire, L. R. (2003). Hippocampal damage equally impairs memory for single items and memory for conjunctions. *Hippocampus, 13*(2), 281-292.

Starkman, M. N., Gebarski, S. S., Berent, S., & Schteingart, D. E. (1992). Hippocampal-formation volume, memory dysfunction, and cortisol-levels in patients with cushings-syndrome. *Biological Psychiatry, 32*(9), 756-765.

Starkman, M. N., Giodani, B., Gebarski, S. S., Berent, S., Schork, M. A., & Schteingart, D. E. (1999). Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. *Biological Psychiatry, 46*(12), 1595-1602.

Starkman, M. N., Giordani, B., Gebarski, S. S., & Schteingart, D. E. (2003). Improvement in learning associated with increase in hippocampal formation volume. *Biological Psychiatry, 53*(3), 233-238.

Stebbins, G. T., Carrillo, M. C., Dorfman, J., Dirksen, C., Desmond, J. E., Turner, D. A., et al. (2002). Aging effects on memory encoding in the frontal lobes. *Psychology and Aging, 17*(1), 44-55.

Steptoe, A., & Ussher, M. (2006). Smoking, cortisol and nicotine. *International Journal of Psychophysiology, 59*(3), 228-235.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society, 8*(3), 448-460.

Stern, Y., Habeck, C., Moeller, J., Scarmeas, N., Anderson, K. E., Hilton, H. J., et al. (2005). Brain networks associated with cognitive reserve in healthy young and old adults. *Cerebral Cortex, 15*(4), 394-402.

Summerfield, C., Greene, M., Wager, T., Egner, T., Hirsch, J., & Mangels, J. (2006). Neocortical connectivity during episodic memory formation. *PLoS Biology, 4*(5).

Summers, C. H., Watt, M. J., Ling, T. L., Forster, G. L., Carpenter, R. E., Korzan, W. J., et al. (2005). Glucocorticoid interaction with aggression in non-mammalian vertebrates: Reciprocal action. *European Journal of Pharmacology, 526*(1-3), 21-35.

Suzuki, W. A., & Amaral, D. G. (2004). Functional neuroanatomy of the medial temporal lobe memory system. *Cortex, 40*(1), 220-222.

Suzuki, W. A., & Eichenbaum, H. (2000). The neurophysiology of memory. *Ann N Y Acad Sci, 911*, 175-191.

Tanabe, H. C., & Sadato, N. (2009). Ventrolateral prefrontal cortex activity associated with individual differences in arbitrary delayed paired-association learning performance: a functional magnetic resonance imaging study. *Neuroscience, 160*(3), 688-697.

Telzer, E. H., Mogg, K., Bradley, B. P., Mai, X. Q., Ernst, M., Pine, D. S., et al. (2008). Relationship between trait anxiety, prefrontal cortex, and attention bias to angry faces in children and adolescents. *Biological Psychology, 79*(2), 216-222.

Tessner, K. D., Walker, E. F., Dhruv, S. H., Hochman, K., & Harnann, S. (2007). The relation of cortisol levels with hippocampus volumes under baseline and challenge conditions. *Brain Research, 1179*, 70-78.

Thompson-Schill, S. L., Jonides, J., Marshuetz, C., Smith, E. E., D'Esposito, M., Kan, I. P., et al. (2002). Effects of frontal lobe damage on interference effects in working memory. *Cognitive Affective and Behavioral Neuroscience, 2*(2), 109-120.

Tisserand, D. J., & Jolles, J. (2003). On the involvement of prefrontal networks in cognitive ageing. *Cortex, 39*(4-5), 1107-1128.

Tisserand, D. J., van Boxtel, M. P. J., Pruessner, J. C., Hofman, P., Evans, A. C., & Jolles, J. (2004). A voxel-based morphometric study to determine individual differences in gray matter density associated with age and cognitive change over time. *Cerebral Cortex, 14*(9), 966-973.

Tisserand, D. J., Visser, P. J., van Boxtel, M. P. J., & Jolles, J. (2000). The relation between global and limbic brain volumes on MRI and cognitive performance in healthy individuals across the age range. *Neurobiology of Aging, 21*(4), 569-576.

Tomita, H., Ohbayashi, M., Nakahara, K., Hasegawa, I., & Miyashita, Y. (1999). Top-down signal from prefrontal cortex in executive control of memory retrieval. *Nature, 401*(6754), 699-703.

Tsai, J., Hurley, A., Osmack, R., Schultz, B., Deleon, M., Marcus, D., et al. (1988). Abnomal pituitary-adrenal response to blood-glucose in patients with Alzheimer's disease. *Clinical Research, 36*(3), A492-A492.

Tsukiura, T., & Cabeza, R. (2008). Orbitofrontal and hippocampal contributions to memory for face-name associations: The rewarding power of a smile. *Neuropsychologia, 46*(9), 2310-2319.

Tulving, E. (1972). Episodic and semantic memory. In E. Tulving & W. Donaldson (Eds.), *Organization of memory* (pp. 381-403). New York: Academic Press.

Tulving, E. (1983). *Elements of episodic memory*. New York: Oxford University Press.

Tulving, E. (1985). How many memory-systems are there. *American Psychologist, 40*(4), 385-398.

Tulving, E. (2002). Episodic memory: From mind to brain. *Annual Review of Psychology, 53*(1), 1-25.

Tulving, E., Kapur, S., Craik, F.I.M., Moscovitch, M., & Houle, S. (1994). Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings. *Proceedings of the National Academy of Science, 91(6), 2016-20.*

Tuvnes, F. A., Steffenach, H. A., Murison, R., Moser, M. B., & Moser, E. I. (2003). Selective hippocampal lesions do not increase adrenocortical activity. *Journal of Neuroscience, 23*(10), 4345-4354.

Urry, H. L., van Reekum, C. M., Johnstone, T., Kalin, N. H., Thurow, M. E., Schaefer, H. S., et al. (2006). Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. *J Neurosci, 26*(16), 4415-4425.

Van Gerven, P. W. M., Meijer, W. A., & Jolles, J. (2007). Education does not protect against age-related decline of switching focal attention in working memory. *Brain and Cognition, 64*(2), 158-163.

Van Gerven, P. W. M., Meijer, W. A., Prickaerts, J. H. M., & Van der Veen, F. M. (2008). Aging and focus switching in working memory: Excluding the potential role of memory load. *Experimental Aging Research, 34*(4), 367-378.

Van Honk, J., Kessels, R. P. C., Putman, P., Jager, G., Koppeschaar, H. P. F., & Postma, A. (2003). Attentionally modulated effects of cortisol and mood on memory for emotional faces in healthy young males. *Psychoneuroendocrinology, 28*(7), 941-948.

Van Honk, J., Tuiten, A., van den Hout, M., Koppeschaar, H., Thijssen, J., de Haan, E., et al. (1998). Baseline salivary cortisol levels and preconscious selective attention for threat - A pilot study. *Psychoneuroendocrinology, 23*(7), 741-747.

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia, 42*(10), 1394-1413.

Van Petten, C., Plante, E., Davidson, P. S. R., Kuo, T. Y., Bajuscak, L., & Glisky, E. L. (2004). Memory and executive function in older adults: relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. *Neuropsychologia, 42*(10), 1313-1335.

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., VanPaesschen, W., & Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science, 277*(5324), 376-380.

Vaughan, L., Basak, C., Hartman, M., & Verhaeghen, P. (2008). Aging and working memory inside and outside the focus of attention: Dissociations of availability and accessibility. *Aging, Neuropsychology, and Cognition, 15*(6), 703-724.

Verhaeghen, P. (2003). Aging and vocabulary scores: a meta-analysis. *Psychol Aging, 18*(2), 332-339.

Verhaeghen, P., & Basak, C. (2005). Ageing and switching of the focus of attention in working memory: Results from a modified N-Back task. *Quarterly Journal of Experimental Psychology Section a-Human Experimental Psychology, 58*(1), 134-154.

Vogel, E. K., McCollough, A. W., & Machizawa, M. G. (2005). Neural measures reveal individual differences in controlling access to working memory. *Nature, 438*(7067), 500-503.

Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: A meta-analysis. *Cognitive Affective & Behavioral Neuroscience, 3*(4), 255-274.

Wagner, A. D., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. E. (1998). Prefrontal cortex and recognition memory - Functional-MRI evidence for context-dependent retrieval processes. *Brain, 121*, 1985-2002.

Wagner, A. D., Poldrack, R. A., Eldridge, L. L., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. E. (1998). Material-specific lateralization of prefrontal activation during episodic encoding and retrieval. *Neuroreport, 9*(16), 3711-3717.

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., et al. (1998). Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity. *Science, 281*(5380), 1188-1191.

Wais, P. E., Squire, L. R., & Wixted, J. T. (2009). In Search of Recollection and Familiarity Signals in the Hippocampus. *Journal of Cognitive Neuroscience, 22*(1), 109-123.

Walhovd, K. B., Fjell, A. M., Reinvang, I., Lundervold, A., Dale, A. M., Eilertsen, D. E., et al. (2005). Effects of age on volumes of cortex, white matter and subcortical structures. *Neurobiology of Aging, 26*(9), 1261-1270.

Walhovd, K. B., Fjell, A. M., Reinvang, I., Lundervold, A., Fischl, B., Quinn, B. T., et al. (2004). Size does matter in the long run - Hippocampal and cortical volume predict recall across weeks. *Neurology, 63*(7), 1193-1197.

Walhovd, K. B., Westlye, L. T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., et al. (2009). Constistent neuroanatomical age-related volume differences across multiple samples. *Neurobiology of Aging, 29*.

Waring, J. D., & Kensinger, E. A. (2009). Effects of emotional valence and arousal upon memory trade-offs with aging. *Psychol Aging, 24*(2), 412-422.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin, 120*(2), 272-292.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience, 18*(1), 411-418.

Williams, P., & Tarr, M. J. (1997). Structural processing and implicit memory for possible and impossible figures. *J Exp Psychol Learn Mem Cogn, 23*(6), 1344-1361.

Wingfield, A., & Stine-Morrow, E. A. L. (2000). Language and speech. In F. I. M. Craik & T. A. Salthouse (Eds.), *Handbook of aging and cognition* (2nd ed., pp. 359-416). Mahwah, NJ: Erlbaum.

Wolf, O. T., Dziobek, I., McHugh, P., Sweat, V., de Leon, M. J., Javier, E., et al. (2005). Subjective memory complaints in aging are associated with elevated cortisol levels. *Neurobiology of Aging, 26*(10), 1357-1363.

Wolf, O. T., Schommer, N. C., Hellhammer, D. H., McEwen, B. S., & Kirschbaum, C. (2001). The relationship between stress induced cortisol levels and memory differs between men and women. *Psychoneuroendocrinology, 26*(7), 711-720.

Wood, N. L., & Cowan, N. (1995). The cocktail party phenomenon revisted - attention and memory in the classic selective listening procedure of Cherry (1953). *Journal of Experimental Psychology-General, 124*(3), 243-262.

Worsley, K. J., Marrett, S., Neelin, P., & Evans, A. C. (1996). Searching scale space for activation in PET images. *Human Brain Mapping, 4*(1), 74-90.

Wright, C. E., Kunz-Ebrecht, S. R., Iliffe, S., Foese, O., & Steptoe, A. (2005). Physiological correlates of cognitive functioning in an elderly population. *Psychoneuroendocrinology, 30*(9), 826-838.

Yehuda, R., Tischler, L., Golier, J. A., Grossman, R., Brand, S. R., Kaufman, S., et al. (2006). Longitudinal assessment of cognitive performance in Holocaust survivors with and without PTSD. *Biological Psychiatry, 60*(7), 714-721.

Yen, S. S. C., & Laughlin, G. A. (1998). Aging and the adrenal cortex. *Experimental Gerontology, 33*(7-8), 897-910.

Yerkes, R., & Dodson, J. (1908). The relation of strength of stimulus to rapidity of habit-formation. *Journal of comparative Neurology and Psychology, 18*, 459-482.

Yesavage, J. A., & Rose, T. L. (1984). The effects of a face-name learning mnemonic in young, middle-aged, and elderly adults. *Experimental Aging Research, 10*(1), 55-57.

Yonelinas, A. P. (2001). Components of episodic memory: the contribution of recollection and familiarity. *Philosophical Transactions of the Royal Society B-Biological Sciences, 356*(1413), 1363-1374.

Yonelinas, A. P. (2002). The nature of recollection and familiarity: A review of 30 years of research. *Journal of Memory and Language, 46*(3), 441-517.

Yonelinas, A. P., Kroll, N. E. A., Quamme, J. R., Lazzara, M. M., Sauve, M. J., Widaman, K. F., et al. (2002). Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. *Nature Neuroscience, 5*(11), 1236-1241.

Yonelinas, A. P., Otten, L. J., Shaw, K. N., & Rugg, M. D. (2005). Separating the brain regions involved in recollection and familiarity in recognition memory. *Journal of Neuroscience, 25*(11), 3002-3008.

Young, A. H., Sahakian, B. J., Robbins, T. W., & Cowen, P. J. (1999). The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology, 145*(3), 260-266.

Young, A. H., Sahakian, B. J., Robbins, T. W., & Cowen, P. J. (1999). The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology, 145*(3), 260-266.

Young, E. A., Abelson, J., & Lightman, S. L. (2004). Cortisol pulsatility and its role in stress regulation and health. *Frontiers in Neuroendocrinology, 25*(2), 69-76.

Zeineh, M. M., Engel, S. A., Thompson, P. M., & Bookheimer, S. Y. (2003). Dynamics of the hippocampus during encoding and retrieval of face-name pairs. *Science, 299*(5606), 577-580.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr Scand, 67*(6), 361-370.

Zola-Morgan, S., & Squire, L. R. (1985). Medial temporal lesions in monkeys impair memory on a variety of tasks sensitive to human amnesia. *Behavioral Neuroscience, 99*(1), 22-34.

APPENDIX I

School of Psychology
University of Dublin, Trinity College
Dublin 2, Ireland

Tel: +353 1 896 1886
Fax: +353 1 671 2006

F.A.O. Shane O'Mara

School of Psychology Research Ethics Committee

3 July 2007

Dear Shane,

Following receipt of signed 'working with adults' forms from the researchers conducting the study (Gillian Cooke and Sinéad Mullally) and confirmation of the 5-year data-storage period, I am pleased to inform you that your application entitled "Studies of memory across the lifespan" has been approved by the School of Psychology Research Ethics Committee.

Yours sincerely,

Kevin Thomas, PhD
Chair,
School of Psychology Research Ethics Committee

School of Psychology
University of Dublin, Trinity College
Dublin 2, Ireland

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Fax: +353 1 671 2006

F.A.O. Joanne Feeney

School of Psychology Research Ethics Committee

1st April 2009

Dear Joanne,

Following receipt of amendments as advised by the Committee, I am pleased to inform you that your application entitled "Lifespan memory changes with affective stimuli" has been approved by the School of Psychology Research Ethics Committee.

Yours sincerely,

Luisa Byrne
Executive Officer
School of Psychology Research Ethics Committee

SCHOOL OF PSYCHOLOGY
Aras an Phairsaigh
Trinity College
Dublin 2

Information leaflet

Lifespan Memory Changes and Affective Stimuli

Introduction My name is Joanne Feeney and postgraduate student in the Institute of Neuroscience and School of Psychology, Trinity College, Dublin, working under the supervision of Dr Shane O'Mara. We are currently carrying out research, which aims to study how memory changes across the lifespan with different types of material to be remembered.

Procedure We are looking for individuals aged between 20 and 29 years, and 40 and 49 years of age. If you agree to participate in this experiment, you will have to perform some simple learning and memory tasks (which are presented either verbally, visually or on a computer screen), and fill in some questionnaires. In addition we are interested in examining the amount of the stress hormone cortisol in your body. This will be assessed by analysing saliva samples. You will be asked to give three samples of saliva during the course of the experiment. This is very quick and easy to do.

In total the whole experiment will last no more than 1 hour.

Benefits There will be no direct benefits to participants from participation in this study. However, the results of this study may further knowledge about how memory function varies across the lifespan.

Risks There are no risks associated with participation in this experiment.

Exclusion from participation You are excluded from participating in this study if any of the following apply:

You are not aged between 20-29 or 40-49 years of age.

You have a history of psychiatric or neurological disorder, drug/alcohol addiction, epilepsy, stroke, head injury, or heart disease.

You have a history of endocrine (hormone) disorder e.g. diabetes, hypothyroidism

You are currently taking steroid medication e.g. hydrocortisone, prednisolone.

Confidentiality Your identity will be confidential. Your name will not be published and will not be disclosed to anyone outside the study group. Your scores will be averaged with those of other people, so nobody outside of the experimenters involved will know how well you did on the tasks. Your data will be stored using a numbered code (e.g. Participant 001) to ensure confidentiality. The data will be

stored in a password locked computer. This data will be kept for 10 years in accordance with guidelines on data protection.

Compensation This study is covered by standard institutional indemnity insurance. Nothing in this document restricts or curtails your rights.

Voluntary participation If you decide to participate in the study, you may withdraw at any time, for any reason. Under the Freedom of Information Act, you have the right to see your scores after the test, if you wish.

Stopping the study You understand that the investigators may withdraw your participation in the study at any time without your consent.

Permission This study has permission from the School of Psychology Ethics Committee.

Further Information For further information, please see contact details below.

Many Thanks,

Joanne Feeney
TCIN,
Lloyd Building,
Dublin 2.
Ph: (01) 896 8411
feeneyj@tcd.ie

Prof. Shane O'Mara
Room 3.43
TCIN
Lloyd Building
Dublin 2.
Ph: (01) 896 1886
smomara@tcd.ie

Psychological support services:

Samaritans	http://www.samaritans.org/	Ph: 1850 60 90 90
Niteline	http://www.niteline.ie/	Ph: 1800 793 793

Informed Consent form

Lifespan Memory Changes and Affective Stimuli

Investigators: Joanne Feeney and Prof. Shane O'Mara

Summary of Involvement: You will be required to complete memory tasks on computer/using pen and paper, in addition to some questionnaires. You will also be asked to give saliva samples for analysis of cortisol levels. The whole process will take no more than 1 hour.

Statement of Consent:

	YES	NO
I have read and understood the information leaflet and consent to take part in this study on a voluntary basis.	☐	☐
I understand that I may withdraw from the study at any time, or be withdrawn by the experimenter at any time, without prejudice to my ethical and legal rights.	☐	☐
I agree to provide saliva samples for analysis of cortisol levels.	☐	☐
I consent to have my data used again in any future study by the experimenters.	☐	☐
I consent to be contacted again about any future studies that may arise.	☐	☐

Participant's signature:_____ Date:_____

Participant's name (printed):_____ Date:_____

Statement of investigator's responsibility: I have explained the nature and purpose of this research study, the procedures to be undertaken and any risks that may be involved. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

INVESTIGATOR'S SIGNATURE:..... Date:.....

Letter of Consent to Participate in Experimental Research in the School of Psychology and Institute of Neuroscience, Trinity College Dublin.

Dear Sir / Madam,

My name is Joanne Feeney and I am a PhD student in the Institute of Neuroscience and School of Psychology, Trinity College, Dublin, under the supervision of Dr Shane O'Mara. We are currently carrying out research, which aims to study how memory changes across the lifespan, and the relationship between memory and cortisol levels. If you agree to participate in this experiment, you will have to perform some simple learning and memory tasks (which are presented either verbally, visually or on a computer screen). In addition, the concentration of the hormone cortisol in your body will be assessed by analysing saliva samples. You will be asked to give three samples of saliva during the course of the experiment. The testing should a little over one hour in total.

Your scores will be averaged with those of other people, so nobody will know how well you did on the task. Your data will be stored using a numbered code (e.g. Participant 001) to ensure confidentiality, and you are free to stop doing the experiment at any stage, and for any reason. Under the Freedom of Information Act, you have the right to see your scores after the test, if you wish.

For further information, my contact details are listed below:

Many Thanks,

Joanne Feeney (feeneyj@tcd.ie)

Joanne Feeney
School of Psychology and TCIN,
Lloyd Building,
Trinity College,
Dublin 2.
Ph: (01) 896 8411

Statement of Consent:

I, _____ (block capitals), have read this and give my informed consent to participant in the experiment.

Signed: _____, Date: _____

TRINITY COLLEGE
Institute of Neuroscience
TCIN *from molecules to mind*

GENERAL MRI DATA CONSENT FORM

Trinity College Institute of Neuroscience, (TCIN) is performing research, utilising an MRI scanner at Trinity College, Dublin 2. These research scans, although not full clinical scans, will be read by a radiologist.

In the unlikely event of an irregularity being found, the radiologist, [Dr William Torreggiani of The Adelaide and Meath Hospital Incorporating the National Children's Hospital (AMNCH), Tallaght] will inform the participants GP, that a proper clinical scan may be required to determine whether or not an irregularity is of clinical significance.

To enable us to perform the research scans the participant agrees to give consent/ permission for:

(i) TCIN to conduct the MRI scan and store MRI scan data of participant;
(ii) TCIN or Principal Investigator, (PI) to contact participants GP;
(iii) TCIN radiographer to send MRI scan data to radiologist acting for TCIN;
(iv) Radiologist to store data in a hospital system with same care as other patient data ensuring participants confidentiality;
(v) Radiologist/ Clinician (acting for TCIN) to contact participants GP;
(vi) TCIN to store data on the study for a period of at least 5 years or as specified in the specific consent form.

A dated standard letter signed by the appropriate Principal Investigator will be sent to all participants GP's, it is the responsibility of the Principal Investigator to ensure that this is sent at least two days before scanning to allow for postal delays. The principal investigator is responsible for their project at all times.

The TCIN designated radiologist will be sent data in a form that allows identification so that if a response is required he can act quickly. This will be stored in the hospital system with the same rigour and attention to confidentiality as all other medical data, as per the rules of that institution. The raw scan data will be stored at TCIN in anonymous form for research purposes as agreed on the consent form of the specific research project.

I agree to the above points and understand that my data will be treated carefully at TCIN and in the hospital system.

Participant Name and Address_____

_____

_____

Signed by Participant:_____

Participants GP Name and Address

_____

_____

Date:_____

Information and Consent

Information on the MRI component of the Study:

a. **What is MRI?** The purpose of functional MRI scanning is to determine which brain regions are activated as someone performs certain tasks. In the MRI scanner there is a very large magnetic field. This magnetic field and radio signals, which are transmitted in the scanner, measure the concentration of water particles within the body, allowing brain functioning relating to behaviour to be measured in terms of blood flow to the brain. The person who is going to be scanned lies on a bed where their head is placed into a device, which has the appearance of a large helmet. When the person has been safely and comfortably secured in this device, the bed is moved slowly into the scanner. When the person's head is in the middle of the magnetic field, radio frequency pulses and magnetic fields are switched on and off to produce a signal, which we use for measuring blood flow.

b. **How long will the scan last?** Individual MRI test runs will last no longer than 15 minutes to minimise fatigue and the entire testing session will be completed within 60 minutes. It is very important that you keep still and, in particular, do not move your head while we are taking an image of your brain. For some images, you will be doing a cognitive task that you will have practiced outside of the scanner. For other images, you will just lie still and relax while we take high-resolution images of your brain. We will explain exactly what you need to do before we start each MRI test run.

c. **What will I be asked while I am in the MRI scanner?** You will be asked to perform cognitive tasks that you will have already practiced with one of the researchers prior to the scanning session. During scanning, we will tell you what task to do before each scan by communicating through the intercom system.

d. **What are the risks associated with MRI?** When operated by appropriately qualified individuals, MRI presents virtually no risk, as there is **NO** exposure to x-rays or radioactivity with this procedure. The noise produced by an MRI exam can be very loud and you will be issued with protective headphones or earplugs to prevent damage to your hearing. The noise produced by the exam has been reported to produce temporary threshold shifts (i.e., decreased ability to hear quiet sounds) in a small percentage of people. Given the confines of an MRI machine, a small percentage of people in the past have reported feeling claustrophobic (fear of being closed in a tight space) when placed into an MRI scanner. Please let us know if you have experienced claustrophobia in the past. During MRI scanning, you will be in contact with the MRI operator via an auditory communication system. This will be used to regularly check your comfort and to allow you to inform us of any problems or concerns. You will also have a "panic button" which you may press at any time to indicate that you wish to stop the scanning procedure.

As the MRI involves a large magnetic field, it is essential that NO METAL BE BROUGHT INTO THE SCANNER WITH YOU.

Items that **must be** removed by individuals before entering the MRI facility include:

- Purse, wallet, money clip, credit cards, cards with magnetic strips;
- Electronic devices such as beepers or cell phones;
- Hearing aids;
- Metal jewellery (in all parts of the body), watches;
- Pens, paper clips, keys, coins;
- Hair barrettes, hairpins;
- Any article of clothing that has a metal zipper, buttons, snaps, hooks, under-wire bras, or metal threads;
- Shoes, belt buckles, safety pins.

Other objects that may be hazardous include:

- Metallic spinal rod
- Plates, pins, screws, or metal mesh used to repair a bone or joint
- Joint replacement or prosthesis
- Metal jewellery such as that used with body piercing.
- Some tattoos or tattooed eyeliner (these alter MR images, and there is a chance of skin irritation or swelling; black and blue pigments are the most troublesome)
- Bullet, shrapnel, or other type of metal fragment
- Metallic foreign body within or near the eye (such an object generally can be seen on an x-ray; metal workers are most likely to have this problem)
- Dental fillings (while usually unaffected by the magnetic field, they may distort images of the facial area or brain; the same is true for orthodontic braces and retainers)

If you have any of these items, please inform us immediately.

e. **Additional Risks?** There may be additional or unknown risks associated with MRI. For example, in very rare cases, the strong magnetic field can induce nerve stimulation (e.g., switching the strong magnetic field gradients during imaging has been reported to cause twitching in the neck muscles). Also, in very rare cases, the radio signals have been reported to cause burns. There may be other risks associated with imaging that are not yet known.

f. **Who should NOT undergo the MRI procedure?** There are some items that may interfere with the Magnetic Resonance Imaging and some that may be **potentially hazardous**. To help us to determine your suitability for an MRI scan and to ensure your safety, please complete the following checklist carefully.

Not all people can have an MRI scan because the strong magnetic field may be hazardous to them. People with:

- Permanent pacemakers
- Prosthetic heart valves
- Implanted cardiac defibrillators
- Certain types of vascular clips

Cannot have an MRI scan

It is essential that you inform the MR operator if you have any metal items in any of the above lists.

g. **Pregnancy and MRI.** For female participants it is also important that you tell us if there is any possibility that you are pregnant. To date there are no known risks of MRI during pregnancy, however as a precautionary safety measure pregnant individuals will not be included in the study. To participate in the current study women of child-bearing potential must be using one of the following acceptable methods of birth-control:

a. oral or transdermal contraceptives
b. barrier (diaphragm or condom) with spermicide
c. intrauterine progesterone contraceptive system
d. levonorgestrel implant
e. medroxyprogesterone acetate contraceptive injection
f. complete abstinence from sexual activity

h. **What if the brain imaging finds some abnormality in my brain?** See General Consent Form

2. You can get more information or answers to your questions about the study, your participation in the study, and your rights, from Dr. Neuman Correia, who can be contacted at 01–414 3862 or 085-722 0977. If your doctor learns of important new information that might affect your desire to remain in the study, he or she will tell you.

CONSENT FORM

MRI Scan Consent

I have been informed of the discomforts and risks that I may reasonably expect to experience as part of this study. I have been informed that when used on appropriately qualified individuals, MRI presents virtually no risk. There will be no exposure to x-rays or radioactivity in this study. I understand that noise produced by this exam could be very loud, and that I will wear earplugs or headphones to prevent damage to my hearing. Even with earplugs, the noise produced by the exam may produce temporary threshold shifts (i.e., decreased ability to hear quiet sounds). I have been informed that I may experience some discomfort from lying in the MRI scanner such as claustrophobia (fear of being closed in a tight space) or tight sensations from having my head restrained to prevent movement. I have been informed that I will also be asked to perform some tasks that I have been trained on, prior to the MRI procedure, which should not cause undue distress.

I have been informed that other risks of injury due to MRI include damage to implanted electronic devices (such as pacemakers), haemorrhage if aneurysm clips are present and trauma if ferrous metal objects are brought too close to the scanner. However, these risks are minimal in a properly administered site. I do not have any of these items in my body.

I have understood these risks and am agreeing to volunteer to participate in this research. I understand that I can withdraw at any time from the study.

PARTICIPANT'S NAME: _____

Please provide us with the details of another person (e.g., next-of-kin) should we need to contact you in the future.

Name of contact person: _____

Phone: _____

PARTICIPANT'S SIGNATURE: _____

Date: _____

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and

fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

PHYSICIAN'S SIGNATURE: _____

Date: _____

Trinity College Institute of Neuroscience
Lloyd Building
Trinity College Dublin
Dublin 2

Dear

Participant '_____' is taking part in a research study, utilising an MRI scanner at Trinity College Institute of Neuroscience, TCD Dublin 2. These research scans, although not full clinical scans, will be read by a clinician.

In the event of an irregularity being found, the clinician, [Dr William Torreggiani of The Adelaide and Meath Hospital Incorporating the National Children's Hospital] will inform you as the participants GP that a proper clinical scan may be required to determine whether or not an irregularity is of clinical significance.

The GP should then contact the participant to advise them that a proper clinical scan, at a hospital, is recommended to check the irregularity.

In the unlikely event that you need to contact us, the following telephone number can be used. (01-8962925).

Sincerely,

Prof. Shane O'Mara

Director of Development
Trinity College Institute of Neuroscience & Dept. of Psychology
Trinity College Dublin
Dublin 2