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Exploring the bases of Hippocampal- and Prefrontal-Based Memory: The effect of Age and Disease

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A thesis submitted for the degree of
Doctor of Philosophy

University of Dublin
Trinity College
2010

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Summary

Memory formation largely depends on normal function of the temporal lobes (particularly the hippocampal complex) and the prefrontal cortex. The relationship between these two regions and the degree to which each region is engaged during different memory tasks is still unclear. Evidence from animal studies suggests abnormal hippocampal functioning in hypothyroidism (Alzoubi, Gerges, & Alkadhi, 2005), and abnormal prefrontal functioning in aging (Allain et al., 2005). This study investigates the nature of the relationship between memory tasks that have been associated with hippocampal and prefrontal cortex (PFC) regions, and examines how this relationship changes when either region is damaged; the hippocampus as a result of hypothyroidism, and the prefrontal cortex as a result of aging. It is hypothesised that specific defects in memory tasks associated with the hippocampus will be observed in hypothyroid patients, while specific deficits in memory tasks associated with both prefrontal- and hippocampal regions will be observed in healthy older adults.

The effects of inadequate thyroid hormone (hypothyroidism) availability on cognitive function and brain activity have been long debated and are still not clearly understood. It is widely believed that declarative memory depends on the medial temporal lobe (MTL) (Milner, Squire, & Kandel, 1998; Scoville, & Milner, 1957). The hippocampus is a thyroid hormone rich region within the MTL, which has been implicated in the hypothyroid-induced cognitive deficits in memory. Burmeister et al (2001) have shown that memory deficits resulting from hypothyroidism could be related to dysfunction of the hippocampus, while others reported that hypothyroidism impacts negatively on associative memory (Miller et al., 2006). Conversely, Zhu et al (2006) found, using an fMRI (functional magnetic resonance imaging) paradigm, that there was a working memory (WM) impairment in those with subclinical hypothyroidism.

In the present study, baseline assessments of the neurocognitive function of hypothyroid participants, prior to hormone-replacement treatment, were compared to control participants using several declarative memory tasks, such as the Face-Name memory task (Zeineh, Engel, Thompson, & Bookheimer, 2003). A number of neurocognitive and neuroimaging studies have shown that the pre-frontal cortex (PFC) is activated during executive function tasks, such as WM tasks (Levy, & Goldman-Rakic, 2000). Given that executive functions, particularly WM, underlies many cognitive functions, we also used the *n*-Back task (Meyer-Lindenberg et al., 2001), among others, to determine if this PFC-dependant task showed deficits in those

participants with hypothyroidism. The results confirmed the presence of specific, hippocampal-based memory deficits in hypothyroidism, and suggested that these deficits impacted PFC-based memory. Subsequent follow-up testing sessions investigated the impact of thyroid hormone replacement on cognitive functions, and identified that there was some functional recovery of baseline deficits associated with this treatment. Though some debate remains as to whether these deficits are fully-reversible.

Damage to the PFC with aging has been confirmed in several studies (Milner et al., 1998), though the relationship between this damage and the interactions with other brain regions is still under debate. Previous studies have proposed that the PFC plays a role in memory tasks in which the associations between items are needed for successful recall, tasks such as the Face-Name task (Mitchell, Johnson, Raye, & D'Esposito, 2000). While these tasks primarily rely on normal hippocampal functioning, aging may disrupt this process through age-related changes in the PFC. As a result, tasks that require the successful activation of the PFC, such as long-term memory retrieval, may be impaired; either due to the diminished connectivity between the hippocampus and the PFC, or because of faulty encoding process in the first instance. The nature of age-related memory impairments across the lifespan were investigated in tasks that have been linked to hippocampal- and PFC-regions. The results verified that there are specific deficits on a number of tasks associated with both hippocampal- and PFC-areas in aging, and identified at what point these emerged. Future studies are needed to confirm whether these deficits are related to reduced hippocampal-PFC connectivity in aging.

Investigations into the impact of disease and age on hippocampal- and PFC-based memory tasks, confirmed that there are specific disease- and age-related impairments in memory. The nature of these deficits was discussed, together with a proposed model to explain the findings.

Abbreviations

ACh – Acetylcholine

AChE – Acetylcholinesterase

AD – Alzheimer's disease

BADS – Behavioural Assessment Of Dysexecutive Syndrome

BFB – Basel Forebrain

BOLD – Blood Oxygen Level Dependent

CPT – Continuous Performance Task

CVLT – California Verbal Learning Test

DART – Dual Attention to Response Task

DG – Dentate Gyrus

EEG – Electroencephalography

EMQ – Everyday Memory Questionnaire

fMRI – Functional Magnetic Resonance Imaging

HADS – Hospital Anxiety and Depression Scale

HF – Hippocampal Formation

IQ – Intelligence Quotient

LT4 – Levothyroxine

LTM – Long Term Memory

LTP – Long Term Potentiation

MMQ – Mundane Memory Questionnaire

MRI – Magnetic Resonance Imaging

mRNA – Messenger Ribonucleic Acid

MTL – Medial Temporal Lobes

MTS – Match to Sample

NART – National Adult Reading Test

PET – Positron Emission Tomography

PFC – Prefrontal Cortex

PSS – Perceived Stress Scale

rCBF – Regional Cerebral Blood Flow

ROCF – Rey-Osterrieth Complex Figure

RT – Reaction Time

SART – Sustained Attention to Response Task

SCH – Subclinical Hypothyroidism

SPECT – Single photon emission computed tomography

SRS – Self Rating Scale

STM – Short Term Memory

T3 – Triiodothyronine

T4 – Thyroxine

TRH – Thyrotrophin-Releasing Hormone

TSH – Thyrotrophin-Stimulating Hormone

WM – Working Memory

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Chapter 1

General Introduction

1.1 Summary

This chapter discusses the general concept of memory, and more specifically neuropsychological measures of memory that have been associated with the medial temporal lobe and prefrontal cortex. The relationship between medial temporal lobe and prefrontal cortex functioning is also discussed, with reference made to models of memory and memory impairments associated with damage to both regions. Lastly, an outline of the proposed studies is offered.

1.2 General Introduction to Memory

Cognition is believed to consist of precise neural systems that involve many, overlapping brain regions. Functions such as concentration, attention, perception, language, memory and executive function, have been mapped to these regions using findings from animal, lesion and functional imaging studies (Samuels, 2008). The identification of the particular regions, or network of regions, associated with learning and memory, allows researchers the opportunity to manipulate memory paradigms and examine the changes in memory in normal and damaged populations.

1.2.1 Short- and Long-Term Memory

In learning and memory research, a division is usually drawn between short-term memory (STM), which holds information for a matter of seconds, and long-term memory (LTM), which stores information on a permanent or semi permanent basis (Kopelman, 2002) (see Figure 1.1). STM lets you hold on to a piece of information for less than a minute and retrieve it during this time. In general, you can retain 5 to 9 in short-term memory (Miller, 1994). Working memory (WM) refers to the structures and processes used for this temporary storage and manipulation.

In contrast, LTM allows people to hold onto items for a matter of hours, days, months, and even years. LTM is subdivided into episodic-, semantic- and implicit-memory (Lezak et al., 2004). Episodic memory concerns information specific to a particular context, such as a time and place; semantic memory, concerns facts taken independent of context; and implicit memory concerns repetitive learning of motor skills. Episodic and semantic memory refers to all types of memories that are consciously available, and include many functions that are examined in neuropsychological measures. These types of memory are encoded by the hippocampus, entorhinal cortex, and perirhinal cortex (structures within the medial temporal lobes; MTL), but consolidated and stored elsewhere in the cortex (Lezak et al., 2004). The primary focus of the current studies is to examine both short and long-term memory in a number of different groups, and to explore the relationship between these types of memory and the regions involved in their consolidation, storage and retrieval.

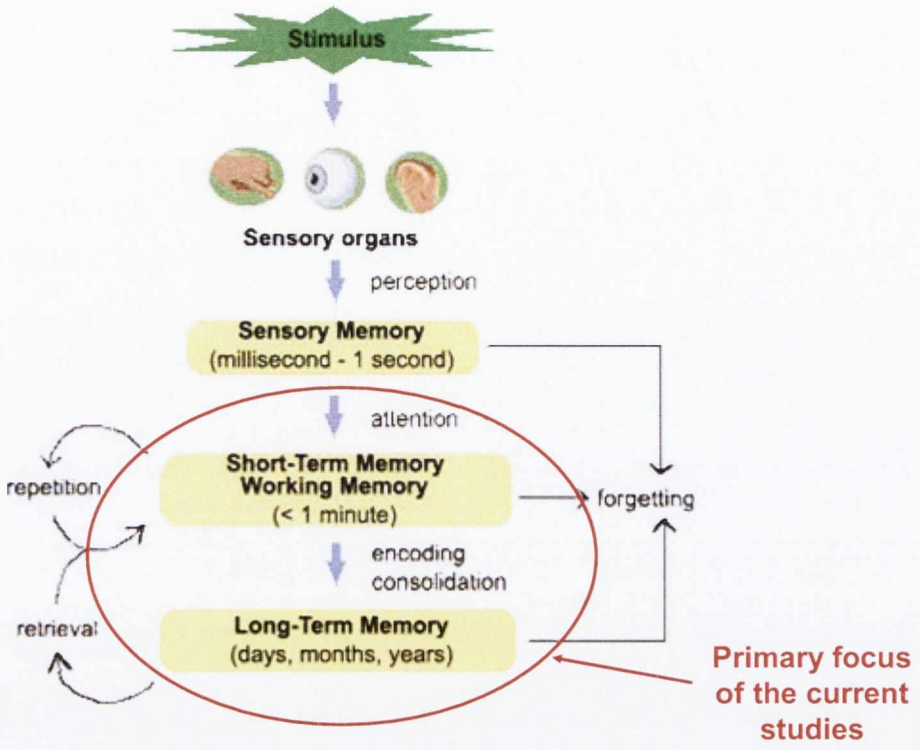

Figure 1.1: Divisions of the memory system. Adapted from http://www.aboutmind.com/memory-brain-neurons-1.shtml

1.2.2 Regions involved in Memory

The PFC and hippocampus are two brain structures that have consistently been reported to play an important role in learning and memory (Squire, 1992). The role of the hippocampus is continuously under review; damage to the MTL, and more specifically the hippocampus, is known to impair memory in humans and animals (Simons et al., 2003). Lesion studies propose that activity in the hippocampus, in particular, underlies the relationship between items – binding all the features associated with an item, or several items, together into a coherent memory trace (Eichenbaum, 2000). fMRI studies have reported activation in the MTL during both encoding and retrieval for spatial memory, navigation tasks and contextual information (see Simons et al., 2003). In addition, there have been several studies that have reported that the magnitude of activation in the hippocampus during encoding/binding processes, correlates with the likelihood that the information will be subsequently recalled (Davachi et al., 2002). However, in all of these processes, it is doubtful that the hippocampus functions on its own, especially during binding; it probably works in conjunction with neocortical regions (Sperling et al., 2003).

The PFC, on the other hand, is associated with planning complex cognitive behaviors, personality expression, decision-making, and moderating correct social behavior. The main function of the PFC is to organise thoughts and actions in accordance with internal goals. These types of functions are referred to as executive functions. As executive functions involve planned or intentional activities, they can break down at any stage. According to Lezak et al. (2004), there are four components that account for executive functioning: 1) volition; 2) planning 3) purposive action; and 4) effective performance. An examination of each of the four components would ascertain at which point or points the deficits occur.

Damage to the PFC has been shown to result in considerable impairment to certain types of memory; it leads to problems with tests of frontal lobe function and contextual information, when there is interference between stimuli, and can lead to confabulation (Simons et al., 2003). Deficits in executive functioning have primarily been associated with frontal lobe damage as is well documented in previous literature; however executive functions are also sensitive to damage in other parts of the brain including the limbic system (Lezak et al., 2004). A recent computational model of PFC functioning has indicated that the PFC may interact with the MTL during LTM, lending support to the view that there are interactions between these two regions that are crucial during many stages of memory encoding and retrieval (Simons et al., 2003). As the PFC has a number of connections with the hippocampus, the relationship between PFC functioning and hippocampal functioning is of extreme interest in memory studies. In order to examine these concepts further, a closer examination of the MTL and PFC is necessary.

1.3 Medial Temporal Lobes (MTL)

The MTL system includes the hippocampus, amygdala and surrounding structures (see Figure 1.2). It has been well established that the MTL is important for declarative memory, but does not appear crucial for working memory (Squire, 1992). Several studies, from animal lesion and electrotophysiology studies, to human amnestic patients studies, propose that the main function of the MTL, and more particularly the hippocampus, is to form relationships/associations between previously unrelated items (Eichenbaum et al., 1996). As the MTL plays a crucial role in binding information together in memory, the theories that describe these processes are relational in nature; they propose that the MTL is important for encoding contextual information, configural information, and relational information (Olson et al., 2006).

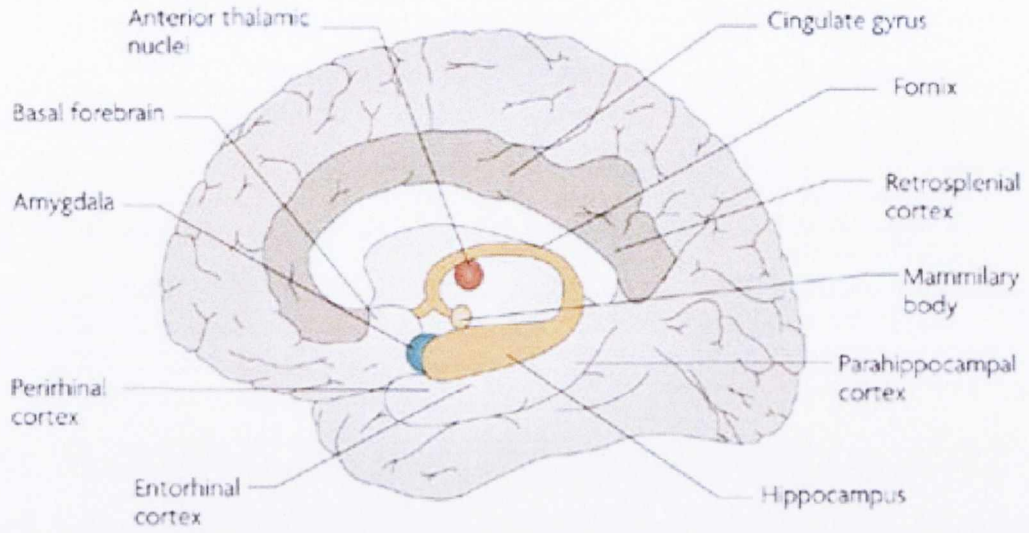

Figure 1.2: The MTL and the hippocampus. The hippocampus lies in the medial temporal lobes, surrounded by the entorhinal, parahippocampal and perirhinal cortices. It is part of Papez's circuit, and so is connected to several subcortical and cortical structures, such as the anterior thalamic nuclei, the mammillary bodies, the septal nuclei of the basal forebrain, the retrosplenial cortex and the parahippocampal cortex. Taken from Bird (2008).

However, there is growing evidence that the MTL does not function alone during episodic memory; and that the nature of the relationship between the MTL and PFC may be more interactive than previously suggested.

1.3.2 Role of the MTL in Episodic Memory

There are several types of memory that the MTL, and especially the hippocampus, have been associated with: matching tasks, memory for learning and remembering faces, memory for past events, both of a personal and more global nature, spatial memory – routes and self-centred movement, and memory of abstract designs (see Figure 1.3). A fundamental element of this episodic/associative memory is the ability to bind information together, e.g. a face and a name (Sperling et al., 2003).

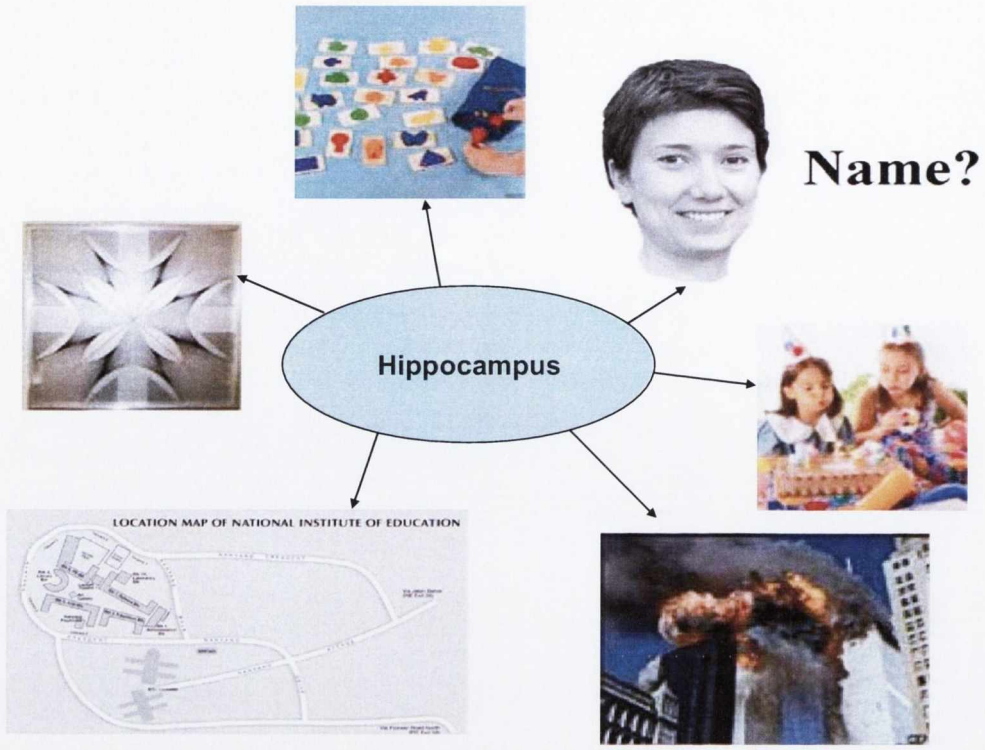

Figure 1.3: The role of the hippocampus. The hippocampus plays an essential role in matching tasks, memory for learning and remembering faces, memory for past events, both personal and more global, spatial memory – routes and self-centred movement, and memory of abstract designs.

This type of associative memory is particularly difficult as it relies upon the novel relationship between items from different domains; verbal (when someone introduces themself) and visual (when you see that persons face). Items are stored in episodic memory in differing degrees of accessibility, and with varying amounts of associated information, which binds them together (Sommer et al., 2005). During encoding there are also certain factors that influence the amount of information that is associated with an item; attention and depth of processing. Attentional theories believe that the impairments in associative memory observed in older adults are due to reduced attentional resources available with age; while the level-of-processing theories suggest that older adults have greater difficulty with the spontaneous use of processes that assist memory (self initiated), though when they are given direction (task driven), these difficulties normally improve (Craik, 2008).

Adding to the debate over what processes underlie episodic memory impairments, is the stage at which episodic memory impairments can be examined. The first involves the initial encoding of episodic memories. Faulty encoding could result from a deficit in the

processes concerned with the initial 'representation' of episodic information (Kopelman, 2002), the point at which this information is taken. Researchers can examine the neural substrates of memory formation by observing brain activity during learning trials and look at the to-be-remembered events (Guo et al., 2005). Secondly, there may be impairment when transferring the information from this initial representation, into LTM; the process by which this takes place will be discussed later. Thirdly, there could be an impairment acquiring the contextual information that needs to be examined; that is, there could be a problem 'binding' the associations together (Kopelman, 2002). Finally, there could be a problem with the storage/retention of the episodic memory, or the process of retrieval of the memory. Kopelman (2002) discusses the idea that retrieval processes are actually very reliant on the initial encoding processes, so if there is an impairment with the initial encoding, then this, in turn, may lead to problems retrieving the information.

There is a lot of dispute in the current literature about the different types of memory (memory for single items vs. associative memory) , and how they relate to each other; comparing the memory for individual items with the relationship between those items allows researchers to look at this in more detail. The subsequent memory (SM) paradigm can be used to explore the nature of the differences in behavioural and neural activity between encoding individual items and associated information, as it provides a correlation between items remembered, and activation during encoding when the associations were formed (Davachi et al., 2002) (see Figure 1.4). SM studies have shown that the degree of activation within the hippocampus during encoding is related to the likelihood for successful later recall, the greater the activation, the more likely people are to successfully recall associative memory pairs. In addition, as evidenced in Figure 1.4, it is also possible to identify different patterns of activation between stimulus types using the SM paradigm. Determining whether there are separate underlying mnemonic systems at play during item and relational memory, or if episodic memory simply reflects different intensities of one encoding systems remains to be decided (Davachi, 2006).

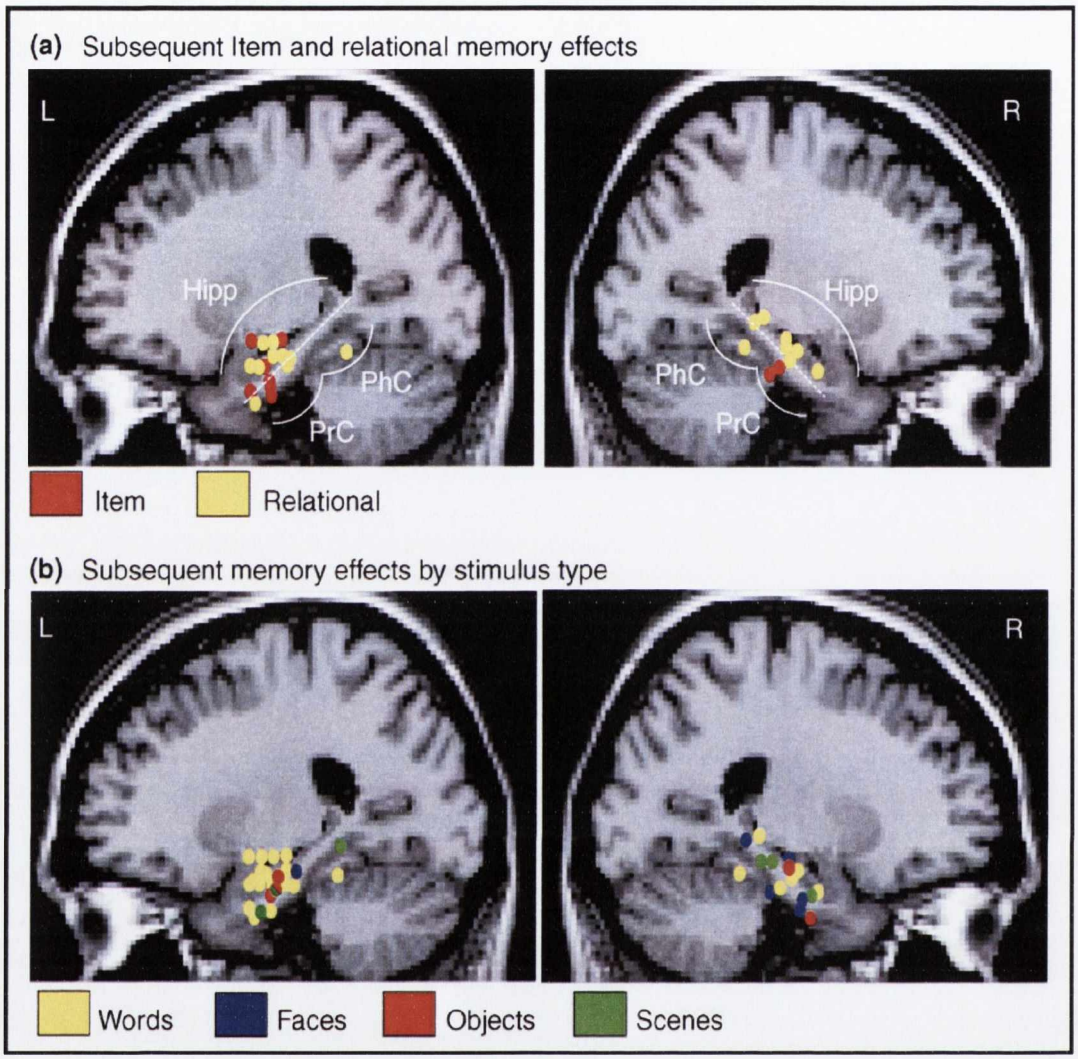

Figure 1.4: Location of medial temporal lobe subsequent memory effects. (a) Peak subsequent memory effects taken from extant studies designed to directly contrast item and relational memory effects. Relational SM effects are predominantly seen in bilateral hippocampus and PhC while item SM effects are commonly seen in PrC. (b) Peak subsequent memory effects plotted by stimulus type. Note the dominance of left lateralized SM effects in studies using verbal stimuli contrasted with bilateral effects for objects and scenes and primarily right lateralized effects for faces. Taken from Davachi (2006).

However, it is important to note that the examination of the binding of items/association between items requires a distinction to be made between recall and recognition memory. Several studies that examined recall and recognition in amnesic patients whose pathology included the hippocampus, found that they had impairments on measures of recall but relatively intact recognition memory (Aggleton et al., 1999; Manns et al., 1999).

Nevertheless, there is a difference between remembering something and knowing something, and studies examining deficits in associative memory need to make that distinction. That said, the possibility that the spared recognition (knowing) reflects a milder form of associative impairment (remembering) can not be ignored (Kopelman, 2002) and should be explored in future research.

1.3.2 Associative Memory and the Face-Name Task

There are several tasks that have been designed to explore the nature of associative memory, and different studies using these tasks have attempted to address the many concerns discussed above. One of the most useful of these tasks is the face-name task (Zeineh et al., 2003). It examines the formation of episodic memories through the use of a set of face-name pairs, and is reported to be one of the most ecologically valid measures of associative memory (Hampstead et al., 2008). Several fMRI studies found that the anterior regions of the hippocampus were preferentially activated during associative memory face-name tasks (Mitchell et al., 2000; Sperling et al., 2001; Zeineh et al., 2003). However, most of these used a block design, which does not allow researchers the opportunity to separate the activation in order to explore the difference between single items and the relationship between those items. Event related fMRI studies using SM paradigms have made this possible.

Sperling et al. (2003), have used the SM design in an event related face-name associative memory task. Their aim was to identify the regions of the brain that were activated during successful encoding (learning a face-name pair and successfully recalling it later), and to determine the relationship between these regions. They believed that the degree of activation in these regions would predict whether a face was successfully recalled or not. It is important to note that unlike the type of face-name task used in the present studies (see Chapter 2 Section 2.3.3.1b), in the Sperling study participants saw 455 face-name pairs, and during a post-scan memory test identified what name (from 2 possible names presented with each face) was originally paired with the face. It could be argued that this type of recall is not free recall, but more likely recognition, and therefore introduces the possible problem of priming into the scenario. Nevertheless, their findings did demonstrate that the magnitude of the relationship between the hippocampus and the PFC may contribute to the probability of successful subsequent associative memory.

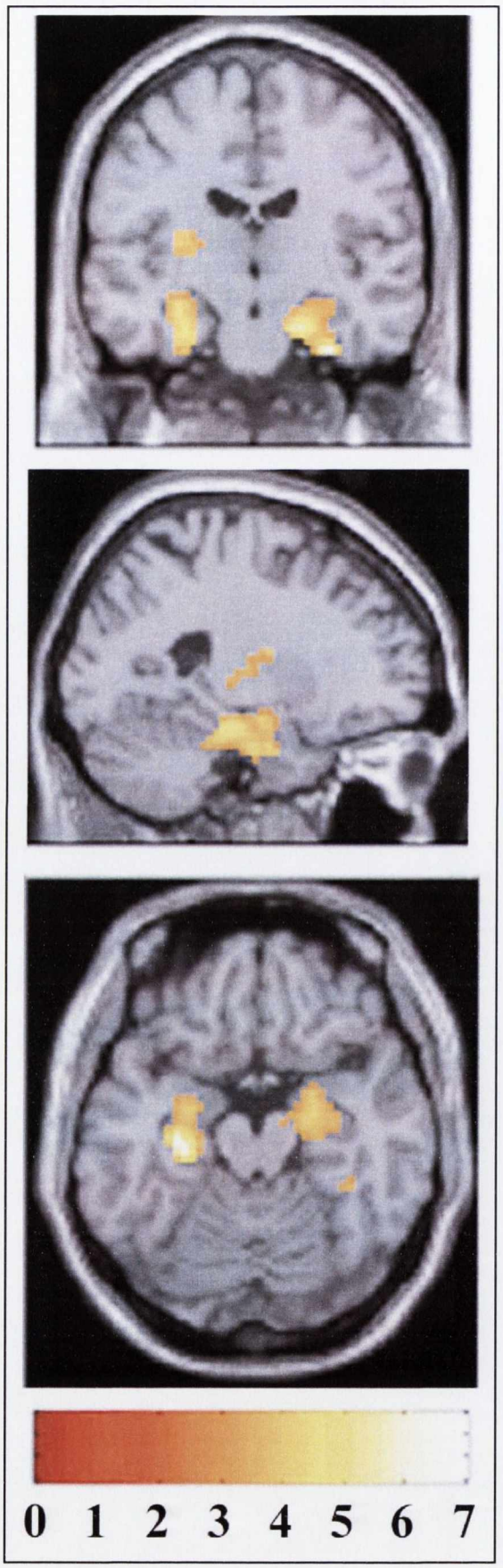

Figure 1.5: Successful vs. Failed Encoding. Statistical activation maps demonstrating greater response during encoding of Face-Name pairs that were subsequently successfully remembered (High Confidence Correct) compared to Face-Name Pairs that were forgotten (Incorrect). Activation within the hippocampal formation is shown in three image planes: coronal (top), sagittal (middle), and transaxial (bottom), and was located in the anterior hippocampus bilaterally, and the right entorhinal cortex. Taken from Sperling et al. (2003).

In Figure 1.5 the maps of activation indicate that there is more activation in the hippocampus and the entorhinal cortex during the encoding of faces that were later remembered correctly. Additionally, they also reported that the activation was at its highest within the first four blocks of encoding; suggesting that this is when the participant's learnt the most number of faces.

In another study that looked at activity within the hippocampus during encoding and retrieval, Zeineh et al. (2003) attempted to directly examine activation patterns within different regions of the MTL. They wanted to determine how activation patterns change within the MTL, during the encoding of face-name pairs. What was extremely novel about this study, was the method they used for unfolding the hippocampal cortex, this allowed them to identify neural activity within the subregions. An example of this 'unfolded' map is presented in Figure 1.6.

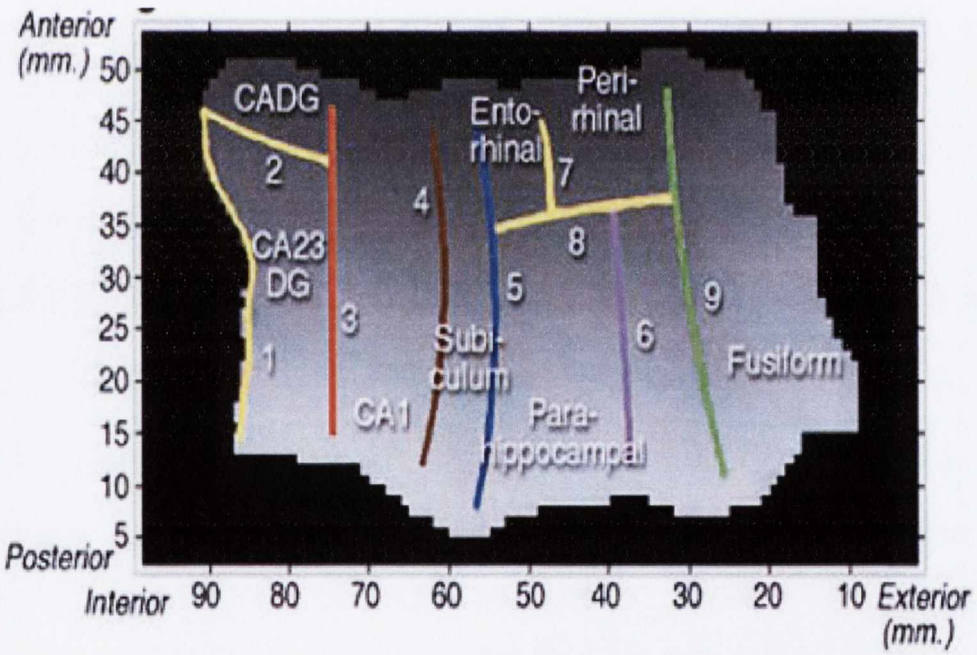

Figure 1.6: A flat hippocampal template was generated by averaging the boundaries between the following subregions across subjects: CA2,3DG, cornu ammonis 2, 3, and dentate gyrus, the initial stages of hippocampal circuitry; Ca 1, cornu ammonis 1, the next step in information flow; Subiculum, the main source of hippocampal ouput; Entorhinal cortex, the gateway of cortical input to the hippocampus and hippocampal output to the neocortex; Perirhinal, neocortex lateral to entorhinal cortex along the anterior collateral sulcus; Parahippocampal, neocortex along the parahippocampal gyrus and posterior collateral sulcus; Fusiform, neocortex along the fusiform gyrus. Numbers 1 to 9 represent division lines between these subregions. Taken from Zeineh et al. (2003).

In a manner similar to that of the present studies, participants had 4 blocks within which to encode the face-name pairs, this allowed the comparison of activity across the block while participants were encoding the face-name pairs, rather than the single learning pairs used in many other studies, such as that conducted by Sperling (2003) and discussed above. By measuring the learning curve, they were able to determine that the nature of hippocampal activity was different during encoding and retrieval. As detailed below in Figure 1.7, during encoding the CA2, CA3 and dendate gyrus appeared to be more active, while the subiculum was more activated during retrieval.

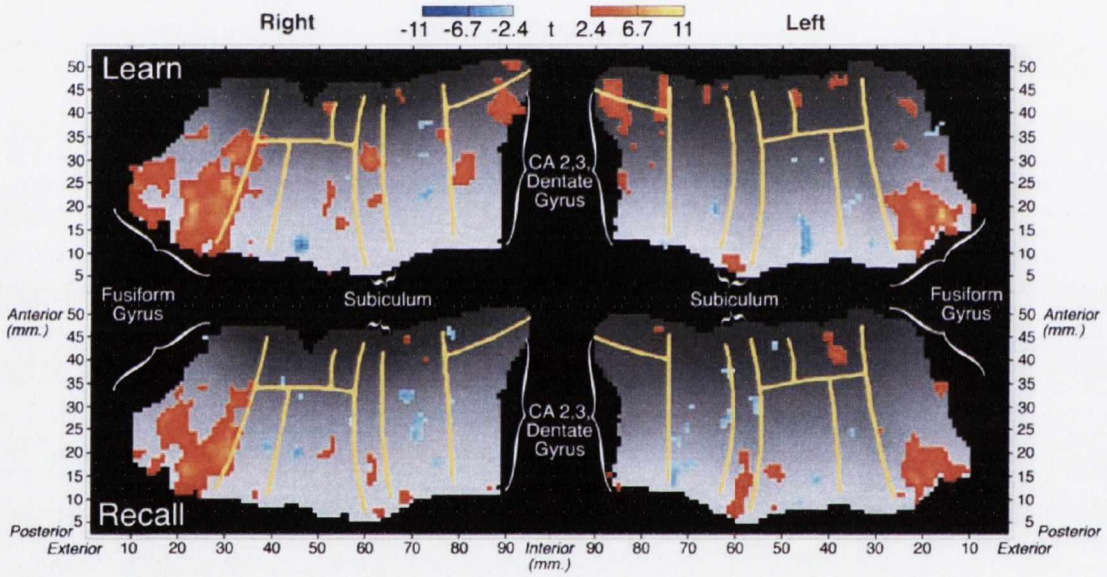

Figure 1.7: Random effects *t* maps (statistical maps of significantly activated regions as seen by fMRI) for incremental performance during learning (top) and recall (bottom).

They suggest that these results indicated that there is a dissociation of activation within the MTL. Activity within the CA2, 3 and dendate gyrus correlates with learning, while activity within the subiculum correlates with retrieval. They also note that as retrieval becomes practiced, the activity within the MTL decreases. However, in turn, activity within the PFC increases during retrieval. Taken together, these studies imply that the MTL plays a role in encoding; however the regions of the MTL that are engaged during encoding changes as associations become more practiced. In addition, the activation within the PFC is stronger

during retrieval and increases overtime with the number of face-name pairs successfully recalled.

1.3.3 Role of the MTL in Working Memory

Until recently, it had been assumed that the MTL structures were primarily associated with encoding and consolidation, and less involved in retrieval (Squire, 1992). Extensive research on H.M., a patient who underwent an MTL resection, has demonstrated that the MTL is crucial for the formation of new episodic memories, following the finding that H.M. was unable to form new memories for events. In addition, though his short-term memory was relatively intact (few seconds), he showed severe deficits on LTM tasks; suggesting that the MTL regions are also crucial for LTM (Ranganath et al., 2005). According to Simons (2003), there is still a lot of debate about the extent of the involvement of the hippocampus in the consolidation and retrieval of LTM, so this suggestion requires further clarification. Additionally, there is growing evidence that during WM, the MTL, and the hippocampal formation in particular, may be involved. Researchers have recently proposed that the binding processes that underlie hippocampal functioning may contribute to the maintenance of information in WM (Braver et al., 2009; Ranganath et al., 2001). Although simple forms of WM may not be affected by MTL damage, it is possible that forms of WM that require associative memory rely on the MTL.

Findings from Olsen et al. (2006) reported that the MTL was important for at least one type of WM: during the formation of memory for relationships or associations between items. Their findings in amnesic patients, proposed that feature memory, memory for locations or objects, did not differ between amnesic and control groups. However, when they tested whether amnesic patients were impaired in associative memory, when they were required to remember an object in a location, they found that their memory was considerably impaired. Additional analyses revealed that this deficit was closely linked to damage in the hippocampus and not the surrounding structures of the MTL (Olson et al., 2006). There is a lot of evidence that associative memory is quite different from simpler forms of memory (Mitchell et al., 2000), and as such the presence of intact memory for simple features offers no information about whether or not memory for the associations between stimuli are also undamaged.

1.3.4 Damage to the MTL

Traditionally, the extent of memory impairment was believed to be proportionate to the extent of damage to the MTL, where all of the MTL structures function as an integral system (Tulving et al., 1997). However, there is growing support for the more recent interactionist view which proposes that many different brain regions are involved in the learning and performance of tasks (Tulving et al., 1997). If this is the case, then it is important to identify which structures/network of structures is involved in various tasks, and the contribution that each structure makes to the various aspects of the task performance. There is also evidence that in those with hippocampal and MTL lesions, plasticity of the brain can lead to reorganisation of function (Becker et al., 1996). "Plasticity" relates to learning by adding or removing connections, or adding cells; it allows the neurons in the brain to compensate for injury (due to disease or age) and adjust their activity in response to new situations or changes in their environment (see Stein, 2000). This in turn lends more support to the notion that there is an interactive network of connections underlying memory, and supports Tulving's interactionist view.

There have been many studies that have looked at the impact of MTL lesions on memory, and while the results are varied, they do offer great insight into the nature of MTL damage. For instance, while the notion that STM does not rely upon the MTL is prevalent (Ryan et al., 2004), Ranganath and Blumenfeld (2005) suggest that perhaps not all forms of STM are spared in patients with MTL lesions. Previous studies have indicated that MTL lesion patients have intact STM for instructions, concentration, and attention levels when performing complex tasks. In addition, they also have intact STM for simple visual shapes (Cave et al., 1992, cited in Ranganath et al, 2005). Nevertheless, these studies do not examine the memory processes that are probably uniquely processed by the MTL. Accordingly, Ranganath et al. (2005) proposed that it would be more beneficial to investigate STM for materials that are closely linked to the MTL, such as complex figures (see Figure 1.3 for more examples). Ranganath et al. (2005) reviewed a number of such studies and found that, in all but one, patients with MTL lesions had STM impairments across maintenance delays as short as 2-10 seconds.

Consequently, damage to the MTL cannot be examined in isolation. Studies that examine the effects of disease or age for example, on tasks that have been associated with MTL functioning, should also include tasks that have been associated with PFC functioning, such as working and short-term memory, as many of the skills used on a day-to-day basis

may actually rely on the interaction between these two regions. This provides the means by which to study the nature of the relationship between the two regions, and allows the identification of both global- and/or region-specific memory impairments related to disease or age.

1.4 Prefrontal Cortex

The PFC is in the anterior region of the frontal lobes, and can be divided into anterior- (APFC), dorsolateral- (DLPFC), ventrolateral- (VLPFC), and medial- (MPFC) prefrontal cortex (see Figure 1.8). It is primarily responsible for executive functions, such as planning, inhibition, and organisation of material. Planning is central to many of the tests examined in the current studies, the ability to look ahead, identify changes in goal directed behaviour, and execute the necessary behaviour are all key areas that need to be examined. In addition, in order to plan efficiently the participant must have good impulse control and a reasonably intact memory, as well as the ability to sustain attention for long periods of time. Many of the theories of WM state that it involves some of the planning processes such as decision making and attentional control. These functions are considered to "act at the highest levels of cognition to optimise performance on everyday tasks" (Allain et al., 2005, p. 4). Without these abilities, people could not orchestrate simple behaviours such as cooking or dressing (Royall et al., 1992). Understanding how the brain controls these processes is continuously under review; in particular the design of ecologically valid tests of executive functioning has been difficult (Norris et al., 2000). In addition, there is great difficulty understanding scores on tests of executive functions in light of their importance for patient outcomes; transferring results from a battery of tests that is conducted in a lab environment to real world situations can prove problematic.

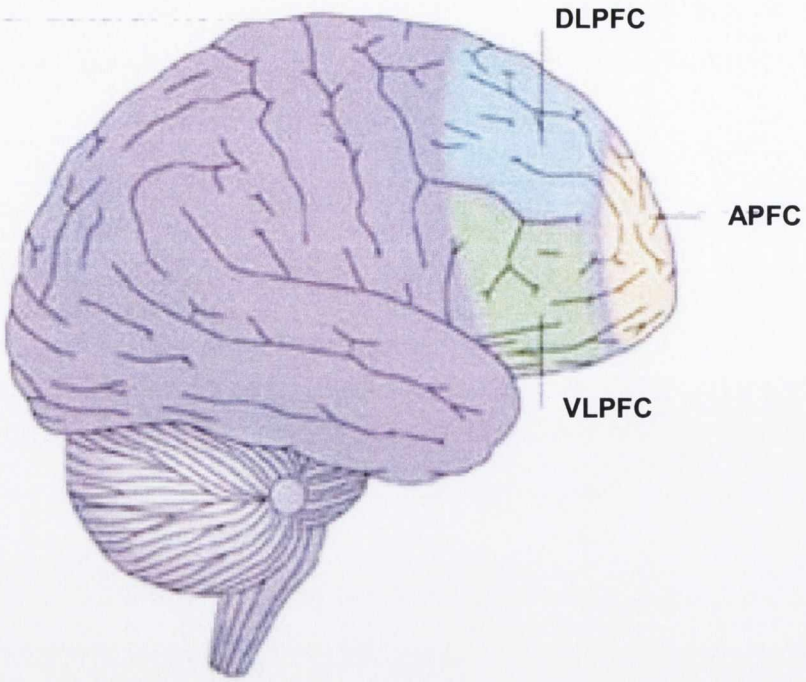

Figure 1.8: The prefrontal cortex can be divided into anterior (APFC), dorsolateral (DLPFC), ventrolateral (VLPFC), and medial (MPFC – not shown) regions. Adapted from Simons & Spiers (2003)

The frontal lobes appear to be particularly susceptible to the degenerative effects of age; several post-mortem and neuroimaging studies have reported that deterioration is seen earlier and more severely in the frontal lobes than other cerebral regions (for a review, see Tisserand et al., 2003). As a result, there are age-related cognitive impairments found in many tasks that have been associated with PFC functioning, such as working memory or planning abilities (Amieva et al., 2003); understanding the role that the PFC plays in these tasks is of paramount importance.

1.4.1 Role of the PFC in Working Memory

WM involves the manipulation of information held, or the maintenance of that information, while dealing simultaneously with incoming stimuli (Grady et al., 2000), and is required for the performance of time-limited tasks, such as learning, planning, reasoning and comprehension (Missonnier et al., 2004). There are three main processes involved in WM; the encoding of incoming information via sensory processing (vision, hearing, etc), storing this information in short-term, and the activation of executive processes which

operate on this short-term information (Missonnier et al., 2004). The executive processes involved include the online manipulation of the information held, inhibition of responses in response to the information held, and coordinating the appropriate responses to the information held. While working memory is fundamental for complex cognition, there are several different frameworks detailing how the working memory system actually works (McCabe et al., 2005).

The model of WM proposed by Baddeley (1992; 1986) (see Figure 1.9) outlines a three-level model of working memory. The first step is the 'central executive'; which is a modality-specific, limited short-term buffer located in the visual cortex and the posterior parietal cortex. It allocates processing abilities (Missonnier et al., 2004), for e.g. it is involved in selective attention, response inhibition, and coordinating the subsystems of WM. As a result, there is a reciprocal relationship between the central executive and the second level of WM, which includes the 'phonological loop', the 'visuospatial sketchpad', and in a later model, the 'episodic buffer' (Baddeley, 2000). The phonological loop is also modality-specific; it holds speech based information in a temporary storage system, allowing rehearsal of this information if required. There are two parts: a short-term phonological store which holds auditory information, though it is subject to rapid decay and an articulatory rehearsal component that allows the rehearsal of this information. The phonological loop may play a key role in the acquisition of vocabulary, particularly in the early childhood years (Baddeley et al., 1998). The visuospatial sketchpad is reported to hold spatial and visual information. It temporarily stores and manipulates information, such as shapes and colours, or the location or speed of objects in space. It has also been reported to be involved in tasks which involve planning of spatial movements, such as planning a journey through a building (Baddeley, 2000).

The episodic buffer links information across domains to form integrated units of visual, spatial, and verbal information and sequential ordering, and is related to long-term memory (Baddeley, 2000). It perhaps is the stepping stone between information that is held in either the phonological loop or the visuo-spatial sketchpad and long term memory formation (Baddeley et al., 2002). There are also other models of WM, they suggest that the three processes are differentiated by those that are automatic ('bottom up', pre-attentive processes), and those that are voluntary ('top-down', attention demanding) (see Tomita et al., 1999)

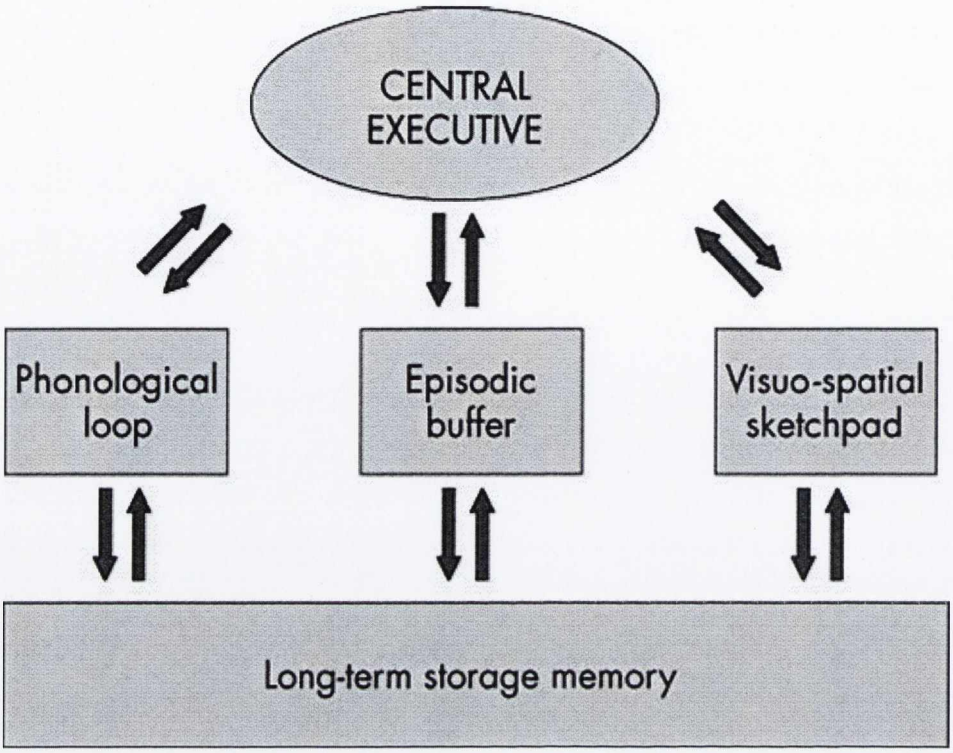

Figure 1.9: Baddeley's model of memory (2000). Figure taken from http://www.psypress.com/groome/figures/fig%206.9.jpg

Models of WM have proposed that there are several different types of relationship between memory systems and focal attention (the part of WM that is currently being processed); some suggest that there are two distinct systems, one which deals with items within focal attention, and the other which deals with passive memory representations (see works of James, 1890). While others believe that there is a long-term memory (LTM) system, a working memory system and the current focus of attention (see Baddeley, 1986). This view-point sees WM as a limited-capacity system that maintains a small number of items outside of focal attention; these items are more accessible than those in LTM. McElree (McElree, 1996, cited in McElree, 2001) states that focal attention is only able to maintain the last item processed, or items if they are coded into chucks that form a single processing epoch. In order to examine working memory, many people suggest that levels of attention must also be examined. What's more, there is the need to account for the relationship between attention and WM, and the amount of information that can be attended to at one time, which as previously mentioned, is limited. As a result, the exchange that occurs between focal attention and WM when incoming information exceeds the span of attention,

also needs to be investigated, as it is unlikely that all stimuli can be maintained in the focus of attention at once (McElree, 2001).

Other models focus on the control processes involved in WM, including maintaining, storing, preventing interference, updating the information and ultimately using it. The model proposed by Braver et al. attempts to explain WM components in terms of underlying neurobiologically based computational mechanisms; they focus on the fact that the ability to exert control over WM varies, e.g. with age, and that their model could be used to explain this variation (Braver et al., 2009; Braver et al., 2003; Locke et al., 2008).

The core of WM is controlled processing, the ability to flexibly adapt behaviour to task demands, this favours the processing of task relevant information and goal-compatible behaviour. The model suggests that there is a growing trend to emphasise PFC involvement in cognitive control rather than WM. They propose that cognitive control operates via two distinct operating modes; proactive control, and reactive control (Braver et al., 2003). Both modes are distinct on a number of properties; computational properties, neural substrates, temporal dynamics, and information processing. By distinguishing between both modes it is possible to look at the inconsistencies in inter-individual and intra-individual differences in WM abilities, the variation between WM tasks, the impairments reported using these tasks, the mechanisms by which the model explains all of these, and the noncognitive variables that might also play a role. Systems that are known to underlie WM include the PFC (proactive cognitive control), MTL (binding), dopamine (DA) (updating), and the anterior cingulate cortex (ACC) (performance monitoring). During proactive control sustained activity should be evident in the PFC and should be present across all events. During reactive control PFC activity is transient and present only for events where reactivation is required.

According to Braver et al. (Braver et al., 2009), the neural network framework can simulate human performance in cognitive tasks using principles of processing that are similar to those believed to apply to the brain. As is shown in Figure 1.10, information is represented as graded patterns of activity over populations of simple units, processing takes place as the flow of activity from one set of units to another, and learning occurs through the modification of the connection strengths between these units (Locke et al., 2008). They put forward that cognitive controlled processing arises from the interactions

between the specialised processing subsystems in the brain. These subsystems should not be considered in isolation, rather a number of core brain systems play critical roles in WM.

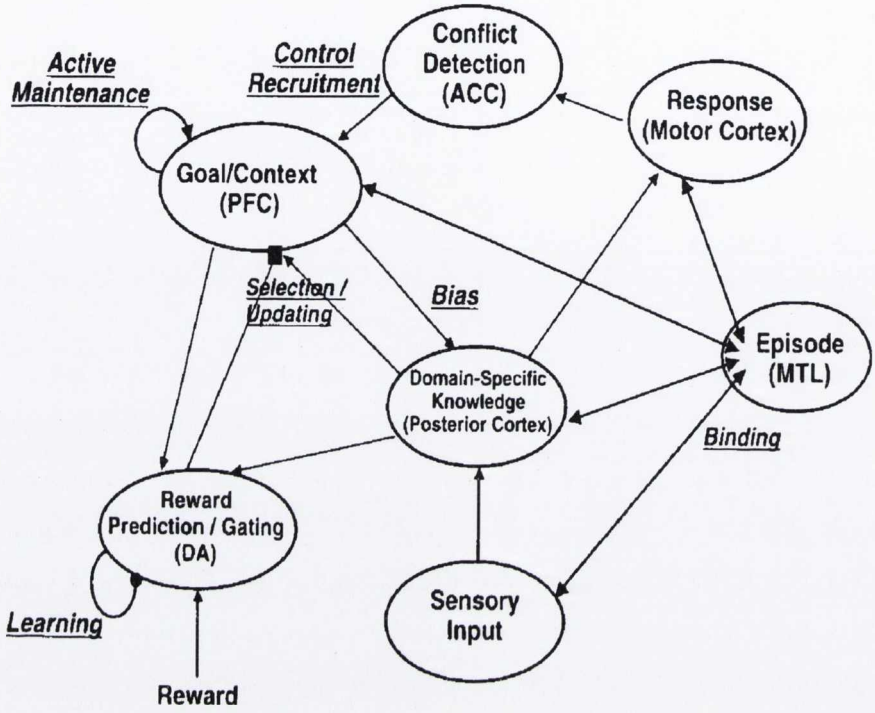

Figure 1.10: The neural network framework proposed by Braver et al. (2007)

In particular, they propose that representations of context information are housed within the DLPFC, and are actively maintained there when task demands require such active maintenance, as is the case of tasks such as the n-back or Stroop task. The PFC is especially influential because of its extensive connections with other brain regions and its specialised processing abilities. The DA projections to DLPFC are proposed to regulate the access to such context information, protecting this information from the interfering effects of noise over intervals in which the information must be sustained, while at the same time allowing for the appropriate updating of such context information when needed. In addition the DA system is postulated to regulate the contents on the PFC via an updating mechanism sensitive to reinforcement contingencies; this can be examined in tasks that include a reward component. The MTL region aids PFC functions through rapid associative binding of active representations throughout the brain, especially important during the face-name and n-back tasks. While the ACC is hypothesised to modulate the general responsiveness of the PFC through a performance monitoring mechanism – this

continuously indexes the need for top-down control via a computation of ongoing processing conflict (Braver et al., 2009). But what happens when the context representation is impaired? And what effect might this have on measures of context representation? The computational model predicts that individuals and populations with impairments in either or both DL-PFC or the DA system should demonstrate specific patterns of impaired cognitive control related to the processing of context.

1.4.2 Working Memory and the n-Back Task

By the *n*-back task, researchers have explored the amount of information that can be held in memory while simultaneously processing new information. In addition, the issue of how information is exchanged between memory and focal attention when the attentional capacity has been exceeded can be examined. As can the relationship between the different regions of the brain involved in the cognitive control processes of the task. The *n*-back task requires determining whether an item (number, face, etc) matches the *n*-th item back (e.g. 1-back, 2,-back etc) in a serially presented list of numbers. What it means is that participants must preserve the *n*-th item back, while continuing to process the incoming stimuli. While it sounds easy, the reality is that the participants must continuously update their response set as each new item is presented. Thus as each new item is met, the *n*-th item changes from a target to a distracter item, and the item $n - 1$ back becomes the target item etc. The particular version of the *n*-back used in the current studies differs from the standard version of the task; it is a continuous response task, so that at the higher loads (1- and 2-back, as opposed to the 0-back) participants have time to prepare their responses as they know which number of 4 possible numbers (1, 2, 3, or 4) that they must press, but at the 0-back condition they do not, they must make an immediate response to the stimuli on screen. It is different to the usual *n*-back version where one would predict an increase in reaction times; in the case of the present studies, the amount of time to prepare the response increases with load, so as the load increases, the reaction times should decrease (see Chapter 2 Section 2.333c for a full description). According to Callicott et al. this version of the task is designed to compel participants to continuously update their mental set while trying to ensure that there is minimal interference from incoming stimuli (2000). They believe that it "emphasises the 'executive' aspects of WM with continual presentation of incoming stimuli and continual WM response" (p. 1080).

On the other hand, the approach taken by McElree (2000) utilised this task by examining response times to items *n*-back, if items are successfully maintained in focal attention then

they should be available immediately, however if subsequent processing results in the *n*-back item no longer being available in focal attention, then response times to retrieve it will be longer. Other approaches, such as that championed by Baddeley (1996), believe that the *n*-back task utilises control processes, such as sub-vocal rehearsal, to store the current and future n-back targets in a temporary buffer. Imaging studies of the *n*-back task have shown significant activation of Broca's area, among other areas, which increases with increasing *n*, indicating that the subvocal rehearsal required increases with increasing task load (Suchan et al., 2006).

In addition, the *n*-back task can be used to assess temporal order memory, as the participant must make a response only to an item in a particular position. Temporal judgements will be slower if the item has to be recovered from memory rather than focal attention, and may also systematically increase with *n* if order information is required (McElree, 2001). There are two views as to the mechanisms involved in temporal order memory in the *n*-back task. The first suggested that participants begin with the most recent item and serially scan representations backwards in time, implying that memory representations preserve order information (McElree, 2001). The second view postulates that the search process utilises pairwise associative information (Lewandowsky et al., 1989), thus participants draw on the associative relations formed between adjacent items during encoding. Each item is used as a cue for the next item, and so on and so forth. What both approaches have in common is the view that the recovery of information entails a sequence of operations, rather than a unitary operation.

In particular, the capacity of working memory and the cognitive processes that are required to complete switches within working memory. Studies by Sternberg (1969, cited in Garavan, 1998), revealed that we do not have concurrent and instantaneous access to all items currently in working memory, but instead, we must serially compare all items in WM. These comparisons between items in WM require switches between the items, as it has been proposed that WM only allows us to hold one "object" in mind (Garavan, 1998).

1.4.3 Damage to the PFC

Many researchers believe that the PFC has distinct regions that are specialised for different cognitive functions (Wilson et al., 1993). Support for this view comes from several fMRI studies that have reported a lateralisation in the PFC; the left PFC is activated during encoding, while the right PFC is activated during retrieval (Nyberg, McIntosh, Cabeza et

al., 1996), though this may depend upon the type of information being remembered as much as the type of memory process being carried out (Simons et al., 2003). Distinctions between the VLPFC and the DLPFC have also been made; the VLPFC has been shown to be involved in the encoding of episodic memory and the maintenance of the retrieved information, while the DLPFC has been shown to be involved in the organisation of material before encoding and the substantiation, monitoring and assessment of information retrieved from LTM (Simons et al., 2003). However, people with damage to the PFC do not appear to have a problem with measures of recognition of encoded information, implying that the PFC is less important for recognition based retrieval and more important for recollection based retrieval.

Depression, for example, has been shown to effect PFC functioning. According to Harvey et al. (2004) depression is characterised by cognitive deficits, involving mainly memory and executive functions. Updating processes, such as those used in the *n*-back task, were used to examine the impact of increasing load on WM abilities of people with depression. They found that there was a significant impact of depression on performance accuracy at the 1-, 2- and 3-back levels of the *n*-back task.

In another study, Robertson et al. (1997) examined measures of sustained attention, which is an important part of executive control, in patients with traumatic brain injury (TBI). They found that performance on the SART (sustained attention to response task) differentiated a sample of brain injured patients from a normal control group. Further evidence from Dockree et al. (2006) reported that there was a significant impact of TBI on a dual task of sustained attention (DART). Patients had significantly more errors in both the SART and the DART than normal healthy controls. They believe that these errors reflect 'transient drifts' of controlled processing which results in a more automated response. As a result, they suggest that the PFC of the TBI patients may be less capable of managing alertness. Taking all of these findings into account, it is necessary to explore the connectivity between the MTL and PFC in more detail.

Aging is another area that has been shown to impact PFC functioning. In a study that looked at cognitive control processes between young and old healthy individuals, Braver et al. (2002) suggested that there was an underlying decline in the function of the DA system projection to PFC. As a result, this impacts cognitive control across a wide range of cognitive domains, including working memory, attention, and inhibition

1.5 Connections between the MTL and the PFC

Most of the hippocampus's neocortical inputs come from the perirhinal and parahippocampal cortices, through the entorhinal cortex, and most of its neocortical output is through the subiculum, which also projects back to the entorhinal cortex. Connections between MTL regions are hierarchically organized (Shapiro et al., 1997). As shown in Figure 1.11, below, perirhinal and parahippocampal cortices receive sensory input from various neocortical areas, such as the temporal, frontal, and parietal lobes (these regions are responsible for high level, multi-modal processing). This information is projected out to the entorhinal cortex; which supplies the major inputs to the dentate gyrus within the hippocampal formation (dendate gyrus, hippocampus, and subiculum). The dentate gyrus projects to the CA3 region of hippocampus. Within the CA3 region itself, inputs from the dendate gyrus are either projected to other neurons within the CA3, or projected into the CA1 region of hippocampus. In turn, the CA1 then projects to the subiculum, which is the main output structure of the hippocampus.

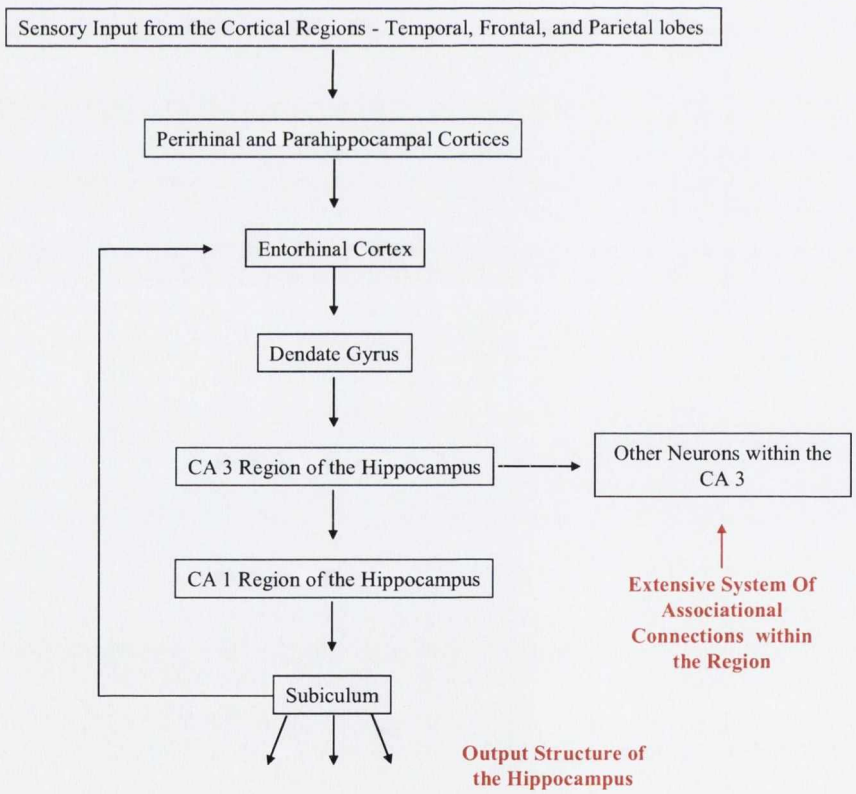

Figure 1.11: Projections into, within, and out of the MTL

Information that comes into the hippocampus will eventually fade over time; however, depending on how interested a person is in the information, then this memory may be strengthened and stored in LTM. It is through the various structures of the limbic system (the hippocampus is one of the brain structures that make up the limbic system), and their influence on the hippocampus and the temporal lobe via Papez's circuit, that this 'strengthening' takes place (see Bear et al., 2007 for more detail). Within this circuit, there are many inter-connections between that the structures within the limbic system. The diagram shown below (Figure 1.12) indicates the route that information travels within this circuit; from the hippocampus to the mammillary bodies of the hypothalamus, then on to the anterior thalamic nucleus, the cingulate cortex, and the entorhinal cortex, before finally returning to the hippocampus.

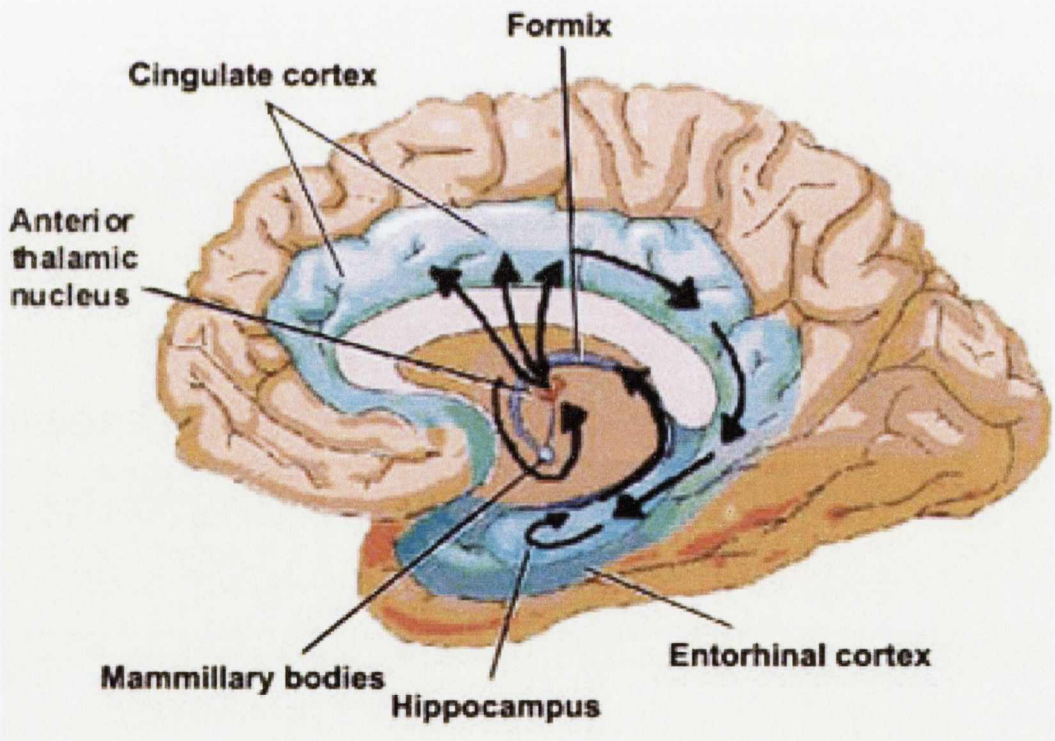

Figure 1.12: Papez's circuit, taken from http://thebrain.mcgill.ca/flash/index_a.html

Once the incoming information to the MTL has passed through this circuit a number of times it is consolidated; e.g. the association between a face and a name is strengthened, so much so that it may stabilise and become independent of the hippocampus (Shapiro et al., 1997). In this case the memories no longer pass through this circuit, but are encoded within

specific areas of the cortex: the same ones where the sensory information that created the memories was initially received (the occipital cortex for visual memories, the temporal cortex for auditory memories, etc.). In fact, there is a lot of evidence to support the idea that the PFC and the MTL are part of a distributed network of brain regions that are involved in memory (Nyberg et al., 2000); consequently, exploring the relationship between the two regions is of great importance.

1.6 Relationship between Episodic- and Working-Memory Systems

There is a lot of support in the current literature demonstrating that the PFC is crucial for the execution of strategic, goal-directed processes. While these processes may not be necessary for episodic memory, there is reason to believe that the PFC serves to increase memory formation, aid retrieval and assess the correctness of the retrieved memories. Cognitive processes, including memory, are believed to be mediated by large-scale neural networks, who's nature may be determined using functional neuroimaging techniques (Nyberg et al., 2000). Tulving (1993) (cited in Nyberg et al., 2000), proposed that in episodic memory, left prefrontal regions work together with more posterior regions during encoding, collectively these regions form lasting memory representations. Conversely, Markowitsch (1995) proposed that upon retrieval, right prefrontal regions interact with posterior regions.

The contribution of each region depends upon the type of memory process (e.g. encoding, recall or recognition), the type of material (e.g. face, name, or complex figure), and the ease of access of the information in memory. There are several methods used to examine the PFC-MTL interactions, for example anatomical disconnection studies in animals have found that the type of memory impairment found differs depending on the route of interaction between the two regions (Gaffan et al., 2002). Functional neuroimaging studies have also reported the activation of both the PFC and the MTL during memory tasks; however these studies have reported that the nature of the activation differs depending upon the demands of the task. For instance, Henson et al. (1999) found that there were different networks activated during encoding and retrieval of words, and that the magnitude of activation evident during encoding of the words predicted whether they would be recalled successfully (see also Figure 1.4 – study by Davachi et al., 2006). Simons (2003) states that, while the interactions between these two regions are apparent

during the encoding of memories, they appear to be more important during the retrieval of memories.

As free-recall episodic memory tasks require participants to tap into the strategic memory processes, damage to the frontal lobes has been shown to impair the initiation of these processes. Using a list learning task, Jetter et al. (1986) found that patients with frontal lobe lesions showed a reduced tendency to classify words semantically on measures of recall, despite being given instructions to do so. Likewise, a similar study found that patients with frontal lobe damage were impaired on levels of free recall and the use of organisational strategies (Gershberg et al., 1995). This reduction in the use of strategies was evident on tests of recall for both unrelated and related items. These findings propose that the impairments seen on measures of free recall in patients with frontal lobe lesions may be triggered, at least in part, by deficits in the use of organisational strategies.

The difficulty in finding evidence to support these theories lies in the challenge of identifying neural responses that reflect actual recovery of event information (free recall). For example, some studies that look at changes in regional cerebral blood flow correlated with successful retrieval of information have found increased activation of the medial temporal lobe (MTL) regions, including the hippocampus, with increased levels of retrieval (Nyberg, McIntosh, Houle et al., 1996). While others have found increased activity in some neocortical brain areas is associated with increased memory performance, and others have found no evidence of differential patterns of activation (Nyberg et al., 2000). Functional connectivity studies (Nyberg et al., 2000) have found evidence that supports the HERA model (hemispheric encoding/retrieval asymmetry model); which proposed that the left PFC was more engaged during encoding of episodic memory, while the right PFC was more engaged during episodic memory retrieval.

Positron emission tomography (PET) studies allow further exploration of this assumption. They have demonstrated that there is a network of common regions that are activated during encoding and retrieval, but more interestingly, have also highlighted the regions that are differentially activated during encoding and retrieval. Tulving (1997) reported that encoding activated the two hemisphere's in a similar pattern, while retrieval activated the right hemisphere to a greater extent than the left. Brassen et al. (2006) examined the network underlying free recall, recognition and forgetting, they found that there was a linear increase in activation from forgetting words, to recognising previously seen words,

to free recall of previously seen words. The hippocampus was activated more during the encoding of subsequently recalled words than forgotten words, while there was no increase for words that were later recognised. While this may reflect differences in the strength of the memories, there could be different networks that are activated during recall and recognition. In contrast, the PFC was most active during the encoding of words that were later recognised then recalled. All of these findings support that idea that there are strong networks linking the PFC and the MTL, the activation of which depends upon the many factors discussed.

1.7 Impetus for the Current Studies

There is considerable evidence to support the relationship between MTL and PFC functioning. Numerous studies have highlighted the neural connections between the two regions, and investigated the input that each region plays in the cognitive functions of the other. While this research has provided considerable insight into the nature of this relationship, the impact of disease and age-related degeneration is less clear. Using a hypothyroid group and a normal healthy comparison group, the present study aims to investigate the impact of hypothyroidism, on MTL and PFC functioning.

A breakdown of the endocrine system can have widespread effects on the body and brain. Hypothyroidism is one example of such a breakdown, and is associated with symptoms which include weight gain, dry skin, cold intolerance and excessive fatigue (Tremont et al., 2000). The endocrine system exerts widespread effects on growth, development, and metabolism; as a result thyroid hormones affect neuronal processing and integration, myelination and glial cell proliferation (Bauer et al., 2002). Despite this, there has been little research conducted on the cognitive deficits associated with hypothyroidism. However, findings form basic research has provided support for the neuropsychological examination of hypothyroidism. Firstly, thyroid hormones are widespread throughout the brain, especially in the amygdala and the hippocampus (Ruel et al., 1985; cited in Bauer et al, 2002). In addition, thyroid hormones have also been detected in high concentrations in cortical areas (Campos-Barros et al., 1996; cited in Bauer et al, 2002). As a result, hypothyroidism has been shown to alter cell numbers, structure and function in the hippocampus and other brain regions in animals, as thyroid hormones are active in regions that subserve memory (Samuels et al., 2007a). These findings would support the hypothesis that adult onset hypothyroidism may be linked to decreased cognitive

functioning in associative- and working-memory tasks that have been associated with the MTL and PFC regions.

However, on the basis of the well known effects of myxedema on neuropsychiatric functioning (Baldini et al., 1997), recent studies have examined the possibility of cognitive dysfunction in even mild forms of hypothyroidism. Normal thyroid functioning plays a critical role in cognitive performance, especially during aging, when the brain becomes increasingly reliant upon hormones and increasingly sensitive to changes in thyroid function (Loosen, 1992; cited in Bono et al, 2004). Neurologically, hypothyroidism has been shown to be related to memory impairment, hallucinations, confusion, psychotic behaviour, and cerebellar ataxia (Bono et al., 2004; Smith et al., 2002). In adults, hypothyroidism has been shown to interfere with memory, concentration, attention and executive functioning, as well as being associated with increased levels of depression and anxiety (Constant et al., 2005). Rivas et al. (2007), state that there is an association between cognitive deficits in hypothyroidism and biochemical and biophysical alterations in the hippocampus. Using electroencephalography (EEG), Khedr et al. (2000) reported that the central nervous system was affected in 78% of their hypothyroid patients. They suggest that hypothyroid patients, even those who are asymptomatic, should undergo electrophysiological studies.

As it is standard practice to treat hypothyroidism with a synthetic thyroid replacement drug, examining whether there is a recovery of function may offer some insight into the impact of hypothyroidism on the brain. Research has found that the brain continues to reorganise itself, by forming new neural connections throughout life. As stated previously, the brain regions are interconnected, and learning may happen through changing the strength of the associations of memories within these regions, by adding or removing connections, or by adding new cells. The expectation is that following treatment, patient's baseline, pre-treatment cognitive impairments would attenuate, allowing an examination of functional recovery in hypothyroidism (Samuels et al., 2007a).

Considering that thyroid dysfunction increases with age, that elderly patients can often present with problems resembling an early dementia (Haupt et al., 1993), and that a history of thyroid dysfunction has been suggested to be a risk factor of developing Alzheimer's disease (Bono et al., 2004), neuropsychological assessment of patients that present with hypothyroidism is warranted. According to Dugbartey (1998), changes in neurocognitive

status associated with hypothyroidism are often overlooked by clinicians; he states that "every individual diagnosed as having this disorder should be referred for comprehensive neuropsychological evaluation in view of the strong risk for cognitive morbidity" (p. 1416). This study allows the opportunity to investigate these deficits in more detail. In addition, this patient population provides an extremely interesting opportunity to examine the "reversible dementia" associated with hypothyroidism and its treatment.

Nonetheless, the group of patients included in the thyroid studies vary considerably in age, from 21 to 64 years of age. Considering the impact that age alone has on the brain in normal healthy adults, it is likely that there may also be age-related impairments that influence cognitive functioning in this group. Consequently, it is important to examine the nature of the impact of age, and identify whether hypothyroid-related impairments remain above the effect of age.

Finally, investigating cognitive dysfunction in normal aging will add weight to these results. As the PFC is particularly sensitive to age-related changes, investigating age-related changes to PFC functioning will allow further differentiation between the thyroid-induced impairments. In addition, by including tests that have been associated with MTL regions, it is possible to examine the relationship between these two regions and establish whether this relationship changes differentially across the lifespan. Long-term, lifespan studies that look at a range of cognitive abilities, using a range of techniques, are needed to bring together much of these findings. However such studies are extremely costly and time consuming; by focusing on a large scale, cross sectional study, that includes people from all educational backgrounds, more consistency may be possible, ultimately bridging some of the gaps in the current literature.

In summary, there are three studies that will be discussed; the first one investigates pre-treatment impairments in hypothyroidism and the impact that age has on these impairments, the second determines whether there is a functional recovery of these cognitive impairments following treatment, and the third one draws on the findings of both of these to identify age-related impairments that are present in a healthy population.

Chapter 2

Examining the Effects of Untreated Thyroid Dysfunction on Cognitive and Affective Measures in Subclinical and Overt Hypothyroidism

2.1 Summary

The effects of inadequate thyroid hormone (hypothyroidism) availability on cognitive function and brain activity have been long debated and are still not clearly understood. The hippocampus is a thyroid hormone rich region within the medial temporal lobes, which has been implicated in the hypothyroid-induced cognitive deficits in memory. In the present study, baseline assessments of the neurocognitive function of hypothyroid participants, prior to hormone-replacement treatment, were compared to control participants using several declarative memory tasks, such as the Face-Name memory task (Zeineh et al., 2003). Given that executive functions, particularly working memory, underlies many cognitive functions, we also used the *n*-Back task (Meyer-Lindenberg et al., 2001), among others, to determine if there were deficits in tasks that have been associated with prefrontal cortex functioning in hypothyroidism. The results confirmed the presence of specific, memory deficits in tasks that have been associated with hippocampal functioning in hypothyroidism, and suggested that these deficits impacted WM deficits. This chapter examines the effects of hypothyroidism on several neurocognitive and neuropsychological measures, and builds upon previous literature. It aims to identify specific impairments associated with memory in hypothyroidism, and to determine if age has an impact on these impairments.

2.2 Introduction

The presence of cognitive dysfunction associated with untreated hypothyroidism has been debated for many years. Results from previous research have proven difficult to interpret as conflicting findings suggest the impairment of different types of memory functions; some studies have reported deficits in WM (Zhu et al., 2006) while others have reported deficits in verbal memory (Miller et al., 2007). While thyroid hormone insufficiency has been shown to interfere with cognitive function in some patients, not all patients develop cognitive difficulties. However, in those subjects that do develop cognitive impairments, some studies suggest that the cognitive dysfunction can be so severe it is defined as "reversible dementia" (Haupt et al., 1993). As a result, this group provides an interesting opportunity to look at adult onset cognitive dysfunction and the possible reversibility of this dysfunction through treatment. In addition, the study may offer some support for researchers who suggest that people with an underactive thyroid glad should be referred for neurocognitive assessment (see Dugbartey, 1998). Consequently, understanding the processes involved in hypothyroidism is of importance.

There is a lack of research into the effects of hypothyroidism on the brain (Gerges et al., 2004) and the subsequent improvement in cognitive functioning following thyroxine therapy (Wekking et al., 2005). Numerous researchers have attempted to identify and isolate the pattern of cognitive impairments associated with hypothyroidism; however many studies have failed to get a clear representation of the cognitive deficits attributed to this disease. There are several reasons for this: small sample size, no control group comparisons, no pre- and post- treatment comparisons, and an inadequate number of neuropsychological tests utilised (Bono et al., 2004; Samuels, 2008). The present study aims to overcome many of these problems by using a relatively large sample size, looking at pre- and post- treatment cognitive profiles, including a control group for comparison, and employing a large battery of neuropsychological tests in order to get a more comprehensible depiction of the specific deficits associated with untreated hypothyroidism, and ultimately classifying a model of hypothyroid dysfunction. Subsequently, an assessment of the treatment effects of hypothyroidism will be presented, in which the debate about functional recovery will be addressed.

2.2.1 Background to Thyroid Dysfunction

Endocrine dysfunction, such as hypothyroidism, results in signs and symptoms that can affect many organs of the body, including the brain (Oatridge et al., 2002). When the thyroid gland is underactive, improperly formed at birth, surgically removed all or in part, or becomes incapable of producing enough thyroid hormone, a person is said to be hypothyroid. Symptoms of hypothyroidism normally include a slowdown in metabolism, fatigue, weight gain, feeling of being cold much of the time, brittle hair and nails, difficulty concentrating and depression. The disease affects both sexes and all ages, however; middle-aged women are most vulnerable (Roberts et al., 2004). About 1 in 50 women and about 1 in 1000 men develop hypothyroidism at some time in their life (Tunbridge et al., 2000), while about 8 in 100 women and 3 in 100 men will develop subclinical hypothyroidism (Lazarus, 2007).

Diagnosing thyroid disease is a process that can incorporate numerous factors, including clinical evaluation, blood tests, imaging tests, and biopsies. Since hypothyroidism is caused by too little thyroid hormone secreted by the thyroid, the diagnosis of hypothyroidism is normally first based upon measuring the amount of thyroid hormone in the blood; these tests measure the amount of TSH (Thyrotrophin-Stimulating Hormone), T3 (free Triiodothyronine), and T4 (Thyroxine) in the bloodstream. The production of T4 and T3 is regulated by TSH, released by the anterior pituitary, and cells of the brain are a major target for T3 and T4 (Kester et al., 2004). In the cells and tissues of the body T4 is converted to T3. In turn, this T3, along with T3 that is secreted from the thyroid gland, which is biologically active and influences the activity of all the cells and tissues of the body (Kester et al., 2004). The function of the thyroid therefore is to regulate the body's metabolism (Smith et al., 2002).

The classification of hypothyroidism is based on when it developed (congenital or acquired), the level of endocrine dysfunction (primary or secondary), and its severity (overt [clinical] or mild [subclinical]) (Roberts et al., 2004). The present study includes people with both clinical and subclinical acquired primary hypothyroidism. The distinction between hypothyroidism and subclinical hypothyroidism (SCH) is normally defined biochemically, with SCH patients displaying normal T4 levels and elevated TSH levels, while the hypothyroid patients display lowered T4 levels and elevated TSH levels. TSH levels that are elevated or above normal are considered indicative of hypothyroidism (normal reference range: TSH 0.4 – 4 mU/l). Free T3 measures the free, unbound levels of

T3 in the bloodstream and is considered more accurate than Total T3. Free T3 is typically lowered in hypothyroidism (normal reference range: 4.5 – 6.5 mU/l). Free T4 measures the free, unbound T4 levels in the bloodstream. Free T4 is typically lowered in hypothyroidism (normal reference range: T4 10 – 25 pmol/l). Because the free levels of T4 represent immediately available hormone, free T4 is thought to better reflect the patient's hormonal status than total T4.

According to Bauer et al. (2008), the most frequently occurring thyroid diseases in adulthood are autoimmune disorders, thus, the most common type of hypothyroidism is autoimmune (Hashimoto's) thyroiditis. Other types of hypothyroidism include acquired primary hypothyroidism resulting from thyroid injury, surgery or irradiation, and secondary hypothyroidism which is acquired as a consequence of a disease that interferes with thyrotrophin-releasing hormone (TRH) (Roberts et al., 2004). Hypothyroidism is usually treated with synthetic thyroid hormone replacement therapy (LT4).

2.2.2 Hypothalamic-Pituitary-Thyroid Axis

The endocrine system is responsible for the internal secretion of a number of biologically active substances and hormones into the blood stream, including the thyroid hormones T3 and T4. These thyroid hormones effect oxygen consumption and changes in metabolism, among other things (Smith et al., 2002). Neuroendocrinology deals with the interactions between the endocrine system and the nervous system, including the brain. In particular, the hypothalamic-pituitary axis, which plays a key role in these interactions; the hypothalamus is responsible for releasing TRH (Thyrotrophin-Releasing Hormone), this results in the release of TSH from the pituitary gland, which in turn, stimulates the release of T3 and T4 from the thyroid gland (see Figure 2.1).

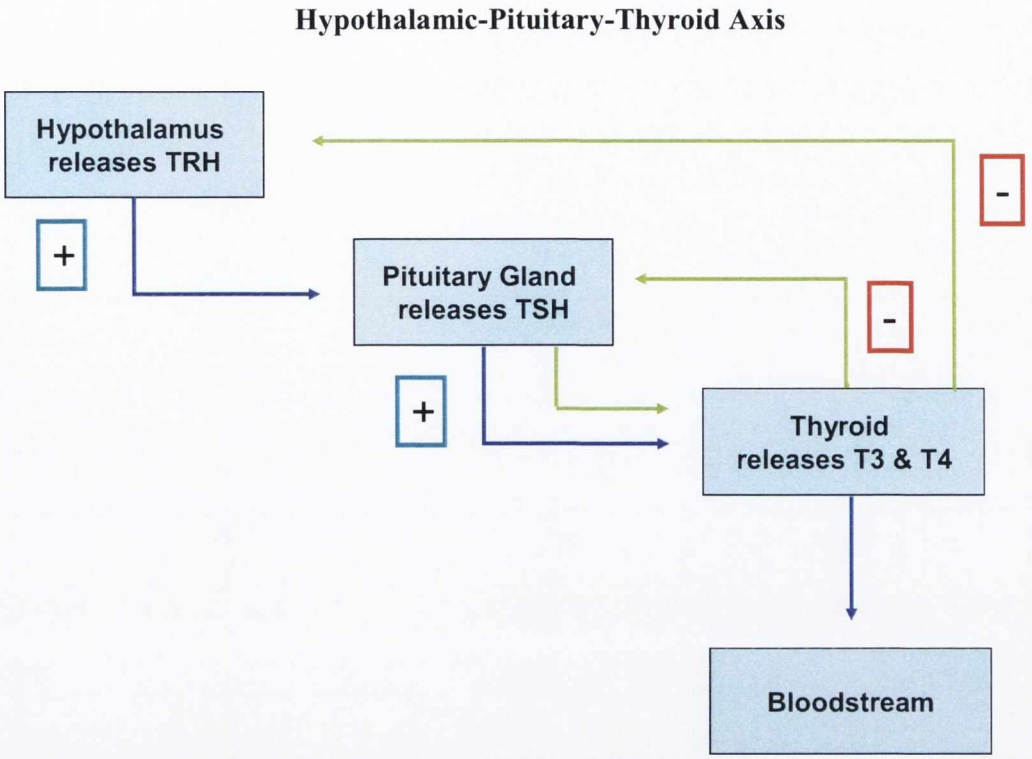

Figure 2.1: TSH levels in the bloodstream rise or fall depending on whether enough thyroid hormone is produced to meet your body's needs. Higher levels of TSH prompt the thyroid to produce more thyroid hormone. Conversely, low TSH levels signal the thyroid to slow down production. The pituitary gland gets its information in several ways. It is able to read and respond directly to the amounts of T4 circulating in the blood, but it also responds to the hypothalamus, which is a section of the brain that releases its own hormone TRH. TRH stimulates TSH production in the pituitary gland. Blue lines indicate the positive relationship and the green lines show the Negative Feedback Loop between the thyroid and the pituitary gland.

The ratio of T4 to T3 secretion in humans is 14:1, and while T4 is produced entirely by the thyroid gland, most circulating T3 is derived by the break-down of T4 in non-thyroid tissues, such as the kidneys and liver (Smith et al., 2002). Once the thyroid hormones enter the brain, they bind with the T3 and T4 receptors that are located throughout the brain, particularly in areas responsible for higher-level cognitive functioning and mood (e.g. PFC and hippocampus) (Davis et al., 2007).

Any alteration in structure, function, and behaviour, as a result of thyroid dysfunction, highlights the role of these hormones in normal development and function, especially of the CNS. Animal studies that have examined the effects of knocking out thyroid hormone genes in mice (TRα $^{-/-}$ mice), found abnormalities in open field and fear conditioning tests, with TRα $^{-/-}$ mice exploring less and freezing more compared to wild type mice (Guadano-Ferraz et al., 2003). Since TRα has been shown to be widely distributed in the amygdala

and hippocampus, Guadano-Ferraz et al. (2003, cited in Bauer et al., 2008) have proposed a role for TRα in hippocampal structure and function and implied that TRα $^{-/-}$ mice display signs of a dysfunctional hippocampal circuitry .

2.2.3 Memory, the Medial Temporal Lobes, and the Pre Frontal Cortex

Research on the action of thyroid hormones in the adult brain has become more prevalent with the advent of improved methods of investigation. Thyroid hormone receptors are prevalent in the adult brain, with the highest biological activity in the younger brain regions, such as the amygdala and the hippocampus, and lower densities in the brain stem and cerebellum (Bauer et al., 2002). While the hippocampus, a thyroid hormone rich region has been implicated in the hypothyroid-induced cognitive deficits in memory, it is also important to look at other structures that are critical for memory, and examine the links between these structures and the hippocampus. The prefrontal cortex (PFC) and hippocampus are two brain structures that are important for learning and memory (Squire, 1992). The role of the hippocampal formation (HF) in learning and memory is continuously under review; it plays a role in declarative memory and is crucial for the encoding and formation of memories. Working memory and other such higher cognitive functions are associated with the PFC. Consequently, understanding the connections between the two regions is of great and ongoing importance as "brain function is characterised by both regional differentiation of function and the necessity to coactivate functionally appropriate cooperative networks for all but the most trivial of tasks" (Meyer-Lindenberg et al.., 2001, p. 1809)

In rodent models, studies have shown that the hippocampus sends projections to the medial PFC (mPFC) (Conde et al., 1995, cited in Sui et al, 2006). Consequently, this pathway has been investigated as an important model of communication between the two regions (Sui et al., 2006), particularly as it is considered to play a critical role for higher cognitive functioning (Laroche et al., 2000). Given that the hippocampus displays a selective vulnerability to adult hypothyroidism (Calza et al., 1997), Sui et al. proposed that this may affect the hippocampal-MPFC pathway. Therefore, cognitive impairments associated with hypothyroidism may be related to the changes within this pathway. Sui et al. (2006) reported that, in hypothyroid induced adult rats, long-term potentiation (LTP) was inhibited not only in the hippocampus, but also in the pathway between the hippocampus and the MPFC. Additionally these inhibitions were rescued by a return to the euthyroid status with T3 replacement. This would imply that the impairments in LTP were associated

with the decrease in thyroid hormones. These findings support those from previous studies that found similar LTP inhibition in the hippocampus (Gerges et al., 2004). While generalisations to connections between the MTL and PFC in humans cannot be made, rodent models do provide an excellent opportunity to examine relationship between the two regions in great detail.

2.2.4 Memory Dysfunction in Hypothyroidism

As discussed below, thyroid dysfunction has been associated with several cognitive impairments in humans, such as, visual-spatial skills, memory, and psychomotor speed, while motor skills, sustained attention, and language appear to be spared (Burmeister et al., 2001; Dugbartey, 1998; Osterweil et al., 1992). Researchers now seem to be leaning towards focusing on the specific deficits associated with thyroid dysfunction. In particular, the role of thyroid dysfunction in changes to associative- and working-memory task performance, which has been examined in both SCH and hypothyroidism. However, there is still debate as to the presence of cognitive impairments in SCH and the need to treat SCH (Zhu et al., 2006). Some researchers believe that SCH and hypothyroidism exist on a continuum (Davis et al., 2007; Gharib et al., 2005; Samuels, 1998), and that the presence of SCH will lead to an eventual diagnosis of hypothyroidism. As a result, they suggest that SCH should be treated to prevent the development of overt hypothyroidism (Owen et al., 2003). In contrast, other researchers reported that there were no clinically relevant benefits following 6 months of treatment for SCH (Kong et al., 2002), and suggest that in those with SCH, treatment is seldom necessary (Chu et al., 2001).

2.2.4.1 Subclinical Hypothyroidism

Although there is little debate that hypothyroidism is associated with cognitive impairments, with some researchers going as far as to suggest that severe hypothyroidism is considered a form of treatable dementia (Delaney, 1982), there are still those who question the impact of SCH on cognitive functioning (Davis et al., 2007). Those diagnosed with SCH are usually asymptomatic, though some have reported weight gain, fatigue and memory loss (Bono et al., 2004). Research by Samuels et al. (Samuels et al., 2007a, 2007b) focused on memory changes in SCH, as memory has been shown to be affected in patients with SCH (Baldini et al., 1997; Jaeschke et al., 1996). They tested three types of memory; declarative memory (associated with medial temporal lobe functioning, MTL), working memory (associated with PFC functioning) and motor learning (associated with cerebellum and basal ganglia functioning). They also included measures of health status

and mood as they can affect cognition. Their results indicated that there were significant differences present in patients with SCH on measures of working memory, including the *n*-back task and the subject ordered pointing task, which they argue are direct effects of the altered thyroid status. While these effects were small, Samuels et al. (2007b) claim that they are clinically relevant. However, there were no differences on the measures of declarative or motor learning. A correlation between working memory decrements and changes in T4 levels was also found, which, they suggest, supports the concept that SCH exists at a point on a continuum, with normal thyroid function on one end and overt hypothyroidism on the other. Baldini et al. (1997) also found impairments in SCH, with an overall decrease in memory performance, and significant differences present on logical memory scores. However neither Jorde et al. (2006), nor Bono et al. (2004) found any significant differences in SCH on cognitive measures as a result of thyroid dysfunction. Jorde et al. found that, while the control subjects had an overall higher composite cognitive score, differences between the control and SCH groups were not significant. They suggested that the reason for this was that the SCH patient's TSH levels were not raised above 10mIU/l

Few studies have investigated thyroid-associated cognitive deficits using fMRI, and given that working memory is considered essential for many cognitive functions (Zhu et al., 2006), investigating the cognitive control processes involved in WM, and determining the nature of these deficits using fMRI in hypothyroidism may clarify some of the arguments surrounding the SCH debate. WM refers to the short-term storage, and online manipulation of information (Baddeley, 1992), and working memory tasks often require people to hold information in short-term memory while performing a mental operation of some description. One such task is the *n*-back task, which is widely used to investigate the neural substrates of WM (Nystrom et al., 2000). In healthy subjects, the *n*-back task reveals a load effect, with different neural responses evident at different levels of the *n*-back task; therefore researchers can use this load effect to determine whether or not the cognitive control-related areas of the brain are functioning properly in hypothyroidism and SCH.

Zhu et al. (2006), examined working memory performance in euthyroid, hyperthyroid and SCH subjects. Performance accuracy of the SCH group was significantly worse in the 2-back condition. There was a common network of activation seen across all subjects; this network included the bilateral middle/inferior frontal gyri (M/IFG), the bilateral dorsolateral PFC (DLPFC), the bilateral pre-motor areas (PreMA), the supplementary

motor area/anterior cingulate cortex (SMA/ACC), and the bilateral parietal areas (PA). This is consistent with previous findings, that have found activation in these differential but interacting regions in the WM *n*-back task (Nystrom et al., 2000). Region-of-interest analyses were then conducted to determine if there was an *n*-back load effect. SCH patients only exhibited a load effect in the PA and the PreMA, unlike the control group who exhibited a load effect in the frontal and PA regions. Zhu et al. (2006) implied that executive functioning of WM was impaired in the SCH group. However it is important to note that they only found differences in WM, the SCH groups performed at control levels on all other measures examined (e.g. associative memory, orientation, and visual reproduction among others).

2.2.4.2 Hypothyroidism

While the debate surrounding the presence of cognitive impairments in SCH continues, there is little debate as to the presence of thyroid-related impairments in overt hypothyroidism. Miller et al. (2007), studied the effects of untreated hypothyroidism on verbal memory, visual memory, attention, and executive functioning, and also included measures of mood status. They found that hypothyroid patients had a significant decrease on their ability to retrieve information after both a short- and long-term delay in the verbal test in comparison to control participants. Interestingly, this group also scored higher on measures of depression. A previous study conducted by Miller et al. (2006), also found verbal memory deficits in hypothyroidism, which improved with treatment. Taken together, these findings would suggest that there is a specific impairment in verbal memory in hypothyroidism, which is reversible with treatment.

Burmeister et al. (2001), also found that there were impairments in verbal memory in patients with hypothyroidism. While this deficit did not affect verbal learning or immediate recall, they did find that hypothyroidism was associated with a decrease in retrieval from memory, and that those with hypothyroidism scored significantly higher on the Beck Depression Inventory (BDI). In this case, the memory deficits were specific to the dysfunction of tasks that have been associated with the hippocampus, which is rich in thyroid hormones. However, there were no differences in executive functioning as measured by the Stroop task, though this may be due to the fact that they used a pen and paper version of the task, making it more difficult to measure reaction times. Using a computerised version of the Stroop task, Constant et al. (2005) found that there were significant differences in reaction times, in the hypothyroid group, in comparison to the

control group, especially on the incongruent trial; they suggested that those with hypothyroidism have greater difficulties using their capacities of inhibition. The presence of the cognitive impairments needs to be interpreted with caution as hypothyroid patients normally display higher levels of depression and anxiety in comparison to control subjects; this matter warrants further investigation.

2.2.5 Relationship between Hypothyroidism and Depression

According to Davis and Tremont (2007), there is an association between hypothyroidism and an increased susceptibility to depression; especially as many of the limbic systems that are involved in depression are rich in thyroid hormones (Bauer et al., 2008). A reduction in thyroid hormones was reported to slow serotonergic neurotransmission, which is associated with depression. The importance of the link between thyroid function and psychiatric disorders is also supported by research that has used TH to treat psychiatric disorders (Bauer et al., 2003). Behavioural results found a significant relationship between TSH levels and hypothyroidism using the BDI (Cleare et al., 1995). In addition, there has also been a link between SCH and depression, with an increased prevalence of depression evident in patients suffering from SCH (Haggerty et al., 1993), suggesting that SCH enhances the risk of depression. However, not all studies reported similar findings; Aslan et al. (2005) found no relationship between hypothyroidism and depression using the Hospital Anxiety and Depression Scale (HADS), and Baldini et al. (1997) found that there was no presence of depressive or anxious symptoms in patients with SCH. So while most studies have found a link between depression and thyroid dysfunction, the relationship between the two remains unclear. Jackson (1998) suggests that the two may not be mutually exclusive disorders; hypothyroidism may result in depressive symptoms, and people who are suffering from depression may have altered thyroid functioning.

2.2.6 Relationship between Hypothyroidism and Stress

The function of the hypothalamic-pituitary-thyroid axis has been reported to be associated with several psychiatric disorders, such as depression and anxiety (Aslan et al., 2005); however, there have been few studies that have examined the effects of stress on thyroid functioning and thyroid-induced cognitive impairments. As low levels of TSH are associated with increased levels of steroid hormone within the hypothalamus-pituitary-adrenal axis, elevated levels of cortisol (which is part of this system) may result in the loss of cells within the hippocampus and in turn negatively effect episodic memory performance (Wahlin et al., 1998). As both Hypothyroidism, and stress have been shown

to diminish health and increase susceptibility to mental disorders; it is important to establish if there is a co-occurrence of stress and hypothyroidism, and if this results in a greater impairment to health and cognitive functioning (Gerges et al., 2004). Previous studies have found that stress in aged rats and humans has a deleterious effect on the hippocampus, probably due to the increased levels of glucocorticoids (McEwen, 1999).

Hypothyroidism is also associated with increased concentration of cortisol (Cleare et al., 1996). It may be that in stress and hypothyroidism, there is a potentiation of the same mechanism or pathway, which in turn impairs memory, and the co-occurrence of both would lead to a greater impairment in memory (Gerges et al., 2004). Gerges et al. found that the combination of stress and hypothyroidism resulted in a greater impairment in memory than either condition alone. The rats that were stressed showed impaired short-term memory but normal learning, while those who were hypothyroid showed a delay in learning ability and an impairment in short- and long-term memory. However, those who were both stressed and hypothyroid displayed a greater impairment in short- and long-term memory than either condition alone. Although the two conditions are different, it is believed that they both affect hippocampal functioning, which in turn results in impaired memory functioning.

2.2.7 Hypothyroidism and the Effects of Aging

While the prevalence of hypothyroidism is known to increase with age (Elliott, 2000), little is known about the effects of hypothyroidism on the adult brain, and the age at which it will have the most impact on cognitive functioning (Tong et al., 2007). Correct thyroid functioning has been said to play a crucial role in cognitive functioning, especially during aging, when the brain has been reported to become more reliant upon hormonal levels and more susceptible to changes in thyroid function (Davis et al., 2003; Loosen, 1992). Perhaps it is possible that hypothyroidism induces an age- and task-dependent impairment of memory. Several studies looking at normal elderly adults found that hypothyroidism was not associated with cognitive impairment (Gussekloo et al., 2004; Jorde et al., 2006), while others found that older adults were more vulnerable to the hypothyroid state than younger adults (Dugbartey, 1998). In contrast, Tong et al. found that the deficits in odour memory and spatial consolidation were more impaired in young hypothyroid mice (2 months) than older hypothyroid mice (15 months) (2007). Taking all of this into account, studies should include an examination of the interaction between age levels, thyroid-induced cognitive impairments, and mood disorders. If there is an age effect of hypothyroidism, then older

adults with cognitive impairments should be checked for thyroid status (Hogervorst et al., 2008).

2.2.8 Conclusions from the Current Literature

One thing that researchers do seem to agree upon is that there is a lack of cohesion in the current literature. According to Constant et al. (2005), the reason for the discrepancy in cognitive deficits and mood disorders, as a result of thyroid dysfunction, reported in the literature is methodological bias. Not all studies used a sufficiently large enough age- and education- matched control group, practice effects for repeated sessions may not have been accounted for, and some of the tests used were insufficiently sensitive enough to measure the cognitive impairments related to hypothyroidism. Furthermore, while several of the studies found an association between cognitive deficits and depression, many of which were discussed here, very few have identified whether the deficits are due solely to the hypothyroid state, or a combination of hypothyroidism and accompanying depression.

It is important to examine the neurocognitive changes associated with both overt and subclinical hypothyroidism. According to Dugbartey (1998), most published reports on hypothyroidism have only focused on limited aspects of cognitive domains. An examination should not be restricted to tests that measure hippocampal functioning, but also include areas of the brain that are linked to the hippocampus, such as the PFC, and tests that can assess if changes seen are due to memory deficits, or problems with other functions such as attention, that could ultimately impact on memory functioning. In addition, caution should be taken to ensure that impairments are not due to differences on measures of depression, anxiety, or stress. Preliminary results have indicated that there is a significant difference between hypothyroid patients and controls at baseline on a number of measures including the HADS, the Rey complex figure test, the Face-name task, and Rivermead Behavioural memory test. Deficits begin to return to normal levels within 3-6 months of treatment (Correia et al., 2009). The hypotheses for the present study are outlined below.

2.2.9 Hypotheses

1. There maybe deficits in associative memory in patients with an underactive thyroid gland in comparison to control subjects; these deficits are probably more pronounced in those who are hypothyroid in comparison to those who are subclinical.
2. There maybe deficits in verbal memory in patients with an underactive thyroid gland in comparison to control subjects; these deficits are likely to be more pronounced in those who are hypothyroid in comparison to those who are subclinical.
3. There maybe deficits in working memory in patients with an underactive thyroid gland in comparison to control subjects; these deficits are likely to be more pronounced in those who are hypothyroid in comparison to those who are subclinical.
4. There maybe differences in executive functioning between the groups.
5. That there maybe differences in measures of attention across the groups.
6. There are differences in scores on affective measures between the groups, with those who are hypothyroid likely to score higher than subclinical participants.

2.3. Methods

2.3.1 Participants

Prospective participants were identified from their medical records having attended the Diabetes Clinic in the Adelaide & Meath Hospital, incorporating National Children's Hospital (AMNCH), Tallaght, which specialises in several endocrine conditions including hypothyroidism. Participants' suitability was based on the evaluation of their blood test results, looking specifically at their T4 and TSH levels. Exclusion criteria included a previous history of ischemic heart disease, stroke, diabetes, head injury, epilepsy, psychiatric illness, significant visual impairment, or pregnancy. Care was taken to avoid testing during periods of significant stress (e.g., death of relative). All study subjects gave their written signed consent to the study, which was approved by the Research Ethics Committee of the School of Psychology, Trinity College Dublin and the Research Ethics Committee of the Adelaide and Meath Hospital and St. James's Hospital (Dublin, Ireland) (a copy of the consent form and the ethics approval letter are in the Appendix I).

Potential participants were contacted by phone call from Dr Neuman Correia (following GP consent) and gave full and informed consent to take part in the study. Two participant groups were formed, a subclinical hypothyroid group (normal free T4 (>11 pmol/l) with elevated TSH (>4 mU/l)) and a hypothyroid group (low free T4 (<11 pmol/l) and elevated TSH (> 4 mU/l), there was also a control group recruited from the local community (normal T4 (11-25 pmol/l) and normal TSH 0.4-4 mU/l). No restrictions were placed on the severity of the patients thyroid failure (i.e. there was no limit set on TSH levels).

2.3.1a Sub-Clinical Hypothyroid Group

This group consisted of 36 out-patients with SCH. The mean age of this group was 50 years and ranged from 24 to 64 years.

2.3.1b Hypothyroid Group

This group consisted of 51 out-patients with hypothyroidism. The mean age of this group was 41 and ranged from 21 to 61 years.

2.3.1c Control Group

A total of 32 participants were recruited from the local community who did not have a known history of brain injury or a medical condition that would affect the results. The mean age of this group was 42 years and ranged from 25 to 61 years.

2.3.2 Experimental Design & Neurocognitive Battery

At diagnosis, an experimental battery of neurocognitive and neuropsychological tests were performed, lasting approximately 2 hours (including an optional 5 minute break after the Sustained Attention to Response Task). LT4 was prescribed as an initial dose of 50 µg/day and subsequently titrated depending on TSH levels (a blood test was routinely carried out 6 weeks post-baseline to ensure the TSH and T4 levels were beginning to return to normal, and at every testing session – adjustments to medication were made as necessary throughout the study depending on these levels).

2.3.3 Neuropsychological Assessment

A comprehensive neuropsychological assessment battery was administered to all participants at baseline. The assessment had two primary aims. Firstly the assessment of declarative memory function (primarily associated with MTL functioning) and secondly the evaluation of executive function (primarily associated with PFC functioning) using both standardised and novel tests as described below. Comparisons were made between groups at baseline in order to identify and elucidate the specific neuropsychological difficulties associated with SCH and hypothyroidism.

Declarative memory (HF) functioning was investigated using several standardised tests as well as some new measures: novel neuropsychological tests included the mundane memory questionnaire (MMQ) (Mangaoang et al., 2004) and Self Rating Scale (SRS). Other tests that are used include the following: Rey-Osterrieth Complex Figure (ROCF) (Osterrieth, 1944; Rey, 1941), Modified Taylor Complex Figure (Hubley et al., 2006), California Verbal Learning Test (CVLT II) (Delis et al., 2000) and the Everyday Memory Questionnaire (EMQ) (Sunderland et al., 1984).

In line with the second aim, several tests were included that concentrated on executive (PFC) functioning: primarily the Behavioural Assessment of the Dysexecutive Syndrome (BADS) test battery (Wilson et al., 2003) which includes items specifically sensitive to the

skills involved in problem solving, planning, and organizing behaviour over an extended period of time. There were also several standardised tests included.

In addition to this there were also several computerised tasks which examined declarative memory and executive function, for sustained attention, memory, and concentration. These included: Face-Name Task (Zeineh et al., 2003), Stroop Task (Stroop, 1935), N-Back Task (Meyer-Lindenberg et al., 2001), Sustained Attention Response Task (Robertson et al., 1997) and the Dual Attention Response Task (Dockree et al., 2006).

The NART (National Adult Reading Test) (Nelson et al., 1991) was also used to identify an estimate of premorbid IQ (Intelligence Quotient) levels and a number of tests which examined the effects of depression, anxiety and stress on the participants were included: HADS (Zigmond et al., 1983), BDI- II (Beck et al., 1996), and the Perceived Stress Scale (PSS) (Cohen et al., 1983). Administration time for each battery was no longer than two hours. All computerised tasks were programmed using E-Prime 1.2 (Psychology Software Tools, Pittsburgh, PA) installed on a Dell Latitude X1 Laptop (screen 26 cm x 16 cm). Participants were positioned approximately 60 cm from the screen for all experiments.

2.3.3.1 Declarative Memory Tests

2.3.3.1a Visual Memory: The Rey-Osterrieth Complex Figure (ROCF)

The RCFT was designed to measure visuospatial ability and visuospatial memory (Meyers, 1995). It was designed by Rey (Rey 1941) and elaborated by Osterrieth (Osterrieth, 1944). It consisted of a 2-dimensional line drawing containing 18 details such as lines, squares, crosses, and triangles. The version used in the present study consisted of four sections; copy, immediate recall, delayed recall (20 minutes later) and recognition trial (15 minutes later). The recognition trail was designed to evaluate the contributions of encoding, storage and retrieval to memory performance (Meyers, 1994). Participants were not forewarned when given the copy instructions that they would have to reproduce the figure from memory. There was a short-delay (2 minutes) and a long-delay (20 minutes) recall, in addition to a further delayed recognition test.

Procedure

For each of the drawing sections of the RCFT the participant was instructed as follows.

Copy - The figure was placed on the table on front of the participant and the instructions were given: "I am going to show you a card on which there is a design that I would like you to copy on this sheet of paper. Please copy the figure as carefully and as accurately as you can. If you think you have made a mistake, don't erase it, just correct whatever you think is wrong".

Immediate recall - The figure was taken away and the participant was given the following instructions: "I am going to ask you to redraw the figure you have just seen on this sheet of paper. Please draw it as carefully and completely as you can. If you think you have made a mistake, don't erase it, just correct whatever you think is wrong".

Delayed recall - After an approximately 20 minute delay the participant was asked to draw the figure again having been given the following instructions: "Do you remember the design I had you copy and draw a little while ago? I would like you to draw it again from memory as carefully and completely as you can on this sheet of paper. Again if you think you have made a mistake, don't erase it; just correct whatever you think is wrong".

At each stage they were given a sheet on which to draw the figure. The participant then had to complete a recognition trial in which 24 items were presented. They had to indicate whether each item was a part of the original figure they had seen (12 were from the original drawing and 12 were new lines drawings).

Scoring

A detailed outline of the scoring for the copy, immediate recall and delayed recall, as well as recognition of the RCFT is given in the appendix (Appendix II). Briefly; the marks for the RCFT are given for both correctness of the details of the figure and their placement (Spreen, 1991). However allowances were made for the fact that it is difficult to draw a straight line without the use of a ruler. The figure was broken down into 18 scoreable items, with 0.5-2.0 points being awarded for each item depending on the accuracy and placement of the item as detailed below.

The recognition trail had a score for the recognition true positives, recognition false positives, recognition true negatives (12- recognition false positives) and recognition false negatives (12- recognition true positives). As a result, a recognition total correct score was calculated (recognition true positives+ recognition true negatives).

A percentage accuracy score was calculated for each of the trials, copy, immediate, delayed and recognition. In addition an overall percentage accuracy score was calculated (Delayed Recall/Copy Trial * 100) in order to remove the effects of the copy trial from the memory trial (Lezak, 1995). For the purpose of this study no examination was made of strategy used in drawing the complex figure.

2.3.3.1b Associative memory: Face-Name Learning and Recall

This task has been utilised as a ecologically valid measure of associative learning, with both behavioural and neuroimaging data suggesting that it is hippocampally driven (Zeineh et al., 2003). Using a face-name association task participants were presented with a series of eight unfamiliar faces each paired with a name, their task was to successfully recall the names associated with each face. In both the encoding and retrieval phases, 8 female faces (selected from a college yearbook and presented in black and white with all hair removed), were positioned 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, whereas in the retrieval phase the names were replaced with the prompt command "Name?" (see Figure 2.2).

Design

The Face-Name task was programmed in E-Prime 1.2 (Psychology Software Tools, Pittsburgh, PA). All names selected had two syllables, were common English female names, and were matched for frequency. A visual attention (distracter) task was included between the encoding and retrieval phases of the Face-Name task. This aimed to prevent sub-vocal rehearsal of the face name pairs between the encoding and retrieval phases in the two experimental conditions (Zeineh et al., 2003). This served to equalize the conditions between the encoding and the retrieval phases. Participants viewed a centrally located fixation cross, enclosed within the black outline of a circle, which changed intermittently into a solid black circle. In total there were four blocks of the encoding-distracter-recall trials and one block of delayed recall. Total task duration was approximately 7 minutes and 40 seconds.

Procedure

Face Name Encoding

During the encoding blocks (see Figure 2.2), participants viewed 8 face-name pairs, presented serially at a rate of one every 3.5 seconds (ISI = 500 ms). They were instructed

to study each face-name pair carefully and to attempt to memorize the name corresponding to each face. The presentation order was consistent across each of the encoding blocks.

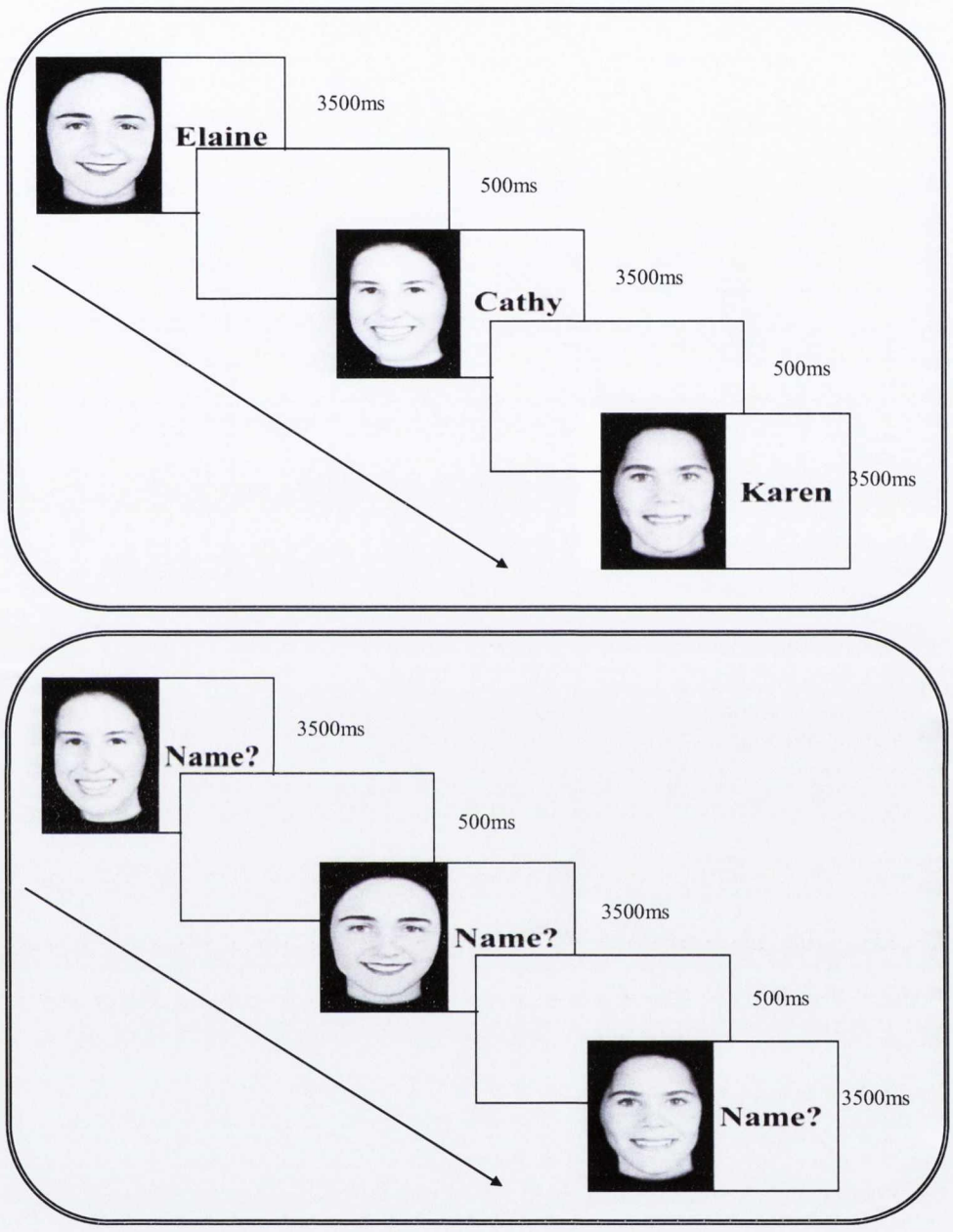

Figure 2.2: (Upper Panel) Face-Name Encoding: Participants viewed each face-name pair for 3.5 seconds (ISI = 0.5s), during which time they attempted to memorize the name corresponding to each face. (Lower Panel) Face-Name Retrieval: Participants were presented with each of the eight previously viewed 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).

Visual Attention Task

Participants focused on the centrally located fixation cross and responded with a button press (the circular button in the middle of the Cedrus RB-530 response pad: see Figure 2.3)

every time the circle and cross-changed to a solid black circle (see Figure 2.3). This change occurred randomly every 1-5 seconds and lasted 0.25 seconds. The duration of each visual attention task block was 154 s. The purpose of this attention task was to prevent face-name pair rehersal.

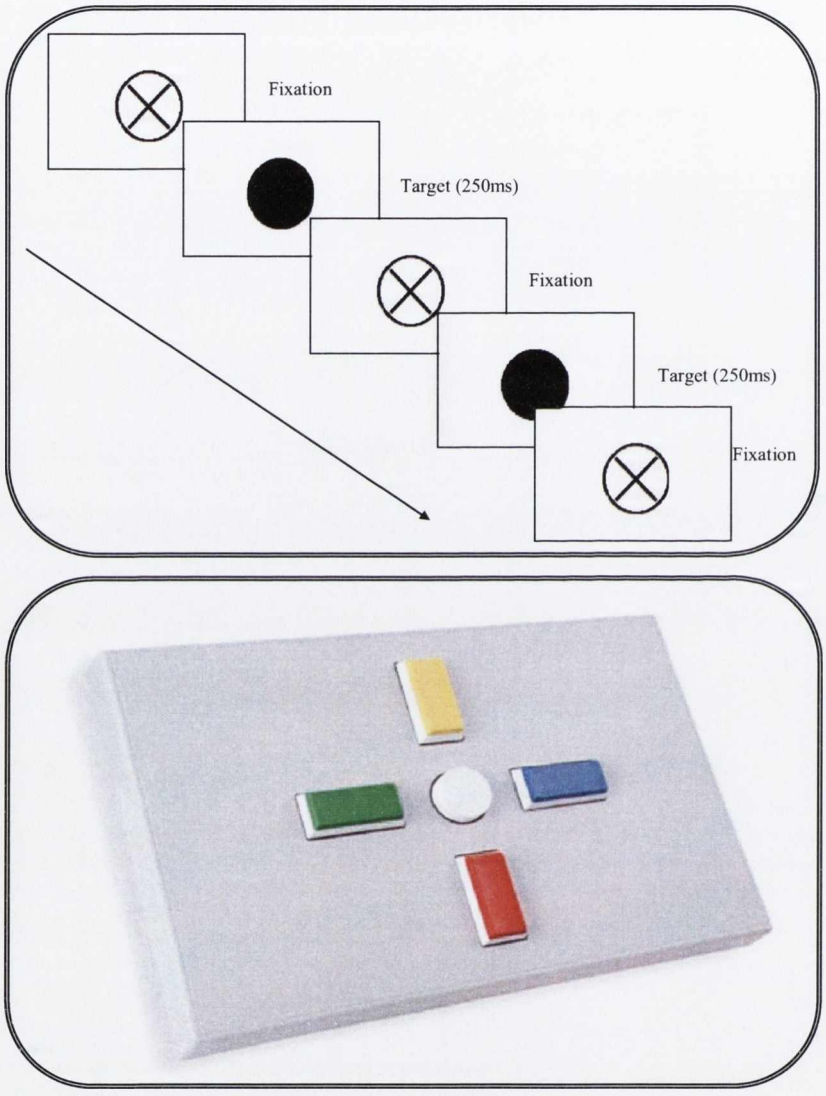

Figure 2.3: (Upper Panel) Visual Attention Task Participants focused on the fixation cross and pressed a button, as quickly as possible, every time it changed to a solid black circle; (Lower Panel) Cedrus RB-530 response pad model. Participants pressed the white circular button every time the circle and cross-changed to a solid black circle.

Face Name Retrieval

Participants serially viewed the 8 faces presented in random order, without the accompanying names (see Figure 2.2). Again, each face was presented for 3.5 seconds (ISI = 500 ms), during which time participants were required to vocally recall the names

corresponding to each of the eight faces. The experimenter recorded correct and incorrect responses; non-responses were recorded as incorrect.

Face Name Delayed Recall

Participants were again presented with the 8 faces presented in random order, after a 15 minute delay, without the accompanying names. Once more they were required to vocally recall the names corresponding to each of the eight faces, and again the experimenter recorded correct and incorrect responses; non-responses were recorded as incorrect.

Scoring

The percentage accuracy score for each block was calculated, as well as the total percentage accuracy (block 1-4) and the delayed recall percentage accuracy.

2.3.3.1c Verbal Memory: California Verbal Learning Test (CVLT-II)

Verbal learning and memory was assessed using the California Verbal Learning Test (CVLT-II) (Delis et al., 2000). The CVLT-II was designed to measure both recall and recognition of two lists of words over a number of immediate- and delayed-memory trials. It can also be used to assess participant's spontaneous use of semantic associations as the list of 16 items contains four words from each of four semantic categories.

Procedure

The immediate trials consisted of five presentations with recall of the 16-item list. Each of the 16 items belonged to one of four semantic categories (Standard version – vegetables, animals, ways of travelling and furniture; Alternative version – tools, fruits, clothing, and insects). After each presentation, the participant recalled all of the words that he/she could remember. Following this an interference list (list B) is read to the participants. The short term delayed recall provided the first free recall of the list. This was followed by short term delayed cued recall which utilised the categories as cues, where participants had to list all of the items in each of the four categories. There is an additional benefit of this type of recall for those who did not make the semantic associations during the learning trials, especially in the later (20 minutes) long-delay trials. Recall of the list is again measured under the free and cued recall trails, and is followed immediately by a recognition trail. During this recognition trial, 44 words are presented and participants had to state whether each word was from List A or not, followed finally by a forced choice recognition.

Scoring

There are several useful ways to score the CVLT-II, all are outlined in the manual (Delis et al., 2000). For example, the level of correct recall on list A trial 1, level of correct recall on list A trials 2-5, total recall (all remembered from trial 1 to 5), semantic cluster ratio, free recall, and cued recall.

2.3.3.2 Self-rating Memory Questionnaires

There is increasing recognition that we should utilise, not only multiple indicators of the constructs we assess, but also self-reports and naturalistic observations (Crawford et al., 2003). In line with this view, the present study has included a number of self-report questionnaires which examined memory.

2.3.3.2a Everyday Memory Questionnaire (EMQ)

Developed by Sunderland et al. (Sunderland et al., 1984) as a subjective measure of memory failure in everyday life, this questionnaire only has 27 items, each scored on a 9-point scale, ranging from "not at all in the last 3 months" to "more than once a day". Higher scores reflect a greater level of self-reported memory problems.

Procedure

Participants were asked to read the instructions and to rate each item of the questionnaire based on how often they felt that it happened to them.

E.G. Not remembering a change in your daily routine, such as a change in the place where something is kept, or a change in the time something happens. Following your old routine by mistake.

There was no time limit applied for completing the EMQ.

Scoring

The score for each of the items was summed to give a total score on the EMQ. The square root of this total score was then calculated according to the guidelines described by Sunderland et al. (1984).

2.3.3.2b Mundane Memory Questionnaire (MMQ)

The MMQ, originally designed to assess memory problems in patients who had undergone a right or left amygdalohippocampectomy (Mangaoang et al., 2004), was used to measure personally relevant episodic memory of a participants typical day over the previous four days prior to testing. It asks participants to write down information about a typical day e.g. "Do you recall getting dressed this morning? If so, what did you wear?" The 12-item questionnaire focuses on the temporal order of everyday events and was designed to measure the rate at which these events are forgotten over four consecutive days. It has previously been shown to be extremely sensitive to the types of everyday memory problems that patients with temporal lobe epilepsy complain of, particularly as it does not ask them to rate their own memory performance, but actually take account of what they have done over the last four days (Mangaoang et al., 2004).

Procedure

The format presented in the present study was the structured MMQ, in which the questions followed the temporal order of a 'normal' daily routine from morning to evening. Participants were asked to read the instructions and to answer each item of the questionnaire. There were two parts to each item; the first just required a yes or a no answer e.g. "Do you recall getting dressed on this day?", if the participant remembered then they circled 'yes', and if they didn't they circled 'no'. The second part required a little bit of detail, e.g. "If so, what did you wear?" the participant was required to write a short response to the question. There was no time limit applied for completing the MMQ. A copy of the MMQ, along with the instructions is presented in Appendix II.

Scoring

The MMQ scoring provides both a score for each of the four days and also a total score. One point was given for each 'Yes' response and also for filling in the specific details following each response. No points were given for 'No' responses and blank spaces. A total score for each day (maximum per day was 24 points) and an overall total score (maximum score 96 – 24 x 4 days) was calculated, where higher scores indicated a greater level of recall.

2.3.3.2c Self-Rating Scale (SRS)

This is a five-point Likert scale designed to assess how well participants rated their own memory. Having completed all of the tests and questionnaires, participants were asked to

rate their own memory ranging from 5 (excellent) to 1 (very bad). A copy of the SRS is provided in Appendix II.

Scoring

The rating given by the participants were used in this task.

2.3.3.3 Executive Functioning

2.3.3.3a Behavioural Assessment of Dysexecutive Syndrome

The Behavioural Assessment of Dysexecutive Syndrome (BADS) (Wilson et al., 2003) is a battery of tests designed to assess the effects of impairments associated with the frontal lobes. These include difficulties with planning, organising, initiating, monitoring, and adapting behaviour. The argument is that the BADS examines these tasks in more complex, real life situations than other methods, highlighting the day-to-day difficulties found with impairments of the frontal lobes (Wilson et al., 2003). Although there are six tests and a questionnaire in the battery, only two tests and the questionnaire were chosen for the present testing battery. There were several reasons for this, firstly time constraints would not allow use of the entire battery, the participants have 15 tests in total to complete, and it was felt that using the entire battery would not be feasible. Secondly, there are many other tests used in the present battery which may utilize many of the same requirements of the excluded BADS tests (these will be discussed later on). Finally, it was important to focus principally on the types of difficulties reported by patients with SCH and hypothyroidism, especially including day-to-day difficulties in memory and executive functioning, for this reason two of the BADS tests were included in this testing battery; the Key Search (KS) and the Zoo Map (ZM). In addition to this, the Dysexecutive questionnaire was also included.

Key Search Test

This task was designed to be analogous to a real-life activity as losing something is normal for everyone and more common in those with brain damage (Wilson et al., 1996). It allows the experimenter to observe the participant's ability to effectively plan an efficient course of action, and also gives the participant the opportunity to monitor their own work as the lines drawn on the sheet indicate whether all the ground has been covered.

Procedure

Participants were presented with an A4-sized piece of paper with a 100mm square in the middle and a small black dot 50mm below. Subjects were told to imagine that the square was a large field in which they have lost their keys. They were asked to draw a line, starting on the black dot, to show where they would walk to search the field to make sure that they found their keys (for more detailed instructions see Wilson et al., 2003). The drawings were scored based upon a number of criteria. Total time taken was recorded using a stop watch.

Scoring

Briefly, the scores were broken up into five elements; (1) entering and leaving the field (corners gained more marks than the middle of the base), (2) patterns compromised of vertical or horizontal parallel lines gained more marks than concentric ones, (3) single planned patterns gained more marks, (4) marks were awarded for drawing a continuous line, attempting to cover all ground and (5) the likelihood of successfully finding the keys.

Zoo Map Test

The Zoo Map Test was designed to assess the ability of the participant to independently formulate and implement a plan (high-demand condition) and to follow a predetermined pattern (low-demand condition) (Wilson et al., 2003).

Procedure

Participants were required to show how they would visit a series of selected places on a map of a zoo, while obeying certain rules outlined in the instructions (see Wilson et al., 2003). These rules included starting at the entrance, finishing at the picnic area and using specific 'paths' in the zoo just once. There were two trials, one in which the selected places can be visited in any order (high-demand), and a second in which the selected places must be visited in a particular order (low-demand). Once the participant had visited each of the chosen places they were given a different coloured pen, this allowed the tester to see in which order they visited the different places (for more detailed instructions see Wilson et al., 2003). Time spent planning and total time taken was recorded using a stop watch.

Scoring

Sequence points were awarded if the participant visited each place in one of the possible four correct sequences. Error points were awarded if the participant deviated from the path,

failed to make a continuous line, visited an inappropriate place, or used designated 'paths' more than once. Error points were then subtracted from sequence points to give a total score for each version; these were subsequently added for an overall score.

DEX Questionnaire

The DEX is a 20-item questionnaire that examines many of the symptoms that have been associated with executive impairment such as planning problems, disinhibition, aggression and distractibility (e.g. 'I act without thinking, doing the first thing that comes to mind') (see Wilson et al., 2003). There are four broad areas of change covered: emotional or personality change, motivational change, behavioural change and cognitive change. The DEX comes in two forms, one for self-rating (the participant) and one for independent rating (by someone who lives with the participant or knows come in very close contact with the participant – not used in the present study due to logistical reasons). All items are rated on a 5-point Likert scale from never (0 points) to very often (4 points).

Procedure

Participants were asked to read each item carefully and rate them according to their personal experience.

Scoring

The scores on all of the items are then summed to give an overall DEX score.

2.3.3.3b Focused Attention

Each of the four encoding and recall trials in the face-name task (see Section 2.3.3.1b) was separated by a thirty second visual attention (distracter) task. Participants were required to respond to a rapid and repetitive visual stimulus. While this sought to prevent sub-vocal rehearsal of the pairs it also offered a brief measure of focused attention.

Procedure

Participants focused on the centrally located fixation cross and responded with a button press (the circular button in the middle of the Cedrus RB-530 response pad: see Figure 2.3) every time the circle and cross-changed to a solid black circle. This change occurred randomly every 1-5 seconds and lasted 0.25 seconds. The duration of each visual attention task block was 154 ms.

Scoring

Both reaction time and percentage accuracy scores were calculated.

2.3.3.3c Working Memory: The n-Back Task (0-Back, 1-Back & 2-Back Levels)

The *n*-back task was programmed in E-Prime 1.2 (Psychology Software Tools, Pittsburgh, PA).

Design, Materials, and Stimuli

In the *n*-back working memory task participants were presented with a series of digits, one at a time, on screen. The stimuli (Meyer-Lindenberg et al., 2001) consisted of grey diamond shapes (16.9° long, 16.9° wide) presented centrally on screen, with a black outline (0.75 pt). These diamonds contained the digits 1, 2, 3 or 4; "1" was located in the top corner (1.2 cm x 0.7 cm (height x base width)), "2" was located in the left corner (1.2 cm x 0.8 cm), "3"was located in the right corner (1.2 cm x 0.8 cm) and "4"was located in the bottom corner (1.2 cm x 0.3 cm). There was also a blank diamond that contained no digit (see Figure 2.4). Responses were recorded using the Cedrus RB-530 response pad which was positioned to the right of the screen.

Procedure

The *n*-back task used in the current studies is a modified version of the standard task (see Callicott et al., 2000; Meyer-Lindenberg et al., 2001). It was a continuous presentation task, in which a stream of digits (1, 2, 3, or 4) was presented on screen. Each stimulus remained on screen for 1800 milliseconds followed by a blank screen (ISI 200ms). There was a pseudo-random sequence to the presentation of the stimuli i.e. in the 0-back condition there was a continual stream of numbers, in the 1-back condition every nine randomly presented numbers were followed by one blank diamond, and in the 2-back condition every nine randomly presented numbers were followed by two blank diamonds. The blank diamonds signalled a pause in the number sequence. The 0-back trial contained 45 stimuli and required 45 responses. The 1-back trail contained 50 stimuli and required 45 responses (don't respond on the first number of each set of numbers). The 2-back trial contained 44 stimuli and required 36 responses (don't respond on the first two numbers of each set of numbers). The 1-back and 2-back conditions were both preceded by a short practice trail. The task lasted in total approximately 6 minutes and 25 seconds. There was a practice block immediately prior to the 1- and 2-back conditions. While reaction times were not reported in either the Meyer-Lindenberg et al. study (2001), or the Callicott et al.

study (2000), they were reposted in the present study for the sake of completeness. Both reaction times and accuracy were recorded automatically by the E-Prime software.

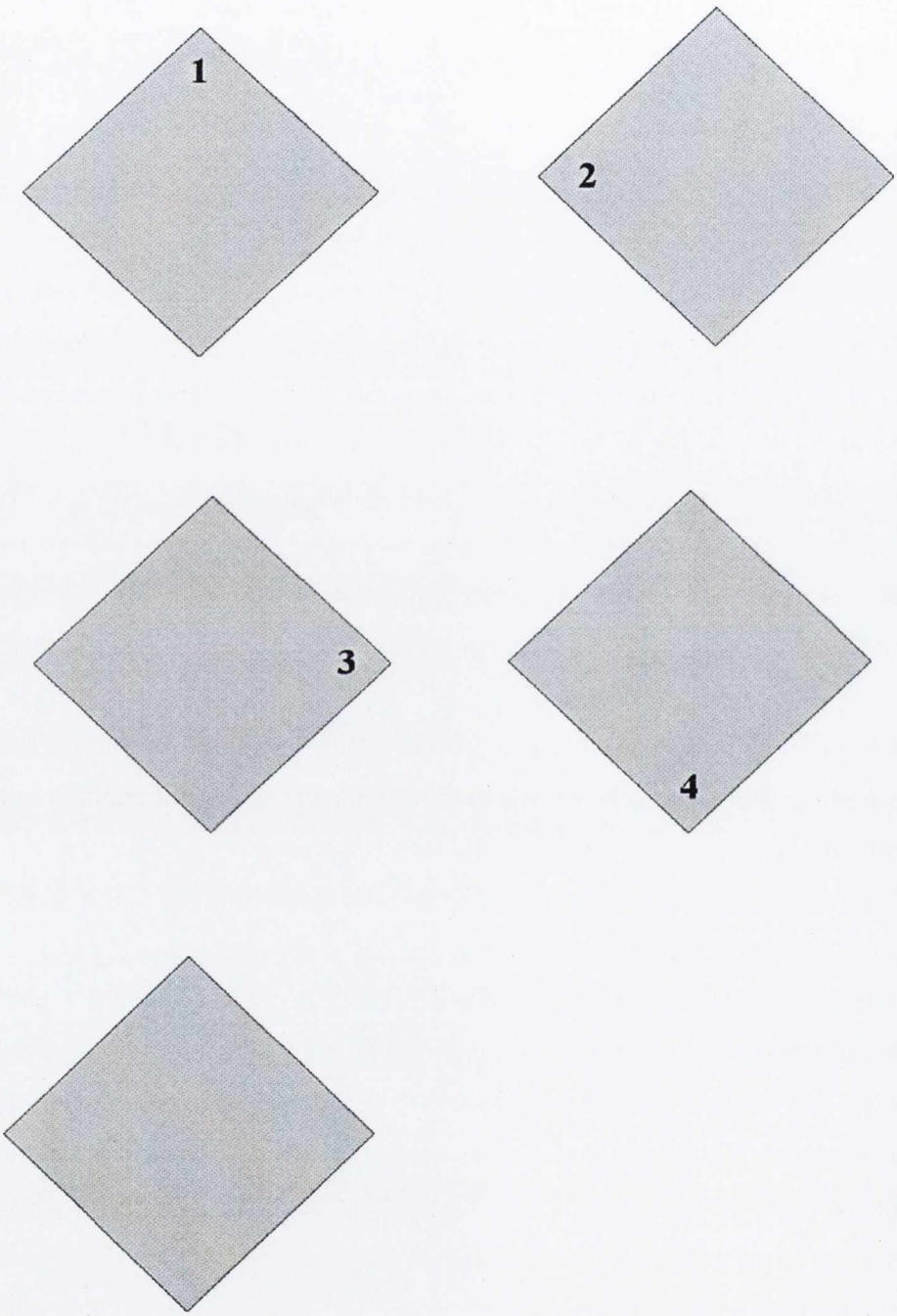

Figure 2.4: (Upper Panels) Numerical n-back stimuli. The numbers 1, 2, 3, and 4 were located in a fixed position within the diamond. (Lower Left Panel) A blank diamond.

0-Back condition (Sensorimotor Control)

Participants were required to press the button corresponding to the number that currently appeared on screen (see Figure 2.5). There were no blank diamonds.

1-Back Condition (Within the Focus of Attention)

Participants were instructed to press the button corresponding to the last number that they saw and not the number currently on screen, i.e. they had to press the number from one trial previous (1-back). In order to do this successfully the participants had to keep the current number and the last number within their working memory, and continuously update this with the presentation of each new number. When they reached a blank diamond, participants were instructed to continue to press the number from the previous trial, however on the next numbered diamond they were not required to make a response (see Figure 2.5). In effect the blank diamond indicated the start of the next number sequence.

2-Back Condition (Outside the Focus of Attention)

In this instance participants were instructed to press the number that was on screen two trials previously (2-back). In order to do this successfully the participants had to keep the current number and the last two numbers within their working memory, again continuously updating it with the presentation of each new number. When they reached a blank diamond, participants were instructed to continue to press the number from two trials previous, however on the next two numbered diamonds they were not required to make a response (see Figure 2.5).

Scoring

Both percentage accuracy scores (availability of an item stored in working memory) and reaction times (ms) (accessibility of that item) were recorded. Responses were recorded on a Cedrus RB-530 response box with four buttons; labelled 1, 2, 3, and 4 (see Figure 2.3). If the participant failed to respond in the 0-back condition then their accuracy score was 0%, in the 1-back condition it was 10% and in the 2-back condition it was 18%. These discrepancies were due to that fact that both in the 1- and 2-back conditions the participants were required to withhold their responses at the start of each set of numbers.

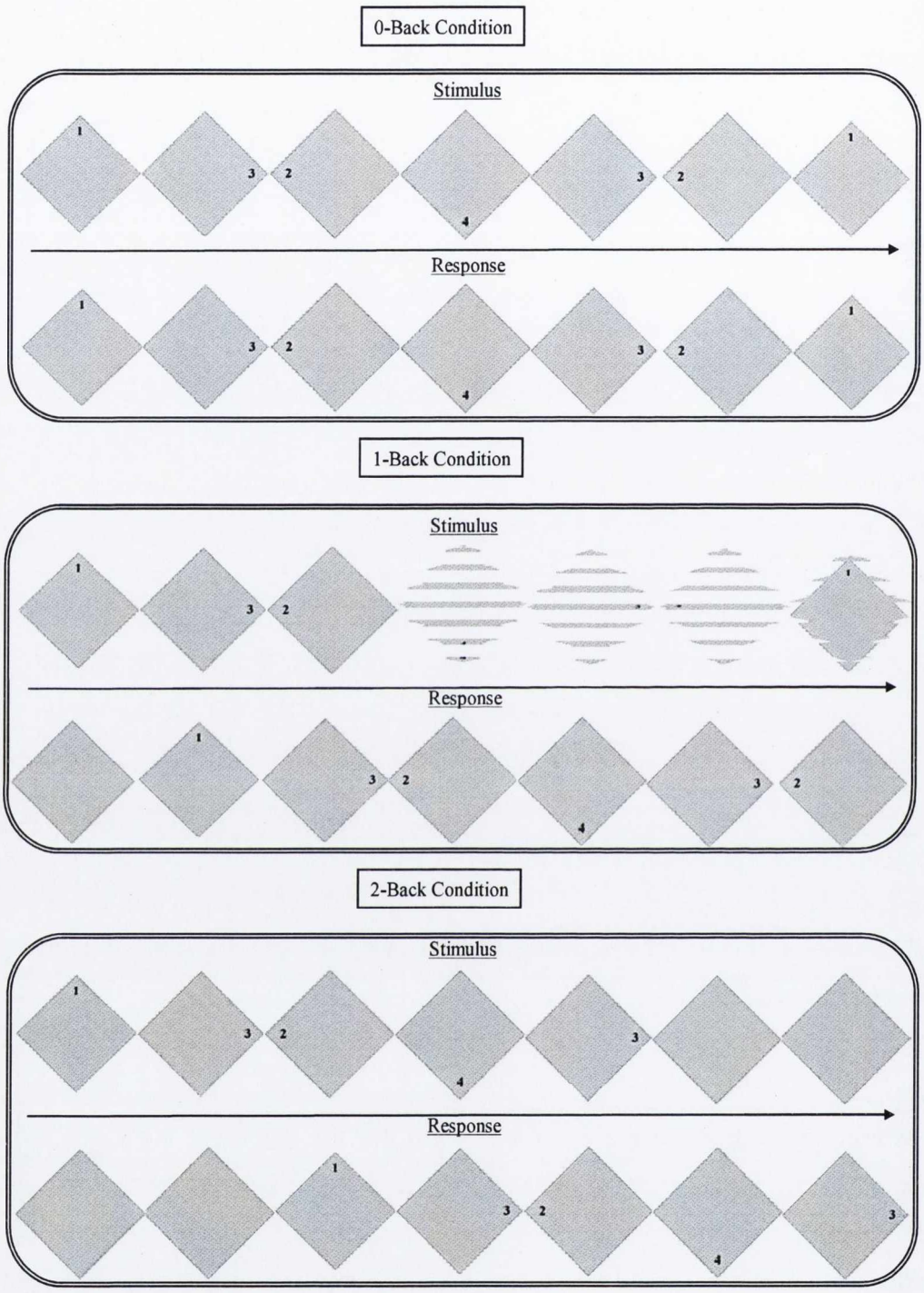

Figure 2.5: (Top Panel) Stimuli and response for the 0-back condition – press the number currently on screen; (Middle Panel) Stimuli and response for the 1-back condition – press the number from one trial previous; (Lower Panel) Stimuli and response for the 2-back condition – press the number from two trials previous.

2.3.3.3d Response Inhibition: The Stroop Task - 'Naming Coloured Words' Version

The Stroop task was programmed in E-Prime 1.2 (Psychology Software Tools, Pittsburgh, PA). This task assessed participant's ability to make an appropriate response when presented with two conflicting stimuli (Stroop, 1935). It is based on the finding that it takes longer to identify the colour of the ink in which a colour name is printed when the ink is a different colour than the colour name itself (e.g. the word red written in blue ink).

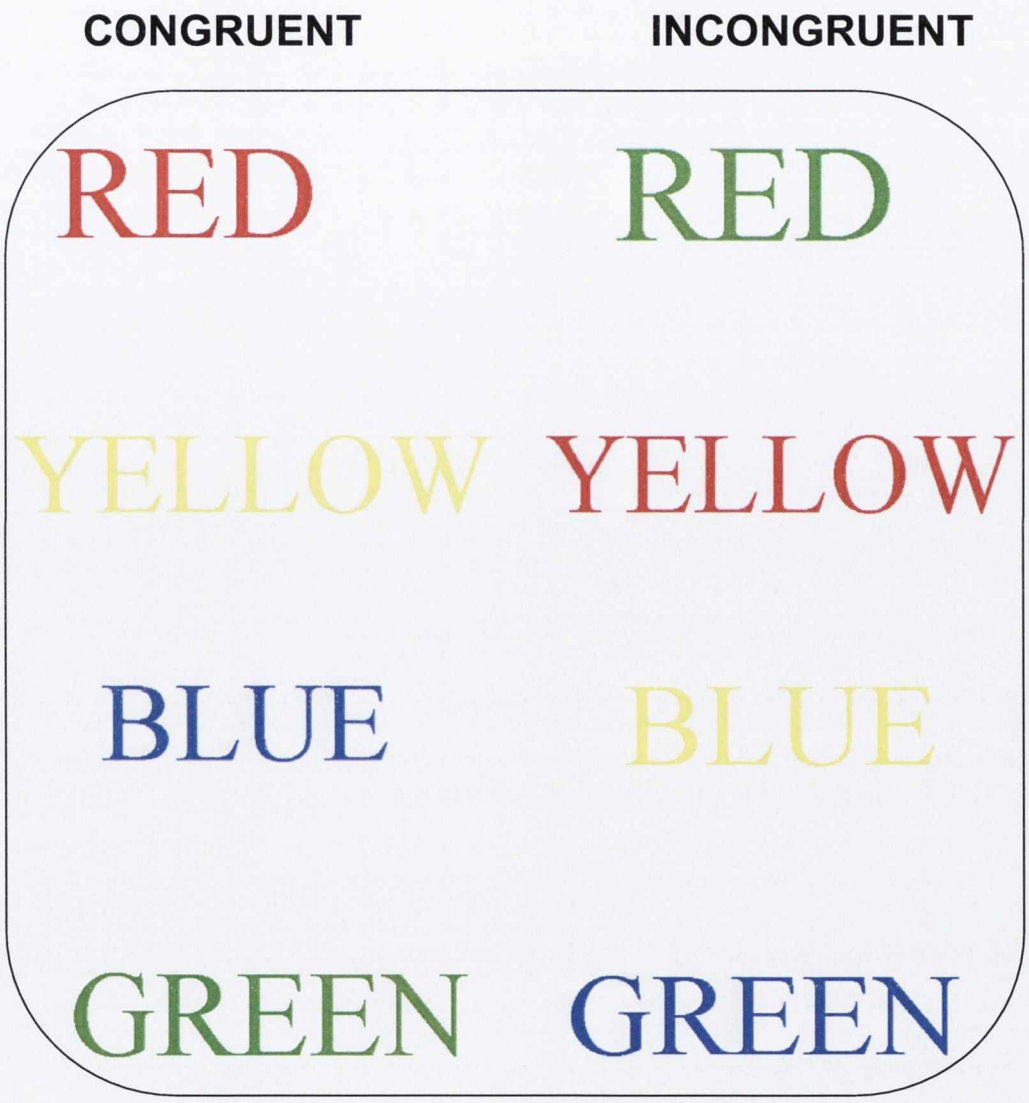

Figure 2.6: Stimuli used in the Stroop Task

Design

During this task participants were presented with four words (RED, YELLOW, BLUE, and GREEN – see Figure 2.6). Each word was presented in one of the four colour fonts (red, yellow, blue, and green; see Figure 2.6). Each word was presented on screen for 1300ms; this was followed by a blank for 300ms. There were 2 blocks in total; each presented 102 words (95 congruent trials and 7 incongruent trials) over a period of 2 minutes 46 seconds (total task duration 5 minutes 32 seconds).

Procedure

The participant's had to press the button on the response pad (see Figure 2.3) that corresponded to the font colour of the word. It was not important what the written word was, all they had to attend to was the colour of the word, e.g. if the word RED was presented in blue font then they had to press the button corresponding to blue on the response pad.

Scoring

Both reaction time and percentage accuracy scores were calculated for both the congruent and incongruent trials. Colour-naming latency is reported to reveal the extent to which processing resources are allocated to the word content

2.3.3.3e Sustained Attention to Response Task (SART)

Sustained attention has been described as the ability to "self-sustain mindful, conscious processing of stimuli whose repetitive, non-arousing qualities would otherwise lead to habituation and distraction to other stimuli" (Robertson et al., 1997). The paradigm developed by Robertson et al. (1997) to test sustained attention was used in the present study; it was a continuous performance task (CPT) which involved frequently pressing a button in response to non-target stimuli and withholding that response to target stimuli. Such a paradigm should be sensitive to mild attentional difficulties.

Design

The SART was programmed in E-Prime 1.2 (Psychology Software Tools, Pittsburgh, PA). Digits were presented in order from '1' though to '9' on a computer screen. The digits were displayed in one of four possible font sizes (11mm, 14mm, 17mm, and 20mm). Each digit was presented on screen for 500ms, this was followed by a fixation for 100ms and then the response cue for 500ms, the trial ended in a fixation of 100ms (see Figure 2.7).

There were 2 blocks in total; each presented 225 digits (25 of each of the 9 digits) over a period of 4 minutes 42 seconds (total task duration 9 minutes 24 seconds). Thus there were 200 go trials and 25 no-go trials in each block.

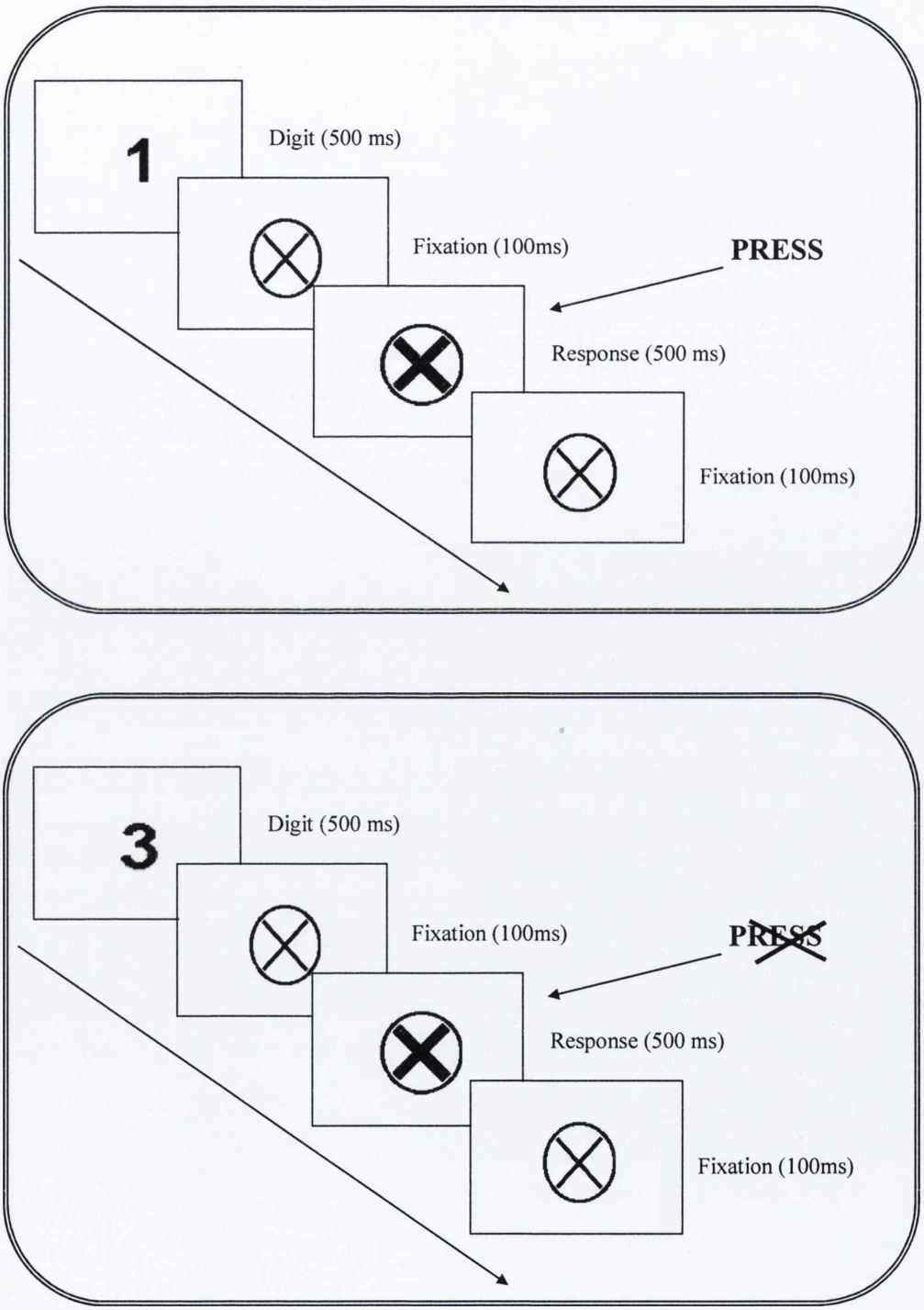

Figure 2.7: (Upper Panel) Sequence of events contained within a go trial on the SART (press the circle button on the response pad at response point); (Lower Panel) Sequence of events contained within a no-go trial on the SART (withholding the response when the number 3 appears on screen).

Procedure

Participants used their preferred hand and were asked to respond as quickly and as accurately as possible. Participants were required to respond (press the circle button on the response pad, see Figure 2.3) to the cue, after every digit except the number 3 (fixed target stimuli). Each participant first underwent a practice trial of 36 digits, 4 of which were target stimuli prior to commencing the first block.

Scoring

Both reaction time and percentage accuracy scores were calculated for both the go and no-go trials. These methods have also been described in detail elsewhere (Dockree et al., 2005; Manly et al., 1999; Robertson et al., 1997).

2.3.3.3f Dual Attention to Response Task

The DART has an additional CPT embedded in the basic design of the SART (described above). As well as responding to all non-target stimuli (go-trials – press the yellow button), and withholding that response to all target stimuli (no-go trials), participants now also have to make an additional response to a third stimuli – grey coloured numbers (grey-trials). When a grey coloured number appeared on screen participants were instructed to press a different button (circle), or continue to withhold their response if a digit 3 appeared on screen. However, in order to challenge only the available processing during the task but not immediately before or after the target stimuli (digit 3), the presentation of grey coloured numbers was restricted to digits 5 through to 9 (Dockree et al., 2006). The reason for this was that errors should then result from attentional lapses and not from response switching (Bellgrove et al., 2004).

Design

The DART was programmed in E-Prime 1.2 (Psychology Software Tools, Pittsburgh, PA). Again each digit was presented on screen for 500ms, this was followed by a fixation for 100ms and then the response cue for 500ms, the trial ended in a fixation of 100ms (see Figure 2.8). The digits were displayed in one of four possible font sizes (11mm, 14mm, 17mm and 20mm). There were 2 blocks in total; both presented 117 digits (13 of each of the 9 digits) over a period of 2 minutes 27 seconds (total task duration 4 minutes 54 seconds). Thus there were 92 go trials, 13 no-go trials and 12 grey trials in each block. The grey digits were created in Microsoft Paint, with a hue of 160 and a luminance of 120.

Procedure

Participants used their preferred hand and were asked to respond as quickly and as accurately as possible. However the instructions also asked the participants to be especially mindful of the grey digits. Each participant underwent at least one practice trial of 36 digits, 4 of which were target stimuli (no-go trial) and 6 of which were grey stimuli, prior to commencing the first block.

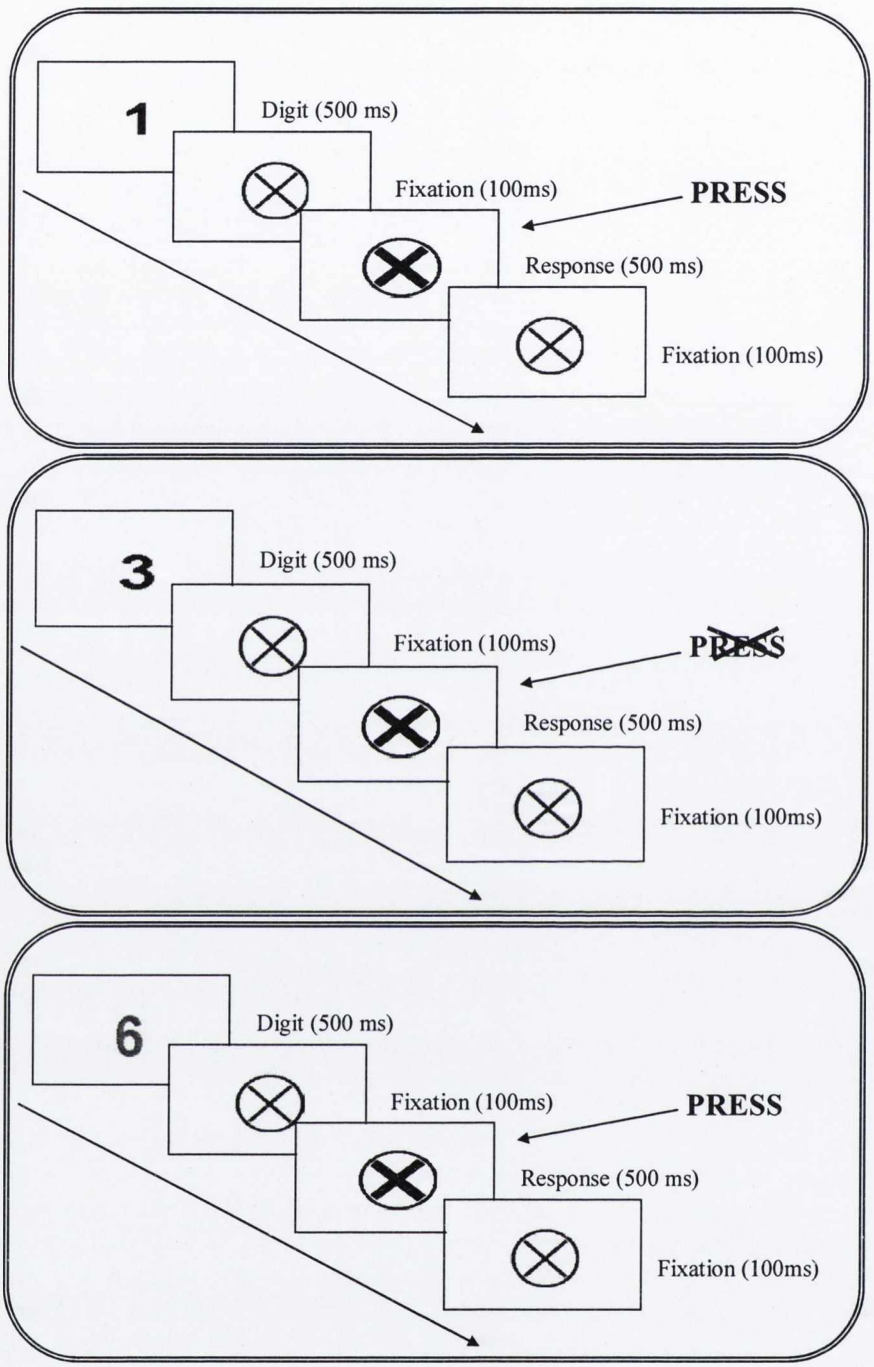

Figure 2.8: (Upper Panel) Sequence of events contained within a go trial on the DART (press the yellow button on the response pad at response point); (Middle Panel) Sequence of events contained within a no-go trial on the DART (withholding the response when the number 3 appears on screen); (Lower Panel) Sequence of events contained within a grey trial on the DART (press the circle button on the response pad at response point).

Scoring

Reaction time, error and percentage accuracy scores were calculated for the go, grey and no-go trials. These methods have also been described in detail elsewhere (Bellgrove et al., 2004; Dockree et al., 2006).

2.3.3.4 Premorbid IQ - National Adult Reading Test 2nd Ed

The National Adult Reading Test (NART) (Nelson, 1982; 1991) was designed to measure premorbid intelligence in elderly adults with possible or probable dementia (Cockburn et al., 2000). However in other studies, including the present study, it has been used for comparison with current intelligence as measured by more comprehensive tests. The usefulness of this test in the assessment of premorbid intelligence depends upon the test providing a sensitive measure of previous familiarity with words (Nelson, 1991), thus words not previously in the participant's vocabulary should be incorrectly pronounced. As the ability to read aloud is generally retained until relatively late in the dementing process, the list consists of 50 relatively short words (see Appendix II) printed in order of increasing difficulty. However they are 'irregular' with respect to the common rules of pronunciation, minimising the possibility of reading them phonetically rather than word recognition. Participants were asked to read aloud the list of words and errors made were recorded. The total errors made were used to calculate the WAIS Predicted Full-Scale IQ score (see Nelson et al., 1991).

2.3.3.5 Affective Measurements

2.3.3.5a Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-assessment scale that was developed for detecting states of depression and anxiety in the setting of a hospital outpatient clinic (Snaith, 2003; Zigmond et al., 1983). It was designed to be brief and easily understood.

Design

The HADS consists of 14 items, 7 that reflect anxiety (e.g. I feel tense or 'wound up') and 7 that reflect depression (e.g. I feel as if I am slowed down). Of the 7 that measure depression, 5 reflected aspects of reduction in pleasure response which is one of the two obligatory states for the definition of depression (Snaith, 2003). Items 1, 3, 5, 7, 9, 11, and 13 reflect anxiety and items 2, 4, 6, 8, 10, 12, and 14 reflect depression.

Procedure

Participants are asked to read each item carefully and circle the reply which comes closest to how they've been feeling in the last week.

Scoring

Each item is measured on four point scale (0-3); scores therefore ranged from 0 to 21 for both anxiety and depression. A score of 7≤ is regarded as being within the normal range. Zigmond and Snaith (1983) have suggested two cut-off scores for detecting depression and anxiety; scores of 8 - 10 are suggestive of the presence of anxiety or depression while scores of 11 and higher indicate the probable presence of anxiety or depression.

2.3.3.5b Beck Depression Inventory II (BDI-II)

The original BDI was designed as an instrument to measure the behavioural symptoms of depression in response to the need for an appropriate system for identifying depression (Beck et al., 1961). The BDI-II (Beck et al., 1996) was a revised version of the original test which was designed in response to publication of the fourth edition of the American Psychiatric Association's "Diagnostic and Statistical Manual of Mental Disorders" in which the many of the diagnostic criteria for Major Depressive Depression had been changed (1994).

Design

It is a 21 item inventory, where each item describes a specific behavioural manifestation of depression (e.g. loss of interest, concentration difficulty, and guilty feelings). Each item is measured on a four point Likert scale (0-3) indicating the degree of severity of the symptoms. In some items there are two alternative statements presented at the same level and are given the same weight (e.g. item 16, 1a and 1b).

Procedure

Participant's were asked to read each group of statements carefully, and to pick the statement that best described the way they were feeling during the previous two weeks, including the day of testing. They had to circle the number beside the statement they picked; in the case where several statements in the group seemed to apply equally well, they were told to circle the highest number for that group.

Scoring

The BDI-II is scored by summing the ratings for the 21 items, with a maximum total score of 63. An index score 0-13 was considered within the minimal range, 14-19 was mild, 20-28 was moderate, and 29-63 was severe.

2.3.3.5c Perceived Stress Scale (PSS)

The Perceived Stress Scale (Cohen et al., 1983) was designed to measure participant's perception of how stressful their lives were over the month prior to testing.

Design

It is a 14-item scale (see Appendix II) which is easy to understand and quite general in nature.

Procedure

Participants were asked to read each question and indicate how often in the last month that the felt or thought a certain way.

E.G. Do you recall getting dressed on this day? If so, what did you wear?

Scoring

Of the 14-items, seven are positive items (4, 5, 6, 7, 9, 10, and 13) and these are reverse scored (0=4, 1=3, 2=2, 3=1, 4=0), and seven are negative items (1, 2, 3, 8, 11, 12 and 14); the scores on all of the items are then summed to give an overall perceived stress score. Though the Perceived Stress Scale is not a diagnostic instrument; there are no score cut-offs.

2.3.4 Analytic Measurement

Using the DPS immulite® 2000 analyser, serum TSH concentrations were measured using a third generation chemiluminescent immunometric assay, free T4 using a competitive analogue immunoassay and thyroid peroxidase (TPO) antibodies using an immunometric assay (CV < 5% for all). TPO antibodies were considered normal if < 35 IU/L, equivocal if 35-90 IU/L and abnormal if >90 IU/L. Reference ranges were drawn from the laboratory reference range.

2.3.5 Statistical Analysis

Analyses were carried out using SPSS (version 15) for PC. All data was expressed as means ± standard error (± SEM), unless specified otherwise. Analysis of Variance (ANOVA) was the primary statistical tool used. When performance on a specific task was repeated across multiple trials and/or testing sessions 'mixed between-within subject ANOVAs' (Tabachnick et al., 2007) were used to compare performance across the

repeated levels and between the groups. Where significant ($p < 0.05$) main effects and interactions were observed and if appropriate, post-hoc analyses were conducted (Bonferroni-Corrected for multiple comparisons). Subsequent one-way ANOVAs compared the dependent variable at each level between the groups and post-hoc analysis identified between which groups the differences lay. In the case of data that was not normally distributed, non-parametric analyses were carried out. In the presence of significance between-group differences, a priori planned comparisons were used to test specific differences between the SCH and control groups (comparison 1) and the Hypothyroid and control groups (comparison 2). A bonferroni adjustment to the alpha level (alpha / no. of comparisons; $0.05 / 2 = 0.025$) was applied to these comparisons, to maintain a reasonable alpha level across all tests. The relationship between TSH levels and all dependent variables was investigated using Pearson correlations, only correlations above 0.3 were reported for the TSH analysis. Where there was a lack of normality in the data it was transformed using a Log_{10} transformation when possible. Where a variable (e.g. age) was suspected to influence performance on a memory test, the dependent variable (DV), a relationship between the variable and the covariate was first examined using correlations and scatterplots. Then a series of ANCOVA's (Analysis of Covariance) were carried out on each dependent variable. As a result, the variation of the DV that is due to the covariate was removed. Preliminary checks were made prior to conducting the ANCOVA to ensure that there was no violation of the assumptions of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and reliable measurement of the covariate. When significant differences were found, the p-value was reported at three levels; $p < 0.05$ (*), $p < 0.01$ (**), and $p < 0.001$ (***).

2.4. Results

2.4.1 Blood Test Results

TSH

In the control group the average TSH values were 1.45 mU/l, ranging from .04 mU/l to 3.61 mU/l; in the subclinical the average TSH values were 8.57 mU/l, ranging from 4.18 mU/l to 15.80 mU/l; and finally in the hypothyroid group the average TSH values were 50.76 mU/l, ranging from 8.29 mU/l to 94.00 mU/l (see Table 2.1).

T4

In the control group the average T4 values were 16.18 pmol/l, ranging from 12.60 pmol/l to 19.20 pmol/l; in the subclinical the average T4 values were 14.85 pmol/l, ranging from 11.00 pmol/l to 23.60 pmol/l; and finally in the hypothyroid group the average T4 values were 6.38 pmol/l, ranging from 3.90 pmol/l to 10.80 pmol/l (see Table 2.1).

Group	Control	Subclinical	Hypothyroid
TSH	1.45 (0.04 – 3.61)	8.57 (4.18 – 15.80)	50.76 (8.29 – 94.00)
T4	16.18 (12.60 – 19.20)	14.85 (11.00 – 23.60)	6.38 (3.90 – 10.80)

Table 2.1: Mean (range) of TSH (mU/l) and T4 (pmol/l) values in the three groups.

2.4.2 Declarative Memory Tests

2.4.2a Visual Memory: The Rey-Osterrieth Complex Figure (ROCF)

There were significant differences found between the groups on the copy trial of the ROCF (percentage accuracy scores) ($f = 7.154$; $df = 2, 116$; $p < 0.01$). Post-hoc analysis indicated that these differences lay between the control and subclinical groups ($p < 0.05$) and the control and hypothyroid groups ($p < 0.01$). However there were no differences seen between the subclinical and hypothyroid groups on the copy trial ($p = .741$) (see Figure 2.9).

Significant differences were also seen on the immediate trial (percentage accuracy scores) ($f = 4.87$; $df = 2, 73$; $p < 0.05$). Again post-hoc analysis indicated that these differences lay between the control and subclinical groups ($p < 0.05$) and the control and hypothyroid groups ($p < 0.05$). There were also no differences seen between the subclinical and hypothyroid groups on the immediate trial ($p = .652$) (see Figure 2.9).

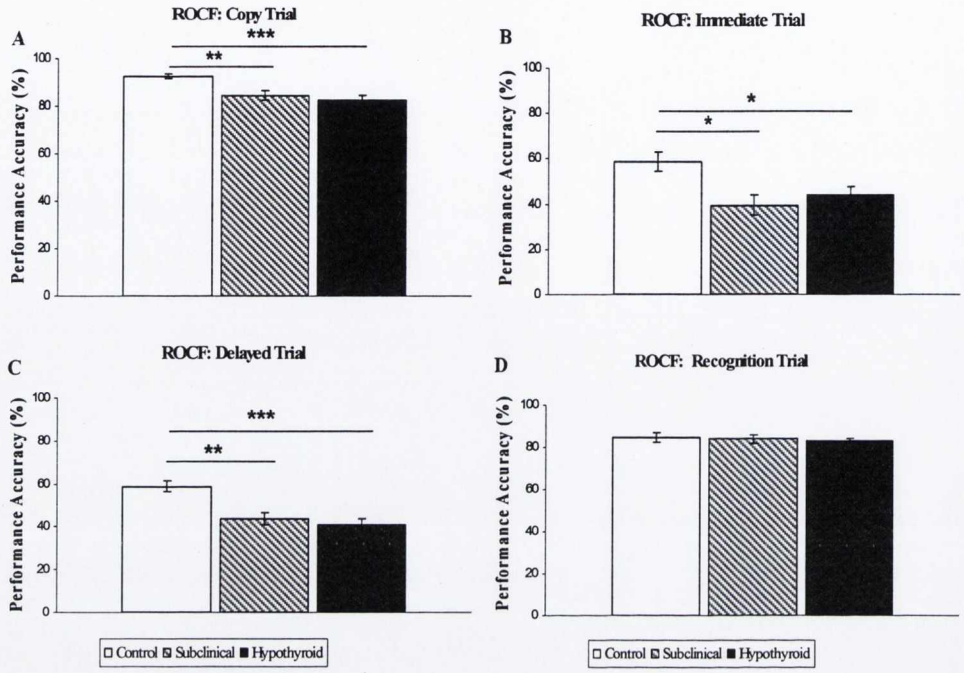

Figure 2.9: The Rey-Osterrieth Figure Task. Mean performance accuracy (percentage) (± SEM) in the control, subclinical hypothyroid and hypothyroid groups. (A) Copy trial, (B) Immediate trial (within 2 minutes), (C) Delayed trial and (D) Recognition trial.

In the delayed trial significant differences are seen once again between the groups (percentage accuracy scores) (f = 10.655; df = 2, 116; $p < 0.001$) with post-hoc tests revealing that these differences lay between the control and subclinical groups ($p < 0.01$) and the control and hypothyroid groups ($p < 0.001$). As with the previous trials, there were no differences found between the subclinical and hypothyroid group (p = .735) (see Figure 2.9).

Analysis of the recognition trial revealed that there were no differences between the groups (f = .272; df = 2, 73; p = .762) (see Figure 2.9).

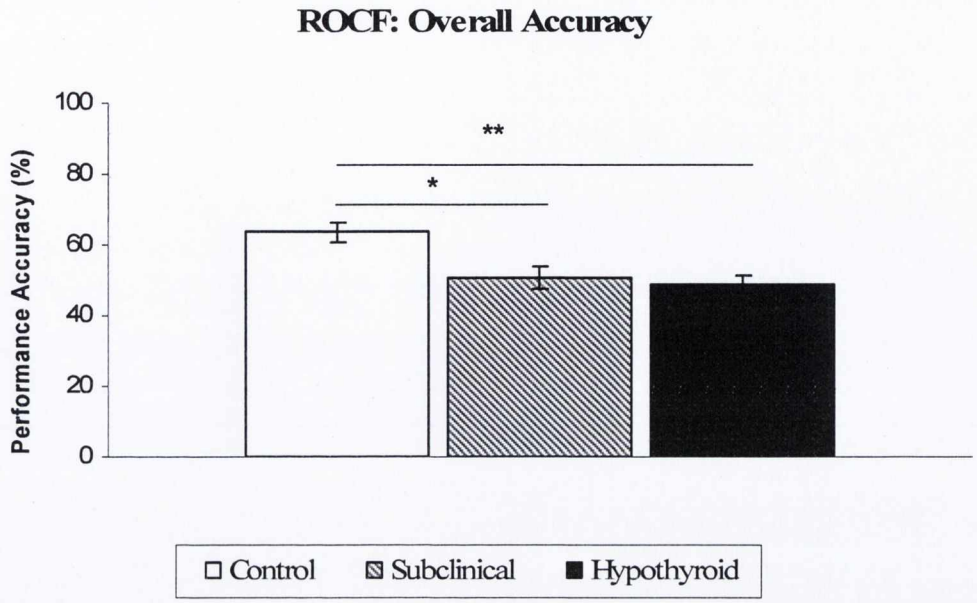

Figure 2.10: The Rey-Osterrieth Figure Task. Mean overall performance accuracy (percentage) (± SEM) in the control, subclinical hypothyroid and hypothyroid groups (Delayed Recall/Copy Trial * 100).

Overall-percentage accuracy scores (designed to measure the delayed recall relative to the initial copy ability) also revealed significant differences between the groups ($f = 7.305$; $df = 2, 116$; $p < 0.01$). The differences between the control and subclinical groups ($p < 0.05$) and the control and hypothyroid groups ($p < 0.01$) remained, though the subclinical and hypothyroid groups did not differ ($p = .851$) (Figure 2.10).

2.4.2b Associative memory: Face-Name Learning and Recall

The results of a repeated measures ANOVA across the four learning trials of the task (blocks 1-4) found that there was a significant difference across the trials as would be expected in a learning task ($f = 56.763$; $df = 2, 116$; $p < 0.001$), there was a significant improvement in accuracy across encoding blocks. Performance at block one was significantly improved by block 2 ($p < 0.001$), 3 ($p < 0.001$) and 4 ($p < 0.001$). Performance at block 2 was significantly improved by block 3 ($p < 0.01$) and 4 ($p < 0.001$). While performance at block 3 was significantly improved by block 4 ($p < 0.001$). There was also an overall significant difference between the groups on their ability to encode and subsequently recall the face-name pairs ($f = 7.763$; $df = 2, 116$; $p < 0.01$), but there was no

significant interaction between the trials and groups ($f = 1.815$; $df = 6, 116$; $p = .095$). The group differences were significantly different between the control and subclinical group ($p < 0.01$) and the control and hypothyroid group ($p < 0.01$), though the subclinical and hypothyroid groups did not differ ($p = .896$) (see Figure 2.11).

A total score was computed of all faces learnt in the encoding trials (blocks 1-4). Group differences were significant ($f = 5.619$; $df = 2, 116$; $p < 0.01$), with control groups remembering significantly more faces than the subclinical group ($p < 0.05$) and the hypothyroid group ($p < 0.01$) (see Figure 2.11 Panel B). Again, as with all of the other face-name analysis, there were no differences seen between the subclinical and hypothyroid group ($p = .780$).

Analysis of the delayed recall using an ANOVA, showed significant differences between the groups to successfully recall the face-name pairs after a 20 minute delay ($f = 5.742$; $df = 2, 116$; $p < 0.01$). Again there were significant differences between the control group and the subclinical group ($p < 0.05$) and the control group and the hypothyroid group ($p < 0.01$) (see Figure 2.11 Panel C), there were no differences seen between the subclinical and hypothyroid group ($p = .719$).

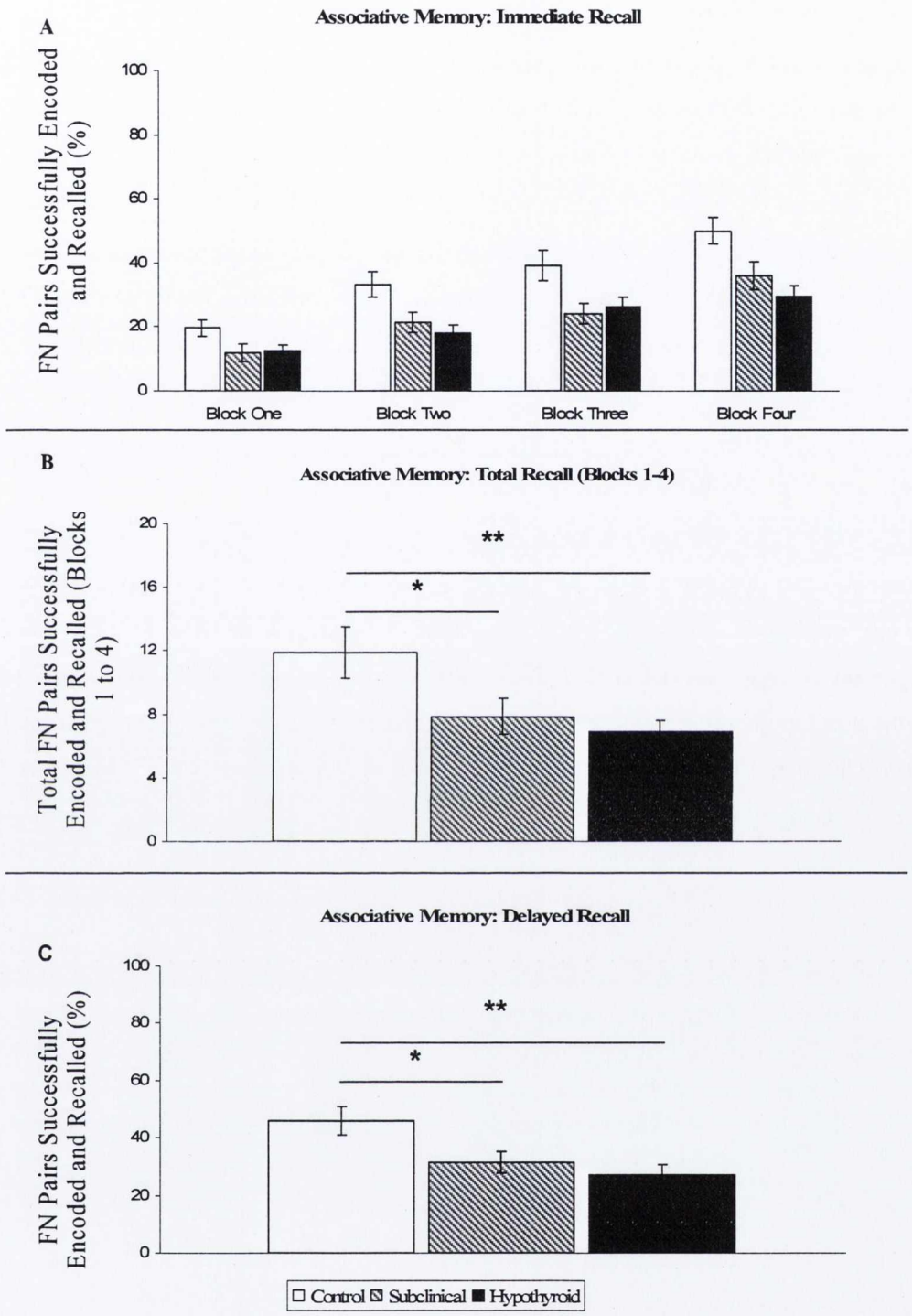

Figure 2.11: Panel A: Mean (± SEM) face-name pairs successfully recalled across each of the four recall blocks; Panel B: Total number of face-name pairs successfully encoded across the 4 learning trials at Session 1 (expressed as Mean ± SEM); Panel C: Mean (± SEM) pairs recalled 30 minutes post learning (i.e. delayed recall).

2.4.2c Verbal Memory: California Verbal Learning Test (CVLT-II)

Verbal learning was measured using the California Verbal Learning Test (CVLT-II), which assesses not only the amount of material learnt but also how learning occurs or fails to occur. There are several trials and trial types. Focusing first on the learning trials for List A (Trials 1-5), there was a significant main effect of trial as would be expected in a learning task ($f = 149.030$; $df = 4, 72$; $p < 0.001$). In a similar fashion to the face-name task, again there is a significant improvement in encoding processes across learning trials as measured by the CVLT. There was a significant improvement from the first trial to block 2 ($p < 0.001$), 3 ($p < 0.001$) 4 ($p < 0.001$), and 5 ($p < 0.001$). Performance at block 2 was significantly improved by block 3 ($p < 0.01$), 4 ($p < 0.001$) and 5 ($p < 0.001$). While performance at block 3 was significantly improved by block 5 ($p < 0.01$). There were no significant differences between blocks 3 and 4, or blocks 4 and 5. There was also a significant main effect of group ($f = 7.808$; $df = 2, 72$; $p < 0.01$), but no interaction between trial type and group ($f = 1.672$; $df = 8, 72$; $p = .105$). Post-hoc analysis found that these differences occurred between the control and subclinical groups ($p < 0.01$) and the control and hypothyroid groups ($p < 0.01$); there were no differences between the subclinical and hypothyroid groups ($p = .945$) (see Figure 2.12).

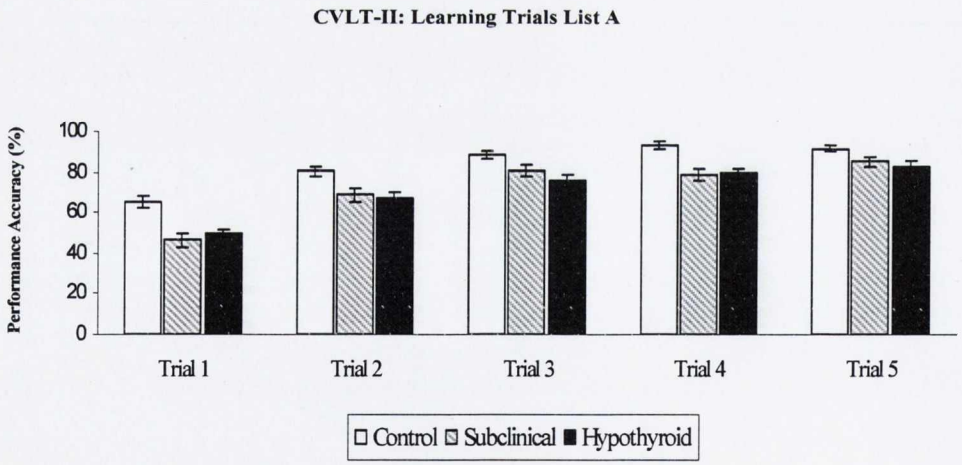

Figure 2.12: Performance accuracy (%) on trials 1-5 of the CVLT-II (expressed as Mean ± SEM).

Next scores on Trial B were examined, again there were significant differences found between the groups on the number of words remembered on Trial B ($f = 4.211$; $df = 2, 72$; $p < 0.05$). It was only the control group and hypothyroid group that were significantly different at post-hoc analysis ($p < 0.05$), there were no significant differences between the control and subclinical group ($p = .08$), or the subclinical and hypothyroid group ($p = .897$) (see Table 2.2).

Group	Control	Subclinical	Hypothyroid
Trial B	55.88 (± 3.53)	44.94 (± 3.10)	43.07 (± 2.67)

Table 2.2: Mean (±) SEM performance accuracy on trial B of the CVLT

Short-delay free and cued recall, along with long-delay free and cued recall were also examined (see Figure 2.13). On the short delay trials there were significant differences between the groups on both the free recall ($f = 8.816$; $df = 2, 72$; $p < 0.001$) and the cued recall ($f = 5.210$; $df = 2, 72$; $p < 0.01$). In the free recall trial there were significant differences between the control group and both the subclinical group ($p < 0.01$) and the hypothyroid group ($p < 0.001$), though there were no differences between the subclinical and hypothyroid group ($p = .932$). However in the cued recall there was only a significant difference between the control and hypothyroid groups ($p < 0.01$), the subclinical and control groups did not differ ($p = .051$), nor did the subclinical and hypothyroid groups ($p = .839$).

The long delay trials also showed significant differences between the groups on both the free recall ($f = 7.261$; $df = 2, 72$; $p < 0.01$) and the cued recall ($f = 5.983$; $df = 2, 72$; $p < 0.01$). However in this instance there were significant differences between the control group and both the subclinical and hypothyroid group in the free recall ($p < 0.05$; $p < 0.01$) and in the cued recall ($p < 0.05$; $p < 0.01$); the subclinical and hypothyroid groups did not differ on long-free or cued recall ($p = .514$; $p = .965$).

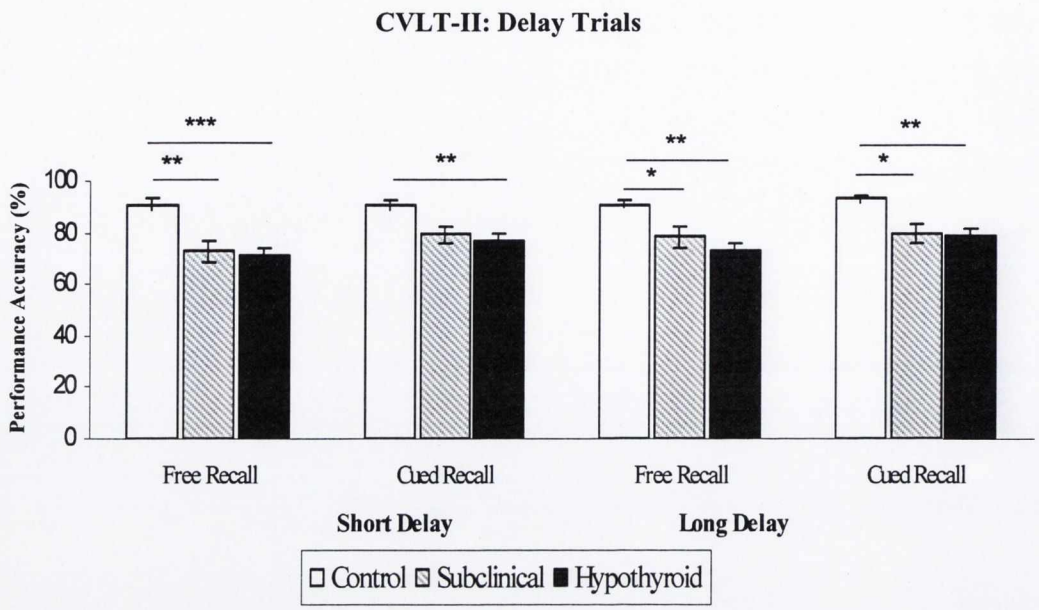

Figure 2.13: Performance accuracy (%) on Delay Trials of the CVLT-II (expressed as Mean ± SEM).

2.4.3 Self-Rating Memory Questionnaires

2.4.3a Everyday Memory Questionnaire

Everyday memory problems were assessed using the EMQ (see Figure 2.14), analysis found that there were significant differences between the groups on their total score (f = 3.359; df = 2, 73; $p < 0.05$). Post-hoc comparisons could not identify where these differences lay, the control group did not differ from the subclinical (p = .977) or hypothyroid groups (p = .145), and the subclinical and hypothyroid groups did not differ from each other (p = .063). Though the hypothyroid group reported more memory problems (M = 6.98, SEM = 0.44) than the subclinical (M = 5.5, SEM = 0.46), and control groups (M = 5.66, SEM = 0.41).

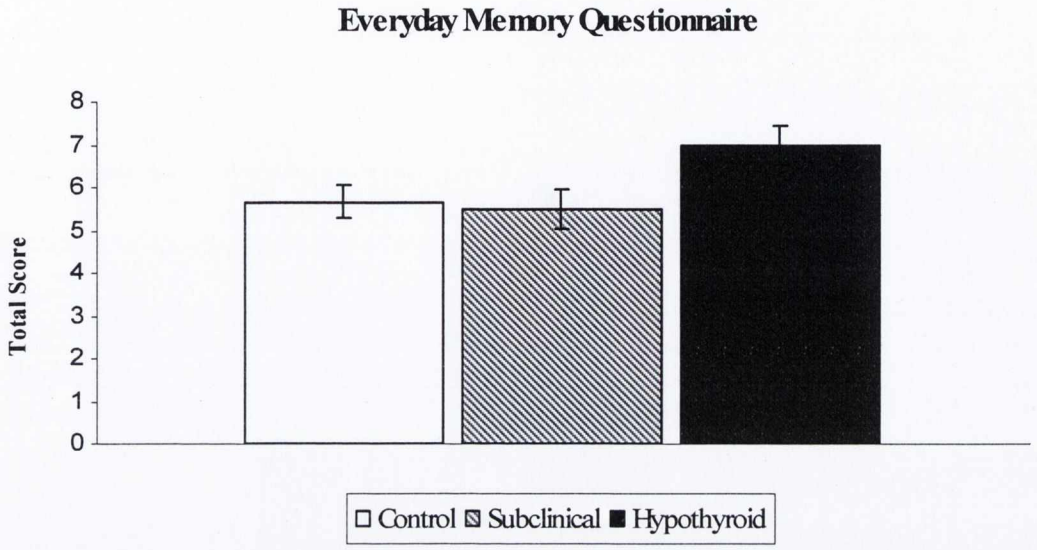

Figure 2.14: Self-reported memory problems on the EMQ (expressed as Mean of the Total Score ± SEM). The Total Score was calculated using the square root of the sum of all of the questions from the EMQ.

2.4.3b Mundane Memory Questionnaire (MMQ)

Memory for mundane everyday tasks was assessed using a repeated measures ANOVA across days (days 1-4) in the control, subclinical and hypothyroid groups. A significant effect of day was found ($f = 28.828$; $df = 3, 116$; $p < 0.001$) as would be expected, with participants remembering more about days 1 then 2, 3 or 4. There was a significant decrease in the amount of information recalled with an increase in day. There were significantly more events remembered at day 1 than 2 ($p < 0.01$), 3 ($p < 0.001$) or 4 ($p < 0.001$). There were significantly more events remembered at day 2 than 3 ($p < 0.01$) or 4 ($p < 0.001$). Finally there were significantly more events remembered at day 3 than 4 ($p < 0.001$). There was no interaction between group and day (= .413; $df = 6, 116$; $p = .87$), however there was a significant overall main effect of group ($f = 5.406$; $df = 1, 116$; $p < 0.05$) (see Table 2.3).

Group	Control	Subclinical	Hypothyroid
Day 1	23.80 (± 0.48)	23.00 (± 0.43)	21.80 (± 0.36)
Day 2	22.40 (± 0.67)	22.59 (± 0.61)	20.59 (± 0.52)
Day 3	22.00 (± 0.72)	21.05 (± 0.65)	19.59 (± 0.55)
Day 4	20.30 (± 0.92)	20.24 (± 0.83)	18.47 (± 0.70)

Table 2.3 Performance accuracy expressed as Mean (± SEM) on MMQ.

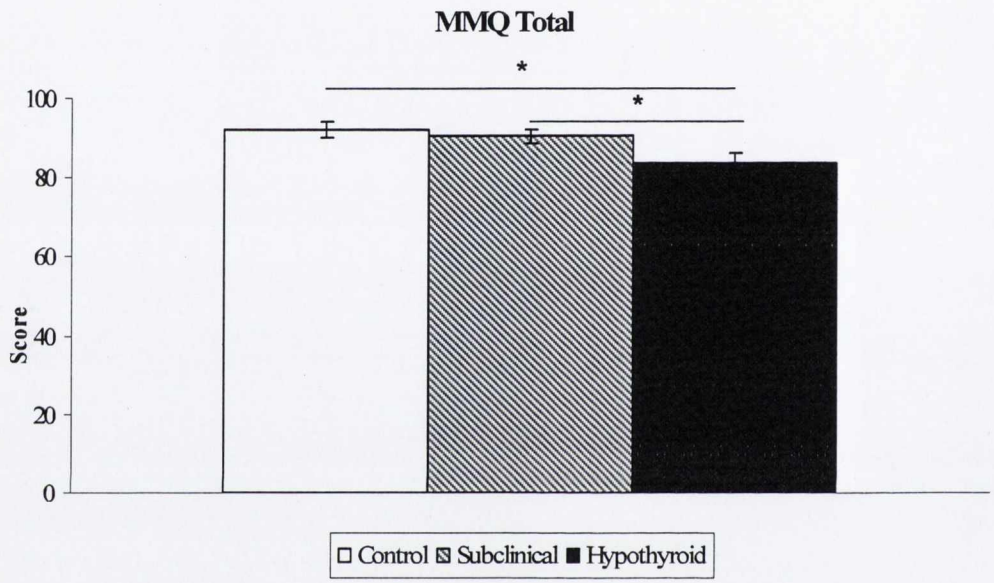

Figure 2.15: Performance accuracy expressed as Mean (± SEM) scores on the MMQ Total score for the control, subclinical and hypothyroid groups.

Post-hoc analysis found that while there was a significant difference between the control groups and the hypothyroid group ($p < 0.05$), and the subclinical group and the hypothyroid group ($p < 0.05$), there were no significant differences between the control group and the subclinical group ($p = .869$) (see Figure 2.15).

2.4.3c Self-Rating Scale (SRS)

A self report of overall memory performance at the end of testing was examined using the SRS. As data was not of parametric quality, non-parametric analysis was carried out. Results on the Kruskal-Wallis test found that there were no differences between the groups in their self-rating of memory performance (χ^2 (2, $N = 75$) = 5.392; $p = .067$).

2.4.4 Executive Functioning

2.4.4a Behavioural Assessment of Dysexecutive Syndrome:

Key Search Test

Executive functioning, as measured by the Key Search Test of the BADS, was analysed using an ANOVA. There were no significant differences between the groups on their ability to draw an efficient path in the Key Search Test (χ^2 (2, N = 66) = 2.61; p = .271).

Zoo Map Test

There were also no significant differences between the groups in the Zoo Map Test (χ^2 (2, N = 66) = .119; p = .942).

DEX

Total scores on the DEX questionnaire, revealed that there were no significant differences between the groups (χ^2 (2, N = 76) = 4.48; p = .106).

2.4.4b Focused Attention

Focused attention (attention trial in the Face-Name task) differences were examined across the groups. There was a significant effect of trial (f = 16.862; df = 3, 109; $p < 0.001$), with all groups improving in accuracy as they progressed through the trials (see Table 2.4). There was no significant main effect of group on the performance accuracy (f = .276; df = 2, 109; p = .759), and no significant interaction (f = .706; df = 6, 109; p = .645).

Group	Control	Subclinical	Hypothyroid
Trial 1	80.74 (± 4.43)	82.22 (± 3.84)	85.92 (± 3.29)
Trial 2	88.70 (± 4.01)	90.56 (± 3.47)	90.82 (± 2.97)
Trial 3	87.59 (± 4.18)	89.17 (± 3.62)	92.45 (± 3.10)
Trial 4	90.19 (± 3.65)	93.06 (± 3.16)	91.84 (± 2.71)

Table 2.4: Mean (± SEM) on performance accuracy (%) for focused attention.

There was also a significant effect of trial (f = 9.087; df = 3, 107; $p < 0.001$), with all groups responding slower as they progressed through the trials (see Table 2.5). However there was no significant main affect of group in reaction time (ms) (f = 1.707; df = 2, 107; p = .186), and no significant interaction (f = 1.809; df = 6, 107; p = .097).

Group	Control	Subclinical	Hypothyroid
Trial 1	219.87 (± 19.98)	198.91 (± 17.55)	252.99 (± 14.99)
Trial 2	244.52 (± 12.89)	256.92 (± 11.32)	264.61 (± 9.67)
Trial 3	245.03 (± 14.26)	249.76 (± 12.52)	264.21 (± 10.69)
Trial 4	243.59 (± 12.51)	259.64 (± 10.99)	268.76 (± 9.38)

Table 2.5: Mean (± SEM) reaction time (ms) for focused attention.

2.4.4c Working Memory: The n-Back Task (0-Back, 1-Back & 2-Back Levels)

Using a repeated measures ANOVA, there was a significant main effect of load (f = 180.551; df = 2, 101; $p < 0.001$) as would be expected. Performance at the zero-back was significantly higher than at the -1back ($p < 0.001$) or 2-back ($p < 0.001$). Performance at the 1-back was also significantly quicker than the 2-back ($p < 0.001$). There was also a significant difference between the groups in performance accuracy across all levels of the *n*-Back task (f = 3.865; df = 2, 101; $p < 0.05$) and a significant interaction between group and level (f =2.680; df = 4, 101; $p < 0.05$). Post-hoc analysis showed that these differences lay between the control and hypothyroid groups only ($p < 0.05$), the control and subclinical groups did not differ (p = .088), nor did the subclinical and hypothyroid groups (p = .927).

Further examination of each level separately, found that there was a significant difference between the groups at the one-back level (f = 4.550; df = 2, 113; $p < 0.05$), and the two-back level (f = 3.556; df = 2, 103; $p < 0.05$), but no difference at the zero-back level (f = .050; df = 2, 113; p = .951). At the one-back level these differences were evident between the control and hypothyroid group ($p < 0.01$), the control and subclinical groups did not differ (p = .190), nor did the subclinical and hypothyroid groups (p = .423). At the two-back ($p < 0.05$) level these differences were evident between the control and hypothyroid group the control and subclinical groups did not differ (p = .061), nor did the subclinical and hypothyroid groups (p = .997) (see Figure 2.16).

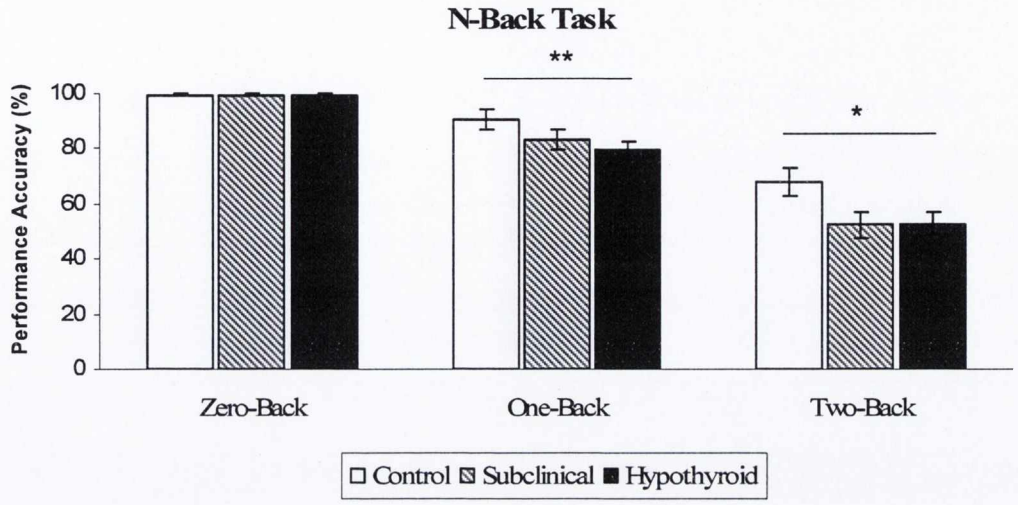

Figure 2.16: Percentage performance accuracy (presented as Mean + SEM) across the 3 levels of the n-back task, zero-, one- and two-back.

The mean "switch cost" in accuracy – accuracy in the 2-back condition minus accuracy in the 1-back condition was also computed and analysed, there were no differences among the groups on their "switch cost" in accuracy ($f = 1.134$; $df = 2, 103$; $p = .326$).

Reaction time analysis (median RT in ms) revealed a significant main effect of load ($f = 77.185$; $df = 2, 80$; $p < 0.001$) as would be expected (see Table 2.6); however, in this case all groups showed quicker reaction times at the 2-back level than the 0-back ($p < 0.001$) and 1-back ($p < 0.001$) level. There was also a significant interaction between the groups across the levels of the *n*-Back task ($f = 2.966$; $df = 4, 80$; $p < 0.001$). However there was no significant main effect of group ($f = 2.347$; $df = 2, 80$; $p = .102$).

Group	Control	Subclinical	Hypothyroid
0-Back	606.52 (± 23.09)	650.15 (± 24.12)	672.90 (± 18.59)
1-Back	502.59 (± 54.56)	579.19 (± 57.10)	673.33 (± 43.94)
2-Back	300.08 (± 37.15)	381.59 (± 38.81)	291.13 (± 29.92)

Table 2.6: Mean (± SEM) reaction time (ms) for the n-back task.

2.4.4d Response Inhibition: The Stroop Task - 'Naming Coloured Words' Version

Tests of normality revealed that the stroop data was not normally distributed, as a result a series of non-parametric analyses were carried out. Where significant results were found a priori planned comparisons were used to test specific differences between the SCH and control groups (comparison 1) and the Hypothyroid and control groups (comparison 2). A bonferroni adjustment to the alpha level (alpha / no. of comparisons; 0.05 / 2 = 0.025) was applied to these comparisons, to maintain a reasonable alpha level across all tests.

There were no differences between the groups in accuracy, for either the congruent condition [χ^2 (2, 114) = 2.375; p = .305] or incongruent condition [χ^2 (2, 114) = 2.159; p = .340]. Differences between the groups were found for the congruent condition for reaction time [χ^2 (2, 114) = 7.206; $p < 0.05$], though not for the incongruent reaction time [χ^2 (2, 114) = .710; p = .701]. Results of the Mann-Whitney planned comparisons found that there were no significant differences between the control group and the subclinical group (Z = -.635; p = .526), however the control group and the hypothyroid group were significant (Z = -2.571; $p < 0.025$) (see Figure 2.17).

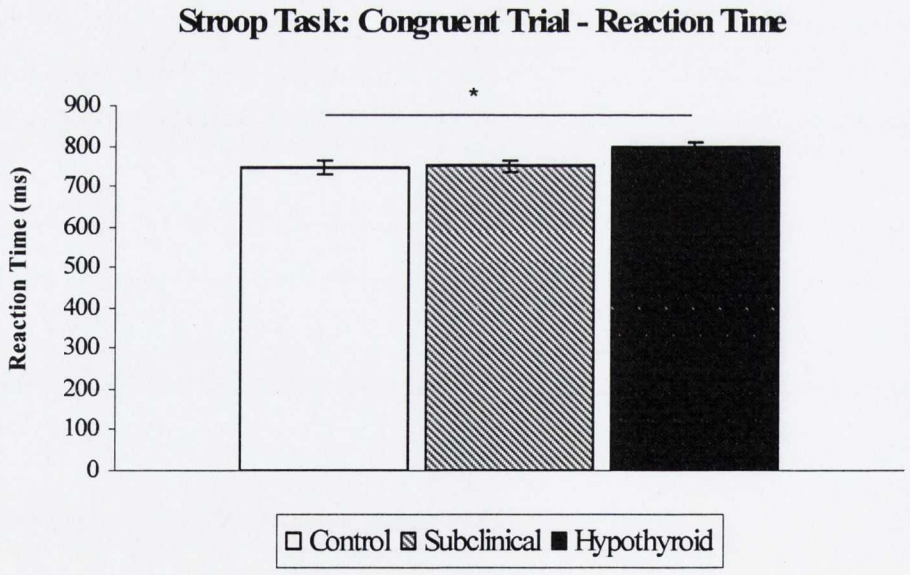

Figure 2.17: Median reaction time (expressed as Median ± SEM) in the control, subclinical and hypothyroid group.

Next the errors of commission were analysed, in the congruent trials there was no significant difference between the groups [χ^2 (2, 114) = 3.387; p = .184]. In the incongruent trial there was also no significant difference in the number of errors committed across the groups [χ^2 (2, 114) = 3.077; p = .215].

2.4.4e Sustained Attention to Response Task (SART)

Tests of normality revealed that the SART data was not normally distributed, as a result a series of non-parametric analyses were carried out. There were two trial types in the SART, go and no-go. For performance accuracy (%) there were no significant differences found between the groups for either the go trial [χ^2 (2, 73) = 1.656; p = .437], or the no-go trial [χ^2 (2, 73) = 5.969; p = .051]. There were also no significant differences found in reaction time (ms) for the go trial [χ^2 (2, 73) = 2.258; p = .323]. Errors of omission (EOO – go trial) and errors of commission (EOC – no-go trial) were also calculated, again there were no differences found on either EOC [χ^2 (2, 73) = .568; p = .753] or EOO [χ^2 (2, 73) = 3.226; p = .199] between the groups.

2.4.4f Dual Attention to Response Task

Tests of normality revealed that the DART data was not normally distributed, as a result a series of non-parametric analyses were carried out. There were three trial types in the DART, go and no-go and grey. For performance accuracy (%) there were no significant differences found between the groups for the go trial [χ^2 (2, 68) = 3.919; p = .141], the no-go trial [χ^2 (2, 68) = 2.164; p = .339], or the grey trial [χ^2 (2, 68) = 4.487; p = .106]. There were also no significant differences found in reaction time (ms) for the go trial [χ^2 (2, 68) = .518; p = .772], or the grey trial [χ^2 (2, 68) = .610; p = .737]. Errors of omission (EOO – go trial and grey trial) and errors of commission (EOC – no-go trial) were also calculated, again there were no differences found on either of the EOC trials [χ^2 (2, 68) = 1.000; p = .606], on the EOO go trial [χ^2 (2, 68) = 2.957; p = .228], EOO grey trial [χ^2 (2, 68) = 4.320; p = .115] between the groups.

2.4.5 Premorbid IQ - National Adult Reading Test 2nd Ed (NART)

Full-scale IQ was measured using the NART, there were significant differences between the groups on their IQ scores (f = 9.768; df = 2, 115; $p < 0.001$). Post-hoc analysis revealed that these differences were between the control group and the hypothyroid group ($p < 0.001$), and also the subclinical group and the hypothyroid group ($p < 0.05$). The control

group and the subclinical group both had higher IQ scores than the hypothyroid group (see Figure 2.18, and Table 2.7).

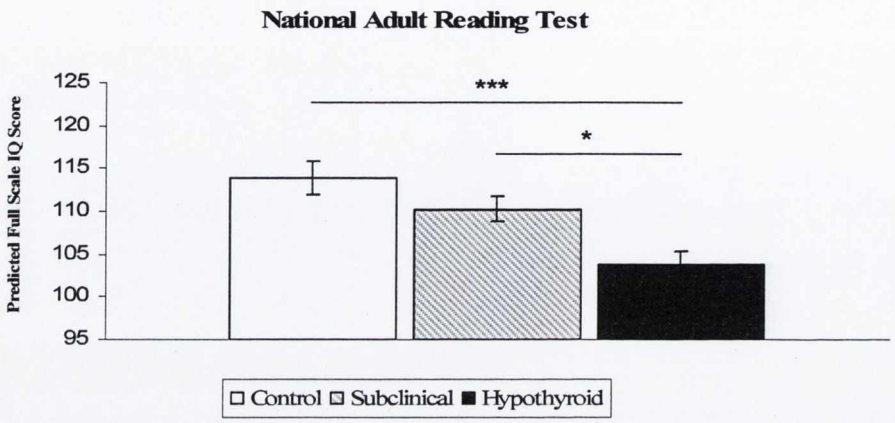

Figure 2.18: Predicted full scale (expressed as Mean ± SEM) IQ, derived using the National Adult Reading Test.

2.4.5.1 Age and Education Profile

To further investigate the differences between the groups, age and education differences were examined. There were significant age differences between the groups on age (f = 10.065; df = 2, 116; $p < 0.001$) (see Table 2.7). The control group was significantly younger than the subclinical group ($p < 0.01$). The hypothyroid group (was also significantly younger than the subclinical group ($p < 0.001$).

However there were no differences between the groups on their years spent in full-time education (f = 1.841; df = 2, 115; p = .163).

Group	Control	Subclinical	Hypothyroid
Age	42.23 (± 1.82)	50.51 (± 1.7)	40.9 (± 1.46)
Gender (M : F)	1 : 30	2 : 35	3 : 48
Education (yrs)	14.07 (± 0.58)	12.68 (± 0.48)	12.97 (± 0.44)
Predicted IQ	113.90 (± 1.93)	110.24 (± 1.45)	103.73 (± 1.60)

Table 2.7 Mean (± SEM) age, years spent in full-time education and predicted IQ scores. Gender ratio (males:females).

2.4.6 Affective Measurements

2.4.6a Hospital Anxiety and Depression Scale

Anxiety and depression was measured using the HADS. Significant differences were found between the groups on the HADS-Depression scale ($f = 6.598$; $df = 2, 116$; $p < 0.01$). Post-hoc analysis revealed that these differences lay between the control and hypothyroid group ($p < 0.01$). There were no significant differences between the control and subclinical groups ($p = .070$), and the subclinical and hypothyroid groups ($p = .385$). Significant differences were also found between the groups on the HADS-Anxiety scale ($f = 7.581$; $df = 2, 116$; $p < 0.01$). Post-hoc analysis revealed that these differences lay between the control and subclinical group ($p < 0.01$) and the control and hypothyroid group ($p < 0.01$), there were no significant differences between the subclinical and hypothyroid groups ($p = .837$) (see Figure 2.19).

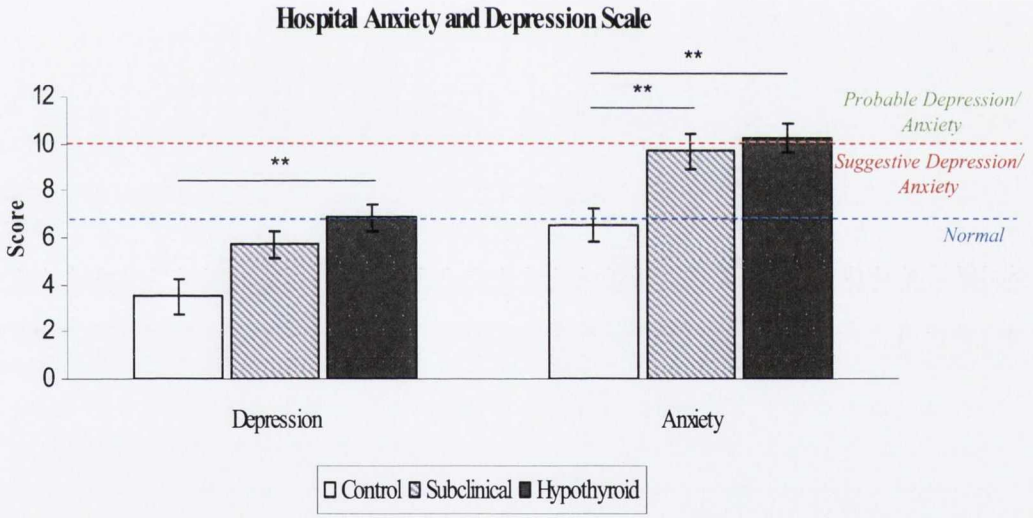

Figure 2.19: Mean (± SEM) score on the HADS across the control, subclinical and hypothyroid groups for both depression and anxiety.

2.4.6b Beck Depression Inventory II (BDI-II)

Depression was also measured using the BDI-II, and again significant differences were found between the groups in their depression scores ($f = 3.44$; $df = 2, 72$; $p < 0.05$). Post-hoc analysis revealed that these differences lay between the control and hypothyroid group

($p < 0.05$); there were no significant differences between the control and subclinical groups $p = .395$), or the subclinical and hypothyroid groups ($p = .467$) (see Figure 2.20).

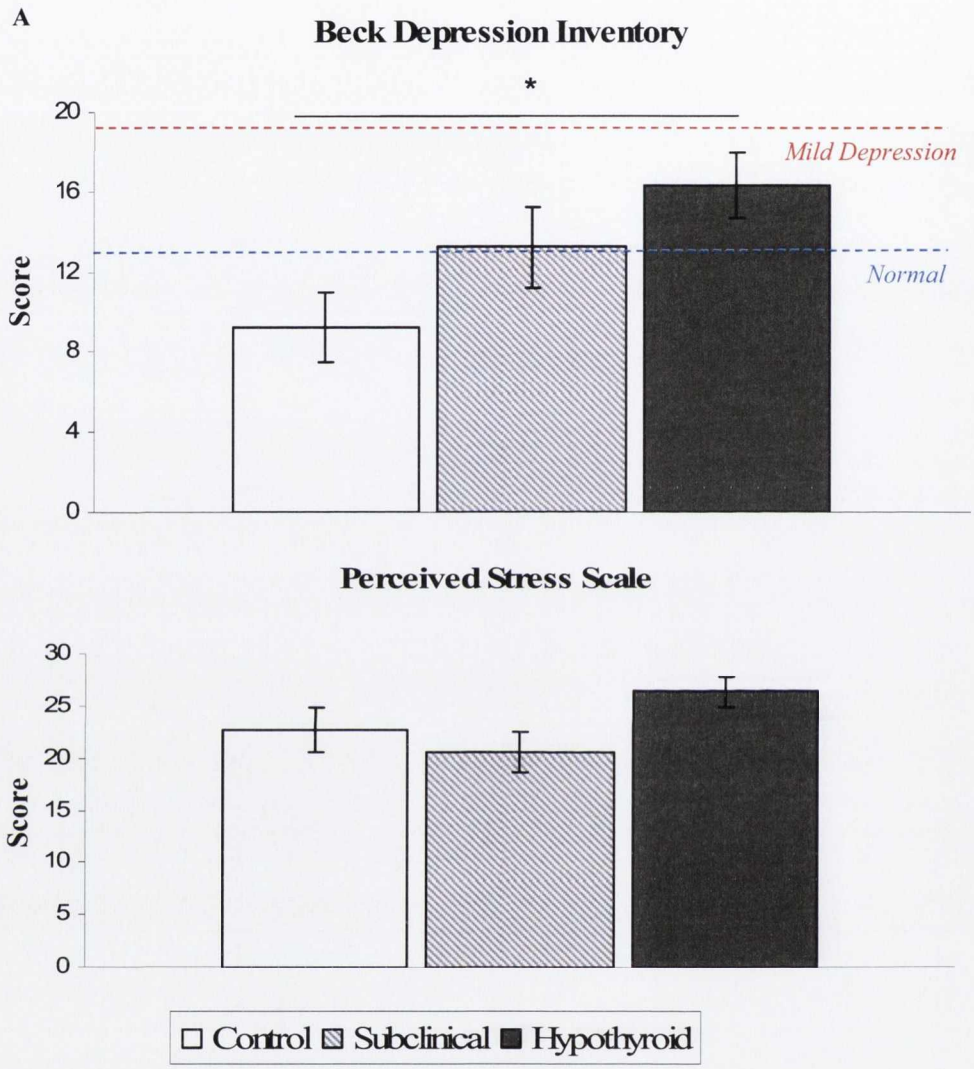

Figure 2.20: Upper Panel: Scores on the BDI in the control, subclinical and hypothyroid groups (expressed as Mean ± SEM). Lower Panel: PSS scores across the groups (expressed as Mean ± SEM).

2.4.6c Perceived Stress Scale (PSS)

Stress was measured in all participants using the PSS, while there were no significant differences found between the groups ($f = 3.037$; $df = 2, 73$; $p = .054$), there does appear to

be a trend showing as indicated in Figure 2.20; subclinical participants appear to report less stress then control and hypothyroid groups .

2.4.7 Age Analysis

As age effects have been reported on many tests of memory in the current literature, and age was significantly different between the groups, significant results were re-analysed in order to ensure that the group effects remained and that no age effects existed in the current data. Only data that was significantly impacted by age is reported. A relationship between age and the DVs was first examined using correlations, and then age at first visit was used as the covariate in ANCOVA analysis of the DVs.

2.4.7.1 Visual Memory: The Rey-Osterrieth Complex Figure (ROCF)

There was a significant, medium, negative relationship between age and delayed recall (r = -.301; n = 118; $p < 0.01$), and also age and overall accuracy (r = -.303; n = 118; $p < 0.01$) on the ROCF, with increase in age associated with decreased performance on recall. When age was included as a covariate in the analysis of the ROCF, a significant effect of age was found in the delayed recall (f = 13.878; df = 1, 114; $p < 0.001$; partial eta squared = .109), however the main effect of group still remained significant (f = 11.516; df = 2, 114; $p <$ 0.001; partial eta squared = .168). There was also a significant effect of age on the overall accuracy score of the ROCF, which is not surprising as it is calculated using the delayed score (f = 13.418; df = 1, 114; $p < 0.001$). A significant main effect of group was also still evident after the inclusion of age as a covariate (f = 7.949; df = 2, 114; $p < 0.01$). A table of the adjusted means for the delayed recall and overall accuracy is presented below.

Group	Control	Subclinical	Hypothyroid
Delayed Recall	57.764 (± 3.05)	47.102 (± 2.88)	39.392 (± 2.38)
Overall Accuracy	62.433 (± 3.07)	54.114 (± 2.91)	47.079 (± 2.40)

Table 2.8 Age-adjusted mean (± SEM) scores on ROCF.

2.4.7.2 Associative memory: Face-Name Learning and Recall

A significant relationship was seen between age and face-name recall at block one (r = -.238; n = 118; $p < 0.01$), block two (r = -.226; n = 118; $p < 0.05$), block three (r = -.408; n = 118; $p < 0.001$), block four (r = -.390; n = 118; $p < 0.001$), and delayed recall (r = -.320; n = 118; $p < 0.001$). When age was included as a covariate in the ANCOVA, it had a significant impact on face-name pair recall (f = 26.16; df = 1, 114; $p < 0.001$; partial eta

squared = .187), however a significant main effect of group still remained (f = 9.936; df = 2, 114; $p < 0.001$; partial eta squared = .148). On the delayed recall trial, a significant effect of age was also seen (f = 16.198; df = 1, 114; $p < 0.001$; partial eta squared = .124), though again the main effect of group remained significant (f = 6.983; df = 2, 114; $p < 0.01$; partial eta squared = .109) (see Table 2.13).

Group	Control	Subclinical	Hypothyroid
Total Recall	34.172 (± 2.66)	27.403 (± 2.52)	19.454 (± 2.08)
Delayed Recall	44.182 (± 4.14)	36.532 (± 3.92)	25.203 (± 3.23)

Table 2.9: Age-adjusted mean (± SEM) scores on face-name task.

2.4.7.3 Working Memory: The n-Back Task

There was also a significant negative relationship between age and accuracy levels of the *n* -back at the 1-back level (r = -.242; n = 118; $p < 0.05$), and the 2-back level (r = -.267; n = 118; $p < 0.01$). The AVCOVA results revealed that age was significantly correlated with accuracy on the 1-back (f = 11.227; df = 1, 110; $p < 0.01$; partial eta squared = .093), and 2-back (f = 8.861; df = 1, 100; $p < 0.01$; partial eta squared = .080) levels of the *n*-back task. However, a main effect of group remained on both the 1-back (f = 6.575; df = 2, 110; $p < 0.01$; partial eta squared = .109) and 2-back levels (f = 4.204; df = 2,100; $p < 0.05$; partial eta squared = .074) above and beyond the effect of age (see Table 2.14).

Group	Control	Subclinical	Hypothyroid
1-Back	89.690 (± 3.67)	85.398 (± 3.43)	73.526 (± 2.94)
2-Back	67.481 (± 4.67)	56.252 (± 4.70)	50.932 (± 3.88)

Table 2.10: Age-adjusted mean (± SEM) scores on *n*-back task

2.4.7.4 Hospital Anxiety and Depression Scale

There was a negative relationship between age at visit and the depression scores of the HADS (r = -.221; n = 118; $p < 0.05$), though no relationship between age and anxiety scores. Depression scores covaried significantly with age (f = 7.347; df = 1, 114; $p < 0.01$; partial eta squared = .067) on the HADS, though once more the main effect of group remained (f = 6.848; df = 2, 114; $p < 0.01$; partial eta squared = .107) (see Table 2.11).

2.4.7.5 Beck Depression Inventory II

The relationship between age and depression scores on the BDI was also significant (r = -.254; n = 74; $p < 0.05$). Age also significantly covaried with depression (f = 5.480; df = 1, 74; $p < 0.05$; partial eta squared = .073), though yet again the group differences on depression scores remained significant (f = 3.322; df = 2, 74; $p < 0.05$; partial eta squared = .087) (see Table 2.11).

Group	Control	Subclinical	Hypothyroid
Depression – HADS	3.312 (± .701)	6.285 (± .663)	6.335 (± .547)
Depression – BDI	8.752 (± 2.118)	14.886 (± 2.065)	15.013 (± 1.456)

Table 2.11 Age-adjusted mean (± SEM) scores on the HADS depression scale and the BDI

2.4.8 TSH Correlations

Pearson product-moment correlations between Log10 TSH levels at session one and all dependent variables were calculated within each group. For the control participants there was a significant medium negative correlation between TSH and MMQ recall score on day 3 (r = -.412, n = 26, $p < 0.05$), with high levels of TSH associated with lower recall scores. There was also a significant medium relationship between TSH and performance accuracy at the 2-back level of the n-back task (r = .447, n = 25, $p < 0.05$), this relationship was positive, indicating that higher TSH levels were associated with better accuracy at the 2-back level of the n-back task. In addition, there was also a significant relationship between TSH levels and switch cost accuracy in the n-back task (r = .447, n = 25, $p < 0.05$). There was also a large positive relationship between TSH levels and reaction time on the grey trial of the DART (r = .665, n = 13, $p < 0.05$).

For the subclinical group there was a significant negative relationship between TSH and MMQ recall on day 1 (r = -3.83, n = 37, $p < 0.05$), indicating that higher levels of TSH was related to lower recall scores. However there was a positive relationship between TSH and face-name performance accuracy at block 1 (r = .419, n = 37, $p < 0.05$), 3 (r = .419, n = 37, $p < 0.05$), and 4 (r = .417, n = 37, $p < 0.05$). There was also a relationship between TSH and total scores on the face-name task (r = .331, n = 37, $p < 0.05$). Reaction time scores on the focused attention task at block 4 were significantly negatively correlated with TSH levels (r = -.361, n = 35, $p < 0.05$). Recall at trial 2 (r = .492, n = 21, $p < 0.05$), short-delay free recall (r = .500, n = 21, $p < 0.05$), short delay cued recall (r = .536, n = 21, $p <$

0.05), and long delay free recall ($r = .549$, $n = 21$, $p < 0.05$) of the CVLT was significantly positively correlated with TSH levels.

In the hypothyroid group, there was a significant correlation between TSH levels and recognition on the Rey complex figure ($r = .490$, $n = 36$, $p < 0.01$), accuracy at the 2-back level of the n-back task ($r = -.309$, $n = 43$, $p < 0.05$), and error scores in the congruent trial of the stroop task ($r = .311$, $n = 48$, $p < 0.05$).

2.4.9 IQ Matched Analysis

As there were significant differences evident on the NART a secondary IQ matched analysis was conducted. A subgroup was selected from all three groups that were IQ matched to determine whether group differences remained when the groups were matched for scores on the NART. Then the control participants in this matched IQ group were compared with the control participants in the non-matched IQ group, ***on all measures from the present*** study to ensure that there were no differences between either of the control groups. There were no significant differences between the two control groups (data not shown). This was extremely important as it was imperative that the subgroup of control participants used for the IQ matched analysis were representation of the group as a whole. This meant that this subgroup of control participants could be legitimately compared to the patient subgroups. There were 22 control participants (Mean IQ = 113.29, SEM = 1.74), 23 Subclinical participants (Mean IQ = 113.61, SEM = 1.73), and 22 hypothyroid participants (Mean IQ = 111.68, SEM = 1.77). Please see Table 2.12 at the end of the results section for details of the baseline cognitive profile of SCH and hypothyroidism following an IQ matched analysis.

2.4.9a Age, Education, IQ

Comparisons were then made on all measures from the current study using the IQ matched groups (N = 66). There were significant age differences between the groups on age ($f = 5.140$; $df = 2, 68$; $p < 0.01$). The control group was significantly younger than the subclinical group ($p < 0.05$). The hypothyroid group was also significantly younger than the subclinical group ($p < 0.05$). There were no differences on years spent in full time education ($f = 2.443$; $df = 2, 68$; $p = .095$) or NART IQ score ($f = .341$; $df = 2, 68$; $p = .712$).

2.4.9b Declarative Memory Tests

Visual Memory: The Rey-Osterrieth Complex Figure (ROCF)

There were no longer significant differences found between the groups on the copy trial of the ROCF (percentage accuracy scores) ($f = 2.139$; $df = 2, 66$; $p = .126$). There were also no differences on the immediate trial ($f = 1.809$; $df = 2, 66$; $p = 177$). In the delayed trial significant differences are seen between the groups ($f = 3.279$; $df = 2, 66$; $p < 0.05$) with post-hoc tests revealing that these differences lay between the control and subclinical groups ($p < 0.05$). There were no differences found between the control and hypothyroid groups ($p = .172$), or the subclinical and hypothyroid group ($p = .817$). Analysis of the recognition trial revealed that there were no differences between the groups ($f = 2.387$; $df = 2, 39$; $p = .105$). There were no significant differences on the overall-percentage accuracy scores (which was designed to measure the delayed recall relative to the initial copy ability) between the groups ($f = 2.444$; $df = 2, 66$; $p = .095$).

Associative memory: Face-Name Learning and Recall

The results of a repeated measures ANOVA across the four learning trials of the task (blocks 1-4) found that there was a significant difference across the trials as would be expected in a learning task ($f = 20.14$; $df = 3, 39$; $p < 0.001$). Performance at block one was significantly improved by block 2 ($p < 0.01$), 3 ($p < 0.001$) and 4 ($p < 0.001$). Performance at block 2 was significantly improved by block 4 ($p < 0.001$). While performance at block 3 was significantly improved by block 4 ($p < 0.01$), There was also an overall significant difference between the groups on their ability to encode and subsequently recall the face-name pairs ($f = 4.064$; $df = 2, 39$; $p < 0.05$), but there was no significant interaction between the trials and groups ($f = 1.756$; $df = 6, 39$; $p = .114$). The group differences were significantly different between the control and hypothyroid group ($p < 0.05$), though the control and subclinical group ($p = .127$), and subclinical and hypothyroid groups did not differ ($p = .921$).

A total score was computed of all faces learnt in the encoding trials (blocks 1-4). Group differences were significant ($f = 3.209$; $df = 2, 66$; $p < 0.05$). Though the post hoc analysis could not reveal where these differences lay; though control groups remembered more faces than the subclinical group ($p = .071$) and the hypothyroid group ($p = .095$). Again, as with all of the other face-name analysis, there were no differences seen between the subclinical and hypothyroid group ($p = .994$). Analysis of the delayed recall using an

ANOVA, showed no significant differences between the groups ability to successfully recall the face-name pairs after a 20 minute delay (f=1.160; df= 2, 66; p = .320).

2.4.9c Verbal Memory: California Verbal Learning Test (CVLT-II)

Focusing first on the learning trials for List A (Trials 1-5), there was a significant main effect of trial as would be expected in a learning task (f= 74.908; df= 4, 34; $p < 0.001$). In a similar fashion to the face-name task, again there is a significant improvement in encoding processes across learning trials as measured by the CVLT. There was a significant improvement from the first trial to block 2 ($p < 0.001$), 3 ($p < 0.001$) 4 ($p < 0.001$), and 5 ($p < 0.001$). Performance at block 2 was significantly improved by block 3 ($p < 0.001$), 4 ($p < 0.001$) and 5 ($p < 0.001$). While there were no differences between block 3, 4 and 5. There was also a significant main effect of group (f = 3.417; df = 2, 34; $p < 0.05$), but no interaction between trial type and group (f= .978; df= 8, 34; p = .456). Post-hoc analysis found that these differences occurred between the control and subclinical groups ($p < 0.05$); there were no differences between the subclinical and hypothyroid groups (p = .809) and the control and hypothyroid groups (p = .108).

Next scores on Trial B were examined, there were no significant differences found between the groups on the number of words remembered on Trial B (f= 1.720; df= 2, 34; p = .194). Short-delay free and cued recall, along with long-delay free and cued recall were also examined. On the short delay trials there were significant differences between the groups on free recall (f= 5.682; df= 2, 34; $p < 0.01$), though not cued recall (f= 2.122; df = 2, 34; p = .135). In the free recall trial there were significant differences between the control group and both the subclinical group ($p < 0.01$) and the hypothyroid group ($p < 0.05$), though there were no differences between the subclinical and hypothyroid group (p = .573).

The long delay trials also showed significant differences between the groups on free recall (f= 4.368; df= 2, 34; $p < 0.05$), though not on cued recall (f= 3.160; df= 2, 34; p = .055). In this instance there were significant differences between the control group and the hypothyroid group in the free recall ($p < 0.05$), the control and subclinical groups (p = .065), and the subclinical and hypothyroid groups (p = .983), did not differ on long-free recall.

2.4.9d Self-Rating Memory Questionnaires

Everyday Memory Questionnaire

Everyday memory problems were assessed using the EMQ, analysis found that there were no significant differences between the groups on their total score ($f = 2.282$; $df = 2, 39$; $p = 116$).

Mundane Memory Questionnaire (MMQ)

Memory for mundane everyday tasks was assessed using a repeated measures ANOVA across days (days 1-4) in the control, subclinical and hypothyroid groups. A significant effect of day was found ($f = 20.929$; $df = 3, 66$; $p < 0.001$) as would be expected, with participants remembering more about days 1 then 2 ($p < 0.01$), 3 ($p < 0.001$) or 4 ($p < 0.001$). They also remembered more at day 2 than day 4 ($p < 0.01$), and at day 3 than day 4 ($p < 0.05$). There was no interaction between group and day (= .709; $df = 6, 66$; $p = .643$), and no significant overall main effect of group ($f = .470$; $df = 1, 66$; $p = .627$).

Self-Rating Scale (SRS)

A self report of overall memory performance at the end of testing was examined using the SRS. As data was not of parametric quality, non-parametric analysis was carried out. Results on the Kruskal-Wallis test found that there were no differences between the groups in their self-rating of memory performance (χ^2 (2, $N = 41$) = 2.902; $p = .234$).

2.4.9e Executive Functioning

Behavioural Assessment of Dysexecutive Syndrome:

Key Search Test

Executive functioning, as measured by the Key Search Test of the BADS, was analysed using an ANOVA. There were no significant differences between the groups on their ability to draw an efficient path in the Key Search Test (χ^2 (2, $N = 36$) = .149; $p = .928$).

Zoo Map Test

There were also no significant differences between the groups in the Zoo Map Test (χ^2 (2, $N = 36$) = 2.99; $p = .223$).

DEX

Total scores on the DEX questionnaire, revealed that there were no significant differences between the groups (χ^2 (2, $N = 42$) = 3.786; $p = .151$).

Focused Attention

Focused attention (attention trial in the Face-Name task) differences were examined across the groups. There was a significant effect of trial ($f = 10.583$; $df = 3, 62$; $p < 0.001$), with all groups improving in accuracy as they progressed through the trials. There was a significant main effect of group on the performance accuracy ($f = 3.428$; $df = 2, 61$; $p < 0.05$), though no significant interaction ($f = .300$; $df = 6, 61$; $p = .936$). Post hoc analysis could not identify where the group difference lay; control vs. subclinical ($p = .055$), control vs. hypothyroid ($p = .079$), and subclinical vs. hypothyroid ($p = .985$).

There was also a significant effect of trial ($f = 8.057$; $df = 3, 61$; $p < 0.01$). However there was no significant main affect of group in reaction time (ms) ($f = 2.166$; $df = 2, 61$; $p = .123$), and no significant interaction ($f = 1.023$; $df = 6, 61$; $p = .366$).

Working Memory: The n-Back Task (0-Back, 1-Back & 2-Back Levels)

Using a repeated measures ANOVA, there was a significant main effect of load ($f = 91.471$; $df = 2, 60$; $p < 0.001$) as would be expected. Performance was significantly more accurate at the 0-back level in comparison to the 1-back ($p < 0.001$) and 2-back ($p < 0.001$) levels. The 1-back level was also significantly more accurate than the 2-back level ($p < 0.001$). There was no significant difference between the groups in performance accuracy across all levels of the *n*-Back task ($f = 1.232$; $df = 2, 60$; $p = .299$) and no significant interaction between group and level ($f = 1.346$; $df = 4, 60$; $p = .257$).

The mean "switch cost" in accuracy – accuracy in the 2-back condition minus accuracy in the 1-back condition was also computed and analysed, there were no differences among the groups on their "switch cost" in accuracy ($f = 1.279$; $df = 2, 60$; $p = .286$).

Reaction time analysis (median RT in ms) revealed a significant main effect of load ($f = 43.938$; $df = 2, 40$; $p < 0.001$) as would be expected, and a significant main effect of group ($f = 4.056$; $df = 2, 40$; $p < 0.05$), with the groups responding quicker at the 2back task load than the 1-back ($p < 0.001$) and the 2-back ($p < 0.001$). The subclinical group responded significantly quicker than the hypothyroid group ($p < 0.05$), though there were no differences between the control group and either the subclinical group ($p = .956$), or the hypothyroid group ($p = .061$). However there was no significant interaction between the groups across the levels of the *n*-Back task ($f = 1.787$; $df = 4, 40$; $p = .139$).

Response Inhibition: The Stroop Task - 'Naming Coloured Words' Version

Tests of normality revealed that the stroop data was not normally distributed, as a result a series of non-parametric analyses were carried out. There were no differences between the groups in accuracy, for either the congruent condition [χ^2 (2, 66) = .634; p = .728] or incongruent condition [χ^2 (2, 66) = 1.806; p = .405]. There were also no differences between the groups for the congruent condition for reaction time [χ^2 (2, 66) = 2.310; p = 315], or for the incongruent reaction time [χ^2 (2, 66) = 2.249; p = .325]. Next the errors of commission were analysed, in the congruent trials there was no significant difference between the groups [χ^2 (2, 66) = 1.168; p = .558]. In the incongruent trial there was also no significant difference in the number of errors committed across the groups [χ^2 (2, 66) = 2.212; p = .331].

2.4.9e Sustained Attention to Response Task (SART)

Tests of normality revealed that the SART data was not normally distributed, as a result a series of non-parametric analyses were carried out. There were two trial types in the SART, go and no-go. For performance accuracy (%) there were no significant differences found between the groups for either the go trial [χ^2 (2, 40) = 2.528; p = .282], or the no-go trial [χ^2 (2, 40) = 1.394; p = .498]. There were also no significant differences found in reaction time (ms) for the go trial [χ^2 (2, 40) = 1.330; p = .514]. Errors of omission (EOO – go trial) and errors of commission (EOC – no-go trial) were also calculated, again there were no differences found on either EOC [χ^2 (2, 40) = .702; p = .704] or EOO [χ^2 (2, 40) = .2.146; p = .342] between the groups.

2.4.9f Dual Attention to Response Task

Tests of normality revealed that the DART data was not normally distributed, as a result a series of non-parametric analyses were carried out. There were three trial types in the DART, go and no-go and grey. For performance accuracy (%) there were no significant differences found between the groups for the go trial [χ^2 (2, 39) = 2.449; p = .294], the no-go trial [χ^2 (2, 39) = .859; p = .651], or the grey trial [χ^2 (2, 39) = 5.742; p = .057]. There were also no significant differences found in reaction time (ms) for the go trial [χ^2 (2, 39) = .779; p = .677], or the grey trial [χ^2 (2, 39) = 1.564; p = .457]. Errors of omission (EOO – go trial and grey trial) and errors of commission (EOC – no-go trial) were also calculated, again there were no differences found on either of the EOC trials [χ^2 (2, 39) = .001; p = .999], on the EOO go trial [χ^2 (2, 39) = 1.497; p = .473], EOO grey trial [χ^2 (2, 39) = 5.583; p = .061] between the groups.

2.4.9g Affective Measurements

Hospital Anxiety and Depression Scale

Anxiety and depression was measured using the HADS. Significant differences were found between the groups on the HADS-Depression scale ($f = 3.488$; $df = 2, 66$; $p < 0.05$). Post-hoc analysis revealed that these differences lay between the control and hypothyroid group ($p < 0.05$); there were no differences between the control and subclinical group ($p = .094$), and the subclinical and hypothyroid group ($p = .950$). Significant differences were also found between the groups on the HADS-Anxiety scale ($f = 3.560$; $df = 2, 6$; $p < 0.05$). Post-hoc analysis revealed that these differences lay between the control and subclinical group ($p < 0.05$); there were no differences between the control and hypothyroid group ($p = .225$), and the subclinical and hypothyroid group ($p = .629$).

2.4.6b Beck Depression Inventory II (BDI-II)

Depression was also measured using the BDI-II, and there were no significant differences were found between the groups in their depression scores ($f = 1.061$; $df = 2, 39$; $p = .356$).

2.4.6c Perceived Stress Scale (PSS)

Stress was measured in all participants using the PSS, there were no significant differences found between the groups ($f = .686$; $df = 2, 39$; $p = .510$).

Test	Associated Area	Trial	Subclinical	Hypothyroid
Visual Memory – ROCF	**Hippocampus**	**Copy**	***No Longer Impaired***	***No Longer Impaired***
		Immediate	***No Longer Impaired***	***No Longer Impaired***
		Delayed	***Impaired***	***No Longer Impaired***
		Recognition	***Not Impaired***	***Not Impaired***
Associative Memory – Face-Name Task	**Hippocampus**	**Immediate**	***No Longer Impaired***	***Remained Impaired***
		Delayed	***No Longer Impaired***	***No Longer Impaired***
Verbal Memory – CVLT	**Hippocampus**	**Immediate**	***Remained Impaired***	***No Longer Impaired***
		Short-Delay	***Remained Impaired***	***Remained Impaired***
		Long- Delay	***Remained Impaired***	***Remained Impaired***
Working Memory – *n*-Back Task	**DLPFC**	**0-Back**	***Not Impaired***	***Not Impaired***
		1-Back	***Not Impaired***	***No Longer Impaired***
		2-Back	***Not Impaired***	***No Longer Impaired***

Table 2.12: Baseline Cognitive Profile in SCH and Hypothyroidism following an IQ matched analysis

2.5. Discussion

In this chapter, the relationship between thyroid dysfunction and memory was assessed. The main aim was to investigate the effects of hypothyroidism on both associative and working memory. In addition, a number of affective measures were included to determine if depression or anxiety was also present. The main findings are listed below:

- Impairments in associative memory were found in patients with an underactive thyroid gland; these impairments were more pronounced in the hypothyroid group than the subclinical group, though this difference was not significant.
- Impairments in verbal memory were found in patients with an underactive thyroid gland, these impairments were more pronounced in the hypothyroid group than the subclinical group, though this difference was not significant.
- Working memory deficits were only found in the hypothyroid group.
- No differences were found on measures of executive functioning or attention between the groups.
- Depression and anxiety scores were significantly higher in patients with an underactive thyroid gland, the differences were more pronounced in the hypothyroid group than the subclinical group, though this difference was not significant.

2.5.1 Associative Memory Impairments in Hypothyroidism

Impairments in memory associated with hypothyroidism were examined. The first hypothesis, that differences in associative memory measures will be found across the groups, was supported. Additionally, it was postulated that these differences would be more pronounced in the hypothyroid group, than the subclinical group, in comparison to the control group; while there deficits appeared to be more pronounced in the hypothyroid group than the subclinical group, they were not significant. Both measures of associative memory used in the current study showed an overall group differences. Results of the ANOVAs found a significant difference between the groups, with the control group scoring significantly higher on the ROCF than both the subclinical and hypothyroid groups on the copy, immediate and delayed trials of the ROCF. However, there were no differences between the subclinical and hypothyroid groups; implying that both groups were equally impaired on these measures of the ROCF. When an overall accuracy score

was calculated, which took into account the initial copy ability and compared the groups on delayed recall, there were still differences between the groups; however they were more pronounced in the hypothyroid group than the subclinical group, though not significantly different. The control group continued to score higher on the overall accuracy in comparison to both the subclinical and hypothyroid groups. Again, this would suggest that while there is a deficit in associative memory present, it is to the same degree in both patient groups. Nevertheless there were no differences evident on the recognition trial of the ROCF, where all the groups performed at the same level.

Hypothyroidism resulted in impaired associative memory as measured by the ROCF in both the subclinical and hypothyroid groups. This supports previous studies that have also found significant differences between the groups on the ROCF (Cooke et al., 2008). In contrast, Miller et al. (2007) found no significant differences between control and hypothyroid groups on the copy and delayed recall trials of the ROCF; their hypothyroid subjects actually performed better than the matched healthy controls on both the copy and delayed recall. Nevertheless, their study did not include the numbers of participants that the present study did, they only tested 10 controls and 14 hypothyroid patients. In addition, they made no adjustment for multiple comparisons; however, in the present study every care was taken to account for multiple comparisons. Taking these strengths into account, the findings from the present study demonstrate that there are specific deficits evident on copy and recall measures of the ROCF in those with an underactive thyroid gland.

However, there were differences between the groups on IQ scores, with the hypothyroid group having a lower IQ score. When a subgroup of all participants were selected based on IQ matched comparisons, there were no longer significant differences between the groups on the copy or immediate trial; however, groups differences still remained on the delayed trial of the ROCF, with the subclinical group performing worse than the control group. Taking into account initial differences in the IQ scores of the groups, there still remains a significant impairment on delayed measures of associative memory.

The second measure of associative memory, the face-name task, also confirmed the presence of impairments in hypothyroidism. Analysis of the four learning blocks illustrated a significant difference between the groups, impairments in associative learning were found in the subclinical and hypothyroid groups, relative to the controls. When the total number of face-name pairs successfully encoded and recalled was examined, these deficits

were significant, with the hypothyroid group showing a more pronounced impairment than the subclinical group, though this difference was not significant. This deficit persisted in the delay trail of the face-name task, where again both the hypothyroid and subclinical participants were significantly impaired in comparison to the control group. In contrast to a number of previous studies, such as Miller et al. (2007), these findings demonstrate that subclinical and hypothyroid patients have a similar and significant difficulty encoding associative information as measured by the face-name task. Subsequently, measures of immediate and delayed recall are impaired. There are few previous studies that have examined cognitive impairments in hypothyroidism using the face-name task; those that have found thyroid dysfunction-induced deficits in associative memory (Cooke et al., 2008; Correia et al., 2007). However, there were differences between the groups on IQ scores, with the hypothyroid group having a lower IQ score. When a subgroup of all participants were selected based on IQ matched comparisons, differences still remained between the groups, with the hypothyroid group showing a significant impairment on face-name recall in comparison to the control group. The impairments in the SCH group were no longer evident. Accordingly, the findings from the present study demonstrate that there is a significant deficit in encoding tasks in hypothyroidism; associative memory, as measured by the face-name task, was significantly impaired.

2.5.2 Verbal Memory Impairments in Hypothyroidism

Verbal memory was also significantly impaired on measures of the CVLT in hypothyroid patients. Comparing learning across the 5 blocks, there was an overall group difference in immediate recall, with the hypothyroid group showing significant impairments relative to the controls. The subclinical group also demonstrated deficits in verbal memory, with significant differences in recall in comparison to the control group. However, there was no learning x group interaction found, suggesting that both the subclinical and hypothyroid groups were equally impaired across the learning trials of the CVLT. This is contrary to the findings from Miller et al. (2007), who found no differences on measures of immediate recall in the CVLT; however, Cooke et al. (2008) found that there were significant differences on immediate recall of the CVLT, with the SCH and hypothyroid group performing significantly worse than control participants. In addition, both Correia et al. (2008) and Samuels et al. (2007b), reported significant impairments in SCH and hypothyroid patients on the immediate recall of a short paragraph. Consequently, the results from the present study confirm that once more, that hypothyroid and SCH patients have specific deficits encoding associative memory.

On measures of short delay, significant differences between the groups were apparent, with both the subclinical and hypothyroid group showing deficits in free recall, and the hypothyroid group showing deficits in levels of cued recall. There was no impairment on the cued recall for the SCH group suggesting that while they are impaired, it may not be to the full extent that the hypothyroid group is, and may also support the suggestion that hypothyroidism exists on a continuum. In the long delay trial there were differences between the groups, in this case though, both the subclinical and hypothyroid group demonstrated a similar and significant impairment on the free and cued recall. These results illustrate the specific deficits in verbal memory that were associated with hypothyroidism, for both SCH and overt groups. Miller et al. (2007), found a similar overall group difference on the CVLT-II, however in their case, the differences were only significant on the short-delay cued recall and the long-delay free and cued recall, probably due to the low number of participants that took part.

The IQ matched comparison found that there were still significant differences between the groups on their recall of the list of 16 words; though these differences lay between the control and subclinical groups only. There were also significant differences seen on both the short- and long- delayed free recall. At both the short and long delay, both the subclinical and hypothyroid groups showed significant impairments. Again this would suggest that the impairments in verbal memory are evident in both patient groups, and are still present when initial IQ differences have been accounted for.

Miller et al. suggested that thyroid dysfunction resulted in a specific deficit in memory retrieval, which appears after a short delay; thus "hypothyroidism is associated with a deficit in synthesis and retrieval of information, rather than the initial formation of the memory (encoding)" (2007, p. 135). While the present study found significant differences in memory retrieval, there were also significant differences in encoding, calling into question the suggestion made by Miller et al.. In comparison, Cooke et al. (2008), who found significant differences between the groups on the CVLT, identified that these impairments were evident during learning, as well as recall trials. This view would support the findings from the present study; there were significant differences on immediate and delayed recall in the face-name task, the ROCF, and the CVLT-II. Once more, these results demonstrate that there are specific encoding deficits evident in patients with hypothyroidism.

2.5.3 Working Memory Impairments in Hypothyroidism

Working memory deficits in hypothyroidism were also identified. However, these were only apparent in the hypothyroid group who were significantly different from the control group on accuracy in both the 1-back and 2-back levels of the *n*-back task. Nonetheless, there were no significant differences on reaction times between the groups, and also no differences on switch cost (2-back – 1-back) on levels of accuracy or reaction time. These findings are concomitant with previous studies, where deficits in working memory using the n-back task were also found (Correia et al., 2007; Samuels et al., 2007b). Though, contrary to the present study, Zhu et al. (2006) found that there were significant impairments in both SCH and hypothyroid patients, using the *n*-back task. However, the subclinical group did show a clear trend towards an accuracy impairment ($p = 0.088$). The contradiction between this study and the present findings is surprising, given that the average age for SCH was 30 in the Zhu study and 50 in the present study. In view of the fact that PFC associated memory decreases with age, deficits are more likely to be present in the SCH participants from the current study. Nevertheless, the number of years spent in full-time education, which is known to impact WM, was considerably higher in the SCH participants from the present study (12.5: 9), perhaps this might account for the discrepancy between the two studies.

As WM deficits were only found in the hypothyroid group, this might again support the idea that hypothyroidism exists on a continuum. With SCH come deficits on measures of associative memory which related to thyroid rich regions of the brain. However, as the disease progresses, the relationship between these thyroid rich-regions and the PFC maybe impacted, resulting in an impairment in measures of WM that have been associated with the PFC.

However, there were differences between the groups on IQ scores, with the hypothyroid group having a lower IQ score. When a subgroup of all participants were selected based on IQ matched comparisons, there were no longer any significant differences between the groups on measures of accuracy on the *n*-back task. Nevertheless, there was a significant group difference on the reaction time of the *n*-back task, with the SCH group responding faster than the hypothyroid group.

It is important to note that, reaction times actually decreased with increasing cognitive load. This is counterintuitive; normally reactions times on the *n*-back task have been shown

to increase with increased cognitive load. Contrary to the design of the standard *n*-back task, this design of this task, which was modified from those of Meyer-Lindenberg et al. (2001) and Callicott et al. (2000), meant that participants had time to prepare their responses for the 1-back and 2-back conditions, as they knew 1- and 2-items in advance what response was required. Accordingly response times decreased as task load increased. In hindsight, it could be argued that this may not in fact be a true *n*-back task as it does not allow for a complete working memory assessment as designed. The automated memory responses that are available as a result of this increase time to prepare the response may be confounded with the memory load increases. While the numbers that had to be kept in mind could have been offline from the WM processes, participants may have been repeating the numbers through the phonological loop. This may indicate that under certain circumstances the phonological loop can be used as a buffer between what is held within and outside of the focus of WM attention.

2.5.4 Executive Functioning and Attention in Hypothyroidism

There were few differences seen in the tasks that measured executive functioning. While there were significant differences seen in the hypothyroid group in the Stroop task, these were only seen in reaction time on the congruent trials. There were no differences in the incongruent trials, in either reaction time or accuracy. Constant et al. (2006) found that hypothyroid participants had significantly slower RT in the Stroop and the emotional Stroop task, suggesting that this was evidence of psychomotor slowing in hypothyroidism. Additionally, in the present study, there were no differences seen on any measure of the BADS that were used. These findings reflect the discrepancy seen in the current literature; some researchers have found significant differences in executive functioning in those with hypothyroidism (Constant et al., 2005), while others have found no deficits (Jorde et al., 2006).

In addition, attention levels were also measured using the focused attention task from the face-name task, the SART, and also the DART. No differences were evident between the groups on any of the measures of attention. This data is similar to that found in the Miller study presented earlier (2007), where there were no differences on measures of sustained attention between hypothyroid and control groups. These findings offer support for the proposed idea that hypothyroidism is associated with specific deficits in MTL associated memory. There were no differences found on measures of attention or speed of processing,

and there were only differences found on measures of accuracy on the *n*-back task, and these were present only in the hypothyroid group.

However, there were differences between the groups on IQ scores, with the hypothyroid group having a lower IQ score. When a subgroup of all participants were selected based on IQ matched comparisons, there were no differences found on the focused attention, stroop, BADS, SART, or DART tasks. Differences found on the reaction times for the congruent trial of the stroop task were no longer evident.

Taken together, all of the findings demonstrate that there are specific, hippocampal-associated memory deficits in hypothyroidism, that these deficits are more marked in hypothyroid patients than SCH patients. They might also suggest that as the disease progresses, there is an impact on areas of the brain that interact with these hippocampal regions.

2.5.6 Hypothyroidism and Affective Measures

It was hypothesised that hypothyroidism would result in higher scores on affective measures. There were significant differences between the groups on measures of depression, with the hypothyroid group scoring significantly higher than the control group on both the HADS depression scale and the BDI. Several studies have found significant differences between the groups on affective measures. In addition to the deficits found in verbal memory retrieval, Miller et al. (2007) also found that those in the hypothyroid group scored significantly higher on the Hamilton Depression Scale, than those in the control group. Group differences were also seen on the HADS anxiety; however in this case, both the subclinical and hypothyroid groups reported significantly higher levels of anxiety. These differences were more pronounced in the hypothyroid group who scored within the probable anxiety range, while the SCH group scored within the suggestive anxiety range. Contrary to these results, there were no differences between the groups on the self-reported levels of stress as measured by the PSS. These findings would suggest that there is a presence of depression and anxiety symptoms in SCH and overt hypothyroidism.

In contrast, a previous study of SCH that only included measures of psychological well being found that there were no differences between control subjects and SCH patients on measures of psychological well being (Bell et al., 2007). However, Miller et al. (2007) noted that the hypothyroid group did not show deficits on any of the measures that are

normally impaired as a result of major depression; these included response inhibition, sustained attention, and cognitive flexibility. In the present study there were also no significant differences on sustained attention or response inhibition as measured by the SART and Stroop task, other than reaction time on the congruent trial. This would suggest that the memory deficits due to thyroid dysfunction are distinct from the cognitive impairments that are normally associated with depression, which is in agreement with several of the studies already discussed (Baldini et al., 1997; Burmeister et al., 2001; Monzani et al., 1993; Nystrom et al., 1988). Findings by Constant et al. (2005, 2006) support this view, while depressive symptoms were evident in patients with hypothyroidism; they were not as intense as those seen in major depression. Accordingly, though significant differences were found in hypothyroid patients on measures of executive functioning and attention, there was no relationship found between these cognitive impairments and depression. This is in line with the findings from the present study; while significant differences were found between the groups on measures of anxiety and depression, the mean scores for depression and anxiety as measured by the HADS and BDI, were only suggestive of mild/probable depression and anxiety; these levels were not found to have a relationship with TSH levels as discussed below.

2.5.7 TSH Correlations with Cognitive and Affective Measures

There was a somewhat contradictory picture found for the relationship between TSH levels and measures used in the current study within each group. There was a significant positive relationship found between TSH levels and recall on the face-name task in the subclinical patients only. With increasing TSH levels (up to 15.80 mU/l), the number of face-name pairs successfully recalled also increased. There was also a significant positive relationship found between TSH levels and several measures of the CVLT in the subclinical group. Yet there was no relationship found in the hypothyroid group, positive or negative for the face-name task or the CVLT. If there was a cut-off point, at which increased TSH levels becomes detrimental to declarative memory recall, then a negative relationship would have been expected in the hypothyroid group. Perhaps the large range of TSH values (8.29 – 94.00 mU/l) in the hypothyroid group is masking this relationship.

A significant positive relationship was found between TSH levels and ROCF recognition in the hypothyroid group. This is inline with the findings from the study given that there were no deficits found on the recognition trial of the ROCF. In this case the increased TSH levels may have been assisting their recognition abilities.

There was a significant positive relationship found between TSH levels and accuracy at the 2-back level of the *n*-back task for the control participants, and a negative relationship found in the hypothyroid group. This would suggest that within the normal range of TSH, increased TSH levels are associated with improved performance accuracy; though outside of this range, increased TSH levels are associated with decreased performance accuracy at the 2-back level. In line with this, there was a significant positive relationship found between TSH and the number of errors committed in the congruent trial of the stroop task in the hypothyroid group; suggesting that increased TSH levels are also associated with increased errors on the stroop task

For the control group, who had TSH levels within the normal range, there was a significant negative relationship found between TSH and recall scores on the MMQ at day 3; accordingly higher TSH levels was related to lower recall scores. While a similar finding was evident for the subclinical participants, there was no relationship between MMQ and TSH levels in the hypothyroid group. Perhaps when TSH levels are within the normal levels of the control group, or near to normal levels of SCH then elevated TSH levels result in lower recall scores; especially considering that there was only a significant impairment on recall for the hypothyroid group. Once outside the normal/near to normal range, the TSH levels fluctuated greatly from one patient to the next, perhaps masking the relationship in the hypothyroid group.

These results are somewhat in line with those in the current literature that found a significant relationship between cognition and TSH. Correia et al. (2009), found that TSH level correlated negatively and significantly with predicted IQ, visuo-spatial construction ability, and visuo-spatial, verbal, associative and working memory. Wahlin et al. (1998), also found that in healthy older adults, TSH levels (within the normal range) correlated positively with episodic memory performance.

2.5.8 Hypothyroidism and the Effects of Aging

The discrepancies between the findings from previous studies may result from a failure to account for age-related cognitive impairments in the populations used. It is a possibility that undetected thyroid dysfunction in the general population could be related to age-related cognitive impairments found across the lifespan (van Boxtel et al., 2004). Though, there is a difficulty in diagnosing thyroid dysfunction in older adults as they are often asymptomatic and are often taking numerous medications which can interfere with thyroid

function tests (Diez, 2002). However, the prevalence of hypothyroidism in older adults ranges from 0.5 – 5 % for overt hypothyroidism, and from 5 – 20 % for SCH (Mariotti et al., 1995). As a result the relationship between thyroid dysfunction and cognitive dysfunction during normal aging is difficult to isolate. It is unclear as to the degree of the relationship between variations in healthy elderly adults thyroid functioning and changes in cognitive functioning (Prinz et al., 1999). Age-related alterations in the HPT axis need to be differentiated from disease-related changes. However, considering the fact that illnesses affecting the HPT axis are more common in older adults this means that is a very difficult problem to overcome (Habra et al., 2005).

Consequently, the impact of age on cognitive performance was examined, as the present study, like Miller (2007) and Burmeister (2001), used younger participants than those often examined in the literature (Nystrom et al., 1988; Osterweil et al., 1992). Some of the current literature proposed that there is an age effect on performance of many of the cognitive tasks used in the present study; differences have been seen even in healthy euthyroid older adults (Craik, 2008). Therefore, it is extremely important to try to isolate the pathological effects from those of normal aging. The relationship between age at visit and the tasks that displayed a significant group difference were examined, and then age was used as a covariate in an ANCOVA on the measures that exhibited a relationship with age.

Associative memory was correlated with age at visit; there was a significant negative relationship between age, and both the delay and overall recall of the ROCF. This would suggest that older participants had more difficulty with retrieval of complex figures such as the ROCF. The adjusted means for the delayed recall of the ROCF indicated that once the effect of age had been accounted for, the mean score for the control and hypothyroid group decreased. The age-adjustment to subclinical group scores increased the mean, probably due to the fact that the subclinical group was older than the control and hypothyroid groups. However, while age was a significant covariate on the delayed recall, the group differences still remained once the age effects had been accounted for. A similar pattern was seen in the overall recall, where the adjusted means were slightly lower for the control and hypothyroid groups, and slightly higher for the subclinical groups; nevertheless, the group differences were still significant.

While, Wahlin et al. (1998) suggested that TSH impacts episodic memory through its influence during encoding and consolidation processes, and may be a more sensitive indicator of cognitive functioning in older adults, Rosselli and Ardila (1991) found that age impacted scores on both the copy and delayed recall trials of the ROCF. While others noted a significant age effect on recall ability of the ROCF (Spreen et al., 1998), with decline beginning in the 30's and dropping steadily until the 70's. At this point it shows a more pronounced drop. For the first time, this study has indicated that there is an age-related impairment in visuo-spatial memory in hypothyroid patients; though the hypothyroid-induced memory impairments remain once age has been accounted for.

The face-name task was another associative measure used in the present study, and once more there was a negative relationship between age and face-name pairs remembered on trials 2-4, and age and delayed recall. This suggests that older adults have greater difficulty with encoding and successfully recalling face-name pairs. When age was included as a covariate in the ANCOVA, it was found to have a significant impact on face-name pairs remembered across the trials. Age adjusted means showed an increase in the subclinical group and a decrease in control and hypothyroid groups on both the total and delayed recall. However, despite the age-adjustment to the means of the groups, there was still a significant difference between the groups on the number of face-name pairs successfully encoded and recalled in the total and delayed recall. Studies by Naveh-Benjamin et al. (2007; 2004) also found age-related decreases in face-name associative memory. Together, these offer further support for the need to account for age-related impairments in associative memory.

Results from the analysis with age and the *n*-back task confirmed that there was also a negative relationship between age and performance accuracy at the 1- and 2-back levels. Performance accuracy decreased as age increased. Although age was a significant covariate in performance accuracy at both the 1- and 2-back levels, the age adjusted means still resulted in significant differences between the groups on both measures (increase in the subclinical group, decrease in the control and hypothyroid group). These findings support those from previous studies that found an impact of age on measures of WM (Van Gerven et al., 2007; Vaughan et al., 2008).

While mood is not considered to be a part of cognition, its effects on cognition can not be ignored, as a result it must be included in any debate of age- and thyroid-altered cognitive

functioning. More importantly, as most studies suggest that there are increased rates of anxiety and depression in hypothyroidism, and that these may improve with LT4 (synthetic levothyroxine) treatment (Samuels, 2008). There was also a negative relationship between depression, as measured by the HADS and the BDI, and age. Older adults reported higher scores on measures of depression. Similar adjustments were made to the mean depression scores in each of the three groups, and despite a significant effect of age on depression, the group differences still remained on both the HADS and the BDI. Interestingly, they also found a positive correlation between TSH and mood symptoms, and while this is consistent with previous findings the effects of TSH on memory performance could have been masked by this relationship. Memory was positively correlated with TSH and negatively correlated with mood symptoms. This would suggest that variations in mood due to effects of TSH do not mediate the effects of TSH on episodic memory. Another study that looked at older adults found that there were no associations between thyroid status and either cognitive function or depressive symptoms (Gussekloo et al., 2004). While their participants did decline over time, there was no relationship between thyroid function and the measures of decline.

Prinz et al. (1999) suggest that healthy older adults need to have thyroid hormones in the high range of the normal levels in order to maintain optimal cognitive functioning, suggesting that variations in thyroid hormone levels can have a significant impact on cognitive functioning even in euthyroid older subjects. Volpato et al. (2002) found that low levels of T4 was a strong predictor of decline in cognitive functioning on orientation and delayed memory. However, other researchers suggest that endogenous hormones do not have an effect on cognitive decline with age (Morley et al., 1997) and that physiological aging is related to normal thyroid functioning (Mariotti et al., 1995). A study of older adults, whose thyroid hormones were within the normal range, found that TSH levels were positively correlated with episodic memory performance (Wahlin et al., 1998), while there were no correlations between T4 levels and episodic memory performance. However, these effects were independent of age, education level, and depressive mood state. Other studies have found similar results, indicating that TSH-memory association is independent of age group (van Boxtel et al., 2004).

Findings from the current study challenge the methodological designs in some of the current literature. In hypothyroidism, there is clearly an additional, age-related deficit in associative and working memory. The debate as to whether and to what degree cognitive

changes are reliant on the aging process or age-associated thyroid dysfunction remains (Chiovato et al., 1997).

2.5.9 Hypothyroidism and its Impact on Hippocampal-Associated Memory

The impact of hypothyroidism on associative memory has been examined in the present study. For the first time, this study has demonstrated that there are specific deficits found in hypothyroidism on the face-name associative memory task. In support of previous studies, deficits were also found using tests of verbal, visuo-spatial, and working memory. It is evident from previous studies that thyroid hormones have an effect on learning and memory, now there is growing evidence that thyroid hormones may play a role in the regulation of neurogenesis, predominantly in the areas of the brain vital for learning and memory (Davis et al., 2007). Thyroid hormones may mediate adult hippocampal neurogenesis, as reported in previous studies (Desouza et al., 2005); accordingly, thyroid hormone deprivation could impact learning and memory through this mechanism (Davis et al., 2007). If this is the case, then hippocampal/MTL based memory should be impaired in hypothyroidism. The results from the current study would support this view; there were specific deficits found on measures of associative memory, despite the impact of IQ and age (see Table 2.13), all of which are linked to hippocampal functioning.

Test	Associated Area	Trial	Subclinical	Hypothyroid
Visual Memory – ROCF	**Hippocampus**	**Copy**	***Impaired***	***Impaired***
		Immediate	***Impaired***	***Impaired***
		Delayed	***Impaired***	***Impaired***
		Recognition	***Not Impaired***	***Not Impaired***
Associative Memory – Face-Name Task	**Hippocampus**	**Immediate**	***Impaired***	***Impaired***
		Delayed	***Impaired***	***Impaired***
Verbal Memory – CVLT	**Hippocampus**	**Immediate**	***Somewhat Impaired***	***Impaired***
		Short-Delay	***Somewhat Impaired***	***Impaired***
		Long- Delay	***Impaired***	***Impaired***
Working Memory – *n*-Back Task	**DLPFC**	**0-Back**	***Not Impaired***	***Not Impaired***
		1-Back	***Not Impaired***	***Impaired***
		2-Back	***Not Impaired***	***Impaired***

Table 2.13: Baseline Cognitive Profile in SCH and Hypothyroidism

Table 2.13 lists the type of abilities that were impaired as a result of hypothyroidism in the present study, and also the groups that were affected at each level of the tasks. There are

clearly deficits found on several measures of immediate and delayed recall, suggesting that both encoding and retrieval processes are impaired. Miller (2006) proposed that the impaired retrieval and intact encoding and recognition abilities found in her study suggest that hypothyroidism does not affect memory globally, but more specifically, and that this might implicate the prefrontal cortex. However findings from the current study are somewhat contradictory. There results from this study found impaired encoding and retrieval, but intact recognition, which implicate the hippocampus/MTL. These findings demonstrate that hypothyroid patients have an impairment in their ability to encode information, and subsequently display impairments on measures of retrieval. However, as the disease progresses, impairments in the PFC may appear.

2.5.9a Is it a problem with "binding"? - Relationship between MTL and PFC in Hypothyroidism

The successful association between items is unlikely to rely solely on the hippocampus; Sperling et al. (2003) suggest that the hippocampus is working to "bind" together different pieces of information from several regions, probably the neocortex, into an organised memory trace. This view is supported by findings that have shown the extensive connections between these two regions. There have been several studies that have examined associative memory in healthy controls, many using the face-name task, in order to determine what role the MTL, especially the hippocampus, and the PFC play in encoding and retrieval. Haxby et al. (1996) reported that the both the right MTL and the right PFC were activated in a PET study during encoding of faces when a new memory was made, but the left PFC was activated during recognition of the faces. They suggested that there was dissociation between neural regions involved in encoding and retrieval. Using a fMRI study, Sperling et al. (2001) found that the hippocampus (part of the MTL) was engaged during encoding. The dorsolateral PFC was also engaged during encoding, suggesting that the PFC also plays a part in associative memory.

Subsequent memory paradigms have demonstrated that the extent of activation during encoding in the hippocampus is associated with later indices of relational memory, however, there is some debate as to whether the hippocampus is associated with later recognition (Davachi, 2006). While few studies actually allow the assessment of successful recall, those that do provide evidence that hippocampal activation during encoding, is correlated with associative memory performance and not recognition. In their 2003 study (Sperling et al.), they suggest that the coordination between the MTL and the

PFC may underlie successful recall – that both were engaged during encoding, and as a result, this network of activation is involved in successfully "binding" together the face and name.

While the findings from the present study did not include an fMRI study, the behavioural results confirm that there are deficits in associative memory which has been associated with the MTL, which likely arise from impairments in the binding/encoding abilities of the hypothyroid patients. Although the role of the PFC in this encoding process cannot be examined directly, the nature of impairments in tasks that have been associated with the PFC in hypothyroidism was examined. Given that the only WM deficits evident from all of the tests that examined tasks associated with PFC-memory were seen in the hypothyroid group, these deficits may result from faulty communication between the PFC and the MTL. If this is the case, that both the MTL and the PFC are needed for successful encoding, then damage to either one, through effects of disease or age-related changes, could impair encoding and therefore reduce the ability to recall the information.

Damage to the PFC, in frontal lobe lesion patients impaired their ability to encode and recall novel faces, and also to identify famous faces (Rapcsak et al., 2001). PFC patients also perform better at cued-recall compared to free-recall (Blumenfeld et al., 2007). MTL lobectomy patients were impaired in their ability recall previously studied faces (Crane et al., 2002). Combined, these studies imply that MTL and PFC structures are essential in the encoding and retention of associative memories. An additional MRI component to this study would allow the examination of the point at which associative memory breaks down; representation, transfer, binding or storage and retrieval. It would also offer the opportunity to examine the nature of the relationship between the MTL and the PFC during associative and working memory processes.

Results from the present study indicate that there was an impaired ability in SCH and hypothyroid patients to successfully encode face-name pairs, to recall components of a complex figure, and recall words from a verbal memory task when compared to control participants; however, there were no impairments on the recognition trial of the complex figure. These results, combined with previous behavioural research and fMRI studies, demonstrate that there are specific, hippocampal-associated, associative memory impairments evident in hypothyroidism. If thyroid dysfunction leads to hippocampal impairment, then this could explain the impairments in working memory also seen in the

present study. Therefore, if MTL – PFC connections are reduced, as a result of hippocampal damage, then this reduced connectivity may account for the impairment in working memory using the *n*-back task found in the current study (see Table 2.17). Few studies that have examined the impairments associated with hypothyroidism have used the necessary tasks, had sufficient participant numbers, or included a suitably matched control group, to allow them to reach such a conclusion. Nevertheless, imaging studies, examining both hippocampal- and prefrontal-dependent memory are necessary to draw any concrete conclusion, though the behavioural results would suggest that it might be a possibility.

2.5.10 Outstanding Methodological Issues and Future Directions

Although the current literature is not extensive nor conclusive, and does not agree on the degree of cognitive impairments linked to hypothyroidism, it is reasonable to suggest that individuals diagnosed with hypothyroidism should be referred for a comprehensive evaluation of neuropsychological and neurocognitive functioning (Dugbartey, 1998). These studies will no doubt add to the debate about whether cognitive deficits are evident in hypothyroidism, and whether SCH patients should be treated. Findings from the present study would suggest that there are significant deficits found on measures of associative memory in SCH, and that this supports the idea that SCH patients should be treated.

In order to avoid methodological bias, the present study assessed the presence of attention and executive dysfunction, along with deficits in associative and verbal memory, all of which have been reported to be impaired in the hypothyroid state. By examining measures of attention and executive function, it provided the means with which to rule out a lack of attentional resources and difficulty planning a response to a task, as the underlying cause for the impairments that were reported. There were no significant differences found on measures off attention and executive function, suggesting that the deficits found were not related to the presence of concomitant attentional of executive dysfunction.

In addition, measures of depression, anxiety, and stress were included; since isolating hypothyroid dysfunction in cognition, above that which may be present with depression, was considered extremely important. In addition, the present study also included many facets of memory retrieval, immediate, free- and cued-recall, short- and long-term delayed recall, and recognition. Any assessment of learning and memory should include delay trials in order to establish whether memories have been stored in the short-term and also the long-term. Including both a short- and long-term delay also allows us to establish whether

participants showed increased time to integrate the information, by comparing the earlier and later performance. However, despite the fact that an extensive neuropsychological battery was used, that the participants were younger, and a relatively-closely age-matched control group was used, there are some limitations to the present study.

A larger number of patients would lend weight to the findings, though getting access to large numbers through one clinic would be difficult. In addition, it was unknown how long prior to diagnosis that the patients were experiencing symptoms, while some reported having no symptoms at all. Further analysis of symptom length/presence may offer some more insight into the nature of the problems found in hypothyroidism. In order to examine the relationship between depression and cognitive impairments in hypothyroidism in greater detail, it would have been beneficial to include measures that looked at emotionally charged memory. For example, Constant et al. (2005) used a supraliminal and subliminal emotional stroop test; while they were unable to demonstrate an interaction between emotional valence and performance on the stroop test, they did find a slowing in performance of the hypothyroid group. Perhaps the use of, for example, a valanced face-name task, or *n*-back task would be of more value. Alternatively, as deficits were found on measures of verbal memory, perhaps the use of a verbal *n*-back task could offer further insight into the nature of the deficits found in hypothyroidism.

2.6 Conclusion

There are specific impairments in neurocognitive function theoretically and experimentally associated with hippocampal function, evident in SCH and overt hypothyroidism. While age was associated with these impairments, the groups remained impaired on all measures when age effects were accounted for. Longitudinal studies are needed to examine whether there is a treatment-related reversal of these impairments in memory. In addition, a further study, examining age-related memory changes in a healthy population, is essential in order to clarify the impact of age on cognition in hypothyroidism.

Chapter 3

Examining the Potential Reversibility of Cognitive and Affective Impairments in Subclinical and Overt Hypothyroidism with Thyroxine Replacement Therapy

3.1 Summary

The results from the previous chapter confirmed the presence of specific, associative memory deficits in hypothyroidism that have been associated with hippocampal functioning, and suggested that these deficits may have impacted WM which has been associated with the PFC. Subsequent follow-up testing sessions investigated the impact of thyroid hormone replacement on cognitive functions, and identified that there was some functional recovery of baseline deficits associated with this treatment. This chapter investigates the long-term effects of hypothyroidism from baseline to six months on treatment. It aims to confirm that cognitive and affective differences seen at baseline are reversible with thyroxine replacement therapy.

3.2. Introduction

3.2.1 Treatment for Hypothyroidism

While findings from previous research support those found in Chapter 2, that thyroid dysfunction is often associated with cognitive impairments and mood disturbances, several studies have reported the reversibility of these cognitive deficits and mood disturbances with thyroid replacement therapy (Miller et al., 2006). Treatment for hypothyroidism usually involves synthetic thyroid hormone replacement therapy, which is highly effective and has a small risk of adverse reactions. While it can take up to 3 months for thyroid levels to return to normal, this can vary from patient to patient. The key to successful management of the disease is careful monitoring of the TH, through regular blood tests, as about 20% of patients are receiving an inadequate thyroxine dose, and another 20% are receiving an excessive dose (Canaris et al.., 2000; Hollowell et al.., 2002). Treatment is usually started at low doses, of approximately 25-50 μg per day, and monitored after the first six weeks of treatment, and then annually or when symptoms arise.

3.2.2 Lack of Cohesion in the Current Literature

In addition to the variation in thyroid recovery, there is no reliable pattern of improvement of cognitive dysfunction and mood disorders, especially as there seems to be a lack of long-term, control-matched, placebo-controlled studies. According to Bono et al. (2004) there is a reduction of the affective and cognitive symptoms of hypothyroidism, as a result of LT4 treatment, in the majority of hypothyroid patients. While LT4 treatment has been shown to bring TSH levels back to within the normal range for both SCH and hypothyroid patients, a lot of researchers dispute that treatment has an effect on clinical symptoms and neuropsychological dysfunction (Jorde et al., 2006). In addition, there is much debate in the literature as to whether SCH should be treated at all (Chu, & Crapo, 2001; Cooper, 2004; Vanderpump, 2003). Chu et al. (2001), report that there are as many placebo-controlled randomised studies that find no decline in symptoms of SCH, as there are studies that find positive benefits of treatment. However, while there are several arguments against treating SCH, it would mean that the progression to overt hypothyroidism would be prevented, treatment might improve the serum lipid profile and reverse the symptoms of mild hypothyroidism (Cooper, 2004). Taking all of these problems into account, the lack of adequately controlled studies, the debate over treating SCH, and the disagreement about the effects of treatment on the symptoms of

hypothyroidism, the biggest difficulty in the current literature appears to be a lack of consistency in the data.

It has been well established that hypothyroidism impairs learning and memory, although there are conflicting reports about the restoration of hypothyroid-induced cognitive impairments following LT4 therapy (Alzoubi et al., 2005). Previous research has found that thyroxine replacement does improve memory in subclinical (Baldini et al.., 1997; Jensovsky et al.., 2002; Osterweil et al.., 1992), and hypothyroid patients (Miller et al.., 2006; Osterweil et al.., 1992); however there is debate as to whether the treatment fully restores the hypothyroid-induced impairments (Jaeschke et al., 1996; Leentjens et al., 1995). In addition, some researchers have found improvements in memory scores following treatment that did not show a deficit at baseline testing (Baldini et al., 1997). This debate is furthered by the fact that in normal elderly subjects, there is a variation in the levels of thyroxin within the normal range, and these variations correlate positively with learning and memory (Prinz et al., 1999).

3.2.2.1 Subclinical Hypothyroidism

Some studies reported that SCH patients have a positive response (Monzani et al., 1993), no response (Jaeschke et al., 1996), and even a negative response to LT4 treatment (Kong et al., 2002). Bono et al. (2004) found that in 36 SCH patients, cognitive and affective status were barely affected by thyroid dysfunction from baseline to 6-months on LT4 replacement therapy. The only statistical difference was on the verbal fluency task; however this change did not correlate with TSH changes after LT4 treatment. In addition there was also an improvement in depression scores. Nonetheless, these results need to be interpreted with caution; neither the verbal fluency nor depression measures were significant at baseline. Bono et al. (2004) suggest that SCH does not correlate with cognitive impairments, but instead may cause an age-related impairment of attentive functions in those with normal cognitive functioning.

In a placebo-controlled, double-blind intervention study with T4 medication for one year, Jorde et al. (2006) found no significant differences between SCH and control participants on any of the cognitive tests at baseline, and no effect of treatment (Bono et al., 2004). The tests used included the Stroop test, the CVLT, the Trail Making test and the Digit Forward and Backward test; they also used the BDI and the General Health Questionnaire to assess affective differences. These results imply that SCH is not related to cognitive or mood

deficits, though the SCH patients included only had serum TSH levels in the 3.5-10.0 mIU/l range. However, they did find that age was a negative predictor of cognitive performance in a multiple linear regression analysis. Unusually, they also found that the control group had higher scores on affective measures than the SCH group, which calls into dispute the links between depression and SCH that other studies have found.

Improvements in logical and visual memory in SCH, were found in a study conducted by Baldini et al. (1997). In SCH patients who were re-examined after 3 months of treatment, there was a significant improvement, compared to baseline scores, using the Weschler Memory scale in logical memory, visual memory, number span, and an overall total memory scores. By three months SCH participants performed at the same level as euthyroid patients. Unlike the present study, this study used a euthyroid goiter group of patients, who were on average 5 years younger than the SCH group, as the matched control participants. However, no indication was given about the length of time that the "control" group were euthyroid. If there is debate about whether cognitive impairments are fully reversible, then using a healthy age-matched control group would lend more weight to these findings.

In a novel experiment, Samuels et al. (Samuels et al., 2007b), induced SCH in a group of euthyroid hypothyroid patients. This allowed comparison between cognitive functioning at the euthyroid and SCH stages; however it did not allow the identification of impairments in untreated SCH and subsequent investigation into the effects of treatment upon baseline deficits. Nevertheless, they did find that during the SCH stage of the experiment, participants reported decreased general health and were impaired on two working memory tasks. In addition, there was a correlation between T4 levels and deficits seen on WM tasks. While the differences they found were small, they believe that they were clinically relevant. Reviewing the literature highlights the discrepancies found across studies and underlines the need to use well controlled, follow-up studies in order to identify consistent patterns in the data.

3.2.2.2 Hypothyroidism

The presence of cognitive deficits and reversibility of these deficits upon treatment appears to be more acceptable in patients with overt hypothyroidism. Verbal memory learning and retention deficits were significantly correlated with hypothyroidism, while these deficits improved with treatment (Osterweil et al., 1992). Monzani et al. (1993) also found that

contextual verbal memory impairments significantly improved with treatment, and levels of depression declined. Some studies have reported that hypothyroid patients did not return to premorbid levels of cognitive functioning, despite being treated for between 6 and 12 months (Bjerke et al., 2001).

Miller et al. (2007) conducted an investigation into the effects of untreated hypothyroidism on verbal memory using the CVLT-II, and extended it further (Miller et al., 2006) to include a follow-up testing session of approximately 6 months after LT4 therapy began. They found that the deficits in verbal memory evident at baseline improved with treatment, there were no significant differences between the control and hypothyroid group at time two. Having controlled for differences in depression scores between the groups, the improvement in verbal memory was still evident.

Conversely, Samuels et al. (2007a) looked at health status, mood and cognition in treated hypothyroid patients. Although their thyroid hormone levels were within the normal range, there were significant impairments in working memory using the n-back task, and motor learning using the pursuit rotor task, in treated hypothyroid subjects. Hypothyroid participants also displayed deficits on the copy trial of a complex figure. Despite this fact, no correlations were found between the different cognitive and affective measures and TSH, T3 or T4 levels. It is important to note that the hypothyroid participants were tested after only 3 months of treatment, perhaps it takes longer for the deficits to reverse. This adds to the debate about the treatment-reversibility of the cognitive deficits associated with hypothyroidism.

3.2.3 Relationship between Hypothyroidism, Depression, and Recovery of Symptoms

Many of the limbic system structures are rich in thyroid hormones, and have been implicated in mood disorders, though the mechanisms and pathways underlying these effects are not clear (Bauer et al.., 2008; Bauer et al.., 2003). It has long been recognised that TRH has distinct acute antidepressant effects in both humans and animals (Zeng et al., 2007). In humans, intravenous administration of TRH triggers rapid remission of major depression (Callahan et al.., 1997), and also produces an antidepressant effect in those with bipolar disorder (Szuba et al., 2005). TRH administration also reduces immobility in the forced-swim test in rats, and enhances the pharmacological effect of antidepressant drugs (Zeng et al.., 2007). Zeng et al. (2007) examined the effects of knocking out thyroid

hormone genes in mice (TRα $^{-/-}$ mice), they found that the TRα $^{-/-}$ mice displayed high levels of TSH serum and reduced TSH biological activity. However, they noted that the anxiety- and depression-like behaviour that is exhibited by the TRα $^{-/-}$ mice may also be due to the reduction in the levels of thyroid hormones available, and not just a result of TRH inactivation. The reason for this is that there is a lot of evidence to support the antidepressant effects of T3 and T4 in both humans and animals (Joffe et al., 2000), and a link between the potentiation of T3 of the actions of serotonin has been demonstrated (Lifschytz et al., 2006). However, while the exact mechanisms of the relationship between depression and thyroid hormones are not known, it is reasonable to accept that there is a thyroid-related antidepressant effect present in humans and animals.

There are several studies that have shown an improvement in depression scores following LT4 treatment. Miller (2006) found that scores on the Hamilton Depression Scale declined following treatment for about 3 months, and while depression was evident prior to treatment, the deficits found in memory were not those usually associated with depression. In a different approach, Wekking et al. (2005) examined levels of mental health and well-being in euthyroid hypothyroid patients (treated for at least 6 months, though it ranged from 6 months to 25 years, median 5.5 years). They found that in comparison to the general population, the patients had significantly lower measures of mental health and well-being. These findings add to the debate about the reversibility of differences on affective measures following LT4 therapy.

3.2.4 Hypotheses

1. Baseline deficits in associative memory should improve with treatment in patients with an underactive thyroid gland, with the subclinical group returning to control levels within 6 months.
2. Baseline deficits in working memory should improve with treatment in patients with an underactive thyroid gland.
3. Self-reported levels of depression and anxiety should improve with treatment in patients with an underactive thyroid gland.

3.3 Methods

3.3.1. Participants

Prospective participants were identified from their medical records having attended the Diabetes Clinic in the Adelaide & Meath Hospital, incorporating National Children's Hospital (AMNCH), Tallaght, which specialises in several endocrine conditions including hypothyroidism. Participant's suitability was based on the evaluation of their blood test results, looking specifically at their T4 and TSH levels. Exclusion criteria included a previous history of ischemic heart disease, stroke, diabetes, head injury, epilepsy, psychiatric illness, significant visual impairment, or pregnancy. Care was taken to avoid testing during periods of significant stress (e.g., death of relative). All study subjects gave their written signed consent to the study, which was approved by the Research Ethics Committee of the School of Psychology, Trinity College Dublin, and the Research Ethics Committee of the Adelaide and Meath Hospital and St. James's Hospital (Dublin, Ireland).

Potential participants were contacted by phone call from Dr Neuman Correia (following GP consent) and gave full and informed consent to take part in the study. Two participant groups were formed, a subclinical hypothyroid group (normal free T4 (>11 pmol/l) with elevated TSH (>4 mU/l)) and a hypothyroid group (low free T4 (<11 pmol/l) and elevated TSH (> 4 mU/l), there was also a control group recruited from the local community (normal T4 (11-25 pmol/l) and normal TSH 0.4-4.0 mU/l).

3.3.1a Sub-Clinical Hypothyroid Group

This group consisted of 22 out-patients with SCH. The mean age of this group was 51 and ranged from 34 to 64 years.

3.3.1b Hypothyroid Group

This group consisted of 27 out-patients with hypothyroidism. The mean age of this group was 43 and ranged from 24 to 61 years.

3.3.1c Control Group

A total of 20 participants were recruited from the local community who did not have a known history of brain injury or a medical condition that would affect the results. The mean age of this group was 44 and ranged from 25 to 61 years.

3.3.2 Experimental Design & Neurocognitive Battery

At each follow-up (3 months and 6 months post-baseline), an experimental battery of neurocognitive and neuropsychological tests were performed, lasting approximately 1.5-2 hours (including an optional 5 minute break after the Sustained Attention to Response Task). Blood tests were routinely carried out each testing session to check whether the TSH and T4 levels had returned to normal, (adjustments to medication were made as necessary throughout the study depending on these levels).

3.3.3 Neuropsychological Assessment

A comprehensive neuropsychological assessment battery was administered to all participants at each session; the assessment had two primary aims. Firstly the assessment of declarative memory function (primarily HF-mediated) and secondly the evaluation of executive function (primarily PFC-mediated) using both standardised and novel tests as described below. Comparisons were made between groups across the three testing sessions in order to identify and elucidate the specific neuropsychological difficulties associated with SCH and hypothyroidism, and their subsequent recovery following LT4 treatment. A description is given below in the case of tests that used different versions or stimuli, all other details can be found in Chapter 2 Section 3 (methods section).

3.3.3.1 Declarative Memory Tests

3.3.3.1a Visual Memory: Complex Figure

See Chapter 2 Section 2.3.3.1a for a complete description of the ROCF. In addition to the ROCF, a comparable additional figure was also used, the Modified Taylor Complex Figure (MTCF) (Hubley et al., 2006). It consisted of a 2-dimensional line drawing containing 18 details such as lines, squares, crosses, and triangles. The version used in the present study consisted of four sections; copy, immediate recall, delayed recall (20 minutes later) and a newly developed recognition trial (15 minutes later). The recognition trail was designed to evaluate the contributions of encoding, storage and retrieval to memory performance (Meyers, 1994). Participants were not forewarned when given the copy instructions that they would have to reproduce the figure from memory. There was a short-delay (2 minutes) and a long-delay (20 minutes) recall, in addition to a further delayed recognition test. The procedure and scoring for the MTCF follows exactly that as described in Chapter 2 Section 2.3.3.1a for the ROCF.

3.3.3.1b Associative memory: Face-Name Learning and Recall

See Chapter 2 Section 2.3.3.1b for a full description of the face-name task. At sessions 2 and 3 different sets of faces were used in the task.

3.3.3.2 Self Rating Memory Questionnaires

See Chapter 2 Section 2.3.3.2 for a full description of these tasks.

3.3.3.2a Everyday memory questionnaire

3.3.3.2b Mundane Memory Questionnaire (MMQ)

3.3.3.2c Self-Rating Scale (SRS)

3.3.3.3 Executive Functioning

See Chapter 2 Section 2.3.3.3 for a full description of these tasks

3.3.3.3a Behavioural Assessment of Dysexecutive Syndrome

Key Search Test

Zoo Map Test

DEX

3.3.3.3b Focused Attention

3.3.3.2c Working Memory: The n-Back Task (0-Back, 1-Back & 2-Back Levels)

3.3.3.2d Response Inhibition: The Stroop Task - 'Naming Coloured Words' Version

3.3.3.2e Sustained Attention to Response Task (SART)

3.3.3.2f Dual Attention to Response Task

3.3.3.4 Premorbid IQ - National Adult Reading Test 2nd Ed (NART)

See Chapter 2 Section 2.3.3.4 for a full description of these tasks.

3.3.3.5 Affective Measurements

See Chapter 2 Section 2.3.3.5 for a full description of these tasks.

3.3.3.5a Hospital Anxiety and Depression Scale (HADS)

3.3.3.5b Beck Depression Inventory II (BDI-II)

3.3.3.5c Perceived Stress Scale (PSS)

3.3.4 Analytic measurement

See Chapter 2, Section 2.3.4 for full details.

3.3.5 Statistical Analysis

Analyses were carried out using SPSS (version 15) for PC. All data was expressed as means ± standard error (S.E.), unless specified otherwise. Analysis of Variance (ANOVA) was the primary statistical tool used. When performance on a specific task was repeated across multiple trials/sessions a 'mixed between-within subject ANOVAs' (Tabacknick & Fidell, 2007) was used to compare performance across the repeated levels and between the groups. Where significant ($p < 0.05$), main effects and interactions were reported and if appropriate, post-hoc analyses were conducted (Bonferroni-Corrected for multiple comparisons). Subsequent one-way ANOVAs compared the dependent variables between the groups and post-hoc analysis identified what groups differed. When there were more than 2 levels in the dependent variable, within group differences were investigated using apriori planned comparisons across each level of the DV (bonferroni corrected for multiple comparisons). When significant differences were found, the p-value was reported at three levels; $p < 0.05$ (*), $p < 0.01$ (**), and $p < 0.001$ (***).

3.4 Results

3.4.1 Blood test results

Subclinical group

The average TSH level at session two for the subclinical group was 3.35 mU/l, ranging from 0.42 mU/l to 7.30 mU/l. The average T4 level was 16.12 pmol/l, ranging from 12.40 pmol/l to 18.80 pmol/l. At session three the average TSH level for this group was 3.36 mU/l, ranging from 0.52 mU/l to 8.19 mU/l. The average T4 level was 16.32 pmol/l, ranging from 12.90 pmol/l to 19.80 pmol/l.

Hypothyroid group

The average TSH level at session two for the hypothyroid group was 4.77 mU/l, ranging from 0.09 mU/l to 17.50 mU/l. The average T4 level was 18.45 pmol/l, ranging from 7.00 pmol/l to 28.70 pmol/l. At session three the average TSH levels for this group was 4.72 mU/l, ranging from 0.11 mU/l to 23.20 mU/l. The average T4 level was 17.98 pmol/l, ranging from 13.00 pmol/l to 30.20 pmol/l.

Note: No blood samples were taken from the control group at session two or session three due to personnel constraints.

Thyroid Hormones	Session	Control	Subclinical	Hypothyroid
TSH	Session 1	1.45 (0.04 – 3.61)	8.57 (4.18 – 15.80)	50.76 (8.29 – 94.00)
	Session 2	N/A	3.35 (0.42 – 7.30)	4.77 (0.09 – 17.50)
	Session 3	N/A	3.36 (0.52 – 8.19)	4.72 (0.11 – 23.20)
T4	Session 1	16.18 (12.60 – 19.20)	14.85 (11.00 – 23.60)	6.38 (3.90 – 10.80)
	Session 2	N/A	16.12 (12.40 – 18.80)	18.45 (7.00 – 28.70)
	Session 3	N/A	16.32 (12.90 – 19.80)	17.98 (13.00 – 30.20)

Table 3.1: Mean (range) of TSH (mU/l) and T4 (pmol/l) values in the SCH and hypothyroid groups. Blood samples were only taken from the control group at session 1.

There was a significant reduction in the TSH levels of both the subclinical ($f = 34.117$; $df = 2, 16$; $p < 0.001$) and hypothyroid ($f = 39.784$; $df = 2, 21$; $p < 0.001$) groups across sessions. By session 2 the mean TSH values for the subclinical group were within the

normal range (< 4 mU/l); this remained the case at session 3. The hypothyroid group were slightly above the normal range and both session 2 and 3. There was also a significant increase in T4 levels across sessions, for both the subclinical (f = 19.071; df = 2, 14; p < 0.001) and hypothyroid groups (f = 60.961; df = 2, 18; p < 0.001). By session 2 the mean T4 values for the subclinical and hypothyroid group were within the normal range (> 11 pmol/l); this remained the case at session 3.

3.4.2 Declarative Memory Tests

3.4.2a Visual Memory: The Rey-Osterrieth Complex Figure (ROCF)

COPY

Changes in performance between the three groups, across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], were assessed. There was a significant main effect of Session (f = 6.22; df = 2, 57; p < 0.01) , There was a significant overall improvement on the copy scores from session 1 to session 2 (p < 0.01), however the scores at session 3 were reduced from those seen at session 2 (p < 0.05). There was also a significant main effect of Group (f = 3.832; df = 2, 57; p < 0.05); however, despite this no significant Group x Session interaction was observed (f = = .2231.447; df = 4, 57; p = .237). Post-hoc analysis found that there were no significant differences between the control and subclinical groups across the three sessions (p = .998), and also no significant differences between the control and hypothyroid groups across the three sessions (though p = 0.058). Differences between the subclinical and hypothyroid groups were significant (p < 0.05) (see Figure 3.1). Across the sessions, the SCH participants displayed the highest accuracy scores, while hypothyroid participants displayed the lowest accuracy.

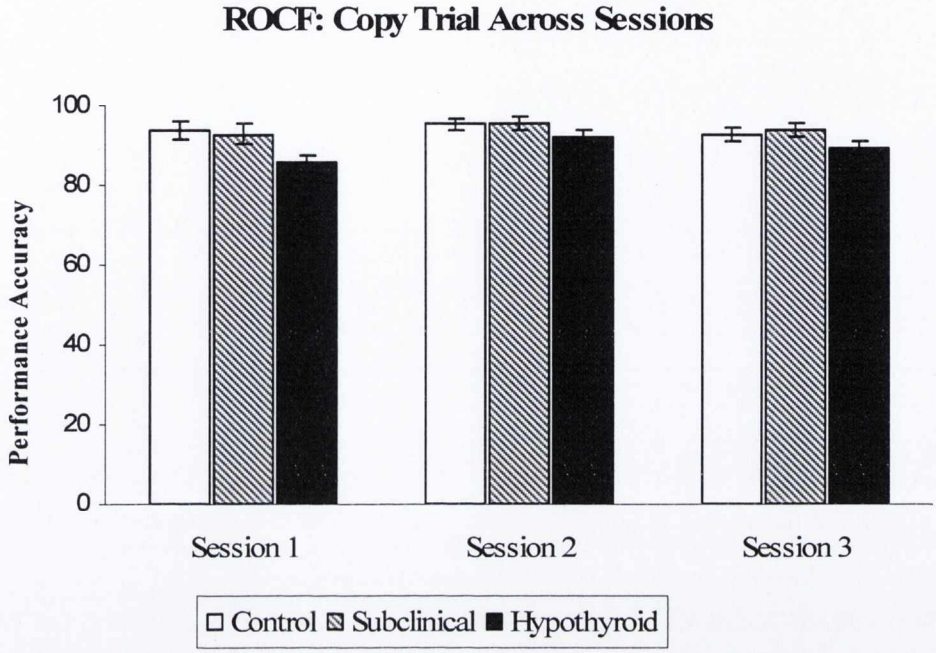

Figure 3.1: Mean Performance Accuracy (± SEM) on the copy trial across the three testing sessions

IMMEDIATE

Changes in performance between the three groups, across the three testing sessions were assessed. Despite strong a main effect of Session ($f = 11.786$; $df = 2, 15$; $p < 0.001$), and a significant Group x Session interaction ($f = 3.203$; $df = 4, 15$; $p < 0.05$) no significant Group effect was found ($f = 2.427$; $df = 2, 15$; $p = .122$). Irrespective of group differences, when scores across session were examined there was a significant improvement from session 1 to session 2 ($p < 0.05$), and also session 1 to session 3 ($p < 0.001$), on the immediate trial of the ROCF. However, there was no improvement from session 2 to session 3 ($p = .358$).

DELAYED

Once again, changes in performance between the three groups, across the three testing sessions were assessed. A similar pattern was seen to that at the copy trial, although there was a strong a main effect of Session ($f = 42.828$; $df = 2, 57$; $p < 0.001$) and Group ($f = 9.168$; $df = 2, 57$; $p < 0.001$), no significant Group x Session interaction was observed ($f = 1.696$; $df = 4, 57$; $p = .156$). Post-hoc analysis found that there were no significant

differences between the control and subclinical groups across the three sessions ($p = .148$), and also no significant differences between the subclinical and hypothyroid groups ($p = .077$); however there were significant differences between the control and hypothyroid groups across the three sessions ($p < 0.001$), with the hypothyroid group consistently displaying a significant impairment on the delayed trial of the ROCF (see Figure 3.2).

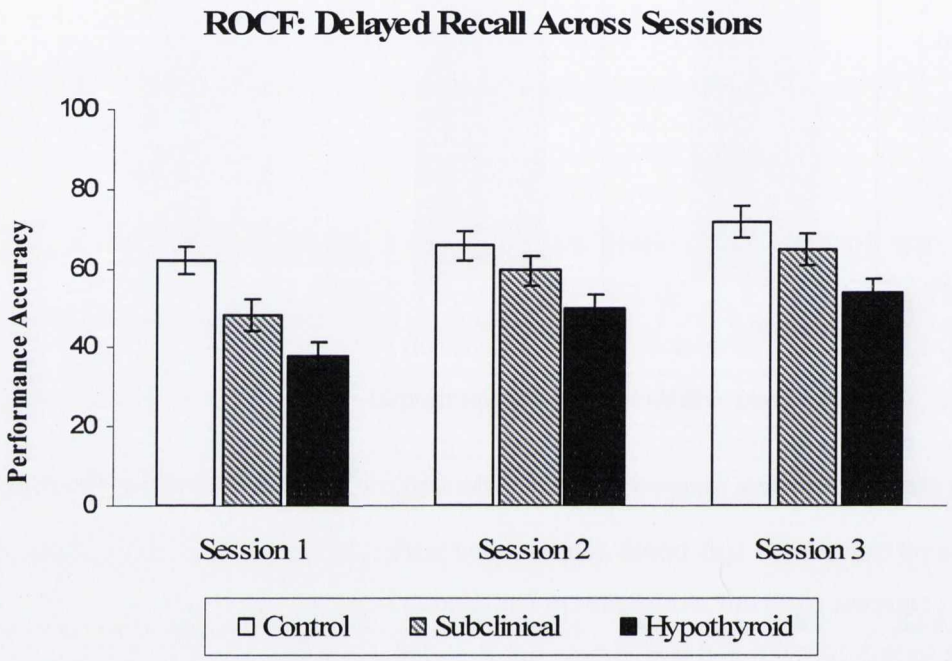

Figure 3.2 Mean Performance Accuracy on Delayed Recall (± SEM) across the three testing sessions.

When scores across session were examined in there was an increasing significant improvement across all sessions; from session 1 to session 2 ($p < 0.001$), session 1 to session 3 ($p < 0.001$), and also session 2 to session 3 ($p < 0.01$) on the delayed trial of the ROCF.

RECOGNITION

Changes in performance between the three groups, across the three testing sessions were assessed; no significant differences were found for the session ($f = 1.937$; $df = 2, 10$; $p = .170$), group ($f = 4.358$; $df = 2, 10$; $p = .063$), or session by group interaction ($f = .170$; $df = 2, 10$; $p = .845$).

OVERALL SCORE

Overall percentage accuracy scores, designed to measure the delayed recall relative to the initial copy ability were assessed across the three sessions. A significant main effect of session was observed ($f = 43.445$; $df = 2, 57$; $p < 0.001$). Pairwise comparisons found that there was an increasing significant improvement across all sessions; from session 1 to session 2 ($p < 0.001$), session 1 to session 3 ($p < 0.001$), and also session 2 to session 3 ($p < 0.001$) on the overall trial of the ROCF. There was also a significant main effect of group ($f = 8.905$; $df = 2, 57$; $p < 0.01$); nevertheless there was no significant interaction between group x session ($f = 1.344$; $df = 4, 57$; $p = .258$). Post-hoc analysis found that the differences between the control group and hypothyroid group remained across the three sessions ($p < 0.001$), as did the differences between the control and subclinical groups ($p < .05$), There were no significant differences between the subclinical and hypothyroid groups ($p = .292$) (see Figure 3.3).

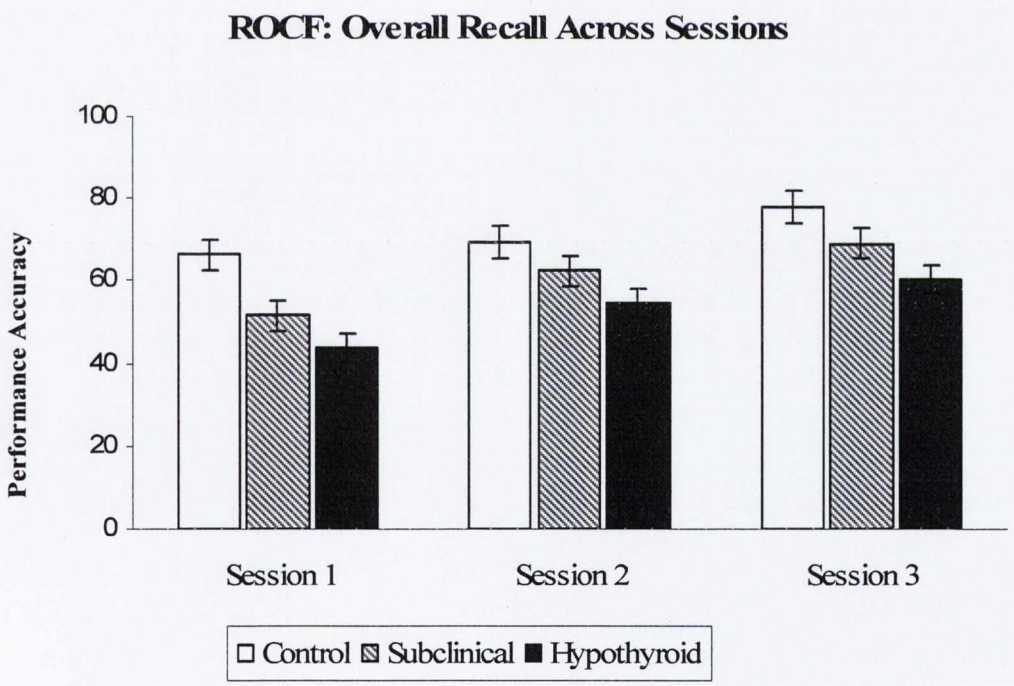

Figure 3.3 Overall Performance Accuracy (Mean ± SEM) across the three testing sessions.

3.4.2b Associative memory: Face-Name Learning and Recall

Changes in performance across the four learning trials between the three groups, across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], were assessed (see Figure 3.4). Despite strong a main effect of Session (f = 21.445; df = 2, 58; $p < 0.001$) and Group (f = 5.373; df = 2, 58; $p < 0.01$), no significant Group x Session interaction was observed (f = 1.955; df = 4, 58; p = .106). Post-hoc analysis found that these differences were between the control and hypothyroid group ($p <$ 0.01) (see Figure 3.4). There were no significant differences between the control and subclinical groups (p = .765), and the subclinical and hypothyroid groups (p = .062). Pairwise comparisons found that there was an increasing significant improvement across all sessions; from session 1 to session 2 ($p < 0.001$), session 1 to session 3 ($p < 0.001$), and also session 2 to session 3 ($p < 0.001$) on the number of face-name pairs successfully recalled. While all groups improved across the sessions, the control group consistently performed better than the subclinical and hypothyroid group across sessions. In addition, the subclinical group consistently performed better than the hypothyroid group across sessions; however, further post hoc analysis could not be conducted on these improvements as the session x group interaction was not significant.

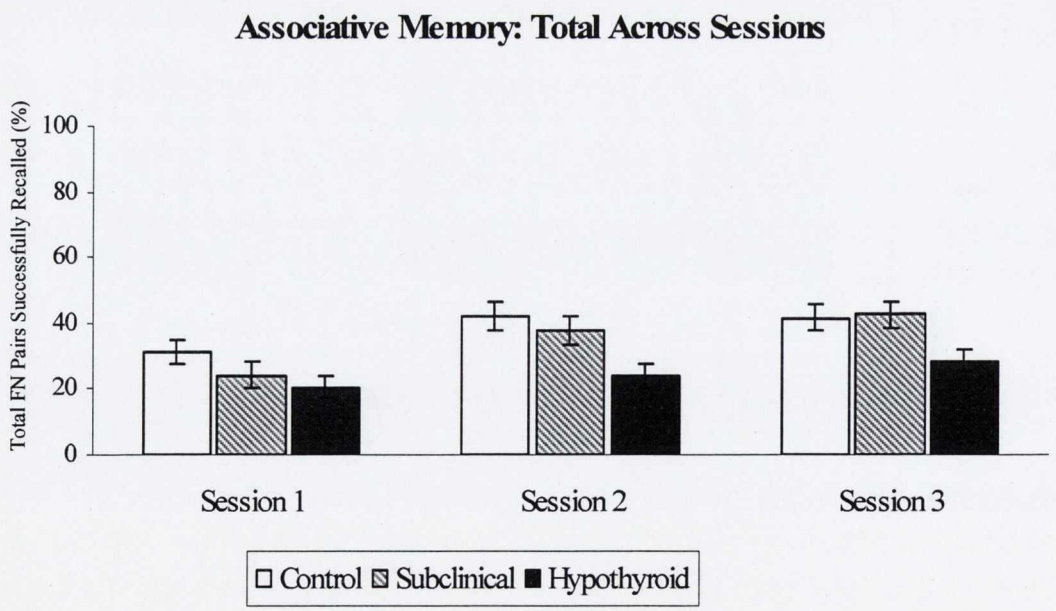

Figure 3.4: Mean (± SEM performance accuracy) Total face-name pairs successfully recalled across each of the sessions.

There were also significant differences across trials ($f = 133.081$; $df = 3, 58$; $p < 0.001$), a significant interaction between trial x group ($f = 3.220$; $df = 6, 58$; $p < 0.01$), a significant interaction between session x trial ($f = 9.051$; $df = 6, 58$; $p < 0.001$) and a significant session x trial x group interaction ($f = 1.862$; $df = 12, 58$; $p < 0.05$). There was a significant increase in the number of face-name pairs recalled across the trials, significantly more pairs were remembered at trial 4 than trial 1 ($p < 0.001$), 2 ($p < 0.001$), and 3 ($p < 0.001$). Significantly more pairs were remembered at trial 3 than trial 1 ($p < 0.001$) and 2 ($p < 0.01$). Finally, significantly more pairs were remembered at trial 2 than trial 1 ($p < 0.01$). Again, all groups remembered more faces with increasing learning trial, though the control group consistently performed better than the subclinical and hypothyroid group. The subclinical group also consistently performed better than the hypothyroid group. For the most part, an increase in session was related to an increase in the number of pairs remembered across trials, with the exception of the first encoding trial of session 3; this was lower than that of both session 1 and session 2.

Improvement in the number of face-name pairs recalled by session three was examined (Total Score Session 3 – Total Score Session 1). There was a significant effect of group with regards to the improvement on pairs recalled by session three ($f = 4.539$; $df = 2, 64$; $p < 0.05$), with the subclinical group remembering significantly more than the hypothyroid group ($p < 0.05$), when controlling for baseline differences (see Figure 3.5). There were no significant differences between the control and subclinical groups ($p = .232$), and the control and hypothyroid groups ($p = .469$).

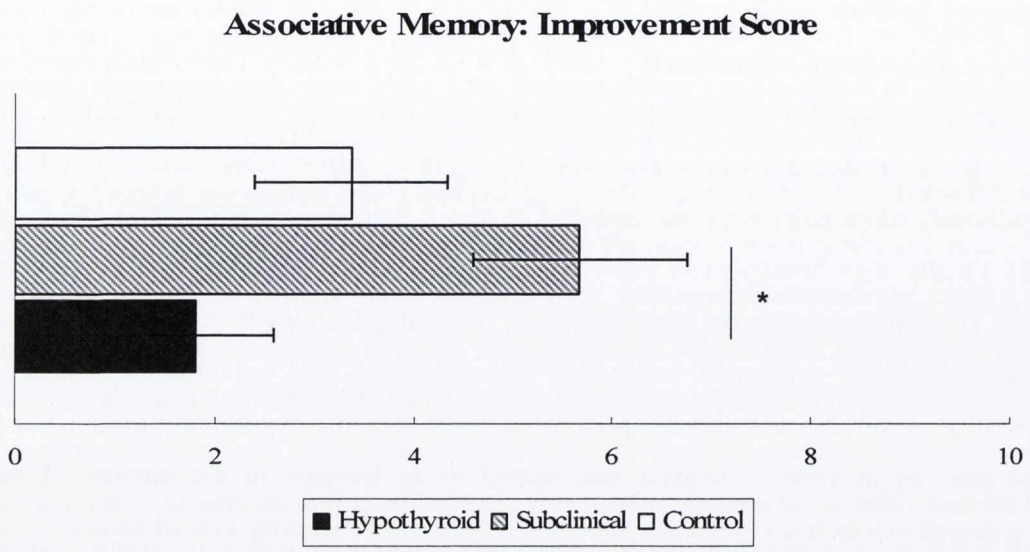

Figure 3.5: Total number of face-name pairs successfully encoded across the 4 learning trials at Session 1 (Pre-Treatment Total Face-Name Learning score, Version 1) subtracted from the total Face-Name score at Session 3 (following 6 months treatment; Total Face-Name Learning Score, Version 3), rendering an associative learning 'Improvement Score' for each of the three groups (expressed as Mean ± SEM).

Delayed recall was examined across the three sessions and between the groups. There was a significant main effect of session (f = 16.075; df = 2, 58; $p < 0.001$) there was an increasing significant improvement in the number of face-name pairs recalled across all sessions; from session 1 to session 2 ($p < 0.01$), and also session 1 to session 3 ($p < 0.001$). However, there was no significant difference between session 2 to session 3 ($p = 0.142$) on the number of face-name pairs successfully recalled in the delayed trial. There was also a significant difference between the groups (f = 4.255; df = 2, 58; $p < 0.05$), but no interaction between session x group (f = .615; df = 4, 58; p = .653). Differences were significant between the control and hypothyroid group ($p < 0.01$) (see Figure 3.6), with the hypothyroid patients showing a significantly reduced performance accuracy. There were no significant differences between the control and subclinical groups (p = .240), and the subclinical and hypothyroid groups (p = .411).

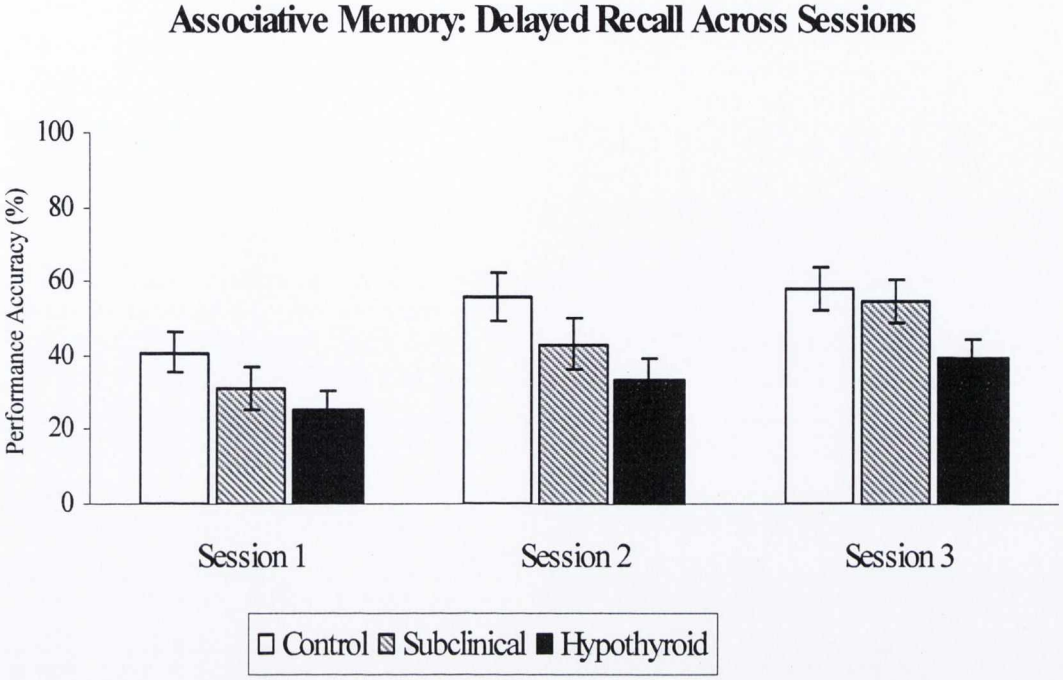

Figure 3.6: Delayed Recall (expressed as Mean ± SEM performance accuracy) across the three sessions

3.4.3 Self-rating Memory Questionnaires

3.4.3a Everyday Memory Questionnaire

While there was a significant interaction between session and group on the EMQ across the three testing sessions ($f = 3.735$; $df = 2, 15$; $p < 0.01$), there was no effect of session ($f = .009$; $df = 2, 15$; $p = .991$) and no effect of group ($f = .611$; $df = 2, 15$; $p = .556$).

3.4.3b Mundane Memory Questionnaire (MMQ)

Examining the total score across the three sessions no significant main effects of session were found ($f = 1.070$; $df = 2, 58$; $p = 0.346$). There was also no significant interaction between session x group ($f = 1.457$; $df = 4, 58$; $p = .220$), and no significant main effect of group ($f = 1.557$; $df = 2, 58$; $p = .220$).

3.4.3c Self-Rating Scale (SRS)

In line with the results found at baseline, there were no significant differences across the three testing sessions in the Self Rating Scale for session ($f = 2.674$; $df = 2, 16$; $p = .084$),

group (f = .411; df = 2, 16; p = .670), or session by group interaction (f = 1.234; df = 4, 16; p = .316).

3.4.4 Executive Functioning

3.4.4a Behavioural Assessment of Dysexecutive Syndrome

Key Search Test

There were no significant effects of group (f = .440; df = 2, 15; p = .652), no significant effects of session (f = .488; df = 2, 15; p = .619), and no significant interaction between group x session (f = 1.398; df = 4, 15; p = .258

Zoo Map Test

There were no significant effects of group (f = .032; df = 2, 15; p = .969), no significant effects of session (f = 3.094; df = 2, 15; p = .060), and no significant interaction between group x session (f = 1.009; df = 4, 15; p = .418).

DEX

There were no significant effects of group (f = 1.093; df = 2, 15; p = .360), no significant effects of session (f = 1.130; df = 2, 15; p = .336), and no significant interaction between group x session (f = .794; df = 2, 15; p = .538).

3.4.4b Focused Attention

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], were assessed between the groups on their total accuracy score (Block 1-4). There was a significant effect of session (f = 3.342; df = 2, 51; $p < 0.05$), but no effect of group (f = .688; df = 2, 51; p= .507), and no interaction between group and session (f = .348; df = 4, 51; p= .845) (see Figure 3.7). There was a significant improvement from session 1 to 3 ($p < .05$); though, there was no improvement from session 1 to 2 (p = 0.341) or session 2 to 3 (p = 0.101).

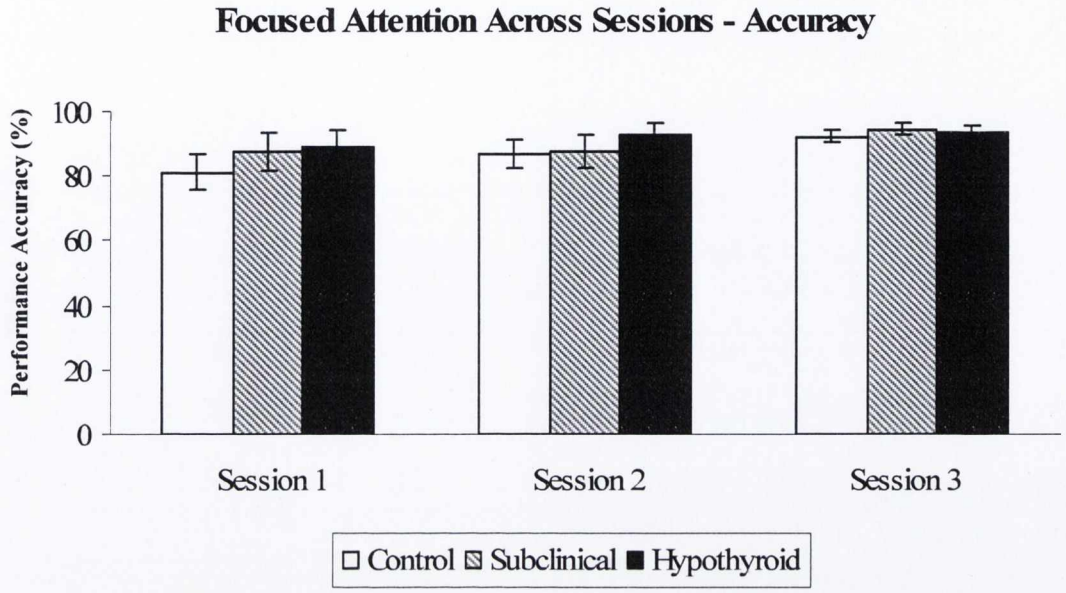

Figure 3.7: Mean (± SEM) performance accuracy on the Focused Attention task across the three testing sessions

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], were assessed between the groups on their Reaction Time (Block 1-4). Again, while there was a significant effect of session (f = 4.190; df = 2, 47; $p < 0.05$), but no effect of group (f = 1.506; df = 2, 47; p = .232), and no interaction between group and session (f = .458; df = 4, 47; p = .766) (see Figure 3.8). There was a significant decrease in RT from session 1 to 2 ($p < .05$), and a significant increase from session 2 to 3 ($p < .01$); though, there was no change from session 1 to 3 (p = 0.516).

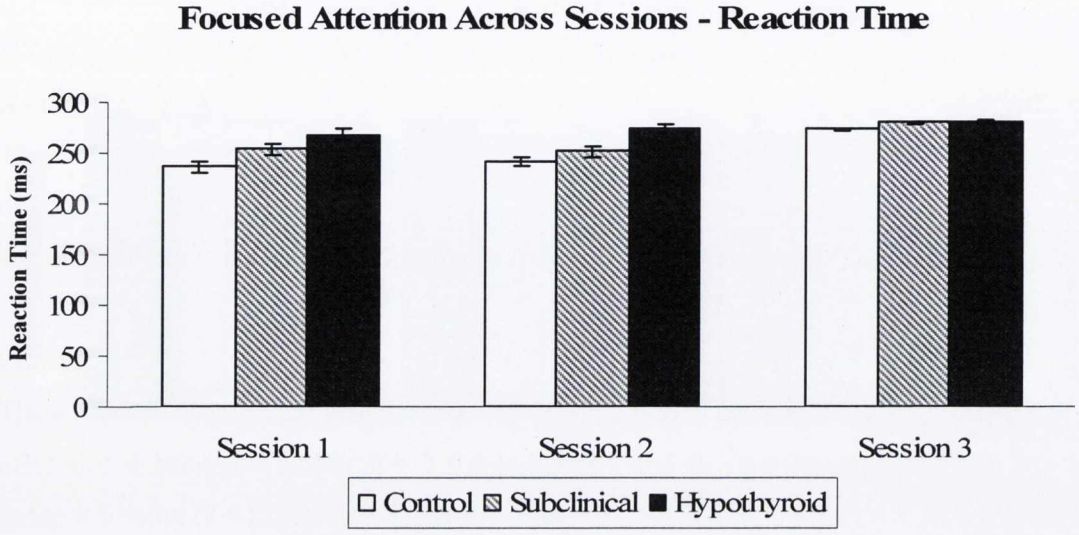

Figure 3.8: Mean (± SEM) reaction time on the Focused Attention task across the three testing sessions

3.4.4c Working Memory: The n-Back Task (0-Back, 1-Back & 2-Back Levels)

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], were assessed between the groups on their accuracy in the *n*-Back task. There was a significant main effect of load ($f = 118.751$; $df = 2, 51$; $p < 0.001$), and a significant main effect of session ($f = 9.710$; $df = 2, 58$; $p < 0.001$), but no significant differences between the groups ($f = 1.720$; $df = 2, 58$; $p = .188$). The 2-back load is significantly more difficult than both the 0-back ($p < 0.001$) and the 1-back ($p < 0.001$), while the 1-back is more difficult than the 0-back ($p < 0.001$). There is a significant improvement in accuracy on the n-back task across sessions, where accuracy at session 1 is significantly improved upon by session 2 ($p < 0.01$), and session 3 ($p < 0.01$). However, there is no significant improvement from session 2 to session 3 ($p = 1.000$).

There was also no significant interaction between session x group ($f = 1.408$; $df = 4, 58$; $p = .236$), load x group ($f = 1.786$; $df = 4, 58$; $p = .136$), or session x load x group ($f = .912$; $df = 8, 58$; $p = .508$). However, there was a significant interaction between session x load ($f = 4.883$; $df = 4, 58$; $p < 0.01$).

The mean "switch cost" in accuracy – accuracy in the 2-back condition minus accuracy in the 1-back condition, across the sessions, was also analysed there were no differences among the groups on their "switch cost" in accuracy across the sessions for session (f = 1.714; df = 2, 58; p = .185), group (f = 1.466; df = 2, 58; p = .239), or the session x group interaction (f = .219; df = 4, 58; p = .927).

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], were assessed between the groups on their reaction time in the *n*-Back task. There was a significant main effect of load (f = 73.521; df = 2, 53; $p < 0.001$); however there was no significant effect of session (f = .053; df = 2, 53; p = .949) or group (f =1.664; df = 2, 53; p = .199). There were also no interaction between session x load (f = 2.128; df = 4, 53; p = .078), session x group (f = .177; df = 4, 53; p = .950), load x group (f = .269; df = 2, 53; p = .898), and session x load x group (f = .645; df = 8, 53; p = .739). Across sessions and groups, all participants were quicker on the 2-back than the 0-back ($p < 0.001$) or 1-back ($p < 0.001$).

The mean "switch cost" in reaction time – reaction time in the 2-back condition minus reaction time in the 1-back condition, across the sessions, was also analysed, there were no differences among the groups on their "switch cost" in reaction time across the sessions for session (f = 1.072; df = 2, 28; p = .349), group (f = 1.468; df = 2, 28; p = .248), or the session x group interaction (f = .721; df = 4, 28; p = .581).

3.4.4d Response Inhibition: The Stroop Task - 'Naming Coloured Words' Version

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], and between the two trial types [Congruent vs. Incongruent], were assessed between the groups on their accuracy in the Stroop task. There was a significant effect of session (f = 7.388; df = 2, 57; $p < 0.01$), and a significant effect of trial type (f = 109.796; df = 1, 57; $p < 0.001$); however there was no effect of group (f = 1.863; df = 2, 57; p = .165). There was also no interaction between session x group (f = 1.385; df = 4, 57; p = .243), type x group (f = .939; df = 2, 57; p = .379), session x type x group (f = .670; df = 4, 57; p = .614), but there was a significant interaction between session x type (f = 12.567; df = 2, 57; $p < 0.001$). Participants responded more accurately at session 3 than session 1 ($p < 0.01$); they also had a significantly higher performance accuracy at for the congruent than incongruent trials ($p < 0.001$).

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], and between the two trial types [Congruent vs. Incongruent], were assessed between the groups on their reaction time in the Stroop task. There was no significant effect of session ($f = 2.180$; $df = 2, 57$; $p = .118$), and no effect of group ($f = 1.566$; $df = 2, 57$; $p = .218$). There was also no interaction between session x group ($f = .381$; $df = 4, 57$; $p = .822$), type x group ($f = .385$; $df = 2, 57$; $p = .682$), session x type x group ($f = .688$; $df = 4, 57$; $p = .615$), or session x type ($f = 2.309$; $df = 2, 57$; $p = .105$). However, there was a significant effect of trial type ($f = 181.984$; $df = 1, 57$; $p < .001$), with the participants responding quicker at the congruent than incongruent trials ($p < .001$),

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], and between the two trial types [Congruent vs. Incongruent], were assessed between the groups on their errors committed in the Stroop task. There was a significant effect of session ($f = 11.6$; $df = 2, 55$; $p < 0.001$), a significant effect of type ($f = 102.185$; $df = 2, 55$; $p < 0.001$), and a significant interaction between session and type ($f = 10.196$; $df = 2, 55$; $p < 0.001$). However there was no significant effect of group ($f = 1.875$; $df = 2, 57$; $p = .163$), no significant interaction between session x group ($f = .714$; $df = 2, 57$; $p = .584$), type x group ($f = 1.271$; $df = 2, 57$; $p = .289$), or session x type x group ($f = 1.046$; $df = 4, 57$; $p = .387$). Participants made fewer errors across the sessions, percentage of errors committed decreased from session 1 to 2 ($p < 0.01$), and from session 1 to 3 ($p < 0.001$). There was no difference in the errors committed between session 2 and 3 ($p = .858$). They also made 25% less errors on the congruent trials than the incongruent trials ($p < 0.001$).

3.4.4e Sustained Attention to Response Task (SART)

The comparisons made across the sessions in accuracy, reaction and errors committed on the go and no-go trial types of the SART found no effect of session and no effect of group, and no significant effect of trial type.

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], and between the two trial types [Go vs. No-go], were assessed between the groups on their accuracy on the SART. There was a significant a significant effect of type ($f = 5.766$; $df = 2, 14$; $p < 0.05$). However there was no

significant effect of effect of session (f = .191; df = 2, 14; p = .828), group (f = .631; df = 2, 14; p = .546), no significant interaction between session x group (f = .079; df = 4, 14; p = .988), type x group (f = .921; df = 2, 14; p = .421), interaction between session and type (f = .197; df = 2, 14; p = .822), or session x type x group (f = .005; df = 4, 14; p = 1.000). Overall, participants were better on the no-go trials than the go-trials ($p < 0.05$).

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)] were assessed between the groups on their reaction time for the go trial of the SART. There was no significant effect of effect of session (f = .765; df = 2, 14; p = .475), group (f = 2.082; df = 2, 14; p = .162), no significant interaction between session x group (f = .413; df = 4, 14; p = .798).

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], and between the two trial types [Go vs. No-go], were assessed between the groups on their errors committed on the SART. There was a significant a significant effect of type (f = 5.508; df = 2, 14; $p < 0.05$). However there was no significant effect of effect of session (f = .512; df = 2, 14; p = .605), group (f = 1.073; df = 2, 14; p = .369), no significant interaction between session x group (f = .034; df = 4, 14; p = .998), type x group (f = .997; df = 2, 14; p = .394), interaction between session and type (f = .141; df = 2, 14; p = .869), or session x type x group (f = .067; df = 4, 14; p = .991). Overall, participants committed more errors on the go than no-go tials ($p < 0.05$).

3.4.4f Dual Attention to Response Task (DART)

The comparisons made across the sessions in accuracy, reaction time, and errors committed on the go, grey and no-go trial types of the DART were examined.

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], and between the three trial types [Go vs. No-go vs. grey], were assessed between the groups on their accuracy on the DART. There was a significant a significant effect of type (f = 4.176; df = 2, 16; $p < 0.05$). However there was no significant effect of effect of session (f = .251; df = 2, 16; p = .780), group (f = .036; df = 2, 16; p = .965), no significant interaction between session x group (f = .396; df = 4, 16; p = .810), type x group (f = 1.269; df = 4, 16; p = .302), interaction between session and type (f = .529; df = 4, 16; p = .715), or session x type x group (f = 1.155; df = 8, 16; p = .340). There was a decrease in accuracy between the go trials and the grey trials ($p < 0.05$).

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], and between the three trial types [Go vs. No-go vs. grey], were assessed between the groups on their errors on the DART. There was a significant a significant effect of type ($f = 3.939$; $df = 2, 16$; $p < 0.05$). However there was no significant effect of effect of session ($f = .614$; $df = 2, 16$; $p = .548$), group ($f = .267$; $df = 2, 16$; $p = .769$), no significant interaction between session x group ($f = .036$; $df = 4, 16$; $p = .456$), type x group ($f = 1.313$; $df = 4, 16$; $p = .288$), interaction between session and type ($f = .443$; $df = 4, 16$; $p = .777$), or session x type x group ($f = 1.061$; $df = 8, 16$; $p = .402$). There was an increase in errors between the go trials and the grey trials ($p < 0.05$).

Changes in performance across the three testing sessions [Session 1 (baseline) vs. Session 2 (3 months) vs. Session 3 (6 months)], and between the three trial types [Go vs. No-go vs. grey], were assessed between the groups on their reaction times on the DART. There was no significant a significant effect of type ($f = 1.607$; $df = 1, 16$; $p = .224$), no significant effect of effect of session ($f = 1.110$; $df = 2, 16$; $p = .343$), group ($f = 1.056$; $df = 2, 16$; $p = .372$), no significant interaction between session x group ($f = .646$; $df = 4, 16$; $p = .634$), type x group ($f = 1.662$; $df = 2, 16$; $p = .230$), session x type ($f = .997$; $df = 2, 16$; $p = .381$), or session x type x group ($f = .968$; $df = 4, 16$; $p = .439$).

3.4.5 Premorbid IQ - National Adult Reading Test 2nd Ed (NART)

Comparisons of NART IQ score across the three sessions and between the three groups found no significant effect of session ($f = 2.393 = 2, 57$; $p = .096$), no significant effect of group ($f = 2.790$; $df = 2, 57$; $p = .070$), and no interaction between session x group ($f = 1.714$; $df = 4, 57$; $p = .152$).

3.4.6 Affective Measurements

3.4.6a Hospital Anxiety and Depression Scale

Comparisons across the three sessions on the depression scores from the HADS found significant effects of both session ($f = 14.028$; $df = 2, 59$; $p < 0.001$), and group ($f = 6.176$; $df = 2, 59$; $p < 0.01$). However there was no significant interaction between session and group ($f = 1.494$; $df = 4, 59$; $p = .208$). Post-hoc analysis revealed a significant difference between the control and hypothyroid groups ($p < 0.01$) and the control and subclinical group ($p < .05$), while there were no differences between the subclinical and hypothyroid group ($p = 1.000$) (see Figure 3.9). There was a significant decrease in the HADS

depression scores across the sessions, there were fewer reported depression symptoms as session 2 ($p < 0.001$) and session 3 ($p < 0.001$), in comparison to session 1.

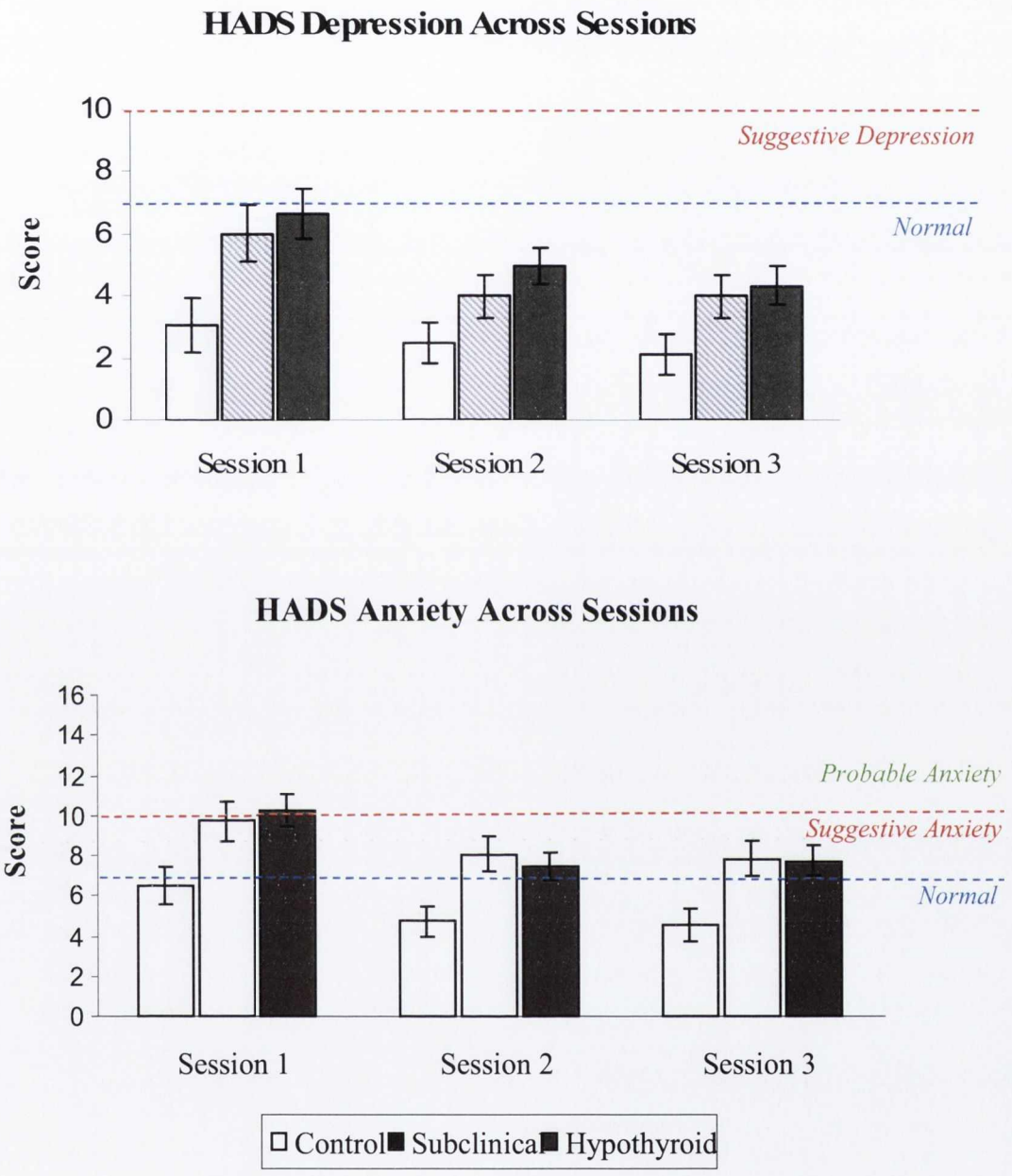

Figure 3.9: Mean (± SEM) score on the HADS across the control, subclinical and hypothyroid groups for both depression and anxiety at Session One, Session Two, and Session Three.

Scores on the anxiety scale of the HADS were also examined across the three sessions. Again, there were significant effects of both session ($f = 12.268$; $df = 2, 59$; $p < 0.001$), and

group (f = 8.732; df = 2, 59; $p < 0.001$), but no significant interaction between session and group (f = 1.101; df = 4, 59; p = .359). In this case though, the post-hoc analysis found significant differences between the control group and both the subclinical ($p < 0.01$), and hypothyroid group ($p < 0.01$), though there were no differences between the subclinical and hypothyroid groups (p = .694) (see Figure 3.9). There was a significant decrease in the HADS anxiety scores across the sessions, there were fewer reported anxiety symptoms as session 2 ($p < 0.001$) and session 3 ($p < 0.001$), in comparison to session 1.

3.4.6b Beck Depression Inventory II

The comparisons made across the sessions on the BDI score found no effect of session (f = .970; df = 2, 16; p = .290) and no effect of group (f = 1.609; df = 2, 16; p = .239), and no interaction between session x group (f = .571; df = 4, 16; p = .686). Baseline differences between the control and hypothyroid group were no longer evident (see Table 3.2).

Group	Control	Subclinical	Hypothyroid
Session 1	9.24 (± 0.70)	13.25 (± 0.75)	16.29 (± 0.61)
Session 2	4.43 (± 1.94)	5.00 (± 1.63)	8.30 (± 1.62)
Session 3	4.57 (± 2.81)	5.50 (± 1.26)	8.60 (± 2.35)

Table 3.2: Mean depression (± SEM) scores on the BDI across the three sessions

3.4.6c Perceived Stress Scale

The comparisons made across the sessions on the PSS score found no effect of session (f = .267; df = 2, 15; p = .768) and no effect of group (f = .270; df = 2, 15; p = .767), and no interaction between session x group (f = 1.141; df = 4, 15; p = .356). This reflected differences found at baseline.

3.4.7 TSH Correlations

Correlations between TSH levels and the dependent variables, at both session two and session three, were calculated separately for each of the patient groups; there were no bloods taken at session 2 or 3 for the control participants.

Session 2:

At session two there were no significant correlations between TSH and any of the measures used for the subclinical group. There was a significant negative correlation between TSH levels and PSS scores, where the higher the TSH level the lower the PSS

scores (r = -.545, n = 15, $p < 0.05$). There was a significant positive correlation between TSH levels and MSRS scores, where the higher the TSH level the higher the MSRS scores (r = .542, n = 15, $p < 0.05$). There was also a significant negative correlation between TSH levels and accuracy on the 0-back level of the n-back task, where the higher the TSH level the lower the 0-back accuracy (r = -.656, n = 30, $p < 0.001$). There was also a significant negative correlation between TSH levels and reaction time on the 2-back level of the n-back task (r = -.415, n = 26, $p < 0.05$), and also reaction time switch cost (r = -.439, n = 26, $p < 0.05$). A positive relationship was found between TSH levels and reaction time in the go trial of the SART task (r = .519, n = 15, $p < 0.05$). There was also a positive relationship between TSH and accuracy on the incongruent trials of the Stroop task (r = .375, n = 30, $p < 0.05$), and a negative correlation between TSH levels and reaction errors on the incongruent trials (r = -.374, n = 30, $p < 0.05$),

Session 3:

At session three there was a significant positive correlation between TSH and reaction time on the 0-back level of the n-back task in the hypothyroid group (r = .408, n = 25, $p < 0.05$).

3.5 Discussion

There were three key aims of this study that investigated the change in memory and mood as a result of treatment for hypothyroidism (LT4 therapy). Firstly, to determine whether associative memory impairments improved with treatment; secondly, to determine whether working memory impairments improved with treatment; and finally, to establish whether depression and anxiety levels decreased with treatment. Changes were examined from baseline (session one), across two follow-up testing sessions, session two (3 months on treatment) and session 3 (6 months on treatment). The main findings are listed below:

- Associative memory impairments seen at baseline in patients with an underactive thyroid gland improved with treatment; however, all participants improved across sessions.
- Working memory impairments seen at baseline in patients with an underactive thyroid gland were no longer present; however, all participants improved across sessions.
- Levels of depression and anxiety decreased in patients with an underactive thyroid gland with treatment; however, a similar pattern of reduced symptoms were also seen in the control group

3.5.1 Associative Memory Following Treatment

It was hypothesised that baseline deficits in associative memory would improve with treatment, and that the subclinical group would improve to control levels by session three. Deficits seen on the ROCF at baseline were examined across the three testing sessions. In the copy trial, there were significant differences in recall accuracy across the three testing sessions. Closer examination of these differences found that by session two, all participants were performing at the same level, significantly better than at session 1; however, there was a significant decrease from session 2 to session 3. While there was an overall group difference, with the subclinical group performing he best, there was no group x session interaction. This would suggest that there was no treatment related improvement in the copy trial of the ROCF.

A previous study found that at 3 months on treatment, hypothyroid subjects still displayed deficits in the copy trial of a complex figure; though there were no differences in the

immediate or delayed recall (Samuels et al., 2007a). However, the participants recruited for the Samuels study were not assessed at baseline; rather they were assessed after 3 months of treatment and compared with normal controls. While this does confirm that there are deficits on the ROCF in hypothyroidism after 3 months of treatment, it allows no comparison for baseline scores and doesn't take into account the nature of repeat test sessions in order to reduce between subjects variability. In addition, there were no adjustments made for multiple comparisons. The strengths of the current study include among others, that it is a repeated measures study comparing memory from baseline, across 2 follow-up testing sessions while adjusting for multiple comparisons. While deficits were evident at baseline in Chapter 2, those who completed the follow-up testing sessions did not reflect this pattern.

A similar pattern was seen on the immediate trial, where baseline scores had also improved by session two; though in this case these general improvements were evident across all of the groups, and were maintained at session 3. However, there were still significant group differences on the delayed recall of the ROCF; the control group scored significantly higher than both the SCH and hypothyroid groups. Nevertheless, there was also a significant effect of session, and no session x group interaction, suggesting that all group improved in their delayed accuracy recall across the sessions. All participants performed significantly better by session 2, and also improved significantly more at session 3. Scores on the recognition trial remained equal between the groups, with no differences found across the sessions.

When the difference between delayed recall and copy ability was taken into account, across the sessions, there was a significant difference between the groups. The control group performed significantly better than both the SCH and hypothyroid groups across the three sessions. There was also an significant increase in the overall score with an increase in session, however, again there was no session x group interaction, suggesting that improvements on the ROCF were not treatment related. These findings are not in agreement with previous studies. Correia et al. (2007), found that deficits on overall accuracy in spatial memory, using the ROCF, were evident at 3 months following treatments in the hypothyroid group. In the same group of patients at 6 months following treatment, deficits remained on the overall accuracy scores in the hypothyroid group (Correia et al., 2008). The present results demonstrate that associative memory, as measured by the ROCF, improved across sessions and markedly so in the subclinical

group, though group differences were still evident between the groups on some measures. These results do not suggest that are significant impairments in associative memory that improve with treatment, accordingly, they do not offer weight to the suggestion that functional impairments in hypothyroidism are reversible.

Associative memory changes were also examined using the face-name task across the three testing sessions. The hypothesis that the deficits evident in memory for face-name pairs at baseline would improve following treatment was not supported. The total number of faces successfully recalled at each session was analysed and group differences were evident; there was a significant impairment in the hypothyroid patient's ability to learn the face-name pairs, when compared to the control groups. There was also a significant effect os session, with more face-name pairs remembered overall between session 1 and 2, session 1 and 3, and also session 2 and 3. While all groups improved across the sessions, the control group consistently performed better than the subclinical and hypothyroid group across sessions. In addition, the subclinical group consistently performed better than the hypothyroid group across sessions; however, further post hoc analysis could not be conducted on these improvements as the session x group interaction was not significant.

An improvement score was also devised that calculated the change in the number of face-name pairs successfully recalled from session one to session three. While all three groups showed an improvement across the sessions, the subclinical group showed the largest improvement, beyond that of control participants. The hypothyroid group performed the worst.

Analysing the delayed recall for the face-name task across sessions, again significant differences were seen between the control and hypothyroid group. There were also significant improvements in recall accuracy across the sessions; however, there were no session x group differences. This suggests that all participants improved across sessions; there is no treatment effect evident in those who completed the follow-up sessions. These findings contradict those of Correia et al. (2007, 2008), who reported that at 3 months there were still significant differences between the control and hypothyroid group in associative memory, while the SCH group were no longer different from the controls within 3 months on treatment. By 6 months, their hypothyroid group remained impaired on the delayed recall of the face-name task. In the current study, associative memory, as measured by the face-name task, improved across all sessions and in all of the groups, though significant

differences remained between the control and hypothyroid groups. These findings do not demonstrate that the associative memory deficits found in hypothyroidism are reversible, at least in SCH, within 6 months of treatment. Finally, they do support the proposition that hypothyroidism exists on a continuum to some degree; this will be discussed in more detail later.

3.5.2 Working Memory Following Treatment

Working memory deficits were evident at baseline in chapter 2, with the control group performing significantly better than the hypothyroid group. The hypothesis that these differences would no longer be evident following treatment was not supported. There was a significant improvement in accuracy scores on the *n*-back WM task across the sessions; though no overall group difference was evident across the sessions. Accuracy scores improved by session 2, and this improvement was maintained at session 3, for all participants. However, there were no significant group differences and no session x group interaction. This would suggest that there was a general improvement across sessions for all participants. There was no treatment related improvement in WM.

These findings do not support those reported by Correia et al. (2008), who found that impairments in working memory in hypothyroid patients, as measured by the n-back task, recovered within 6 months of treatment. They also reported that there were no deficits found in the SCH group at any session, implying that working memory is not impaired in SCH. While the present study found no significant differences in WM in the SCH group, previous studies have found WM deficits. Samuels et al. (2007b) reported a significant impairment in WM (short term memory) in experimentally-induced SCH, and found that there were also decreases in mood status in this group. This study provides support for treating SCH, as the impairments in WM were present when the participants were induced with SCH. However, the participants in the Samuels study (2007b) were not compared to a healthy control group; rather it was a within groups comparison of euthyroid status (for 3 months), and experimentally induced SCH in the same group. While it did reduce between subject variance, it could not take into account the possibility that, while in the euthyroid part of the experiment, participants could be experiencing impairment in WM. In contrast, the present study allowed comparisons to be made to a healthy control group.

Zhu et al. (2006), mentioned previously, also carried out a 6-month follow-up in the SCH group to examine the benefits of LT4 treatment on WM. As executive function plays a key

role in many cognitive operations, treatment should ameliorate the WM impairments seen at baseline, and ultimately benefit the SCH group. While there were differences at baseline, there was no significant difference post-treatment, on performance accuracy of the SCH group. ROI analysis of the common network of activation seen across all subjects found that, following treatment, the SCH exhibited a load effect in the same regions seen in the control group. This study provides both behavioural and fMRI support for treating SCH, as the WM impairments were reversible within 6 months; indicating that there is functional recovery in hypothyroidism.

The results from the present study suggest that there is no affect of hypothyroidism on PFC-associated memory, and that changes found within 6 months are not treatment related. This does not support the suggestion that PFC memory impairments are caused by reduced connectivity with the MTL during hypothyroidism; and that upon treatment, the relationship between the two regions improves and these WM deficits are reversed.

3.5.3 Relationship between Hypothyroidism and Affective Measures Following Treatment

The final hypothesis that self-reported levels of depression and anxiety would improve with treatment was somewhat supported. Depression scores, as measured by the HADS were significantly different across the sessions; there was a significant decrease in depression symptoms reported with and increase in session. However, while there was a significant difference found between the control group and both the SCH and hypothyroid groups, there was also a reduction in the number of symptoms reported by the control group. As there was no session x group interaction, these differences could not be examined further. Though baseline differences between the control and hypothyroid group were still evident across the sessions, the scores for the hypothyroid group are now within the normal range (see Figure 3.10). Previous studies have examined depression and anxiety levels in SCH and hypothyroidism using the HADS, they found a significant decrease in anxiety and depression scores following 3 months of LT4 treatment (Correia et al., 2007). This is somewhat contradictory with previous finding, as Wekking et al. (2005) found that after an average of 5 year treatment, euthyroid patients still displayed significantly higher scores on measures mental health, wellbeing and vitality.

Anxiety levels, as measured by the HADS, were also examined across the sessions. Again there were significant differences between the groups on the anxiety levels; these were

between the control group and both the subclinical and hypothyroid group. There was also a significant decrease in anxiety symptoms reported across sessions, though again there was no session x group interaction, so these differences could not be examined further. Unlike the depression scores, the SCH and hypothyroid groups remained within the suggestive anxiety range at session 2 (3 months) and 3 (6 months) (see Figure 3.10). Contrary to the findings from the present study, Jorde et al. (2006) found that there were no baseline differences on cognitive and affective measures in SCH, and no differences in the SCH patients when they were treated with either a placebo or LT4 replacement. However, they note that there was a major limitation to their study, only those with TSH up to 10mU/l were included. In the present study, the TSH levels in the SCH at baseline ranged from 4.18 – 15.80 mU/l. Perhaps differences would have been evident in SCH patients with higher TSH levels; however, Jorde et al. (2006) did include a broad range of tests and use a large sample of participants.

Findings from the present study demonstrate that there are significant differences in measures of depression and anxiety in hypothyroidism, though there were no treatment related decreases in symptoms. While a relationship between hypothyroidism and depression has been proposed, the mechanisms through which this relationship occurs are not known. Whybrow et al. (1981) suggest that a possible mechanism of action for thyroid replacement therapy maybe through its effects on monoamine neurotransmitter systems, especially as thyroid dysfunction has been linked with abnormalities in noradrenergic neurotransmission. Nevertheless, there is a lack of conclusive studies that have been carried out on adult humans with hypothyroidism.

3.5.4 TSH Correlations with Cognitive and Affective Measures Following Treatment

In the current study, there was little relationship between TSH levels and mood or cognition following treatment. While some measures were significantly related to TSH levels at session 2 in the hypothyroid group, there were few found in the SCH group. There were also few correlations found at session 3. Previous research has found no correlations between TSH, free T3 or free T4 on measures of mood or cognition (Samuels et al., 2007a) following 3 months of treatment in euthyroid hypothyroid group. However they did find a correlation between changes in T4 and changes in WM performance in SCH patients; they believe that this supports the idea that SCH is part of a continuum of thyroid diseases, with milder deficits seen in SCH and greater impairments in hypothyroidism (Samuels et al.,

2007b). Accordingly, there have been suggestions made by The National Academy of Clinical Biochemistry that normal TSH levels should be between 0.5 and 2.0 mlU/l, and that the current levels of 0.4 to 4.0 mlU/l (Baloch et al., 2003) are too wide. This would result in the inclusion of additional patients due to the more narrowly defined normal population, though it may prompt more debate over the decision to treat SCH.

3.5.5 Should Thyroid Dysfunction be Treated?

Conclusions from the current study have not established that the hypothyroid-induced memory deficits are reversible, with improvements, and in some cases full recovery, of impairments evident within 6 months of treatment. In addition, the results offer little support to the notion that hypothyroidism exists on a continuum, and that SCH will eventually lead to hypothyroidism. For the most part, the SCH and hypothyroid groups displayed similar deficits.

In a fMRI study that compared WM abilities at baseline, and following 6 months of treatment, Zhu et al. (2006) found that pre-treatment SCH participants displayed abnormal function within the frontal lobes However, following 6 months of treatment SCH participants recruited all of the same regions as the control participants, indicating that they had normal frontal functioning. While a similar study has not been published using hypothyroid patients, there has been some work done with this group, looking at change in brain size with treatment (Oatridge et al., 2002). Oatridge et al. examined if there were brain changes in patients with hypothyroidism after treatment, and aimed to correlate any changes with serum markers of the disease. While there were only three patients in this group, they did find that as the patients returned to a euthyroid state, the brain increased in size, and the ventricles decreased in size. This increase in the brain size correlated with an increase in T4 levels and a decrease in TSH levels, indicative of a return to the euthyroid state. The decrease in ventricular size was also correlated with an increase in T4 levels and a decrease in TSH levels. They report "a strong correlation between changes in brain and ventricular size and thyroid hormones levels after treatment" (Oatridge et al., 2002, p. 1542). While there is a lack of research using MRI in hypothyroidism, those studies that have used it to examine treatment effects, demonstrate the beneficial effects that thyroid hormone replacement has in hypothyroidism.

In 2004 an expert panel came to the conclusion that there was insufficient data to support an association between SCH and cognition, recommending that patients should not be

treated based on their neurocognitive effects (Surks et al., 2004). This supported a previous decision by an earlier consensus panel led by Vanderpump, who suggested that subclinical patients only be treated when their TSH levels surpass 10 mU/l (1996). However the risk of progression towards overt hypothyroidism is estimated at 5-15% of patients per year, and this increases with the presence of thyroid antibodies (Hendrick et al., 1998). Nevertheless, Gharib et al.(2005), who also advocate for a cautious approach to treatment, raise a very interesting point; they note that "the lack of definitive evidence for a benefit does not equate to evidence for lack of benefit" (p. 583). Reviewing the literature, which contradicts the findings of the present study somewhat, it appears that LT4 therapy improves memory function in SCH patients and validates the opinion that it should be given to all patients diagnosed with SCH and hypothyroidism.

3.5.6 Are Deficits Fully Reversible with Treatment?

There is considerable debate as to whether the deficits in cognitive functioning and mood disorders are fully reversible, as recent studies have suggested that there is only a partial recovery following treatment for hypothyroidism (Dugbartey, 1998). Wekking et al. (2005) examined 141 euthyroid patients, (median duration of treatment 5.5 years), to determine if they exhibited impairments despite a return to the euthyroid level. When compared to standard values, the euthyroid patients displayed reduced performance on measures of complex attention (Paced Auditory Serial Attention Task) and verbal memory (CVLT and Rivermead); they also had significantly lower levels of well-being in comparison to the general population (Symptom Checklist-90 and Rand 36-Item Health Survey). The strength of this study lies in the number of patients examined and the time since they began treatment, after more than five years, impairments were still evident. This finding is also consistent with that of Leentjens et al. (1995), who found that baseline cognitive deficits remained impaired, even with treatment, when compared to control subjects. Additionally, Saravanan et al. (2002) investigated psychological well being in euthyroid patients; they found that even with normal TSH levels, patients still displayed a significant impairment in psychological well being (Saravanan et al., 2002).

It is evident in the present study that not all baseline deficits showed a treatment related improvements within 6 months, previous studies have reported that deficits are still evident even after 5.5 years of treatment (Wekking et al., 2005). A longer follow-up period would help to identify whether the deficits found at baseline in the present study are reversible. Care was taken at every point to account for the multiple testing sessions and comparisons

made between the groups in the statistical analysis, strengthening the findings that did emerge. Nevertheless, the patterns of improvement evident across all of the particpants on all of tasks included, suggest that perhaps it remains to determine when a treatment-related effect will be evident.

3.5.7 What is the Cognitive Profile of Hypothyroidism?

Accounting for the baseline deficits discussed in Chapter 2 and the lack of treatment-related improvements found following LT4 treatment in the current chapter, it id difficult to rectify what the cognitive profile of hypothyroidism is. There were primarily two specific cognitive deficits found in hypothyroidism; one in hippocampal-associated memory and one in PFC-associated memory at baseline. There were significant impairments on several measures of hippocampal-associated memory; deficits were found on measures of visuo-spatial, verbal, and associative memory. There were also significant deficits found on DLPFC-associated memory using the *n*-back working memory task (see Table 2.13). Following 6 months of treatment, there were significant improvements seen in the SCH and hypothyroid group across several measures; however these improvements were evident in all groups and not just the patient groups. While the impairments seen in the SCH group appear to normalised with treatment on all measures, we cannot identify when these improvements took place. Some of those observed in the hypothyroid group were still evident by 6 months, though again it is difficult to rectify this with the general improvement across sessions also seen in the control group. Deficits remained on visuo-spatial memory, as measured by the ROCF, and on associative memory, as measured by the face-name task. This would suggest that hippocampal-associated memory deficits are not fully reversible within 6 months in hypothyroid patients; however, it remains to determine the impact that the treatment had on these deficits (see Table 3.3).

Test	Associated Area	Subclinical	Hypothyroid
Visual Memory – ROCF	**Hippocampus**	***Normalised***	***Remains Impaired***
Associative Memory – Face-Name Task	**Hippocampus**	***Normalised***	***Remains Impaired***
Working Memory – *n*-Back Task	**DLPFC**	***No Deficit at Baseline***	***Normalised***

Table 3.3: Behavioural changes in SCH and hypothyroidism within 6 months of LT4 therapy

Considering the relationship between the PFC and the hippocampus, some might suggest that the improvement in WM at 6 months is due to the improvement in hippocampal functioning following LT4 treatment. However, verifying such a statement would require further investigation, using methods such as fMRI and functional connectivity. Nevertheless, certain conclusions can be reached from the data found in the current study. There were specific deficits found in hypothyroidism, primarily on hippocampal-associated memory tasks, while these improvements on these tasks were not treatment related, they did not fully recover within 6 months of treatment.

3.5.8 Outstanding Methodological Issues

The primary issue with the current study is that it was difficult to identify treatment related improvements in memory, above and beyond that of practice across sessions. The present study was limited by the number of patients who took part in all sessions, reducing the sample size quite dramatically: at 6 months there were 22 SCH and 27 hypothyroid patients, along with 20 control participants. A fourth testing session was originally included to examine the deficits after 12 months of treatment but could not be included in the analysis due to the difficulty in bringing patients back for follow-up appointments. Perhaps the subset of patients who completed the follow-up sessions was not representative of the overall population. The relatively few males were not intended for example. Every patient who met the inclusion criteria was approached and asked to participate in the study; however, there were considerably fewer men diagnosed with hypothyroidism during the study than women, resulting in a gender bias in the numbers recruited. However, this is not unusual in hypothyroidism, as it is significantly more prevalent in women (Roberts et al., 2004). While the present study did have an intensive set of measures (each of the testing sessions lasted about 2 hours), which allowed the rigorous examination of cognitive deficits and mood disorders. However, it was never the intention to examine global cognitive changes, but more subtle specific deficits that were hypothesised to occur with hypothyroidism, following the review of previous animal and human studies of thyroid dysfunction. Accordingly, significant differences were not found across the sessions, perhaps due to the reduced participant numbers.

The present study included measures that offered a more sensitive and hypothetical driven examination of cognition than many of the previous studies; this was reflected in the findings, impairments were primarily hippocampal-associated (declarative memory), though mild deficits were found in frontally driven tasks (working memory). This supports

the current view that hypothyroid-related memory impairments are not of a global nature, but more specific. Bauer (2008) even goes as far as to suggest that the impairments are specifically deficits in retrieval and not attention. The present findings extend this suggestion, by proposing that retrieval deficits are present, but these are due to faulty encoding processes in the first instance. However, the findings did not support a treatment-related reduction in those deficits.

While differences in anxiety levels remained, the deficits on the cognitive measures evident in the current study appear to be distinct from those associated with mood disorders, in which patients typically experience broad executive difficulties (Miller et al., 2007). In addition, while improvements were seen with LT4 treatment, there were also improvements seen in the control group. Given that LT4 treatment cannot exactly reproduce the physiological function of thyroid hormones (Bauer et al., 2008), this may offer an explanation for the continued impairments evident in the hypothyroid group once they returned to a euthyroid state.

3.5.9 Future Directions

To-date there have been few functional imaging studies of hypothyroidism; those published have mainly used techniques that assess cerebral blood flow and metabolism. Though, unlike the behavioural studies discussed in chapter 2 and 3, the most consistent findings from the SPECT and PET studies have been global, diffuse hypoperfusion, and not specific patterns of activity that would be expected given the data from behavioural studies. Nevertheless, the decrease in regional cerebral blood flow appears to be more prominent in the parietal lobe, though whether these decreases persist after a return to the euthyroid state remains to be answered (Krausz et al., 2004). While the studies are limited in number, they have offered some promising insights into the thyroid-brain relationship (Bauer et al., 2008).

First and foremost, verifying the pre-treatment behavioural deficits seen in the current study using fMRI would lend weight to the findings. Replicating the results would require the use of very well designed event-related fMRI tasks, which would allow researchers to identify the successfully encoded face-name pairs from those that were subsequently forgotten. In addition, the use of a delayed recall task, whilst in the MRI scanner, would offer the benefit of looking at blood oxygenation level-dependent (BOLD) activity patterns during LTM retrieval. Examining the nature of the WM deficits in more detail might also

indicate whether there are altered levels of BOLD activity in the PFC as a result of hypothyroidism. Post-treatment fMRI follow-up scans would also be useful to determine whether there are changes evident in the BOLD activity between the groups, though treatment-related behavioural improvements across the sessions were not found.

Investigating the relationship between hippocampal and PFC connections in hypothyroidism could also prove quite an interesting topic to investigate in the future, perhaps using functional connectivity. This may identify altered connections evident in hypothyroidism, and also the nature of the change in the networks between the two structures as a result of treatment using follow-up MRI studies.

Furthermore, as age had a significant impact on hypothyroid cognitive performance, it would be extremely useful to examine the effects of age on hippocampal- and PFC-based tasks across the lifespan. This might then allow further clarification of the exact nature of the impairments evident in hypothyroidism.

3.6 Conclusion

Samuels (2008) reviewed a large number of studies that investigated cognitive deficits in a range of thyroid dysfunctions. She made three conclusions; firstly, that global cognitive impairments are not seen in thyroid disease; secondly, that key impairments in specific cognitive domains are not usual in thyroid disease; and finally, that understated impairments in specific cognitive domains are likely to exist in thyroid disease (mainly in WM and executive function). While these statements may not fully reflect the findings from the present study, they do agree with them somewhat. The current study demonstrates that global cognitive impairments are not evident in hypothyroidism, but deficits of a more specific nature are found in both SCH and hypothyroidism. Analysing the results from the present study, it would appear that these deficits are primarily found in hippocampal- and PFC-based memory tasks, and are more marked in hypothyroid than SCH patients. However; these deficits were not reversible upon treatment, with SCH patients returning to normal levels within 6 months of treatment, and hypothyroid patients improving, but still showing impairments in hippocampal based tasks. It remains to be determined whether these deficits are fully-reversible, and to what extent treatment can improve associative and working memory deficits found at baseline.

Chapter 4

Associative- and Working-Memory Changes throughout the Lifespan

4.1 Summary

It is well documented that memory declines with age, though the rate at which different types of memory functions declines appears to vary across the lifespan. This rate depends upon the type of memory function that is being tested (e.g. WM), whether it is STM or LTM being tested, and the measures used to test memory (recall Vs recognition). Studies that have investigated age-related decline in associative memory have differentiated between memory for single units and memory for the relationship between those units (Naveh-Benjamin, 2000). There is also considerable support for the decline in WM across the lifespan, with investigators focusing more recently on the amount of information that can be held in the focus of attention, and the age-related cost that there might be in switching between items inside and outside of the focus of attention (Van Gerven et al., 2008). This chapter builds upon the previous findings; firstly, that there was an age-associated impact on cognitive functioning in patients with an underactive thyroid gland; and secondly, that there was a relationship between memory impairment on tasks that have been associated with hippocampal- and PFC-regions in hypothyroidism. The main aim of the current chapter is to explore the relationship between both of these findings in a healthy population; it examines the nature of the relationship between age and associative- and working-memory changes throughout adulthood.

4.2 Introduction

4.2.1 Memory across the Lifespan

It has generally been accepted that memory declines gradually over the lifespan, with most people beginning to report memory problems by their early sixties (Craik, 2008); in contrast, some studies have reported that memory problems are evident by the time people reach their thirties (Park et al., 2002). Accordingly, there is a lot of debate in the current literature about age-related decline in memory, about the types of memory functions involved, whether these losses can recover, and about whether memory impairments impact other cognitive functions.

According to Luo and Craik (2008), there are five major memory systems that need to be considered, and the rate at which these systems deteriorates differs across the lifespan. They state that episodic and working memory decline quite rapidly, while general knowledge, memory for habitual tasks and perceptual information remain relatively intact. There is still considerable debate about the reasons for this differential rate of decline, though some suggestions have been put forward. One suggestion, is that as we age we have increased difficulty with self-initiated processing of large amounts of information; the other is that as we age we have increased difficulty when specific information is required (Craik, 2008). The latter explanation may offer some insight into the age-related deficits seen in the hypothyroid study (Chapter 2), that older people experience impairments in memory that requires the retrieval of specific information, such as someone's name when they see their face.

What is known and agreed upon is that not all types of memory are affected equally; age-related decline tends to be less pronounced in short-term memory span tasks, and recognition tasks; whereas a more marked decline has been documented in tasks involving free or cued recall, which necessitate the precise and conscious recollection of information (Kessels et al., 2003) Additionally, there is also a more marked decrease in WM tasks (Grady et al., 2000). There are several suggestions about the processes that underlie age-related memory decline (see Light, 1991 for a review); perhaps it is a general slowing of cognition (Salthouse, 1996); or an age-related decline in attentional resources (see Craik, 2008); alternatively, it may be a reduction in the efficiency of inhibitory processes; or increased difficulty in associating or binding aspects of an event together (Chalfonte et el, 1996), or even as a result of synaptic loss (Backman, 2008). Alternatively, it could be a

combination of all of the above, each explanation accounting for the differential rate of decline from one memory system to the next. An examination the types of memory that are likely to decrease with age is necessary.

4.2.2 Associative Memory Decline in Adulthood

The ability to put a face to a name is one of the most common problems reported by people as they age (Scanlan et al., 1997; Yesavage et al., 1984). Associative memory involves binding items/information/stimuli (e.g. a face and a name) together so that relationships form between the items to aid their recall. The ability to bind pieces of information together is necessary for successful day-to-day functioning, for example, remembering who you have told a story to so that you do not tell them again (Kersten et al., 2008). Creating this association between, for example, the features of an item is necessary, as the representations of the item (e.g. colour and shape) are located on distinct feature maps in the brain (Kersten et al., 2008). Accordingly, in order to remember the item more efficiently, it is necessary to create a relationship between the feature maps of that item. Difficulties in episodic memory could stem from problems with the initial encoding of information, or its retrieval, or even both. Age-related deficits in binding and binding errors have been reported by several researchers and will be discussed below.

Findings from associative memory studies supports the idea that there are age-related deficits in associative memory, and that these are linked to declines in hippocampal and PFC functioning (Kersten et al., 2008). Since binding in memory has been reported to rely upon the functioning of the hippocampus and the PFC (Eichenbaum, 2000; Glisky et al., 2001), and both of these regions are known to be particularly sensitive to the effects of aging (Raz et al., 1998), then older adults may exhibit increased binding errors compared to younger adults. Chalfonte et al. (1996) reported that older adults were impaired on measures of binding features of a stimulus together (picture of an object and it's location in a grid). In addition, Mitchell et al. (2000) found that not only did older adults exhibit deficits in binding of objects and locations, but that this deficit was related to changes in the functioning of the hippocampus and PFC.

In a series of experiments Kersten (2008) reported that older adults had an impairment binding people with the actions that they performed in a series of videos. They did not believe that this was due to a failure to encode the information presented (actors engaging in a behaviour), nor was it a difficulty in remembering the features of the information; but

rather an age-related impairment in associative memory or binding. This is consistent with the associative deficit hypothesis proposed by Naveh-Benjamin (2000).

4.2.2a Associative Deficit Hypothesis (ADH)

Previous research has shown that it is more difficult for older adults to maintain episodic information (binding information to contextual elements); as an explanation for this deficit, the associative deficit hypothesis proposed that aging results in a decline in the ability to bind new pieces of information (Naveh-Benjamin, 2000). This hypothesis distinguishes between memory for single units and memory for the association/relationship between these units. Accordingly, older adults show a greater impairment on associative memory, as their ability to create these associations, and to subsequently retrieve them is impaired. As a result, there are age-related decreases in the efficiency of associative memory abilities across the lifespan, due to the extent to which the creation or use of associations is required (Naveh-Benjamin et al., 2004).

This deficit has been reported across many types of stimuli: word pairs (Castel et al., 2003); picture pairs (Naveh-Benjamin et al., 2003); face pairs (Bastin et al., 2006); and face-name pairs, arguably one of the most ecologically valid measures of episodic memory (Naveh-Benjamin et al., 2004). Nevertheless, the source of this associative memory deficit is still under debate; studies have proposed that it is due to poor strategy use, reduced speed of processing, reduced attentional resources, and problems with inhibition (see Kilb et al., 2007). However, many of these studies do have something in common; they use paradigms that examine memory for the individual components (e.g. names) separate to memory for the associations (e.g. face-name pair).

4.2.2b Support for the ADH

There have been several studies conducted by Naveh-Benjamin et al. that have offered support for the associative deficit hypothesis (Kilb et al., 2007; Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2007; Naveh-Benjamin et al., 2004; Naveh-Benjamin et al., 2003). While their 2003 study found that, using tests of recognition with picture pairs, older adults were impaired on associative memory tests, they also found that this impairment decreased when familiar information was used (information that was already in memory), improving older adults subsequent encoding and retrieval. They extended these findings in the 2004 study, which attempted to look at more ecologically valid information, i.e. face-name pairs,

as many older adults complained that they had difficulty remembering the names of people they had not seen in a while.

They proposed that older adults have difficulty remembering someone's name when they saw their face because this ability relies upon the initial encoding event; they believe that this ability, to bind the face and the name together, is faulty in older adults. Support for this view came from their studies that examined both the encoding and retrieval of associative information, along with the separate recognition of the individual faces and names; while there was no impairment in name recognition, and only a small impairment in face recognition, there was a significant decline in the ability to recognise the associations between the names and faces. As a result, findings that emerged from these studies supported the idea that, rather than a generalised slowing down in memory, older adults had specific impairments on measures of associative memory (Naveh-Benjamin et al., 2004).

The underlying processes of this associative deficit in older adults was examined to determine if it was due to a reduction in the attentional resources available to them (Naveh-Benjamin et al., 2004). Divided attention studies have examined this concept and proposed that older adults should have a greater deficit in associative memory when their attentional resources are challenged, if the associative deficit is related to changes in attention across the lifespan. Kilb et al. (2007) used the divided versus full attention paradigm in young and older adults; having manipulated attention levels at encoding, they found that there was no relationship between the associative deficit and attention. Including a divided attention paradigm did not cause a greater impairment to memory for associations than to memory for items in either age group. They suggested that the deficit might result from a decreased efficiency in the use of associative strategies (see Naveh-Benjamin et al., 2007). Kilb et al. (2007) concluded that, the associative memory deficit evident in older adults results from problems when binding information together, especially considering that with increasing age, people do not make full use of the strategic processes which are mediated by the frontal lobes. Accordingly, older adults can not adequately organise the information to be learnt.

In support of this idea, other studies have proposed that the binding processes, which play a central role in associative memory, are principally mediated by the PFC (Glisky et al., 2001). As a result, older adult's deficits in associative memory may be linked to changes in

PFC functioning. Moscovitch (1994) believes that both the PFC and the MTL function collectively to encode information in both a strategic and automatic manner, a view that is supported by several studies. These divided attention studies indicate that the PFC requires more attentional resources than the MTL (Cabeza et al., 2000). Neuroimaging studies also support the role of the PFC during encoding processes in associative memory, and report that there is a differential pattern of activity in the PFC between younger and older adults (Cabeza et al., 2000).

Kilb et al. (2007) add to the debate by proposing that the associative deficit may also be due to the age-related changes in the hippocampus. As the hippocampus plays a key role in associative memory that involves binding processes and binding processes are negatively affected with age; as a result hippocampal activity during associative memory should also show a deficit in older adults compared to younger adults. In line with this idea, Mitchell et al. (2000) found that the hippocampus showed greater activation in younger adults than older adults during the encoding of associative information. However, they also found a similar pattern of activation within the PFC, suggesting that the deficits in PFC activation in the older adults may mediate the deficits in hippocampal activation; the explanation proposed was that the PFC held the associative information until the hippocampus was engaged. Kilb proposed, that these findings, in addition to those found in their own study, imply that "the associative deficit of older adults is mediated by both automatic and strategic processes" (2007, p. 1171). This proposition supports that of others, who report that the frontal lobes are important for strategic binding, and the hippocampus is important for automatic binding (Moscovitch, 1994).

PET studies, that measured regional cerebral blood flow during the encoding and recognition of faces, reported that the MTL, especially the hippocampus, demonstrated increased activation during the encoding of new memories compared with during recognition in younger adults (see Grady et al., 1995). Interestingly, Nyberg et al. reported that the PFC was activated during both conditions; during encoding the left PFC was activated, while during recognition the right PFC was activated (1996). When a similar study was carried out in young and older adults there was a differential pattern of activity in the MTL with age (see Grady et al., 1995 for a review). Whereas, the MTL was activated during encoding in younger adults, there was a lack of significant activations in the MTL during encoding in the older adults. Patterns of functional interactions during encoding were also examined; these found that in young adults, the strongest correlation

was between the right hippocampus and the anterior cingulate, while in older adults the right hippocampus was correlated with activity in the left parahippocampal gyrus. Grady et al. (1995) suggest that the lack of activation in the older adults during encoding implies that the impaired recognition was related to the failure to encode the faces properly in the first instance, and highlight the possibility that older adults may have difficulties binding information/items together. Impaired recognition was also seen in an fMRI study comparing young and older adults; they found that the older adults performed significantly worse on measures of recognition than the younger adults (Miller et al., 2008).

There is considerable evidence to suggest that there are impairments in associative memory across the lifespan. It would appear that these problems result from an inability to effectively bind associative information, either through a reduction in attentional resources or through a reduction in the efficient use of processing strategies.

4.2.3 Working Memory Decline in Adulthood

It has been reported in many studies that WM declines with age (Craik, 2008). Some studies found that older adults had a reduction in their WM storage abilities (Foos, 1989). According to Baddeley's model, this should result in activation differences in visuo-spatial regions of the brain. Evidence to support this was found in neuroimaging WM studies, where differences in activation in older adults were reported; these changes were found in the extra-striate cortex and the temporal lobes (Cabeza et al., 1997a), and would suggest that there are age-related impairments in sensory information processing (Missonnier et al., 2004). Nevertheless, these studies do not have the temporal resolution that allows researchers to examine short-term memory storage at the millisecond level. Electrophysiological studies can provide a method with which to explore these processes, as they have a much higher temporal resolution than MRI.

Event-related potential analysis of performance in young adults on an adapted version of the n-back task conducted by Missonnier et al.. (2003) revealed a significant positive-negative waveform (PNwm) which occurs 140-280ms post stimulus onset. The amplitude of this component is modulated by WM load and the authors suggest that it represents a novel electrophysiological index of WM load. In order to investigate age-related electrophysiological changes in WM processes, Missonnier et al. (2003) used the same neuropsychological paradigm to compare the density of this newly identified PNwm component in young and healthy elderly individuals. Although the elderly had slower

reaction times and poorer performance on the 2-back task than the younger participants the authors point out that it is unlikely that these behavioural differences are reflective of inefficient or slowed WM processes. In contrast they identified WM related electrophysiological changes in the elderly in the latency and amplitude of the PNwm component. The significant increase in latency reported in older adults is thought to reflect late visual processing which is known to increase with age (McEvoy et al., 2001, cited in Missonnier et al, 2003). With regard to amplitude whilst both groups displayed comparable amplitudes in the 1-back task, the amplitude increased with WM load in the 2-back task in the younger participants; no such increase was evident in the elderly. As this difference was observed mainly over parietal electrodes, in line with the compensation hypothesis, the authors propose an age-related impairment in ability to recruit posterior cortical neurons with increased WM load.

Several studies have investigated the relationship between WM and focal attention, investigating the point at which information transfers from one to the other. When incoming information exceeds the span of attention, then successful performance necessitates moving information between memory and focal attention (McElree, 2001). Using the *n*-back task, the relationship between aging and switching the focus of attention in WM was examined in younger and older adults (Verhaeghen et al., 2005). They found that there were no differences in reaction times (RT) for focus switching – that is, the difference in RT between the 1-back condition and the 2-back condition. Once general slowing was taken into account, there was no switch cost related to the move from focal attention to items stored in working memory. They also found that there was no differences on measures of accuracy for the 1-back condition, but once outside the focus of attention ($N>1$), there was a switch cost in the accuracy. However, this difference was only related to the switching process (difference between $N=1$ and $N=2$), when N increased beyond 2 there was no further cost in accuracy. They suggested that these results imply that there is an age-related deficit in tasks that require some form of focus switching, and suggest that this is the root of age-related differences found in other studies that use focus switching, such as dual-task performance (see Verhaeghen et al., 2003).

There are several well supported findings about changes in PFC with aging (Cabeza et al., 2000); older adult's memory deficits have often been attributed to structural and functional changes in the frontal lobes (West, 1996); atrophy in the aging brain has been shown to be more prominent in the PFC (Raz et al., 1998); and older adults generally have reduced

activation in the frontal lobes during both encoding and retrieval (Cabeza et al., 1997a). During episodic memory retrieval Cabeza (2002) reported that younger adults had activation predominantly in the right PFC, while older adults had activation in both the left and right PFC. Further clarification of the differential activation patterns is necessary.

4.3.2a Differential Patterns of Activation across the Lifespan

Activation patterns in the LPFC at encoding and retrieval can often differ, it would appear that the LPFC is less activated in older adults during many encoding tasks, and more activated during many retrieval tasks. A study by Anderson et al. (2000) found that aging may increase the attentional load of a task, and thus negatively affect memory function, thereby reducing the ability to engage in elaborate encoding carried out by the LPFC. As a result, this increased attentional load reduces the amount of time, or the processing resources available for encoding, perhaps by reducing the activity in the LPFC regions (Grady et al., 2000). Whereas, the increased LPFC activity seen during retrieval tasks in older adults, may reflect the increased demand for attentional processes needed in order to recall previous stimuli. McIntosh (1999) also reported that older adults recruited additional regions within the brain, and that those regions were related to performance.

Other studies support the idea that older adults have difficulties initiating memory strategies. Grady et al. (1998) found that older adults did not show as much activation in the PFC as task difficultly increased, whereas younger adults were better able to activate the PFC with increasing difficulty. Additionally, they also found that the older adults showed reduced activation of the MTL. Taken together, Grady suggests that older adults have difficulty initiating memory strategies.

While some studies have found similar patterns of activation in young and old using fMRI (Schacter et al., 1996), others have found altered patterns across the lifespan (Cabeza et al., 2000), often attributing the changes in older adults to an increased need to perform the task adequately (Grady et al., 2000). This has led to the proposal that perhaps this increased activation may be a compensatory mechanism (Cabeza et al., 2000); however, this idea remains speculative. While some researchers believe that age-related decreases reflect cognitive impairments and increases reflect functional compensation (Cabeza et al., 1997a), others believe that decreases in activation reflect more efficient processing (Karni et al., 1995). The key question to ask is, whether this increased activation in older adults aids their ability to perform the task. In order to answer this question, a carefully planned

out experiment is required that would allow the identification, not only of items that are recalled, but also the point at which these successfully recalled items were encoded.

4.2.4 The Notion of Cognitive Reserve

Researchers have proposed the idea that humans have a "cognitive reserve"; Stern (2002) suggests that as we age we can offer some protection against the effects of aging. Passive models have been proposed; that state that the brain has a reserve capacity against which damage may have an effect. There are differences in the brain reserve capacity of each person, so one person can reach their threshold before another (Satz et al., 1993); beyond this threshold clinical or functional impairments will emerge. Methods of measuring brain reserve capacity have not been confirmed, though they might include examining brain size or counting the number of synapses (Stern, 2002).

Alternatively, active models of reserve include the "brain reserve hypothesis", which is used to explain the dissociation between cognitive and functional impairments on one side and pathological brain changes and damage on the other side (Christensen et al., 2007). It states that those who have a high pre-morbid intelligence level, are well educated and active across the lifespan will have a 'reserve capacity' which will act as a buffer against the effects of disease and aging on the brain (Coffey et al., 1999, cited in Christensen et al, 2007). This reserve works by recruiting brain networks that might underlie the use of different cognitive approaches. Nevertheless, findings in this area are not all in agreement about the relationship between education and intelligence and a possible brain reserve. Christensen (2007) found that education did not buffer against the effects of cognitive decline in people with high levels of atrophy; while Staff et al. (2004) found that education and occupation do act as a buffer, allowing cognitive function to be maintained into old age.

A second active model of brain reserve is that of compensation. Several studies looking at activation within the brain during cognitive tasks in patients with Alzheimer's disease (AD) and age-matched controls, found that there was an increased and more extensive pattern of activation in the AD patients (Grady et al., 1993). They suggest that as AD pathology impairs the patient's abilities to complete the task using the same networks or brain regions as the controls, they compensate by recruiting different brain regions. If increased activity is a result of a compensatory mechanism, then it is very important to determine exactly how the activity in the additionally recruited areas is related to the

behaviour (Grady et al., 2000) i.e. does it actually lead to improved/comparable performance on cognitive tasks.

4.2.5 Flaws in the Current Research

There have been several studies that have attempted to look at changes in associative and working memory, identifying both encoding and retrieval, in young and older adults; however many of these studies have failed to successfully address the methodological issues associated with neurocognitive research. The primary measure of recall has been cued recall and recognition; few studies have included measures of free recall of encoded material. For example, in their 2004 study, Naveh-Benjamin et al. used several types of forced choice recognition; for face recognition, name recognition and face-name recognition. However, there was no measure of free- or cued-recall. Even in MRI studies that claim to examine episodic encoding mechanisms, it is often delayed recognition tasks that are used to identify successfully encoded material (see Miller et al., 2008; Rand-Giovannetti et al., 2006). For this reason, it is extremely important to include measures of free recall in aging studies, so that conclusions reached about successful encoding processes are based on successful encoding events, and not on subsequent measures of recognition.

In addition, many of the studies reviewed in the current chapter have only included two groups; young and old adults. There is a lack of research that looks at memory changes across the entire adult lifespan. Those that do include several groups do not include all age ranges (18 years to late adulthood). While comparing young and old groups is sufficient in research that is designed to establish *whether* deficits occur, identifying *when* these deficits occur requires the use of adults of all ages.

There are several studies which have emphasised the importance of schooling, arguing that the strong association between education level and performance on various neuropsychological measures is more important than the effects of age (Gomez-Perez et al., 2006). They especially believe that attention and executive function are particularly sensitive to education. One of the most common general findings in neuropsychological research and gerontological research on cognitive aging has been the major role of education in explaining individual differences in verbal and non-verbal cognition (Schaie, 1996, cited in Morgan et al., 2008). Accordingly, the use of education-matched participants in aging research cannot be ignored.

The current study aims to address many of these issues. Associative- and working-memory will be investigated in aging, using tests of both recall and recognition, in an attempt to identify the differential rate at which these types of memory decline. Subjects will be closely matched for education and IQ levels, and will include people from across the lifespan (18-64).

4.2.6 Hypotheses

1. There are significant effects of age on associative memory abilities across the lifespan, with significant differences appearing by the forties.
2. There are no significant effects of age on working memory across the lifespan.

4.3 Methods

4.3.1 Participants

4.3.1a Experiment 1: Pilot

Data from 111 healthy participants aged between 18-64 years who had taken part in previous studies were compared in the face-name and *n*-back task. The 20's group consisted of 44 participants (Range = 18 – 28, Mean = 21.55, Std Dev = 3.01), the 30's group had 15 participants (Range = 30 – 39, Mean = 34.80, Std Dev = 3.14), the 40's group had 24 participants (Range = 40 – 49, Mean = 45.79, Std Dev = 3.00), and the 50+ group had 28 participants (Range = 50 – 66, Mean = 56.21, Std Dev = 5.43).

4.3.1b Experiment 2: Lifespan Study

137 healthy participants aged between 18-64 years took part in this study (see Table 4.1 for demographic information of all age groups). Subjects were recruited from the local community, college notice boards and e-mails, and recruitment posters. All participants were fluent English speakers. Exclusion criteria included a previous history of Ischemic heart disease / stroke / diabetes / head injury / epilepsy / psychiatric illness / significant visual impairment or pregnancy. The study was approved by the Trinity College School of Psychology ethics review committee. Written, informed consent was obtained prior to the commencement of the testing and participants were compensated for travel expenses (a copy of the consent and ethical approval is included in Appendix I). The young adulthood group consisted of 47 participants (Range = 18 – 29, Mean = 24.17, Std Dev = 3.31), the 30's group had 31 participants (Range = 30 – 39, Mean = 34.19, Std Dev = 2.94), the 40's group had 33 participants (Range = 40 – 49, Mean = 43.93, Std Dev = 3.00), and the 50+ group had 28 participants (Range = 50 – 64, Mean = 55.07, Std Dev = 4.29).

4.3.2 Experimental Design & Neurocognitive Battery

A battery of neurocognitive associative and working memory tasks was performed which lasted approximately 1 hour. An estimate of pre-morbid intelligence was obtained using the National Adult Reading Test (Nelson, 1982), and self-reported mood and well-being were obtained using the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) and a self-rating scale was used to identify how good participants felt that their own memory was following completion of the study (Self-Rating scale). In addition, declarative

memory function (primarily hippocampal-mediated) and working memory function (primarily prefrontally-mediated) were assessed.

4.3.3 Neuropsychological Assessment

4.3.3.1 Premorbid IQ - National Adult Reading Test 2nd Ed (NART)

Described previously, see Chapter 2, Section 2.3.3.4.

4.3.3.2 Affective Measurement - Hospital Anxiety and Depression Scale (HADS)

Described previously, see Chapter 2, Section 2.3.3.5a.

4.3.3.3 Associative Memory Tasks

4.3.3.3a Face-Name Learning and Recall Task

Described previously, see Chapter 2, Section 2.3.3.1b. Additional changes to the design are described below.

Recognition: Faces

Following the delayed recall, participants were presented with 16 faces, 8 new faces and the 8 faces from the task; they had to correctly identify all 8 faces that they had previously seen and all 8 new faces. They also had to rate their certainty on a confidence scale that ranged from 1 (most confident) to 6 (least confident). Levels of certainty were collapsed during analysis.

Name Recall

A free recall of the names was then conducted, where participants had to list aloud all the names that they could remember from the task, again the experimenter recorded correct and incorrect responses. Levels of certainty were collapsed during analysis.

Recognition: Names

Then participants were presented with 16 names, 8 new names and the 8 names from the task; they had to correctly identify all 8 names that they had previously seen and all 8 new names. They also had to rate their certainty on a confidence scale that ranged from 1 (most confident) to 6 (least confident).

Scoring

The percentage accuracy score for each block was calculated, the delayed recall percentage accuracy as well as name recall accuracy. In addition ***Hits*** (correctly identifying a face that was previously seen), ***Misses*** (not identifying a face that was previously seen), ***Foils*** (correctly identifying a face that was not previously seen) and ***False Positives*** (incorrectly identifying a face that had not been previously seen as one that had been previously seen) scores for the face and name recognition were calculated. An overall Face Recognition and Name Recognition accuracy was also calculated ((Hit-False Positives) / 8) *100).

4.3.3.3b Picture-Word Task

Design

The Picture-Word task was programmed in E-Prime 1.2 (Psychology Software Tools, Pittsburgh, PA). The materials used in this task were taken from those used in the Snodgrass and Vanderwart study (1980); each picture was paired with a word.

Procedure

Picture-Word Encoding

During the encoding blocks, participants viewed 20 picture-word pairs, presented serially at a rate of one every 3.5 seconds (ISI (blank) = 500 ms). They were instructed to study each picture-word pair carefully and to attempt to memorize the word corresponding to each picture (see Figure 4.1). They were told that their memory of the pairs would be tested at some point in the testing session. The presentation order was consistent across the encoding block for each participant.

Focused Attention

Described previously, see Chapter 2 Section 2.3.3.3b.

Picture-Word Retrieval

Participants serially viewed the 20 pictures presented in sequential order, without the accompanying words (see Figure 4.1). Again, each picture was presented for 3.5 seconds (ISI (blank) = 500 ms), during which time participants were required to vocally recall the words corresponding to each of the 20 pictures. The experimenter recorded correct and incorrect responses; non-responses were recorded as incorrect.

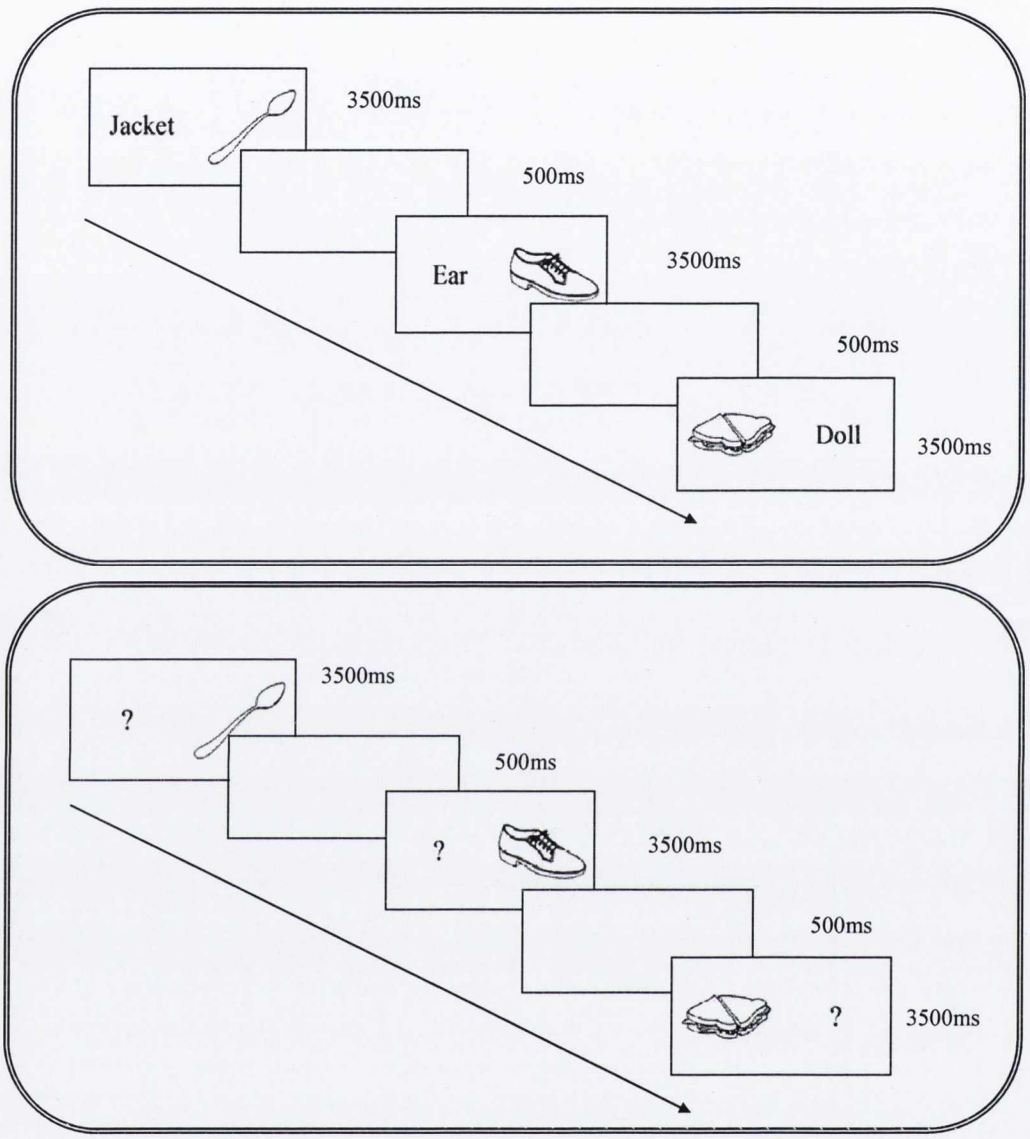

Figure 4.1: (Upper Panel) Picture-Word Encoding: Participants viewed each picture-word pair for 3.5 seconds (ISI = 0.5s), during which time they attempted to memorize the word corresponding to each picture. (Lower Panel) Picture-Word Retrieval: Participants were presented with each of the previously viewed pairs (same, reversed order or recombined). They were required indicate if each pair was part of the original task or not. Each picture was viewed for 3.5 seconds (ISI = 0.5 s).

Picture-Word Delayed Recall

Participants were again presented with the 20 picture-word pairs (taken from http://titan.cog.brown.edu:8080/TarrLab/stimuli/objects/svlo.zip/view) presented in

sequential order, after a 15 minute delay. The picture-word pairs were presented in three different formats; as originally seen in the encoding trial, 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). So in this case the participants had to indicate, by pressing one of two buttons on the laptop, whether the pair was part of the original task or not. Correct and incorrect responses were recorded.

Scoring

In the immediate recall trial the number of correct picture-word pairs (as noted by the experimenter) was transformed into a performance accuracy score (%) ((Recall score/20) * 100). In the delayed trial the number of correct picture-word pairs were recorded and also computed into a delayed performance accuracy score (%) ((Recall score/20) * 100).

4.3.3.4 Working Memory Tasks

4.3.3.4a n-Back Task (0-Back, 1-Back & 2-Back Levels)

Described previously, see Chapter 2, Section 2.3.3.3c.

4.3.3.4b Match-to-Sample Task

The Match-to-Sample (MTS) task was programmed in E-Prime 1.2 (Psychology Software Tools, Pittsburgh, PA).

Design, materials, and stimuli

In the Match-to-Sample working memory task participants were presented with a series of stimuli, one at a time, on screen (taken from http://titan.cog.brown.edu:8080/TarrLab/stimuli/novel-objects/poss-imp.zip/view). The stimuli consisted of black line drawings (see Figure 4.2) presented centrally on screen. Responses were recorded using the Cedrus RB-530 response pad which was positioned to the right of the screen.

Procedure

Working Memory task

There was a countdown for 3 seconds (ISI = 0.5s) prior to the presentation of each stimulus. A cue stimulus then appeared on screen for 1 second, followed by a fixation (jitter: 7, 9, 11 or 13s). The target stimulus then appeared on screen until the participant responded; they had to indicate whether the cue stimulus and target stimulus matched

(press number 1 button) or not (press the number 2 button). Each stimulus remained on screen until a response was made. The trial contained 20 cue stimuli and 20 target stimuli and required 20 responses. The task was preceded by a short practice trail (5 sets of stimuli). Reaction times and accuracy were recorded automatically by the E-Prime software.

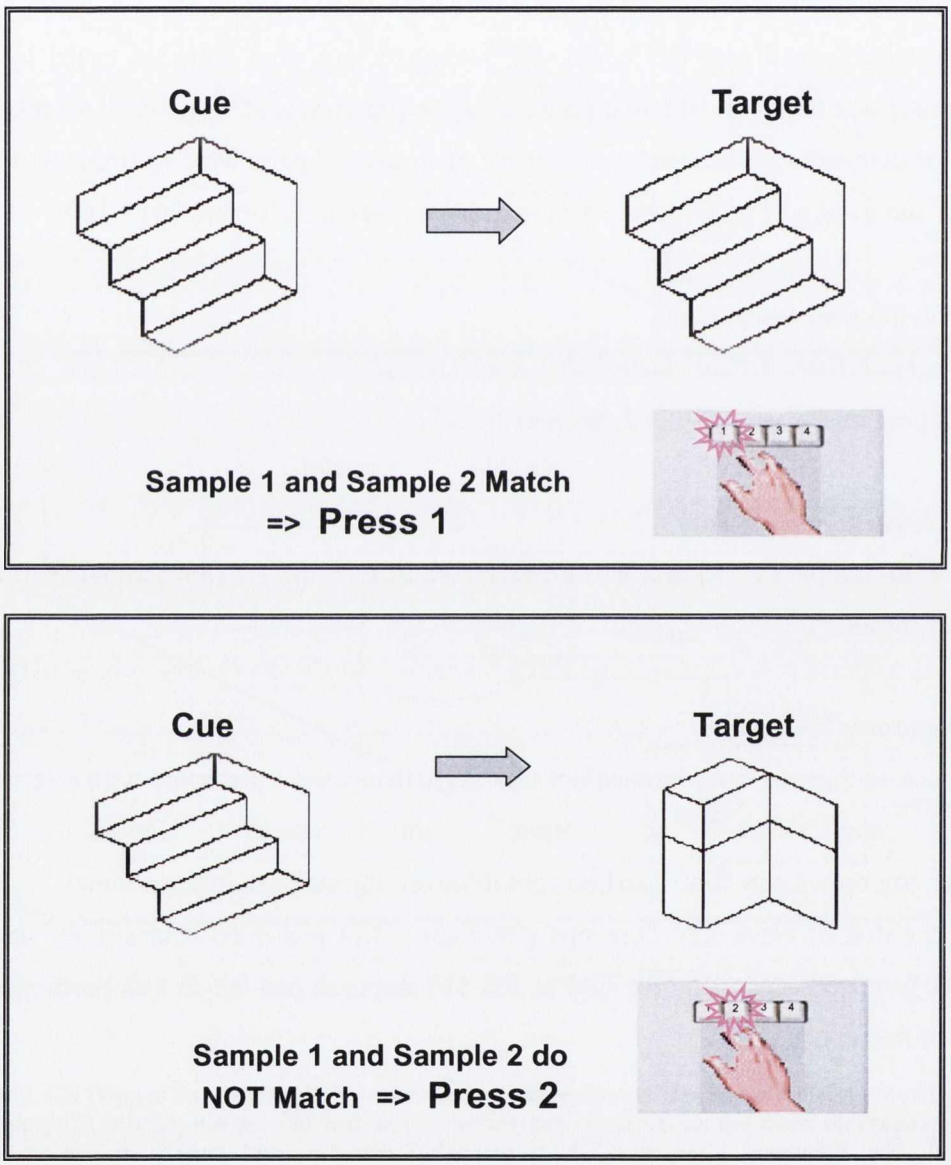

Figure 4.2: Stimuli presented during the Match-to-Sample task. (Upper Panel) When the cue matched the target stimuli the participants had to press the number 1 button. (Lower Panel) When the cue did not match the target stimuli the participant had to press the number 2 button.

Delayed Recognition

At this point, participants were shown an item on the computer screen (for an indefinite amount of time) and were instructed to identify if they had seen it before as part of the task of if it was a new line-drawing on the response sheet that they were given. They also had to rate their certainty on a confidence scale that ranged from 1 (most confident) to 6 (least confident). Once they had made a decision they had to press the spacebar to move the task along to the next picture. In total there were 35 stimuli, 25 that had been part of the task (either in the training (5) or the main trial of the task (20)), and 10 new stimuli.

Scoring

A percentage accuracy score was calculated for the training trial and the main trial of the task. In the recognition trial Hits (correctly identifying a stimulus that was previously seen), Miss (not identifying a stimulus that was previously seen), Foil (correctly identifying a stimulus that was not previously seen) and False Positive (incorrectly identifying a stimulus that had not been previously seen as one that had been previously seen) scores for the face and name recognition were calculated. An overall recognition accuracy score was also calculated ((Hit-False Positive) / 25) *100).

4.3.4 Statistical Analysis

Analyses were carried out using SPSS (version 15) for PC. All data was expressed as means ± standard error (S.E.), unless specified otherwise. Analysis of Variance (ANOVA) was the primary statistical tool used. When performance on a specific task was repeated across multiple trials a 'mixed between-within subject ANOVAs' (Tabacknick & Fidell, 2007) was used to compare performance across the repeated levels and between the groups. Where significant ($p < 0.05$), main effects and interactions were reported and if appropriate, post-hoc analyses were conducted. Subsequent one-way ANOVAs compared the dependent variables between the groups and post-hoc analysis identified what groups differed. When there were more than 2 levels in the dependent variable, within group differences were investigated using apriori planned comparisons across each level of the DV (Bonferroni-Corrected for multiple comparisons). Where a variable (e.g. IQ) was suspected to influence performance on a memory test (DV), a relationship between the variable and the covariate was first examined using correlations and scatterplots. Then a series of ANCOVA's (Analysis of Covariance) were carried out on each dependent variable. As a result, the variation of the DV that is due to the covariate was removed. Preliminary checks were made prior to conducting the ANCOVA to ensure that there was

no violation of the assumptions of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and reliable measurement of the covariate. When significant differences were found, the p-value was reported at three levels; $p < 0.05$ (*), $p < 0.01$ (**), and $p < 0.001$ (***).

4.4 Results

4.4.1 Experiment 1: Pilot Data

Data was available from 111 participants from a number of previous studies who had completed both the face-name and *n*-back tasks. Differences across four age-groups were examined (young adulthood, 18-29; thirties, 30-39; forties, 40-49; fifties plus, 50-64).

4.4.1a Associative memory: Face-Name Learning and Recall

Analysis across the four learning blocks of the face-name task revealed a significant effect of block ($f = 101.905$; $df = 3, 107$; $p < 0.001$), a significant effect of age ($f = 53.968$; $df = 3, 107$; $p < 0.001$), and a significant interaction between age and block ($f = 12.88$; $df = 9, 107$; $p < 0.001$). Post hoc analysis showed that those in the young adulthood group remembered significantly more face-name pairs then those in their 30's ($p < 0.001$), 40's ($p < 0.001$), and the 50+ group ($p < 0.001$). The 30's group also performed significantly better than those in the 50+ group ($p < 0.05$). Separate analysis was then conducted at each block to identify where these differences lay (see Figure 4.3).

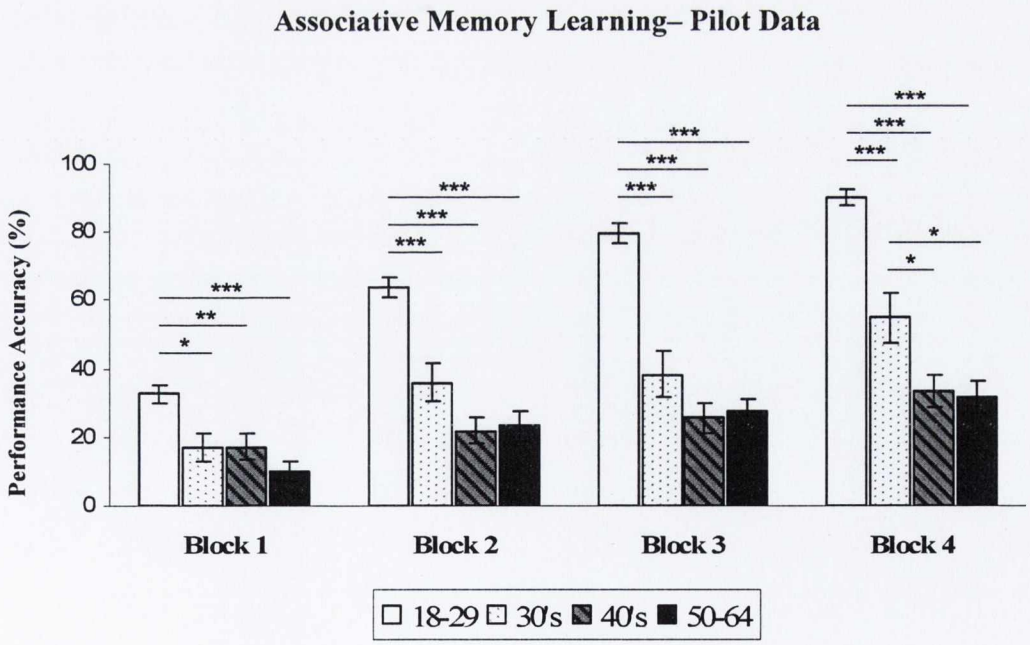

Figure 4.3: Performance accuracy across the four learning blocks of the Face-Name task (expressed as Mean ± SEM) for each of the age groups.

Group differences were significant at block one ($f = 11.662$; $df = 3, 110$; $p < 0.001$), with those in the young adulthood group performing significantly better than those in their 30's ($p < 0.05$), 40's ($p < 0.01$), and the 50+ group ($p < 0.001$). At block two group differences were significant once again ($f = 32.33$; $df = 3, 110$; $p < 0.001$); those in the young adulthood group were also significantly different to those in their 30's ($p < 0.001$), 40's ($p < 0.001$), and the 50+ group ($p < 0.001$). Analysis of block three found that there were also significant differences at this point in the number of face-name pairs successfully recalled ($f = 54.786$; $df = 3, 110$; $p < 0.001$). A similar pattern was seen at block three as seen in the previous two blocks, with those in the young adulthood group performing significantly better than those in their 30's ($p < 0.001$), 40's ($p < 0.001$), and the 50+ group ($p < 0.001$). Block four differences were also significant between the age-groups ($f = 58.398$; $df = 3, 110$; $p < 0.001$), and again there were significant between the young adulthood group and those in their 30's ($p < 0.001$), 40's ($p < 0.001$), and the 50+ group ($p < 0.001$). However, those in their 30's were also significantly better at face-name recall then those in the 40's ($p < 0.05$), and the 50+ group ($p < 0.05$).

When a face-name improvement score was calculated (recall at block 4 – recall at block 1), there were significant differences between the groups on their improvement scores ($f = 29.743$; $df = 3, 110$; $p < 0.001$). Post hoc tests revealed that the younger participants (Mean = 4.598; S.E.M. = .240) showed the most improvement across the blocks in comparison to those in their 30's (Mean = 2.867; S.E.M. = .411; $p < 0.01$), those in their 40's (Mean = 1.292; S.E.M. = .325; $p < 0.001$), and those in the 50+ group (Mean = 1.790; S.E.M. = .301; $p < 0.001$). Those in the 30's group also showed significant improvement in comparison to those in their 40's ($p < 0.05$). Overall, the older groups improved less than the younger groups across the blocks.

Delayed recall was then assessed between the groups, significant differences were found ($f = 14.293$; $df = 3,73$; $p < 0.001$), with those in the young adulthood group were also significantly different to those in their 30's ($p < 0.01$), 40's ($p < 0.001$), and the 50+ group ($p < 0.001$) (see Figure 4.4).

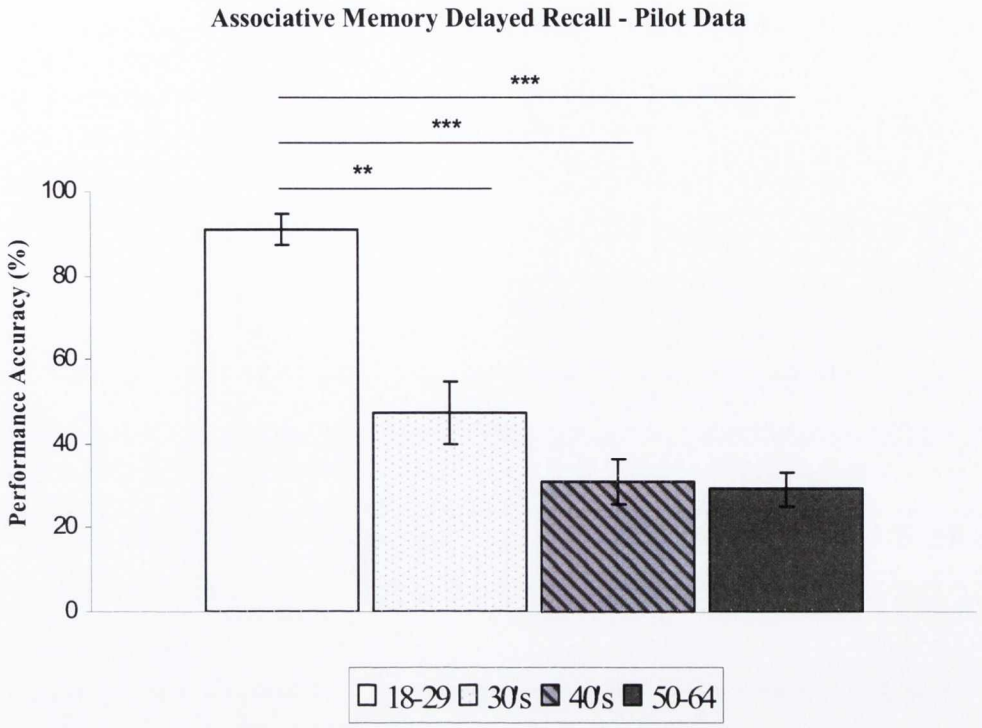

Figure 4.4: Performance on delayed recall of the Face-Name task (expressed as Mean ± SEM) for each of the age groups.

4.4.1b Working Memory: The n-Back Task (0-Back, 1-Back & 2-Back Levels)

Differences in working memory were tested using the *n*-back task between the four age-groups. There was a significant difference in participants accuracy levels across the three levels of the task (0-back, 1-back and 2-back) ($f = 66.05$; $df = 2,65$; $p < 0.001$), however there was no significant effect of age-group and no significant interaction between age-group and level on the *n*-back task (see Figure 4.5).

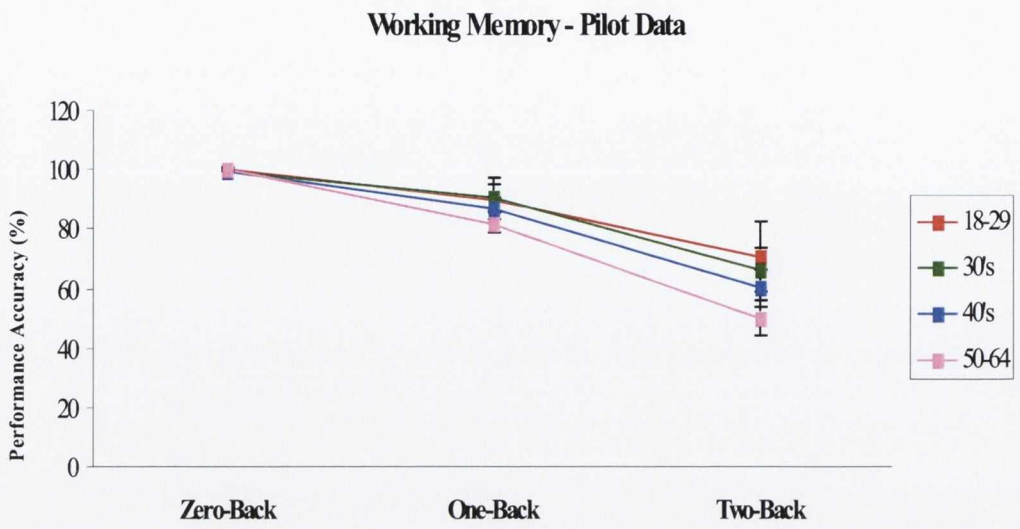

Figure 4.5: Performance on the *n*-Back task (expressed as Mean ± SEM) for each of the age groups.

4.4.1c Relationship between Associative and Working Memory

The relationship between performance at the 2-back level of the *n*-back task and total number of face-name pairs successfully recalled was examined. Overall, there was a significant positive relationship between performance accuracy at the 2-back level and the number of face-name pairs remembered ($r = .514$, $n = 113$, $p < 0.001$) (see Figure 4.6). When the relationship was investigated within each age group, only the 50-64 group had a significant positive relationship between the two variables ($r = .449$, $n = 24$, $p < 0.05$).

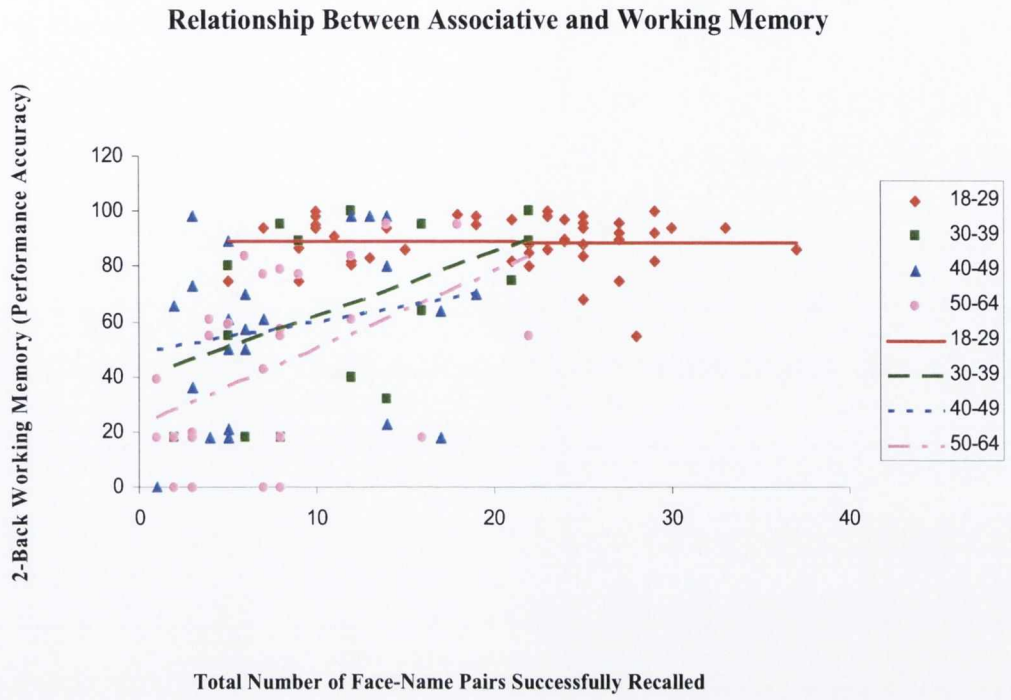

Figure 4.6: Relationship between performance accuracy on the 2-back level of the n-Back task and the total number of face-name pairs recalled

4.4.1d Premorbid IQ - National Adult Reading Test 2nd Ed (NART)

Data was also available for predicted IQ using the NART; significant differences were found on IQ between the groups (f = 6.607; df = 3,96; $p < 0.001$). Post-hoc analysis revealed that those in the young adulthood group had a significantly higher IQ scores as measured by the NART then those in the 30's ($p < 0.05$), 40's ($p < 0.01$), and 50+ groups ($p < 0.05$). As a result, the face-name and n-back tasks were reanalysed in order to determine if IQ scores impacted performance on both tasks.

4.4.1e Relationship between Associative Memory and IQ

When IQ was included as a covariate in the ANOVA, there was no longer a significant difference across the blocks of the face-name task. There was a significant interaction between block and age-group (f = 7.632; df = 9,92; $p < 0.001$), a significant main effect of age-group (f = 35.215; df = 3,92; $p < 0.001$), and also a significant main effect of IQ score (f = 6.840; df = 1,92; $p < 0.05$).

4.4.1f Relationship between Working Memory and IQ

Analysis of the n-back task, with IQ score included as a covariate, demonstrated that there was still a significant effect of accuracy across the levels of the task ($f = 10.901$; $df = 2,58$; $p < 0.001$), and a significant interaction between accuracy across the levels and IQ score ($f = 6.316$; $df = 2,58$; $p < 0.01$). There was also a significant main effect of IQ scores ($f = 10.551$; $df = 1,58$; $p < 0.01$).

4.4.2 Experiment 2: Lifespan Study

Results from a different cohort are now discussed. There were no significant differences in the number of males and females between the age groups and also no difference in the predicted IQ scores across the groups (see Table 4.1). However there were significant differences in the years spent in full-time education ($f = 8.794$; $df = 3, 124$; $p < 0.001$), with those in their 30's having spent significantly more time in full-time education than the 18-29 group ($p < 0.05$), those in their 40's ($p < 0.001$) and those in the 50-64 group ($p < 0.001$). There were also no differences in the depression or anxiety scores across the groups as measured by the Hospital Anxiety and Depression Scale, and no difference in the self-reported memory scores (SRS) (see Table 4.1).

Age Group	18-29 (n=47)	30-39 (n=30)	40-49 (n=34)	50-64 (n=26)
Gender (M : F)	17 : 30	13 : 17	12 : 22	9 : 17
Education (yrs) *	17.30 (± 2.30)	19.77 (± 2.66)	16.11 (± 4.04)	15.73 (± 3.70)
Predicted IQ	117.15 (± 5.89)	118.19 (± 6.46)	116.26 (± 7.64)	118.08 (± 7.32)
HADS Anxiety	6.66 (± 0.59)	6.03 (± 0.6)	6.32 (± 0.57)	5.85 (± 0.58)
HADS Depression	2.64 (± 0.32)	2.67 (± 0.47)	3.65 (± 0.52)	2.38 (± 0.31)
SRS	3.43 (± 0.11)	3.22 (± 0.20)	3.03 (± 0.16)	2.88 (± 0.19)

Table 4.1: Demographic information, HADS scores, and self-rating scores for each age-group. * There were significant differences seen on years spent in full-time education, all other variables were not significantly different between the groups.

4.4.2.1 Associative memory

4.4.2.1a Face-Name Learning and Recall

There were several types of trials in the Face-Name task including immediate face-name pair recall (encoding), delayed face-name pair recall, delayed name recall, name recognition, and face recognition. Firstly, the learning phase (blocks 1-4) was analysed.

There was a significant main effect of block (f = 146.761; df = 3, 133; $p < 0.001$), there was also a significant main effect of age group (f = 20.839; df = 3, 133; $p < 0.001$). However these differences must be interpreted with caution in light of the significant interaction between block and age group (f = 5.612; df = 9, 133; $p < 0.001$). Post-hoc analysis found that there were no significant differences between the 18-29 group and those in their 30's, however the 18-29 group successfully recalled significantly more faces than those in their 40's ($p < 0.001$), and those in the 50-64 group ($p < 0.001$). Those in their 30's also successfully recalled significantly more faces than those in their 40's ($p < 0.01$), and those in the 50-64 group ($p < 0.001$). There were no significant differences between the number of pairs recalled by those in their 40's and the 50-64 groups. In order to identify at which point the groups differed, a series of one-way ANOVAs were carried out at each block between the age groups. The number of face-name pairs successfully recalled by each group at each block is displayed in Figure 4.7.

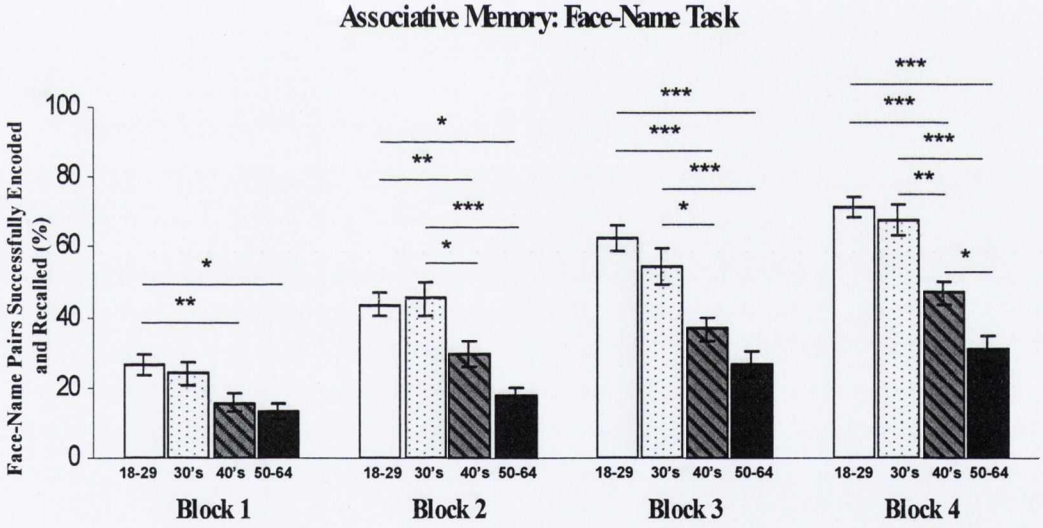

Figure 4.7: Performance Accuracy (Mean ± SEM) face-name pairs successfully recalled across each of the four recall blocks.

There were significant differences at block one in the number of face-name pairs successfully recalled (f = 5.285; df = 3, 133; $p < 0.01$). Those in the 18-29 group remembered more face-name pairs then those in their 40's ($p < 0.05$) and those in the 50-

64 group ($p < 0.01$). There were also significant differences at block two in the number of face-name pairs successfully recalled ($f = 11.987$; $df = 3, 133$; $p < 0.001$). At block two those in the 18-29 group remembered more face-name pairs then those in their 40's ($p < 0.05$) and those in the 50-64 group ($p < 0.01$), and so too did those in their 30's ($p < 0.05$, $p < 0.001$ respectively). At block three, again there were significant differences in the number of face-name pairs successfully recalled ($f = 16.371$; $df = 3, 133$; $p < 0.001$). These differences were once again significant between those in the 18-29 group and those in their 40's ($p < 0.001$) and those in the 50-64 group ($p < 0.001$). A similar pattern was evident between those in their 30's and both those in their 40's ($p < 0.05$) and those in the 50-64 group ($p < 0.001$). And finally, in block four, there were also significant differences in the number of face-name pairs successfully recalled ($f = 24.439$; $df = 3, 133$; $p < 0.001$) between the groups. As with blocks two and three, those in the 18-29 group were significantly different to those in their 40's ($p < 0.001$) and those in the 50-64 group ($p < 0.001$), as were those in their 30's ($p < 0.01$, $p < 0.001$ respectively). However this time the 40's were also significantly different to those in the 50-64 group ($p < 0.05$).

Delayed Recall

Face-Name Pair Recall

There was a 20 minute delayed recall trial, and differences between the groups were examined at this point. Significant differences in the number of face-name pairs recalled in the delay trial were evident between the groups ($f = 26.224$; $df = 3, 133$; $p < 0.001$). Post-hoc analysis revealed that again these differences were between the 18-29 group and those in their 40's ($p < 0.001$) and 50-64 ($p < 0.001$) and also those in their 30's and the 40's ($p < 0.01$) and 50-64 groups ($p < 0.001$). There were no differences between those in the 40's and those in the 50-64 groups in the number of face-name pairs successfully recalled on the delay trial (see Figure 4.8).

Name Recall

Prior to the recognition each participant had to do a free recall of the names, there was a significant difference in the number of names freely recalled between the groups ($f = 4.773$; $df = 3, 116$; $p < 0.01$), with those in the 18-29 group remembering more than those in the 50-64 group ($p < 0.01$). Those in their 30's also remembered more names than those in the 50-64 group ($p < 0.05$) (see Figure 4.8).

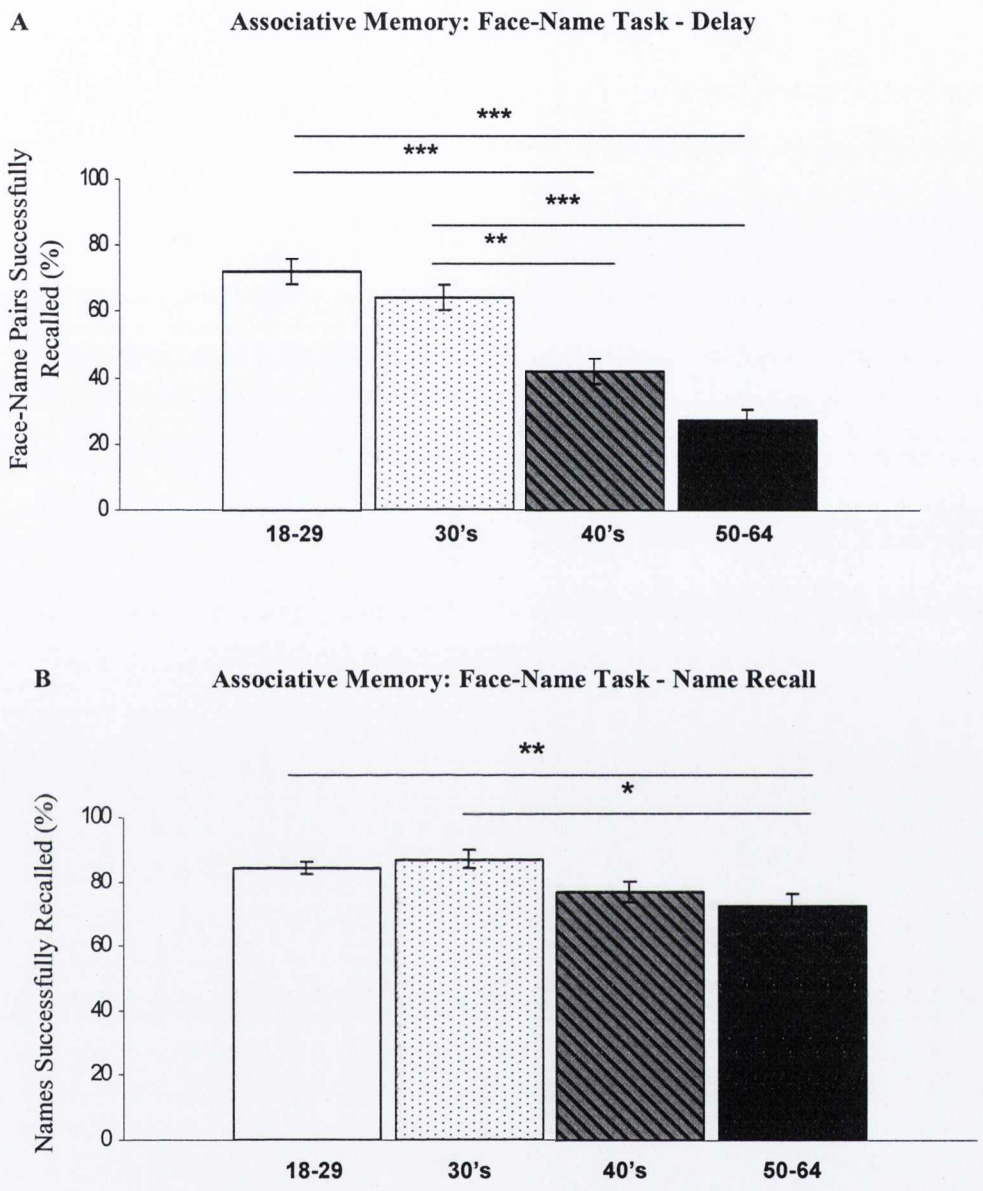

Figure 4.8: Performance Accuracy (Mean ± SEM) face-name pairs successfully recalled. (Panel A) Delayed Recall. (Panel B) Name Free-Recall

Recognition

Face Recognition

Face recognition was examined next; there were significant differences between the groups on their ability to correctly identify the 8 faces that were in the task and the 8 new faces ($f = 6.499$; $df = 3, 116$; $p < 0.01$). These differences only lay between the 18-29 and the 50-64

groups ($p < 0.01$) and the 30's and the 50-64 groups ($p < 0.05$) (see Figure 4.9). In order to identify where these differences lay, a series of one-way ANOVAs were run on the Hits (correctly identifying a face that was previously seen), Miss (not identifying a face that was previously seen), Foil (correctly identifying a face that was not previously seen) and False Positive (incorrectly identifying a face that had not been previously seen as one that had been previously seen) scores of the face recognition.

There was s significant difference on the Hits score ($f = 8.623$; $df = 3, 132$; $p < 0.001$), with the 18-29 yr olds ($p < 0.001$) and those in their 30's ($p < 0.001$) identifying significantly more of the previously seen faces then the 50-64 yr olds. There was also a significant difference between the age groups on the Miss score ($f = 7.783$; $df = 3, 132$; $p < 0.001$), with the 50-64 yr olds missing significantly more than the 18-29 yr olds ($p < 0.001$) and those in their 30's ($p < 0.001$). With the Foils score there was no significant difference in the age groups ability to correctly identify those faces that had not been previously seen. However, in the False Positives score, there were significant differences between the groups ($f = 2.894$; $df = 3, 132$; $p < 0.05$). In this case the only groups that differed were the 18-29 yr olds and those in their 40's ($p < 0.05$). Nevertheless, all groups performed well above chance levels.

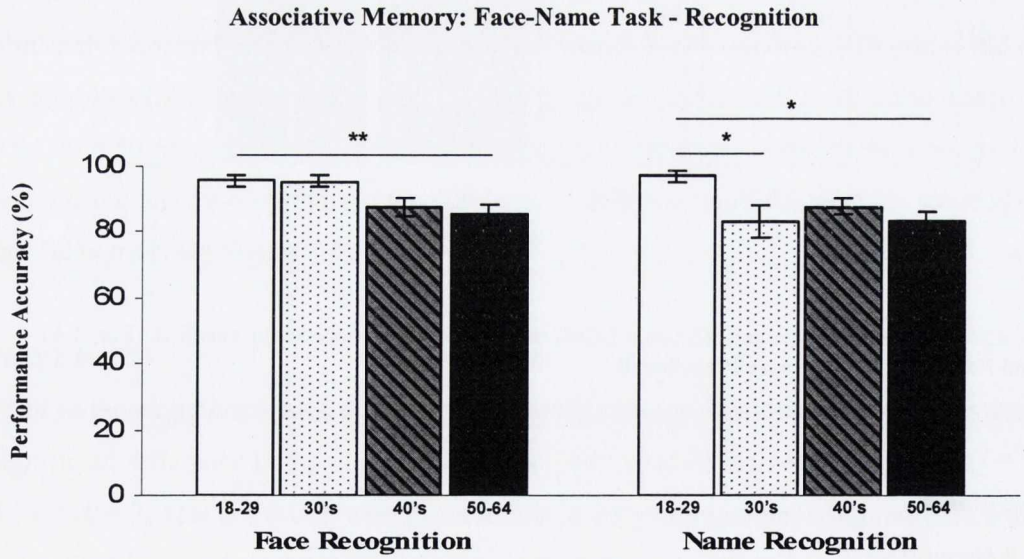

Figure 4.9: Performance Accuracy (Mean ± SEM) on face recognition and name recognition

Name Recognition

Name recognition was then examined, and there were significant differences again between the groups on their ability to correctly identify the 8 names that were in the task and the 8 new names ($f = 3.951$; $df = 3, 116$; $p < 0.05$). Interestingly, these differences were between the 18-29 yr olds and both those in their 30's ($p < 0.05$) and the 50-64 groups ($p < 0.05$) (see Figure 4.9). In order to identify where these differences lay, a series of one-way ANOVAs were run on the Hits (correctly identifying a name that was previously seen), Miss (not identifying a name that was previously seen), Foil (correctly identifying a name that was not previously seen) and False Positive (incorrectly identifying a name that had not been previously seen as one that had been previously seen) scores of the name recognition.

There was a significant difference on the Hits score ($f = 3.064$; $df = 3, 76$; $p < 0.05$), with the 18-29 yr olds ($p < 0.05$) identifying significantly more of the previously seen names then the 50-64 yr olds. There was also a significant difference between the age groups on the Miss score ($f = 3.064$; $df = 3, 76$; $p < 0.05$), with the 50-64 yr olds missing significantly more than the 18-29 yr olds ($p < 0.05$). With the Foils and False Positives scores there were no significant differences in the age groups. Nonetheless, all groups performed well above chance levels.

4.4.2.1b Picture-Word Task

In addition to the Face-Name task participants also completed the Picture-Word task. There was an immediate and delayed recall of the 20 Picture-Word pairs (see Figure 4.10).

Immediate Recall

In the immediate recall there were significant differences between the groups on the number of picture-word pairs correctly recalled ($f = 13.978$; $df = 3, 127$; $p < 0.001$). Those in the 18-29 yr old group remembered more words than those in their 40's ($p < 0.001$) and those in the 50-64 yr old group ($p < 0.001$). The 30's also remembered more pairs than those in their 40's ($p < 0.05$) and those in the 50-64 yr old group ($p < 0.05$).

Delayed Recall

In the delayed recall there were significant differences between the groups on the number of picture-word pairs correctly recalled ($f = 6.715$; $df = 3, 122$; $p < 0.001$). Those in the 18-29 yr old group remembered more words than those in their 40's ($p < 0.01$) and those in

the 50-64 yr old group ($p < 0.05$). The 30's also remembered more pairs than those in their 40's ($p < 0.05$) but there was no difference between the 30's and those in the 50-64 yr old group.

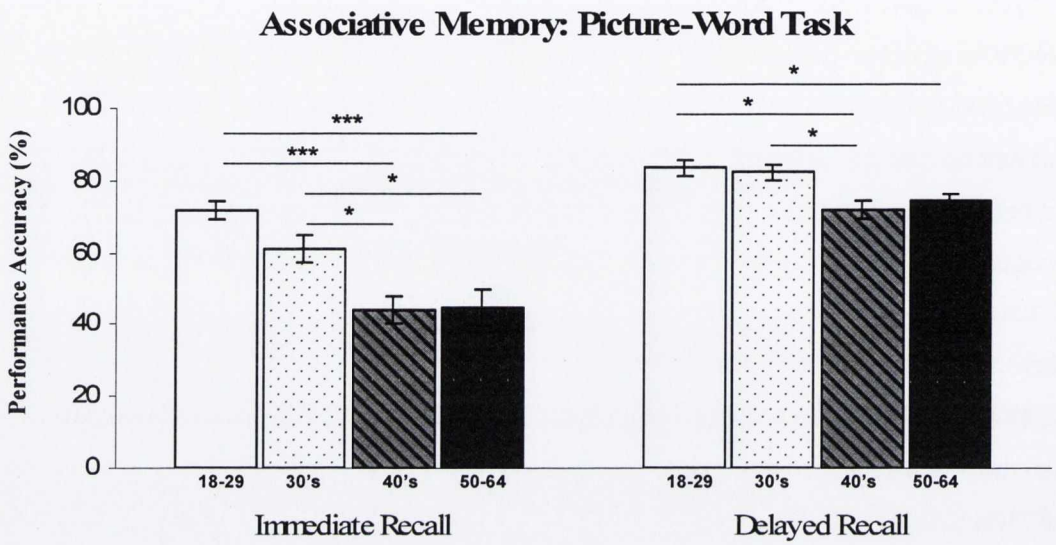

Figure 4.10: Percentage performance accuracy on the Immediate and Delayed recall trials of the Picture-Word Task (expressed as Mean ± SEM).

4.4.2.2 Working Memory

4.4.2.2a The n-Back Task (0-Back, 1-Back & 2-Back Levels)

Accuracy

Using a repeated measures ANOVA, there was a significant main effect of memory load on the *n*-Back ($f = 155.845$; $df = 2, 124$; $p < 0.001$) as would be expected; however, there were also significant differences between the groups in performance accuracy across all loads of the *n*-Back task ($f = 10.801$; $df = 3, 124$; $p < 0.001$) and a significant interaction between group and load ($f = 13.443$; $df = 6, 124$; $p < 0.001$). Post hoc tests identified that the 40's performed significantly worse then those in the 18-29 group ($p < 0.01$) and those in their 30's ($p < 0.01$). Those in the 50-64 group were also significantly different to those in the 18-29 group ($p < 0.001$) and those in their 30's ($p < 0.01$).

In order to identify where these differences lay a series of one-way ANOVAs were conducted, these identified a significant difference between the groups at the 1-back level

(f = 10.208; df = 3, 124; $p < 0.001$) and the 2-back level (f = 15.183; df = 3, 124; $p < 0.001$), but no difference at the 0-back level (see Figure 4.11). At the 1-back level those in their 40's were less accurate than those in the 18-29 yr old group ($p < 0.01$) and those in their 30's ($p < 0.01$). Those in the 50-64 yr old group were also less accurate than those in the 18-29 yr old group ($p < 0.001$) and those in their 30's ($p < 0.001$). At the 2-back level those in their 40's were less accurate than those in the 18-29 yr old group ($p < 0.001$) and those in their 30's ($p < 0.01$). Those in the 50-64 yr old group were also less accurate than those in the 18-29 yr old group ($p < 0.001$) and those in their 30's ($p < 0.001$).

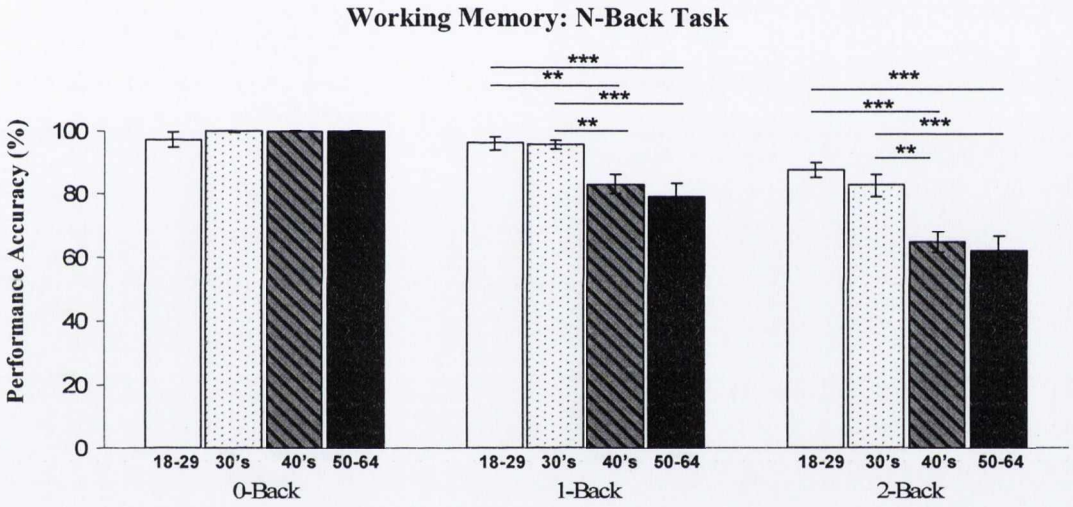

Figure 4.11: Percentage performance accuracy (presented as Mean + SEM) across the 3 levels of the n-back task, zero-, one- and two-back.

In addition to this, within groups comparisons were investigated to determine if there was a significant difference on performance accuracy across the three load levels of the task. Young adults differed significantly across the 3 levels of the *n*-back task (f = 22.871; df = 2, 84; $p < 0.001$). Pairwise comparisons showed that the young adults performed significantly worse at the 2-back level then both the 0-back ($p < 0.001$) and 1-back ($p < 0.001$). Those is the 30's group also differed significantly across the 3 levels of the *n*-back task (f = 21.152; df = 2, 60; $p < 0.001$). Pairwise comparisons showed that the 30's

performed significantly better at the 0-back level then both the 1-back ($p < 0.05$) and 2-back ($p < 0.001$), there was also a significant decrease in their performance from 1-back to 2-back ($p < 0.01$). The forties group also differed significantly across the 3 levels of the *n*-back task ($f = 63.161$; $df = 2, 56$; $p < 0.001$). Pairwise comparisons showed that the 40's performed significantly better at the 0-back level then both the 1-back ($p < 0.001$) and 2-back ($p < 0.001$), there was also a significant decrease in their performance from 1-back to 2-back ($p < 0.001$). While those in the 50+ group also differed across task load ($f = 39.515$; $df = 2, 48$; $p < 0.001$). Pairwise comparisons showed that the 50's+ performed significantly better at the 0-back level then both the 1-back ($p < 0.001$) and 2-back ($p < 0.001$), there was also a significant decrease in their performance from 1-back to 2-back ($p < 0.001$).

The mean "switch cost" in accuracy – accuracy in the 1-back condition minus accuracy in the 0-back condition was also computed and analysed, again there was a significant differences among the groups on their "switch cost" in accuracy ($f = 17.336$; $df = 3, 124$; $p < 0.001$). The 18-29 yr old group had a significantly lower switch cost than those in their 40's ($p < 0.001$) and 50+ ($p < 0.001$) (see Figure 4.12). Additionally those in their 30's had a significantly lower switch cost than those in their 40's ($p < 0.01$) and 50+ ($p < 0.001$).

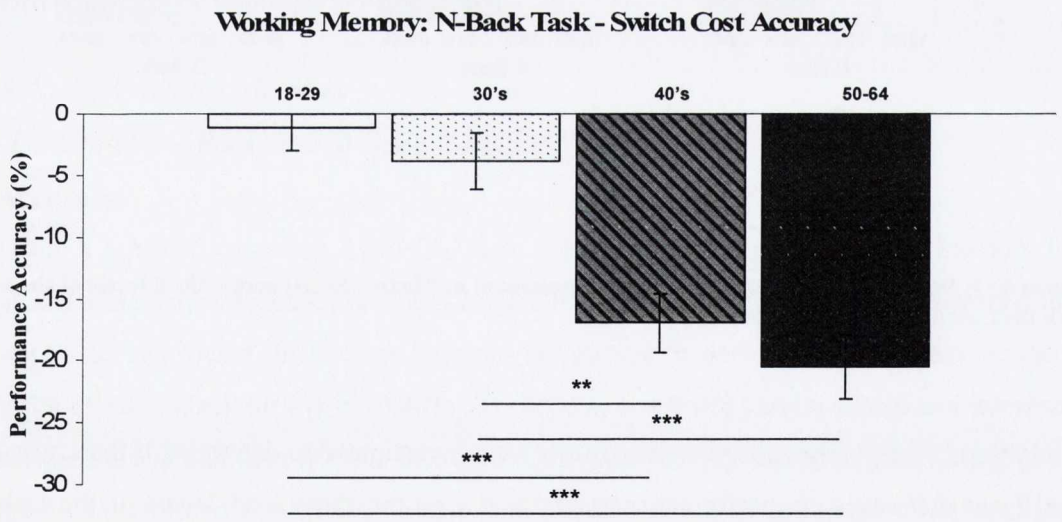

Figure 4.12: Switch Cost (1-back – 0 back; presented as Mean + SEM) across the age groups for accuracy

Reaction Time

Reaction time analysis (median RT in ms) revealed a significant main effect of load (f = 137.439; df = 2, 125; $p < 0.001$). There was also a significant main effect of group (f = 20.833; df = 3, 123; $p < 0.001$) and an interaction between the groups across the loads of the n-Back task (f = 6.601; df = 6, 123; $p < 0.001$). The differences between the groups were identified to be between the 18-29 yr old group and those in their 40's ($p < 0.001$) and the 50-64 yr old group ($p < 0.001$), and also between the 30's and those in their 40's ($p < 0.001$) and the 50-64 yr old group ($p < 0.001$).

Further examination of each level separately, found that there was a significant difference between the groups in their reaction time at the zero-back level (f = 18.275; df = 3, 128; $p < 0.001$), at the one-back level (f = 19.273; df = 3, 128; $p < 0.001$) and at the two-back level (f = 7.989; df = 3, 125; $p < 0.01$) (see Figure 4.13). At the zero-back level the 18-29 yr old group was significantly quicker than those in their 30's ($p < 0.05$) 40's ($p < 0.001$) and the 50-64 yr old group ($p < 0.001$). The 30's were also significantly quicker than the 50-64 yr old group ($p < 0.01$). At the one-back level the 18-29 yr old group, and the 30's were significantly quicker than those in their 40's ($p < 0.001$; $p < 0.001$) and the 50-64 yr old group ($p < 0.001$; $p < 0.001$). Finally in the two-back level those in their 20's and 30's were both significantly quicker than those in their 40's ($p < 0.01$; $p < 0.05$) and 50+ ($p < 0.01$; $p < 0.01$).

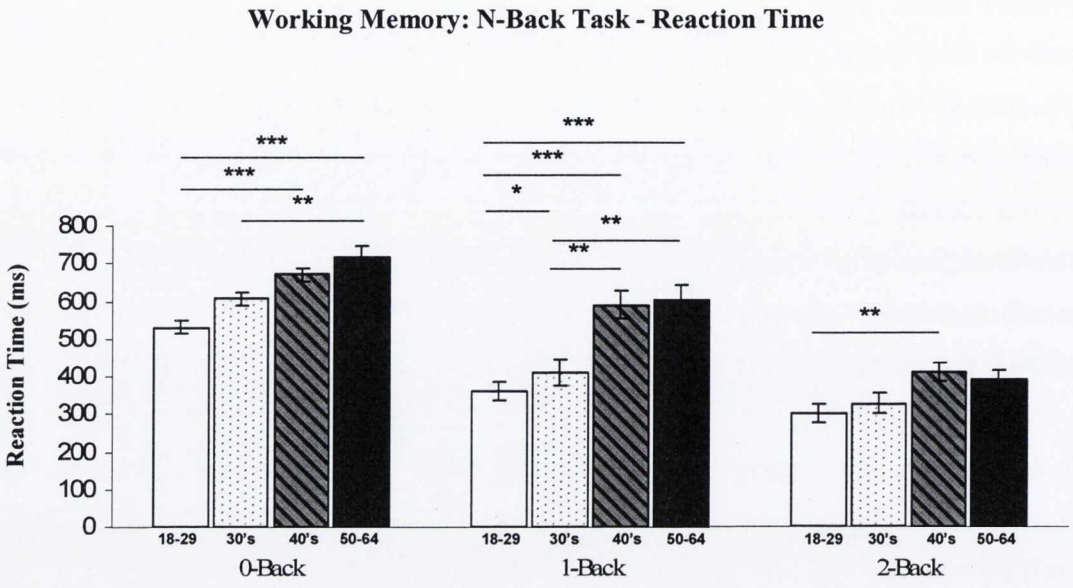

Figure 4.13: Reaction time (expressed as Mean ± SEM) across the three trials of the n-back task.

In addition to this, within groups comparisons were investigated to determine if there was a significant difference on reaction times across the three load levels of the task. Young adults differed significantly across the 3 levels of the *n*-back task ($f = 55.052$; $df = 2, 84$; $p < 0.001$). Pairwise comparisons showed that the young adults performed significantly quicker at the 2-back level then both the 0-back ($p < 0.001$) and 1-back ($p < 0.01$), and also at the 1-back level compared to the 0-back ($p < 0.001$). Those is the 30's group also differed significantly across the 3 levels of the *n*-back task ($f = 51.022$; $df = 2, 60$; $p < 0.001$). Pairwise comparisons showed that the 30's performed significantly slower at the 0-back level then both the 1-back ($p < 0.001$) and 2-back ($p < 0.001$), they were also significantly slower at the 1-back in comparison to the 2-back ($p < 0.001$). The forties group also differed significantly across the 3 levels of the *n*-back task ($f = 33.558$; $df = 2, 56$; $p < 0.001$). Pairwise comparisons showed that the 40's performed significantly quicker at the 2-back level then both the 0-back ($p < 0.001$) and 1-back ($p < 0.001$). While those in the 50+ group also differed across task load ($f = 25.801$; $df = 2, 48$; $p < 0.001$). Pairwise comparisons showed that the 50's+ performed significantly quicker at the 2-back level then both the 0-back ($p < 0.001$) and 1-back ($p < 0.001$). These results need to be interpreted

with caution, please see Chapter 2 pages 60, 85 and 107, and the discussion section below for further analysis.

4.4.2.2b The Match-to-Sample Task

In the training trial of the Match-to-Sample task there was a significant difference between the groups ($f = 7.137$; $df = 3, 127$; $p < 0.001$), with the 50-64 yr old group performing significantly worse than those in the 18-29 group ($p < 0.001$), those in their 30's ($p < 0.01$) and those in their 40's ($p < 0.01$) (see Figure 4.14). Nevertheless there were no significant differences between the groups on the task itself ($f = .842$; $df = 3, 127$; $p = .473$).

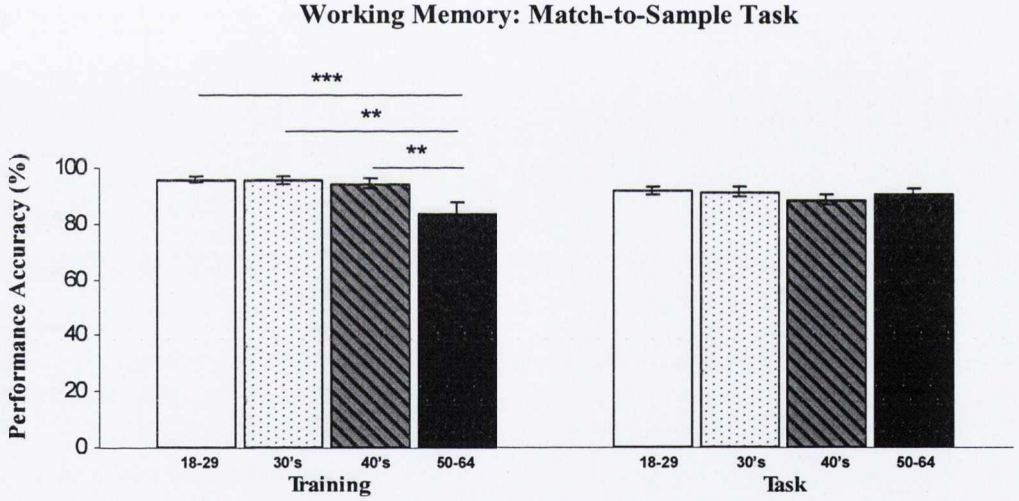

Figure 4.14: Performance accuracy (expressed as Mean ± SEM) on the training trial and during the task for the Match-to-Sample task.

Group	18-29	30's	40's	50-64
Recognition	46.98 (± 1.88)	44.80 (± 2.19)	45.25 (± 2.04)	41.76 (± 2.03)

Table 4.2: Performance accuracy (expressed as Mean ± SEM) on delayed recognition

A delayed recognition trial followed, and again there were no significant differences between the groups in their ability to recognise the stimuli that they had and had not previously seen (f = .507; df = 3, 110; p = .678) (see Table 4.2). However, when the response types were categorised according to hits, misses, foils and false positives group differences emerged. There was a significant difference between the groups on the number of foils correctly identified (f = 4.227; df = 3, 130; $p < 0.01$), with those in the 18-29 group identifying significantly more foils then those in the 40's ($p < 0.05$). The number of false positives committed between the groups was also significantly different (f = 4.703; df = 3, 127; $p < 0.01$), with those in the 18-29 group committing significantly fewer false positives then those in the 40's ($p < 0.05$), and those in the 50-64 group ($p < 0.05$).

NOTE

Although there were no significant differences between the groups on their IQ score as measured by the NART, each analysis was re-run with IQ as a covariate in order to determine if the age-groups differed above and beyond the possible effect that IQ might have on the performance scores.

4.4.2.3 Relationship between Associative memory and IQ

4.4.2.3a Face-Name Task

IQ had a significant impact on the immediate recall of the face-name task, as a significant effect of IQ (f = 19.798; df = 1, 129; $p < 0.001$; partial eta sq = 0.133), was found. However, despite the inclusion of IQ as a covariate, there still remained a significant main effect of age-group (f = 25.038; df = 3, 129; $p < 0.001$; partial eta sq = 0.368) on the total performance accuracy across the learning trials of the face-name task. There was also a significant effect of IQ on the delayed recall (f = 22.388; df = 1, 129; $p < 0.001$; partial eta sq = 0.148), though the age effects still remained (f = 30.726; df = 3, 129; $p < 0.001$; partial eta sq = 0.417).

IQ was also a significant covariate in name free-recall (f = 5.564; df = 1, 128; $p < 0.05$; partial eta sq = 0.042), and again, the main effect of age-group was still significant (f = 4.784; df = 3, 128; $p < 0.01$; partial eta sq = 0.101). Despite the effects of IQ on the different measures of recall, there was no effect of IQ on face recognition, or name recognition. See Table 4.3 below for the IQ adjusted means.

Group	18-29	30's	40's	50-64
Total F-N Recall	51.08 (± 2.29)	47.95 (± 2.98)	32.47 (± 2.75)	21.18 (± 3.09)
Delayed F-N Recall	71.76 (± 3.10)	63.23 (± 4.03)	43.05 (± 3.72)	25.93 (± 4.18)
Name Free-Recall	84.08 (± 2.06)	83.40 (± 2.68)	77.07 (± 2.47)	72.31 (± 2.83)

Table 4.3: IQ-Adjusted performance accuracy (expressed as Mean ± SEM) on the face-name task

4.4.2.3b Picture-Word Task

The effects of IQ on associative memory were also assessed in the picture-word task. Differences between the age groups on immediate recall remained when IQ was included as a covariate ($f = 13.6$; $df = 3, 123$; $p < 0.001$; partial eta sq = 0.249), though IQ did have a significant effect on recall accuracy ($f = 8.864$; $df = 1, 123$; $p < 0.01$; partial eta sq = 0.067). Delayed recall performance also remained significantly different between the age-groups when IQ was included as a covariate ($f = 6.372$; $df = 3, 123$; $p < 0.001$; partial eta sq = 0.139), though again, in this case, IQ also had a significant effect on recall ($f = 22.753$; $df = 1, 123$; $p < 0.001$; partial eta sq = 0.162). See Table 4.4 below for the IQ adjusted means.

Group	18-29	30's	40's	50-64
Immediate Recall	71.69 (± 3.09)	58.05 (± 4.06)	45.43 (± 3.87)	44.29 (± 4.19)
Delayed Recall	83.55 (± 1.80)	81.64 (± 2.31)	73.39 (± 2.29)	73.32 (± 2.45)

Table 4.4: IQ-Adjusted performance accuracy (expressed as Mean ± SEM) on the picture-word task

4.4.2.4 Relationship between Working Memory and IQ

4.4.2.4a n-Back Task

IQ had a significant impact on accuracy scores for the 1-back ($f = 19.101$; $df = 1, 120$; $p < 0.001$; partial eta sq = 0.137), and 2-back ($f = 17,654$; $df = 1, 120$; $p < 0.001$; partial eta sq = 0.128) levels of the *n*-back task; reaction time at the 1-back level ($f = 8.257$; $df = 1, 120$; $p < 0.01$; partial eta sq = 0.064); and switch cost accuracy in reaction time ($f = 5.594$; $df = 1, 119$; $p < 0.05$; partial eta sq = 0.045). Regardless of the inclusion of IQ as a covariate, differences between the groups still remained on accuracy at the 1-back ($f = 11.554$; $df = 3, 120$; $p < 0.001$; partial eta sq = 0.224) and 2-back ($f = 16.390$; $df = 3, 120$; $p < 0.001$; partial eta sq = 0.291) levels; reaction time at the 1-back ($f = 13.712$; $df = 3, 120$; $p < 0.001$; partial eta sq = 0.254); and finally reaction time switch cost ($f = 6.808$; $df = 3, 119$; $p < 0.001$; partial eta sq = 0.146). See Table 4.5 below for the IQ adjusted means.

Group	18-29	30's	40's	50-64
Accuracy 1-B	95.94 (± 2.14)	95.83 (± 2.66)	84.25 (± 2.64)	78.25 (± 2.82)
Accuracy 2-B	87.55 (± 2.73)	82.31 (± 3.39)	65.79 (± 3.36)	60.64 (± 3.59)
Reaction Time 1-B	365.83 (± 27.14)	425.42 (± 33.67)	575.32 (± 32.83)	606.11 (± 35.57)
RT Switch Cost	-63.35 (± 24.25)	-71.23 (± 30.24)	169.08 (± 28.96)	216.90 (± 31.41)

Table 4.5: IQ-Adjusted performance accuracy (expressed as Mean ± SEM) on the *n*-back task

4.4.2.4b Match-to-Sample Task

IQ was not a significant covariate in the match-to-sample training scores or task scores.

4.4.2.5 Relationship between Associative and Working Memory

The relationship between performance at the 2-back level of the *n*-back task and total number of face-name pairs successfully recalled was examined. Overall, there was a significant positive relationship between performance accuracy at the 2-back level and the number of face-name pairs remembered ($r = .466$, $n = 128$, $p < 0.001$) (see Figure 4.15). When the relationship was investigated within each age group, only the 30's group had a significant positive relationship between the two variables ($r = .409$, $n = 31$, $p < 0.05$).

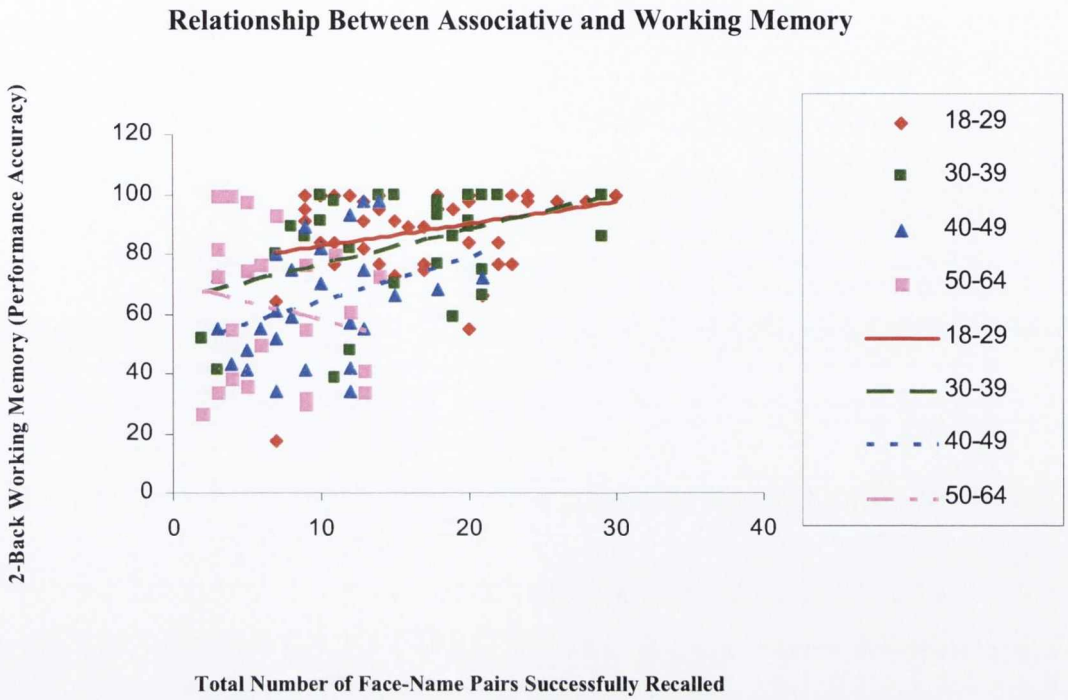

Figure 4.15: Relationship between performance accuracy on the 2-back level of the n-Back task and the total number of face-name pairs recalled

4.5 Discussion

In this chapter, the relationship between age and associative- and working-memory was examined across the lifespan. A number of affective measures were also included, in addition to a measure of pre-morbid IQ, to determine if depression, anxiety, or IQ was associated with the age-related cognitive impairments. The main findings are listed below:

- Impairments were found on both measures of associative memory between the age groups; these deficits emerged in the 40's group.
- Impairments were found on one measure of working memory between the age groups; these deficits emerged in the 40's group.
- There was no significant difference on measures of depression or anxiety across the age groups. In addition, the age groups did not differ on IQ levels.

4.5.1Pilot Study Results

Results from the pilot study indicated that there was a significant difference between the age groups on the face-name associative memory task. Age had a significant impact on free- and delayed-recall, with deficits emerging by the 30's. On the other hand, there was a significant impact of IQ on these results, suggesting that participants should be carefully matched for IQ in aging studies. There were no significant differences between the age groups on performance accuracy in the *n*-back task; suggesting that WM deficits would not be evident in these age groups (18-64). Nevertheless, there was a significant relationship between performance on the face-name task and performance at the 2-back level of the *n*-back task; suggesting that there may be common underlying regions that serve associative- and working-memory.

4.5.2 The Present Findings and the Current Literature - Associative Memory Impairments across the Lifespan

The first hypothesis (which was based both upon current literature and findings from the pilot data) that age would have a significant effect on associative memory, with deficits appearing by the forties, was supported. There were two tests used to examine this hypothesis, the face-name task, and the picture-word task. There were several associative memory constructs measured by the face-name task; the first, encoding across the blocks (1-4), was significantly different between the groups. Those in their 40's and those 50+

were significantly impaired at remembering the face-name pairs then those in their 20's and 30's. There were also significant differences in the delayed recall trial, where again the 40's and 50+ groups remembered significantly less face-name pairs than the 20's and 30's groups. Free recall of the names was then tested; however in this case, only those in the 50+ group differed significantly than the 20's and 30's. A similar pattern was seen on measures of face-recognition, with those in the 50+ group showing impairments in the overall recognition score. Finally, differences in name-recognition were examined, and differences were again significant between the groups, however this time the 30's and 50+ groups differed significantly than those in the 20's group. Performance on the face-name task was significantly impaired with increasing age, significant deficits in associative memory appearing in the 40's.

There is some debate in the literature about name recall abilities in older adults, and whether they do have a particular impairment in remembering proper names, or whether their performance is just inferior to that of younger adults. Cued recall does not provide information about individual components – making it difficult to determine if poor performance is from an inability to access associations or poorer memory of the individual components. However in the present study, free-, cued-, and recognition-memory were all assessed. The findings from the current study support those reported in previous studies, where researchers found that there was a decrease in memory performance on a face-name test, with younger adults remembering the most pairs, and older adults remembering the least, with middle-age adults performing at an intermediate level (Yesavage et al., 1984). One of the many strengths of the current study is that, not only does it confirm that there are associative memory impairments in encoding abilities evident with increasing age, but it also identifies that these encoding deficits emerge in the 40's (the fifth decade of life).

While the 2004 study by Naveh-Benjamin et al. attempted to examine these ideas, they only used a recognition test for the individual components along with the associative face-name pairs; they did not include free recall of the names, or a cued recall of the face-name pairs. All of their measures were forced choice recognition. They argued that other studies have found impairments on name recall when they used free- or cued-recall measures, and not recognition. They believe that recognition tests provide older adults with the necessary cues and environmental support; this meant that they did not have to self initiate the retrieval of the names, and resulted in performance levels that reflected those of the younger adults. Although the use of the recognition paradigm does allow them to identify

if older adults have a deficit recognising associative information, it does not allow them to determine if these deficits are due to faulty encoding processes, or deficits with the long-term storage of the information. Contrary to this, the design of the present study allows for the discrimination between encoding and retrieval impairments. It is important to note that despite the fact that they used a recognition paradigm, there were still significant impairments found in the older adults on associative memory.

They also found that older adults showed a small but significant deficit in face recognition, similar to that found in the present study. While the average age of their older group was 72 years of age, the present study found that these impairments emerged in the 50-64 year old group. However, while Naveh-Benjamin et al. (2004) found that there were no differences on name recognition, and felt that these results revealed situations in which older adults performed on a par with younger adults, the present findings did not lend support to these results. There was a small but significant impairment on name recognition in those over 50. There are several previous studies that have also found age-related differences in name recognition (Evrard, 2002; Maylor, 1997). However, it must be noted that the 30's group also demonstrated a significant impairment on name recognition; a finding which does not reflect the current literature or any of the other associative memory findings from the current study.

Associative memory was also assessed using the picture-word task, and differences between the groups were examined. There were significant differences on the immediate recall between those in the 20's and 30's group with those in the 40's and 50+ group. In the delayed recall, there were significant differences in the number of picture-word pairs remembered, with those in the 40's group remembering significantly fewer than those in the 20's and 30's groups. Those in the 50's also performed significantly worse, though only in comparison to those in the 20's group. The first hypothesis was also supported using the picture-word task, with significant differences emerging in the 40's.

Recognition has also been examined in other studies; they reported that older adults do exhibit deficits in associative memory, but they do not exhibit deficits in tests of recognition; accordingly, they do remember the different components from associative memory (e.g. picture and words), but they have difficulty pairing the components together (correctly remembering the picture-word pairs) (Guo et al., 2005; Kersten et al., 2008). In contrast, Crook and Larrabee (1992), found that impairments in face recognition were

evident by the fifth decade of life, and were especially pronounced by the seventh decade. Additionally, Lott et al. (2005) also found differences in face recognition in older adults; while there was a decline in face recognition with age, they only included elderly adults from 64 years to 102 years. Therefore it is difficult to identify at which point across the lifespan these deficits first appear. Collectively, the results from the present study offer considerable weight to the findings from the current literature. Deficits in older adult's associative memory emerge in the 40's; at this point there is only a deficit in the participant's ability to bind information together, and as a result there are significant impairments on both immediate and delayed recall. It is not until the 50's that deficits in recognition of associative information appear.

Identifying the cognitive processes that underlie these associative memory changes is somewhat difficult. There are clearly differences in the number of face-name pairs remembered by the age groups across the 4 encoding blocks; the younger groups learn more face-name pairs across the 4 blocks than the older groups. Perhaps the younger participants are more motivated to learn the faces or the older participants have a lower expectation as to their possible performance levels. Initiating the appropriate encoding strategy required to successfully perform the task, or an inability to spontaneously change the encoding strategy used, may be a reason for the deficits seen in the associative memory tasks. Perhaps if the participants had been told to make a semantic decision about the stimuli, thus encouraging a deeper level of processing during encoding, then their retrieval scores would have been improved. The levels-of-processing effect improves memory regardless of age, but may lead to greater improvements in the older adults (Grady et al., 2000). This is consistent with the idea that there are age-related decrements in activity in brain networks during memory tasks in which older adults show impairment; though during tasks in which the older adults perform relatively well, or on a par with younger adults, they show a similar or increased activation pattern (Schacter et al., 1996).

4.5.3 *The Present Findings and the Current Literature - Working Memory Impairments across the Lifespan*

The second hypothesis (which was based both upon current literature and findings from the pilot data), that there are no effects of age on working memory, and again there were two tests used to examine this hypothesis, the *n*-back task and the match-to-sample task, was supported with the findings of the match-to-sample task, and only somewhat by the findings of the *n*-back task.

Based upon the results from the pilot data, WM deficits were not expected in the *n*-back task, though it is important to note that these findings are not in agreement with much of the current literature. However, differences between the groups were significant on the *n*-back task, with those in their 20's and 30's performing significantly better than those in their 40's and the 50+ group on performance accuracy at the 1-back and 2-back levels. There was also a significant difference in the switch-cost in accuracy form the 1-back to 2-back between both the 20's and 30's in comparison to the 40's and 50+. Analysing RT across the task, significant differences were seen between the groups. Across the 0-back, those in the 20's group performed significantly quicker than those in their 30's, 40's and 50+. While at the 1- and 2-back levels, both the 20's and 30's were significantly quicker than the 40's and 50+ groups. The results of the *n*-back task did not support the hypothesis, findings from the present study found that significant differences in WM emerged in the 40's.

WM tasks offer a useful means to test the relationship between age and frontal lobe function, since the PFC plays an important role in WM, and age has been shown to have a detrimental effect on the PFC functioning. Findings from the present study suggest that there are some age-related differences in WM. In the *n*-back task, accuracy at both the 1- and 2-back levels was significantly different, and these differences emerged by the 40's and remained significant up to 64 years of age (upper age limit). Interestingly, the switch cost in accuracy was also significantly different with age; these differences are evident in the 40's and 50+ groups on measures of accuracy. This implies that with increasing age, people experience greater difficulty switching between items held inside the focus of attention and items held outside the focus of attention.

Similar findings have been reported in previous studies that used the *n*-back task; significant differences were found on the ability to switch between items held in the focus of attention, and items held in WM (Van Gerven et al., 2007). They found that these differences were evident by middle age (mean age = 56 years), and state that "the effect seems to be purely attributable to aging" (pg. 162), as participants were carefully screened for age-related health problems. In an additional study, this group offered further evidence for the distinction between items held within the focus of attention, and items held outside the focus of attention (Vaughan et al., 2008). They found that there was an increase in response times from when one item was held in WM, to when there was two or more items stored. Combined, findings from the present study, and previous research (Vaughan et al.,

2008; Verhaeghen et al., 2005), suggest that in demanding tasks, like the *n*-back task, the limit of the focus of attention is 1 item.

There was also a significant difference on RTs across all levels of the *n*-back task, though the 20's and 30's performed significantly quicker then those in their 40's and the 50+ group at each level of the task. Using the standard *n*-back task, reaction times normally increase with task load because infrequent targets are used; however, in the present study a continuous response task was used (similar to that used by Meyer-Lindenberg et al. (2001)). The subjects were able to prepare their response prior to the stimulus onset for the 1- and 2-back conditions, which they cannot do in the 0-back condition. As a result, their response times decreased with increasing task load. In addition, they were also more motivated to respond faster at the higher levels i.e. 2-back relative to 1-back, as this way they can dump the outdated information faster and concentrate on the in-coming input physically, by moving their hand over to the next stimuli. Accordingly response times decreased as task load increased. In hindsight, it could be argued that this may not in fact be a true *n*-back task as it does not allow for a complete working memory assessment as designed. The automated memory responses that are available as a result of this increase time to prepare the response may be confounded with the memory load increases. While the numbers that had to be kept in mind could have been offline from the WM processes, participants may have been repeating the numbers through the phonological loop. This may indicate that under certain circumstances the phonological loop can be used as a buffer between what is held within and outside of the focus of WM attention.

Unlike the findings from Van Gerven et al., the results of the present study did not reflect those found in the work carried out by Verhaeghen et al. (2005). While they found that there were no age-related impairments in RT, the present study found significant differences between both the young adults and those in their 30's, in comparison to both those in the 40's and 50-64 groups at the 1- and 2-back levels. At the 0-back level, where subjects had no time to prepare their response, those in the 20's performed significantly quicker than those in their 30's, 40's and 50+. Verhaeghen also found no difference on accuracy at the 1-back level, which is not in agreement with the present study, but did find that there was a significant switch cost in accuracy, which was also evident in the present study. There are several differences between the two studies; the present study required participants to constantly update their memory and continuously respond to the stimuli on screen, while those in the Verhaeghen study did not have to continuously update (they only

had to press at every *n*-th item); secondly, the present study only included up to *N*=2 back, while the Verhaeghen study required participants to work up to *N*=5 back, the inclusion of *N*>2 allowed the comparison of more than one level outside of the focus of attention. As a result, Verhaeghen et al. (2005) were able to deduce that the age-related impairments were only related to the switching costs between the 1- and 2-back levels, as age differences in accuracy did not increase from *N*=2 to *N*=5.

Using a modified version of the n-back task, older adults were reported to have a difficulty maintaining the processing manipulations required by the 1-back task (Dobbs et al., 1989), a result that was also found in the present study. Furthermore, they found that age was a reliable predictor of performance at the 1- and 2-back level, while education was a reliable predictor of performance only at 2-back level. They concluded that while there were differences in the findings across studies on the speed and strength of the processing system, aging studies have demonstrated that there is a decrease in the speed at which processing changes can be achieved.

Nevertheless, despite significant age-related differences found on several measures of the *n*-Back task, and during the training trial of the MTS task, there were no differences found on test trial of the MTS task in any age group, which does support the hypothesis. Perhaps the differences found in the results of these WM tasks is due to the fundamental difference in their memory requirements; while the MTS task required participants to hold an item in memory for a period of time while processing the next stimulus, the *n*-Back task required participants to continually manipulate and update the information held in memory. Looking at the results from the present study, it would appear that there is only an age-related deficit in those tasks that require the person to continuously manipulate and update the information held in memory. Perhaps the difference between the results of the two WM tasks lies in the complexity of the operations required to complete them successfully. Perhaps the use of a task that has an equal memory requirement of the *n*-back task would verify that these deficits are present.

Lastly, studies have investigated the impact of education on memory performance across different age groups; Economou et al. (2006) found that age and education affected both working and delayed memory scores. As a result, education has been seen to have a defensive influence on age-related cognitive impairments (Christensen et al., 2007). Nevertheless, Van Gerven et al. (2007), mentioned previously, found that there was no

relationship between education and the effect of age on the switch cost in the *n*-Back task . Though, the older adults who were in the high education group had larger RTs in comparison to the older adults who were in the low education group. They suggest that there may be an intentional slowing down in the high education group in an effort to maintain a high level of accuracy. While the impact of education on memory was not included in the present study every care was taken to match participants as closely as possible for years spent in full-time education. Nevertheless, the impact of IQ on memory performance was investigated. IQ significantly impacted both associative and WM findings, however the effects of age remained when IQ had been accounted for. This suggests that there is a specific age-related deficit in both associative and WM that emerges in the 40's.

4.5.4 Summary of the Current Findings

Age has a significant effect on associative memory; for the most part, these deficits appear in the forties, and continue to decline across the lifespan (see Table 4.6). In addition, there was also a significant effect on a high demand WM task (the *n*-Back task); once again, these differences appeared in the forties (see Table 4.6). Taken together, these findings would suggest that deficits in associative and working memory tasks that have been reported in previous studies first emerge in the 40's. While there was a significant effect of IQ on both associative and working memory tasks, the age-related impairments remained above the effects of IQ.

Test	Associated Area	Trial	Age Effects
Associative Memory – Face-Name Task	**Hippocampus**	**Face-Name Pair Free-Recall**	***Above 40***
		Delayed Face-Name Pair Free-Recall	***Above 40***
		Delayed Name Free-Recall	***Above 40***
		Delayed Face Recognition	***50 +***
		Delayed Name Recognition	***30's and 50 +***
Associative Memory – Picture-Word Task	**Hippocampus**	**Immediate Free-Recall**	***Above 40***
		Delayed Recall	***Above 40***
Working Memory – *n*-Back Task	**DLPFC**	**0-Back Accuracy**	**None Found**
		1-Back Accuracy	***Above 40***
		2-Back Accuracy	***Above 40***
Working Memory – Match-to-Sample Task	**DLPFC**	**Immediate Accuracy**	**None Found**
		Delayed Accuracy	**None Found**

Table 4.6 Cognitive profile of aging – Identification of the specific memory impairments that accompany aging, and the point at which these emerge across the lifespan.

In particular, the deficits in the 40's appear to be related to encoding processes, as impairments were evident on measures of immediate free-recall. Consequently, while those in their 40's had no difficulty recognising the individual components of associative memory, the relational information between those components was impaired. Furthermore, there was a significant difficulty switching between items in the *n*-back task that emerged in the 40's. Taken together, these findings propose that there may be a down regulation in connectivity between the MTL and the PFC with aging, and that this appears in the 40's; however, confirming this proposal requires further investigation.

The relationship between associative memory and working memory was also assessed; data from the pilot study suggested that there was a significant relationship between positive relationship between performance at the 2-back level of the *n*-back task and the total number of face-name pairs remembered. While a medium positive relationship was found in the current study across all age groups (see Figure 4.15), once the analysis was separated by group, the significant relationship between the two variables only held for those in their 30's. While it has been hypothesised that a positive relationship between the two tasks could indicated that successful performance on both requires activation of similar brain regions, we cannot make any conclusions form the current data. An in-depth MRI analysis would be needed to confirm this hypothesis.

4.5.5 Outstanding Methodological Issues

One of the great strengths of the current study is the age range of participants included, and the number of participants in each age-group. In order to be able to identify the point at which associative memory deficits appeared, the present study included adults from 18-64 years of age. Few previous studies have analysed memory changes across several groups from the adult lifespan; most have compared a young and old group, failing to include those of middle-age. It is at this point that the associative memory deficit appears in the current findings. In addition, there was a concerted effort made to ensure that there were adequate numbers of subjects included in each age group. This meant that the effect of age across adulthood could be examined. However, the present studied did not include people over 64 years of age. This exclusion was primarily due to logistical reasons. It would have been extremely beneficial to include those beyond 64 years to determine if associative and working memory abilities continue to decrease in the elderly, as suggested in much of the current literature.

As previously mentioned many tests of episodic memory use recognition trials rather than free-recall trials. Unlike in the current study, those in Cabeza's study were shown two items, one previously seen and one new (2000). They tested people's memory for items using a recognition task and for context, by examining the order in which the items were presented. Older adults showed impairment on memory for items, but an even larger impairment in temporal order associative memory. It is important to note that recognition can have many different bases, such as familiarity or recollection, and these may relate to different types of information (McIntosh et al., 1997; Nyberg et al., 2000). Separation of these concepts may provide more insight into the recognition impairments in older adults.

According to Gomez-Perez et al. (2006), there are attentional changes across the lifespan; these allow for greater selectivity and speed of processing during childhood and adolescence, and generally less selectivity and increased slowing during later adulthood. There was no measure of attention included in the present task, other than the 0-back level of the *n*-back task. Perhaps inclusion of a specific measure of attention would offer some insight into the processes underlying the age-related impairments in memory found in the current study. Alternatively, using a divided attention face-name task could confirm that the deficits found are not due to a reduction in the attentional processes available.

There were also some analytical flaws in the current study. The analysis of the *n*-back task did not include an investigation of differences in general slowing with age. Verhaeghen et al. (2005) transformed their reaction time data to account for the effects of general slowing across the lifespan, as a result they found no age-related differences in RT on the *n*-back task. Perhaps if a similar transformation had been included in the present study, the age-related impairments in WM would not have been evident.

Unlike the studies discussed in Chapter two and three, the present study did not include any measures of thyroid hormones, which have been reported to be associated with changes in cognition. It would be beneficial to include analysis of thyroid functioning in order to assess the impact of thyroid hormones across the lifespan, as hormonal changes, in addition to aging, may explain age-cognition patterns. This is of particular interest as several hormone levels shift with age (Morley et al., 1997).

4.5.6 Future Directions

There is some evidence to support the idea that cognitive training interventions can help reduce the impairments seen in associative memory (Yesavage et al., 1990). There are several types of training programs that can be used; practice, imagery, and the use of memory aids are among some of the methods. By using imagery based mnemonics, older adults could use a more effective strategy to organise and encode associative memory; this could in turn aid face-name recall. Using one of these mnemonic training strategies, Yesavage found that there was an improvement on memory performance scores following training; however, each age group improved at the same rate, so pre-treatments differences in associative memory were still evident (1984). In their 1990 study, they found that training improved both face-name and list recall, though there was a lot of variability in the data, suggesting that there is a substantial difference in peoples abilities to benefit from the training (Yesavage et al.). Both age and premorbid cognitive functioning were found to account for quite a lot of these differences, which implies that future training programs should account for the possible interaction between types of training available and the age group to which it is offered, and also the participants premorbid cognitive performance. In addition, examining associative memory using a concurrent associative memory task would allow researchers the opportunity to create interference with the associations and assess that impact that this would have on associative memory in younger and older adults. Tasks that also require binding and involve activation of the same regions as associative memory could be used.

Findings of age-related impairments in the current study are based entirely on neuropsychological measures. Evidence shows that the model of intact versus damaged memory function seen in older adults may be accompanied by a corresponding model of reduced and increased activity in the brain areas responsible for memory (Grady et al., 2000). A logical next step in the current study would be to examine associative and working memory using fMRI. The challenge would be to verify whether additional activations reported in other studies are present, and determine if these reflect a compensatory mechanism of sorts, or whether it simply reflects a more scattered pattern of activation in older adults.

However, age-related changes in neural activation have been shown to be partly attributable to age-related changes in neural connectivity according to Cabeza et al. (1997b). Perhaps analysis of functional connectivity, rather than BOLD activity, would

represent a more direct assessment of the interactions between brain regions during episodic memory; especially considering that McIntosh et al. (1997) found that functional interactions between frontal and posterior regions were related to level of recovery.

4.6 Conclusion

Impairments in episodic memory are often the first sign that something may be wrong, and may possibly be a marker for mild cognitive impairment (Backman, 2008). Reviewing the findings of the current study it would appear that there is a significant effect of age on episodic memory; this impairment appears in the fifth decade and continues to decrease well into the seventh decade. There is also a significant effect of age on working memory; again this impairment appears in the fifth decade and continues to decrease into the seventh decade. Mechanisms through which these deficits may occur were discussed, highlighting the common neural mechanisms that underlie both associative and working memory. These focused primarily on the relationship between MTL and PFC functioning. It remains to determine whether these neuropsychological deficits will be mirrored in magnetic resonance imaging studies.

Chapter 5

General Discussion & Conclusions

5.1 Summary

This chapter outlines the main findings from the current studies; the hypothyroid-induced impairments in cognitive functioning found in chapter 2, to the follow-up examination seen in chapter 3, and the subsequent examination into age-related impairments in PFC and MTL associated functions in chapter 4. There is a discussion on how these findings contribute to the current literature, taking into account both the strengths of the studies, and the outstanding methodological issues. The chapter concludes with a proposed model to account for these findings, and recommended future directions that should be considered in light of the suggested model.

5.2 Synopsis of Results

Recent lesion and neuroimaging studies have suggested that there is an interaction and overlap in function between the structures of the frontal lobes and the MTL that are involved in memory formation (Kopelman, 2002). The present studies examined this suggestion in two populations, a diseased population (subclinical hypothyroidism and overt hypothyroidism) and an aging population (normal healthy controls across the lifespan). The main aim was to explore the nature of the deficits in both groups, and determine if there was a relationship between the findings from each and the interconnections between the PFC and the MTL regions. The main findings are listed below.

- There is a specific deficit in MTL-based memory in patients with an underactive thyroid gland. These deficits are more pronounced in patients with hypothyroidism than SCH.
- While there are deficits in PFC-based memory, these are only present in the hypothyroid group.
- There is some functional recovery of these deficits in SCH patients within 6 months, though deficits remained in the hypothyroid group; however; it was difficult to determine the extent of these improvements above those seen with practice in all participants across sessions.
- The findings lend some support to the suggestion that hypothyroidism exists on a continuum.
- There are specific deficits found on MTL- and PFC-based memory tasks with age. These deficits primarily emerge in the 40's.

5.2.1 Specific Deficits Associated with Hypothyroidism

In Chapter 2, cognitive deficits were investigated in newly diagnosed hypothyroid patients, with both subclinical and overt hypothyroidism. The hypothesis stated that there were specific impairments on measures of prefrontal and MTL functioning; these measures included associative memory, verbal memory, and WM. In addition, the impact of depression, anxiety, and age on hypothyroidism was also considered. The findings lend support to previous studies that have advocated the role of the MTL and PFC in hypothyroid-associated memory impairments.

There were significant impairments found on several measures of associative memory, which is chiefly associated with hippocampal/MTL functioning. Observing the specific types of hippocampal memory that were affected, it would appear that the deficits were primarily at the encoding level, and were greater in those with overt hypothyroidism than SCH. There appear to be difficulties making associations/forming relationships between items in memory in people with untreated hypothyroidism. This problem "binding" information together results in impairments on recall across a wide range of hippocampal-based tasks. On measures of immediate recall in the face-name task, there was a significant deficit in the hypothyroid patient's ability to form the associations between the face-name pairs. In addition, their subsequent delayed recall was also impaired; these retrieval problems are probably due, primarily, to the difficulty they experienced at the encoding level. This supports previous findings that reported a specific deficit in hypothyroidism using the face-name task (Cooke et al., 2008; Correia et al., 2009), and demonstrates that this deficit stems from a problem encoding the associative information.

Further support for this view comes from the results of the Rey complex figure test, performance of which is also hippocampal related. There was a significant impairment in the hypothyroid patient's ability to recall the elements of the ROCF, and this impairment was more severe in those with overt hypothyroidism. These deficits were evident at the copy, immediate, and delayed trials for both patient groups, though they were more pronounced in the overt hypothyroid group. However, there were no impairments on the recognition trial, which has primarily been associated with the PFC. This offers further confirmation that the impairments associated with hypothyroidism result from a deficit in relational information, as memory for the individual items, as measured by the recognition task, was unaffected. It also offers further support for the proposal that PFC associated memory undergoes little or no damage in hypothyroidism, as recognition tasks are thought to be PFC-based.

On measures of verbal memory; deficits were also evident, though they were more marked in the overt hypothyroid group. Hypothyroid patients were significantly impaired on immediate, short- and long- delayed free recall, and also on short- and long-delayed cued recall. These findings indicate that the MTL-related deficits in hypothyroidism are quite severe, as they impact several types of recall. This is the first time that this deficit in encoding associative information has been confirmed on several measures. Taken together, these findings suggest that the deficits were primarily due to impaired encoding abilities

resulting from an alteration in the functioning of the MTL, and more specifically the hippocampus.

As a result of the "altered" hippocampal functioning, the projections from the hippocampus to the PFC may be altered or reduced in number; this could explain the deficits seen on the WM task. There were significant impairments evident in performance accuracy at the 1- and 2-back levels of the *n*-back task; though these were only evident in the hypothyroid group and not the SCH group. These results indicate that the magnitude of thyroid dysfunction present is related to the incidence of PFC dysfunction; the greater the thyroid hormone insufficiency is in the MTL, the more likely the occurrence of PFC associated memory problems. This idea lends weight to the suggestion that hypothyroid associated memory impairments are mainly due to the dysfunction of the MTL, and that there is little or no dysfunction in the PFC itself. If the network between the hippocampus and the PFC is not functioning properly, then performance on PFC-based tasks could also be at risk. However, these findings are in total contrast to those of Zhu et al. (2006), who found a significant deficit in WM in hypothyroidism using the *n*-back task, and no impairments in associative memory using the Wechsler Memory Scale—Chinese revision.

The findings from this study also support previous studies that found a link between hypothyroidism and measures of depression, and anxiety. Depression scores were significantly higher on two different measures of depression in the overt hypothyroid group. In addition, anxiety levels were significantly higher in both patients groups; though more marked in the overt hypothyroid group. Considering that depression, stress and anxiety have all been shown to have a detrimental effect on memory (Potter et al., 2009), the relationship between high depression and anxiety scores and thyroid-related memory impairments warrants further investigation.

Lastly, a significant relationship between age and memory deficits in hypothyroidism was found. Taking the impact of age into account, there were still impairments present on measures of associative and working memory. This would suggest that age and thyroid status have a differential outcome on cognitive functioning; nonetheless, this effect requires further examination. Overall, the findings from the Chapter 2 offer further and more extensive evidence of a specific, hippocampal-associated, memory deficit in hypothyroidism, and a secondary decrease in PFC functioning. The ability to recover from these deficits is highly controversial and remains to be determined.

5.2.2 Functional Recovery in Hypothyroidism

If hypothyroidism results in impaired functioning of the hippocampus due to decreased thyroid hormone expression, then treatment for hypothyroidism should improve hippocampal functioning; however, there was little evidence of this in the follow-up cognitive results discussed in Chapter 3. There was a significant improvement found in both the SCH and hypothyroid groups, on a number of cognitive and affective measures. However, there was also a significant improvement on many of the test measures in the control group. For this reason it is difficult to determine the nature of the treatment related improvements, above those evident due to practice.

Following treatment for 6 months, the deficits observed in the SCH group at baseline had all normalised. The hippocampal-associated memory functions, as measured by the ROCF and the face-name task, both showed improvements by 6 months, with SCH patients performing at control levels. However, while the hypothyroid patients showed considerable improvements, they were still not performing at control levels on the hippocampal-associated tasks following 6 months of treatment (ROCF and face-name task). Nevertheless, it is important to interpret these results with caution as there were few group x task x session interactions, indicating that all groups improved across sessions regardless of treatment. An improvement in hippocampal functioning following treatment may be related to the improved performance on the DLPFC based tasks utilised in the study; as the WM deficits present in the hypothyroid group at baseline, were no longer evident. This would suggest that within 6 months of treatment, the hippocampus had recovered sufficiently to reverse the impairments seen in WM, through the reciprocal relationship between the PFC and the hippocampus. However, confirmation of this cannot be made given the fact that the present study only included measures of neuropsychological function. Further examination of this, using fMRI is required.

There are two conclusions that can be reached from these findings; the first is that there does appear to be some degree of improvement in cognitive deficits found in hypothyroidism following 6 months of treatment. Impairments that were evident at baseline are reduced, and some have disappeared, within 6 months, suggesting that the hippocampal-associated memory impairments related to hypothyroidism may recover functionally. The second conclusion that can be reached is that these findings offer some support for the opinion that hypothyroidism exists on a continuum; from normal thyroid function at one end, to subclinical function in the middle, and finally to overt hypothyroid

function. The differential rate at which the SCH and hypothyroid groups were impaired, coupled with the differences in their improvement at 6 months, and the evidence of deficits still present in the hypothyroid group following 6 months of treatment, suggest that these deficits do occur along a continuum. Nevertheless, the results found in the present study need to be replicated, and an interaction between the groups, task and session, is required to confirm this suggestion.

5.2.3 Specific Deficits Associated with Aging

Although the exact neural mechanisms that prompt cognitive aging across the lifespan are not fully appreciated, there is evidence to suggest that dysfunction of the hippocampal formation may be related to memory decline in older adults (Kessels et al., 2003). Given that this region of the brain plays an important role in the encoding of new information, associative encoding and recall of face-name pairs and picture-word pairs was investigated across the adult lifespan. In addition, considering that the frontal lobes also participate in the intentional encoding of information (Stebbins et al., 2002), PFC functioning was explored using the *n*-back WM task and the MTS task. The hypotheses stated that associative memory and WM abilities decrease at a differential rate with age, with deficits likely to appear in the 40's in associative memory, but later in WM. The first hypothesis was supported, there were significant deficits found with age, on measures of associative memory. In contrast, the results of the second hypothesis were somewhat contradictory; while there were no deficits on the MTS-WM task across the age-groups, there were significant impairments found on the *n*-back WM task as early as the 40's.

There is considerable support from the results of the Chapter 4, for the presence of a specific encoding deficit present by the 40's (the fifth decade of life). There was a significant, increasing impairment in free recall on the both the face-name and picture-word tasks across the lifespan. These deficits first emerged in the 40's group, indicating that by their 40's people have a significant difficulty forming associations between items. In addition, there were also significant impairments in delayed recall on both tasks, and again this deficit emerged in the 40's. In contrast, there were no impairments on either face- or name-recognition in the 40's group, these deficits did not emerge until the sixth decade (50-64 group). Taken together, these finding suggest that by the fifth decade people will experience a significant difficulty with binding information together, resulting in impairment on measures of associative memory; conversely their memory for the individual items remains unimpaired, as reflected by the intact recognition abilities in the

40's. These findings are important as they demonstrate that both the associative- and working-memory deficits emerge by the 40's.

With regards to the PFC associated tasks, there were conflicting findings from this study. Despite the fact that there were no significant impairments on the WM, or on the delayed recognition component of the MTS task, there were significant differences on several measures of the *n*-back task across the age groups. Performance accuracy at the 1- and 2-back levels was significantly impaired with age; these deficits emerged by the 40's, which was contrary to what was expected. In addition, the switch cost (accuracy at the 2-back level minus accuracy at the 1-back level), was significantly different in the 40's group. RT also increased with age and across blocks; once more, these deficits emerged by the 40's, at the 0-, 1-, and 2-back levels. There were also significant differences in the RT switch cost; these emerged by the 40's. Two conclusions can be drawn from these findings. The first, that there is an increasing difficulty with high demand WM tasks across the lifespan; by the 40's significant differences emerge. Secondly, these results contribute to the growing literature which examines the capacity of focal attention (Van Gerven et al., 2008; Vaughan et al., 2008; Verhaeghen et al., 2005). Considering the findings of the present study, they lend support to the suggestion that there is a limit to people's focus of attention, and this limit is one item (Garavan, 1998). Though, this limit does appear to be age-dependent; by their 40's people have difficulty maintaining more than one item in their focus of attention, instead they have to switch between their focus of attention and items held in WM. This finding is unique to the present study as most previous studies have only used a young and old group, and were unable to determine when this difficulty emerged, but rather only that it did emerge with age.

To conclude, there are significant specific age-related deficits in associative- and working-memory; for the most part, these deficits appear by the 40's. Further examination of the role that MTL-PFC network dysfunction performs in these deficits is required.

5.3 Contribution to the Literature

There are several findings from these studies that contribute to the current literature. For example, the nature of the associative memory changes found in hypothyroidism, and the confirmation that these changes remain despite the presence of an effect of age; to the identification of the age at which people appear to become vulnerable to focal attention

switches. These findings contribute to both the associative and working memory literature, as well as to wider issues about the impact of age and depression on memory.

5.3.1 *Associative Memory and the Current Findings*

First and fore-most, a specific deficit in associative memory based tests was found in patients with hypothyroidism. There have been several studies that have attempted to identify the nature of the cognitive impairments associated with hypothyroidism. Samuels et al. (2008) reviewed several population-based studies that examined the effect of untreated hypothyroidism on mood and cognition. They reached three main conclusions; firstly, global cognitive impairment that affects several domains is not found in adult-onset hypothyroidism. The findings from the present study would support this conclusion. For the first time, it has been shown that there is a specific deficit associated with hypothyroidism on several measures of encoding abilities, including associative information, verbal information and encoding elements of a complex figure. Considering the link between the hippocampus and thyroid status, and the generally held view that an intact hippocampus is essential for encoding, one could conclude that thyroid dysfunction impacts encoding abilities in those with an underactive thyroid gland. In contrast, Samuels et al. (2008) also state that significant deficits in specific cognitive domains are not usual in studies of thyroid dysfunction. The findings from the current study do not support this conclusion; there are quite definite, specific and significant impairments on measures of MTL associated memory tasks. However, they conclude that there are subtle cognitive deficits that are specific to WM and executive functioning. While similar findings of deficits in WM were found in the current study, the suggestion has been put forward that these deficits are simply related to altered connectivity between the MTL and the PFC.

Examining at the involvement of the PFC in more detail; during encoding, some theories suggest that the PFC plays an essential role in guiding the spontaneous organisation of information throughout encoding and retrieval of memories (della Rocchetta et al., 1993). These "organisations" create the relationship between items during encoding, and in turn promote the memory for associations among the items (Blumenfeld et al., 2007). While the results of the present study do not make any attempt to rule out the role of the PFC in encoding, they do suggest that the encoding deficits found in hypothyroidism are not due to PFC dysfunction. There were no deficits found on measures of attention or executive functioning, other than accuracy on the *n*-back task, suggesting that the PFC was functioning at a normal or near-normal level in the hypothyroid patients. This is

concomitant with some of the current studies that reported no deficits on measures of executive functioning (Miller et al., 2006). Nevertheless, confirmation of this cannot be made without further investigation, especially given that our findings are not in agreement with those of Zhu et al. (Zhu et al., 2006), who found a significant impairment on WM in SCH patients, and no impairments on associative memory.

Encoding deficits were not limited to the hypothyroid study. There was a similar pattern of deficits found in both the thyroid and lifespan study, though the investigation of the nature of associative memory was more in depth in the lifespan study. Several researchers have reported that as people age they demonstrate an affinity towards encoding information in a more general way, rather than the detailed manner seen in young adults (Erngrund et al., 1996). This concept could offer some insight into the age-related impairments found in the healthy lifespan study. There was a considerable deficit found in associative memory across the age groups; for the first time we show this deficit emerged in the 40's and was exclusively related to encoding problems. Considering that the 40's group had no deficits in face or name recognition, and no deficits on free recall of the names, there appears to be no impairment in this group with retrieval of the individual items; the difficulty lies with the association of information between the items. These results strengthen those found by Naveh-Benjamin et al. (2004) who found that older adults had a specific deficit in memory for associative information. Unlike our study, they did not examine this effect across the lifespan; instead they compared a young and old group, making it difficult to identify at which point in the lifespan this deficit develops. The inclusion of so many age groups is one of the novel strengths of the current study.

Considering that there is an impact of thyroid status on cognitive functioning, and given our findings that age also impacts cognitive functioning, we examined the impact of age on the cognitive deficits found in hypothyroid patients. Previous studies have investigated the impact of thyroid status on cognitive functioning in healthy older adults; while some found no relationship between thyroid hormones and cognition in older adults (Fonda et al., 2005), others found that there was a relationship between TSH levels and episodic memory (Wahlin et al., 1998). Interestingly though, Whalin et al. (1998) found that this relationship between TSH levels and episodic memory was independent of age. The findings from the current study support those of Whalin et al.; while there was a significant impact of age on cognitive functioning in the face-name, ROCF and *n*-back tasks, there was no significant interaction between age and group on any of these measures. This would indicate that the

hypothyroid-induced memory impairments were independent of age. These findings have not been previously reported across the range of years included in the present study.

5.3.2 *Working Memory and the Current Findings*

Deficits observed in WM were only evident in the untreated hypothyroid patients and do not support those found by earlier studies (Samuels et al., 2007b; Zhu et al., 2006). While Zhu et al. (2006) reported that untreated SCH patients had abnormal functioning in the frontal lobes which was related to impaired WM, the current study did not find significant impairments in the SCH group. However, there were several differences between the present study and that conducted by Zhu et al. There were only 11 SCH patients at baseline, and only 6 completed the 6 month follow-up MRI scan; the nature of the task design was different, in the Zhu et al. study there were only 10 numbers in each block, and the subjects had to respond with their hands to indicate which number was 1- or 2-back allowing no measurement of reaction time using a serial response box. Nevertheless, it is interesting that while Zhu et al. (2006) found significant impairments in the SCH group, the hypothyroid group performed significantly worse at the 2-back level than all of the groups; again this offers some support to the idea that hypothyroidism exists on a continuum.

Ranganath and D'Esposito (2001) suggest that regions within the MTL play differential roles in memory; they found that the hippocampus was activated after a delay period during a WM task, while the parahippocampal gyrus exhibited short-lived activation during encoding and retrieval trials of WM and LTM. Additionally, they propose that the hippocampal 'binding processes' that aid encoding and retrieval, also support the active maintenance of novel information; offering additional support for the role of the MTL in WM. Considering these findings, the WM deficits found in the present study could be related to hippocampal associated changes as a result of hypothyroism, and not hypothyroid-related frontal lobe dysfunction.

Furthermore, the results from the analysis of attention and executive function in the hypothyroid groups from the current study, offers support to earlier studies that also reported no deficits on measures of executive function. Jorde et al. (2006) found that there was no significant impairment found in hypothyroid patients on measures of attention, sustained attention and executive function. Taken together, all of these results suggest that hypothyroid-related memory impairments are primarily MTL based. While deficits were

found in WM these may be related to the reduced connections between the MTL and PFC in hypothyroidism, consequently these deficits should disappear with thyroid hormone replacement therapy. However, confirmation of this would require extensive fMRI and connectivity studies in the future.

Very few studies have examined WM deficits across the lifespan; instead there is an inclination to compare a young and old group. However, in the present study, WM was examined across a wide age range, allowing identification of when the deficits first appear. Based on the findings from the pilot data, the hypothesis predicted that there would be no deficits in WM until later in life. This hypothesis is not in agreement with some of the current literature, which reports that there are considerable impairments on several measure of WM across the lifespan (Dobbs et al., 1989; Economou et al., 2006; Missonnier et al., 2004). Contradictory findings emerged from the present study that both support and oppose the existing literature. There were no significant differences discovered in the MTS task, which is contrary to previous studies (see Resnick et al., 2007); however there were significant differences found across the lifespan on the *n*-back WM task; we reported age-related decreases in accuracy emerging at the 40's. Dobbs et al. (1989) reported that there was a significant effect of load across the age groups. Similar to the current studies, they included a wide range of age groups; they examined these effects in people between 30 and 70+, and found an age-related decrease in the mean number of digits that participants recalled before committing an error. They reported that significant deficits appeared in the 60's. An equivalent decrease in performance accuracy was seen across the lifespan in the present study; however we reported that this deficit emerged as early as the 40's.

Our findings also strengthen more recent studies that have examined the limits of focal attention using the *n*-back WM task. Van Gerven et al. (2007) examined the capacity of focal attention, the part of WM that is currently being processed, by focusing on the switch cost between the 1- and 2-back levels. In their 2007 study, they reported that there was a reduced ability to switch between a 1 and 2 item lag, and that this deficit was detectable by middle age (50-60 years). However, they reported that these deficits could not control for the increased memory load; as a result they investigated the effect of memory load in more detail. By manipulating the 1-back task (single-digit vs. two-digits), Van Gerven et al. (2008) concluded that the switching of focal attention accounted for the disproportionate accuracy decrements in older adults, and not memory load. Although, the current studies did not manipulate the 1-back condition, they did find a significant age-related decrease in

focus switching, in both accuracy and RT, suggesting that there are age-related sacrifices in response speed and accuracy in WM tasks, and that these emerge in the 40's.

5.3.3 Other Contributions

There are several other implications of the current findings, from both the thyroid and lifespan study. Firstly, findings from the investigation into the effects of hypothyroidism on cognition offers further support for two key proposals; that hypothyroidism exists on a continuum and that there is some treatment-related functional recovery evident within 6 months (though the present findings need to be interpreted with caution). Samuels (1998) considers SCH to be a stage in the development of hypothyroidism; with that in mind, she argues the case for the treatment of SCH in order to prevent this progression, though offers little in the way of cognitive experimental evidence. In line with her conclusion, the present study goes further to offer evidence of a significant impairment in memory in patients with SCH, though the deficits are more marked in those with hypothyroidism. Inferring from the current findings, that the magnitude of thyroid dysfunction directly impacts the degree of cognitive deficits found; it would appear that the greater the thyroid dysfunction the greater the impairments on measures of associative-, and possibly working-memory. These findings support those from previous studies that consider thyroid function to exist along a continuum, from healthy, to subclinical, and finally to hypothyroid (Gharib et al., 2005).

Consequently, this offers support for the view that thyroid dysfunction should be treated, even in those with SCH (Gharib et al., 2005; Owen et al., 2003). Particularly given the findings that not only do the deficits in cognitive abilities discontinue, but that there appears to be some functional recovery of these abilities within 6 months for SCH. While there were still deficits evident in the hypothyroid group at the 6 month follow-up, these had improved from baseline. Nevertheless, there were also improvements evident on many of the memory measures used in the control group, suggesting that there is also a practice effect at play. It is difficult to determine why this is the case as different versions of almost all of the tests were used at every session, and there was 3 months between each session.

The relationship between thyroid hormones, depression, and anxiety has often been debated, but the current findings offer further insight into this relationship. There is a considerable lack of cohesion in the current literature; some studies report that there is no association between thyroid hormone dysfunction and affective measures (Aslan et al.,

2005; Jorde et al., 2006), and others found a relationship between TSH increases and mood decreases (Bono et al., 2004) though Kong et al. report a worsening in anxiety scores following treatment for hypothyroidism (2002). Though there is considerable debate in the literature, the present results offer support for the occurrence of depression and anxiety in patients with hypothyroidism. Anxiety scores were significantly higher in those with SCH and hypothyroidism, in comparison to control subjects, though they were more marked in the hypothyroid group. In contrast, depression was only significantly higher in the hypothyroid group. Once again, it would appear that the magnitude of thyroid dysfunction is related to the presence of depression and anxiety, especially considering the positive relationship that was found between increased TSH levels and increased depression and anxiety scores in the present study.

Results from the present study also offer considerable insight into the impact of IQ on memory abilities, in both a diseased and healthy aging population. There is considerable evidence in the literature to support the relationship between development of congenital hypothyroidism and decreased IQ scores (Kempers et al., 2006), however the relationship is not so clear in adult onset hypothyroidism, especially given the lack of studies that include a measure of IQ. Samuels et al. (2007a) found no differences between a hypothyroid and control group on measures of general intelligence. While there was a significant difference between the groups on IQ in the thyroid study, the control group and the subclinical group had significantly higher IQ scores than the hypothyroid group, the mean for all groups was above the general population mean (100) (Nelson et al., 1991). The subsequent IQ-matched group analysis confirmed that most hypothyroid-associated impairments were still present following control of IQ differences. Accordingly, careful consideration was taken in the aging study to match participants based on their predicted IQ scores on the NART. While there were no significant differences between the age groups on IQ scores, an examination of associative- and working-memory deficits found that there was a relationship between IQ scores and associative- and working-memory. However, the deficits between the age groups remained above the impact of IQ on both associative and working memory tests. These findings lend weight to the current literature; age-related impairments in associative and working memory are not solely due to the influence of IQ on test performance.

On the whole, the results from the lifespan study identify the point at which deficits in associative- and working-memory appear. While many studies have confirmed the

presence of these deficits, few studies have been able to pinpoint when they first emerge. In addition, the results confirmed that there is a specific deficit in memory in hypothyroidism and aging; the memory impairments discovered in both studies are not due to a general slowing of cognition, but rather a more specific, hippocampal-PFC based impairment in associative and working memory.

5.4 Outstanding Methodological Issues and Future Directions

5.4.1 Hypothyroid Studies

While every care was taken to avoid any methodological problems there are some points that should be addressed. Recruitment in the hypothyroid study took place over 2.5 years in an out-patient endocrine clinic; nevertheless, it was entirely reliant upon the detection of patients with newly developed SCH and overt hypothyroidism that had not been put on any thyroid hormone replacement treatment. As many of the referrals to the clinic came from G.P.s working in the local community, there was a considerable amount of new patients referred to the clinic that had already been put on thyroid replacement medication. As a result the number of patients in each group was unequal. In addition, the number of patients that completed the follow-up session was smaller than expected; there was great difficulty getting patients to return to follow-up sessions and a planned third follow-up session at 12 months could not be included in the present analysis due to an insufficiency in the numbers who completed all four sessions. Given that patients were tested at 6 months following treatment, a full reversal of the hippocampal-based memory deficits in the hypothyroid group may be evident at a later time point. Future studies should include an additional follow-up session at 9 and 12 months post-treatment; this may be enough time to observe a complete functional recovery in the hypothyroid patients that is already present in the SCH patients by 6 months. It would also lend further weight to the concept the hypothyroidism exists on a continuum, and would allow further exploration of this idea.

A possible confounding effect in the blood test results is that the range of TSH values reported in the present study was fairly broad. Some studies have restricted the range of TSH levels to ensure that there is less variation in the data, for example Samuels et al. (2007b) restricted the inclusion of SCH patients to those with TSH above 10 mU/l, while we include SCH patients with TSH between 4.18 – 15.80 mU/l. However, they recognise that such a restriction may limit the results as those with mild SCH are not included. In the

present study, follow-up blood tests results were only included in the control group at the 12 month time-point to confirm that they were still euthyroid. In hindsight, this was not ideal as the drop-out rate resulted in this session being excluded from the analysis; future studies should also measure the control participant's thyroid hormones at each testing session. Though it is important to note, that all blood tests were done on the day of testing, or within a few days of testing; as a result they do give an accurate reflection of the thyroid function at testing.

The nature of the recruitment for hypothyroid patients meant that there was the possibility of a sampling bias. Subjects were only recruited from one out-patient clinic in a Dublin-based hospital. There was an attempt to recruit from another Dublin-based hospital during the study, but the lack of resources available there meant that it was not feasible; however, in the future it would be beneficial to extend the recruitment processes to other hospitals within the city to reduce the possibility of a sampling bias. In addition, the nature of hypothyroidism is such that it is more prevalent in women than men (Hollowell et al., 2002); as a result the participants included in the present study were predominantly female. Nevertheless, this was not a conscious effort to exclude men from the study; it was merely that fewer men were diagnosed during the recruitment time-frame.

There are ethical issues to consider in with-holding treatment from patients, and while there may be a placebo effect found, this may not be significant enough to reduce the risks associated with not treating the disease. Accordingly, a placebo intervention was not included in the present study, though Cooper et al. (1984) found that symptoms related to SCH improved in 8/14 patients treated with thyroid replacement therapy and in only 3/12 SCH patients treated with a placebo.

While several aspects of associative and working memory were examined in the hypothyroid study, including free and delayed recall and recognition, there was no inclusion of measures of temporal order in the present study. Temporal order memory assessment includes examining when, where and how things happened, and has been shown to be reliant upon the frontal lobes (Cabeza et al., 2000). As a result, Cabeza et al. suggest that that context memory is particularly sensitive to aging. Considering that prevalence of hypothyroidism increases with age (Cooper, 2004), and differential activation patterns have been found within the frontal lobes in patients with SCH (Zhu et al., 2006), it would be interesting to include an assessment of temporal order memory in

future studies of hypothyroidism. Especially considering there were no human studies reported in the current literature that examined the possibility of deficits in temporal order memory in hypothyroidism.

The findings from the present study support the presence of deficits in MTL associated memory in hypothyroidism; nevertheless, these finding were based on neuropsychological measures and do not include an MRI examination of hippocampal and frontal activity during encoding and retrieval of associative- and working-memory tasks. There are few imaging studies that have examined the direct impact of hypothyroidism on the brain, the small number of studies that have been conducted used single photon emission computed tomography (SPECT) (see Krausz et al., 2007; 2004) or (PET) (Constant et al., 2001). Despite the shortage of studies, the results have indicated that hypothyroidism is associated with changes in cerebral metabolism, with a possible localisation to the frontal systems (Davis et al., 2007); these findings are consistent with several neuropsychological studies showing significant thyroid-induced impairments in executive functioning (Zhu et al., 2006). Taken together, the literature presented here highlights the role of the hippocampus and the PFC in the encoding of information in hypothyroidism; however, confirmation of this is required in future fMRI studies. In addition, while there is a degree of functional recovery in hypothyroidism in the present study, it would be extremely beneficial to determine if there is a corresponding change in functional activity; a "neural recovery" in hypothyroidism may be possible.

5.4.2 Lifespan Study

There are few studies in the literature that have included age-groups from across the adult lifespan; while the current study limits the age range to 18-64 years, excluding the oldest of the old, it does include all ages within that range, allowing comparisons to be made across adulthood, and also allowing the identification of the point at which impairments first appear. Though, this study was cross-sectional in nature; as a result it only allows predictions to be made as to the nature of age-related declines. Without the inclusion of longitudinal studies, such a prediction cannot be confirmed.

There was also some concern about the faces used in the present studies, and the relationship with age. Face-name encoding and recall was the main test of associative memory, and while there were age- and disease-related deficits in associative memory found, the faces used were only young faces, taken from a college yearbook and

undergraduate photo bank. No older faces were included in the task, which meant that no comparisons could be made between age group of participants and age group of stimuli. However, previous studies have found that older adults are as accurate in the recognition of young faces, than in the recognition of old faces (Backman, 1991; Bartlett et al., 1991), which supports the use of only young faces in the current study.

An interesting addition to the current study would be an intervention study to determine if training strategies attenuate memory deficits found with aging. Strategies that improve processing speed or provide additional processing resources might reduce age-related impairments. Verhaeghen et al. (1992) examined the effectiveness of memory training for elderly participants in a meta-analysis of pre-to-post test gains on episodic memory tasks in healthy subjects aged 60 or above. Gains were significantly larger in training groups, than in both control and placebo groups, suggesting that older adults may benefit from training to improve their memory. Considering that thyroid hormone levels change with age, and that there is an increased prevalence of hypothyroidism with age (van Boxtel et al., 2004), it would have been extremely beneficial to include an analysis of thyroid hormone function in the lifespan study. However, due to the fact that many of there participants were tested in the evening and at weekends, there was insufficient access to the services required to include these measures.

Considerable support was found in the present study for the limit of one item in the focus of attention; however the n-back task in both the thyroid and lifespan study did not include a memory load beyond 2 items back. Findings from a study by McElree (2001), that used up to three items back, support those from the present study; that focus of attention can only hold one item. While a study that included up to five items back also reached the a similar conclusion (Verhaeghen et al., 2005).

While the present study has offered more insight into the cognitive psychology of aging, it does not offer direct support for the neuroscience of aging. Bridging the gap between these two areas can be resolved by examining the links between cognitive and cerebral aging. While the findings from the current study do not extend to examining hippocampal activations, there was evidence of age-related impairments in free recall, and somewhat so in recognition in associative memory. It would be of huge benefit to extend these findings to the MRI scanner, and determine what activity patterns are seen in the hippocampus. While few published studies have allow the specific comparison of correctly recalled

encoding events, those that have reported that hippocampal activity was correlated with subsequent associative memory performance (see Davachi, 2006).

SM paradigms have been used to determine if hippocampal functioning also supports later recall and item recognition. As previously reported, hippocampal activation correlated with later recall in a SM paradigm, but if there was also a relationship between hippocampal activation and recognition then this would support the idea that there is a single general encoding process (Davachi, 2006). Davachi found that hippocampal activity was not related to items that were later recognised. Though activity in the PrC was related to later item recognition and not associative memory (Ranganath et al., 2004; Sperling et al., 2003). Davachi suggests that these findings strengthen the idea that there are separate encoding processes at work; while the PrC supports encoding of individual features of an item, the hippocampus supports the associative binding between the individual features (2006). However, she does suggest that it might be more beneficial to examine the different forms of representations within the regions of the MTL, and how these regions are involved in associative memory formation.

Investigating the coordination between the MTL and the PFC during encoding and retrieval, through the use of SM paradigms, might offer support for the proposed relationship between decreased activity in these regions that have emerged from the current literature. Neuroimaging studies have indicated that the DLPFC is involved in this organisation (Blumenfeld et al., 2006), especially during "manipulation" tasks, such as the *n*-back, that require information to be sequenced during active maintenance in WM. However, there is a lot of debate as to whether the DLPFC is involved in LTM encoding. Considerably more studies report the involvement of the VLPFC in LTM encoding (Blumenfeld et al., 2007); however, most of the studies have used recognition and not actual recall as a means of calculating the subsequent memory performance. If the DLPFC works by strengthening the relationship between items, then recognition tasks, rather than retrieval tasks, might mask the role of the DLPFC in LTM encoding. Blumenfeld and Ranganath (2006) found that DLPFC activation supports LTM formation by creating these associations between items during their organisation; functional connectivity analyses found that there was increased activity between the DLPFC and regions that represent the items that are to be organised.

Future studies should identify if there are age-related changes not only in functional activity but also in structural MRI scans. Good et al. found specific evidence for structural grey matter changes in the brain with aging (2001). These changes were both global, and more specifically at the regional level; they found accelerated loss in the parietal lobes, pre- and post-central gyri, insula and the anterior cingulated. Interestingly, they found relative preservation in the many regions of the MTL, which was in accordance to that found by Raz et al. (Raz et al., 1998). These investigations might offer some insight into the natures of the relationship between the MTL and the PFC both during aging and in disease.

5.5 Model to Explain Findings

The hippocampus and surrounding MTL regions are critical for episodic memory, with the hippocampus being particularly important in associative learning (Davachi et al., 2002). Considering that associative memory impairments are evident in both the hypothyroid study and the lifespan study, there may be a change in or down regulation of activity within the MTL that affects memory function. Additionally, the nature of the reciprocal relationship between the MTL and the PFC suggests that damage to one region may be related to a change in neural activity in the other. While confirmation of this requires further studies using MRI, a proposed model will be presented that might elucidate to the underlying mechanisms of action that leads to decreased cognitive functioning in both aging and hypothyroidism.

5.5.1 Braver Model of Cognitive Control

As mentioned in Chapter 1, a model of WM has been proposed by Braver et al. (2007), which attempts to specify essential WM components in terms of underlying neurobiologically based computational mechanisms of cognitive control. Shown again in Figure 5.1, this framework outlines the relationship between the interconnected regions involved in WM. The PFC enables the representation and active maintenance of context information; these are representations that are important in situations where there is strong competition for response selection e.g. the Stroop- or *n*-back-task. In situations when the same context must be repeatedly accessed, this must occur through full reactivation of the information each time it is needed. As a result, there is interdependency between the PFC and the MTL for successful task performance. Locke et al. (2008) propose that cognitive control subserves both mnemonic and control functions. This is one of the main differences from the classical Baddeley model (2000) which separates representations of storage and retrieval.

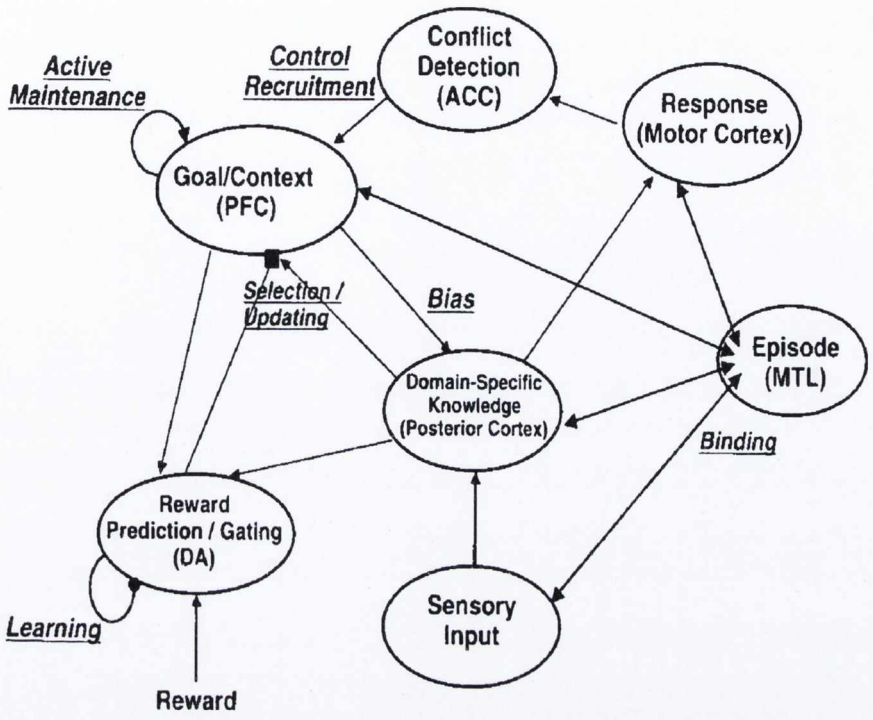

Figure 5.1 Brave et al (2007) model of dual mechanisms of cognitive control. The lines with single arrowheads reflect excitatory interconnections between the regions, while the encoding and retrieval of traces via episodic memory are shown by the lines with double arrowheads. The line that ends in a square reflects the ability of dopaminergic (DA) projections to adjust gate inputs into the PFC.

The active maintenance of context within the PFC occurs via local recurrent connectivity, the DA system is postulated to regulate this active maintenance by gating the entrance of information into the PFC. DA also plays a role in learning, as the DA system can self-organise to develop the appropriate timing of gating signals, this in turn enables the appropriate updating and maintenance of relevant context representations. According to Braver et al. (2007) the timing of gating signals is learned through a reward prediction learning mechanism associated with the midbrain DA system, which enables selection of task-relevant information as context, due the association of that information with the potential for future reinforcement (e.g., being able to recall someone's name in a social situation).

While their model focuses on a WM task, which they use to test the computational mechanisms proposed, it has not thus far been used to examine associative memory. However, they do state that there are reciprocal relationships between the PFC, which is primarily involved in WM, and the MTL, which is primarily involved in associative

memory. In addition, as discussed previously, there has been extensive evidence in the literature to support the role of the PFC in episodic memory, and the MTL in WM (see Chapter 1, Section 1.6). This strengthens the idea that this model could be used to explore the nature of the relationship between these two regions in other types of memory, and the impact that damage in one region (due to age or disease), may have on cognitive function of the other. In addition, it provides a possible neurotransmitter system through which memory functioning may be altered – DA.

There is extensive evidence to suggest that DAergic changes play a role in cognitive decline associated with aging - the cognitive triad model (Backman et al., 2000; Fischer et al., 2010; Morcom et al., 2010). Backman et al. (2000) reported that episodic memory was strongly related to D2 binding, and suggested that this may signify a functional influence of DA through the parallel cortical-striatal-pallidal-thalamic circuits in the brain. Using a spatial WM task, Fischer et al (2010) reported that there was a load-dependent WM effect in PFC regions, along with age-related reductions in BOLD activity within the same regions. They suggest that reductions in DAergic neurotransmission produces decreased neural efficiency. Further support for this idea comes from their findings that younger adult who were given a DA antagonist had reduced accuracy on the WM task, along with reduced load-dependent activation of the PFC. Moreover, Morcom et al. (2010) extend this idea to identify a link between DA, episodic memory networks and aging using a SM paradigm. While they found no behavioural differences during encoding, they did report age- and DA drug-related effects on brain activity in the PFC and MTL during episodic encoding.

The effects of DA in hypothyroidism are less well known, in fact there few studies that have looked at the impact of DA on thyroid function. However, those that do suggest that DA can suppress serum TSH levels (Haugen, 2009). It is through the hypothalamic-pituitary-axis, that DA exerts it effect, activating dopamine D2 receptors. As DA plays a central role in the model proposed by Braver et al., it would be interesting to determine whether there are alterations to the DA system in hypothyroidism, the extent to which this might impact cognitive functioning, and subsequent changes in DA following treatment for hypothyroidism.

Taken collectively, the model of cognitive control, and the role of DA in the model, may offer a model within which to investigate the influence of age- and disease-related changes

on PFC and MTL functioning. While the current results do not offer conclusive support for this, future MRI studies could tie up the findings from the present study, and the proposed model to account for these differences. By examining fMRI data, and conducting psychophysiological interactions (PPI) between activity in the PFC and MTL during either the *n*-back task or the face-name task, further support could be gained for this model. This is discussed further below.

5.5.2 Examining the relationship between the PFC and MTL

A common generalisation that has emerged from the data is that "stronger associative binding relies more heavily on hippocampal processing and on neocortical-hippocampal functioning" (Guo et al., 2005, p. 163). If this is the case, and hippocampal functioning is decreased due to age, disease, or both, then neocortical-hippocampal connectivity could also be reduced. In a previous study that investigated age-related memory decline between young and old adults, Small et al. (2002, p. 293) found "direct evidence that hippocampal function declines with age, and that diminished hippocampal function—reflecting cell number or cell physiology— underlies age-related memory decline". In addition, as the subregions of the hippocampus are interconnected, this in turn means that the hippocampus functions as a circuit – accordingly, damage to any subregion will disrupt global hippocampal function (Small et al., 2002). Furthermore, studies that have explored the affect of hypothyroidism on the MTL reported that thyroid hormone knockout mice had dysfunctional hippocampal circuitry, and proposed that thyroid hormones are involved in hippocampal structure and function (Bauer et al., 2008). Accordingly, the decline in memory associated with normal aging or hypothyroidism may be due to alterations in the synaptic connectivity between the MTL and the neocortex. In turn this may lead to both associative and working memory deficits, though the neurotransmitter system/systems involved in these deficits is not clear.

An interesting method for examining the relationship between BOLD activity in various regions is PPI. This method attempts to explain responses, in one neuronal area, in terms of an interaction between the influence of another area and some experimental (sensory or task-related) parameter (Friston et al., 1997). These interactions can be based solely on experimental factors (i.e., psychological interactions – face-name recall), or they can be based on interactions among neurophysiological measurements (i.e., physiological interactions – TSH levels). Friston et al. note that "the degree to which the activity in one area can be predicted, on the basis of activity in another, corresponds to the contribution of

the second to the first, where this contribution can be related to effective connectivity" (1997, p. 218). By examining the interaction between regions, it allows us to determine how this relationship changes with the experimental or psychological context. This method could offer significant support for the Braver et al. model of cognitive control, as it would allow for the direct examination of activity in one region (e.g. PFC), and how it is influenced by activity in another region (e.g. MTL), during an experimental task (*n*-back task performance). It would also offer the opportunity to determine if the nature of this relationship changes with age or disease.

5.5.3 Predictions

Firstly, focusing on the face-name task, using PPI, we could look at the relationship between hippocampal activation and activity within the PFC during encoding of face-name pairs. Perhaps the strength of the correlation between the areas will reflect the increase in the number of face-name pairs encoded? Previous literature has suggested that there is a dissociation of activity within the MTL during associative memory (Small et al., 2002), therefore focusing on regions that have been shown to be involved in encoding processes is necessary. Regions that have shown SM effects for associative information include the anterior hippocampus and the entorhinal cortex; activity in these regions predicted later recall, especially during the encoding stages. As such, the nature of hippocampal activity should change with increased encoding, as associative information moves from being more MTL based to more PFC based. Comparing the interactions between these regions using PPI, during encoding and later recall, would allow direct investigation of this claim. Perhaps the change in the nature of the relationship between the MTL and PFC will be reflected in changes of the PPI correlations?

Secondly, the investigation of the reverse relationship, from the PFC to the MTL, during associative- and working memory may also lend weight to the present results. It was hypothesised that the WM deficits found in hypothyroidism were due largely to the influence of "faulty" hippocampal connectivity. However, the examination of the reverse must also be conducted in order to confirm this hypothesis. It is possible that deficits in the PFC functioning might mediate deficits found on MTL functioning, in turn impacting associative- and working-memory performance. This might be especially true for age-related deficits found on both WM and associative memory, especially considering that there is significant support for the decline of the PFC with aging (Cabeza, 2002; Naveh-Benjamin et al., 2007; Naveh-Benjamin et al., 2004). These studies have reported

decreased activity in the LPFC during encoding, and increased activity in the LPFC during retrieval for older adults. It could be that there is less communication between the PFC and MTL during encoding with aging, and as a result, the older adults are more reliant on this reported increase in PFC activity during retrieval in order to perform the task. An examination of the current face-name- and *n*-back-task using fMRI and PPI could offer confirmation of many of the suggestions offered throughout this study.

While thyroid hormones are not involved directly in PFC functioning, they may affect frontal activity through the relationship between the MTL and the PFC. The data presented in the current studies proposes that during hypothyroidism, hippocampal functioning is decreased, but PFC functions at normal, or near normal levels. However, when communication between the two regions is required, for example during encoding, then there may be a decrease in activity found in both the MTL and the PFC. Consequently, decreased cognitive functioning may be evident, with significant impairments found in both PFC based memory tasks and MTL based memory tasks, though the deficits are likely to be more marked in MTL based tasks. Correlational analysis, such as that offered by PPI, would allow direct comparison of activity within these regions in people with altered TSH levels. This would permit the examination of the influence of the thyroid hormones on PFC and MTL functioning.

There is no confirmation in the present study for the proposed relationship between DA, thyroid hormones, and aging, though the studies discussed do offer some support for this relationship. Future examination of this relationship might be possible; combining neuroimaging with a pharmacological intervention might offer some insight into these mechanisms. It would involve the administration of a drug or respective placebo before volunteers undergo a cognitive task in PET or fMRI (Thiel, 2003). However, unlike in animal neuroimaging, human pharmacological challenges are always systemic; as a result they will affect every brain region containing the respective receptors. It is only by modulation of task-induced activity, that a pharmacological action can be localised. Morcom et al. (2010), discusses several studies that have already examined the effects of DAergic neurotransmission on memory. Combined, these studies support the potential for the use of DA pharmacological fMRI studies in age- and disease-related memory research.

fMRI studies examining the nature of the associative memory deficits found in hypothyroidism and aging have already commenced. Using newly diagnosed hypothyroid

patients and age-matched controls, it is hypothesised that differences in BOLD activity using fMRI will reflect the associative memory deficits found in hypothyroidism. In addition, using a young group (20's) and an older group (40's – as this is the point at which associative memory deficits occur and are solely related to faulty encoding processes), it is hypothesised that differences in patterns of BOLD activity will also reflect the behavioural associative memory deficits in the aging group. Additionally, we expect to see greater activation during encoding of faces-name pairs that are successfully recalled, than face-name pairs that are subsequently forgotten. Nevertheless, we expect to see differential patterns of activation in the hypothyroid and aged subjects, in comparison to control subjects; as it is hypothesised that hypothyroidism is a reversible model of some aspects of organic aging. Accordingly, while both the hypothyroid patients and the older adults may recruit the same regions, the rate at which, and degree to which they recruit them may differ. Although, follow-up scans in the hypothyroid subjects, should confirm whether there is 'neural recovery' of these deficits.

5.6 Final Thoughts

Taken together, the findings from the present studies suggest that there are specific, deficits found on measures of neurocognitive functioning in hypothyroidism and in aging; these deficits are primarily found in hippocampal- and PFC-based memory tasks. In aging, it was possible to identify the point at which these deficits first emerged. The deficits reported in hypothyroidism recovered somewhat with treatment, though whether a full reversal of impairments will be found remains unclear. Recovering function in aging remains a controversial issue. Exploring the mechanism through which aging and hypothyroidism exerts its effect on associative and working memory using MRI may hold the key to answering the many issues that still remain. However, "the hippocampus continues to fascinate, challenge, beguile, and frustrate those who seek to understand its 'role' in memory" (Tulving et al., 1997, p. 209).

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Appendix I:

Ethical Approval and Consent Forms

Hypothyroid Study

Patient Information and Consent

1. **Title of study:** Cognitive function in endocrine disorders.

2. **Introduction:** Patients with thyroid disorders, diabetes, excessive calcium in the blood, growth hormone deficiency and patients who are receiving cortisol treatment often notice difficulty concentrating or find they do not think as clearly as they used to. Recently developed tests have given us the opportunity to find out in more detail how these hormone disturbances influence the brain.

3. **Procedures:** Should you decide to take part, we would give you a brief set of memory questionnaires in the Institute of Neurosciences in Trinity College Dublin. Some subjects will also be asked to undergo a completely non-invasive brain scan. The scanning technique is called MRI (magnetic resonance imaging), and is painless, safe and lasts about 60 minutes. Importantly, MRI uses a magnetic field and there is no radiation involved. The scanning is also conducted in the Institute of Neurosciences in Trinity College Dublin. If you are taking part in the study because you have an underactive thyroid, we would ask you to repeat the tests 3 months after starting thyroid hormone replacement.

4. **Benefits:** The study will have no direct benefit to the individual participant but the results may benefit subsequent patients.

5. **Risks:** There are no risks associated with these tests.

6. **Exclusion from participation:** Your doctor has told you that you cannot be in this study if any of the following are true:
    1. You are less than 18 or more than 70 years old
    2. You are pregnant
    3. You have another illness that might influence results
    4. You are on other medications that might influence results

7. **Alternative treatment:** Taking part in this study will make no difference to the way in which you are treated.

8. **Confidentiality:** Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone who is not involved in the evaluation/investigation.

9. **Compensation:** Your doctors are covered by standard medical malpractice insurance. Nothing in this document restricts or curtails your rights.

10. **Voluntary Participation:** You have volunteered to participate in this study. You may quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits, which you had before entering the study.

11. **Stopping the study:** You understand that your doctor may stop your participation in the study at any time without your consent. However, you will be offered follow up in the clinics similar to other patients not in the study.

12. **Permission:** The trial has hospital Research Ethics Committee approval.

13. **Further 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

14. 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

Title of research study: Cognitive function in endocrine disorders

1) Cognitive Testing Consent:

This study and this consent form have been explained to me. My doctor has answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study.

I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this agreement.

PARTICIPANT'S NAME:

PARTICIPANT'S SIGNATURE:

Date:

Date on which the participant was first furnished with this form:

2) 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: _____

(Keep the original of this form in the participant's medical record, give one copy to the participant, keep one copy in the investigator's records, and send one copy to the sponsor (if there is a sponsor).

ETHICS LETTER

ETHICS LETTER

Lifespan Study

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 Dr Sinéad Mullally and I am a postdoctoral fellow 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. 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 total the whole experiment will last no more than 40 minutes.

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 (and those of the team working on this project) are listed below:

Many Thanks,

Sinéad Mullally (smullall@tcd.ie)

Sinéad Mullally
School of Psychology and TCIN,
Lloyd Building,
Trinity College,
Dublin 2.
Ph: (01) 896 8471

Statement of Consent:

I, _____ (block capitals), have read this and give my informed consent to participant in the experiment.

Signed: _____, Date: _____

ETHICS LETTER

Appendix II

ROCF Scoring Guidelines

NART Word List

Perceived Stress Scale

Self Rating Scale

Mundane Memory Questionnaire

Rey Complex Figure Test

Scoring Guidelines:

Correct –

Placed properly: - 2 points

Placed poorly: - 1 point

Distorted or incomplete but recognisable -

Placed properly: - 1 point

Placed poorly: - 1/2 point

Absent or not recognisable -

- 0 points

Details	Copy	Immediate	Delay
1. Cross upper left corner, outside of rectangle			
2. Large rectangle			
3. Diagonal cross			
4. Horizontal midline of 2			
5. Vertical midline			
6. Small rectangle, within 2 to the left			
7. Small segment above 6			
8. Four parallel lines within 2, upper left			
9. Triangle above 2 upper right			
10. Small vertical line within 2, below 9			
11. Circle with three dots within 2			
12. Five parallel lines with 2 crossing 3, lower right			
13. Sides of triangle attached to 2 on right			
14. Diamond attached to 13			
15. Vertical line within triangle 13 parallel to right vertical line of large triangle			
16. Horizontal line within 13, continuing 4 to right			
17. Cross attached to low centre			
18. Square attached to 2,lower centre			
TOTAL SCORE			

Recognition:

_____ True positives = Sum of items 2, 5, 7, 8, 9, 12, 13, 15, 19, 20, 22, 24 that were circled

_____ False Positives =Sum of items 1, 3, 4, 6, 10, 11, 14, 16, 17, 18, 21, 23 that were circled

_____ True negatives = 12 – False positives

_____ False Negatives = 12 – True Positives

_____ Total Correct = True Positives + True Negatives

National Adult Reading Test 2nd Edition

NART WORDS	
Ache	Simile
Debt	Aeon
Psalm	Cellist
Depot	Zealot
Chord	Abstemious
Bouquet	Gouge
Deny	Placebo
Capon	Façade
Heir	Aver
Aisle	Leviathan
Subtle	Chagrin
Nausea	Détente
Equivocal	Gauche
Naïve	Drachm
Thyme	Idyll
Courteous	Beatify
Gaoled	Banal
Procreate	Sidereal
Quadruped	Puerperal
Catacomb	Topiary
Superfluous	Demesne
Radix	Labile
Assignate	Phlegm
Gist	Syncope
Hiatus	Prelate

Perceived Stress Scale

Answer/Record Sheet

Initials: _____ **Date:** _____

Group: _____ **Testing session:** _____

Participant Number: [ ]

Score: [ ]

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate *how often* you felt or thought a certain way. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each question fairly quickly. That is, don't try to count up the number of times you felt a particular way, but rather indicate the alternative that seems like a reasonable estimate.

For each question chooses from the following:

0 = never
1 = almost never
2 = sometimes
3 = fairly often
4 = often

1. In the last month, how often have you been upset because of something that happened unexpectedly? _____

2. In the last month, how often have you felt that you were unable to control the important things in your life? _____

3. In the last month, how often have you felt nervous and "stressed"? _____

4. In the last month, how often have you dealt successfully with irritating life hassles? _____

5. In the last month, how often have you felt that you were effectively coping with important changes that were occurring in your life? _____

6. In the last month, how often have you felt confident about your ability to handle your personal problems? _____

7. In the last month, how often have you felt that things were going your way? _____

For each question chooses from the following:

0 = never
1 = almost never
2 = sometimes
3 = fairly often
4 = often

8. In the last month, how often have you found that you could not cope with all the things that you had to do? _____

9. In the last month, how often have you been able to control irritations in your life? _____

10. In the last month, how often have you felt that you were on top of things? _____

11. In the last month, how often have you been angered because of things that happened that were outside of your control? _____

12. In the last month, how often have you found yourself thinking about things that you have to accomplish? _____

13. In the last month, how often have you been able to control the way you spend you time? _____

14. In the last month, how often have you have you felt difficulties piling up so high that you could not overcome them? _____

SRS Scoring

Answer/Record Sheet

Initials: _____ **Date:** _____

Group: _____ **Testing session:** _____

Participant Number: [ ]

Score: [ ]

Having completed this questionnaire and survey, how would you rate your memory overall?

Excellent	Good	Neither Good nor Bad	Not so Good	Very Bad
5	4	3	2	1

Circle the response you feel is most appropriate.

MMQ
Answer/Record Sheet
Initials: _____ Date: _____ Group: _____ Testing session:_____

Participant Number: **Score:**

When answering the following questions, please only write your answer if you are certain that it is correct.
Please do not guess or try to make up an answer.
We are interested in how well you can remember everyday activities.

ACTIVITIES				
Do you recall getting dressed on this day? If so, what did you wear?	Yes No	Yes No	Yes No	Yes No
Do you recall going to work on this day? If so, how did you get there?	Yes No	Yes No	Yes No	Yes No

Do you recall what the weather was like on this day? **If so, describe how it was?**	Yes No	Yes No	Yes No	Yes No
Do you recall having a coffee break on this day? **If so, at what time?**	Yes No	Yes No	Yes No	Yes No
Do you recall receiving any letters on this day? **If so, how many did you receive?**	Yes No	Yes No	Yes No	Yes No
Do you recall meeting any friends on this day? If so, what were there names?	Yes No	Yes No	Yes No	Yes No
Do you recall eating lunch on this day? **If so, what did you eat and drink?**	Yes No	Yes No	Yes No	Yes No
Do you recall doing any shopping on this day? **If so, which shops did you visit?**	Yes No	Yes No	Yes No	Yes No

Do you recall doing any reading on this day? **If so, what did you read?**	Yes No	Yes No	Yes No	Yes No
Do you recall doing any work around the house on this day? If so, what work did you do?	Yes No	Yes No	Yes No	Yes No
Do you recall watching TV on the evening of this day? **If so, what did you watch?**	Yes No	Yes No	Yes No	Yes No
Do you recall making any phone calls on the evening of this day? **If so, how many calls did you make?**	Yes No	Yes No	Yes No	Yes No