Short- and Long-Term Memory: Effects of Ageing and Genetic Risk and Resilience to Alzheimer's Disease

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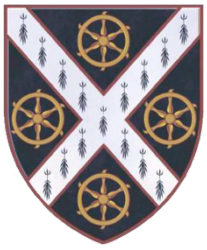
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Abstract

Healthy memory processes are essential for leading a normal life. In particular, this thesis will focus on short-term memory (STM) and long-term memory (LTM). STM is our ability to store limited amounts of information over short periods of time, while LTM refers to our capacity to retain near-unlimited amounts of information over prolonged periods of time. Traditionally, these two types of memory have been studied independently. As a result, our knowledge of the relationship between them has remained limited. In this thesis, I develop well-controlled tasks to compare STM and LTM for the same type of information, formed during equivalent encoding circumstances, and reported in similar ways. Results show that STM and LTM for the same type of information are indeed related. Furthermore, by studying both STM and LTM in cognitively healthy young, middle-aged and older adults, I show that the relationship between these two memory functions remains stable across normal ageing, suggesting some degree of overlap in the underlying neural mechanisms. I also attempt to characterise this relationship in individuals who are at an increased genetic risk of developing Alzheimer's disease, namely, carriers of the apolipoprotein E gene (APOE) ε4 allele, although limited sample size hinders the interpretation of findings. In Chapter 1 of this thesis, I review the literature that supports STM-LTM dichotomy, in addition to studies that suggest similarities between these memory functions. I also provide an overview of the effects of healthy ageing on STM and LTM, and how these memory functions change in the presence of different APOE alleles. In Chapters 2 and 3, I focus on healthy ageing and its effects on STM and LTM. In Chapter 2, these effects are studied in APOE ε2 carriers and non-carriers. In Chapter 3, I introduce two novel continuous-report tasks that enable analogous probing of both types of memory in order to measure the relationship between them. This task is employed in Chapter 4 to assess memory performance in middle-aged APOE ε4 carriers and non-carriers, with an aim to use similar tasks to characterise the effects of this allele on memory in the future. In Chapter 5, I discuss the implications of my findings and the areas in which this research could be extended and improved.

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Declarations

Data presented in Chapter 2 were partially collected while I was a research assistant in the Brain and Cognition Lab prior to starting my DPhil, and another research assistant also contributed to some data collection. I completed the recruitment of participants and data collection during the first year of my DPhil and analysed the data presented in Chapter 2.

The study described in Chapter 4 included a collaboration with Dr Claire Lancaster and Dr Chris Hinds, who developed ‘The Gallery Game’, used as one of the tasks in the study. Data from the game was initially stored on their servers, and I analysed pre-processed data based on the metrics computed through their standard pipeline.

Impact of Covid-19

As so many things over the past year, my research was adversely impacted by the pandemic. I was unable to carry out a study that had been designed, programmed, and ready for piloting. This study was planned to investigate the neural signatures of encoding and retrieval of short- and long-term memories.

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List of Abbreviations

ACE-III – Addenbrooke's Cognitive Examination-III

AD – Alzheimer's disease

apoE – apolipoprotein E

APOE – apolipoprotein E gene

APP – amyloid precursor protein

ATS, ATS_{Mod} – ANOVA-type statistic, modified ANOVA-type statistic

BBB – blood-brain barrier

BDI-II – Beck Depression Inventory-II

BOLD – blood oxygen level-dependent signal

CSF – cerebrospinal fluid

EEG – electroencephalography

fMRI – functional magnetic resonance imaging

GDS – Geriatric Depression Scale

LTM – long-term memory

MCI – mild cognitive impairment

MEG – magnetoencephalography

MMSE – Mini-Mental State Examination

MTL – medial temporal lobe

MRI – magnetic resonance imaging

PET – positron emission tomography

PFC – prefrontal cortex

RAVLT – Rey Auditory Verbal Learning Test

STM – short-term memory

Chapter 1. General Introduction

Healthy memory processes are the cognitive pillars of what we consider a normal life. They enable us not just merely to live in the flash of a moment but to perceive our existence as a continuous flow of time, from the present, reflecting on the past and anticipating the future. Of the many aspects of our lives that depend on memory are executive functions, such as the ability to plan our actions (Baddeley, 2003), and the concept of self (Tulving, 2002). Therefore, memory is what allows us to build our future based on past experiences.

This thesis will focus on short-term memory (STM) and long-term memory (LTM) functions. STM is our ability to store limited amounts of information over short periods of time (Atkinson & Shiffrin, 1968). It stitches our sensory experiences from one moment to the next in the rapidly changing world around us by maintaining sensory information that is no longer present in the environment. In addition, STM stores sensory as well as abstract information for mental manipulation. Although the two definitions are often used interchangeably (Aben et al., 2012), STM is the storage aspect of working memory, which also encompasses executive functions that enable mental manipulation (Baddeley, 1983). In contrast, LTM refers to our ability to store near-unlimited amounts of information over prolonged periods of time. In particular, this thesis will focus on episodic LTM (thereafter, LTM), or memory for temporally dated personal events (Tulving, 1972), which allows us to integrate our past and present experiences to optimise our behaviour, to have a concept of self and to imagine the future (Tulving, 2002).

1.1. The Basis for the STM-LTM Dichotomy

The idea that STM and LTM are two separate memory systems has been around since at least the end of the 19th century. For example, in the *Principles of Psychology*, James (1890) distinguished primary and secondary memory. While primary memory (STM),

according to James (1890), was an extension of the present that has not left conscious awareness, secondary memory, or memory proper (LTM), involved recollection of information that has been absent from consciousness.

In later years, the STM-LTM dichotomy was supported by other prominent theorists in the field, such as Atkinson and Shiffrin (1968) and Baddeley and Hitch (1974), although the exact relationship between STM and LTM differed between their models. For example, in the model described by Atkinson and Shiffrin (1968), maintenance of information in STM was required for the transfer of information to LTM. In contrast, Baddeley and Hitch (1974) suggested that it was the manipulation of information in working memory that was required for the formation of long-term memories.

An important piece of evidence to support the dichotomy came from early lesion studies, which showed that STM and LTM were dependent on different brain structures. Through careful neuropsychological assessment of patients, such as K.F. and H.M., it was shown that lesions to distinct brain areas can impair one type of memory while sparing the other (Milner et al., 1968; Scoville & Milner, 1957; Shallice & Warrington, 1970; Squire, 2009; Warrington & Shallice, 1969). For example, K.F., who was involved in a motorbike accident as a child in which he sustained an injury to his left parietal and occipital lobes, had an impaired verbal STM span, while his LTM seemed to be intact (Shallice & Warrington, 1970; Warrington & Shallice, 1969). In contrast, in the extensively studied case of H.M., who underwent an extreme surgery to remove a large part of his medial temporal lobe (MTL) bilaterally in an attempt to treat intractable epilepsy, STM was relatively spared with almost a complete inability to form new long-term memories (Milner et al., 1968; Scoville & Milner, 1957; Squire, 2009).

The emergence of neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), has highlighted the involvement

of different brain areas in STM and LTM. Namely, the prefrontal cortex (PFC), in addition to basal ganglia and other stimulus modality-dependent areas (e.g., parietal and occipital cortices in visual STM), was implicated in STM (e.g., Braver et al., 1997; Owen, 1999; Smith et al., 1995, 1996). In contrast, MTL structures were shown to be important for both encoding and retrieval of long-term memories (for a review of early studies, see Schacter & Wagner, 1999).

At the cellular level, single-unit recordings and developments in cell biology shed light on the differences in the neural mechanisms supporting STM and LTM storage. It was shown that neurons in the PFC of macaque monkeys fired continuously during the maintenance period of an oculomotor STM task, scaling with memory load (e.g., Funahashi et al., 1989). This suggested that short-term memories were maintained actively, by sustained firing of cells. In contrast, long-term potentiation, the stable and long-lasting strengthening of synapses, which was discovered in the dentate gyrus of the rabbit after short periods of conditioning (Bliss & Lømo, 1973), was suggested to be the mechanism for the storage of information in LTM (Morris, 2003; Nicoll, 2017; Teyler & DiScenna, 1987). It enabled passive long-lasting storage of information, without the need for sustained firing of neurons (notably, whether long-term potentiation alone is sufficient and necessary for LTM is still a topic under investigation, e.g., see Abraham et al., 2019).

There was also behavioural evidence to suggest that STM and LTM preferentially encoded different types of information. Verbal short-term memories, for example, have been shown to rely on acoustic features of verbal stimuli, with more ordering errors made when retrieving a list of words that were acoustically, as compared to semantically, similar (Baddeley, 1966a). In contrast, the success of long-term learning of word order in a similar study was impaired by the semantic similarity of words in the list, with no effect of acoustic

similarity (Baddeley, 1966b). This has led to the notion that long-term memories were inherently less detailed as compared to short-term memories (e.g., Biderman et al., 2019).

Altogether, the evidence available was interpreted to suggest that STM and LTM were two separate memory systems that were localised to different brain regions, employed different neural mechanisms and stored different types of information. This has led to the study of STM and LTM largely being carried out independently. However, the development of new, more specific and sensitive memory tasks, together with improved understanding of neuroimaging methods and data analysis techniques have modified this picture.

1.2. Similarities Between STM and LTM

More recent lesion studies have shown that damage to the MTL, and in particular the hippocampal formation, also affects STM (Olson, Moore, et al., 2006; Olson, Page, et al., 2006; Pertzov et al., 2013; Watson et al., 2013; Zokaei, Nour, et al., 2019), suggesting that the overlap between STM and LTM in the brain is greater than previously thought. The use of standard neuropsychological tests, which were not finetuned to functions of the MTL, may explain why impairments in STM after MTL damage were not detected in early studies. For example, STM impairments have been found to be particularly severe in MTL patients when associations between items and their features, or object-feature bindings, had to be remembered (Olson, Moore, et al., 2006; Olson, Page, et al., 2006; Pertzov et al., 2013; Watson et al., 2013; Zokaei, Nour, et al., 2019). In one study, patients with bilateral damage to the MTL, including the hippocampus, showed worse memory for object-location associations compared to controls after a memory delays of one and eight seconds (Olson, Page, et al., 2006). Participants' memory for these associations was tested by asking them to report if a probe item (a picture of a real-life object) had appeared in the probed square on a nine-square grid before the delay. In contrast, patients' performance was as good as that of

controls when only single features, namely, a location or an item identity, were probed (Olson, Page, et al., 2006). Furthermore, findings from several other studies, which used sensitive continuous-report instead of forced-choice measures, have supported these findings. These studies have shown that, in contrast to controls, hippocampal lesion patients, regardless of lesion aetiology and whether it was bilateral or unilateral, made disproportionately more mis-binding errors by placing probe items in locations of other items in the memory array seen before the delay in multi-item trials (Pertzov et al., 2013; Watson et al., 2013; Zokaei, Nour, et al., 2019). Mis-binding errors fully accounted for the increased magnitude of placement errors in patients compared to controls. In contrast, patients' location memory was as precise as that of controls, with a similar average distance from the original to the reported location, when only one item had to be remembered, especially after a short one-second delay (Pertzov et al., 2013; Zokaei, Nour, et al., 2019). This suggests that the MTL is involved in binding object identities and their locations in STM (Zokaei, Nour, et al., 2019). Although it has been suggested that these results may be explained by the special role of the hippocampus in spatial memory in general (Baddeley et al., 2010), one of the studies also found mis-binding errors when orientation of coloured bars was tested (Pertzov et al., 2013), suggesting a general role of the MTL in feature binding in STM.

Neuroimaging studies have also supported the involvement of the MTL in feature binding in STM. The increasing spatial resolution of MRI in particular was instrumental in mapping changes in blood oxygen level-dependent signal (BOLD) during short-term memory tasks to this brain area. For example, one group combined an elegant STM task with a multivoxel pattern similarity analysis to find that only voxels in the right hippocampus showed increased pattern similarity during the encoding and maintenance of object-position associations in correct as opposed to incorrect trials, suggesting that the hippocampus was involved in the successful encoding and maintenance of these associations (Libby et al.,

2014). In their task, participants were asked to learn and remember positions of four different everyday items on a nine-by-nine square grid over a delay period of 11 seconds. However, the probe that followed the delay contained a twist. In one third of trials, participants were simply shown a probe display that preserved the relationship between objects and their positions on the grid (a match probe). However, on the other two-thirds of trials, the probe display either contained a swap in positions between two of the items (a mismatch-swap probe) or a misplacement of one of the items by one position (a mismatch-position probe). In all three cases the probe display was rotated by 90 degrees from the original, and participants had to identify the probe type. Performance was therefore highly dependent on participants' knowledge of which item appeared in which exact position in the original display, ensuring that brain areas involved in the encoding and maintenance of object-position associations were challenged during the task (Libby et al., 2014).

In support for the findings of behavioural studies, it has been shown using fMRI that the hippocampus was also involved in the successful encoding of more complex associations between non-spatial stimuli. For example, in each trial of the study by Piekema et al. (2009), participants were asked to remember a memory array of three pairs of photographs presented consecutively on the screen. The pairs were a combination of two photographs of male faces or houses, or a face and a house. Following a jittered eight to 20-second delay, participants were presented with a memory probe, which contained either one of the original pairs that appeared before the delay or was a combination of two photographs from separate pairs. They had to indicate if the probe pair matched any of the pairs seen before the delay. Right hippocampal BOLD was elevated during the successful encoding of face-house pairs as compared to face-face or house-house pairs, suggesting that the hippocampus was involved in the successful encoding of between-domain information to STM (Piekema et al., 2009).

Accumulating evidence from neuroimaging studies suggests that the PFC, traditionally implicated in STM, the hippocampus and sensory areas may flexibly interact during encoding, storage and retrieval of short- and long-term memories. As discussed in section 1.1., even the early lesion and neuroimaging studies have implicated occipital and parietal areas in STM (e.g., E. E. Smith et al., 1996; Warrington & Shallice, 1969). Although to this date it remains controversial how exactly short-term memories are stored, there is a solid body of evidence to suggest that the maintenance of highly accurate visual STM representations relies on the interaction between the prefrontal and the occipital cortices, with PFC cells controlling these representations based on task demands and surround suppression in occipital cells supporting their granularity (for a review, see Serences, 2016). In addition, it has been suggested that sensory areas are activated not only during encoding but also during retrieval of long-term memories, and that the presence of visual distractors impairs LTM retrieval (Barsalou, 2008; Buckner & Koutstaal, 1998; Nyberg et al., 2000; Wais et al., 2010). However, to my knowledge, only one study has examined the involvement of sensory areas in the reinstatement of fine-grained visual LTM representations, which are routinely tested during STM tasks, to date (Bosch et al., 2014). Using multivoxel pattern analysis of fMRI data, the authors of this study have shown that representations of previously learned oriented visual gratings could be detected in early visual areas after corresponding tone cues, and that the activation in the hippocampus was associated with the strength of reactivation in the occipital cortex (Bosch et al., 2014). This suggests that the hippocampus is involved in the reinstatement of fine-grained visual representations in early visual areas during LTM retrieval. Finally, it has been shown in a number of studies that the interactions between the PFC and the hippocampal formation are crucial for coordinating the retrieval of context-appropriate information from LTM (for a review, see Eichenbaum, 2017), suggesting another similarity between STM and LTM.

Studies have also found more similarities between STM and LTM at the cellular level. Although, as discussed in section 1.1., persistent spiking in the PFC during the STM delay period has been considered the hallmark of STM maintenance (e.g., Curtis & D'Esposito, 2003; Luck, 2008), an increased understanding of neuroimaging techniques as well as cellular and molecular mechanisms underlying memory functions has shown that STM does not always involve spiking activity (for a review, see Masse et al., 2020). Some of the STM states are activity-silent (Stokes, 2015), which has been attributed to short-term synaptic plasticity arising from the build-up of calcium ions in presynaptic terminals (Mongillo et al., 2008; Zucker & Regehr, 2002). Such plasticity may last from several hundred milliseconds to several minutes (Zucker & Regehr, 2002) and does not require changes in synaptic proteins or gene expression characteristic to long-term plasticity (Bliim et al., 2016; Dudek & Fields, 1999). This suggests that the two types of memory do not necessarily utilise different types of brain mechanims. It may therefore be possible to view the two types of memory as a continuum, with short-term memories being strengthened to form long-term memories by additional molecular mechanisms.

Recent studies have shown that semantic information can also be incorporated into short-term memories, while long-term memories can be as precise in visual detail as short-term memories. For example, by combining intracranial electroencephalography (EEG) recordings, a model for semantic similarity and a deep neural network of visual object features, one group has found that both visual and semantic information was encoded into STM and maintained in a stable form during a seven-second delay period (J. Liu et al., 2020). Intracranial EEG was recorded while human participants were performing a delayed match-to-sample STM task with images of real-life objects as stimuli. Although semantic information of item identity was encoded after visual object features, both types of information contributed to the recordings during the delay period. This was interpreted by the

authors of the study as an integration of visual features and semantic knowledge about the item from LTM, which enabled the maintenance of stable representations in STM over time (J. Liu et al., 2020). There is also a long-standing assumption that LTM relies on semantic information as a result of which visual long-term memories lack detail (e.g., Biderman et al., 2019). However, a study that utilised continuous report tasks to investigate STM and LTM for colour of pictures of everyday objects found that with repeated exposure to stimuli, which, considering everyday life, is an ecologically valid approach, delayed reports of item colour on a continuous scale were as close to the original as short-term memories tested after a one-second memory delay (Miner et al., 2020). This suggests that, at least in certain contexts, visual features are also encoded with high fidelity to LTM.

The evidence discussed in this section suggests that STM and LTM are more similar than previously thought, and that many of the differences assumed by previous studies are at least partially a result of methodological limitations or task demands. On the other hand, there are still many differences between these two memory functions at both molecular and brain levels. One way to disentangle these differences is to study individuals who experience STM or LTM loss, such as during healthy and pathological ageing. In case of a significant overlap between these two memory functions, it is likely that both types of memory will be affected in tandem, with a preserved relationship between them across ageing. In contrast, if the mechanisms underlying STM and LTM are sufficiently independent, it is likely that the relationship between these two memory functions will eventually break down.

1.3. STM and LTM Decline in Normal Healthy Ageing

Both STM and LTM decline with normal healthy ageing. Verbal, location and pattern span have been shown to decrease with an increasing age of participants from 55 to 85 years cross-sectionally (Fournet et al., 2012). In addition, studies that utilised sensitive continuous-

report measures have shown that short-term memories of older adults are also less precise, with larger memory errors produced on analogue measures as compared to young adults (Peich et al., 2013; Pertzov et al., 2015; Zokaei, Grogan, et al., 2020). It remains controversial whether older adults, similarly to lesion patients discussed in section 1.2., also produce more mis-binding errors (Peich et al., 2013; Pertzov et al., 2015). However, a recent large cross-sectional study suggests that this may also be the case, although the incidence of mis-binding errors in healthy older adults is lower than that in patients (Zokaei, Grogan, et al., 2020). Similarly, LTM is also vulnerable to ageing. LTM has been shown to decline in older age both cross-sectionally (Henson et al., 2016; Nilsson et al., 1997; Rönnlund et al., 2005) and longitudinally (Gorbach et al., 2017; Rönnlund et al., 2005). Studies utilising sensitive continuous report measures have also shown lower memory resolution in older as compared to young adults (Korkki et al., 2020; Salvato, Patai, & Nobre, 2016). Similarly to STM, decline in LTM precision has been shown to be the major factor responsible for the increase in response errors with age (Korkki et al., 2020). Notably, although major theories attempting to explain age-related memory decline emphasise deficits in associative memory (e.g., T. Chen & Naveh-Benjamin, 2012; Naveh-Benjamin, 2000; Naveh-Benjamin & Mayr, 2018), results obtained using sensitive continuous report tasks have shown that memory of older adults declines in resolution even for single items (e.g., Zokaei et al., 2020), suggesting that multiple mechanisms may be behind age-related decline in STM and LTM.

Multiple age-related changes in brain structure and function have been associated with changes in memory at older age. Given the STM-LTM dichotomy, discussed in section 1.1, these changes have been studied mostly independently for the two memory functions. As discussed in section 1.2., both STM and LTM likely involve complex interactions between the PFC, the hippocampal formation and sensory areas. It might therefore be possible that

normal ageing alters the structure and function of these brain areas and functional relationship between them.

Most studies to date have focused on the neural mechanisms underlying what can be defined as working memory rather than STM decline with ageing. As a result, a number of studies have reported associations between age-related decreases in grey and white matter in the PFC and impaired cognitive control processes (e.g., inhibition of distracting information) during working memory tasks (for an overview, see Zanto & Gazzaley, 2019). Similarly, a decline in recruitment of the PFC compared to young adults, as measured using fMRI, during working memory tasks has been associated with reductions in performance at older age (for a recent meta-analysis, see Yaple et al., 2019). In contrast, increased functional recruitment, especially bilaterally, of this brain area has been associated with preserved performance in the older group, suggesting an existence of a compensatory strategy to recruit additional control mechanisms in an attempt to preserve performance in older adults (e.g., Mattay et al., 2006; Toepper et al., 2014). Most of these studies have combined fMRI with well-validated tasks, such as n-back or delayed match-to-sample. However, such tasks normally involve crude categorical stimuli, such as letters, numbers or other visual objects. Hence, it is not clear whether structural or functional changes in the PFC alone can account for the deficits in encoding and maintenance of fine-grained representations, such as spatial locations and orientations, seen with ageing (e.g., Pertzov et al., 2015).

Hippocampal volume loss has been implicated in age-related decline in LTM both longitudinally (Gorbach et al., 2017) and cross-sectionally (Henson et al., 2016). This could explain why older adults produce more STM mis-binding errors, as discussed previously (e.g., Peich et al., 2013; Zokaei et al., 2020). In addition, as compared to their young counterparts, decreased functional recruitment, as measured using changes in fMRI BOLD signal, of the hippocampus during LTM encoding has been found in older adults (Pudas et al.,

2013). In contrast, older individuals with preserved performance in this study showed increased BOLD signal in the hippocampus, suggesting that preserved functional activity in this area may lead to spared performance at older age (Pudas et al., 2013). In addition, well-performing older adults also showed increased recruitment of the PFC, which may be interpreted as an involvement of additional brain resources in an attempt to preserve performance at older age (Nyberg, 2017; Pudas et al., 2013). Several other studies have shown that age-related parietal and hippocampal deficits are associated with failures to successfully reinstate vivid long-term memories, which may be the mechanism for impaired LTM retrieval in older adults (Folville et al., 2020; Trelle et al., 2020). Nevertheless, it is still in question whether structural and functional alterations in hippocampal, PFC and parietal structures are the sole contributors to lowered LTM resolution in older adults.

Visual impairments may additionally or alternatively contribute to the decline in visual STM and LTM precision in late adulthood. Older age is associated with a range of visual impairments, including in visual acuity, contrast sensitivity and motion perception (Owsley, 2011; Spear, 1993). These changes may arise due to the reduced availability of gamma aminobutyric acid, the main inhibitory neurotransmitter of the brain, with ageing, which contributes to the weakening of surround suppression and, in turn, distinctiveness of neural responses to different stimuli in older adults (Chamberlain et al., 2021; Pitchaimuthu et al., 2017). In addition, occipital cortex is not spared when it comes to grey matter loss with ageing (Jorge et al., 2020). If, as discussed previously, precise encoding of STM and LTM representations relies on sensory areas, older adults may not be able to encode visual representations to STM and LTM with the granularity available to younger adults.

Changes in long-term synaptic plasticity with ageing may additionally impact LTM. Evidence from animal studies suggests a decline in hippocampal long-term potentiation in old animals (for a review, see Lister & Barnes, 2009). These changes may be associated with

reduced availability of brain-derived neurotrophic factor with ageing, also observed in humans (Miranda et al., 2019). This suggests that at old age, long-term memories may be disproportionally affected as compared to short-term memories.

1.4. STM and LTM Decline in Pathological Ageing

1.4.1. Alzheimer's Disease and Memory

Alzheimer's disease (AD), the most common neurodegenerative disorder, affects both STM and LTM (Jahn, 2013). Age is the greatest risk factor for developing AD, with the prevalence of approximately 5.3 percent in people aged 65 to 74 years, which increases to 13.8 percent in those aged between 75 and 84 years, and to 34.6 percent in those aged 85 years and older (Alzheimer's Association, 2021). As it leads to a complete loss of independence, which calls for round-the-clock care of those affected, with much of the burden on healthy working-age family members, AD inflicts huge economic costs to the society (Alzheimer's Association, 2021; Winblad et al., 2016). As the human population is ageing, the prevalence of AD is estimated to double by 2050 (Alzheimer's Association, 2021), as will the costs associated with it, unless effective treatments become available.

AD is usually diagnosed late, once the pathology becomes so severe, it can no longer be compensated for by the cognitive reserve (Stern, 2012). However, in most cases pathological changes begin in middle age and accumulate over many years, with several studies showing brain and cognitive decline up to a decade before diagnosis (e.g., Tondelli et al., 2012; Wilson et al., 2011). Unless AD treatments, when they become available, can reverse a significant amount of neurodegeneration enabling patients to regain independence, they are unlikely to have a substantial impact on the economic costs of AD. Nevertheless, if we were able to monitor cognitive and brain health of ageing individuals, changes could be

detected much earlier, soon after individuals diverge from a trajectory normal to their age, and treatments could halt the disease progression and maintain independence in everyday life.

Early detection of AD could be achieved with the help of neuroimaging and cerebrospinal fluid biomarkers. For example, AD is characterised by progressive loss of neurons, starting in the perirhinal cortex, progressing towards other MTL structures, such as the entorhinal cortex and the hippocampus, and eventually spreading to the neocortex (Braak & Braak, 1991). The loss of hippocampal grey matter volume in AD, as measured using structural MRI, has been shown in a number of studies (for a meta-analysis, see F. Shi et al., 2009), and has been associated with memory decline in this group (e.g., Kramer et al., 2004; Sexton et al., 2010). Recently, normative differences in hippocampal volume across the adult age range have been characterised in a large cohort of participants from the UK BioBank (Nobis et al., 2019). Such benchmarking may enable the use of hippocampal volume metrics for early AD detection. Similarly, β-amyloid (Aβ) plaques and neurofibrillary tangles of hyperphosphorylated microtubule protein tau are two other hallmarks of AD (Ewers et al., 2012; Lautner et al., 2014). Both of these proteins can be detected in the brain using PET and in the cerebrospinal fluid (CSF) acquired during a lumbar puncture (Dubois et al., 2014). However, both PET and MRI are very expensive and not widely available, making them unsuitable for the screening a large proportion of the elderly population. In addition, the lumbar puncture is an invasive procedure and may not be appealing to many people for general screening purposes.

A cheaper and more accessible alternative to neuroimaging or lumbar punctures could be cognitive measures. Most standard neuropsychological tests have been developed with patients in mind and may therefore be too crude to detect subtle early changes in cognition, masked by cognitive reserve (Stern, 2012), in pre-clinical AD. In addition, it has been shown that, even in patients, continuous-report tests may be more sensitive to the effects of drug

treatments on performance as compared to standard tests of digit span (Zokaei et al., 2015). Furthermore, AD patients show a characteristic pattern of STM impairment also found in MTL lesion patients as measured using sensitive analogue measures (Liang et al., 2016). Therefore, by developing custom tasks to tap into MTL functions and combining them with a wide availability of computers and smartphones, we could develop cheap and convenient screening measures for at-risk populations. One such group is carriers of ε4 allele of the apolipoprotein E gene.

1.4.2. Apolipoprotein E and Genetic Risk of AD

The apolipoprotein E gene (APOE) is based on chromosome 19 in humans. In contrast to other vertebrates (Huebbe & Rimbach, 2017; McIntosh et al., 2012), human APOE is polymorphic and has three major allelic variants, ε2, ε3 and ε4, which are translated to different apolipoprotein (apoE) isoforms, apoE2, apoE3 and apoE4 (Y. Huang & Mahley, 2014; Mahley & Rall, 2000). The three APOE alleles are found at varying frequencies within different human populations (Farrer, 1997). Across people, APOE ε2 is the least common allele, followed by APOE ε4, while APOE ε3 is the most widespread. In people of European descent, APOE ε2, ε4 and ε3 are present in 8.4, 13.7 and 77.9 percent of individuals, respectively (Farrer, 1997). As a single APOE allele is inherited from each parent, most individuals are either heterozygous (ε2/ε3, ε2/ε4 or ε3/ε4) or homozygous (ε2/ε2, ε3/ε3 or ε4/ε4) APOE carriers.

APOE ε4 allele is the strongest genetic risk factor for developing sporadic late-onset AD (Farrer, 1997). The presence of this allele increases the risk of AD by up to three times in heterozygous carriers and up to 15 times in homozygous carriers of European descent, as compared to ε3 homozygotes (Farrer, 1997). The relationship between APOE and AD risk is stronger in Asians and weaker in African Americans (Farrer, 1997). A similar relationship has

also been observed between APOE ε4 and the age of onset of AD, with a reduction by approximately three to nine years with every ε4 allele (Corder et al., 1993; Sando et al., 2008).

The rare APOE ε2 allele, on the other hand, has been shown to half the risk of AD in both homozygous and heterozygous carriers when paired with ε3, as compared to two ε3 alleles (Farrer, 1997). Despite the presence of a protective allele in APOE ε2/ε4 carriers, the risk for this group is increased two to three times as compared to ε3 homozygotes (Farrer, 1997).

1.4.3. The Numerous Roles of ApoE

ApoE is a 299-amino acid 34-kDa protein. It is secreted mostly by hepatocytes in the liver and astrocytes in the brain, but is found also in many other tissues throughout the body, where it is produced either by local cells (e.g., adipocytes in adipose tissue) or macrophages (Y. Huang & Mahley, 2014; Kockx et al., 2018; Mahley, 2016; Mahley & Rall, 2000). In the brain, neurons and microglia also produce apoE, mostly in response to stress (Xu et al., 2006). The abundance of apoE across the body hints at its biological significance.

The primary role of apoE is to transport lipids, including cholesterol, across the body and the brain and to regulate their uptake by cells (Y. Huang & Mahley, 2014; Kockx et al., 2018; Mahley & Rall, 2000). This is achieved by the binding of apoE to plasma lipoprotein particles and cell-surface lipoprotein receptors, such as the low-density lipoprotein receptor and the apoE receptor-2 (Y. Huang & Mahley, 2014). In addition, apoE is also involved in regulating the inflammatory response and the formation of adipose tissue (Ali et al., 2005; Kockx et al., 2018; Zhi et al., 2006). In the brain, in part due to the importance of lipids and cholesterol in cell membranes and myelin, apoE is involved in neural development, synaptic plasticity, and neuronal repair and regeneration via various pathways (Mahley & Rall, 2000).

Differences between the three major apoE isoforms arise from amino acid substitutions at positions 112 and 158 that affect their folding and function. In apoE2, both positions are occupied by cysteine molecules, in apoE3—a cysteine (112^{th}) and an arginine (158^{th}), and apoE4 contains two arginine residues. These seemingly minor differences are sufficient to affect the folding of the resulting protein structures, and in turn, their ability to bind lipoproteins and other molecules (J. Chen et al., 2011; Frieden & Garai, 2012; Y. Huang & Mahley, 2014; Mahley & Rall, 2000; Zhong & Weisgraber, 2009). This results in functional differences among isoforms as well as differential susceptibility to certain disorders in their carriers, including AD. For example, compared to ε3 carriers, individuals who carry ε2 are at a greater risk of developing hyperlipoproteinemia and cerebral amyloid angiopathy (Greenberg et al., 1998; Mahley, 2016). In contrast, ε4 carriers are prone to developing cardiovascular disease, cerebral amyloid angiopathy and AD (Greenberg et al., 1998; Mahley, 2016).

1.4.4. ApoE in AD Pathology

A wide range of potential mechanisms have been proposed through which apoE may be involved in AD pathology.

1.4.4.1. ApoE is Involved in Aβ Deposition. The presence of APOE ε4 allele is associated with a more extensive accumulation of Aβ plaques in both healthy and AD brains. It has been shown using PET that both healthy older adults and AD patients with APOE ε4 show increased levels of Aβ in the brain as compared to homozygous APOE ε3 carriers (Gonneaud et al., 2016; Kantarci et al., 2012). Similarly, significant Aβ accumulation, as measured using PET, has been found up to 20 years earlier, in their fifties, in APOE ε4 carriers as compared to non-carriers (Fleisher et al., 2013). Levels of Aβ in the cerebrospinal

fluid have also been found to be related to APOE genotype in both AD patients and healthy control subjects (Castellano et al., 2011; Prince et al., 2004). Significantly lower levels of this peptide have been found in APOE ε4 carriers as compared to non-carriers (Castellano et al., 2011; Prince et al., 2004), which may indicate reduced Aβ clearance and its accumulation in the form of plaques (Blennow & Hampel, 2003; Castellano et al., 2011).

Aβ pathology in APOE ε4 carriers may be caused by increased production and reduced clearance of Aβ by apoE4 as compared to the other isoforms (Zhao et al., 2018). It has been shown that apoE may stimulate, in an isoform-dependent manner, the production of the amyloid precursor protein (APP), a multi-functional transmembrane protein also involved in the formation and functioning of synapses (Müller et al., 2017), with most APP produced when apoE4 was available, and least when apoE2 was present *in vitro* (Y.-W. A. Huang et al., 2017). Endocytosis of APP into cells, where it is cleaved to produce Aβ, may also be apoE-dependent (Zhao et al., 2018). A more efficient endocytosis of APP has been observed in the presence of apoE4 as compared to apoE3, resulting in an increased production of Aβ (Ye et al., 2005). In addition, out of the three isoforms, apoE4 has been associated with the least efficient Aβ clearance, followed by apoE3, and apoE2 being the most efficient (Castellano et al., 2011). This may relate to isoform-specific ability of free, non-lipoprotein-bound APOE, to bind Aβ, which is then internalised into cells and broken down, with a less stable complex formed by apoE4 as compared to apoE3 *in vitro* (LaDu et al., 1994). However, due to the low availability of free apoE, differential binding of receptors by lipoprotein-bound apoE isoforms may play a more important part in mediating Aβ clearance. For example, apoE and Aβ may bind and therefore compete for the same receptors required for Aβ uptake by cells for degradation, with apoE4 being a stronger antagonist than the other two isoforms (Verghese et al., 2013). Finally, apoE may also facilitate both intracellular and extracellular Aβ breakdown per se, with more efficient proteolysis induced by apoE2 and apoE3 compared

to apoE4 (Jiang et al., 2008). The higher efficiency may be related to greater availability of apoE, as found in post-mortem brain tissue samples of APOE ε2 as compared to APOE ε4 carriers, with intermediate levels in APOE ε3 carriers (Conejero-Goldberg et al., 2014).

1.4.4.2. ApoE Mediates Aβ Cytotoxicity. APOE ε4 carriers may be more vulnerable to Aβ toxicity as compared to ε3 homozygotes or ε2 carriers. It has been shown that cognitive performance, including on measures of visual and verbal memory, of older adult carriers of APOE ε4 may be more affected by the increased levels of Aβ than that of APOE ε3/ε3 or ε2/ε3 carriers (Kantarci et al., 2012). Only APOE ε4 carriers in this study showed a significant decline in memory and visuospatial abilities with increasing levels of PET Aβ (Kantarci et al., 2012). Similarly, at cell level, pericytes, the smooth muscle cells lining the blood vessels, of individuals with APOE ε4 allele are more vulnerable to Aβ toxicity *in vitro* (Wilhelmus et al., 2005), suggesting that Aβ toxicity may be involved in the breakdown of the blood-brain barrier (BBB). A post-mortem analysis of brain slices from frontal cortices of AD patients has shown that those who carried at least one copy of ε4 had a greater degeneration of pericytes and also leakier BBB, as indicated by higher levels of plasma-derived molecules outside the blood vessels of the brain (Halliday et al., 2016). Impairments in the BBB have been associated with cognitive decline irrespective of APOE genotype or Aβ pathology (Nation et al., 2019)

1.4.4.3. ApoE is Involved in the Breakdown of the BBB Independently from Aβ. The isoform-dependent involvement of apoE in the breakdown in the BBB may also occur via Aβ-independent pathways. A study on healthy older individuals, which utilised dynamic contrast-enhanced MRI, has shown that APOE ε4 carriers had leakier BBBs, in particular in the MTL region, compared to APOE ε3 homozygotes, and this effect was independent from

CSF and PET markers of AD (Montagne et al., 2020). Greater decline in cognitive performance, as measured using the Clinical Dementia Rating Scale, was also associated with increased permeability of the blood-brain barrier in APOE ε4 but not APOE ε3 carriers in this study (Montagne et al., 2020).

1.4.4.4. ApoE is Involved in the Hyperphosphorylation of Tau. ApoE isoforms may also differentially modulate the formation of neurofibrillary tangles, another hallmark of AD. Several studies using APOE knockout mice have shown that the addition of human apoE in the presence of Aβ increases the formation of neurofibrillary tangles as compared to Aβ alone, suggesting that apoE is involved in the phosphorylation of tau (e.g., Hou et al., 2020; Shi et al., 2017). However, until recently, it was not clear whether apoE isoforms can modulate the formation of neurofibrillary tangles independently of Aβ pathology. Several studies using human post-mortem tissue preparations and biomarker neuroimaging on living participants with or without AD diagnosis have shown that, indeed, although tauopathies in the absence of Aβ plaques may be less related to the APOE genotype (Farfel et al., 2016), in the presence of Aβ plaques, APOE ε4 carriers show levels of phosphorylated tau beyond those found in non-carriers with a similar degree of Aβ pathology (Farfel et al., 2016; Therriault et al., 2020; Yu et al., 2014). In addition, apoE isoforms can influence cognitive performance via phosphorylated tau in addition to (Yu et al., 2014) and independently from Aβ (Weigand et al., 2021), with worse cognitive performance in APOE ε4 carriers as compared to non-carriers.

It is not entirely clear exactly how apoE isoforms contribute to tau phosphorylation at the molecular and cellular levels. ApoE has been shown to induce tau pathology via its effects on inflammation, potentially in an isoform-dependent manner, with more phosphorylated tau found in cells treated with apoE4 as compared to apoE3 and apoE2 (Hou et al., 2020).

Similarly, the presence of apoE may facilitate the phosphorylation of tau via the innate immune response (Y. Shi et al., 2019), which is explored in greater detail in section 1.4.4.6. ApoE may also interact directly with tau. For example, apoE3 has been shown to bind to tau with much greater affinity than apoE4 *in vitro*, which may prevent the formation of helical tau filaments that then accumulate to form neurofibrillary tangles (Strittmatter et al., 1994). However, future studies are required to explore the effects of apoE isoforms on the phosphorylation of tau.

1.4.4.5. ApoE Mediates Energy Metabolism. Glucose, metabolised by mitochondria, is the main source of energy in the brain. Reduced glucose metabolism is one of the hallmarks of AD (Banerjee et al., 2015), and there may also be differences among APOE ε2, ε3 and ε4 carriers in glucose metabolism. For example, one study has shown that mitochondria in astrocyte cells of mice that have undergone targeted APOE gene replacement to produce either human apoE3 or apoE4 behaved differently under stress (Schmukler et al., 2020). While astrocytes of APOE ε3 mice performed as expected by removing damaged mitochondria via autophagy, mitochondria of APOE ε4 mice showed less degradation, indicating that defunct mitochondria were present in astrocytes of APOE ε4 animals, resulting in decreased energy production (Schmukler et al., 2020). Similar results were found by another study that analysed human post-mortem brain tissue, with decreased concentrations of proteins that regulate mitochondrial dynamics in samples from APOE ε4 carriers as compared to non-carriers (J. Yin et al., 2020). Furthermore, the levels of these proteins were related to cognitive performance prior to death, as measured using the Clinical Dementia Rating Scale (J. Yin et al., 2020), providing a link between mitochondrial function and cognition. Finally, apoE4 is the least structurally stable of the three isoforms, and fragments resulting from its proteolytic cleavage may be toxic to mitochondria, directly affecting their

function and glucose metabolism in cells, contributing to the development of AD (Chang et al., 2005; Muñoz et al., 2019; Nakamura et al., 2009). As shown using mouse models of human APOE and human cell lines, the most efficient energy metabolism is achieved in the presence of apoE2, followed by apoE3, with apoE4 resulting in the least efficient energy production (Wu et al., 2018).

1.4.4.6. ApoE is Involved in the Innate Immune Response. ApoE may also induce neurodegeneration via the innate immune response. In a healthy brain, the appearance of AD biomarkers or damaged cells evokes a response from microglia that, in addition to engulfing these cells or proteins, release pro-inflammatory cytokines to increase the immune response (Solé-Domènech et al., 2016). However, after the task has been accomplished, the inflammatory response is downregulated to restore normal function. In contrast, inflammation persists in AD brain (for a review, see Kloske & Wilcock, 2020). With a help of mouse models, it has been shown that apoE induces tau-related neurodegeneration by activating microglia (Y. Shi et al., 2019). However, more research is required to understand how this may be modulated by different apoE isoforms.

1.4.4.7. ApoE Mediates Synaptic Plasticity. Finally, apoE4 may affect memory via synaptic mechanisms, such as reduced neurite outgrowth and synaptic plasticity, which may interact with AD pathology. In humans, reduced dendritic spine density in post-mortem samples of dendrite gyrus have been found in APOE ε4 carriers with and without AD, as compared to non-carriers (Ji et al., 2003). Similarly, lower levels of pre-synaptic proteins, a proxy for lower synaptic density, were found in the superior temporal gyrus tissue of healthy APOE ε4 carriers compared to non-carriers in another autopsy study (Love et al., 2006). In contrast, APOE ε2 carriers had higher levels of postsynaptic proteins, suggesting higher

synaptic density (Love et al., 2006). Studies on human APOE replacement mice also found reduced dendritic spine density and length (Dumanis et al., 2009; Ji et al., 2003), in addition to lower dendritic branching and synaptic activity (Klein et al., 2010; Wang et al., 2005, although see Korwek et al., 2009), in APOE ε4 as compared to APOE ε3 animals. Notably, at least one study has claimed that these effects were present in the absence of any other pathological changes (Wang et al., 2005), suggesting marked differences in otherwise healthy animals. In contrast, APOE ε2 mice displayed the highest dendritic spine density and length (Dumanis et al., 2009), and the presence of ε2 allele lessened the detrimental effects of ε4 on synaptic activity in APOE ε2/ε4 mice (Klein et al., 2010). Finally, apoE and AD pathology may have interactive effects on memory. Long-term potentiation in human APOE ε4 replacement mice was more impaired by Aβ oligomers than in APOE ε3 mice, with APOE ε2 mice being the most resistant to the effects of Aβ pathology (Trommer et al., 2005).

1.4.5. APOE and Memory in Healthy Adults

Given the many pathways in which apoE is involved in the functioning of a healthy brain and in pathological processes involved in AD, it is not surprising that differences in memory performance have been observed in individuals carrying different APOE alleles. However, observations do not always follow the expected pattern of better performance in APOE ε2 carriers, who are more resilient to AD, and worse performance in their APOE ε4 counterparts, who are at a greater risk of developing this neurodegenerative disorder. The variability in findings may result from the genuine complexity of the effects of this gene on cognition, changing with age and affecting different memory domains to a different degree. However, methodological choices, such the age range, the number of participants tested and the sensitivity of memory tests used, may add further variability to findings (O'Donoghue et

al., 2018). The following sections will provide an overview of the relationship between different APOE alleles and STM and LTM functions with these complexities in mind.

1.4.5.1. APOE ε2 and Memory. There has been surprisingly little research on the relationship between the protective APOE ε2 allele and memory. From the relatively small number of studies conducted to date, discussed in detail in Chapter 2, most have found positive effects of this allele on STM and LTM, in particular longitudinally and in older age (e.g., Hyman et al., 1996; Rajan et al., 2019; Wilson et al., 2002). In addition, a recent cross-sectional study, which utilised a sensitive continuous-report STM task already discussed in previous sections in relation to MTL functions and ageing (Pertzov et al., 2015; Zokaei, Nour, et al., 2019), supported these findings by also showing a STM advantage in ε2 carriers across adulthood (Zokaei et al., 2021). In contrast, several other studies have found no benefits of carrying APOE ε2 as compared to APOE ε3/ε3 on STM or LTM, regardless of participants' age (e.g., Chiang et al., 2010; Marioni et al., 2016). It may also be possible that at young age APOE ε2 carriers have equivalent memory abilities to their at-risk ε4 counterparts (Alexopoulos et al., 2011). However, as no ε3 control group was recruited for the study in question, it is hard to interpret these findings fully. The null findings in these studies may be at least partially accounted for by other factors, such as a small sample size (Alexopoulos et al., 2011), a broad age range of participants tested (Chiang et al., 2010), or crude neuropsychological measures used (Marioni et al., 2016). Therefore, overall, it seems that APOE ε2 may have subtle positive effects on both STM and LTM, which are more readily detectable using sensitive tasks, large samples and longitudinal measurement at older age.

Neuroimaging studies suggest that while APOE ε2 allele may have protective effects on the MTL structures, there may be functional similarities between the brain of APOE ε2 and ε4 carriers (for a review, see Suri et al., 2013). Several MRI studies have shown larger

hippocampal volumes or slower hippocampal decline longitudinally in APOE ε2 carriers as compared to ε3 homozygotes in middle and older age (e.g., Chiang et al., 2010; Hostage et al., 2013, although see Den Heijer et al., 2002), and as compared to ε4 carriers in early adulthood (Alexopoulos et al., 2011). This fits well with the preserved STM and LTM performance in ε2 carriers discussed above. In contrast, functional connectivity during an episodic memory task and at rest, as measured using MRI, has been shown to be similar in ε2 and ε4 carriers as opposed to ε3 homozygotes aged 32 to 55 years (Trachtenberg, Filippini, Cheeseman, et al., 2012; Trachtenberg, Filippini, Ebmeier, et al., 2012). These findings are surprising in the context of AD risk. However, as BOLD signal is an indirect measure of brain activity and reflects increased blood oxygenation resulting from the dilation of blood vessels, it may also reflect vascular differences between groups. Indeed, compared to APOE ε3 homozygotes, both ε2 and ε4 carriers are at an increased risk to develop cerebral amyloid angiopathy (Greenberg et al., 1998), which affects the integrity of blood vessels and increases the risk of stroke in both groups. This suggests that both behavioural and neuroimaging findings in relation to APOE ε2 should be interpreted with caution, as they may reflect both the reduced susceptibility to AD and the increased susceptibility to vascular changes that may lead to otherwise poor brain health.

1.4.5.2. APOE ε4 and Memory. Many more studies have been conducted to date to investigate the relationship between APOE ε4 allele and STM and LTM functions. As APOE has been shown to increase the risk of developing AD, many of the studies have focused on older adults. In many of the studies, individuals who belong to this age group and carry ε4 allele have been shown to have worse STM and LTM performance compared to APOE ε3 homozygotes (e.g., Marioni et al., 2016; Wilson, Schneider, et al., 2002; for a review, see O'Donoghue et al., 2018).

An outstanding issue in the literature is whether deficits in older adults are due to pre-clinical AD pathology, which has been termed the prodromal hypothesis (e.g., Foster et al., 2013; Quintas et al., 2014; G. E. Smith et al., 1998), or are characteristic to APOE ε4 carriers irrespective of impending AD, the cognitive phenotype hypothesis (e.g., Greenwood et al., 2005; Greenwood & Parasuraman, 2003). Several studies that examined individuals with mild cognitive impairment (MCI) and AD in addition to healthy controls, all genotyped for APOE, have shown that the relationship between memory and APOE ε4 was only present in the patient groups (Foster et al., 2013; Quintas et al., 2014; G. E. Smith et al., 1998). At least two of these studies involved previous longitudinal follow-up, which allowed the exclusion of individuals that had developed cognitive deficits from the control groups prior to the present assessment (Quintas et al., 2014; G. E. Smith et al., 1998). The authors therefore concluded that memory deficits found in older APOE ε4 carriers were a result of prodromal AD, suggesting that previous studies may have inadvertently included APOE ε4 carriers that were already cognitively impaired (Foster et al., 2013; Quintas et al., 2014; G. E. Smith et al., 1998). In partial support for the prodromal hypothesis, several longitudinal studies have also found a steeper decline in memory over time in middle-aged to older ε4 carriers as compared to non-carriers, suggesting that deficits develop over time (Blair et al., 2005; Caselli, Dueck, Locke, Sabbagh, et al., 2011), although a meta-analysis of the effects of APOE ε4 on memory functions in this age group has yielded null effects (Lancaster et al., 2017). In addition, a recent meta-analysis has found that there was no overall difference in cognitive performance, including memory, between younger APOE ε4 carriers and non-carriers, showing a lack of support for the presence of a cognitive phenotype at young age (Weissberger et al., 2018).

Due to cognitive reserve, alterations in cognition, especially if measured using crude neuropsychological tests, are often discovered later than those in the brain (Stern, 2012). Therefore, neuroimaging studies may help us understand the differences observed in memory

performance between APOE allele carriers. A number of studies have shown smaller hippocampal volumes and steeper longitudinal hippocampal volume loss in healthy middle-aged and older carriers of APOE ε4 compared to non-carriers (e.g., Cacciaglia et al., 2018; Den Heijer et al., 2002; although see Hostage et al., 2013, who only found differences in AD and MCI but not healthy participants), which predicts longitudinal memory decline in this group (Gorbach et al., 2020). In contrast, few studies have observed any structural differences in the MTL region between young APOE ε4 carriers and non-carriers (e.g., O'Dwyer et al., 2012; but not Filippini et al., 2009; Matura et al., 2014). Therefore, it seems that structural decline in APOE ε4 carriers in the MTL region begins later in life, contributing to memory loss and potentially representing prodromal AD.

A number of studies have found increased fMRI BOLD signal in the brain of older APOE ε4 carriers compared to non-carriers during STM tasks and LTM encoding, including in the MTL and the PFC (e.g., Bondi et al., 2005; Filbey et al., 2010; L. M. Nichols et al., 2012; Scheller et al., 2017). This pattern of results has been suggested by some authors to represent compensatory mechanisms in response to emerging structural changes in the brain (Bondi et al., 2005), an interpretation similar to that found in the ageing literature, as discussed in section 1.3. However, fMRI studies on young adults have also shown a similar pattern of results, both during functional fMRI and at rest (e.g., Filippini et al., 2009; Matura et al., 2014; Trachtenberg, Filippini, Cheeseman, et al., 2012; Suri et al., 2015; although see C. J. Chen et al., 2013 for the effects of STM task difficulty). This suggests the presences of functional brain differences between APOE ε4 carriers and ε3 homozygotes at young age, which may explain the phenotypic effects of ε4 on memory performance. However, as already discussed in the previous section, BOLD response does not necessarily represent neural activity. Literature outlined in sections 1.4.4.2. and 1.4.4.3 suggests that apoE3 and apoE4 isoforms have different effects on the integrity of blood vessels of the brain. As a

result, differences in fMRI activity between ε3 and ε4 carriers may be at least partially explained by differences in vascular health and potentially vascular risk. Indeed, one study has shown that differences in cerebrovascular reactivity to carbon dioxide, which was significantly lower in young APOE ε4 carriers as compared to APOE ε3 homozygotes, accounted for up to 70 percent of the difference in the hippocampal BOLD response between the two groups during LTM encoding (Suri et al., 2015).

Surprisingly, given the findings discussed above, a number of studies have found STM and LTM advantages in APOE ε4 carriers. Most of these studies involved young and middle-aged individuals (e.g., Mondadori et al., 2007; Zokaei et al., 2017). This, in relation to detrimental effects of this allele in later life, has led some authors to suggest that APOE ε4 is an example of antagonistic pleiotropy – a gene exerting beneficial effects at reproductive age, leading to an increased probability of survival and reproduction of its carrier, followed by detrimental effects later in life (Han & Bondi, 2008; Tuminello & Han, 2011). However, a recent study with a large sample of participants aged 18 to 88 years tested cross-sectionally provided little evidence to support the presence of antagonistic pleiotropy in APOE ε4 carriers in relation to LTM (Henson et al., 2020). Furthermore, given that studies that found positive effects in early adulthood did not measure cognition longitudinally, some of the advantageous effects of APOE ε4 in early life may also represent a cognitive phenotype that interacts with AD pathology in late adulthood. One such case could be a STM advantage found in APOE ε4 carriers as compared to ε3 homozygotes after short maintenance periods (Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020). A recent cross-sectional study with a large sample of participants has shown that this advantage was present across adulthood in APOE ε4 carriers (Zokaei, Grogan, et al., 2020). In combination with deficits in LTM in older age, advantages in STM across the lifetime in APOE ε4 carriers may suggest a degree of mechanistic independence between STM and LTM.

1.5. Aims of the Thesis

Our knowledge of the relationship between STM and LTM functions has remained limited. Both STM and LTM are affected by normal and pathological ageing. Studying the impact of these processes on the relationship between the two memory functions may shed light on the level of mechanistic overlap between them. The primary aim of this thesis is to examine the relationship between STM and LTM using sensitive and comparable continuous-report measures in the context of healthy and pathological ageing. Chapters 2 and 3 of this thesis focus on healthy ageing. Chapter 3 introduces two novel continuous-report tasks that enable analogous probing of both types of memory in order to measure directly the relationship between them. This task is employed to test individuals who are at an increased risk of developing AD, APOE ε4 carriers, in Chapter 4, with a hope that similar tasks can help to differentiate phenotypic and prodromal effects of this allele in the future.

Chapter 2. Short- and Long-Term Memory in APOE ε2 Carriers and Non-Carriers in Early and Late Adulthood

Abstract

The rare ε2 allele of the APOE gene has been shown to reduce the risk of incidence and to increase the age of onset of AD in its carriers. However, its relationship with STM and LTM is not well understood. The study described in this chapter utilised two sensitive continuous-report tasks to assess STM and LTM for object-location associations in young and older APOE ε2/ε3 and ε3/ε3 carriers. Overall, the results suggest little difference between the two gene groups across memory measures. Nevertheless, older adults performed significantly worse than the young group across the board. The effects of APOE ε2 on memory may be subtle. Therefore, future studies should recruit larger samples and utilise longitudinal designs in order to track the effects of this allele on STM and LTM in mid to late adulthood. Due to differences between tasks used, the relationship between STM and LTM could not be examined in this study. Future studies should therefore utilise tasks that enable comparable assessment of both short-and long-term memories.

2.1. Introduction

As discussed in Chapter 1, the rare ε2 allele of the APOE gene has been shown to reduce the risk of incidence and to increase the age of onset of AD in its carriers (Corder et al., 1993; Farrer, 1997; Poirier et al., 1993). However, in contrast to the AD risk-increasing ε4 allele, ε2 has attracted less investigation since the publication of first association studies between APOE gene and AD (Corder et al., 1993; Farrer, 1997; Poirier et al., 1993; Suri et al., 2013). As a result, our knowledge of the relationship between this allele and memory is rather limited.

There may be various reasons for the lack of research on the APOE ε2 allele. Firstly, the rarity of the ε2 allele, present in only approximately eight percent of the general population (C. C. Liu et al., 2013), complicates the recruitment of research participants. Furthermore, only 0.8 percent of the general population are homozygous for this allele (Farrer, 1997), making studies with large balanced samples of APOE ε2/ε2 and ε2/ε3 carriers near impossible. In addition, as discussed in Chapter 1, the benefits of APOE ε2 may also come with costs. For example, APOE ε2 allele, similarly to APOE ε4, is overrepresented in individuals with certain neurological disorders, such as cerebral amyloid angiopathy (Greenberg et al., 1998). This may complicate the interpretation of findings from both cognitive and neuroimaging studies, as effects of vascular changes may confound the results. Finally, there may be a natural bias to focus research on the risk factors, such as APOE ε4, as they may provide a more straightforward route to understanding the neuropathology of AD. However, research on the resilience factors may be equally as important, as it may shed light into how AD can be avoided, for example, by upregulating molecular pathways that promote brain health.

The study of the effects of APOE ε2 on cognitive functions may also be complicated by the lack of suitable tools to detect them. For example, most of the studies that investigated memory of APOE ε2 carriers to date have utilised standard neuropsychological tests (see below). Although these tests are invaluable for measuring cognitive decline in individuals who have suffered a haemorrhagic stroke, they may be too crude to detect potentially subtle differences in performance between otherwise cognitively healthy individuals with different APOE alleles cross-sectionally, resulting in inconsistent findings.

The strongest evidence for the protective effects of APOE ε2 allele on both STM and LTM comes from large longitudinal studies. One of these has assessed a sample of 5807 adults over the age of 65 years, including 48 carriers of APOE ε2/ε2 and 782 carriers of

APOE ε2/ε3 alleles (Rajan et al., 2019). APOE ε2/ε2 was associated with less global cognitive decline, as measured using a combined score derived from the Mini-Mental State Examination (MMSE), tests of immediate and delayed episodic recall, perceptual speed and general orientation, over a period of 10 years than APOE ε3/ε3 (Rajan et al., 2019). However, the advantage in the rate of cognitive decline in ε2/ε3 carriers only emerged later in life, after the age of 75 years (Rajan et al., 2019). Both APOE ε2/ε2 and APOE ε2/ε3 carriers also showed significantly slower decline in episodic memory measures (immediate and delayed) than APOE ε3/ε3 carriers, while preservation of performance on the MMSE was also found in APOE ε2/ε3 carriers (Rajan et al., 2019). Overall, these findings suggest that the protective effects of APOE ε2 allele may influence both STM and LTM, particularly in older age.

According to another study, with four- and seven-year follow-ups, older adults over the age of 65 years were also less likely to show impairments in LTM in subsequent follow-ups if they carried at least one copy of the APOE ε2 allele, as compared to two APOE ε3 alleles (Hyman et al., 1996). LTM in this study was measured using delayed recall of words (Hyman et al., 1996). This study tested 1,899 individuals, 11 of whom were APOE ε2/ε2 and 285 were APOE ε2/ε3 carriers (Hyman et al., 1996).

A study with a six-year follow-up on a slightly younger sample of 47 to 68-year-olds has shown that Caucasians carrying one or two copies of the APOE ε2 allele displayed less decline in the delayed word recall task than homozygous APOE ε3 carriers (Blair et al., 2005). This effect was small, potentially due to the relatively young age of participants, but significant. However, African Americans with APOE ε2 did not show a similar preservation of performance on this task (Blair et al., 2005). Nevertheless, in both groups, the presence of APOE ε2 was associated with a smaller negative change in performance on the Digit Symbol Substitution Test than the presence of two APOE ε3 alleles (Blair et al., 2005). Apart from

other cognitive domains, this task is thought to test working memory, as it requires maintaining number-symbol pairings as well as the task instructions (Jaeger, 2018).

Finally, APOE ε2 carriers over the age of 65 years also showed preserved memory as compared to APOE ε3 carriers over an eight-year follow-up period (Wilson, Bienias, et al., 2002). Memory score in this study was derived from performance on a word list memory, and immediate and delayed story recall tasks (Wilson, Bienias, et al., 2002), suggesting advantages in both STM and LTM in APOE ε2 carriers. Of 669 participants that took part in this study, 86 were heterozygous or homozygous for APOE ε2 (Wilson, Bienias, et al., 2002). Overall, the findings of the studies discussed above suggest that the protective effects of APOE ε2 allele may influence both STM and LTM, from middle to older age.

Preserved performance on memory measures in APOE ε2 carriers as compared to APOE ε3 homozygotes has also been observed cross-sectionally. One of the earliest studies investigating the relationship between APOE alleles and cognition in older adults found that homozygous and heterozygous APOE ε2 carriers recalled more words in the word list learning test than homozygous APOE ε3 carriers (Helkala et al., 1995). As this test involved selective cueing of words that had been forgotten, the authors suggested that APOE ε2 carriers showed superior learning abilities as compared to APOE ε3 homozygotes (Helkala et al., 1995). Although a slightly better performance of APOE ε2 carriers was also observed in the immediate and delayed visual reproduction test, during which participants had to reproduce complex figures from memory, this effect was not statistically significant (Helkala et al., 1995). This study tested 916 participants, 76 of whom carried one or two copies of the ε2 allele (Helkala et al., 1995).

Another study investigated cognition of young participants aged 23 to 24 years and their mothers, aged 42 to 67 years, and found a STM advantage in APOE ε2 carriers (Sinclair

et al., 2017). In total, 118 participants took part in the study, 33 of whom had at least one APOE ε2 allele (Sinclair et al., 2017). The authors reported slightly better performance in ε2 carriers than homozygous ε3 carriers on the immediate recall of the Rey Auditory Verbal Learning Test (RAVLT) and the episodic list learning task (Sinclair et al., 2017). This effect was stronger in the young group than in mothers (Sinclair et al., 2017). Participants with APOE ε2 did not show better performance on any of the delayed recall measures, suggesting that ε2 benefits in this study were reserved to STM.

In a much larger recent study, Zokaei et al. (2021) tested 854 adult participants of various ages, 300 of whom were APOE ε2/ε3 carriers, using a sensitive continuous-report STM task, and found a memory advantage in APOE ε2 carriers. During the task participants first viewed one or three coloured fractal objects presented on a black background, followed by a memory delay of either one or four seconds, during which only the black background was presented. Following the delay, two probe items were shown, and participants' memory for object identity and location was measured by asking them to select the item they saw before the delay and place it back to its remembered location (Zokaei et al., 2021). This task has been shown to be sensitive to hippocampal damage in previous studies (Pertzov et al., 2013; Zokaei, Nour, et al., 2019). APOE ε2/ε3 carriers showed superior performance compared to APOE ε3/ε3 homozygotes across the age range, with significantly smaller location errors in high-load three-item trials (Zokaei et al., 2021). In contrast, there were no differences between groups on location memory in low-load one-item trials, or when object identity was assessed using a categorical measure (Zokaei et al., 2021). This suggests that APOE ε2 carriers of any age have an advantage as compared to non-carriers on tasks that tax the hippocampal function. In addition, sensitive and challenging continuous-report tasks, such as this, may be particularly useful to assess memory differences between APOE ε2 carriers and non-carriers.

A memory advantage in APOE ε2 carriers as compared to APOE ε4 carriers has also been observed in clinical populations. In a cross-sectional study, which tested 36 APOE ε2/ε3, 72 APOE ε3/ε3 and 72 APOE ε4 carriers (both homozygous and heterozygous) who had MCI and AD, participants with APOE ε2 performed better than age- and diagnosis-matched APOE ε4 carriers on memory tests, which included a combined score from Visual Association Test A, and RAVLT immediate and delayed recall (Groot et al., 2018). Although they also showed slightly better performance than APOE ε3 homozygotes, the difference between groups did not reach statistical significance. In contrast, APOE ε2/ε3 carriers performed worse than the other two groups on non-memory cognitive tests of attention and executive control (Groot et al., 2018). The MRI findings from this study showed that compared to homozygous ε4 carriers, ε2/ε3 carriers were less affected by hippocampal atrophy. However, they also displayed otherwise worse brain health, characterised by larger brain volumes affected by white matter hyperintensities and microbleeds than ε4 carriers and ε3 homozygotes, respectively (Groot et al., 2018). This suggests that APOE ε2 may selectively protect memory functions and medial temporal lobe structures, such as the hippocampus, that support them.

Other studies have found no difference between APOE ε2 and APOE ε3 carriers on memory measures. For example, a small longitudinal study, which included regular biannual follow-ups for a period of two years, showed that episodic memory, as measured using a delayed story recall from the Wechsler Memory Scale, declined at a similar rate in APOE ε2 carriers and APOE ε3 homozygotes (Chiang et al., 2010). This was despite APOE ε2 carriers showing a slower rate of hippocampal atrophy than the APOE ε3 group (Chiang et al., 2010). However, this study tested only a moderate sample of 134 healthy adults aged 55 to 90 years, 27 of whom were APOE ε2/ε3 carriers (Chiang et al., 2010). Therefore, the broad age range

of participants, the short follow-up period, as well as the insufficient statistical power may have concealed any differences in the cognitive trajectory between groups. The discrepancy between neural and cognitive findings could also be explained by cognitive reserve (Stern, 2012), as participants were highly educated (Chiang et al., 2010).

Similarly, a small cross-sectional study on 33 young adults in their twenties found no difference on memory performance between 17 APOE ε2 and 16 APOE ε4 carriers (Alexopoulos et al., 2011). Their memory was measured using the Inventory for Memory Diagnostics, which included tests of working memory, learning, delayed recall, verbal memory and visual memory (Alexopoulos et al., 2011). However, similarly to the study by Chiang et al. (2010), carriers of APOE ε2 had larger hippocampal volumes than their APOE ε4 counterparts (Alexopoulos et al., 2011). This suggests that neuropsychological tests may not be able to detect differences in performance in small samples of young healthy individuals. However, the presence of larger hippocampal volumes in APOE ε2 carriers early in life may contribute to their superior memory later in life. This study did not have a homozygous APOE ε3 control group.

A very large cross-sectional study on 18,377 individuals aged between 18 and 94 years, 111 of whom were APOE ε2/ε2 and 2194 APOE ε2/ε3 carriers, also found no benefits of ε2 allele on memory performance (Marioni et al., 2016). Memory in this study was assessed using a combined score from an immediate and a delayed paragraph recall from the Wechsler Logical Memory Test (Marioni et al., 2016). It might therefore be possible that healthy APOE ε2 carriers indeed show equivalent memory performance to APOE ε3 homozygotes on standard neuropsychological tests when measured cross-sectionally. Protective effects of APOE ε2 may be more apparent longitudinally (e.g., Blair et al., 2005; Rajan et al., 2019; Wilson, Bienias, et al., 2002) and with more sensitive continuous-report measures of memory (Zokaei et al., 2021; see Table 2.1 for a summary).

Table 2.1. Summary of studies that investigated memory performance of healthy ε2 carriers.

Study	Age	Sample size	Study type	Length of follow-up	Measure type	Effect of ε2 on memory
Alexopoulos et al. (2011)	18-30	33	Cross-sectional	-	Neuropsychological	Null (compared to ε4)
Blair et al. (2005)	47-68	7,895	Longitudinal	6 years	Neuropsychological	Positive
Chiang et al. (2010)	55-90	134	Longitudinal	2 years	Neuropsychological	Null (LTM)
Helkala et al. (1995)	65<	916	Cross-sectional	-	Neuropsychological	Positive (learning)
Hyman et al. (1996)	65<	1,899	Longitudinal	4 years, 7 years	Neuropsychological	Positive (LTM)
Marioni et al. (2016)	18-94	18,377	Cross-sectional	-	Neuropsychological	Null
Rajan et al. (2019)	65<	5,807	Longitudinal	10 years	Neuropsychological	Positive
Sinclair et al. (2017)	23-24, 42-67	118	Cross-sectional	-	Neuropsychological	Positive (STM)
Wilson, Bienias, et al. (2002)	65<	669	Longitudinal	8 years	Neuropsychological	Positive
Zokaei et al. (2021)	18<	854	Cross-sectional	-	Cognitive	Positive (STM)

A study that investigated individuals over the age of 90 years suggests an interesting relationship among the APOE ε2 allele, cognition and the brain at old age (Berlau et al., 2009). Eighty-two participants over the age of 90 years, 11 of whom were APOE ε2 carriers, attended regular cognitive assessments every six months followed by a post-mortem brain investigation. It was found that APOE ε2 carriers, who did not have an AD diagnosis prior to death, were more likely to meet neuropathological criteria for AD than their APOE ε3 counterparts (Berlau et al., 2009). More strikingly, APOE ε2 carriers also displayed similar levels of neuropathological markers of AD as APOE ε4 carriers (Berlau et al., 2009). This suggests that cognition of APOE ε2 carriers may be more resistant to AD pathology than that of APOE ε4 carriers despite similar brain pathology. On the other hand, this particular protective effect of APOE ε2 allele on cognition may be reserved to the oldest old, as the relationship between APOE alleles and survival breaks down after the age of 90 (Bathum et al., 2006).

The aim of the study described in the current chapter was, therefore, to compare cross-sectionally STM and LTM performance of young and older APOE ε2/ε3 and ε3/ε3 carriers using two sensitive continuous-report tasks. The first of the two tasks was the well-validated Oxford Memory Test, performance on which has been shown to be sensitive to age (Pertzov et al., 2015), medial temporal lobe damage (Liang et al., 2016; Pertzov et al., 2013; Zokaei, Nour, et al., 2019), and subtle genetic differences among different APOE groups (Zokaei et al., 2021; Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020). This task allowed the measurement of STM for two different loads (one or three items) after two different delay intervals (one or eight seconds). The second task was developed in-house to measure explicit LTM retrieval. This task involved two stages. During stage one, participants learned associations between objects (one or two) and scenes. During stage two, which followed after a delay of approximately 20 minutes, participants performed a surprise explicit

LTM retrieval test. Both tasks focused on contextual spatial associations between objects and their locations, measured on a continuous scale. In addition, a categorical two-alternative forced-choice measure of item identity was also used.

Based on the findings from previous studies, it was expected that APOE ε2/ε3 carriers, especially at older age, would show a memory advantage over their APOE ε3/ε3 counterparts in both STM and LTM. This advantage would manifest in particular in greater memory resolution when reporting object locations. It was also expected that there would be marked age-related differences in memory performance, as discussed in Chapter 1, with worse memory for object identities and locations in older as compared to young participants.

2.2. Methods

2.2.1. Participants

The study was approved by the Medical Sciences Interdivisional Research Ethics Committee of the University of Oxford (Ethics Approval Reference: R45359/RE003) and complied with the Declaration of Helsinki.

Participants were recruited based on their APOE genotype via the NIHR BioResource (https://bioresource.nihr.ac.uk/). In total, 46 APOE ε2/ε3 and 47 APOE ε3/ε3 carriers were recruited to take part in this study. To be included in the analysis, participants were required to display healthy levels of cognitive performance. Therefore, two participants were excluded from the analysis due to Addenbrooke's Cognitive Examination-III (ACE-III, see section 2.2.2.) score lower than 88/100, the highest recommended cut-off to detect cognitive impairment (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013). The final sample consisted of 22 young ε2/ε3 (21-36 years), 22 older ε2/ε3 (61-82 years), 22 young ε3/ε3 (22-36 years) and 25 older ε3/ε3 (62-78 years) carriers (the exact gene group membership of the excluded participants is not disclosed to avoid their unblinding). One older participant self-reported

colour blindness. Because task performance was not contingent on colour vision and their performance did not differ from other participants in their group, their data were included in the analysis. The remaining participants had normal or corrected-to-normal vision by self-report. All participants were fluent in written and spoken English and comparable on years of education (Table 2.2). Finally, both groups of older participants had comparable ACE-III scores and depression scores, as measured using the Geriatric Depression Scale (GDS, Brink et al., 1982; Table 2.2).

Table 2.2. Descriptive information for participants included in the analysis.

	Young		Older			
Measure	APOE ε2/ε3	APOE ε3/ε3	APOE ε2/ε3	APOE ε3/ε3	Statistic	*p*
N	22	22	22	25	$X^2(3) = 0.30$	.96
Male/female	11/11	10/12	11/11	12/13	$X^2(3) = 0.12$	.99
Age	28.77 (4.63)	29.68 (4.65)	68.86 (5.88)	69.52 (4.82)	$U_{Young} = 219$ $U_{Older} = 248$	.60 .57
Education	16.68 (2.03)	15.98 (1.98)	15.50 (3.04)	16.44 (2.87)	$F(3, 87) = 0.94$	.42
Handedness (L/R)	4/18	1/21	0/22	5/18	-	.06
ACE-III total	-	-	95.68 (2.80)	96.80 (3.04)	$U_{Older} = 201$	.11
GDS Depression	-	-	0.54 (1.10)	0.56 (1.26)	$U_{Older} = 308.5$	.37
GDS Apathy	-	-	0.54 (0.67)	0.40 (0.76)	$U_{Older} = 320$	.26
Dementia in first degree relatives	0	0	5	7	-	.74*

Note: ACE-III = Addenbrooke's Cognitive Examination III, GDS = Geriatric Depression Scale; Age, years in education, ACE-III, and GDS scores are presented as *M* (*SD*). Where test statistics are not provided, Fisher's Exact Test (two-tailed) for count data was used due to 5 or fewer observations per condition; * - comparison between older APOE ε2/ε3 and APOE ε3/ε3 carriers only.

2.2.2. Stimuli, Tasks and Procedures

This study consisted of two computer-based tasks, identical to those described by Zokaei et al. (2019), to measure STM and LTM performance (Figure 2.1 and Figure 2.2, respectively).

In the STM task, participants viewed one or three coloured fractals (1 or 3 seconds, respectively) presented on a black background. Following a delay of either 1 or 8 seconds, the identity and location of one of these fractals was probed.

The LTM task had two stages: A Learning stage was followed by a surprise Explicit LTM retrieval stage. In the Learning stage, participants learned object-scene associations by searching for one or two images of everyday objects within photographic scenes. After a break of approximately 20 minutes following this stage, participants were presented with the surprise Explicit LTM retrieval stage. In this stage, participants viewed previously learned scenes and were probed about identities and locations of objects presented in those scenes during the Learning stage.

The order of the STM and LTM tasks was counterbalanced across participants. Tasks were presented using a Dell OptiPlex 9030 All-in-One touch screen computer with a 1920-by-1080 pixels resolution (53.0 by 29.7 cm), using a Cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent_2000.php) and MATLAB Release 2015b (the MathWorks Inc., Natick, MA, USA).

Older participants underwent cognitive assessment using ACE-III during the break between the two stages of the LTM task. The ACE-III tests attention, memory, verbal fluency, language, and visuospatial abilities. The highest recommended cut-off of 88/100 (Hsieh et al., 2013) was selected, below which participants were excluded from the analysis. Two older participants failed to meet the inclusion criterion.

Finally, all participants completed an online questionnaire, which included questions on demographic information, family history of dementia, and physical and mental health. In the interest of time and to keep them preoccupied to prevent any rehearsal, young participants completed this questionnaire during the break between the two stages of the LTM task, while older participants completed this questionnaire at the end of the study.

2.2.2.1. Short-Term Memory Task

2.2.2.1.1. Stimuli. A set of 60 coloured fractals were used as stimuli in this task. Throughout the task, fractals were presented on a black background (RGB [0, 0, 0]). Their size was restricted to 120 by 120 pixels. Fractal locations were set randomly within several constraints: they appeared at least 120 pixels from the edges and 200 pixels from the centre of the screen, with a minimum distance of 270 pixels from the centres of other fractals in three-item trials.

2.2.2.1.2. Procedure. At the beginning of each trial in the STM task (Figure 2.1), participants viewed a memory array of either one or three fractals for 1 or 3 seconds, respectively. The array was followed by a memory delay of either 1 or 8 seconds, during which only the black background (RGB [0, 0, 0]) was presented. Following the delay, participants viewed two probe fractals arranged vertically along the centre of the screen. One of these fractals had appeared in the memory array before the delay (target) while the other had not (foil). Participants were asked to select the target fractal (identification) and place it in its remembered location as precisely as they could (localisation). They had unlimited time to respond.

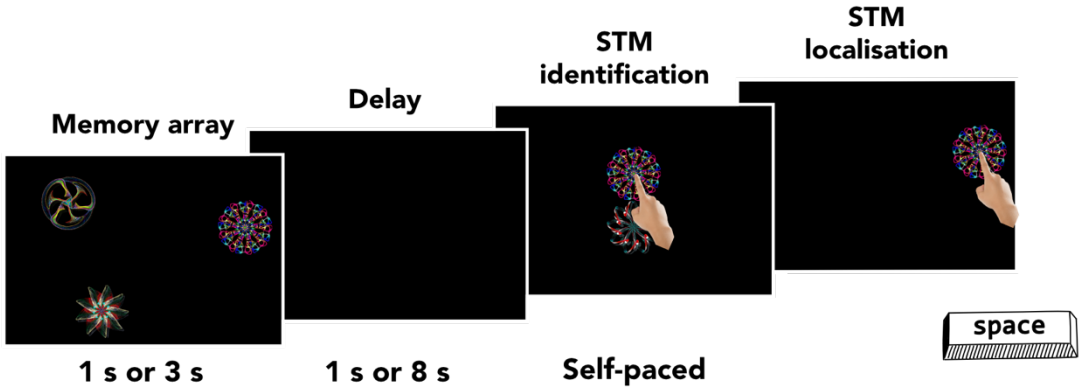


Figure 2.1. Short-term memory (STM) task schematic. Each trial in the STM task began with a memory array of either one or three coloured fractals presented on a black background (1 s or 3 s, respectively), followed by a delay of 1 or 8 s, during which only the black background was presented. The delay was followed by a memory probe: participants had to identify the object that was presented on the screen before the delay out of two shown at the centre of the screen (STM identification) and place it to its remembered location (STM localisation).

There were two blocks of 50 trials, separated by a break. Each block consisted of 16 one-item and 34 three-item trials. Half of these trials incorporated a 1-second memory delay, while an 8-second memory delay was used in the remaining half. Each fractal was presented two to three times per block. All participants completed eight practice trials prior to the task to familiarise themselves with the procedure.

2.2.2.2. Long-Term Memory Task

2.2.2.2.1. Stimuli. Coloured photographs of indoor and outdoor scenes and images of everyday objects were used as stimuli in the LTM task. The scene set consisted of photographs from the Brain and Cognition Laboratory's in-house repository. Ninety-six scenes were randomly selected from a pool of 165 scenes for each participant. They were presented at a resolution of 1125 by 844 pixels (31 by 23.2 cm) surrounded by a grey background (RGB [0.5, 0.5, 0.5]).

The object set consisted of images of everyday objects from Brady et al. (2008) supplemented by additional objects obtained using Google Image Search and processed to remove backgrounds when necessary. A total of 256 objects were randomly drawn from a pool of 415 coloured objects for each participant. They included a range of household, food, and clothing items, as well as toys, tools, kitchenware, and sports equipment. All object images were visually distinct from one another and easy to name. Objects were no larger than 50-by-50 pixels and had an equal probability of appearing in all four quadrants of the scene. Object locations were randomly selected with several restrictions: objects were at least 50 pixels away from the edges and from the centre of the scene, and there was a minimum of 200 pixels between the centres of objects in two-object trials.

2.2.2.2.2. Procedure. This task consisted of two stages: Learning (Figure 2.2A) and Explicit LTM retrieval (Figure 2.2B). Explicit LTM retrieval always followed the Learning stage after a break of approximately 20 minutes.

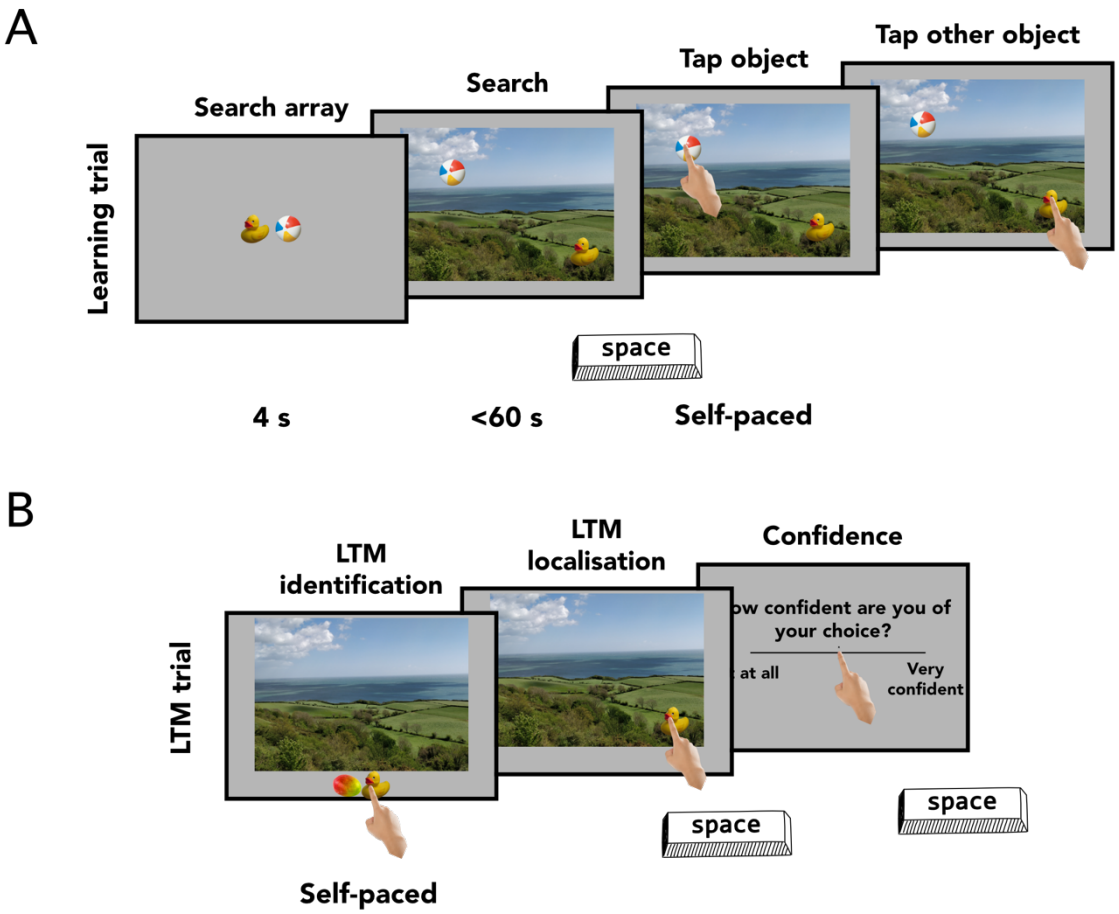


Figure 2.2. Schematic for the two stages of the Long-term memory (LTM) task: Learning (A) and Explicit LTM retrieval (B). Each trial in the Learning stage (A) began with a search array, which contained either one or two everyday objects presented on a grey background (4 s). The search array was followed by the search display. Here, object(s) from the search array were embedded within the scene. Participants had to find the object(s), press the space bar once they had done so, and tap on each of the object(s) to indicate their location. The trial timed out after 60 s if no action was taken. Each trial in the Explicit LTM retrieval stage (B) began with a LTM probe. Here, participants were shown one of the scenes from the Learning stage with two objects below and were asked to select the object that appeared within that scene during Learning (LTM identification) and place it in its remembered location within the scene (LTM localisation). They pressed the space bar to confirm the location. Following LTM localisation, participants were presented with a continuous confidence rating scale on their performance. They had to indicate their confidence from Not confident at all to Very confident. Participants pressed the space bar to complete the trial.

Learning: Each Learning (Figure 2.2A) trial began with a search array of either one or two objects arranged horizontally along the centre of a grey screen (RGB [0.5, 0.5, 0.5]) shown for 4 seconds. These object(s) then reappeared within a scene at random locations. Participants' task was to search for the object(s), press the space bar once they had found them, and indicate the location of each object by tapping on it with their finger. If there were two objects in the search array, participants were instructed not to press the spacebar until both objects were found. A new trial started automatically after object locations were successfully indicated. The trial timed out after 60 seconds if no response was made.

There were four blocks of 96 trials. All object and scene combinations were repeated across the four blocks in randomised order to facilitate learning. Each block consisted of 32 1-item and 64 2-item trials. Participants were encouraged to take breaks between the blocks. All participants completed a minimum set of ten practice trials prior to the start of the task to familiarise themselves with the procedure. If required, they could repeat the set of practice trials until they were comfortable with the task.

Explicit LTM retrieval: Each Explicit LTM retrieval (Figure 2.2B) trial began with an LTM probe. The probe consisted of a scene with two objects presented below. One of these objects had appeared within the scene during the Learning stage (target) while the other object was novel (foil). Participants were asked to select the object they remembered within the scene (identification) and place it in its remembered location as precisely as they could (localisation). They had unlimited time to respond and pressed the spacebar to confirm their response. Following localisation, participants provided a rating to indicate their overall confidence on identification and localisation on a continuous scale from "*Not confident at all*" to "*Very confident*". Finally, they pressed the space bar to confirm their rating and proceed to the next trial.

2.2.3. Design

2.2.3.1. STM Task. The STM task utilised a 2 × 2 × 2 × 2 mixed factorial design with age group (young, older) and gene group (APOE ε2/ε3, APOE ε3/ε3) as between-subject factors and Set size (1 object, 3 objects) and delay length (1 s, 8 s) as within-subject factors. I measured identification accuracy, the proportion of trials in which objects were correctly identified, and localisation error, estimated using the Euclidean distance between the original object location and the reported location.

2.2.3.2. LTM task. The learning task utilised a 2 × 2 × 2 × 4 mixed factorial design with age group (young, older) and gene group (APOE ε2/ε3, APOE ε3/ε3) as between-subject factors and set size (1 object, 2 objects) and block (1, 2, 3, 4) as within-subject factors. I measured search accuracy, the proportion of trials in which the object(s) were successfully found, and search time, the time it took to successfully find the objects indicated by the space bar press in accurate trials.

The explicit LTM retrieval task utilised a 2 × 2 × 2 mixed factorial design with age group (young, older) and gene group (APOE ε2/ε3, APOE ε3/ε3) as between-subject factors and set size (1 object, 2 objects) as the within-subject factor. I measured identification accuracy, the proportion of trials in which objects were correctly identified, and localisation error, the Euclidean distance between the original object location and the reported location.

2.2.4. Data Analysis

2.2.4.1. Data pre-Processing. Data were pre-processed and analysed using MATLAB Release 2018b (the MathWorks Inc., Natick, MA, USA) and R version 4.0.2 (2020) on R Studio version 1.3.1093.

Trials were excluded from the analysis if response times to identify the target objects were faster than 100 milliseconds and if objects were placed outside the scene boundaries in LTM task. Explicit LTM retrieval trials that tested stimuli from Learning trials in which objects were not found in block four were also excluded. In total, less than one percent of trials were excluded from the STM and approximately two percent of trials were excluded from the LTM data analysis. Additionally, only the trials in which targets were accurately identified (accurate trials) were included in localisation error analysis.

2.2.4.2. Main Analyses. Data violated the assumption of normality of the residuals required to carry out the analysis of variance (ANOVA). Therefore, lambda values were derived for STM identification accuracy, STM localisation errors, search accuracy, search time, LTM identification accuracy and LTM localisation errors using *MASS* package (v. 7.3-51.6). Data were then transformed using appropriate Box-Cox transformations based on these lambda values (Box & Cox, 1982; Osborne, 2010) using *car* package (v. 3.0-10). Mixed factorial ANOVAs were then computed using the *afex* package (v. 0.28-0, Singmann et al., 2018). Where significant deviations from sphericity occurred, as measured using Mauchly's test, Greenhouse-Geisser correction was applied. Any follow-up comparisons were performed using *emmeans* package (v. 1.5.1, Lenth, 2018) with *p* values Dunn-Šidák-adjusted for multiple comparisons. Where additional follow-up comparisons were required, paired and independent samples t-tests were computed as appropriate using *stats* package (v. 4.0.2).

2.2.4.3. Localisation Errors at Chance. I used a data-driven approach to estimate localisation error at chance level separately for LTM and STM. To start, I randomly shuffled each participant's localisation response coordinates across all trials and calculated a new localisation error from the original target location to the shuffled response location for every

trial. I repeated this procedure for 1000 iterations in total for each participant per each memory type (STM, LTM), calculating the mean localisation error per iteration. I then calculated the mean across all iterations for each participant and the mean across participants for each memory type, which are the estimates for localisation error at chance for each memory task.

2.2.4.4. Relationship Between LTM Localisation Errors and Confidence Judgements

Judgements. I also looked at the relationship between LTM localisation errors and confidence judgements. Confidence is prone to individual biases (Fleming & Lau, 2014). For example, some individuals might be more modest than others, reporting on average lower confidence. To eliminate biases, I z-scored (normalised) confidence data per participant, resulting in a similar centre value across participants. I then computed Spearman's correlation between LTM localisation errors in accurate trials and normalised confidence for each participant. Localisation errors were chosen as it was expected that they would have a more meaningful relationship with confidence than identification accuracy, which was a binary measure. Correlation coefficients were then normalised using Fisher's z test with *psych* package version 1.8.4 on R (Revelle, 2018). Normalised coefficients were subjected to a two-way between-subjects ANOVA, with age group (young, older) and gene group (APOE ε2/ε3, APOE ε3/ε3) as between-subject factors, performed using *afex* package version 0.22-1 for R (Singmann et al., 2018). Follow-up tests were performed using *emmeans* package version 1.3.0 for R (Lenth, 2018), and α level was Dunn-Šidák-adjusted for two tests. I only used data from two-object trials in this analysis to provide more stable estimates due to larger trial numbers in this condition.

2.2.4.5. Sources of Localisation Errors. Finally, two separate three-parameter two-dimensional mixture models were fitted to the pre-processed localisation error data from accurate STM and Explicit LTM retrieval trials per participant using the maximum likelihood estimation on MemToolbox2D (Grogan et al., 2020) and MATLAB release 2018b (the MathWorks Inc., Natick, MA, USA). The three parameters were memory imprecision, the proportion of guesses, and the proportion of swap (or mis-binding) errors. This model is similar to that described by Bays, Catalao and Husain (2009) but tailored to two-dimensional data. Data were not normally distributed, violating the assumptions required to run the ANOVA, and were therefore transformed using the procedure described in section 2.2.3.2. prior to the analysis.

Model estimates per participant for STM imprecision and the proportion of guesses were subjected to a 2 × 2 × 2 × 2 mixed factorial ANOVA with age group (young, older) and gene group (APOE ε2/ε3, APOE ε3/ε3) as between-subject factors and set size (1 object, 3 objects) and delay length (1 s, 8 s) as within-subject factors. The proportion of swap errors could only be estimated for 3-item trials and therefore a 2 × 2 × 2 mixed factorial ANOVA with age group (young, older) and gene group (APOE ε2/ε3, APOE ε3/ε3) as between-subject factors and delay length (1 s, 8 s) as a within-subjects factor was conducted.

Similarly, estimates for LTM imprecision and the proportion of guesses were subjected to a 2 × 2 × 2 mixed factorial ANOVA with age group (young, older) and gene group (APOE ε2/ε3, APOE ε3/ε3) as between-subject factors and set size (1 object, 3 objects) as a within-subject factor. A two-way ANOVA with age group (young, older) and gene group (APOE ε2/ε3, APOE ε3/ε3) as between-subject factors was used to analyse the proportion of swap errors in 2-item trials.

Follow-up tests were performed using *emmeans* package version 1.3.0 for R (Lenth, 2018), with α level Dunn-Šidák-adjusted for multiple comparisons.

2.3. Results

2.3.1. Short-Term Memory

2.3.1.1. Identification Accuracy. There were three significant main effects on STM identification accuracy: an effect of age group, $F(1, 87) = 9.30$, $p = .003$, $\eta^2_P = .10$, set size, $F(1, 87) = 665.93$, $p < .001$, $\eta^2_P = .88$, and delay length, $F(1, 87) = 16.31$, $p < .001$, $\eta^2_P = .16$. Overall, older adults were less accurate than young adults, and participants' performance was worse in 3-item trials as compared to 1-item trials and after an 8-s delay as compared to a 1-s delay (Figure 2.3A). However, these main effects were complemented by significant Age group × Set size, $F(1, 87) = 12.36$, $p < .001$, $\eta^2_P = .12$, and Set size × Delay length interactions, $F(1, 87) = 6.49$, $p = .01$, $\eta^2_P = .07$. Follow-up tests revealed that the main effects of age group and delay length were driven by participants' performance in 3-item trials (Age group: $t(162) = 4.55$, $p < .001$; Delay length: $t(162) = 4.69$, $p < .001$) but not 1-item trials (Age group: $t(173) = 0.31$, $p = .76$; Delay length: $t(173) = 1.20$, $p = .23$). There was no main effect of gene group (Table 2.3). Both gene groups were equally capable of identifying target objects. None of the other two-, three- or four-way interactions reached statistical significance (Table 2.3).

Table 2.3. Effects on STM identification accuracy that did not reach statistical significance.

Effect	Statistic	p	η^2_P
Gene group	$F(1, 87) = 2.37$	.13	.03
Gene group × Age group	$F(1, 87) = 0.67$	.42	.01
Gene group × Set size	$F(1, 87) = 0.22$	.64	.002
Gene group × Age group × Set size	$F(1, 87) = 0.24$	.62	.003
Age group × Delay length	$F(1, 87) = 0.35$	.55	.004
Gene group × Delay length	$F(1, 87) = 0.96$	.33	.01
Gene group × Age group × Delay length	$F(1, 87) = 3.69$	.06	.04
Age group × Set size × Delay length	$F(1, 87) = 1.05$	.31	.01
Gene group × Set size × Delay length	$F(1, 87) = 0.79$	.38	.01
Gene group × Age group × Set size × Delay length	$F(1, 87) = 1.56$	.22	.02

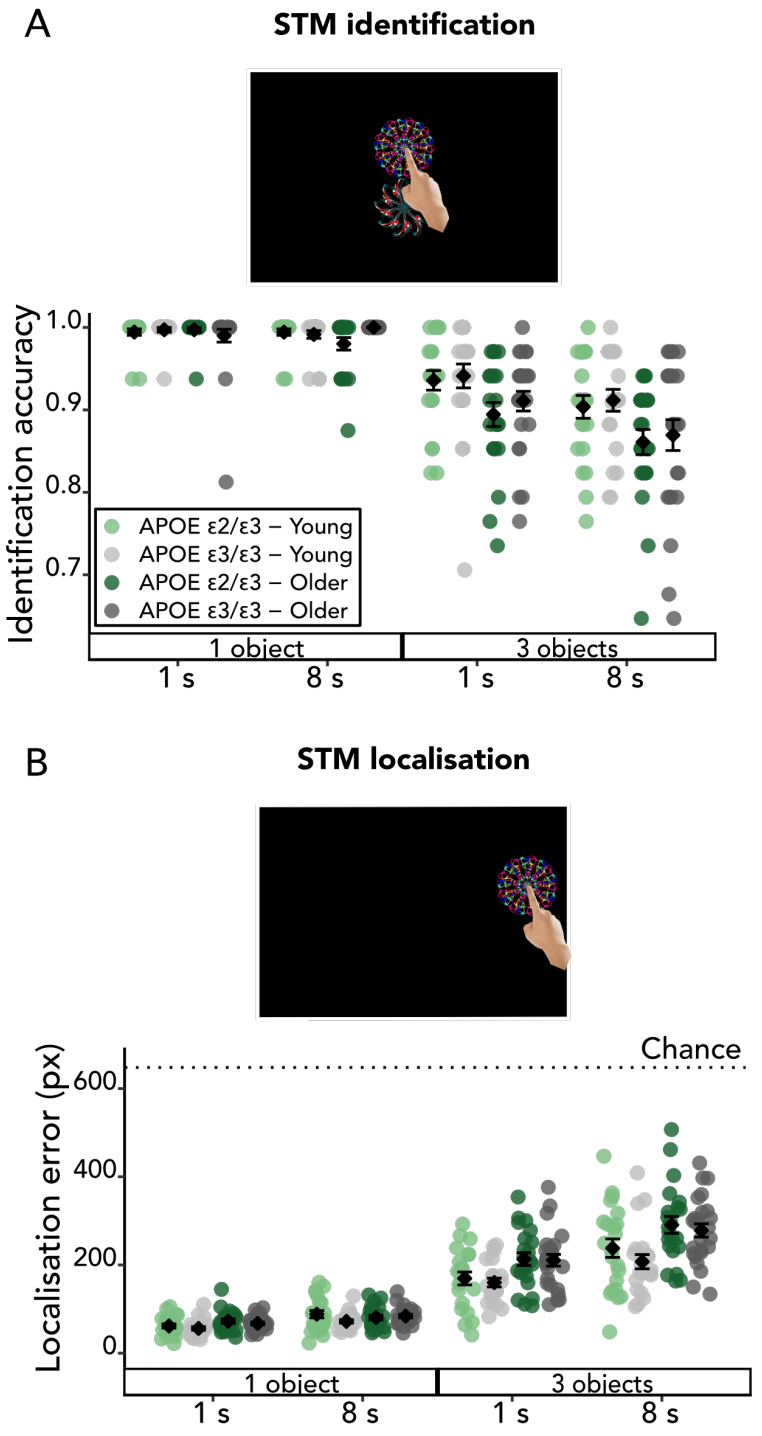


Figure 2.3. Short-term memory (STM) task results: A – Identification accuracy, B – Localisation error. Coloured dots represent participant means (light green – young APOE ε2/ε3, dark green – older APOE ε2/ε3, light grey – young APOE ε3/ε3, dark grey – older APOE ε3/ε3 carriers), diamonds represent group means and error bars are standard errors of the group means. Dotted line represents the average localisation error if participants performed at chance.

2.3.1.2. Localisation Error. There were significant main effects of age group, $F(1, 87) = 11.38$, $p = .001$, $\eta^2_P = .12$, set size, $F(1, 87) = 1478.31$, $p < .001$, $\eta^2_P = .94$, and delay length, $F(1, 87) = 149.44$, $p < .001$, $\eta^2_P = .63$, on localisation errors. Overall, older adults produced larger localisation errors than young adults, and all participants performed worse in 3-object trials as compared to 1-object trials and after an 8-s memory delay as opposed to a 1-s memory delay (Figure 2.3B). However, these main effects were complemented by significant Age group × Set size, $F(1, 87) = 8.58$, $p = .004$, $\eta^2_P = .09$, and Set size × Delay length interactions, $F(1, 87) = 4.38$, $p = .04$, $\eta^2_P = .05$. Follow-up tests revealed that the main effect of age group was driven by participants' performance in 3-item trials, $t(124) = -4.30$, $p < .001$. The direction of the effect was similar in 1-item trials, but it did not reach statistical significance, $t(124) = -1.81$, $p < .001$, $p = .07$. Similarly, the difference in performance between the two delay lengths emerged more strongly in 3-item trials than in 1-item trials, $t(90) = 2.07$, $p = .04$, although in both cases the difference was statistically significant ($t(172) = -10.48$, $p < .001$ and $t(172) = -7.63$, $p < .001$, respectively). There was no main effect or interactions involving gene group (Table 2.4), indicating that the two gene groups showed similar localisation performance (Figure 2.3B). There were no other significant two-, three- or four-way interactions (Table 2.4).

Table 2.4. Effects on STM localisation error that did not reach statistical significance.

Effect	Statistic	p	η^2_P
Gene group	$F(1, 87) = 0.51$	.48	.01
Gene group × Age group	$F(1, 87) = 0.29$	.59	.003
Gene group × Set size	$F(1, 87) = 0.05$	.82	<.001
Gene group × Age group × Set size	$F(1, 87) = 0.49$	.49	.01
Age group × Delay length	$F(1, 87) = 1.68$	.20	.02
Gene group × Delay length	$F(1, 87) = 0.21$	.65	.002
Gene group × Age group × Delay length	$F(1, 87) = 1.85$	.18	.02
Age group × Set size × Delay length	$F(1, 87) = 3.36$	.07	.04
Gene group × Set size × Delay length	$F(1, 87) = 1.41$	.24	.02
Gene group × Age group × Set size × Delay length	$F(1, 87) = 0.35$	.56	.004

2.3.1.3. Sources of STM Localisation Error

2.3.1.3.1. Imprecision. There was a significant main effect of age group on memory imprecision, $F(1, 87) = 6.64$, $p = .01$, $\eta^2_P = .07$. Overall, memory imprecision was higher in older adults than in young adults (Figure 2.4A). However, this effect was accompanied by a significant Age group × Delay interaction, $F(1, 87) = 4.40$, $p = .04$, $\eta^2_P = .05$. This interaction reflected that older adults were only significantly less precise than young adults after a 1-s memory delay, $t(108) = -2.64$, $p = 0.01$, while performance was comparable between age groups after an 8-s memory delay, $t(108) = -1.24$, $p = 0.22$. There was also a significant main effect of memory delay, $F(1, 87) = 151.83$, $p < .001$, $\eta^2_P = .64$. Memory imprecision was higher after an 8-s delay than 1-s delay (Figure 2.4A). Similarly, there was also a significant main effect of set size, $F(1, 87) = 451.96$, $p < .001$, $\eta^2_P = .84$. Higher memory load of 2 items lead to higher imprecision than 1-item load (Figure 3A). Finally, there was no main effect or interactions involving gene group (Table 2.5), indicating that memory precision was similar between the two gene groups (Figure 2.4A). None of the other two-, three- or four-way interactions reached statistical significance (Table 2.5).

Table 2.5. Effects on memory imprecision that did not reach statistical significance.

Effect	Statistic	p	η^2_P
Gene group	$F(1, 87) = 0.71$	.40	.008
Gene group × Age group	$F(1, 87) = 0.25$	.62	.003
Age group × Set size	$F(1, 87) = 0.53$	.47	.01
Gene group × Set size	$F(1, 87) = 0.04$	.85	<.001
Gene group × Age group × Set size	$F(1, 87) = 0.09$	.77	<.001
Gene group × Delay length	$F(1, 87) = 2.10$	.15	.02
Gene group × Age group × Delay length	$F(1, 87) = 3.52$	.06	.04
Set size × Delay length	$F(1, 87) = 0.24$	.62	.003
Age group × Set size × Delay length	$F(1, 87) = 0.85$	.36	.01
Gene group × Set size × Delay length	$F(1, 87) = 1.02$	.32	.01
Gene group × Age group × Set size × Delay length	$F(1, 87) = 0.30$	.59	.003

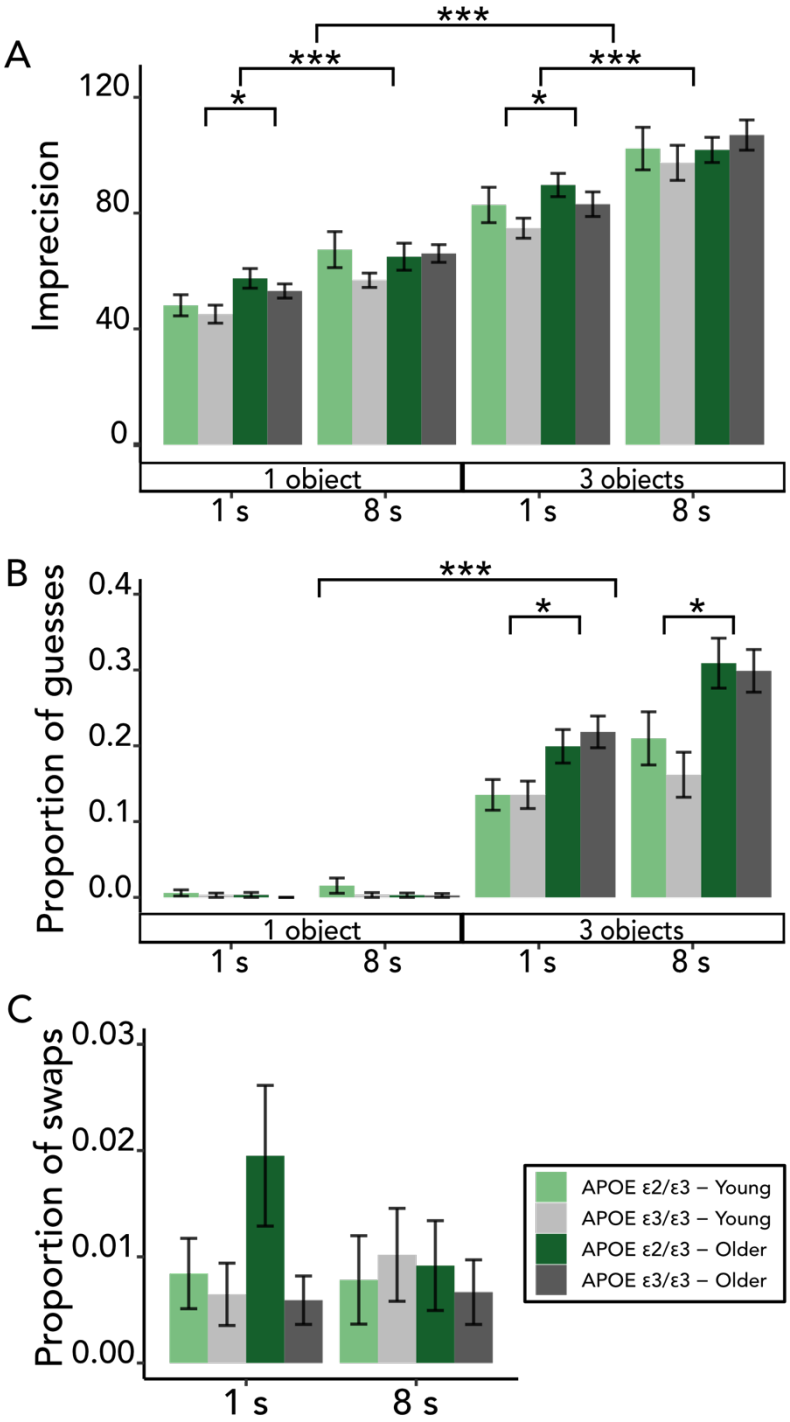


Figure 2.4. Mixture model results for STM data. A – Memory imprecision, B – Proportion of guesses, C – Proportion of swap errors. Coloured bars represent group means (light green – young APOE ε2/ε3, dark green – older APOE ε2/ε3, light grey – young APOE ε3/ε3, dark grey – older APOE ε3/ε3 carriers) and error bars are standard errors of the mean. * $p < .05$, *** $p < .001$.

2.3.1.3.2. Guesses. There was a significant main effect of set size on the proportion of guesses, $F(1, 87) = 1459.59$, $p < .001$, $\eta^2_P = .94$. The proportion of guess responses was higher in 3-item trials than in 1-item trials (Figure 2.4B). Although the main effect of age group was not statistically significant (Table 2.6), there was a significant Age group × Set size interaction, $F(1, 87) = 6.64$, $p = .01$, $\eta^2_P = .07$. The interaction reflected that although there was no difference between age groups in 1-item trials, $t(173) = 1.20$, $p = .23$, older adults guessed significantly more than young adults in 3-item trials, $t(173) = -2.32$, $p = .02$ (Figure 2.4B). The main effects of gene group and memory delay did not reach statistical significance (Table 2.6), indicating that overall APOE ε2/ε3 and ε3/ε3 carriers showed a similar amount of guessing regardless of the length of the memory delay (Figure 3B). Finally, there were no other significant two-, three- or four-way interactions (Table 2.6).

Table 2.6. Effects on the proportion of guess responses that did not reach statistical significance.

Effect	Statistic	p	η^2_P
Age group	$F(1, 87) = 0.59$	.45	.01
Gene group	$F(1, 87) = 0.82$	.37	.01
Gene group × Age group	$F(1, 87) = 0.32$	.57	.004
Gene group × Set size	$F(1, 87) = 0.44$	.51	.005
Gene group × Age group × Set size	$F(1, 87) = 0.13$	.72	.002
Delay length	$F(1, 87) = 2.87$	.09	.03
Age group × Delay length	$F(1, 87) = 0.03$	.86	<.001
Gene group × Delay length	$F(1, 87) = 0.85$	.36	.01
Gene group × Age group × Delay length	$F(1, 87) = 1.13$	.29	.01
Set size × Delay length	$F(1, 87) = 0.35$	.56	.004
Age group × Set size × Delay length	$F(1, 87) = 0.01$	.92	<.001
Gene group × Set size × Delay length	$F(1, 87) = 0.21$	.64	.002
Gene group × Age group × Set size × Delay length	$F(1, 87) = 0.08$	.78	<.001

2.3.1.3.3. Swaps. Overall, the proportion of swap errors was very low (Figure 2.4C). None of the main effects or interactions were statistically significant (Table 2.7), suggesting that swapping was unaffected by participants' age, gene group membership, or delay length (Figure 2.4C).

Table 2.7. Effects on the proportion of swap errors that did not reach statistical significance.

Effect	Statistic	p	η^2_P
Gene group	$F(1, 87) = 0$	.97	<.001
Age group	$F(1, 87) = 0.63$	.43	0.01
Gene group × Age group	$F(1, 87) = 0.07$	.79	<.001
Delay length	$F(1, 87) = 0.25$	.62	.003
Gene group × Delay length	$F(1, 87) = 0.38$	.54	.004
Age group × Delay length	$F(1, 87) = 0.08$	.78	<.001
Gene group × Age group × Delay length	$F(1, 87) = 1.52$	.22	.02

2.3.2. Long-Term Memory

2.3.2.1. Learning

2.3.2.1.1. Search time. There was a significant main effect of block on search time, $F(2.11, 179.40) = 337.56$, $p < .001$, $\eta^2_P = .80$. Pairwise comparisons showed that participants became quicker at finding objects with every block (block 1 – block 2, $t(255) = 9.24$, $p < .001$; block 2 – block 3, $t(255) = 11.41$, $p < .001$; block 3 – block 4, $t(255) = 9.06$, $p < .001$, Figure 2.5A). In addition, there was a significant main effect of age group, $F(1, 85) = 146.49$, $p < .001$, $\eta^2_P = .63$, which reflected that older adults were overall slower at finding objects within scenes (Figure 2.5A). There was also a significant Age group × Block interaction, $F(2.11, 179.40) = 5.92$, $p = .003$, $\eta^2_P = .06$. This interaction reflected that search times of older adults decreased more than those of young adults from block 1 to block 4, $t(175.88) = -3.77$, $p < .001$. However, based on a significant Age group × Set size × Block interaction, $F(2.81, 238.77) = 3.60$, $p = .02$, $\eta^2_P = .04$, the two-way interaction was only significant in 1-

but not 2-item trials ($F(2.06, 174.77) = 11.55$, $p = .002$, $\eta^2_P = .12$ and $F(2.64, 224.18) = 1.11$, $p = .56$, $\eta^2_P = .01$, respectively), indicating that across blocks older adults showed a steeper reduction in search time than young adults in 1- but not in 2-item trials. In addition, there was a significant main effect of set size, $F(1, 85) = 274.43$, $p < .001$, $\eta^2_P = .76$. Participants' responses were slower when two objects had to be found (Figure 2.5A). This effect was accompanied by a significant Age group × Set size interaction, $F(1, 85) = 8.54$, $p = .004$, $\eta^2_P = .09$. The interaction reflected that the difference between set size conditions was greater in older than in young participants, $t(286.18) = 10.06$, $p < .001$ (Figure 2.5A), although in both cases the difference was statistically significant ($t(85) = -14.17$, $p < .001$ and $t(85) = -9.40$, $p < .001$, respectively). Finally, there was no main effect of gene group or any other interactions (Table 2.8). Participants' genotype did not affect their search times.

Table 2.8. Effects on search time that did not reach statistical significance.

Effect	Statistic	p	η^2_P
Gene group	$F(1, 85) = 1.11$	.30	.01
Gene group × Age group	$F(1, 85) = 2.36$	.13	.03
Gene group × Set size	$F(1, 85) = 0.49$	.48	.01
Gene group × Age group × Set size	$F(1, 85) = 0.10$	.76	.001
Gene group × Block	$F(2.11, 179.40) = 0.91$	.41	.01
Gene group × Age group × Block	$F(2.11, 179.40) = 0.31$	.75	.004
Set size × Block	$F(2.81, 238.77) = 0.72$	.53	.01
Gene group × Set size × Block	$F(2.81, 238.77) = 0.58$	.62	.01
Gene group × Age group × Set size × Block	$F(2.81, 238.77) = 0.73$	.53	.01

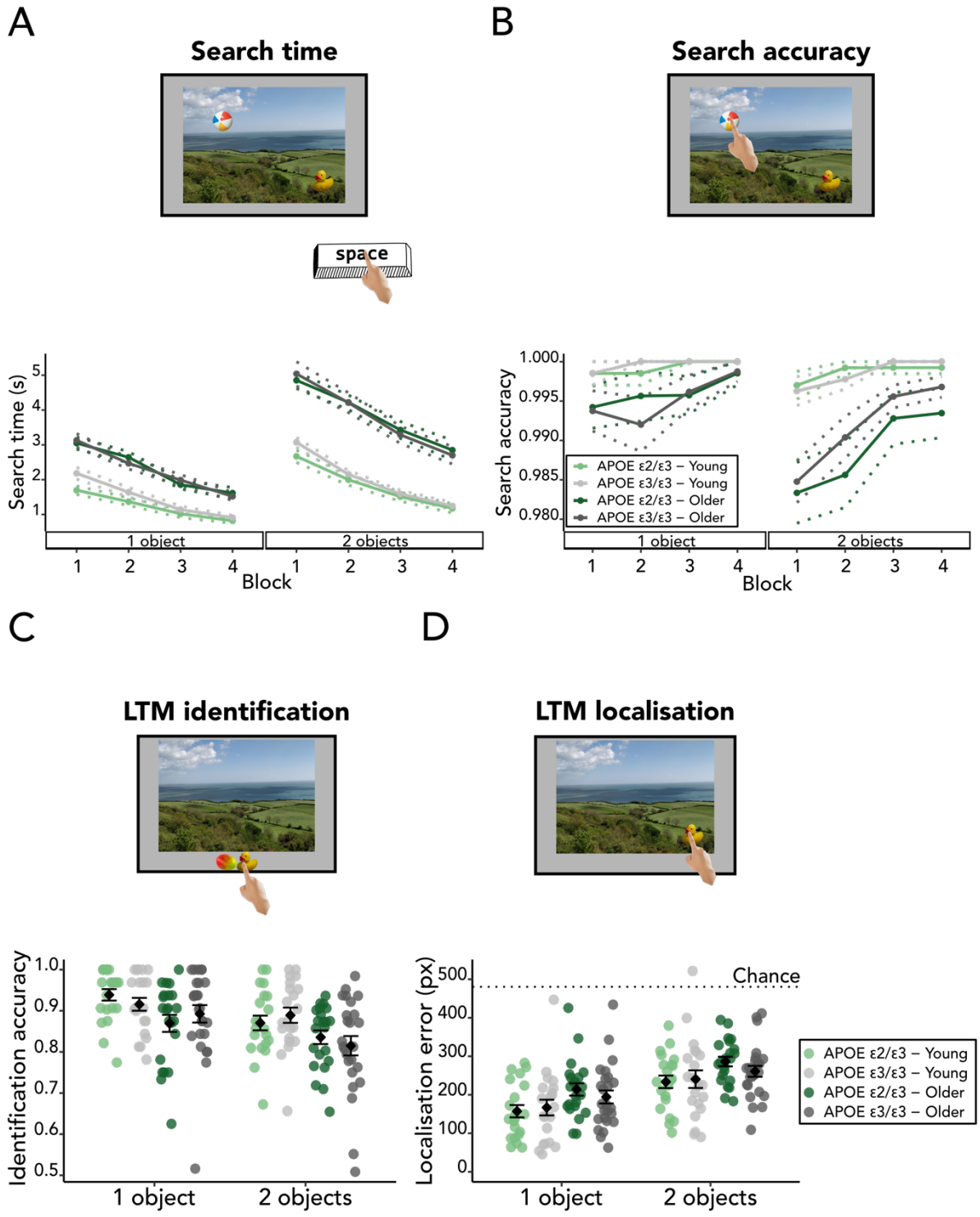


Figure 2.5. Long-term memory (LTM) task results: A – search time, B – search accuracy, C – Identification accuracy, D – Localisation error. In A and B, solid lines represent group means while dotted lines represent standard errors of the group means (light green – young APOE ε2/ε3, dark green – older APOE ε2/ε3, light grey – young APOE ε3/ε3, dark grey – older APOE ε3/ε3 carriers). In C and D, coloured dots represent participant means (light green – young APOE ε2/ε3, dark green – older APOE ε2/ε3, light grey – young APOE ε3/ε3, dark grey – older APOE ε3/ε3 carriers), diamonds represent group means and error bars are standard errors of the mean.

2.3.2.1.2. Search Accuracy. There was a significant main effect of block on search accuracy during the Learning stage, $F(2.63, 223.62) = 16.98$, $p < .001$, $\eta^2_P = .17$. Pairwise comparisons showed that participants' search accuracy increased across the first three blocks (block 1 – block 2, $t(255) = -2.49$, $p = .06$; block 2 – block 3, $t(255) = -2.87$, $p = .02$) and stabilised after (block 3 – block 4, $t(255) = -1.10$, $p = .69$, Figure 2.5B). There was also a significant main effect of age group on search accuracy, $F(1, 85) = 31.70$, $p < .001$, $\eta^2_P = .27$, as well as a significant Age group × Block interaction, $F(2.63, 223.62) = 3.80$, $p = .02$, $\eta^2_P = .04$. Although older participants showed lower search accuracy than their young counterparts (Figure 2.5B), their performance improved more from block 1 to block 4 than that of the young group, $t(147.55) = 2.86$, $p = .004$ (Figure 2.5B). In addition, there was a significant main effect of set size, $F(1, 85) = 35.80$, $p < .001$, $\eta^2_P = .30$, accompanied by a significant Age group × Set size interaction, $F(1, 85) = 15.30$, $p < .001$, $\eta^2_P = .15$. Overall, object search was less accurate in 2-item trials than in 1-item trials (Figure 2.5B). However, the interaction reflected that older participants' performance was significantly impaired by the increase in set size, $t(85) = 7.19$, $p < .001$, while young participants' performance was not, $t(85) = 1.43$, $p = .16$ (Figure 2.5B). There was also a significant Set size × Block interaction, $F(2.19, 186.02) = 4.48$, $p = .01$, $\eta^2_P = .05$. This interaction reflected that the difference in search accuracy between 1- and 2-item trials decreased significantly from block 1 to block 4, $t(88) = 2.47$, $p = .02$ (Figure 2.5B). Finally, there was no main effect of gene group or any other significant interactions (Table 2.9). Participants' genotype did not affect their search accuracy.

Table 2.9. Effects on search accuracy that did not reach statistical significance.

Effect	Statistic	*p*	η^2_P
Gene group	$F(1, 85) = 0.001$	.98	<.001
Gene group × Age group	$F(1, 85) = 0.0004$	.97	<.001
Gene group × Set size	$F(1, 85) = 0.05$	.83	<.001
Gene group × Age group × Set size	$F(1, 85) = 0.41$	.52	.005
Gene group × Block	$F(2.63, 223.62) = 0.57$	.61	.01
Gene group × Age group × Block	$F(2.63, 223.62) = 0.09$	.95	.001
Gene group × Set size × Block	$F(2.19, 186.02) = 0.34$	.73	.004
Age group × Set size × Block	$F(2.19, 186.02) = 1.19$	.31	.01
Gene group × Age group × Set size × Block	$F(2.19, 186.02) = 1.29$	.28	.02

2.3.2.2. Explicit Retrieval

2.3.2.2.1. Identification Accuracy. There was a significant main effect of age group, $F(1, 85) = 8.50$, $p = .005$, $\eta^2_P = .09$, as well as set size, $F(1, 85) = 51.54$, $p < .001$, $\eta^2_P = .38$, on LTM identification accuracy. Older adults were less accurate when identifying target objects than young adults, and all participants were less accurate in 2-item trials as compared to 1-item trials (Figure 2.5C). The main effect of gene group was not statistically significant, $F(1, 85) = 0.04$, $p = .83$, $\eta^2_P < .001$, indicating that the two gene groups showed similar identification accuracy. However, there was a significant three-way Gene group × Age group × Set size interaction, $F(1, 85) = 7.64$, $p = .007$, $\eta^2_P = .08$. Follow-up tests revealed that this interaction reflected different patterns of results in young and older participants. In the young group, the difference in identification accuracy between 1- and 2-item trials (the set size effect) was significantly greater in APOE ε2/ε3 carriers as compared to APOE ε3/ε3 homozygotes, t(29.87) = 2.32, p = .03 (Figure 2.5C). In contrast, the magnitude of the set size effect did not differ significantly between the two gene groups of older adults, t(44.12) = -1.63, p = .11, although the effect was trending towards the opposite direction, with a smaller set size effect in APOE ε2/ε3 carriers than in APOE ε3/ε3 carriers (Figure 2.5C). Finally, there were no other significant interactions: Gene group × Age group, $F(1, 85) = 0.15$, p

= .70, η^2_P = .002; Gene group × Set size, $F(1, 85) = 0.18$, $p = .67$, $\eta^2_P = .002$; Age group × Set size, $F(1, 85) = 0.09$, $p = .76$, $\eta^2_P = .001$.

2.3.2.2.2. Localisation Error. There was a significant main effect of age group on localisation errors, $F(1, 85) = 7.13$, $p = .01$, $\eta^2_P = .08$. Older adults produced larger localisation errors than young adults (Figure 2.5D). In addition, there was a significant main effect of set size, $F(1, 85) = 164.87$, $p < .001$, $\eta^2_P = .66$. Overall, participants produced larger average localisation errors in 2-item trials than in 1-item trials (Figure 2.5D). However, the effect of gene group was not statistically significant, $F(1, 85) = 0.33$, $p = .57$, $\eta^2_P = .004$. APOE ε2/ε3 and APOE ε3/ε3 performed similarly on LTM localisation (Figure 2.5D). Finally, there were no significant two- or three-way interactions: Gene group × Age group, $F(1, 85) = 0.78$, $p = .38$, $\eta^2_P = .01$; Gene group × Set size, $F(1, 85) = 0.07$, $p = .79$, $\eta^2_P < .001$; Age group × Set size, $F(1, 85) = 0.81$, $p = .37$, $\eta^2_P = .009$; Gene group × Age group × Set size interaction, $F(1, 85) = 0.01$, $p = .94$, $\eta^2_P < .001$.

2.3.2.2.3. Relationship Between Localisation Error and Confidence Judgements. There was a marginally significant main effect of age group on the mean correlation coefficients between LTM localisation error and normalised localisation confidence per participant, $F(1, 85) = 3.85$, $p = .05$, $\eta_p^2 = .04$. Older adults had a higher mean Fisher z-transformed correlation coefficient than young adults, $t(57) = -3.12$, $p = .008$ (Figure 2.6B), indicating that their confidence judgements were less negatively correlated with their LTM localisation performance than those of young adults. In other words, older participants were less able to judge their performance than young participants, producing higher confidence ratings after large errors and lower confidence ratings after small errors than young participants. However, this effect was accompanied by a significant Age group × Gene group

interaction, $F(1, 85) = 6.17$, $p = .02$, $\eta_p^2 = .07$. This interaction reflected that the difference between age groups was only statistically significant in APOE ε2/ε3, $t(85) = 3.10$, $p = .003$, but not APOE ε3/ε3 carriers, $t(85) = -0.37$, $p = .71$ (Figure 2.6A). The main effect of gene group was not statistically significant, $F(1, 85) = 0.03$, $p = .87$, $\eta_p^2 < .001$.

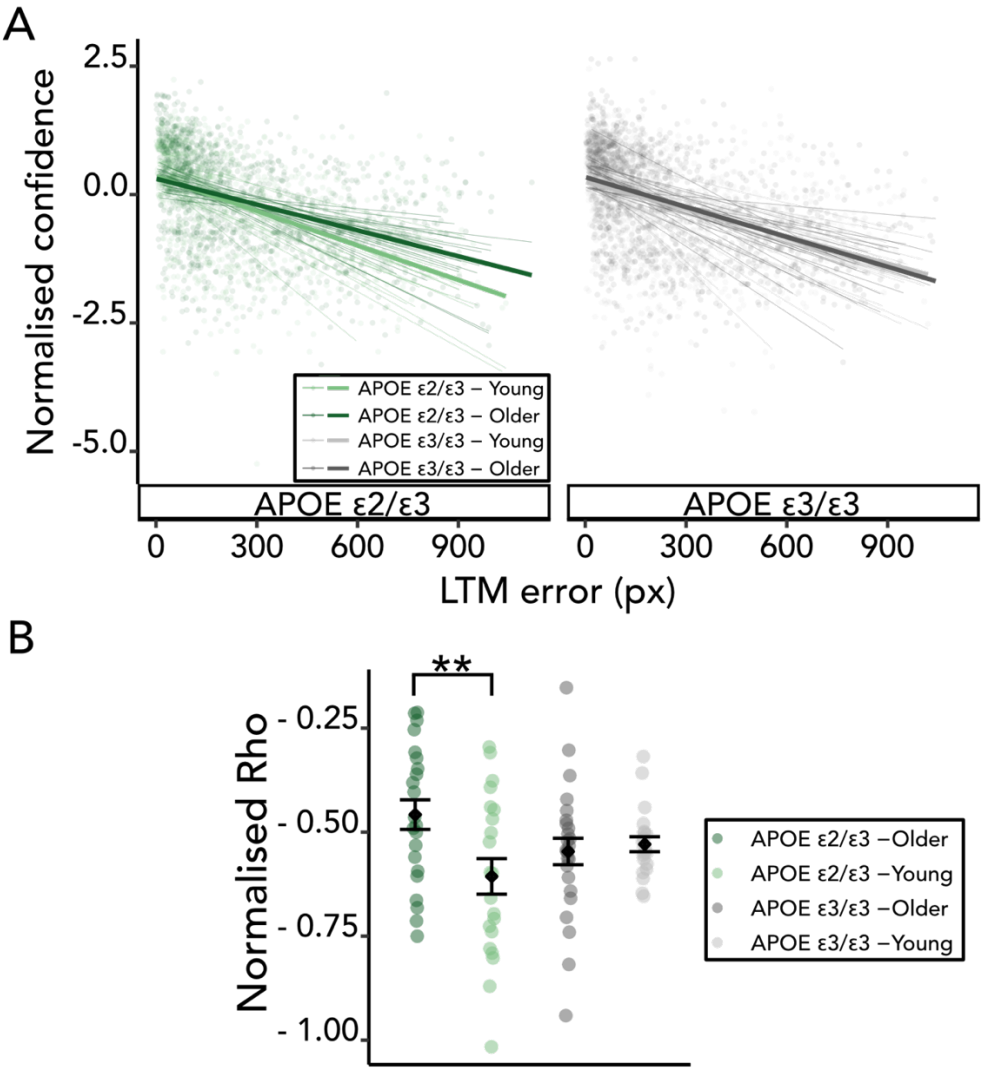


Figure 2.6. Correlation between LTM localisation error and confidence ratings (A) and the difference in normalised average correlation coefficients among groups (B). A – coloured dots represent participants' responses(light green – young APOE ε2/ε3, dark green – older APOE ε2/ε3, light grey – young APOE ε3/ε3, dark grey – older APOE ε3/ε3 carriers), thin coloured lines represent linear regression lines per participant, and thick coloured lines represent linear regression lines per group. B – Coloured dots represent participant means, diamonds represent group means and error bars are standard errors of the mean. ** $p < .01$.

2.3.2.2.4. Sources of LTM Localisation Error

Imprecision: There was a significant main effect of set size on memory imprecision, $F(1, 85) = 15.11$, $p < .001$, $\eta_p^2 = .15$. Participants were more imprecise in 2-object trials than in 1-object trials (Figure 2.7A).The effects of age group, $F(1, 85) = 0.71$, $p = .40$, $\eta_p^2 = .01$, and gene group, $F(1, 85) = 0.14$, $p = .71$, $\eta_p^2 = .002$, were not statistically significant, indicating that neither participants' age nor gene group membership affected the precision of their long-term memories (Figure 2.7A). Finally, there were no significant interactions: Gene group × Age group, $F(1, 85) = 2.03$, $p = .16$, $\eta_p^2 = .02$, Gene group × Set size, $F(1, 85) = 1.29$, $p = .26$, $\eta_p^2 = .02$, Age group × Set size, $F(1, 85) = 0.42$, $p = .52$, $\eta_p^2 = .005$, Gene group × Age group × Set size, $F(1, 85) = 2.90$, $p = .09$, $\eta_p^2 = .03$.

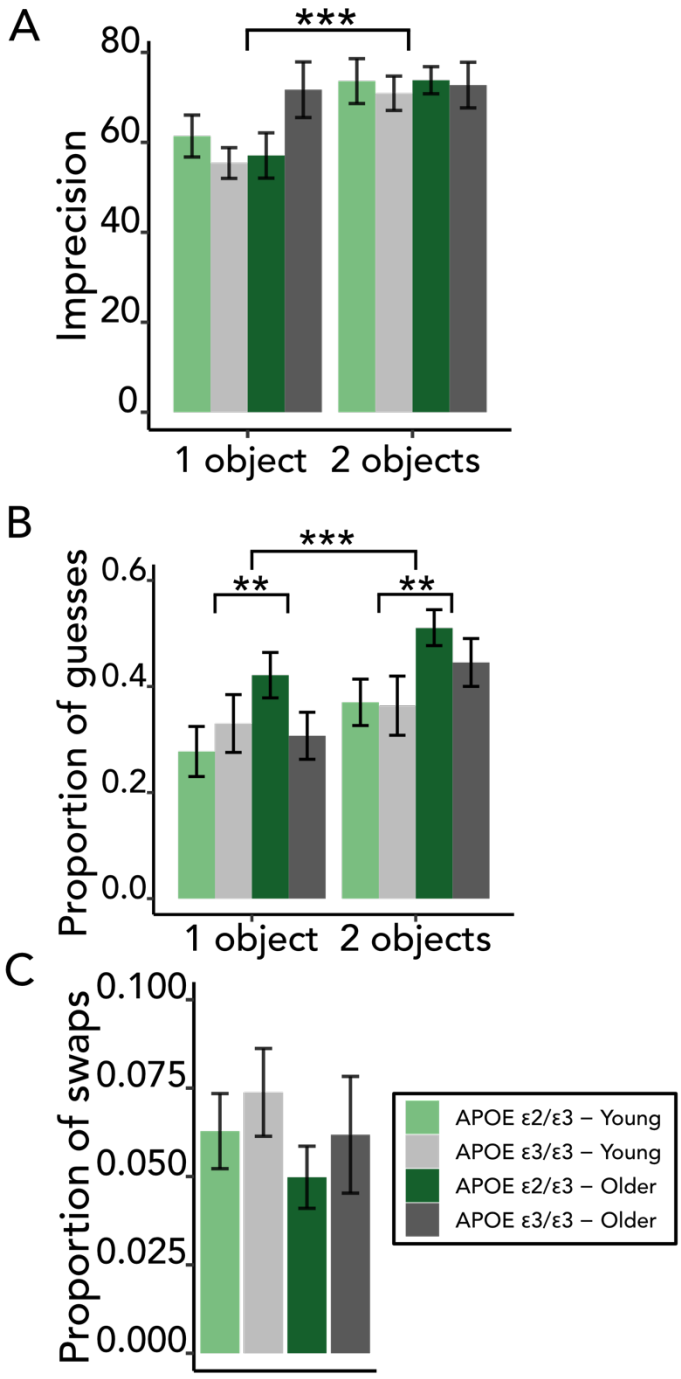


Figure 2.7. Mixture model results for LTM data. A – Memory imprecision, B – Proportion of guesses, C – Proportion of swap errors. Coloured bars represent group means (light green – young APOE ε2/ε3, dark green – older APOE ε2/ε3, light grey – young APOE ε3/ε3, dark grey – older APOE ε3/ε3 carriers) and error bars are standard errors of the mean. ** $p < .01$, *** $p < .001$.

Guesses: There was a significant main effect of age group on the proportion of guesses, $F(1, 85) = 7.37$, $p = .008$, $\eta_p^2 = .08$. Older participants guessed more than young participants (Figure 2.7B). There was also a significant main effect of set size, $F(1, 85) = 14.66$, $p < .001$, $\eta_p^2 = .15$. Participants guessed more in 2-object trials as compared to 1-object trials (Figure 2.7B). There was no main effect of gene group, $F(1, 85) = 0.78$, $p = .38$, $\eta_p^2 = .01$, indicating an equivalent proportion of guesses in APOE ε2/ε3 and ε3/ε3 carriers. Finally, none of the interactions reached statistical significance: Gene group × Age group, $F(1, 85) = 1.37$, $p = .25$, $\eta_p^2 = .02$, Gene group × Set size, $F(1, 85) = 0.30$, $p = .58$, $\eta_p^2 = .004$, Age group × Set size, $F(1, 85) = 0.39$, $p = .53$, $\eta_p^2 = .005$, Gene group × Age group × Set size, $F(1, 85) = 3.51$, $p = .06$, $\eta_p^2 = .04$.

Swaps: Overall, the proportion of swap errors was very small (Figure 2.7C). There was no main effect of age group, $F(1, 85) = 1.36$, $p = .25$, $\eta_p^2 = .02$, or gene group, $F(1, 85) = 0.07$, $p = .80$, $\eta_p^2 < .001$, on the proportion of swap errors, indicating that neither participants' age, nor the APOE allele combination affected the proportion of swap errors produced. Gene group × Age group interaction was also not statistically significant, $F(1, 85) = 0.81$, $p = .37$, $\eta_p^2 = .009$.

2.4. Discussion

The current study utilised two sensitive continuous-report tasks to compare cross-sectionally STM and LTM performance of young and older APOE ε2/ε3 and ε3/ε3 carriers. Based on the protective effects of the APOE ε2 allele from AD, and the evidence from previous studies that found positive effects of this allele on memory (e.g., Rajan et al., 2019; Zokaei et al., 2021), I expected to see better performance in its carriers as compared to APOE ε3 homozygotes. In particular, I expected older carriers of APOE ε2 to show better

performance on those aspects of both tasks that were designed to challenge hippocampal function, namely, localisation stages of the 3-item STM and the 2-item LTM trials. As both STM and LTM are negatively affected by normal healthy ageing (e.g., Korkki et al., 2020; Pertzov et al., 2015; Zokaei et al., 2020), I also expected to see deficits in performance in older adults across the board.

Contrary to expectations, the results showed overall little effect of APOE alleles on memory performance. Participants in both APOE ε2/ε3 and ε3/ε3 groups showed an equivalent ability to learn and remember the identities and locations of objects over both very short (one-second), slightly longer (eight-second), and long (20-minute) time scales. This was true for both young and older adults. These findings are surprising given the sensitivity of the tasks used, one of which has been validated on both small and large samples of APOE ε2 and ε4 carriers previously (Zokaei et al., 2017, 2021; Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020). Nevertheless, they fit well with other studies that found no benefits of APOE ε2 allele on memory (Alexopoulos et al., 2011; Chiang et al., 2010; Marioni et al., 2016). It is therefore possible that, if present, any direct benefits of this allele on memory may be subtle and require both sensitive tasks and much larger samples to be detected, such as in the study by Zokaei et al. (2021), or longitudinal assessment of participants, such as in the study by Wilson, Bienias et al. (2002). It is also possible that, at the brain level, some of the older APOE ε2 but not ε3 carriers show signs of brain pathology, such as asymptomatic haemorrhages as a result of cerebral amyloid angiopathy (Greenberg et al., 1998). Although microbleeds may not cause symptoms, they may slightly lower cognitive performance (Poels et al., 2012). Unaccounted variability in other cognitive functions, such as visuospatial attention (Lancaster, Forster, et al., 2017), may therefore add noise to the measurement of memory performance in small samples. This variability may average out in larger samples leading to observable memory advantages in APOE ε2 carriers (Zokaei et al., 2021).

As expected, older adults showed impaired STM performance as compared to the young group. Although their performance on object identification and localisation was only slightly poorer than that of young adults in one-item STM trials, they performed significantly worse in high-load three-item trials across both one- and eight-second delays. This is consistent with findings from another study utilising similar memory measures (Pertzov et al., 2015), suggesting poorer memory in older than in young adults. Results of the two-dimensional mixture modelling (Grogan et al., 2020), showed that the increase in localisation errors in older adults, as compared to young adults, was due to a decrease in memory precision (in one-second delay trials) and an increase in the amount of guessing (in three-item trials), in agreement with previous literature (Peich et al., 2013; Zokaei, Grogan, et al., 2020). This increase was not related to errors in binding item identities to specific locations (swap errors), which have been previously linked to the presence of hippocampal pathology (Pertzov et al., 2013; Zokaei, Nour, et al., 2019).

Older adults also showed impaired performance compared to young adults on the LTM task. In the Learning stage, they were slower and less successful at finding objects within scenes, regardless of the search array size. This may be due to changes in vision, or impairments in spatial attention or cognitive control, which may prevent them from effectively perceiving or allocating attention in the scene to find objects (e.g., Borges et al., 2020; Hommel et al., 2004; Owsley, 2011). However, having started from a worse baseline, older adults showed a steeper improvement in performance than the young group across Learning blocks. During the explicit LTM retrieval stage, they showed lower identification accuracy and larger localisation errors across both one- and two-item memory loads for successfully searched objects. Based on the results of the two-dimensional mixture model (Grogan et al., 2020), the two age groups only differed in their guessing rates, suggesting that older adults struggled to retrieve items from memory and were therefore guessing more. This

is in contrast to the other studies that also utilised continuous-report tasks to assess LTM for locations (Korkki et al., 2020; Nilakantan et al., 2018). These studies found a decrease in LTM precision but not an increase in guessing rates when comparing older and young adults (Korkki et al., 2020; Nilakantan et al., 2018). The discrepancy between the findings of these and the current study may arise due to different retention intervals used. While Korrki et al. (2020) tested participants' memory after a 30-second interval, and Nilakantan et al. (2018) utilised a 90-second interval, in the current study memory retrieval was tested approximately 20 minutes after the Learning stage. Therefore, future studies may wish to look more carefully and compare memory precision and guessing rates across different time spans, ideally, using an equivalent experimental design as used in the current study, differing only in the time points for interrogating memories.

However, there were two instances when participants' gene group significantly interacted with their age group to predict performance. The first of these was finding that young APOE ε2/ε3 carriers were more susceptible to the effects of set size than their APOE ε3/ε3 counterparts when identifying target objects from LTM. Although the difference was not statistically significant in the older group, the effect was to the opposite direction: older APOE ε2/ε3 carriers were less affected by an increase in set size than ε3/ε3 carriers. This could indicate a disadvantage in young and an advantage in older APOE ε2/ε3 carriers compared to ε3/ε3 carriers. As discussed in Chapter 1, it has been proposed that the ε4 allele of the APOE gene may be an example of antagonistic pleiotropy: the allele exerts beneficial effects early in life and detrimental effects later in life (Han & Bondi, 2008; Tuminello & Han, 2011). A cautious and speculative possibility is that the result described here suggests that APOE ε2 may show an opposite effect: a disadvantage early in life and an advantage later in life. Indeed, it has been shown that ε2 was overrepresented in prenatal deaths and more common in babies born too small for their gestational age (Becher et al., 2006; Jacobs

et al., 2016). Therefore, there is a small possibility that this allele may be associated with slightly worse cognitive outcomes early in life (Goisis et al., 2017), which are then outweighed by more successful cognitive ageing. However, no such interaction was observed for the more sensitive measure of localisation error in this study, which suggests that the result should be interpreted with caution.

Additionally, age group interacted with gene group to predict the relationship between LTM localisation errors and subjective confidence ratings in accurate trials. Only older APOE ε2 but not ε3 carriers showed a disadvantage in their ability to judge their performance as compared to younger counterparts. The mismatch between performance and cognitive ratings has been observed in older adults previously (Shing et al., 2009). In this study, participants first learned a list of word pairs that were then tested. In some of the test trials (lure trials), one of the words in the pair was replaced by a novel word. According to the authors, older adults relied on familiarity with a single word from the pair, producing false alarms to lures when only one of the words had been learned previously, with high confidence (Shing et al., 2009). In the current study, confidence ratings of older APOE ε2 carriers were less related to performance than those of APOE ε3 homozygotes, when contrasted to young adults. In the absence of lure trials in the study, this suggests that older APOE ε2 carriers may be more susceptible to age-related changes in metacognition. To my knowledge, no study has been conducted to investigate this topic to date. Nevertheless, given that APOE ε2 carriers may be more susceptible to microbleeds than APOE ε3 homozygotes (Greenberg et al., 1998), this may result in differences in metacognition between the two groups. This warrants further investigation.

There were several limitations to the study described in this chapter. Firstly, the relatively small sample size may have been insufficient to detect differences between gene groups. However, as discussed in section 2.1., the recruitment of APOE ε2 carriers is

challenging due to the rarity of this allele in the general population. Secondly, although both tasks measured memory resolution using sensitive analogue scales, there were notable differences between the tasks in the nature of the stimuli to be remembered, their surrounding context, and set size conditions. Strict direct comparisons between STM and LTM therefore were not warranted. It is possible that different APOE alleles also differentially affect STM and LTM. For example, it has been shown that the presence of APOE ε4 may relate to better STM and worse LTM performance in its carriers than in ε3 homozygotes (Zokaei, Čepukaitytė, et al., 2019). It is not clear if and how the relationship between STM and LTM would be modulated by the protective APOE ε2 allele.

Therefore, future studies should implement sensitive continuous-report STM and LTM tasks in longitudinal designs. These tasks should be designed to enable comparable measurement of STM and LTM, which would allow to examine the relationship between STM and LTM across ageing in cohorts with risk and resilience factors for AD. In particular, they would be useful in large population studies, as the endless number of potential stimuli available in online repositories, such as images of objects and scenes, would allow to measure memory without marked effects of repeated testing, and the tasks could be customised to fit into the study protocol by adjusting their length. Such measures would provide granularity and continuity to memory monitoring longitudinally.

2.5. Conclusions

The current chapter described a study that investigated the relationship between the protective ε2 allele of the APOE gene and STM and LTM in healthy young and older individuals. Two separate continuous-report tasks allowed to probe participants' memories after very short (one-second), short (eight-second) and long (20-minute) delay intervals. Overall, APOE ε2 carriers did not show a STM or a LTM advantage as compared to

homozygous ε3 carriers. However, there were marked deficits across measures in older compared to young adults, regardless of their gene group. Future studies should employ comparable STM and LTM measures to study the relationship between these two types of memory longitudinally in different APOE allele carriers.

Chapter 3. Short- and Long-Term Memory and Their Relationship Across Adulthood

Abstract

Due to the proposed dichotomy between STM and LTM, these two memory functions have been studied largely independently. As a result, few studies have examined the relationship between them using comparable methodologies. Both STM and LTM decline with normal healthy ageing. However, it is not clear whether they decline to a similar degree, or one of them is affected disproportionately. The study presented in this chapter employed two novel continuous-report tasks that enabled analogous probing of contextual spatial short- and long-term memories in order to quantify behaviourally the relationship between these two memory functions. Young, middle-aged and older participants completed these tasks. Older participants performed worse than their young counterparts across all measures. In contrast, middle-aged participants performed as well as the young group. Despite the decline in both memory functions across the age range, the relationship between them remained stable. Furthermore, STM performance was the only factor that significantly predicted LTM performance. Overall, the results suggest that there is a significant degree of overlap between STM and LTM for the same type of information. Future studies should use similar tasks to examine the mechanisms underlying STM and LTM variability.

3.1. Introduction

Given the proposed dichotomy between STM and LTM, discussed in Chapter 1, these two memory systems have been studied largely independently using different methodologies. As a result, only a relatively small number of studies have attempted to compare and contrast them and explore their relationship using consistent experimental approaches and equivalent stimulus materials.

To investigate the role of STM in supporting LTM formation, studies have manipulated STM maintenance in delayed-match-to sample tasks and subsequently tested LTM-based performance (Bergmann et al., 2013; Ranganath et al., 2005). In these tasks, trials began with a presentation of a line drawing of an abstract three-dimensional object followed by a delay and then a probe object. Participants indicated whether the probe object matched the item before the delay. The delay ranged from two to 13 seconds across studies and, in some trials, included an interruption by an intervening line-counting task (Bergmann et al., 2013; Ranganath et al., 2005). Following the completion of the STM task, items from non-match trials were tested in a surprise LTM recognition test in which participants indicated whether they had seen the object shown on the screen during the STM task. Performance in the LTM recognition test was markedly impaired when the disruption by the intervening line-counting task occurred during the first two and a half seconds of the STM delay period as compared to the no-disruption condition (Bergmann et al., 2013; Ranganath et al., 2005). In contrast, no such impairment was observed if the disruption occurred later in the delay, after a period of at least four seconds had elapsed (Bergmann et al., 2013; Ranganath et al., 2005). These studies provide suggestive evidence for the causal role of the STM maintenance period in aiding the formation of long-term memories (Bergmann et al., 2013; Naveh-Benjamin & Jonides, 1984).

Two studies measuring brain activity during variants of these tasks without disruptions provide further support for the causal influence of STM maintenance on LTM formation (Khader et al., 2007; Ranganath et al., 2005). The first of these utilised EEG (Khader et al., 2007). When examining event-related potentials over occipital and posterior temporal electrodes during the STM delay, the authors observed enhanced neural activity for objects that were later remembered during the surprise LTM recognition test as compared to those that were forgotten. Importantly, the enhancement was only significant for up to one

and a half seconds from the onset of the STM delay, which was in line with the importance of the early delay period described in other studies (Bergmann et al., 2013; Ranganath et al., 2005). The second study used fMRI and similarly found blood oxygenation level dependent (BOLD) signal increases in the dorsolateral PFC and the hippocampus for the remembered items during the early but not later stages of the STM delay (Ranganath et al., 2005; however due to the low temporal resolution of fMRI this finding might be difficult to replicate, e.g., see E. A. Nichols et al., 2006). Altogether, it has been suggested that STM maintenance, in particular its early stages, is important for the establishment of long-term representations (Khader et al., 2007; Ranganath et al., 2005). Furthermore, the strength of these representations may rely on the successful interactions between the PFC, the hippocampus and the occipital cortex (Khader et al., 2007; Ranganath et al., 2005).

The role of STM maintenance on LTM has been questioned by other authors who used change-detection tasks with naturalistic stimuli and similarly manipulated STM maintenance (Fukuda & Vogel, 2019). In the first of the tasks, trials began with a memory array of three everyday objects, evenly spaced around the centre of the screen, presented for 150 milliseconds. The memory array was followed by a 1500-millisecond or a 2400-millisecond memory delay. The delay was either blank or included a 50-millisecond interruption by a mask composed of novel everyday objects rapidly flashing on the screen. The mask was limited to the locations of objects in the memory array and had an onset of zero, 100, 300, 600 or 1500 milliseconds after the offset of the memory array. Following the delay, participants' STM was probed by presenting an object at the centre of the screen and asking them to indicate if the object had been presented in the memory array. Following this task, participants completed a LTM recognition test for previously unprobed items. The second task was similar but tested memory for two-item arrays that were followed by a blank delay of 500, 1500 or 4500 milliseconds. Another manipulation in the latter task was to repeat

a portion of the stimuli thrice across trials. In contrast to studies discussed above (Bergmann et al., 2013; Ranganath et al., 2005), the authors found that regardless of the length of an uninterrupted maintenance period available, performance in the subsequent LTM recognition test was unchanged (Fukuda & Vogel, 2019). Performance was diminished only by a mask presented at the onset of the STM delay (Fukuda & Vogel, 2019), which may have interfered with the encoding of information, and therefore impaired both immediate and delayed performance. In contrast, recognition performance was improved by the repetition of stimuli thrice throughout the task. The authors concluded that STM maintenance did not contribute to LTM encoding (Fukuda & Vogel, 2019). However, the nature of the stimulus materials may have contributed to the different outcomes in this and the previous studies. The study by Fukuda and Vogel (2019) used recognisable and nameable everyday items as stimuli, while the studies discussed above used abstract line drawings (Bergmann et al., 2013; Khader et al., 2007; Ranganath et al., 2005). It is likely that the processing of representations of everyday objects is less vulnerable to subsequent interruptions of visual nature than abstract shapes, and therefore neither STM nor LTM formation was affected. After all, our brain has evolved to deal at speed with non-abstract objects (e.g., a lion lurking in the tall grass). Hence, the impact of the STM delay cannot be discounted based on this study. In contrast, it should be explored in future studies if increasing the complexity of abstract stimuli modulates the amount of uninterrupted STM delay required for the formation of long-term memories.

It has been suggested that it is the STM capacity that determines encoding to LTM (Fukuda & Vogel, 2019). In another change-detection task of this study, a four- or an eight-item display of coloured squares was shown to participants for 150 milliseconds in each trial followed by a 900-millisecond delay. Participants had to judge, based on their STM, if a single probe item presented after the delay had the same colour as an item presented at that location 900 milliseconds earlier. Their visual STM capacity was estimated from accuracy on

this task. Identical trial procedures were then incorporated into a separate encoding task. While performing change-detection, participants were subjected to a set of uniquely spatially arranged four- and eight-item displays (15 each) over 16 blocks, with each display repeated twice per block in random order. In a subsequent recognition test, participants viewed the encoded displays in addition to novel displays and reported if these were new or old. The authors found that there was a significant correlation between STM capacity, as measured using the first task, and recognition performance for eight- but not four-item displays (Fukuda & Vogel, 2019). Notably, this result was not affected by whether participants had explicit instructions that their LTM for displays would be tested (Fukuda & Vogel, 2019). The authors concluded that STM capacity acted as a bottleneck and limited the ability to encode long-term memories, as only when STM capacity was challenged using a high load of eight items did STM capacity and LTM recognition performance correlate (Fukuda & Vogel, 2019). However, it may also be possible that both STM and LTM are affected by a bottleneck, without the causal role of STM in limiting LTM encoding.

STM and LTM may share qualitative similarities. Brady et al. (2013) used continuous report measures, described in Chapters 1 and 2, to assess memory for object colour on both short and long time scales. Separate tasks were used for STM and LTM. In both types of tasks, participants viewed and were asked to remember the identities and colours of everyday objects presented on the screen. The authors found that participants' long-term memories were no less precise than their short-term memories for multi-item arrays (Brady et al., 2013). They concluded that both STM and LTM share the lower limit on fidelity (Brady et al., 2013). If further degradation occurs over time, representations simply become too noisy to be consciously remembered forcing participants to guess, as was evident from the increased guessing rate but preserved precision in the LTM task (Brady et al., 2013). Overall, this suggests that STM and LTM may not only share a limit on the encoding capacity but also on

the quality with which representations can be stored, hinting towards some degree of overlap in the neural machinery underlying STM and LTM systems.

Ageing studies provide another useful line of investigation for probing the relationship between STM and LTM. As discussed in Chapter 1, both STM and LTM decline considerably in later adulthood. However, it is not clear whether they decline to a similar degree, or one of them is affected disproportionately. Three studies that attempted to answer this question are discussed below.

Van Geldorp et al. (2015) used a delayed match-to-sample task to create associations between two pairs of face and house stimuli and test them after both short and long delays in young, middle-aged and older adults. LTM was measured by adding a surprise two-alternative forced-choice task after the initial task. They found that older adults performed worse than both young and middle-aged groups on both tasks, while there was no difference between young and middle-aged adults in performance (Van Geldorp et al., 2015). In addition, neither STM nor LTM was disproportionately affected in older adults, as indicated by a lack of significant interaction between age group and memory type, providing no evidence for a differential rate of decline with ageing (Van Geldorp et al., 2015). However, LTM performance of older adults was near chance, making it possible that any putative interactions may have been masked by task difficulty.

Lugtmeijer et al. (2019) attempted to avoid floor effects by using a two-back STM task with easy to name objects as stimuli. In this task, young and older adults first performed the usual two-back task, where they had to press a button if an object shown on the screen matched the one seen two trials before. Instead of being presented centrally, each object appeared at one of the four quadrants of the screen. Although this was irrelevant for the STM task, memory for object-quadrant associations was tested in a subsequent surprise LTM task. During this task participants were shown those same objects and had to report whether they

appeared at the same or a different quadrant. Older adults performed worse in both STM and LTM tasks (Lugtmeijer et al., 2019). There was also a significant correlation in young but not older adults when comparing performance in the two tasks separately for each age group. The authors concluded that the relationship between the two cognitive functions was different in young and older adults (Lugtmeijer et al., 2019). However, while the n-back task tested memory for object identities, the LTM task tapped on object-quadrant associations. Although both non-associative and associative types of memory are affected by ageing, the latter might be particularly vulnerable to its effects (Naveh-Benjamin, 2000; Peich et al., 2013; Van Geldorp et al., 2015). Hence, the lack of association between short- and LTM performance in older adults might not result from an altered relationship between the two types of memory in general, but rather be the outcome of the differential effects of ageing on associative and non-associative memories.

The third study, conducted by Korkki et al. (2020), avoided this problem by testing associative memory for object-colour bindings on both short and longer timescales. Participants performed two separate continuous-report tasks. In the STM task, they were first shown a display with three coloured objects on a grey background for three seconds, followed by a memory delay of one second. The delay consisted of a colour noise mask (first 100 milliseconds) succeeded by a centrally presented fixation cross (the remaining 900 milliseconds). Following the delay, one of the objects appeared in its original location on the screen in a randomly allocated colour, and participants had to readjust the colour to match that of the original object in the memory array. In contrast, in the LTM task, participants viewed five displays of three coloured objects (nine seconds for each display) separated by an interval of one second. The last display was succeeded by a 30-second delay, during which participants performed an interfering task of counting backwards by three. The colour-report task then followed. Participants had to readjust the colours of all 15 objects they had

observed in the preceding displays. Continuous report tasks employed in this study allowed the authors to compute memory precision and guessing rates. They found a decrease in memory precision, but no change in guessing levels, from young to older adults in both STM and LTM (Korkki et al., 2020). While STM precision predicted LTM precision in older adults, this was not the case for the young group. However, the relationship between STM and LTM precision did not differ significantly across age groups, as demonstrated by a lack of a significant interaction between age group and STM precision when predicting LTM precision (Korkki et al., 2020). Nevertheless, LTM precision declined disproportionately with age as compared to STM precision, as evident from the deficit in LTM in older adults, which persisted after accounting for the decline in STM (Korkki et al., 2020). This reflects that the neural underpinnings of the two memory systems may not be entirely coextensive, resulting in different levels of susceptibility to the effects of ageing. However, the relationship between STM and LTM may have been understated in this study. The two types of memory were measured using separate tasks, which could have led to differential encoding of stimuli. Furthermore, the sequential retrieval of object-colour associations could have added more variability to the LTM data as compared to the STM data due to a greater interference from previously recalled stimuli (Kiyonaga et al., 2017; Makovski & Jiang, 2008; Sun et al., 2017). This may be particularly problematic for older adults that are prone to interference from stimuli in previous trials (Weeks et al., 2020), diminishing the strength of association between STM and LTM in this group. Nevertheless, the continuous report tasks used in this study add significant sensitivity and granularity to the measurement of STM and LTM.

The aim of the study presented in this chapter was to compare, with a high degree of granularity and sensitivity, performance across age groups on STM and LTM tasks, which utilise the same stimulus material and response demands and test memories for the same type of information. In particular, the study focused on spatial contextual associations between

objects and scenes. Memory for this type of information is thought to be dependent on the MTL function (Esfahani-Bayerl et al., 2016; Pertzov et al., 2013; Yonelinas, 2013; Zokaei, Nour, et al., 2019) and is particularly vulnerable to ageing (Naveh-Benjamin, 2000; Naveh-Benjamin & Mayr, 2018; Pertzov et al., 2015). This type of association is also of ecological relevance for remembering the identities and locations of objects in everyday contexts. The experimental approach therefore builds on the findings reviewed above, but also brings significant innovation and introduces a greater level of experimental control that overcomes many of the limitations of the studies to date.

Two tasks were designed for this study to probe object-location associations using sensitive continuous report as well as two-alternative forced-choice measures. The STM task comprised two types of trials: Learning-STM and Learning-only. Both types of trials began with a memory array containing one or three everyday objects presented within a photographic scene, followed by a memory delay. In Learning-STM trials, the delay was followed by a memory probe. Participants were asked to identify the object that appeared in the scene previously and place it in its remembered location. In Learning-only trials, participants were not immediately probed about object identity or location. The two types of trials were intermixed, and their order was randomised and unpredictable, avoiding the possibility of differential encoding of the memory array. LTM for the identity and location of objects in Learning-only trials was tested using an equivalent probe in a subsequent surprise LTM task, performed 20 minutes after the completion of the STM task. In addition, I collected subjective confidence ratings from participants on their LTM performance in each trial, which allowed me to explore how LTM performance and confidence measures were related across age groups.

Participants from three age groups completed the tasks: young, middle-aged and older. Analysis focused on characterising the effects of ageing on different behavioural

indices of STM and LTM to shed light on their degree of association or dissociation within the limits of a cross-sectional design. I expected to see increasing deficits with advancing age for both STM and LTM for the contextual associations. Based on the previous literature on the involvement of the MTL and the hippocampus in associative memory across both short and long timescales, as discussed in Chapter 1, I expected to see a positive relationship between STM and LTM performance. However, this relationship may be weaker in the older age group due to other age-related changes in brain function within and outside of the MTL, as discussed in Chapter 1.

3.2. Methods

3.2.1. Participants

The study was approved by the Medical Sciences Interdivisional Research Ethics Committee of the University of Oxford (Ethics Approval Reference: R56404/RE001) and complied with the Declaration of Helsinki.

In total, 65 healthy volunteers took part in this study. Participants were a mixture of university students and members of the local community recruited via the Oxford Psychology Research (OPR) participant recruitment scheme, Friends of OxDARE participant registry (https://www.oxdare.ox.ac.uk/), Daily Information website, or word of mouth. All gave written informed consent, and either received course credit or were reimbursed at a rate of £10 per hour for participation. Five participants were excluded from the analysis: two participants due to poor performance (see section 3.2.5. below), one participant due to an experimenter error (data were overwritten), and two participants due to low scores on the ACE-III (see section 3.2.3. below).

The final sample consisted of 60 healthy adults: 20 young (19-39 years), 20 middle-aged (41-58 years), and 20 older (62-79 years) (Table 3.1). They had normal or corrected-to-

normal visual acuity and normal colour vision by self-report. The three groups were comparable on years of education and depression scores, as measured using the Beck Depression Inventory-II (BDI-II, Beck, Steer, & Brown, 1996). Middle-aged and older adults exhibited no signs of cognitive impairment, as measured using ACE-III (Table 3.1).

Table 3.1. Descriptive information for the final 60 participants included in the analysis.

	Young	Middle-aged	Older	*p*
n	20	20	20	-
Male/Female	11/9	6/14	9/11	.28
Age	25.2(4.9)	49.6 (7.0)	70.8 (4.4)	-
Years in education	17.8 (2.4)	17.5 (3.4)	16.8 (4.6)	.66
BDI-II	6.6 (5.8)	3.9 (5.9)	5.5 (4.2)	.27
ACE-III Total	-	96.5 (2.8)	96.2 (2.1)	.67

Note: BDI-II = Beck Depression Inventory-II, ACE-III = Addenbrooke's Cognitive Examination III. Age, years in education, BDI-II and ACE-III scores are presented as *M* (*SD*).

3.2.2. Stimuli

Coloured photographs of complex indoor and outdoor scenes and images of everyday objects were used as stimuli. The scene set consisted of a combination of royalty-free images from https://unsplash.com and photographs from the Brain and Cognition Laboratory's in-house repository of photographs by current and previous lab members. Ninety-six scenes were randomly selected from a pool of 192 scenes for each participant. They were presented at a resolution of 1125 by 844 pixels (31 by 23.2 cm) surrounded by grey background (RGB [0.5, 0.5, 0.5]).

A total of 368 objects were randomly drawn from a pool of 422 coloured objects for each participant. The pool was derived from a combination of experimental stimulus sets (Brady et al., 2008; Brodeur et al., 2010) and object images available through Google Images, processed to remove backgrounds when necessary. All object images were visually distinct

from one another and easily nameable. They included a range of household, food, and clothing items, as well as toys and sports equipment.

Objects were sized to fit within a region of 75-by-75 pixels and had an equal probability of appearing in all four quadrants of the scene. Their locations were randomly selected with several restrictions: objects were at least 50 pixels away from the edges and from the centre of the screen, and there was a minimum of 500 pixels between the centre of each object in three-object trials.

Stimuli were presented on a Dell OptiPlex 9030 All-in-One touchscreen computer with a 1920-by-1080 pixels resolution (53.0 by 29.7 cm), using the Cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent_2000.php) and MATLAB Release 2015b (the MathWorks Inc., Natick, MA, USA).

3.2.3. Tasks and Procedures

The study consisted of two tasks, in which participants reported the identity and location of objects associated with scenes based on their short- or long-term memories for those associations. Participants made responses directly on a touchscreen using their finger.

In the first task, participants explored scenes with one or three embedded objects for 5 seconds. In half of the trials, they were probed about the identity of an object in the scene and reproduced its location after a memory delay (STM condition; Figure 3.1A). In the remaining half of the trials, they explored the scene in a similar fashion, but the probing of object identity and location was deferred until a later task, in order to assess LTM for the same type of information.

The second task was a surprise test of LTM retrieval performed after a break of approximately 20 minutes. Participants viewed previously learned scenes and were probed

about the identity and location of an object in a similar fashion as in the first task, but this time based on their long-term memory (LTM condition; Figure 3.1B).

During the break between tasks, middle-aged and older participants completed the ACE-III, which was used to screen participants for cognitive impairment (see section 2.2.2. for more details on ACE-III). I used the highest recommended cut-off of 88/100 (Hsieh et al., 2013), below which participants were excluded from the analysis (see section 3.2.1. above).

Finally, all participants completed an online questionnaire on demographic details, and their general physical and mental health. Young participants completed this questionnaire during the break between tasks to keep them similarly engaged as middle-aged and older participants (who completed ACE-III). The latter two groups responded to the online questionnaire at the end of the session.

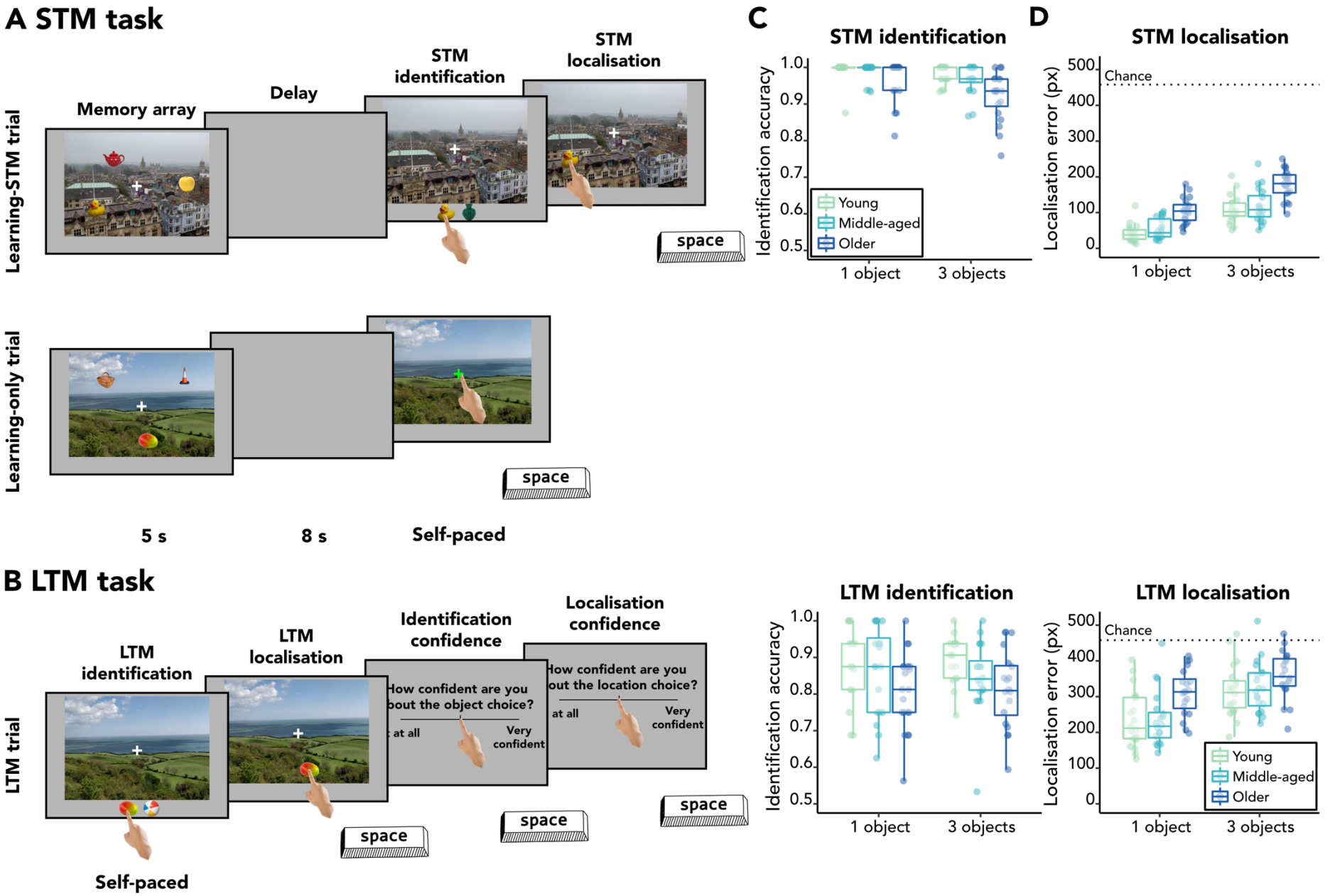

A STM task
Learning-STM trial
Memory array
Delay
STM identification
STM localisation
space
Learning-only trial
space
5 s
8 s
Self-paced
B LTM task
LTM trial
LTM identification
LTM localisation
Identification confidence
Localisation confidence
How confident are you about the object choice?
at all
Very confident
How confident are you about the location choice?
at all
Very confident
space
space
space
Self-paced
C
STM identification
Identification accuracy
1.0
0.9
0.8
0.7
0.6
0.5
Young
Middle-aged
Older
1 object
3 objects
D
STM localisation
Localisation error (px)
500
400
300
200
100
0
Chance
1 object
3 objects
LTM identification
Identification accuracy
1 object
3 objects
LTM localisation
Localisation error (px)
Chance
Young
Middle-aged
Older
1 object
3 objects

Figure 3.1. Short-term memory (STM) and Long-term memory (LTM) task schematic and Identification and Localisation results (C, D). Each trial in the STM task (A) started with a memory array (5 s), which included a scene with either one or three embedded objects, followed by a delay (8 s). In Learning-STM trials, the delay was followed by a memory probe (self-paced) in which participants were asked to select the object they had seen in the memory array before the delay as fast as they could out of the two presented below the scene (STM identification) and place it back to its original location as precisely as they could (STM localisation). In contrast, in Learning-only trials, the delay was followed by only the scene from the memory array and participants were asked to tap on the green fixation cross presented at the centre (self-paced). Participants pressed the space bar to complete the trial. Each trial in the LTM task (B), which followed 20 minutes after the STM task, began with an identical memory probe, which probed memories of learning-only trials (self-paced). Following LTM localisation, participants were presented with two continuous confidence rating scales on object identification and localisation confidence, respectively. They had to indicate their confidence from *Not confident at all* to *Very confident*. Participants pressed the space bar to move from localisation to confidence ratings and to complete the trial. In both memory probes, one of the objects had always appeared in the corresponding memory array while the other object was completely novel. Identification and localisation performance is shown in panels C and D, respectively (STM at the top and LTM at the bottom). Coloured dots represent participant means (light green – young, light blue – middle-aged and dark blue – older participants), lines inside boxes represent group medians, hinges represent first and third quartiles, and whiskers represent values that fall outside the interquartile range (*IQR*) but within 1.5 * *IQR* from each hinge. Dots outside the whiskers are outliers.

3.2.3.1. Short-Term Memory Task. A schematic of the combined learning and STM task (hereafter, STM task) is shown in Figure 3.1A. There were two types of trials: trials in which participants reported the identity and location of an object embedded within a scene following a short delay (Learning-STM) and trials in which participants only learned the object-scene association to be probed later in the study (Learning-only).

All trials began with a presentation of a memory array in which either one or three objects were placed within the scene. The array appeared for 5 seconds. Participants had to find the embedded object(s) and remember their identity(ies) and location(s). The memory array was followed by a delay of 8 seconds, during which participants were presented with a blank grey screen (RGB [0.5, 0.5, 0.5]). After this initial trial phase, the two trial types differed.

In Learning-STM trials, the delay was followed by a STM probe. The scene from the memory array appeared with two objects below. One of these objects had previously been embedded in the scene (target), while the other was a novel object (foil). Participants had to identify the target item by tapping on it (identification) and then place it as precisely as they could in its original location within the scene (localisation). This part of the task was self-paced. Participants were encouraged to respond as quickly as they could when choosing the target object (identification) and to prioritise precision when reproducing its location (localisation). Once they were satisfied, they pressed the spacebar to proceed to the next trial.

In Learning-only trials, the scene from the memory array was presented again, without the embedded objects, with a green fixation cross at the centre. In these trials, participants tapped the fixation cross and pressed the spacebar to continue to the next trial. Participants would subsequently be probed about their long-term memory regarding these object-scene associations in the later, surprise task.

This task consisted of two blocks of 48 trials each. One third of trials in each block contained one object, while the remaining two thirds contained three objects. Half of the trials were Learning-only, and the other half were Learning-STM. The two trial types were randomly intermixed across the two blocks. All participants completed a minimum set of eight practice trials prior to the task to become familiar with the procedures. If required, they could repeat the set of practice trials until they were comfortable with the task.

3.2.3.2. Explicit Long-Term Memory Retrieval. After the 20-minute break, participants completed a surprise explicit LTM retrieval task (Figure 3.1B).

In each trial participants were probed about their LTM for the identity and location of objects from Learning-only trials. The structure of the trial was similar to the memory probe during Learning-STM trials. A previously studied scene appeared with two objects below. One of the objects had been previously embedded in the scene (target), while the other one was a novel object (foil). Participants chose the target object (identification) and dragged it to its remembered location (localisation). Once they were satisfied with their response, they pressed the space bar.

Participants then completed two consecutive confidence rating scales, one for identification and one for localisation, respectively. They reported confidence in their performance on a continuous scale from "*Not confident at all"* (left) to "*Very confident"* (right) by moving the scale bar on the screen.

This task consisted of one block of 48 trials. Trials appeared in a randomised order, so that scenes that had contained one or three objects were randomly intermixed.

3.2.4. Design

This study utilised a 3 × 2 × 2 mixed factorial design with age group (young, middle-aged, older) as a between-subjects factor and memory condition (STM, LTM) and set size (1 or 3 objects) as within-subject factors. Dependent variables were identification accuracy (the proportion of correctly identified trials) and localisation error (the Euclidean distance between the target location and the response location).

3.2.5. Data Analysis

Data were pre-processed and analysed using MATLAB Release 2018b (the MathWorks Inc., Natick, MA, USA) and R version 4.0.2 (2020) on R Studio version 1.3.1093. Trials were excluded from analysis if response times to identify the target object were faster than 100 milliseconds or if localisation responses occurred outside the scene boundaries. In total, approximately one percent of trials were excluded. Additionally, only the trials in which targets were accurately identified (accurate trials) were included in localisation-error analysis. Finally, participants were only included in the analysis if their STM localisation performance was within three standard deviations from the group mean, indicating they were able to perform the task. As a result, two young participants were excluded from all analyses due to poor performance in one-object STM trials (see section 3.2.1. above). I also performed a version of the analysis where trials in which performance was more than three standard deviations away from the participant's mean per set size and memory condition were excluded from the analysis, which yielded comparable results.

3.2.5.1. Comparing Short- and Long-Term Memory Performance Across Age Groups

3.2.5.1.1. Identification Accuracy and Localisation Error. Two separate 3 × 2 × 2 (Age group [young, middle-aged, older] × Memory type [STM, LTM] × Set size [1 or 3 objects]) mixed factorial models were used to explore identification accuracy and localisation error.

As identification accuracy and STM localisation error data were not normally distributed, I used nonparametric rank-based statistical tests, implemented using *nparLD* package version 2.1 on R (Noguchi et al., 2012), for identification accuracy and localisation error analyses, and any follow-up tests for significant interactions. ANOVA-type statistics (*ATS*) were reported due to their suitability for smaller samples, and modified *ATSs* (ATS_{Mod}) with Box approximation were used for the between-subjects factor (age group), as recommended for independent observations (Brunner & Puri, 2013; Noguchi et al., 2012). Where multiple comparisons were made between the three age groups (young vs middle-aged, young vs older, middle-aged vs older), Mann-Whitney U tests were used, and α level was Bonferroni-adjusted for three comparisons.

3.2.5.1.2. Localisation Performance at Chance. I used a response-driven approach to estimate localisation error at chance. To start, I randomly shuffled each participant's localisation response coordinates across all trials and calculated a new localisation error from the original target location to the shuffled response location for every trial. I repeated this procedure for 1000 iterations in total for each participant per each memory type (STM, LTM), calculating the mean localisation error per iteration. I then calculated the mean across all iterations for each participant, the mean across participants for each memory type and the overall mean across memory types, which is the estimate for localisation error at chance.

3.2.5.2. Relationship Between STM and LTM Localisation Errors Across Age Groups.

To explore the relationship between STM and LTM localisation errors across age groups and to test whether age group modulated this relationship, I fitted a general linear model (GLM) to LTM localisation error data per participant (participants' mean LTM localisation errors) from three-object trials. Three-object trials were used because they comprised two-thirds of the overall trial number and the averages were therefore more robust to noise. The model included mean STM localisation error per participant and age group as predictor variables, and STM localisation error × Age group (young, middle-aged, older) interaction.

3.2.5.3. Relationship Between Long-Term Memory Localisation Errors and Confidence.

I also looked at the relationship between localisation errors in LTM and localisation confidence judgements. Confidence is prone to individual biases (Fleming & Lau, 2014). For example, some individuals might be more modest than others, reporting on average lower confidence. To eliminate biases, I z-scored confidence data per subject, resulting in a similar centre value across subjects. I then computed Spearman's correlation between LTM localisation errors and normalised localisation confidence for each participant. Correlation coefficients were then normalised using Fisher's z test with *psych* package version 1.8.4 on R (Revelle, 2018). Normalised coefficients were subjected to a one-way between-subjects ANOVA, performed using *afex* package version 0.22-1 for R (Singmann et al., 2018), with age group (young, middle-aged, older) as the between-subjects factor. Follow-up comparisons between age groups (young vs middle-aged, young vs older, middle-aged vs older) were performed using *emmeans* package version 1.3.0 on R (Lenth, 2018), and α level was Bonferroni-adjusted for three comparisons. I only used data from three-object

trials, which comprised two-thirds of the overall trial number, in this analysis to obtain more reliable estimates.

3.2.5.4. Sources of Localisation Error. A three-parameter two-dimensional mixture model was fitted to the pre-processed localisation error data from accurate trials using the maximum likelihood estimation on MemToolbox2D (Grogan et al., 2020) and MATLAB release 2018b (the MathWorks Inc., Natick, MA, USA). The three parameters were memory precision, the proportion of guesses and the proportion swap (or mis-binding) errors. This model is identical to that described in Chapter 2 and is tailored to two-dimensional data. As the number of trials per participant was insufficient to achieve good model fits, I collapsed data across participants and plotted model fits per memory type (STM, LTM) for each age group (young, middle-aged, older). Only model fits for data in 3-item trials are reported for simplicity. Finally, as no inferential statistics could be performed on these data and therefore only descriptive comparisons are reported.

3.3. Results

3.3.1. Short- and Long-Term Memory Performance

3.3.1.1. Identification Accuracy. The non-parametric model revealed a significant main effect of age group on identification accuracy, $ATS_{Mod}(1.83, 48.29) = 8.98$, $p < .001$. Follow-up Mann-Whitney U tests showed that under $\alpha = .017$, older adults were significantly less accurate than both young, $U = 7500.50$, $z = 3.69$, $p < .001$, and middle-aged adults, $U = 7208.50$, $z = 2.66$, $p = .008$ (Figure 3.1C). However, there was no difference in accuracy between young and middle-aged adults, $U = 6711.00$, $z = .96$, $p = .34$ (Figure 3.1C). There were also significant main effects of memory condition, $ATS(1, \infty) = 240.25$, $p < .001$ and set size, $ATS(1, \infty) = 16.63$, $p < .001$, accompanied by a significant Set size × Memory condition

interaction, $ATS(1, \infty) = 5.96$, $p = .01$. Overall, participants were less accurate when identifying objects in the LTM than in the STM condition (Figure 3.1C). However, the interaction reflected that the difference in accuracy between one- and three-object trials was only statistically significant in STM, $ATS(1, \infty) = 33.76$, $p < .001$, but not LTM condition, $ATS(1, \infty) = 0.01$, $p = .91$ (Figure 3.1C). None of the other two- or three-way interactions reached statistical significance: Age group × Set size: $ATS(1.90, \infty) = 1.04$, $p = .35$, Age group × Memory condition: $ATS(1.99, \infty) = 0.05$, $p = .95$, Age group × Set size × Memory condition: $ATS(1.89, \infty) = 1.43$, $p = .24$.

3.3.1.2. Localisation Error. There was a significant main effect of age group on localisation error, $ATS_{Mod}(1.89, 51.03) = 21.61$, $p < .001$. Follow-up Mann-Whitney U tests showed that under $\alpha = .017$, older adults produced significantly larger localisation errors than both young, $U = 5434.00$, $z = -3.43$, $p < .001$, and middle-aged adults, $U = 5557.00$, $z = -3.01$, $p = .003$ (Figure 3.1D). There was no difference in the magnitude of localisation errors between young and middle-aged adults, $U = 6303.00$, $z = -0.47$, $p = .64$ (Figure 3.1D). There were also significant main effects of memory condition, $ATS(1, \infty) = 1080.58$, $p < .001$, and set size, $ATS(1, \infty) = 141.98$, $p < .001$, accompanied by a significant Set size × Memory condition interaction, $ATS(1, \infty) = 5.85$, $p = .02$. The interaction reflected that although overall memory errors were larger in LTM than in STM trials and in three-object trials than in one-object trials (Figure 3.1D), the difference between set size conditions was proportionally greater in STM, $ATS(1, \infty) = 209.26$, $p < .001$, as compared to LTM, $ATS(1, \infty) = 40.40$, $p < .001$, at $\alpha = .025$. However, when differences in localisation errors between set size conditions (1-object trials – 3-object trials) were compared directly between STM and LTM, the difference was not statistically significant, $ATS(1, \infty) = 1.28$, $p = .26$ ($M_{STM} = -69.24 \pm 40.32$, $M_{LTM} = -72.59 \pm 84.77$). There were no other significant interactions: Age group ×

Memory condition, $ATS(1.96, \infty) = 1.93$, $p = .14$, Age group × Set size, $ATS(1.96, \infty) = 1.02$, $p = .36$, and Age group × Set size × Memory condition, $ATS(1.98, \infty) = 2.02$, $p = .13$.

3.3.2. Relationship Between Short- and Long-Term Memory

As I was interested in whether participants' age group mediated the relationship between STM and LTM localisation errors, I first fitted a GLM that included both the age group and the interaction term. The model showed that STM localisation errors significantly predicted LTM localisation errors, $F(1, 54) = 10.20$, $p = .002$. Namely, participants who produced large STM localisation errors were also more likely to produce large LTM localisation errors (Figure 3.2). On the other hand, the main effect of age group or the interaction between age group and STM localisation errors were not statistically significant, $F(2, 54) = 0.17$, $p = .84$, and $F(2, 54) = 0.23$, $p = .80$, respectively. This indicated that the magnitude of STM localisation errors and not participants' age group best accounted for the magnitude of LTM localisation errors, and that participants' age group did not mediate the relationship between STM and LTM localisation errors (Figure 3.2).

I then simplified the model by first removing the interaction term and then the age group. This did not significantly impair model fit ($p = .80$ and $p = .95$, respectively) and further supported the idea that STM localisation errors alone significantly predicted LTM localisation errors, $F(1, 58) = 17.23$, $p < .001$, $R^2 = .23$, $R^2_{\text{Adjusted}} = .22$.

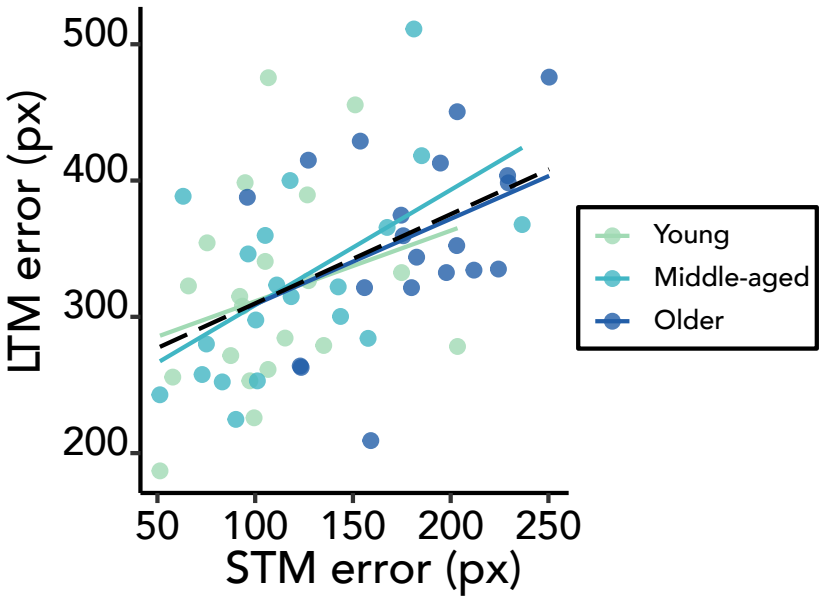


Figure 3.2. The relationship between STM and LTM localisation errors (px) across age groups. Coloured dots represent participant means and coloured lines represent regression lines per age group (light green – young, light blue – middle-aged and dark blue – older participants). Dashed black line represent model fit across groups. The data shown are from three-object trials.

3.3.3. Relationship Between Long-Term Memory and Confidence

There was a significant main effect of age group on the correlation coefficients between LTM localisation error and normalised localisation confidence per participant, $F(2, 57) = 4.92$, $p = .01$, $\eta_p^2 = .15$. Pairwise comparisons showed that under Bonferroni-adjusted $\alpha = .017$, young adults had a significantly lower mean Fisher z-transformed correlation coefficient than older adults, $t(57) = -3.12$, $p = .008$, while there was no difference between young and middle-aged, $t(57) = -1.81$, $p = .18$, and middle-aged and older adults, $t(57) = -1.31$, $p = .39$ (Figure 3.3A). This suggested that confidence judgements of older adults were less strongly negatively associated with their LTM localisation performance than those of young adults. In other words, when localisation errors were small, they reported lower confidence than young adults. In contrast, they produced higher confidence ratings than young adults when their errors were large (Figure 3.3B).

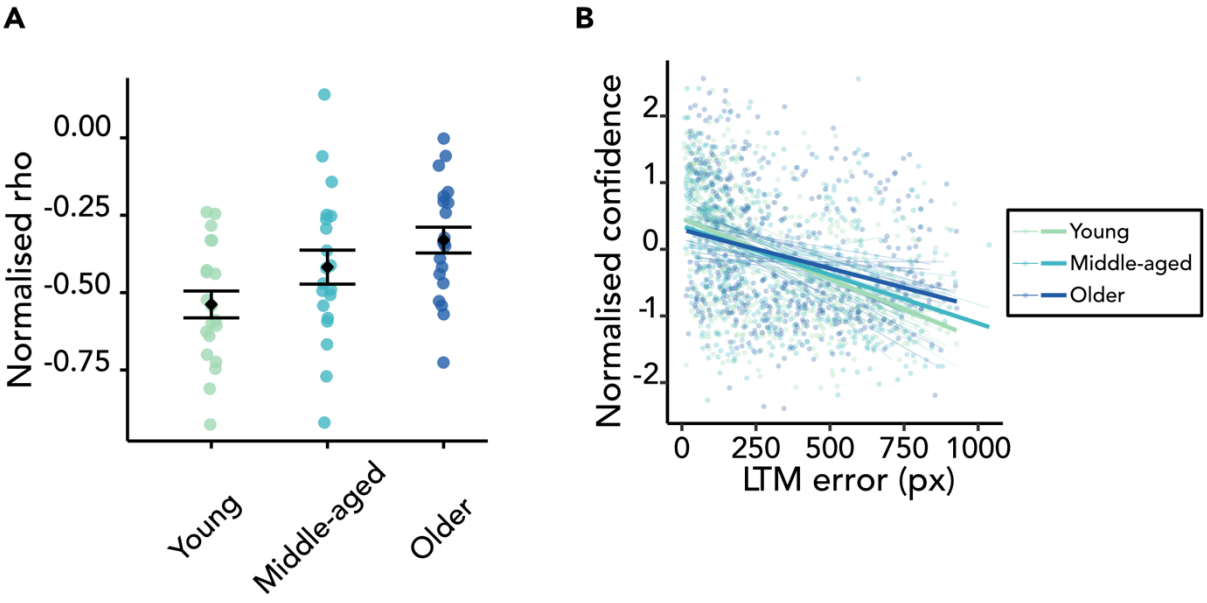


Figure 3.3. Normalised correlation coefficients (rho) per age group (A) and the relationship between LTM localisation errors and normalised confidence ratings per participant (B). A – coloured dots (light green – young, light blue – middle-aged and dark blue – older participants) represent correlation coefficients per participant, black diamonds represent group means and error bars are standard errors of the mean. B – Coloured dots represent LTM localisation errors and confidence ratings per trial, thin coloured lines represent linear regression lines per participant and thick lines represent linear regression lines per age group. The data shown are from three-object trials.

3.3.4. Sources of Localisation Error

As shown in Figure 3.4, all groups showed similar localisation error distributions. The most pronounced effect was the increase in the probability of guessing from STM to LTM. There was also a slight increase in the probability of guessing from young and middle-aged adults to older adults. Similarly, the standard deviation of memory precision was larger for LTM as compared to STM, indicating lower memory precision in LTM. Precision decreased gradually across age groups in STM and was lower, as indicated by larger standard deviation of memory precision, in older adults as compared to the other two groups in LTM. Finally, the probability of swap errors was low, but increased in older adults in STM as compared to the other age groups.

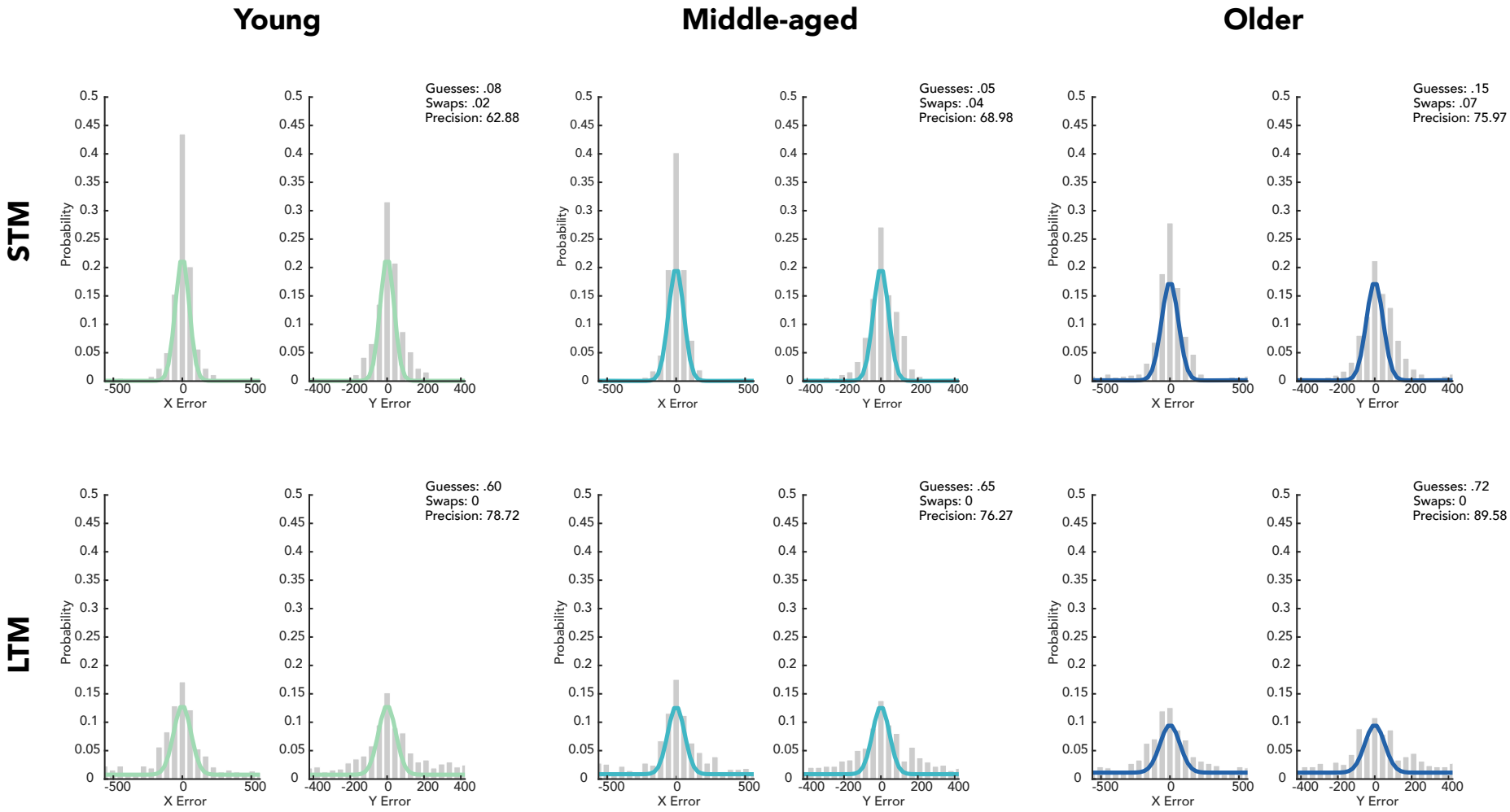


Figure 3.4. Mixture model fits per age group (from left to right: young, middle-aged and older) and memory condition (top: STM, bottom: LTM). Model was fitted to 3-item trial data. Models were fitted separately for each dimension (X Error and Y Error). Model parameters (guesses, swaps and precision) are shown at the top right corner of each plot.

3.4. Discussion

The current cross-sectional study utilised two novel continuous report tasks to investigate the effects of healthy ageing on STM and LTM performance in a sensitive and comparable way. The analogous encoding and probing of memories in the two tasks also allowed to examine the relationship between STM and LTM across the age range. It was expected that performance on both tasks will decline with the increasing age of participants, and that STM and LTM will show a relationship that will weaken with the increasing age of participants.

In line with expectations, older adults showed impairments in STM and LTM performance. Both their ability to recall identities and locations of objects within scenes was diminished as compared to the young group. In contrast, middle-aged adults were comparable in performance to young adults across the board. These findings are consistent with previous reports of STM and LTM impairments from the age of 60 years (e.g., Korkki et al., 2020; Lugtmeijer et al., 2019; Pertzov et al., 2015; Van Geldorp et al., 2015). Therefore, it may be possible that age-related memory decline starts later in life, after this age. However, given the design of the current study, it cannot be ruled out that changes in memory functions start earlier, in mid adulthood, becoming substantial enough to be measured cross-sectionally with a relatively small sample after the age of 60 years. This idea is consistent with findings from larger studies, which showed a gradual decline in STM and LTM performance with an increasing age of participants (e.g., Henson et al., 2016; Zokaei et al., 2020). Notably, both middle-aged and older adults showed comparable performance on the ACE-III, which is a standard neuropsychological test of cognition, providing evidence for the sensitivity and utility of continuous report tasks used in this study for measuring differences in memory functions across groups of otherwise healthy adults.

Regardless of the age group, there was a sharp decline in participants' performance from STM to LTM trials. Participants were less accurate when identifying objects from LTM than from STM. An equivalent pattern of results was observed for object locations within scenes: participants produced larger localisation errors in LTM than in STM trials. This is not unexpected given the long delay separating the learning and the probe stages in the LTM task, as well as the single exposure learning, which may have resulted in a significant degree of forgetting over time. Previous studies have demonstrated better LTM performance when multiple encoding opportunities were available (e.g., Fukuda & Vogel, 2019; Miner et al., 2020), which may enable long-term synaptic potentiation (Abraham et al., 2019).

There was a positive relationship between STM and LTM localisation errors, which was comparable across the three age groups. Regardless of the timescale, memories for bound representations, such as object-location associations, are thought to rely on the MTL, including the hippocampus, as discussed in Chapter 1 (e.g., Kolarik et al., 2018; Yonelinas, 2013; Zokaei et al., 2019). Therefore, given the involvement of the MTL, the presence of this relationship is not unexpected. Nevertheless, to my knowledge, this is the first time both STM and LTM have been assessed for the same type of contextual spatial associations encoded in a truly analogous way. STM localisation errors accounted for 22 percent of variance in LTM localisation errors. It may be that some of the variance was lost due to forgetting over the LTM delay period, which resulted in increased LTM localisation errors, as discussed above. Nevertheless, in contrast to the effect of participants' age group, this effect was statistically significant. This suggests that, in the current study, variability in STM alone significantly accounted for the variability in LTM. This variability may have originated from processing during encoding or maintenance stages of the STM task, which were identical for both Learning-STM and Learning-only trials. This should be explored in future studies, for example, by systematically varying the lengths of encoding and delay periods or measuring

variability in the neural signatures during these periods using EEG and correlating them with performance. Additionally, there may be other mechanisms that govern variability in both memory systems. For example, apart from their ability to bind item-location associations and the granularity with which they can store location information in both STM and LTM, as discussed in Chapter 1, participants' performance may be limited by their ability to exert selective attention in a goal-directed manner to encode and maintain associations. The ability to bind associations can be assessed using mixture modelling on the localisation error data (e.g., Grogan et al., 2020), which can reveal any presence of mis-binding or swap errors. In addition, participants' perceptual precision could be measured by incorporating immediate report trials (e.g., Korkki et al., 2020). Furthermore, a separate basic visual attention task, based on the theory of visual attention (e.g., Espeseth et al., 2014), could be used in future studies as a benchmark for participants' attentional abilities, and performance on this task could be used to account for attentional influences on STM and LTM performance.

In contrast to the findings of the current study, Korkki et al. (2020) have reported that the effect of age group on LTM precision persisted even after accounting for the decrease in STM precision. This discrepancy in findings between the two studies may be attributed to differences in the tasks used to measure STM and LTM, as discussed in section 3.1. above. While the current study employed tasks with analogous encoding and probing of short- and long-term memories, Korkki et al. (2020) utilised two different tasks for the two types of memory. This could have weakened the relationship between STM and LTM measures in their study. Alternatively, the relationship between STM and LTM may look different when looking at the overall error as compared to the sources of error, such as memory imprecision of the proportion of guesses, which should be explored in future studies.

The relationship between STM and LTM measured in the current study was similar across the three age groups, suggesting that both STM and LTM decline at a similar rate with

advancing age. As mentioned previously, the involvement of the MTL and the hippocampus in STM and LTM (e.g., Kolarik et al., 2018; Yonelinas, 2013; Zokaei et al., 2019), as well as alterations in visual functions with age (Chamberlain et al., 2021; Jorge et al., 2020; Pitchaimuthu et al., 2017), may explain why the two types of memory may have a similar vulnerability to ageing. Given that ageing is also associated with declining long-term potentiation (Bettio et al., 2017; Lister & Barnes, 2009), one may expect that older participants' LTM would be disproportionally affected as compared to STM. Nevertheless, these effects may be additive and not affect the relationship between STM and LTM.

Interestingly, the memory load affected not just STM but also LTM localisation performance: participants produced larger localisation errors in three-item trials as compared to one-item trials in both tasks. This is surprising given that, in contrast to STM, LTM is thought to have a near-unlimited capacity (Brady et al., 2008). However, this could be explained by a limited encoding window. In the study by Brady et al. (2008), although characteristics of hundreds of different objects were encoded to LTM, a three-second time window was dedicated for the encoding of each object. In contrast, the current study utilised a constant five-second window in both one- and three-item trials, during which participants searched for items within scenes and encoded their identities and locations. It is therefore possible that the constant encoding window of five seconds in the current study has contributed to a reduced per-item encoding in three-item as compared to one-item trials, resulting in consequences on localisation performance across both STM and LTM. In contrast, there was no difference in identification accuracy between set size conditions in LTM trials. This suggests that long-term memories for object identities were less affected by the limited encoding window than short-term memories. Potentially, other mechanisms, such as familiarity, which does not require detailed representations of stimuli (Schurgin, 2018), may have contributed to object identification performance in LTM trials.

Modelling of memory errors may yield more sensitive measures of memory performance (e.g., Zokaei, Sillence, et al., 2020). Although, given the limited number of trials, only per group modelling could be performed in the current study, without drawing inferences, such data may suggest potential avenues for exploration in future studies. The two-dimensional mixture model (Grogan et al., 2020) results suggest that, across both types of memory, larger localisation errors in older as compared to young adults may have resulted from both memory imprecision and increased guessing rates. This differs from findings by Korkki et al. (2020) and Nilakantan et al. (2018), which suggest that memory imprecision alone accounted for the increase in location errors in older as compared to young adults in STM (Korkki et al., 2020) and LTM (Korkki et al., 2020; Nilakantan et al., 2018). As discussed in Chapter 2, differences between findings of the current and previous studies may relate to the length of retention intervals used in the different tasks. Namely, the current study utilised longer retention intervals in both STM and LTM tasks, potentially resulting in greater forgetting over time in older adults. This should be explored in future studies by systematically varying retention intervals. Importantly, apart from structural changes in the hippocampus (e.g., see Bettio et al., 2017 for a review), ageing is associated with a decline in long-term potentiation that is required for the formation of long-term memories (Bettio et al., 2017; Lister & Barnes, 2009). Therefore, increased guessing as a result of forgetting may be an important marker of ageing. Finally, in STM-only trials, older adults were also more likely to place objects in the location of other objects in the memory array, or to perform swap errors. Swap errors, as well as the loss in memory precision, may indicate the presence of subtle hippocampal pathology in the older group (Pertzov et al., 2013, 2015; Zokaei, Nour, et al., 2019). However, given the limitations of per group modelling, these findings warrant a replication.

Modelling may also shed some light on the potential sources of the increase in localisation errors from STM to LTM. Results suggest that the difference in localisation errors between the two memory conditions may have arisen mostly from an increase in guessing. This is consistent with the idea that participants forgot more information over time, discussed above. In slight contrast to previous literature (Brady et al., 2013), memory precision also declined from STM to LTM, although not by much. This suggests that STM and LTM may indeed have similar limits on fidelity (Brady et al., 2013). It would be valuable to replicate these finding, as well as explore the relationship between STM and LTM precision in future studies, ideally, by using tasks similar to those described in the current chapter with a much greater number of trials to model performance of each participant.

There was a relative mismatch between older adults' LTM localisation performance and their confidence judgements compared to the young group. Older adults seemed less sure when judging their performance, providing less relevant confidence ratings than young adults for localisation errors of the same magnitude. In contrast, one previous study has found that older adults, due to their reliance on familiarity, were overconfident about their memory performance, providing high confidence ratings for false positive responses (Shing, Werkle-Bergner, Li, & Lindenberger, 2009, described in Chapter 2). Given the non-directional deficit, the reduced ability of older adults to judge their performance in the current study may reflect declining meta-cognitive abilities. Alternatively, it may simply reflect that older adults found the task more difficult than the young group. Indeed, based on the mixture model results, older participants may have guessed more than the young group. Guess responses are likely to be followed by low-confidence judgements regardless of their accuracy. This deficit in older adults may be ameliorated by multiple opportunities to learn object-scene associations, as in the study by Salvato et al. (2016), where older adults were as good at evaluating their performance as their young counterparts. Finally, middle-aged adults did not differ

significantly from either of the two groups, suggesting that although they performed as well as young adults on the task, they may have found it slightly more challenging.

One of the potential limitations of this study was that, apart from controlling for self-reported visual abilities, there were no objective measures of visual functions and processing speed. Older adults have been shown to have difficulty ignoring distracting stimuli (Babu et al., 2014). This, in combination with the slower processing speed (Owsley, 2013) and the five-second encoding window, may have disproportionately disadvantaged older adults while they were searching for objects in memory displays. This could have led to disadvantages in localisation performance across memory conditions, in particular, as older adults may have not had as much time as the other two groups to explicitly learn object locations after the objects have been found. However, this did not alter the relationship between STM and LTM across age groups. Nevertheless, more objective measures of visual functions and processing speed should be included in future studies investigating the effects of ageing on memory using the current task.

Future studies could focus on finding the source of impairments in performance in older adults in these tasks. Encoding and early maintenance during the STM delay could play a major part (Craik & Rose, 2012), especially based on the finding that STM localisation errors alone could predict LTM localisation errors irrespective of the age group. However, retrieval of information might also be affected by ageing (Rhodes et al., 2019). The contributions of these processing stages to age-related alterations in memory performance could be investigated by adapting tasks that enable analogous assessment of both STM and LTM performance to neuroimaging. In particular, neuroimaging techniques that allow high temporal resolution, such as EEG or magnetoencephalography (MEG), may provide the means to measure differences between the age groups at different processing stages of STM and LTM on a millisecond timescale (Uhlhaas et al., 2017). For example, it is not known if

the attenuation of parietal P300 component in older adults, which correlates with participants' STM performance (McEvoy et al., 2001; Saliasi et al., 2013), also relates to their LTM performance. Finally, due to a high number of potential stimuli, which are available in online repositories, these tasks may be a useful tool to measure changes in memory longitudinally. If validated and benchmarked, the sensitivity of such tasks may be useful for memory monitoring in older adults as steeper decline in STM and LTM over time may indicate cognitive impairments.

EEG and MEG could also be used to investigate the neural underpinnings of the differences and similarities between STM and LTM processing in similar tasks. It could be expected that event-related potentials in the early and the late delay stages of the STM task would differ for the remembered vs forgotten objects in LTM, which would provide support to findings from previous studies (Khader et al., 2007). Furthermore, based on the existing theories of storage and retrieval of short- and long-term memories, discussed in Chapter 1 (Abraham et al., 2019; Fuster & Alexander, 1971; Serences, 2016; Stokes, 2015), we may expect to see both differences and similarities in the neural signatures measured during the retrieval of object identities and locations from STM and LTM.

By adapting tasks described in the current study for fMRI and lesion studies, it would be possible to identify the brain networks that support STM and LTM for object-location associations. As discussed previously, one of the potential areas of the brain involved in both types of memory may be the MTL, and in particular the hippocampus (Liang et al., 2016; Pertzov et al., 2013; Zokaei, Nour, et al., 2019). Assessment of performance on such tasks in healthy volunteers, in combination with fMRI for spatial resolution, and in patients (e.g., for limbic encephalitis, see Pertzov et al., 2013; for hippocampal lesions, see Zokaei et al., 2019) would enable the finetuning of the tasks for use with pre-clinical and clinical groups, such as Alzheimer's disease patients or individuals at risk of developing this neurodegenerative

disorder, who might experience disproportional decline in LTM as compared to STM due to accelerated long-term forgetting (Weston et al., 2018). It may be that such groups would show a dissociation between STM and LTM performance as compared to healthy controls. The use of such tasks would also enable tracking of STM and LTM changes longitudinally and in a more sensitive way than permitted by the standard neuropsychological measures.

3.5. Conclusions

In conclusion, this is the first study to my knowledge to investigate STM and LTM performance and the association between the two types of memory encoded in an identical way utilising analogous sensitive continuous report measures across different age groups. The findings suggest that both STM and LTM decline in late adulthood and that LTM decline might be driven by impairments in STM processing. Finally, the two memory systems may share at least some of the underlying neural machinery for processing object-location associations, as indexed by their relationship and shared vulnerability to the effects of ageing.

Chapter 4. Short- and Long-Term Memory and Their Relationship in Apolipoprotein E ε4 Carriers and Non-Carriers

Abstract

The relationship between APOE ε4 allele and memory functions is not well understood. Based on studies that utilised sensitive continuous-report tasks, there may be a dissociation between STM and LTM performance in APOE ε4 carriers due to an interaction between phenotypic and prodromal effects of this allele on memory. Furthermore, APOE ε4 carriers may also show increased forgetting of information over time. The study presented in the current chapter examined forgetting as a function of decline in performance from short to long timescales, as well as across different intervals within LTM, in middle-aged APOE ε3/ε3, ε3/ε4, and ε4/ε4 carriers. This was done using the STM and LTM tasks described in Chapter 3, in addition to a smartphone app task, titled the Gallery Game, which enabled assessment of memory performance for object-swipe associations across days. APOE ε4 carriers did not show any differences in memory performance on the in-house STM and LTM tasks. Furthermore, APOE genotype did not alter the relationship between STM and LTM in this study. Surprisingly, ε4 carriers produced fewer errors per learning session on the Gallery Game as well as showed superior recall performance after seven to eight days of retention for non-living objects, suggesting a slight STM and LTM advantage in this group. The length of the STM delay interval used in the current study may explain the lack of difference between APOE groups in the in-house STM task. In addition, many middle-aged APOE ε4 carriers may not yet show decline in memory, which may explain the superior performance of APOE ε4 carriers on some of the other measures in the current study. Future studies should utilise both short and longer delay intervals, in combination with larger samples, to explore the relationship between different APOE alleles and memory.

4.1. Introduction

As discussed in Chapter 1, the literature on the relationship between APOE gene and cognition is riddled with mixed findings, with studies finding positive, negative, as well as null effects of APOE ε4 on STM and LTM. This variability in reported results may be due to various reasons, including the use of crude neuropsychological tests to assess memory in healthy individuals and small samples that often include very few homozygous APOE ε4 carriers (O'Donoghue et al., 2018).

A more coherent picture emerges from studies utilising sensitive continuous-report measures of STM and LTM and balanced samples. Several studies using variants of a continuous-report STM task described in Chapter 2, which has also been shown to be sensitive to MTL damage (Pertzov et al., 2013; Zokaei, Nour, et al., 2019), have found an STM advantage in middle-aged and older APOE ε4 carriers (Zokaei et al., 2017; Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020). During the task, participants first viewed one or three coloured fractal objects presented on a black background, followed by a blank memory delay of either one or four (Zokaei, Grogan, et al., 2020), or one or eight seconds (Zokaei et al., 2017; Zokaei, Čepukaitytė, et al., 2019). After the delay, two probe items were shown, and participants' memory for object identity and location was measured by asking them to select the item they saw in the memory array and place it back in its remembered location.

The results suggest an STM advantage in middle-aged and older APOE ε4 carriers, particularly at high loads and short maintenance durations. This was found in two of the studies, with better STM for locations in APOE ε4 carriers as compared to APOE ε3 homozygotes after a short one-second delay in three-item trials (Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020). The first of these studies tested a sample of 66 older participants, and the advantage was found only in the 22 homozygous ε4 carriers (Zokaei,

Čepukaitytė, et al., 2019). In contrast, the second study included a large sample of 1277 individuals in their mid-twenties to early seventies, 405 of whom were ε4 carriers, and the advantage was present in a combined group of APOE ε4 carriers, the majority of whom (359) were heterozygous for APOE ε4 (Zokaei et al., 2020). In addition to better memory for locations, better memory for object identities in APOE ε4 carriers was also observed in this study (Zokaei et al., 2020). However, a slightly different pattern of results, with better memory for locations after an eight-second delay only in male but not female APOE ε4 carriers, was reported in the third study (Zokaei et al., 2017), suggesting that memory advantage may also be present after longer delay durations. This study tested a sample of 60 middle-aged individuals, an equal number of whom were carriers of APOE ε3/ε3, ε3/ε4 and ε4/ε4 (Zokaei et al., 2017). It is not clear why there is a discrepancy between findings of this and the other two studies using similar methodologies (Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020). It has been suggested that females, including APOE ε4 carriers, are more likely to be affected by AD (Altmann et al., 2014; Farrer, 1997). Therefore, it could be speculated that the extent of the memory advantage in APOE ε4 carriers is modulated by the risk of developing AD (due to or independently from prodromal changes). Individuals at a reduced risk, such as males, may show a memory advantage spanning longer maintenance periods. However, this was not observed in the other two studies (Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020). Taken together, more weight should be placed on the consistent findings of the first two studies, one of which was large-scale.

Overall, the presence of an STM memory advantage in middle-aged and older adults is consistent with the cognitive phenotype hypothesis, discussed in Chapter 1, according to which different APOE alleles affect cognition throughout life (e.g., Greenwood et al., 2005, 2014). However, longitudinal studies including young adults are required to test whether STM advantages are also present at young age and remain relatively stable across life. In

addition, or alternatively, better performance after short delays and equivalent performance after longer delays in STM tasks in APOE ε4 carriers may signal increased forgetting in this group (Zokaei, Grogan, et al., 2020). Accelerated long-term forgetting has been observed in APOE ε4 carriers and may be related to prodromal AD (Weston et al., 2018; Zimmermann & Butler, 2018; Zokaei, Grogan, et al., 2020). Hence, increased forgetting over the longer STM delay periods may also be consistent with the prodromal hypothesis (Foster et al., 2013; G. E. Smith et al., 1998). Finally, based on the studies that separated heterozygous and homozygous participants, it seems that heterozygous carriers of APOE ε4 may show more variability in performance across studies as compared to homozygous carriers, with larger samples required to detect significant differences in memory from non-carriers in this group (Zokaei et al., 2017; Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020). This should be explored further, as the variability in the heterozygous group may shed light on what makes some APOE ε4 carriers vulnerable and others resilient to AD. Finally, studying homozygous and heterozygous participants separately, in particular in smaller samples, may lead to more consistent results.

To date, two studies utilising sensitive continuous-report measures to test contextual spatial LTM of APOE ε3/ε3, ε3/ε4 and ε4/ε4 carriers have been conducted with mixed findings (Salvato, Patai, McCloud, et al., 2016; Zokaei, Čepukaitytė, et al., 2019). The first study by Salvato et al. (2016) focused on middle-aged individuals, while the second study by Zokaei, Čepukaitytė, et al. (2019) tested older participants. Both studies began with a learning task, during which participants searched for real-life objects embedded in complex photographic scenes (one item per scene in Salvato et al. (2016) and either one or two items in Zokaei, Čepukaitytė, et al. (2019)). The same object-scene combinations were presented in random order over four consecutive blocks to maximise learning.

Following the learning task, the procedures diverged between the two studies. After a break of 30 minutes that followed the learning task, participants in the study by Salvato et al. (2016) performed an LTM-guided attentional orienting task. Every trial of this task began with a centrally presented fixation cross shown for 1000-1500 milliseconds and followed by one of the previously searched scenes. After 1000-1500 milliseconds since scene onset, either a stop sign or the object initially learned within that scene was flashed on the screen for 100 milliseconds. The object appeared either at its learned location or anywhere on the opposite side of the scene. Participants pressed a mouse button as soon as they detected the object and refrained from pressing if they saw the stop sign. Participants' gaze was maintained on the central fixation cross throughout the task. This task was followed by an explicit LTM retrieval task. Participants were shown one of the learned scenes and asked to indicate using a cursor the remembered location of the object. This was followed by confidence ratings and a three-alternative forced-choice task to test object identity.

The authors found comparable performance across the APOE groups in both the LTM-based orienting of attention and the explicit LTM retrieval of locations (Salvato, Patai, McCloud, et al., 2016). However, when the relationship between performance on these two tasks was measured, both heterozygous and homozygous APOE ε4 carriers showed weaker association between explicit memory and orienting than non-carriers (Salvato, Patai, McCloud, et al., 2016). These results suggest that middle-aged APOE ε4 carriers may not yet show deficits in either explicit LTM or LTM-guided attention, especially if only one item has to be remembered within a scene. However, unlike non-carriers, they may rely less on explicit LTM representations for attentional orienting (Salvato, Patai, McCloud, et al., 2016). The pattern of results is compatible with either a prodromal or a cognitive-phenotype account.

The study by Zokaei, Čepukaitytė, et al. (2019) utilised the task described in Chapter 2 to test LTM. Following a 20-minute break after the learning task, participants completed a surprise explicit LTM retrieval test. In each trial, one of the scenes from the learning task was shown on the screen with two objects presented below. Participants had to select the object they recalled in that scene and place it in its remembered location. The authors found that, when two items had to be remembered, homozygous APOE ε4 carriers showed a location memory disadvantage for the item tested when compared to heterozygous APOE ε4 carriers and non-carriers (Zokaei, Čepukaitytė, et al., 2019). This suggests that LTM deficits may emerge later in life, consistent with the prodromal hypothesis (Foster et al., 2013; G. E. Smith et al., 1998), and affect carriers with a double dose of the gene more than those with a single dose. However, without testing long-term memories of young participants, the presence of a cognitive phenotype, characterised by poorer LTM for item-location associations, cannot be excluded. Nevertheless, some indirect support for the prodromal hypothesis comes from other studies suggesting no difference between APOE ε4 carriers and non-carriers at young age (for a meta-analysis, see Weissberger et al., 2018), and acceleration of memory decline in middle-aged adults over a six-year follow-up (Caselli, Dueck, Locke, Hoffman-Snyder, et al., 2011).

The studies discussed above suggest that middle-aged and older APOE ε4 carriers may show a different pattern of STM and LTM performance as compared to non-carriers. Namely, although they are able to report item locations with greater precision after a short delay of one second (Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020), this advantage may or may not persist for longer delays of eight seconds (Zokaei et al., 2017; Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020). Furthermore, delays extending to 20 minutes, in combination with higher memory loads, as used in the LTM task described above, may lead to worse performance in at least the older APOE ε4 carriers (Zokaei, Čepukaitytė, et al., 2019). This pattern of results is consistent with the idea of

accelerated forgetting in APOE ε4 carriers (Zokaei et al., 2020). However, no study to date has investigated this phenomenon for the same type of information over both short and long timescales.

Testing forgetting over retention intervals spanning days may also be a promising way to detect pre-Alzheimer's pathology. Accelerated long-term forgetting of the 15-item word list from the Auditory–Verbal Learning Test has been observed after a seven-day retention intervals in both young asymptomatic individuals who are predisposed to developing autosomal dominant (familial) AD (Weston et al., 2018) and asymptomatic middle-aged homozygous APOE ε4 carriers (Zimmermann & Butler, 2018), while their immediate and 30-minute recall was no different from that of controls. This suggests that differences between healthy and at-risk groups might be exaggerated with longer retention intervals.

A novel smartphone task, the Gallery Game, developed by Lancaster et al. (2020) was therefore included in the current study to complement the STM and LTM tasks described in Chapter 3. The task assesses forgetting of object identity and swiping direction associations across multiple retention intervals. The task was designed to measure the MTL function, as the representations formed and tested during the task are associative in nature (Davachi, 2006; Lancaster et al., 2020), although this dependency is yet to be validated empirically.

There are several advantages of using the Gallery Game to measure long-term forgetting (Lancaster et al., 2020). Firstly, it only requires a commitment of a few minutes per day and can be performed in the comfort of one's own home, reducing the demand on participants and potentially increasing their compliance. Furthermore, the use of a large set of different images enables testing of long-term forgetting multiple times over multiple retention intervals but without confounding the results by recalling the same information multiple times, unlike the Auditory–Verbal Learning Test described above (Elliott et al., 2014). In the

current study, a 21-day protocol was used to test memory after one, three, five, seven and ten days.

The Gallery Game allows the implementation of another potential measure to detect early behavioural signs of neurodegeneration. Stimuli used in this task come from two categories: living and non-living. While non-living objects tend to be easily discriminable due to form-to-function mapping, living objects share many similar perceptual features such as eyes and limbs (Lancaster et al., 2020). The perirhinal cortex has been implicated in distinguishing confusable objects, such as living items, from one another (e.g., Bussey et al., 2002; Tyler et al., 2013). This brain area is also one of the first ones to be affected by AD pathology, even before the hippocampus (Braak & Braak, 1991). Accordingly, the ability to distinguish confusable objects has been shown to be impaired in AD patients, who produce more false-positive responses, identifying novel distractors as previously seen, to living as compared to non-living objects (Kivisaari et al., 2013). Therefore, the relative rate of false-positive responses (false alarms) to living vs non-living objects may provide a sensitive marker of early pathological changes in middle-aged APOE ε4 carriers as a result of prodromal AD (Foster et al., 2013; G. E. Smith et al., 1998).

The aims of the study presented in the current chapter were therefore to quantify forgetting as a function of decline in performance from short to long timescales, as well as across different intervals within LTM, in middle-aged APOE ε3/ε3, ε3/ε4, and ε4/ε4 carriers using sensitive continuous report tasks described in Chapter 3 and the Gallery Game (Lancaster et al., 2020). All three tasks test associative memory, which has been shown to be affected by AD (e.g., Kessels et al., 2005; Liang et al., 2016; Parra et al., 2010, 2015). In addition, the Gallery Game may specifically target perirhinal pathology, putatively providing a very early marker of AD pathology (Lancaster et al., 2020).

Given that APOE groups may differ in both cognitive phenotypes and susceptibility to prodromal brain changes, I expected to see better performance, in particular in homozygous APOE ε4 carriers, on STM for locations, with smaller memory errors than those of non-carriers, in line with STM studies discussed above (Zokaei et al., 2017; Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020), and the cognitive phenotype hypothesis (Greenwood et al., 2014; Greenwood & Parasuraman, 2003). This effect may be more apparent in difficult three-item trials. In contrast, I predicted worse performance in the homozygous carrier group on LTM, with larger memory errors, as in Zokaei, Čepukaitytė, et al. (2019), indicating increased forgetting over time as a result of prodromal AD (Foster et al., 2013; G. E. Smith et al., 1998). This effect might be subtle due to most of the participants being middle-aged, as although AD pathology may start developing up to a decade before diagnosis (Tondelli et al., 2012; Wilson et al., 2011), it is likely to be subtle and not present in all participants, even in the homozygous APOE ε4 carrier group, approximately 10 percent of whom may never develop AD (Farrer, 1997). However, I expected the difference among gene groups to be amplified in the Gallery Game due to the accelerated long-term forgetting over retention intervals, previously observed in middle-aged APOE ε4 carriers on verbal tests of memory (Zimmermann & Butler, 2018). Finally, I predicted ε4 carriers to commit more false alarms than ε3/ε3 carriers when remembering living as compared to non-living items, which would be an indication of an early perirhinal atrophy in this group, consistent with the prodromal hypothesis (Foster et al., 2013; G. E. Smith et al., 1998).

4.2. General Methods

4.2.1. Participants

The study was approved by the Medical Sciences Interdivisional Research Ethics Committee of the University of Oxford (Ethics Approval Reference: R61052/RE001) and complied with the Declaration of Helsinki.

In total, 79 participants aged 46-69 years (mean = 54.25) were recruited based on their genotype via Oxford Biobank (www.oxfordbiobank.org.uk) to take part in this study. All gave written informed consent and were reimbursed at a rate of £10 per hour for participation and any travel expenses. The sample consisted of 31 APOE ε3/ε3, 31 APOE ε3/ε4 and 17 ε4/ε4 carriers who, as well as the researchers, were blind to their APOE genotype. Two participants were excluded from all analyses: one due to ACE-III score lower than 88, the highest recommended cut-off to detect cognitive impairment (Hsieh et al., 2013), and one due to history of traumatic brain injury, which may have confounded the results (the exact gene group membership of excluded participants is not disclosed to prevent their unblinding). The remaining sample included 31 APOE ε3/ε3, 30 APOE ε3/ε4 and 16 ε4/ε4 carriers. Three participants from one of the groups reported having abnormal vision due to keratoconus, colour blindness and astigmatism, respectively. However, as they showed average or above average performance as compared to the rest of the gene group, these participants were not excluded from the analysis. One additional participant from a different group also reported colour blindness and was excluded from the in-house (STM-LTM) task analysis due to poor performance (see section 4.3.1.4. for details). The remaining participants had normal or corrected-to-normal vision by self-report. Finally, all were fluent or native English speakers and were comparable on age, years of education, ACE-III Attention and Memory scores, digit span, blood pressure, depression and anxiety scores (see section 4.2.2. for details and Table 4.1 for descriptive information). The groups differed significantly on ACE-III Language,

Fluency, and total scores (Table 4.1). However, as memory tasks used in the study assessed visual memory and participants were able to understand and perform these tasks, ACE-III Language and Fluency scores were not included as covariates in the analysis.

Table 4.1. Descriptive information for participants included in the analysis.

	Gene group				
Measure	APOE ε3/ε3	APOE ε3/ε4	APOE ε4/ε4	Statistic	*p*
N*	31	30	16	$X^2(2) = 5.48$	.06
Male/female	16/15	14/16	4/12	$X^2(2) = 2.65$	.27
Age	53.97 (5.31)	55.00 (5.50)	53.37 (4.59)	$F(2, 74) = 0.52$	.60
Education	15.52 (3.41)	16.07 (3.56)	17.06 (2.23)	$X^2(2) = 2.61$	.27
Handedness (L/R)	2/29	2/28	4/12	-	.14
ACE-III Attention	17.48 (.93)	17.76 (0.63)	17.81 (0.54)	$X^2(2) = 3.29$	.19
ACE-III Memory	25.42 (.96)	25.03 (1.40)	25.69 (0.60)	$X^2(2) = 3.38$	.18
ACE-III Fluency*	12.10 (1.47)	12.93 (1.31)	13.12 (0.81)	$X^2(2) = 8.13$	.02
ACE-III Language*	25.22 (1.06)	25.77 (0.50)	25.37 (1.20)	$X^2(2) = 6.84$	.03
ACE-III Visuospatial	15.61 (0.62)	15.57 (0.77)	15.81 (0.54)	$X^2(2) = 1.97$	.37
ACE-III total*	95.84 (2.56)	97.07 (2.38)	97.81 (2.14)	$X^2(2) = 8.37$	.02
Dementia in parents	7	10	5	-	.65
Digit span forward	11.52 (1.94)	12.33 (1.97)	11.81 (2.74)	$X^2(2) = 2.19$	.33
Digit span backward	8.00 (3.80)	8.6 (3.34)	8.12 (2.52)	$X^2(2) = 1.27$	.53
Smokers	1	2	0	-	.80
Drinkers	27	26	14	-	>.99
Blood pressure (systolic)	124.27 (13.48)	126.83 (16.45)	124.09 (16.63)	$F(2, 73) = 0.20$	.82
Blood pressure (diastolic)	81.16 (7.67)	81.41 (11.41)	82.03 (8.46)	$F(2, 73) = 0.06$	.94
BDI-II	5.10 (8.20)	2.70 (3.38)	2.69 (2.49)	$X^2(2) = 0.68$	.71
STAI (State)	26.98 (8.23)	24.40 (4.16)	26.50 (5.73)	$X^2(2) = 1.76$	.41
STAI (Trait)	34.06 (11.20)	29.40 (7.39)	34.31 (8.33)	$X^2(2) = 4.34$	.11

Note: ACE-III = Addenbrooke's Cognitive Examination III, BDI-II = Beck Depression Inventory-II, STAI - State-Trait Anxiety Inventory. Age, years in education, ACE-III, BDI-II and STAI scores are presented as *M* (*SD*). Where test statistics are not provided, Fisher's Exact Test for count data was used due to 5 or fewer observations per condition. *Indicates variables for which the groups differed significantly ($p < 0.05$).

4.2.2. Tasks and Procedures

Upon their arrival to the testing facilities and signing the consent form, participants were given a verbal overview of the upcoming tasks. This was followed by an introduction and completion of the STM task described in Chapter 3 (also see section 4.3.1.2.). In the break preceding the LTM tasks (see Chapter 3 and section 4.3.1.2.), participants completed the ACE-III. Blood pressure measurements followed the completion of the LTM task. Participants' blood pressure was measured to account for cardio-vascular influences on performance, as APOE ε4 has been associated with an increased risk for cardiovascular diseases (Bennet et al., 2007) that may affect brain health (e.g., Yin et al., 2012). The blood pressure was measured twice using the left arm, with measurements separated by a short break. The average systolic and diastolic blood pressure readings per group are reported in Table 4.1. Blood pressure measurements were followed by the State-Trait Anxiety Inventory (STAI, Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Once this questionnaire was completed, participants were guided through the installation of the Mezurio app and the Gallery Game and completed a set of practice trials guided by the app (see section 4.4. below). If all procedures described above were completed within two and a half hours, participants provided their demographic and health information using an online questionnaire administered via the Qualtrics platform (https://www.qualtrics.com/). Otherwise, participants completed this questionnaire at home.

4.3. Experiment 1: Comparison Between Short- and Long-Term Memory

4.3.1. Methods

4.3.1.1. Participants. One additional participant was excluded from the analysis due to computer failure that resulted in data loss. The remaining sample included 31 APOE ε3/ε3,

29 ε3/ε4 and 16 ε4/ε4 carriers. The groups remained comparable on the baseline measures described in section 4.2.1.

4.3.1.2. Stimuli, Tasks and Procedure. The STM and LTM tasks used were the same as those described in Chapter 3 (also shown in Figure 4.1) with minor modifications. Firstly, participants recruited for this study were on average younger than the older group described in Chapter 3. As middle-aged participants performed as well as young participants in that study, I increased the number of trials to 120 in the STM task and 60 in the LTM task to obtain better estimates of performance. Half of the STM trials were Learning-only, and the other half were Learning-STM. Out of the 60 trials per memory condition, 16 contained one object, while the remaining 44 were three-object trials. To minimise fatigue, the STM task was divided into three blocks of 40 trials and the LTM task contained two blocks of 30 trials. Furthermore, additional objects were added to match the increased number of trials (object acquisition and pre-processing steps are outlined in Chapter 3). In total, 416 objects were randomly drawn from a pool of 515 objects for the two tasks for each participant.

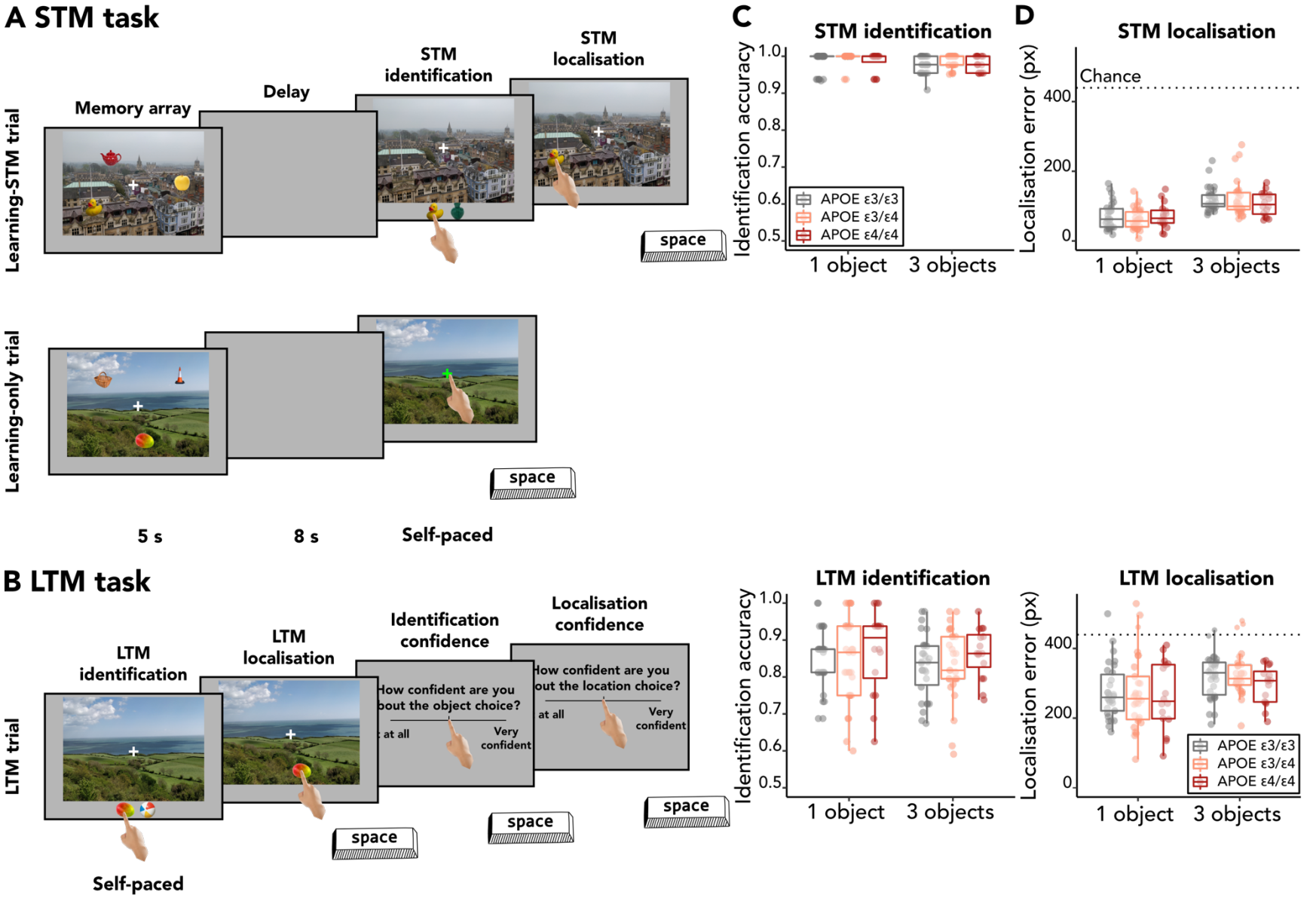

A STM task
Learning-STM trial
Memory array
Delay
STM identification
STM localisation
space
Learning-only trial
space
5 s
8 s
Self-paced
B LTM task
LTM trial
LTM identification
LTM localisation
Identification confidence
Localisation confidence
How confident are you bout the object choice?
at all
Very confident
How confident are you out the location choice?
at all
Very confident
space
space
space
Self-paced
C
STM identification
Identification accuracy
1.0
0.9
0.8
0.7
0.6
0.5
APOE ε3/ε3
APOE ε3/ε4
APOE ε4/ε4
1 object
3 objects
D
STM localisation
Localisation error (px)
Chance
400
200
0
1 object
3 objects
LTM identification
Identification accuracy
1 object
3 objects
LTM localisation
Localisation error (px)
400
200
0
APOE ε3/ε3
APOE ε3/ε4
APOE ε4/ε4
1 object
3 objects

Figure 4.1. Task schematic (A, B) and Identification (C) and Localisation results (D). Each trial in the Short-term memory (STM) task (A) started with a memory array (5 s), which included a scene with either one or three embedded objects, followed by a delay (8 s). In Learning-STM trials, the delay was followed by a memory probe (self-paced) in which participants were asked to select the object they had seen in the memory array before the delay as fast as they could out of the two presented below the scene (STM identification) and place it back to its original location as precisely as they could (STM localisation). In contrast, in Learning-only trials, the delay was followed by only the scene from the memory array and participants were asked to tap on the green fixation cross presented at the centre (self-paced). Participants pressed the space bar to complete the trial. Each trial in the Long-term memory (LTM) task (B), which followed 20 minutes after the STM task, began with an identical memory probe, which probed memories of learning-only trials (self-paced). Following LTM localisation, participants were presented with two continuous report confidence rating scales on object identification and localisation confidence, respectively. They had to indicate their confidence from *Not confident at all* to *Very confident*. Participants pressed the space bar to move from localisation to confidence ratings and to complete the trial. In both memory probes, one of the objects had always appeared in the corresponding memory array while the other object was completely novel. Performance on these tasks is shown in panels C (Identification) and D (Localisation). Coloured dots (grey – APOE ε3/ε3, orange – APOE ε3/ε4, red – APOE ε4/ε4) represent participant means, lines inside boxes represent group medians, hinges represent first and third quartiles, and whiskers represent values that fall outside the *IQR* but within 1.5 * *IQR* from each hinge. Dots outside the whiskers are outliers.

4.3.1.3. Design. This study utilised a 3 × 2 × 2 mixed factorial design with gene group (APOE ε3/ε3, APOE ε3/ε4, APOE ε4/ε4) as a between-subjects factor and memory condition (STM, LTM) and set size (1 or 3 objects) as within-subject factors. Dependent variables were identification accuracy (the proportion of correctly identified trials) and localisation error (the Euclidean distance between the target location and the response location).

4.3.1.4. Data Analysis. Data were pre-processed and analysed following the procedure described in Chapter 3. During the pre-processing, less than one percent of trials were excluded. The participant with self-reported colour blindness that was excluded from the analysis (see section 4.2.1) performed with identification accuracy more than 3 standard deviations below the group mean for one-object STM trials.

4.3.2. Results

4.3.2.1. Short- and Long-Term Memory Performance

4.3.2.1.1. Identification Accuracy. The non-parametric ANOVA-type test showed that the main effect of gene group was not statistically significant, $ATS_{Mod}(1.85, 45.68) = 0.97$, $p = .38$. Regardless of their APOE genotype, participants were equally accurate when identifying target objects (Figure 4.1C). However, there were significant main effects of memory condition, $ATS(1, \infty) = 487.68$, $p < .001$ and set size, $ATS(1, \infty) = 18.86$, $p < .001$. Participants showed higher identification accuracy in STM and one-object trials (Figure 4.1C). None of the two- or three-way interactions reached statistical significance: Gene group × Memory condition: $ATS(1.87, \infty) = 2.22$, $p = .11$, Gene group × Set size: $ATS(1.97, \infty) = 0.04$, $p = .96$, Memory condition × Set size: $ATS(1, \infty) = 0.005$, $p = .94$, Gene group × Set size × Memory condition: $ATS(1.68, \infty) = 0.28$, $p = .72$.

4.3.2.1.2. Localisation Error. The non-parametric ANOVA-type test showed that the main effect of gene group was not statistically significant, $ATS_{Mod}(1.81, 42.42) = 0.46$, $p = .62$. Regardless of their gene group membership, participants produced localisation errors that were similar in magnitude (Figure 4.1D). However, there were significant main effects of memory condition, $ATS(1, \infty) = 1171.51$, $p < .001$ and set size, $ATS(1, \infty) = 110.71$, $p < .001$, accompanied by a significant Memory condition × Set size interaction, $ATS(1, \infty) = 7.02$, $p = .008$. Participants showed smaller localisation errors in STM and one-object trials, respectively (Figure 4.1D). However, the interaction reflected that the relative difference between localisation errors in one- and three-object trials was greater in STM, $ATS(1, \infty) = 99.53$, $p < .001$, as compared to LTM condition, $ATS(1, \infty) = 21.17$, $p < .001$ (Figure 4.1D), although when the mean difference between 1- and 3-object trials was contrasted between memory conditions, there was no significant difference, $z = 1360$, $p = .73$. None of the remaining two- or three-way interactions were statistically significant: Gene group × Memory condition: $ATS(1.99, \infty) = .45$, $p = .63$, Gene group × Set size: $ATS(1.86, \infty) = 1.95$, $p = .15$, Gene group × Set size × Memory condition: $ATS(1.55, \infty) = 0.02$, $p = .95$.

4.3.2.2. Relationship Between Short- and Long-Term Memory. The model showed that participants' STM localisation errors significantly predicted LTM localisation errors, $F(1, 69) = 11.60$, $p = .001$. Namely, participants who produced larger STM localisation errors also produced larger LTM localisation errors (Figure 4.2). On the other hand, the main effect of gene group, and the interaction between gene group and STM localisation error were not statistically significant, $F(2, 69) = 0.22$, $p = .81$, and $F(2, 69) = 0.14$, $p = .87$, respectively. This indicated that the magnitude of STM localisation errors and not participants' gene group best accounted for the increase in LTM localisation errors, and that participants' gene group

did not mediate the relationship between STM and LTM localisation errors, respectively (Figure 4.2).

I then simplified this model by first removing the interaction term and then the gene group. This did not significantly impair model fits (p = .87 and p = .38, respectively) and further supported the idea that the variation in STM localisation errors across participants alone could explain differences in LTM localisation performance, $F(1, 73) = 18.51$, $p < .001$, $R^2 = .20$, $R^2_{\text{Adjusted}} = .19$.

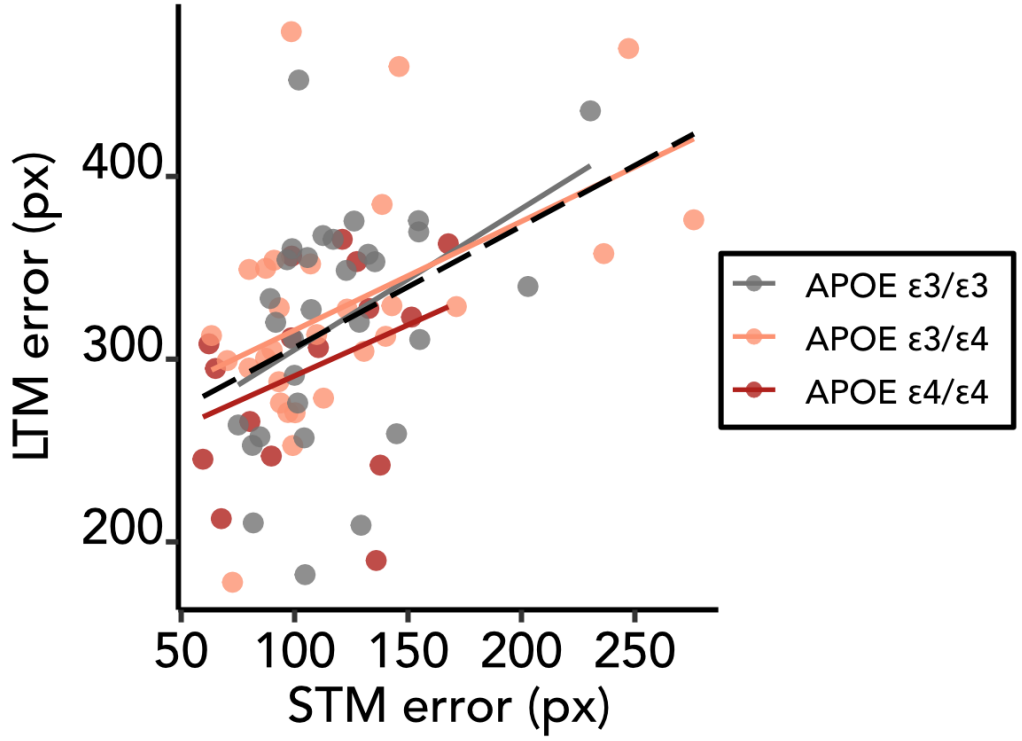


Figure 4.2. The relationship between STM and LTM localisation errors (px) across gene groups. Coloured dots represent participant means and coloured lines represent linear regression lines per age group (grey – APOE ε3/ε3, orange – APOE ε3/ε4, red – APOE ε4/ε4). Dashed black line represent model fit across groups. The data shown come from three-object trials only.

4.3.2.3. Relationship Between Long-Term Memory and Confidence. There was no main effect of gene group on the magnitude of correlation coefficients between LTM localisation error and normalised localisation confidence per participant, $F(2, 72) = 0.22$, $p = .80$, $\eta_p^2 = .006$. In all three gene groups, participants' performance on LTM localisation was similarly negatively correlated to their subjective confidence judgements (Figure 4.3), indicating an equivalent ability to judge performance in all three gene groups (Fisher z-transformed correlation coefficients: APOE ε3/ε3 $M = -.39$, $SD = .04$, APOE ε3/ε4 $M = -.42$, $SD = .04$, APOE ε4/ε4 $M = -.41$, $SD = .04$).

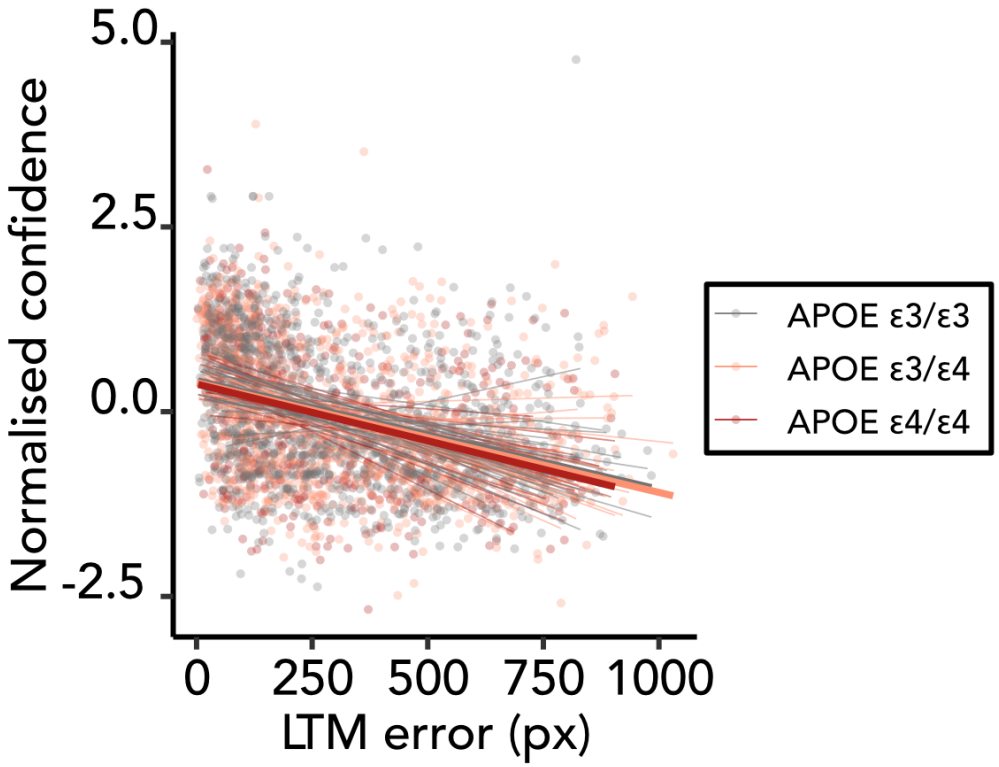


Figure 4.3. The relationship between LTM localisation errors and normalised confidence ratings per participant. Coloured dots represent LTM localisation errors and confidence ratings per trial (grey – APOE ε3/ε3, orange – APOE ε3/ε4, red – APOE ε4/ε4), thin coloured lines represent regression lines per participant, and thick lines represent regression lines per group. The data shown come from three-object trials only.

4.4. Experiment 2: The Gallery Game

As differences among gene groups may become larger at longer retention intervals, participants were asked to contribute their responses to a three-week smartphone app game called the Gallery Game developed by Lancaster et al. (2020). This task enabled remote testing of participants' memory across retention intervals ranging from one to 10 days.

4.4.1. Methods

4.4.1.1. Participants. One of the participants described in section 4.2.1. was unable to install the Mezurio app on their smartphone. From the 76 remaining participants who were able to install the app, data were not available for six owing to incompatibilities between the app and a new operating system release. The remaining sample included 29 APOE ε3/ε3, 24 APOE ε3/ε4 and 16 APOE ε4/ε4 carriers. The groups remained comparable on baseline measures described in section 4.2.1.

4.4.1.2. Tasks and Stimuli. Gallery Game has three inbuilt tasks: Learning, Recognition and Recall (Figure 4.4).

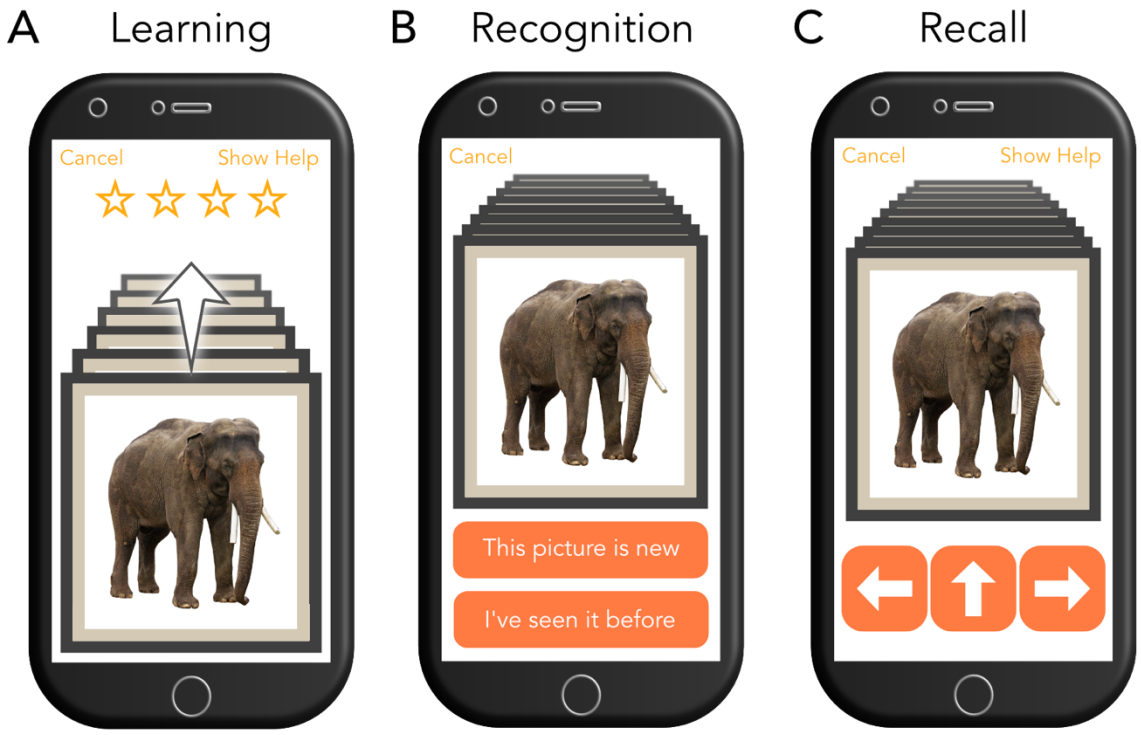


Figure 4.4. Gallery Game schematic. The task had three stages: Learning (A), Recognition (B) and Recall (C). During Learning (A), participants learned to associate a swiping movement with images of living and non-living objects presented within a frame on their smartphone screen. The first time an image was shown, it appeared with an arrow that indicated a swiping direction (left, up or right) associated with that object. Participants had to swipe towards the direction of the arrow using their finger. After a correct response, another image was shown. In subsequent iterations, previously seen objects appeared without arrows and participants had to reproduce their swiping direction from memory. However, if an incorrect response was made, the arrow was presented again. The number of objects to be remembered increased from one to six with each task iteration. A golden star was awarded for every successfully completed iteration (100 percent correct). The Learning stage was stopped once a criterion of five correct responses out of seven presentations was achieved for all objects. The Recognition (B) and Recall (C) stages followed one, three, five, seven or ten days later. During the Recognition stage (B), all six objects from a corresponding Learning session were shown, in addition to six novel objects. Participants had to indicate, by tapping on one of the two buttons bellow the image, if the image was new or seen before. In the Recall stage (C) images from the corresponding Learning session were shown again, and participants had to indicate for each image the swipe direction associated with it by tapping on one of the three arrows (left, up, right) shown below the image. Every image was repeated three times in this session.

4.4.1.2.1. Learning. During the Learning task (Figure 4.4A), participants learned object-swipe associations. The task involved participants viewing images of living (e.g., racoon, bear) and non-living (e.g., armchair, cupboard) objects presented on a white

background within a frame (Figure 4.4A). Each task included three living and three non-living objects that were matched on visual complexity and familiarity (see section 4.4.1.3). The first time an image was shown, it appeared with an arrow pointing left, up or right. Participants had to perform a swiping action towards the cued direction with their finger. Subsequent presentations of the objects omitted the direction cues to test participants' immediate recall for object-swipe associations. However, if at some point the response was incorrect, another learning trial was triggered for that object, with the corresponding direction cue appearing again. Arrow directions were randomised for each task but constrained to couple objects from the same semantic category (e.g., birds, clothing) with different swipe directions, to ensure that objects from the same category are not all coupled with the same direction. In addition, the congruency between object orientation and arrow direction was balanced.

The number of objects to be remembered increased from one to six with each task iteration, so that six new items were introduced in each Learning session. The order of object presentation was randomised in each iteration. Participants were given positive feedback (a gold star) with every successfully completed iteration (100 percent accuracy on all object-swipe associations tested). The learning task was stopped once a criterion of five correct responses out of seven presentations was achieved for all objects. This was done to ensure that all participants had equivalent LTM representations before their memories were tested in subsequent tasks (Lancaster et al., 2020). Therefore, the exact number of iterations and trials varied based on participants' performance.

4.4.1.2.2. Recognition. The Recognition task (Figure 4.4B) involved sorting of objects based on whether they were previously seen or new. Six objects from the corresponding Learning task, which occurred one, three, five, seven or ten days earlier

(Figure 4.5), were presented with six matched distractors in random order. Matching was based on object familiarity, visual complexity and category to create confusable target-distractor combinations (Lancaster et al., 2020). To respond, participants tapped on one of the two buttons (*"This picture is new"* or *"I've seen it before"*).

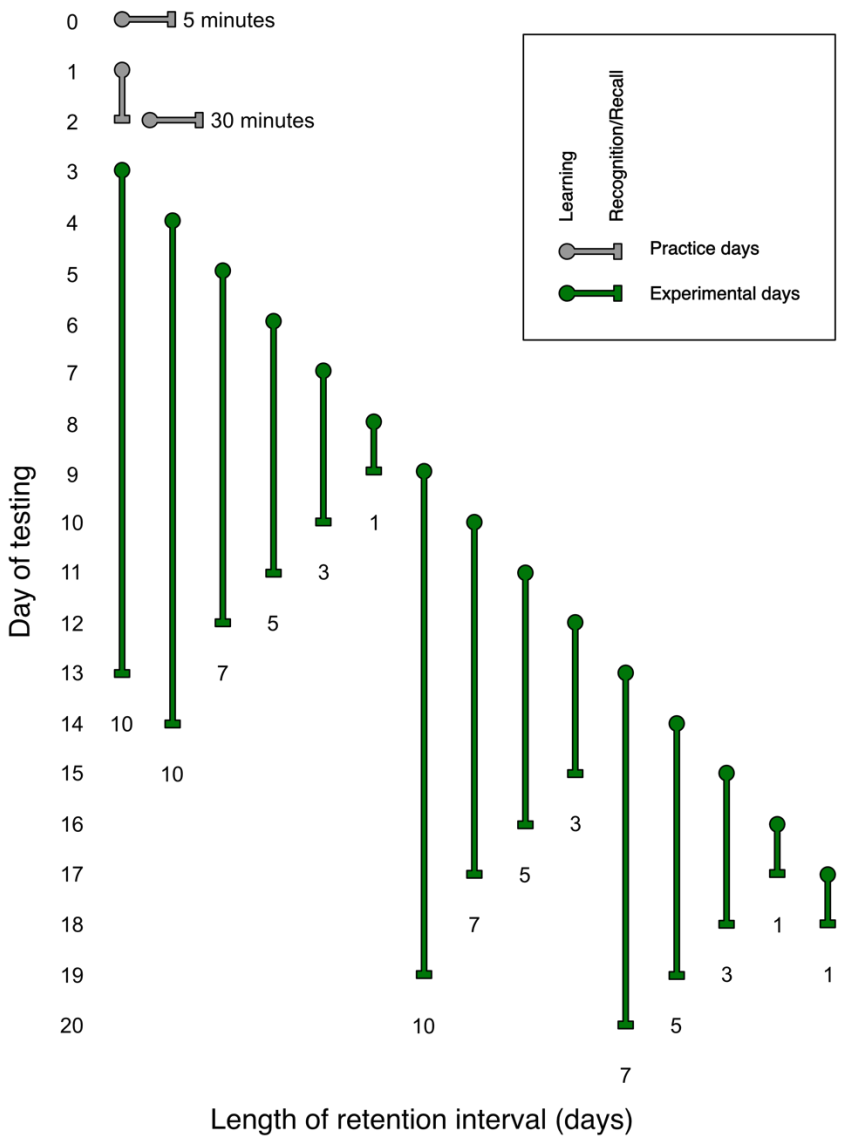


Figure 4.5. Schedule. The default schedule for the tasks. Bubbles represent the Learning task while blocks represent the Recognition and Recall tasks. Practice days are shown in grey while experimental days are shown in green. In total, the schedule took 21 days to complete. The first session was performed inside the testing facilities.

4.4.1.2.3. Recall. Recognition was directly followed by the Recall task (Figure 4.4C). In this task, participants were asked to report the swipe direction they remembered for each object from the corresponding Learning task. Objects appeared in random order thrice during the Recall session. To respond, participants tapped on one of the three arrows (pointing left, up and right) presented below the picture.

4.4.1.3. Stimuli. This version of the game used object images from Shutterstock (n = 1200) (https://www.shutterstock.com, Lancaster et al., 2020). The compressed file size of object images in JPEG format was used as a proxy for object visual complexity (e.g., Donderi & McFadden, 2005; Machado et al., 2015). Furthermore, concept familiarity (Brysbaert et al., 2011) was estimated by Lancaster et al. (2020) using published word frequency from year 1999 to 2009 extracted from Google Ngram (Michel et al., 2011). Stimulus category (e.g., mammals, vegetables, clothing) as well as orientation (left/right/up) were also coded by Lancaster et al. (2020). Finally, objects from these categories were further divided to living and non-living.

4.4.1.4. Procedure. Participants were asked to install the Mezurio App on their own smartphones to play the Gallery Game. This app was available to download free of charge from the Apple App Store and Google Play. Once the installation of the app was completed, participants were provided with and entered their unique nine-digit identification code. They were then prompted to select the convenient time to perform the task daily for the next three weeks on their smartphone and completed a practice session.

The first three days of the schedule (including the first session in the testing facilities, day zero) were dedicated for practice (Figure 4.5). Participants practiced all three tasks (Learning, Recognition, Recall) thrice across the practice days with an example strategy

shown at the end of each practice session. This was done to aid learning and reduce variation between participants in the type of strategies used (Lancaster et al., 2020).

Performance was measured on the remaining 18 days (days three to 20; Experimental days; Figure 4.5). Participants received daily notifications from the app at their chosen time to complete the tasks. If tasks were not completed within 16 hours after the prompt, they expired, and the schedule adapted to omit Recognition and Recall for the missed Learning task. Otherwise, Learning was separated from the corresponding Recognition and Recall tasks by an interval of one, three, five, seven or ten days. This led to participants completing a Learning task every day and a Recognition and a Recall task every day from day nine of the schedule (Figure 4.5).

4.4.1.5. Data Analysis. Data were pre-processed using the pipeline described by Lancaster et al. (2020). Data were analysed using R version 4.0.2 (2020) on R Studio version 1.3.1093.

To examine the effects of increasing delays on recognition and recall performance and to account for variability in response delays (the response window was 16 hours from the prompt), data were grouped to five retention intervals from the first experimental day (Figure 4.5, green): 1–2, 3–4, 5–6, 7–8, 10–11.

This study used a mixed factorial design with gene group (APOE ε3/ε3, APOE ε3/ε4, APOE ε4/ε4) as the between-subjects factor and object type (living, non-living) and retention interval (1–2, 3–4, 5–6, 7–8 or 10–11 days) as within-subject factors.

4.4.1.5.1. Learning. The key measure for the Learning task was the number of immediate recall errors participants made per learning task before they reached the learning criteria. As data did not meet the assumption of normality of the residuals required for

parametric testing using the ANOVA, I used nonparametric rank-based statistical tests, implemented using *nparLD* package version 2.1 on R (Noguchi et al., 2012), described in Chapter 3. *ATS* were reported for the main effects of object type (living, non-living) due to their suitability for smaller samples, and ATS_{Mod} with Box approximation were used for the between-subjects factor of gene group (APOE ε3/ε3, APOE ε3/ε4, APOE ε4/ε4), as they are recommended for independent observations (Brunner & Puri, 2013; Noguchi et al., 2012). Where multiple comparisons were made among the three groups (APOE ε3/ε3, APOE ε3/ε4, APOE ε4/ε4), Mann-Whitney U tests were used, and α level was Bonferroni-adjusted for three comparisons. An additional analysis was also performed with retention intervals, in which participants produced more than three standard deviations the number of errors from the mean, removed. As this analysis yielded equivalent results, only the original analysis without outlier exclusion is reported.

4.4.1.5.2. Recognition. Due to imperfect compliance, 4.12 percent of trials were missing from the Recognition task data.

Hits: One of the three measures for Recognition was hits, trials in which objects were correctly recognised as seen before. The proportion of hit for living and non-living object at different retention intervals was computed using the following formula:

$$Hits = \frac{N_{Hits}}{N_{Hits} + N_{Misses}}$$

where *N* stands for number. The data violated the assumption of normality of the residuals required for the ANOVA. Due to the mixed factorial design, the *nparLD* package (Noguchi et al., 2012) was used for the analysis. As this package cannot be used with missing data, package *mice* version 3.11.0 (Buuren & Groothuis-Oudshoorn, 2011) was used to impute missing values. Importantly, degrees of freedom for multiple non-parametric tests could not be obtained using this package, as it requires the use of general linear models for

analysis, and therefore only a single imputation was performed. The new dataset was then subjected to a mixed factorial model using *nparLD*. The independent variables were object type (living, non-living), retention interval (1–2, 3–4, 5–6, 7–8 or 10–11 days) and gene group (APOE ε3/ε3, APOE ε3/ε4, APOE ε4/ε4). Wilcoxon signed-rank test for paired samples and Mann-Whitney U test were used for follow-up pairwise comparisons, with α level Bonferroni-adjusted for the number of tests. A mixed factorial ANOVA was computed in parallel by excluding the missing values to make sure the results were consistent across the two types of analysis.

False alarms: It was expected that APOE ε4 carriers, and in particular those who carry two copies of this allele, would produce more false alarms to living as compared to non-living distractors than participants who are homozygous for ε3. Due to the relatively infrequent occurrence of false alarms in early retention intervals, where the proportion of hits was high (see Figure 4.7), the data were collapsed across retention intervals (Lancaster et al., 2020). False alarm rates were then computed for living and non-living objects separately using the following formula:

$$FA = \frac{N_{FA}}{N_{FA} + N_{CR}}$$

where *N* stands for number, *FA* stands for false alarms and *CR* stands for correct rejections. The two false alarm rates were combined into one measure, by deriving the ratio between false alarms for living and non-living objects (Lancaster et al., 2020). A ratio of < 1 would indicate a greater incidence of false alarms to non-living objects, ratio = 1 – an equal incidence, and ratio of > 1 would indicate a greater incidence of false alarms to living objects. The data were then subjected to a parametric between-subjects ANOVA, with gene group (APOE ε3/ε3, APOE ε3/ε4, APOE ε4/ε4) as the independent variable.

Recognition sensitivity: Recognition sensitivity *d'* (Macmillan & Creelman, 2005) was also computed for living and non-living objects separately using a log-linear correction

to avoid ceiling and floor effects (Hautus, 1995; Lancaster et al., 2020). The following formula was used:

$$d' = qnorm(Hits) - qnorm(FA)$$

where *d'* stands for sensitivity, *qnorm* stands for log-linear correction, *Hits* stands for the proportion of hits, and *FA* stands for the proportion of false alarms. These data were also subjected to a non-parametric mixed factorial model using *nparLD,* as they did not meet the assumption of normality of the residuals required for the ANOVA. There were two independent variables: object type (living, non-living) and gene group (APOE ε3/ε3, APOE ε3/ε4, APOE ε4/ε4).

4.4.1.5.3. Recall. Due to imperfect compliance, 4.41 percent of trials were missing from the Recall task data. Recall accuracy was defined as the proportion of trials in which swipes were correctly recalled. The data violated the assumption of normality of the residuals required to conduct the ANOVA. As for the analysis of hits, a non-parametric model was used to analyse the data, after a single imputation of missing values (see section 4.4.1.5.2 above for details). The independent variables were object type (living, non-living), retention interval (1–2, 3–4, 5–6, 7–8 or 10–11 days) and gene group (APOE ε3/ε3, APOE ε3/ε4, APOE ε4/ε4). A mixed factorial ANOVA was computed in parallel by excluding the missing values to ensure the results were consistent across the two types of analysis.

4.4.2. Results

4.4.2.1. Learning. Although not perfect, the overall compliance for engaging with the app daily was high, with on average 89.45 percent (*SD* = 17.68) of 90 stimuli encoded across participants. A Kruskal-Wallis test showed that compliance did not differ significantly among

the three gene groups, $X^2(2) = 0.86$, $p = .65$ (APOE ε3/ε3: $M = 85.59$ percent, $SD = 22.37$; APOE ε3/ε4: $M = 92.08$ percent, $SD = 14.20$; APOE ε4/ε4: $M = 92.50$ percent, $SD = 11.12$).

Spearman's correlation showed that the average number of immediate recall errors did not scale significantly with the total number of stimuli encoded, $r_s = -.20$, $p = .09$. Participants who learned more stimuli by completing more learning sessions neither produced more errors as a result of interference from learnt stimuli nor showed significant benefits from practice effects.

The non-parametric model showed a significant difference among the gene groups in the average number of errors made per learning task, $ATS_{Mod}(1.93, 50.29) = 5.26$, $p = .009$. Follow-up pairwise comparisons using Mann-Whitney U tests (with Bonferroni adjusted $\alpha = .017$) showed that APOE ε3/ε3 carriers made significantly more immediate recall errors per learning task as compared to APOE ε3/ε4 carriers, $U = 941.00$, $p = .005$, $r = .39$ (Figure 4.6). The difference between APOE ε3/ε3 and APOE ε4/ε4 carriers was in the same direction but did not reach statistical significance under the adjusted α threshold, $U = 750.00$, $p = .05$, $r = .29$ (Figure 4.6). There was also no difference between APOE ε3/ε4 and APOE ε4/ε4 carriers in the number of immediate recall errors they made on average per learning task, $U = 460.00$, $p = .38$, $r = .14$ (Figure 4.6). Furthermore, there was no difference in immediate recall errors made between living and non-living objects, $ATS(1, \infty) = 0.16$, $p = .69$, or a Gene group × Stimulus type interaction, $ATS(1.99, \infty) = 0.73$, $p = .48$.

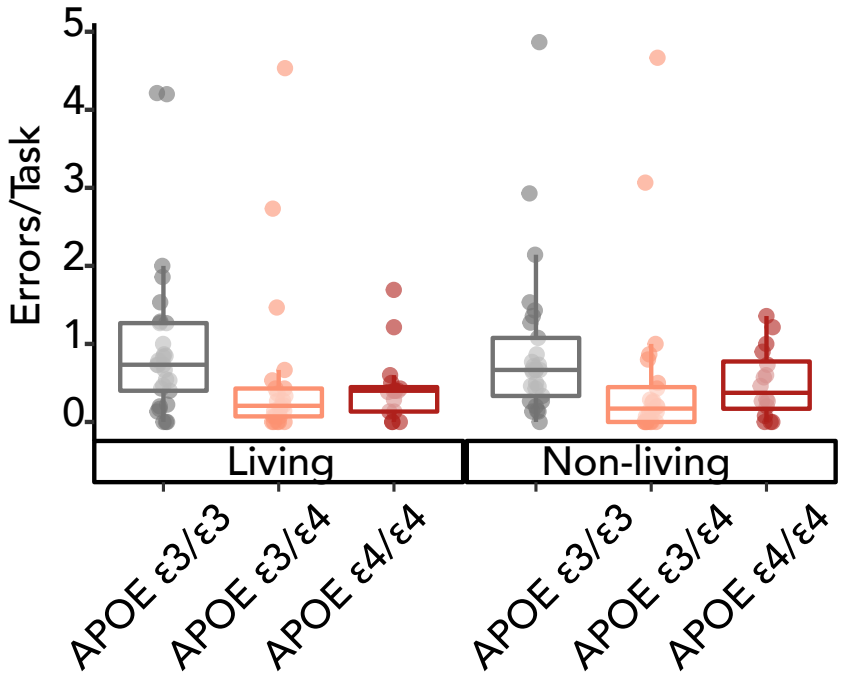


Figure 4.6. Average number of immediate recall errors across learning sessions. Coloured dots (grey – APOE ε3/ε3, orange – APOE ε3/ε4, red – APOE ε4/ε4) represent participant means, lines inside boxes represent group medians, hinges represent first and third quartiles, and whiskers represent values that fall outside the *IQR* but within 1.5 * *IQR* from each hinge. Outliers are dots outside the whiskers.

4.4.2.2. Recognition. On average, participants completed 139.84 recognition trials (*SD* = 41.87). The number of trials completed did not differ significantly among the three groups, $\chi^2(2) = 0.35$, $p = .83$ (APOE ε3/ε3: $M = 135.92$, $SD = 47.38$; APOE ε3/ε4: $M = 146.12$, $SD = 35.60$; APOE ε4/ε4: $M = 137.25$, $SD = 41.79$). One APOE ε3/ε3 carrier who only learnt 12 object-swipe associations did not complete any recognition or recall trials and was therefore excluded from further analyses.

4.4.2.2.1. Hits. The non-parametric model showed that there was no main effect of genotype on the proportion of hits, $ATS_{Mod}(1.84, 43.18) = 0.02$, $p = .97$. However, there was a significant main effect of retention interval, $ATS(3.79, \infty) = 109.07$, $p < .001$. Accuracy

declined, with changes accentuated over the initial set of retention intervals (Table 4.2, Figure 4.7). In addition, there was a significant main effect of object type, $ATS(1, \infty) = 6.68$, $p = .01$. The proportion of hits was overall higher for living as compared to non-living objects ($M = .82$, $SD = .20$ and $M = .78$, $SD = .22$, respectively). However, this main effect was accompanied by a significant Retention interval × Object type interaction, $ATS(3.70, \infty) = 10.01$, $p < .001$. The interaction reflected that the main effect of object type was driven by participants' performance after 10 to 11 days of retention, with significantly lower proportion of hits for non-living as compared to living objects, $z = 1118.00$, $p < .001$, at $\alpha = .01$ (Figure 4.7). There was no difference between living and non-living objects at other retention intervals at $\alpha = .01$, although the difference after 7–8 days was in the same direction (1–2 days: $z = 66.00$, $p = .40$; 3–4 days: $z = 379$, $p = .68$; 5-6: $z = 500.00$, $p = .18$; 7–8 days: $z = 813.50$, $p = .02$, Figure 4.7). In addition, there was a significant Gene group × Object type interaction, $ATS(1.92, \infty) = 3.54$, $p = .03$. Three further separate tests per gene group revealed that, at Bonferroni-adjusted $\alpha = .017$, only APOE ε3/ε3 carriers showed a lower proportion of hits for non-living as compared to living objects, $ATS(1, \infty) = 10.09$, $p = .001$. APOE ε3/ε4 and ε4/ε4 carriers showed an equivalent performance on both types of objects, $ATS(1, \infty) = 2.06$, $p = .15$ and $ATS(1, \infty) = .02$, $p = .89$, respectively. There were no other significant interactions: Gene group × Retention interval: $ATS(6.90, \infty) = 0.42$, $p = .88$; Gene group × Retention interval × Object type: $ATS(6.82, \infty) = 1.22$, $p = .28$. Similar results were obtained from the parametric mixed factorial ANOVA after exclusion of missing values.

Table 4.2. Results of pairwise comparisons for the proportion of hits across retention intervals.

Retention intervals	*z*	*p*
1–2 to 3–4 days	1990.50	<.001
1–2 to 10–11 days	6629.00	<.001
3–4 to 5–6 days	5005.50	<.001
5–6 to 7–8 days	3456.50	.50
7–8 to 10–11 days	3225.50	.11

Note: Bonferroni-adjusted α = .008.

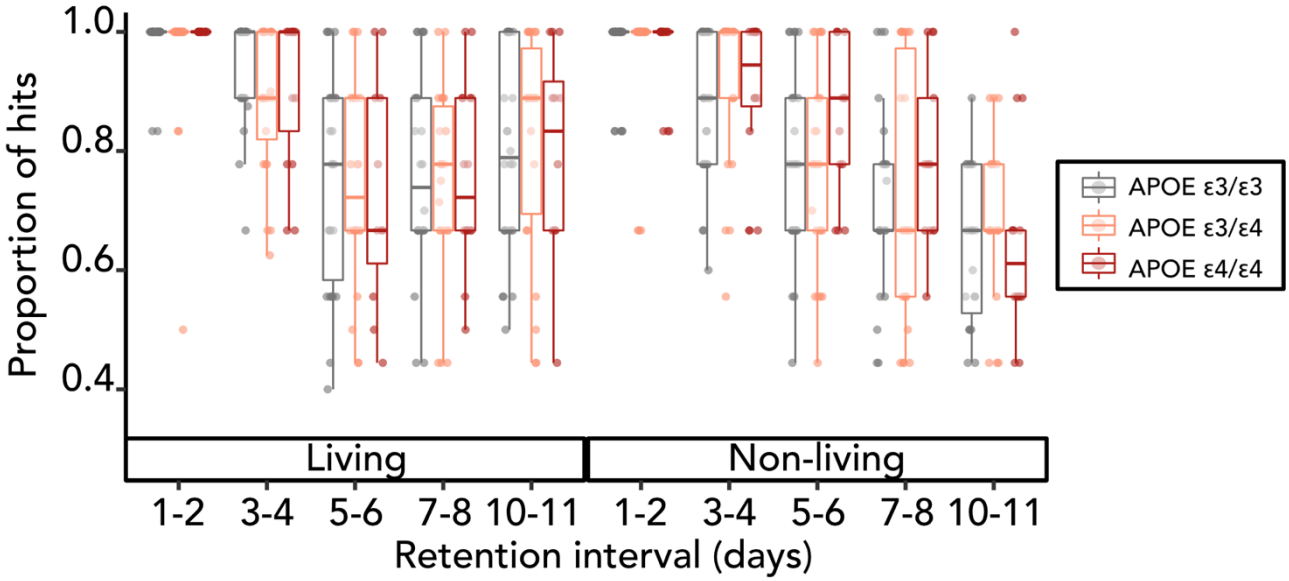


Figure 4.7. Proportion of trials in which objects were correctly identified as seen before (hits) across retention intervals and object types (living, non-living). Coloured dots (grey – APOE ε3/ε3, orange – APOE ε3/ε4, red – APOE ε4/ε4) represent participant means, lines inside boxes represent group medians, hinges represent first and third quartiles, and whiskers represent values that fall outside the *IQR* but within 1.5 * *IQR* from each hinge. Dots outside the whiskers are outliers.

4.4.2.2.2. False alarms. On average, participants produced more false alarms to living as compared to non-living objects, with an average ratio >1 for all groups (APOE ε3/ε3: M = 1.22, SD = 0.17; APOE ε3/ε4: M = 1.24, SD = 0.14; APOE ε4/ε4: M = 1.22, SD = 0.15). However, a between-subjects ANOVA showed that there was no significant difference among gene groups in false alarm ratios, $F(2, 65) = 0.12$, $p = .89$, $\eta^2_P = .004$ (Figure 4.8).

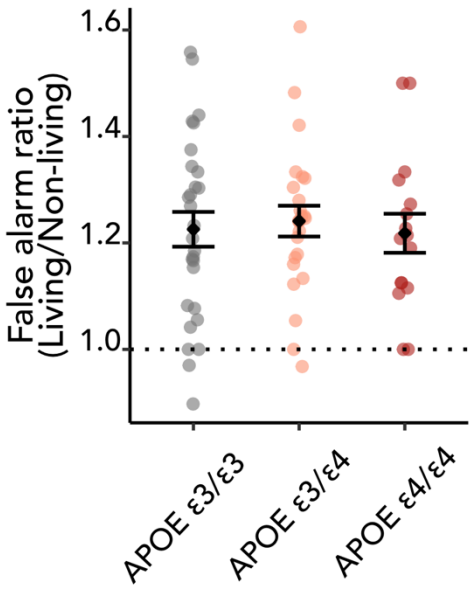


Figure 4.8. The ratio between false alarm rate for living and non-living objects. Coloured dots (grey – APOE ε3/ε3, orange – APOE ε3/ε4, red – APOE ε4/ε4) represent participant means; black diamonds represent group means; error bars represent standard error of the mean.

4.4.2.2.3. Recognition sensitivity. Recognition sensitivity *d'* is shown in Figure 4.9. A Kruskal-Wallis test showed that the bias did not differ significantly among the gene groups, χ^2 (2) =1.49, p = .48 (APOE ε3/ε3: Mdn = 0.93, IQR = 0.44; APOE ε3/ε4: Mdn = 0.90, IQR = 0.67; APOE ε4/ε4: Mdn = 1.32, IQR = 0.71). The mixed non-parametric model showed that the difference among gene groups in recognition sensitivity (*d'*) was not statistically significant, $ATS_{Mod}(1.92, 49.61) = 2.17$, p = .13. However, there was a significant main effect of object type, $ATS(1, \infty) = 30.61$, $p < .001$. Sensitivity was higher for non-living as

compared to living objects (Figure 4.9). There was no significant Gene group × Object type interaction, *ATS*(1.84, ∞) = 1.59, p = .20.

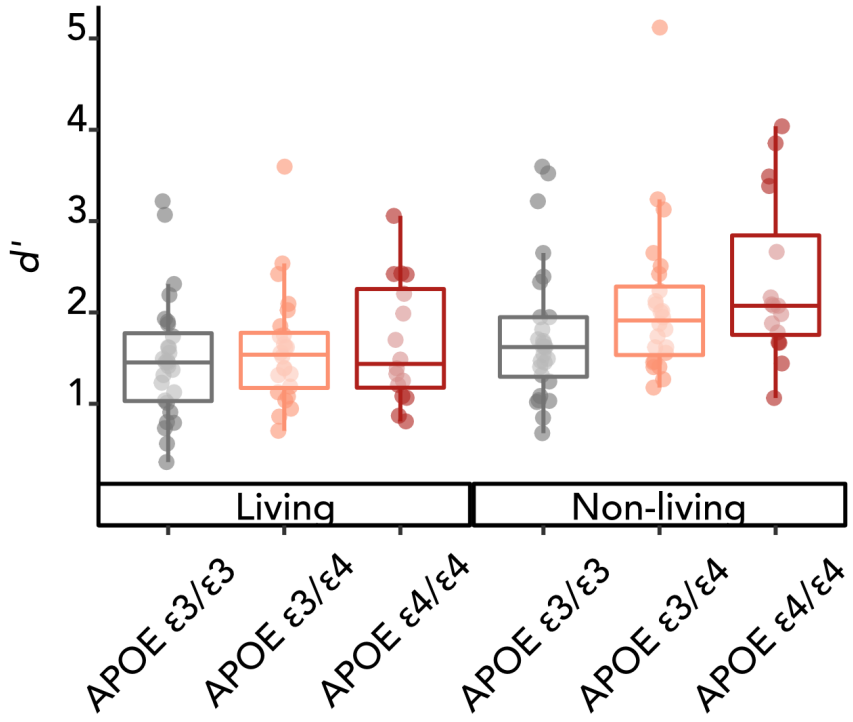


Figure 4.9. Recognition sensitivity (*d'*) across object types (Living, Non-living). Coloured dots (grey – APOE ε3/ε3, orange – APOE ε3/ε4, red – APOE ε4/ε4) represent participant means, lines inside boxes represent group medians, hinges represent first and third quartiles, and whiskers represent values that fall outside the *IQR* but within 1.5 * *IQR* from each hinge. Outliers are dots outside the whiskers.

4.4.2.3. Recall. On average, participants completed 68.82 recall trials (*SD* = 21.01). The number of trials completed did not differ significantly among the three groups, $\chi^2(2) = 0.85$, p = .65 (APOE ε3/ε3: *M* = 66.21, *SD* = 23.72; APOE ε3/ε4: *M* = 72.42, *SD* = 17.74; APOE ε4/ε4: *M* = 68.00, *SD* = 21.02).

The main effect of gene group on recall accuracy did not reach statistical significance, $ATS_{Mod}(1.86, 44.70) = 2.73$, p = .08. The three groups had a similar recall accuracy for object-swipe associations. However, there was a significant main effect of retention interval,

ATS(3.69, ∞) = 43.34, $p < .001$. This main effect reflected the decline in recall accuracy with increasing length of retention (Figure 4.10). In particular, the decline in performance was accentuated between the first two retention intervals and stabilised after (Table 4.3). In contrast, there was no main effect of object type, *ATS*(1, ∞) = 0.01, $p = .92$. Recall accuracy was also similar for both living and non-living objects (Figure 4.10). Although Gene group × Retention interval, *ATS*(7.03, ∞) = 0.77, $p = .62$, Gene group × Object type: *ATS*(1.80, ∞) = 32, $p = .70$ and Retention interval × Object type, *ATS*(3.75, ∞) = 1.75, $p = .14$, interactions were not statistically significant, there was a significant three-way interaction between the retention interval, object type and gene group, *ATS*(7.05, ∞) = 2.04, $p = .04$. Follow-up tests per object condition revealed that there was a significant interaction between gene group and retention interval for non-living objects, *ATS*(6.81, ∞) = 2.13, $p = .04$, although this interaction did not survive the Bonferroni correction at $\alpha = .025$. Nevertheless, there was no significant interaction between the two variables for living objects, *ATS*(6.65, ∞) = 0.63, $p = .72$. Follow-up tests on the interaction that was significant before the correction reflected that APOE ε4/ε4 carriers were more accurate than APOE ε3/ε3 carriers when recalling non-living object-swipe associations after 7–8 days of retention, $U = 520.00$, $p = .007$, $r = .41$. Similar results were obtained from the parametric mixed factorial ANOVA after exclusion of missing values.

Table 4.3. Results of pairwise comparisons for the recall accuracy across retention intervals.

Retention intervals	*z*	*p*
1–2 to 3–4 days	6261.00	<.001
1–2 to 10–11 days	8052.00	<.001
3–4 to 5–6 days	4403.50	.19
5–6 to 7–8 days	5038.50	.03
7–8 to 10–11 days	4044.00	.79

Note: Bonferroni-adjusted $\alpha = .008$.

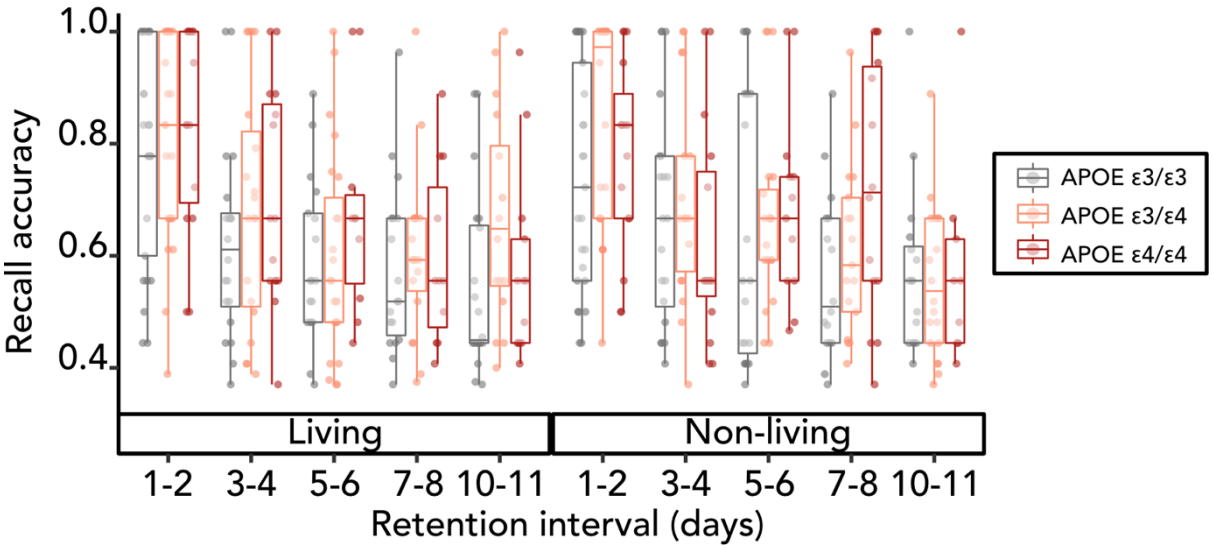


Figure 4.10. Recall accuracy across retention intervals and object types (Living, Non-living). Coloured dots (grey – APOE ε3/ε3, orange – APOE ε3/ε4, red – APOE ε4/ε4) represent participant means, lines inside boxes represent group medians, hinges represent first and third quartiles, and whiskers represent values that fall outside the *IQR* but within 1.5 * *IQR* from each hinge. Outliers are dots outside the whiskers.

4.5. Relationship Between Measures Across Experiments

4.5.1. Methods

To compare performance on the in-house (STM-LTM) tasks and the Gallery Game, I looked at the relationship between analogous measures across the two experiments. For example, the number of immediate recall errors made during the Learning stage of the Gallery Game may relate to performance on STM trials, Recognition hits may be similar to object identification in LTM, and Recall accuracy might be related to localisation errors. To quantify the strength of these relationships, I computed Spearman's correlations, which do not rely on the assumption of normality of the measures.

4.5.2. Results

4.5.2.1. Immediate Recall Errors and STM Identification. Spearman's correlation showed no correlation between the average number of immediate recall errors produced by

participants during the Learning task of the Gallery Game and STM identification accuracy, r_s = .001, p = .99 (Figure 4.11A).

4.5.2.2. Immediate Recall Errors and STM Localisation. There was a weak but statistically significant positive correlation between the average number of immediate recall errors and STM localisation errors, r_s = .24, p = .05. Participants who performed worse on STM localisation, producing larger errors, also conducted more errors during the Learning task of the Gallery Game (Figure 4.11B).

4.5.2.3. Recognition and LTM Identification. The proportion of hits in the Gallery Game did not correlate significantly with LTM identification accuracy, r_s = .17, p = .16 (Figure 4.11C).

4.5.2.4. Recognition and LTM Localisation. However, there was a significant moderate negative correlation between hits in the Gallery Game and LTM localisation error, r_s = -.35, p = .004. Participants who produced larger LTM localisation errors also showed lower proportion of hits (Figure 4.11D).

4.5.2.5. Recall and LTM Identification. Recall accuracy in the Gallery Game did not correlate significantly with LTM localisation error, r_s = .14, p = .24 (Figure 4.11E).

4.5.2.6. Recall and LTM Localisation. There was, however, a significant moderate negative correlation between recall accuracy in the Gallery Game and LTM localisation error, r_s = -.32, p = .008. Participants who produced larger LTM localisation errors also showed lower recall accuracy (Figure 4.11F).

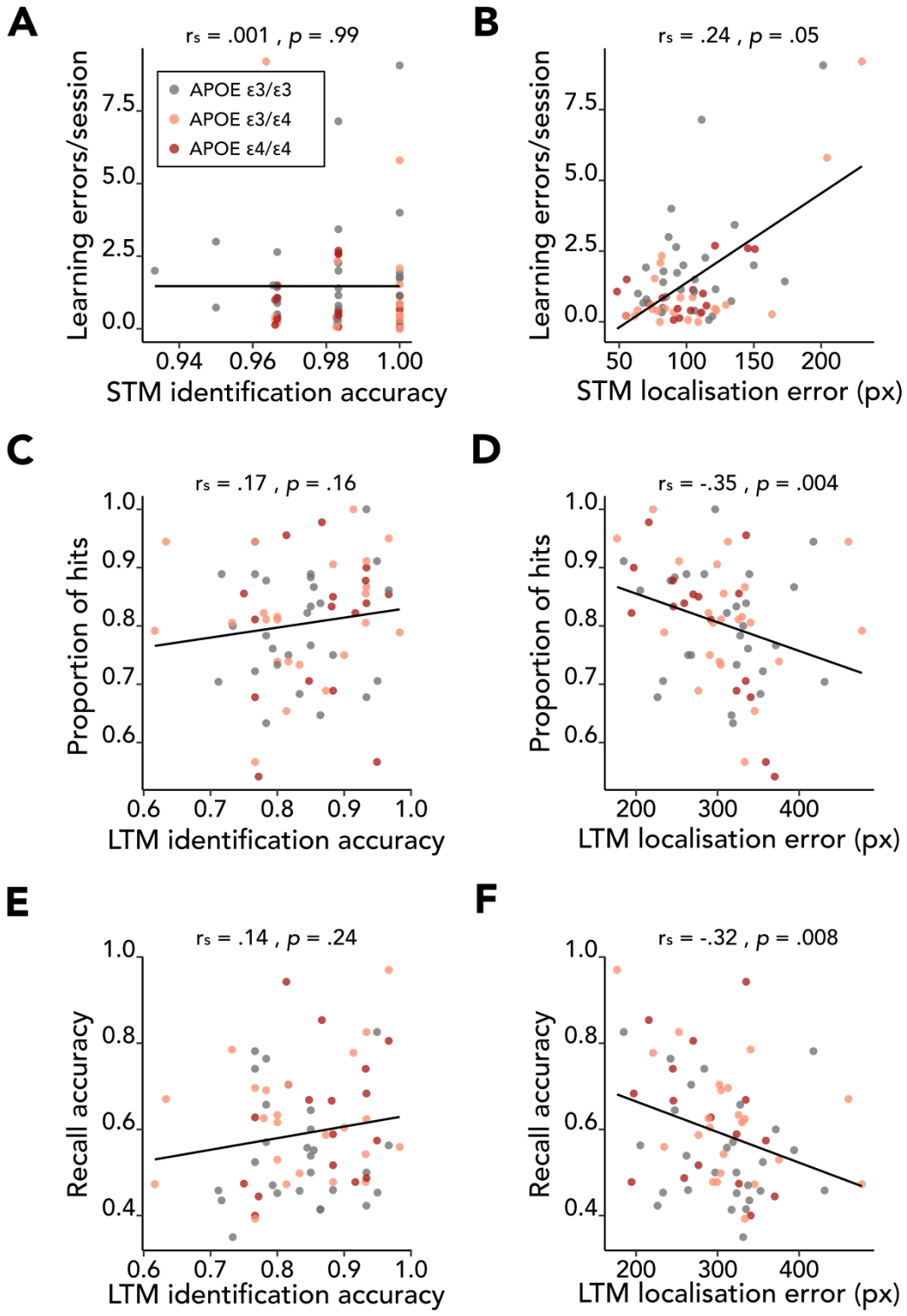


Figure 4.11. Scatterplots of the relationship between A) STM identification accuracy and Gallery immediate recall errors during Learning; B) STM localisation error and Gallery immediate recall errors during Learning; C) LTM identification accuracy and proportion of Gallery Recognition hits; D) LTM localisation error and proportion of Gallery Recognition hits; E) LTM identification accuracy and Gallery Recall accuracy (proportion correct); F) LTM localisation error and Gallery Recall accuracy (proportion correct). Coloured dots represent participant means (grey – APOE ε3/ε3, orange – APOE ε3/ε4, red – APOE ε4/ε4) and black lines represent linear regression lines for demonstration.

4.6. Discussion

The studies described in the current chapter investigated the relationship between performance on STM and LTM tasks in groups with different APOE alleles. I predicted better STM performance in APOE ε4 carriers, in particular the homozygous group, as compared to non-carriers, suggesting a presence of distinct cognitive phenotypes (Greenwood et al., 2014; Greenwood & Parasuraman, 2003). In contrast, I expected APOE ε4 carriers to show slightly worse performance on the LTM task, in a gene dose dependent manner, which may be further exaggerated across the retention intervals of the Gallery Game, indicating the presence of prodromal AD pathology (Foster et al., 2013; G. E. Smith et al., 1998). Finally, I expected APOE ε4 carriers to show an increased false alarm rate as compared to non-carriers to living as compared to non-living objects indicating early perirhinal atrophy, also due to prodromal AD (Foster et al., 2013; G. E. Smith et al., 1998).

Contrary to the predictions, there were no differences among the APOE groups in the STM task performance. APOE ε3/ε3, ε3/ε4 and ε4/ε4 carriers showed both similar identification accuracies and localisation errors. This is consistent with findings of similar studies that found better performance in APOE ε4 carriers only after short, one-second, but not after longer, eight-second, delays (Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020). This suggests that the memory advantage in APOE ε4 carriers may be limited to very short maintenance durations, not measured in the current study, and is diminished if information is maintained for longer. Indeed, the processes underlying STM maintenance over short and prolonged durations may be different. For example, amnesic patients with damage to the MTL performed as well as controls after a one-second memory delay on a STM task (E. A. Nichols et al., 2006). The task required remembering identities of faces, one at a time, presented on a computer screen (E. A. Nichols et al., 2006). In contrast, they were significantly worse after a memory delay of seven seconds and when long-term recognition

for the same faces was tested (E. A. Nichols et al., 2006). This indicates that the maintenance of information over prolonged periods of time may be more reliant on the MTL than when information is only maintained for a second. It may therefore be that the neurobiological basis of the STM advantage in APOE ε4 carriers lies outside of the MTL. For example, it could be that altered calcium homeostasis in APOE ε4 carriers (Veinbergs et al., 2002) may modulate excitatory synaptic transmission in the PFC (Mongillo et al., 2008), improving performance of participants after short maintenance durations. This idea should be explored further in future research. Finally, future studies should incorporate both short and longer delay intervals to assess APOE allele-related differences in STM.

Contrary to the hypothesis, the three APOE groups also did not differ in their performance on the LTM task. This finding is consistent with studies that found null effects of APOE polymorphism on LTM in middle-aged individuals (e.g., Marioni et al., 2016; Salvato et al., 2016). This may suggest that otherwise healthy individuals with APOE ε4 do not show LTM deficits as compared to their ε3 counterparts at middle age. Alternatively, differences among middle-aged individuals may be too subtle to be measured cross-sectionally with a small sample. Indeed, greater longitudinal decline in LTM has been observed in middle-aged ε4 carriers using standard neuropsychological measures (e.g., Blair et al., 2005; Caselli & Dueck, 2009).

In addition, there was no interaction between gene group and memory condition in the main analysis, or gene group and STM localisation error interaction in the regression analysis. The presence of such interactions would indicate an altered relationship between STM and LTM among APOE groups. This relationship could be altered by disproportionally large LTM localisation errors as compared to STM localisation errors in APOE ε4 carriers, indicating greater forgetting over time. However, the absence of any interactions suggests that neither homozygous nor heterozygous APOE ε4 carriers showed increased forgetting in the

current study as compared to ε3 homozygotes. This is in contrast to studies that found increased forgetting in middle-aged APOE ε4 carriers across STM delay intervals (Zokaei, Grogan, et al., 2020) and after one week of retention (Zimmermann & Butler, 2018). As increased forgetting may be associated with prodromal AD (Zimmermann & Butler, 2018; Zokaei, Grogan, et al., 2020), the findings of the current study may be interpreted as a preserved relationship between STM and LTM in APOE ε4 carriers, and an absence of prodromal changes in this group. However, as discussed above, the lack of differences among APOE groups in STM and LTM, resulting in the preserved relationship between the two memory systems as observed here, may also have alternative explanations.

Findings from the Gallery Game also did not provide evidence for accelerated long-term forgetting in APOE ε4 carriers in this study. However, heterozygous carriers of this allele made fewer immediate recall errors per Learning task than APOE ε3/ε3 carriers, with a similar trend in the homozygous carrier group, potentially indexing better STM for object-swipe associations. This is consistent with findings of studies that found a STM advantage in APOE ε4 carriers (Zokaei et al., 2017; Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020), though, in contrast to these studies, items appeared in random order and responses were self-paced in the Gallery Game. This meant that the time between the appearance of the stimulus and the response was variable, and no time-specific patterns of performance could be established. In addition, there was no main effect of gene group on Recognition and Recall measures across retention intervals. In fact, homozygous ε4 carriers were better than non-carriers at recalling swipe directions for non-living objects after a retention interval of seven to eight days. This may suggest that middle-aged APOE ε4 homozygotes may also show an advantage in LTM, which may be more consistent with the idea of a cognitive phenotype (Greenwood et al., 2014; Greenwood & Parasuraman, 2003), rather than the presence of prodromal AD with an increased long-term forgetting in APOE ε4 carriers (Zimmermann &

Butler, 2018). It is difficult to reconcile the latter result with the increased risk of AD in ε4 carriers (Corder et al., 1993; Farrer, 1997; Poirier et al., 1993). Some authors have suggested that APOE gene is an example of antagonistic pleiotropy and provides a selective advantage to its carriers at a young age that reverses after the reproductive age (Han & Bondi, 2008; Tuminello & Han, 2011). It might therefore be that the results of the current study on middle-aged individuals fit into the antagonistic pleiotropy framework. However, given the relatively small sample size of the study, these findings should be generalised with caution.

APOE ε4 carriers did not show a significantly increased false alarm rate or decreased recognition sensitivity for living objects as compared to non-living objects. As suggested by Lancaster et al. (2020), an increased number of false alarms to confusable living objects may signal perirhinal atrophy. If this relationship holds – it is yet to be empirically validated – the current pattern of null results would suggest no significant prodromal atrophy in the perirhinal cortex in middle-aged adults as a function of APOE risk groups. Alternatively, the presence of pathology may be very subtle, and the current study did not have enough statistical power to detect it with a cross-sectional design.

Although the Gallery Game, as well as the in-house STM and LTM tasks, has been designed to assess the functioning of the MTL (Lancaster et al., 2020), all three tasks are yet to be validated empirically. Nevertheless, the correlational analysis of the measures across the tasks suggests that they may challenge similar brain substrates. In particular, localisation but not identification performance on the STM and the LTM task was related to immediate recall errors, recognition hits and recall accuracy of the Gallery Game. This could be explained by the nature of the tasks. In the in-house tasks, participants were expected to form contextual spatial associations between objects and scenes after a single exposure to stimuli. Therefore, when probed, especially after a 20-minute delay preceding the LTM task, participants could have relied on familiarity when judging object identity. However, in order to perform well on

localisation, they had to explicitly remember which object appeared in which location, bound object-context associations. In contrast, during the Learning phase of the Gallery Game, participants were exposed to the same object-swipe associations multiple times. It is therefore likely that when they retrieved object identity during the Recognition phase of the Gallery Game, which followed after a long retention interval, their performance relied on explicit representations that may have also included the associated swipe direction. Therefore, participants' performance was correlated on aspects of both tasks that involved explicit associative memories regardless of the timescale. In addition, the neural mechanisms underlying familiarity also differ from those for recollection, as suggested by the preserved familiarity-based performance but not recollection in amnesic MCI patients (Besson et al., 2015). Finally, as several associative memory tasks have been validated in MTL lesion studies (Pertzov et al., 2013; Zokaei, Nour, et al., 2019), this provides some confidence in the utility of tasks used in the current study to assess MTL functions.

Although there were limited markers of performance differences among the three gene groups in the current study, this was unlikely to be due to insensitivity of the tasks used. As shown in Chapter 3, the STM and the LTM task also reliably detected age-related differences in memory performance. Furthermore, similar tasks were used in the past to successfully detect APOE allele-related differences in older adults (Zokaei, Čepukaitytė, et al., 2019).

One of the limitations of this study was a relatively small sample size and, in particular, a small number of APOE ε4/ε4 carriers. Overall, APOE effects on cognition are variable and may be subtle in healthy individuals. For example, one of the studies on STM found an advantage in APOE ε4 carriers with a partial eta-squared of .004, which is a small effect size (Zokaei, Grogan, et al., 2020). As discussed in section 4.1., advantages in STM may be phenotypic, and therefore should be common in APOE ε4 carriers (O'Donoghue et

al., 2018), which suggests that the effects found were very subtle. Therefore, it is possible that the current study did not have enough statistical power to detect them. In contrast, deficits in LTM are likely to be due to prodromal AD, as they are more consistently found in older participants (Caselli et al., 2009; Caselli & Dueck, 2009; Zokaei, Čepukaitytė, et al., 2019). Prodromal effects might not be as common in middle-aged adults, which suggests that the sample size should be larger to consistently detect any significant effects (O'Donoghue et al., 2018). In addition, due to a small number of APOE ε4/ε4 carriers recruited for this study, I could not investigate gender differences. Males and females may experience different effects of APOE alleles on cognition and brain health. For example, advantages in middle-aged male APOE ε4/ε4 carriers have been observed in STM in one study (Zokaei et al., 2017), although this has not been replicated in other studies (Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020). In contrast, given the heightened risk of Alzheimer's disease in females (Alzheimer's Association, 2018), the prodromal effects on LTM would likely be more apparent in this group compared to males. Therefore, future studies with larger samples should investigate the effects of gender in APOE ε4 carriers and non-carriers.

Despite the lack of consistent effects of APOE alleles on memory of middle-aged individuals in this study, it continues to be a fascinating topic with a lot of potential to aid early detection of AD. Future studies utilising similar tasks to those described in this chapter, after appropriate validation and fine-tuning in relation to the MTL functions and AD pathology, should implement longitudinal designs on larger samples of participants. Because of the near-endless availability of potential scene and object stimuli, such tasks could be used repeatedly in regular intervals to measure changes in memory over time, with reduced effects of practice. In particular, the use of continuous-report measures may help to detect early changes in STM and LTM, while steeper decline in memory resolution over time may indicate prodromal AD. Then, when treatments become available to halt AD progression,

they could be applied early to prolong the independence and life expectancy of affected individuals. Unfortunately, given the small number of homozygous APOE ε4 carriers and potential drop out over time, this may not be feasible with the study described in this chapter, although this has been an intention before the start of the study.

Future studies on APOE should incorporate both short and long STM delay intervals in combination with neuroimaging. Such studies may not only shed light on the neural substrates underlying the STM advantage found in homozygous APOE ε4 carriers after short memory delays (Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020), but also on the differences in neural activity between groups and how it evolves over the duration of the maintenance period. For example, it may be that APOE ε4 carriers differ in neural activity from non-carriers in the early stages of the memory delay, but not necessarily as a compensatory mechanism for MTL decline (Wishart et al., 2006; Zokaei, Čepukaitytė, et al., 2019), but rather as a supplement to other task-related activity, yielding better STM performance in this group. In relation to the studies discussed in Chapter 3 (Khader et al., 2007; Ranganath et al., 2005), the neural activity in the early stages of the STM maintenance period may also be less related to LTM performance in APOE ε4 carriers as compared to non-carriers.

4.7. Conclusions

The current chapter described a study that investigated the relationship between different alleles of the APOE gene and STM and LTM in healthy middle-aged individuals. The use of comparable continuous report tasks allowed to measure the relationship between STM and LTM in APOE ε3/ε3, ε3/ε4 and ε4/ε4 carriers. In addition, the combination of three different tasks allowed to probe participants' memories over seconds, minutes and days. Overall, neither the heterozygous nor the homozygous ε4 carrier group showed worse

performance than ε3 homozygotes, and the presence of APOE ε4 allele did not alter the relationship between STM and LTM. On the contrary, heterozygous ε4 carriers produced fewer errors per day while learning object-swipe associations for the Gallery Game, suggesting better STM. In addition, homozygous carriers performed better than non-carriers at the recall of swipe directions for non-living objects after a 7–8-day interval, suggesting a slight advantage in LTM in this group. These results, postulating better memory performance in ε4 carriers, are more consistent with a cognitive phenotype or antagonistic pleiotropy in this group. Future studies should employ longitudinal designs with a wider range of STM delay intervals in combination with neuroimaging to study the relationship between memory and APOE.

Chapter 5. General Discussion

The overarching goal of this thesis was to assess, with a high degree of sensitivity and granularity, the relationship between STM and LTM performance, in order to improve our understanding of the extent of the mechanistic overlap between these two memory functions. Both STM and LTM are affected by normal ageing, genetic variability and pathological processes related to AD (Jahn, 2013; G. E. Smith et al., 1998; Zokaei et al., 2021; Zokaei, Grogan, et al., 2020). However, the way these processes influence the relationship between STM and LTM has not been appropriately examined. I therefore studied short- and long-term memories for contextual spatial associations cross-sectionally across ageing and in different APOE allele carrier groups, who were at a normal, decreased or increased genetic risk to develop AD. In the presence of a high degree of mechanistic overlap between these two memory functions, I expected to see a preserved relationship between STM and LTM across different age and APOE gene groups. However, if there are substantial differences in the neural substrates underlying these two memory functions, I expected to see a dissociation between STM and LTM performance in older and at-risk groups.

5.1. STM and LTM are Affected by Normal Ageing, With a Stable Relationship Across Age Groups

Studies described in Chapters 2 and 3 investigated STM and LTM in the context of normal ageing. Chapter 2 focused on a study that utilised two sensitive continuous-report tasks to measure cross-sectionally the differences in STM and LTM performance between young and older adults. Similar tasks to the ones used in this study have been shown to be sensitive to the effects of ageing in previous studies (e.g., Pertzov et al., 2015; Salvato et al., 2016). Older adults displayed significant impairments in performance across all measures as compared to the young group. This is in agreement with findings from a number of previous

studies that found deficits in both STM and LTM with an increasing age of participants (Henson et al., 2016; Korkki et al., 2020; Peich et al., 2013; Pertzov et al., 2015; Salvato, Patai, & Nobre, 2016). However, the two tasks utilised in this study, although both testing object-location associations on an analogue scale, differed in many aspects, including the encoding procedure, the type of stimuli used and memory load. This did not allow direct examination of the relationship between STM and LTM. Therefore, two novel continuous-report tasks, which utilised analogous stimulus materials and comparable encoding and probing of short- and long-term memories, were designed for the study described in Chapter 3. In this study, three age groups were compared: young, middle-aged and older. Once again, older adults performed worse than young adults across the board. Interestingly, there was no difference between young and middle-aged adults in any of the measures, suggesting that memory declines significantly only after the age of 60 years, which is in agreement with the findings from several other studies (Gorbach et al., 2017; Pertzov et al., 2015; Van Geldorp et al., 2015). In contrast, although middle-aged and older participants had comparable scores on ACE-III, middle-aged adults showed significantly better performance on the two memory tasks, showing the utility of these tasks for sensitively assessing memory of healthy adults. As both tasks tested associative memories, the ageing effect may be related to atrophic changes in the hippocampus that also escalate after this age and relate to memory performance (Gorbach et al., 2017). The regression analysis of participants' performance showed that STM localisation error, but not participants' age group, significantly predicted LTM localisation error. This suggests that there is a significant relationship between STM and LTM, at least for the same type of information encoded in an analogous way, that is preserved with ageing. This, in turn, may mean that there is also a significant degree of overlap between these two memory functions at a neural level. This is consistent with a number of other studies that found evidence for some degree of common constraints between STM and LTM, may it be

their capacity (Forsberg et al., 2020; Fukuda & Vogel, 2019) or fidelity limits (Brady et al., 2013; Miner et al., 2020). However, there was one type of relationship that did change with age: older participants were less able to judge their LTM localisation performance compared to the young group. In contrast to another study, the current study did not find that older adults were overconfident on their judgements (Shing et al., 2009). Rather, they were less aware of their performance, which may reflect task difficulty.

5.2. Genetic Resilience to AD has Limited Effects on Memory at Young and Older Age

Chapter 2 also examined the relationship between the neuroprotective APOE ε2 allele and STM and LTM functions. It was found that the presence of APOE ε2 allele did not improve STM or LTM performance of its carriers, contrary to its protective effects from AD on the brain (Suri et al., 2013). Both young and older APOE ε2 carriers showed an equivalent performance to APOE ε3 homozygotes across the board, with the exception of LTM identification accuracy, where young APOE ε2 carriers showed worse performance than APOE ε3 carriers, while this effect trended towards the opposite direction in older individuals. It could be speculated that APOE ε2 may have slight negative effects on cognition at young age, which are then compensated for by increased survival of its carriers at older age, with the opposite suggested for APOE ε4 in the antagonistic pleiotropy hypothesis (Han & Bondi, 2008; Tuminello & Han, 2011). However, in light of otherwise null results on the more sensitive continuous-report measures, it is more likely that this effect has occurred by chance. Overall, most studies that associated APOE ε2 with better memory performance in the past were either measuring older participants' memory longitudinally (Blair et al., 2005; Helkala et al., 1996; Wilson, Bienias, et al., 2002) or included a large cross-sectional sample (e.g., Zokaei et al., 2021). This suggests that the effects this allele exerts on memory are likely to be subtle, with the current study not having a sufficiently large

statistical power and longitudinal follow-up of participants to detect them. In addition, and rather surprisingly, older APOE ε2 carriers, in contrast to APOE ε3 homozygotes, showed a decline in the ability to judge their LTM localisation performance, similarly to older adults in the study described in Chapter 3. If this effect is related to task difficulty, as previously speculated, this may suggest that older carriers of APOE ε2 allele, despite an equivalent memory performance, were more challenged by this task. Indeed, despite the protective effects of this allele from AD, as compared to APOE ε3 carriers, some APOE ε2 carriers may show otherwise worse brain health at old age due to the increased risk of cerebral amyloid angiopathy, which causes vascular lesions in the brain (Greenberg et al., 1998). Indeed, this has been shown to be the case for older individuals with MCI and AD (Groot et al., 2018).

5.3. Genetic Risk of AD has Null or Positive Effects on STM and LTM and Does not Affect the Relationship Between Them at Middle-Age

In Chapter 4, the STM and LTM were compared among middle-aged carriers of APOE ε3/ε3, ε3/ε4 and ε4/ε4. This study utilised the continuous report STM and LTM tasks described in Chapter 3, in addition to a novel smartphone task developed by collaborators and titled the Gallery Game (Lancaster et al., 2020), which enabled measurement of associative long-term memories across days. Although it was expected that participants with ε4 would show signs of increased forgetting of information over time, from STM to LTM and over longer retention intervals of the Gallery Game, this was not the case. Groups did not differ on their STM and LTM performance on the in-house tasks, with a preserved relationship between STM and LTM localisation errors across the three groups. STM localisation error alone explained a significant degree of variance in LTM localisation error, a finding comparable to that described in Chapter 3. Although bearing APOE ε4 significantly reduces the age of onset of AD, in the vast majority of individuals it is diagnosed in their 70s or later

(Corder et al., 1993; Sando et al., 2008). Therefore, most APOE ε4 carriers may show an equivalent performance to non-carriers at middle-age, which may explain the current results. In contrast, APOE ε4 carriers made fewer immediate recall errors while learning object-swipe associations of the Gallery Game, hinting towards better STM. Contrary to expectations, this group was also more accurate than the ε3/ε3 carriers when recalling object-swipe associations after seven to eight days of retention, suggesting a slight LTM advantage in individuals who are at a greater genetic risk of developing AD at middle age. It is hard to reconcile this finding with the existing theories of the effects of APOE ε4 on cognition (i.e. prodromal (e.g., Foster et al., 2013; Quintas et al., 2014; G. E. Smith et al., 1998) or phenotypic (e.g., Greenwood et al., 2005; Greenwood & Parasuraman, 2003)) or the increased risk of AD in its carriers (Farrer, 1997). One could argue that, as participants were middle-aged, these effects may fit within the antagonistic pleiotropy framework, with an advantage of carrying APOE ε4 early in life (Han & Bondi, 2008; Tuminello & Han, 2011). However, a recent large cross-sectional study has shown little support for the presence of antagonistic pleiotropy in ε4 carriers (Henson et al., 2020). Therefore, these findings warrant a replication, as, due to the small sample size, they may have occurred by chance. Finally, the comparison of participants' performance on living, as compared to non-living objects, which was expected to reveal the presence of any perirhinal pathology (Lancaster et al., 2020), did not yield any differences.

5.4. Implications and Future Work

To my knowledge, this is the first time the relationship between STM and LTM was examined using truly comparable continuous-report tasks and stimulus materials. Based on the findings presented in Chapters 3 and 4, this relationship exists, with STM localisation errors predicting a significant proportion of variability in LTM localisation errors across participants. In addition, the findings from Chapter 3 also suggest that this relationship is

preserved across healthy ageing, hinting towards potentially overlapping neural mechanisms underlying these two memory functions that decline with age. However, what determines this relationship is not exactly clear. Both STM and LTM representations were encoded in an identical way and maintained for the initial eight-second memory delay. The probing of information was also analogous, although differentiated by the length of time separating the memory array and the probe. Variability in performance between participants may have therefore arisen from processing during any of these three stages. Ageing has a wide range of effects on the brain, including on the structure and function of the MTL (Gorbach et al., 2017; Henson et al., 2016; Trelle et al., 2020) and the occipital cortex (Chamberlain et al., 2021; Jorge et al., 2020; Pitchaimuthu et al., 2017). The former is thought to support the binding of features in both STM and LTM (Watson et al., 2013; Zokaei, Nour, et al., 2019), as well as coordinate the reinstatement of long-term memories via pattern completion (Horner et al., 2015), while the latter may support the quality of fine-grained representations in both STM and LTM (Bosch et al., 2014; Serences, 2016), making them likely targets for modulating the variability in both STM and LTM. Future studies should examine the structural integrity of these brain areas and how they relate to STM and LTM measured using analogous methods. In addition, neurophysiology methods, such as MEG on healthy individuals or intracranial EEG on pre-surgery patients, which can record brain activity from the surface and deep in the brain (e.g., Solomon et al., 2019; Tesche & Karhu, 2000), may allow measuring how activity in both the MTL and the occipital cortex during such tasks relate to the variability in STM and LTM.

It remains unknown whether the relationship between STM and LTM changes with pathological ageing. As suggested by the findings of the study described in Chapter 4, this relationship may remain stable even in the presence of the APOE ε4 allele. However, this study also did not find any differences in performance between APOE groups on the in-house

STM and LTM tasks, suggesting that they did not show signs of prodromal AD. Previous studies have found better STM performance in APOE ε4 carriers as compared to non-carriers after very short one-second memory delays, which may represent a cognitive phenotype (Zokaei, Čepukaitytė, et al., 2019; Zokaei, Grogan, et al., 2020). In addition, one patient study has also found that amnestic MTL lesion patients performed as well as controls on a STM task after one- but not seven-second memory delay (E. A. Nichols et al., 2006). It could therefore be speculated that the maintenance of information over very short periods of time may be independent from the MTL. This would explain how older APOE ε4 homozygotes, who showed impaired LTM performance as compared to ε3 homozygotes, were able to maintain superior STM performance after one-second memory delay in one of the previous studies (Zokaei, Čepukaitytė, et al., 2019). Therefore, future studies comparing the relationship between STM and LTM among different groups of participants should also include trials with one-second memory delay, as this may involve less neural overlap with LTM and enable better detection of any dissociations in performance. With proper validation, similar tasks could be used for AD screening of healthy individuals.

In future studies, it may also be valuable to explore the relationship between APOE and environmental risk factors in predicting STM and LTM performance. For example, APOE ε4, which was once the only type of APOE present in humans (Drenos & Kirkwood, 2010; Fullerton et al., 2000; Hanlon & Rubinsztein, 1995; Huebbe & Rimbach, 2017), may be less harmful in certain conditions, such as low environmental temperatures (its frequency in Lapland is approximately 31 percent [Corbo & Scacchi, 1999]), high physical mobility, and low or unstable caloric intake (ε4 is still abundant in African hunter-gatherers, such as Khoi San, 37 percent, and Bantu, 29 percent, [Singh et al., 2006]). Therefore, it is likely that lifestyle factors, such as a healthy diet, intermittent fasting and exercise, would also modulate the relationship between STM and LTM. Collecting and analysing such data in the future may

allow to account for differences in performance among APOE ε4 carriers, especially at middle age.

5.5. Limitations

The studies described in this thesis suffered from several important limitations. The first of these is the small number of research participants and the lack of any longitudinal follow-up in studies on the relationship between APOE alleles and memory. Although participant recruitment was determined by their availability in the two databases used (Oxford BioBank [https://www.oxfordbiobank.org.uk] and UK BioResource [https://bioresource.nihr.ac.uk]) and the time constraints of the DPhil, the small sample sizes did not allow me to elucidate some of the controversies in the literature about the relationship between APOE alleles and memory, as I had set out to do. Small cross-sectional studies are abundant in the APOE literature, contributing to the controversy surrounding the relationship between this gene and cognition (O'Donoghue et al., 2018). One future possibility would be to create a collaborative multi-site project in order to spread the efforts of recruitment and maximise the sample size, which would also enable a longitudinal follow-up of participants. Alternatively, the development of online versions of tasks may enable the recruitment of large samples of participants remotely, as it removes the need to travel, which is often time-consuming and deters participants from taking part in studies (successful examples include Zokaei et al., 2020, 2021).

To minimise fatigue and the need for a second study visit, lower numbers of trials were used in the tasks than would have been ideal in order to perform mixture modelling of behavioural performance. This was especially true for the study described in Chapter 3, where only model results per age group were reported. Mixture modelling of memory performance provides additional valuable information, especially in the context of

pathological processes. For example, using variants of the STM task described in Chapter 2, it has been shown that, in contrast to healthy controls, AD patients made more mis-binding errors, while Parkinson's disease patients guessed more (Zokaei, Sillence, et al., 2020). As this kind of modelling has never been performed on STM and LTM data from analogous tasks in relation to ageing, this may have been an excellent opportunity to do it.

There are also several ways the memory tasks described in this thesis could have been improved. For example, both one- and three-item trials in the STM and LTM tasks described in Chapters 3 and 4 had a five-second encoding window, which may have resulted in set size effects for both STM and LTM. Although not a major limitation, a matched encoding window for the number of items (e.g., three seconds for one item, and nine seconds for three items), may have also reduced the large amount of guessing reported for LTM. In addition, when testing groups with known differences in perceptual processing, such as young and older adults, as in studies described in Chapters 2 and 3, additional trials with an immediate reporting to measure perceptual precision should be included (e.g., Korkki et al., 2020). This would enable quantification of the extent of perceptual impairments in older adults and draw stronger conclusions about the origins of the relationship between STM and LTM measured by these tasks.

5.6. Conclusions

To conclude, this thesis examined STM and LTM performance cross-sectionally across healthy ageing, and in the presence of genetic risk and resilience factors for AD, in order to determine the relationship between these two memory functions, as measured using sensitive continuous-report measures. The findings suggest that STM and LTM for the same type of contextual spatial information are related, and that this relationship remains stable with normal ageing. This implies similarities in the neural machinery underlying these two

memory functions, but further validation studies are required to confirm this. Small sample size in studies on different APOE carrier groups hindered the interpretation of findings. However, the novel analogous STM-LTM tasks, in combination with neuroimaging techniques and in the context of lesion studies, may be useful for the investigation of memory processes and development of sensitive cognitive screening methods for AD.

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