Apolipoprotein ε4 and Attentional Control: Understanding the Trajectory of Cognitive Ageing from Mid-life.

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DECLARATION

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I hereby declare that this thesis has not been and will not be, submitted in whole or in part to another University for the award of any other degree.

Signature:……

Date:……...

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APOLIPOPROTEIN E4 AND ATTENTIONAL CONTROL: UNDERSTANDING THE TRAJECTORY OF COGNITIVE AGEING FROM MID-LIFE.

The greatest genetic factor in how well we age cognitively is Apolipoprotein E (*APOE*), a single nucleotide polymorphism with three allelic variants: epsilon-2, epsilon-3 and epsilon-4 (hereafter ε2, ε3, ε4). The ε4 allele is associated with an increased risk of cognitive disadvantage in later life, however, the effects of this variant are not isolated to old-age, with some studies reporting cognitive advantages in youth. This thesis investigates the influence of *APOE* ε4 on cognition from mid-adulthood, a point in the lifespan when the detrimental effects of this allele may be emerging.

This thesis begins with a systematic review and meta-analysis of the literature to-date, and suggests attention may be sensitive to ε4 differences in mid-adulthood, however, effects of the allele are not consistently shown, perhaps due to methodological limitations including the use of insensitive neuropsychological batteries (Chapter 1). Next, behavioural paradigms providing a sensitive index of both selective (Chapter 2) and executive attention (Chapter 3), suggest many attentional processes are intact in mid-age (45-55 years) ε4 carriers. Subtle deficits, however, are apparent on prospective memory (PM) and Stroop-switch paradigms, indicating a goal maintenance disadvantage. In addition, a proxy of cognitive reserve was found to moderate the effects of ε4 on executive attention in mid-adulthood (Chapter 4). Follow-up research used paradigms that target the distinct processes supporting focal and non-focal PM to interrogate the profile of change observed in mid-age ε4 carriers, identifying a profile of disadvantage consistent with that observed in pathological ageing (Chapter 5). PM, however, was not found to differentiate ε4 carriers in older individuals at heightened risk of converting to dementia (Chapter 6). Collectively, this research provides evidence for a profile of accelerated ageing in ε4 carriers, with subtle disadvantages apparent in executive attention by the end of the 5th decade.

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1. General Introduction

Ageing is inevitably associated with some degree of cognitive decline; however, there are considerable individual differences, both in the extent and rate of cognitive ageing. The consequences of cognitive ageing, including reduced occupational performance and impairment in the ability to live independently, motivate investigation into factors influencing the trajectory of age-related change (Salthouse, 2012). Furthermore, with a rising proportion of elderly in the population (Office for National Statistics, 2012), the societal impact of cognitive ageing is increasing. This thesis focuses on understanding the role of the Apolipoprotein-E (*APOE*) epsilon-4 genetic variant, an established risk factor for poor cognitive ageing, on cognitive performance in mid-adulthood.

This general introduction first provides a brief overview of the profile of cognitive change characteristic of both healthy and pathological ageing, before introducing the *APOE* gene and the domain-specific effects associated with the ε4 variant in older-adulthood. Specifically, attentional control differences are reported in *APOE* ε4 carriers on sensitive, nuanced measures of cognition; therefore how differences within individual attentional processes integrate with existing theoretical models of controlled cognition is discussed. The introduction then reviews evidence for *APOE* ε4 genotype effects in youth, and the impact these have on theoretical accounts of the association between ε4 and cognitive decline. A rationale for studying the emergence of ε4 effects from mid-adulthood is provided, followed by the key research aims and article outlines.

1.1 Cognitive ageing: adopting a lifespan approach

Age-related decline is not consistent across cognitive domains; however, the profile of change characteristic of 'healthy' ageing is well established in the literature. Whilst 'crystallised' or accumulated cognition (e.g. semantic memory, vocabulary) is relatively resistant to age-related decline, more 'fluid' abilities (e.g. executive function (EF), memory, attention, speed of processing) are vulnerable to decline (Kievit et al., 2014; Salthouse, 2009; Salthouse, Atkinson, & Berish, 2003; Schaie, 2005). Corresponding changes within the brain, both structural (atrophy, loss of white matter integrity) (e.g. Bartzokis, 2004; Lockhart & DeCarli, 2014; Raz & Rodrigue, 2006) and functional (e.g. Davis, Dennis, Daselaar, Fleck, & Cabeza, 2007; Motes, Biswal, & Rypma, 2011), offer a biological basis for observed cognitive decline. Importantly, the region of these brain changes associate with the differential profile of decline across cognitive domains; medial temporal and frontal lobe structures are sensitive

to change early in the ageing trajectory, in accordance with the vulnerability of memory and EF to age-related decline (Fjell, McEvoy, Holland, Dale, & Walhovd, 2014; Raz et al., 2005).

There is some overlap between healthy cognitive ageing and the profile of change associated with late-onset sporadic Alzheimer's disease (LOAD), the most prevalent form of dementia (Kalaria et al., 2008; Rizzi, Rosset, & Roriz-cruz, 2014). While impairment in learning and memory is the most salient feature of this disease, EF, attention, language, and perceptual-motor skills all demonstrate significant decline as the disease progresses (American Psychiatric Association, 2013). In addition to neurodegeneration, LOAD is associated with the accumulation of Braak pathology in the neocortex (amyloidosis, phosphorylated tau), with substantial build up in frontal and medial temporal lobe regions (Braak & Braak, 1991; Okamura et al., 2014; Thal, Attems, & Ewers, 2014). The accumulation of amyloid and phosphorylated tau however, is not limited to individuals diagnosed with AD, but also present in healthy older adults (e.g. Bennett et al., 2006; Fornicola et al., 2014; Jack et al., 2010). Furthermore, the greatest risk factor for AD is age (Kawas, Gray, Brookmeyer, Fozard, & Zonderman, 2000), supporting the need to consider both healthy and pathological ageing along a continuum to further understanding of individual differences in cognitive decline (Walhovd, Fjell, & Espeseth, 2014).

Adopting a lifespan approach is necessary for establishing factors influencing how well we age cognitively (Walhovd et al., 2014). Although there is some inconsistency in the trajectory suggested by longitudinal and cross-sectional research, a continuous process of age-related cognitive decline is reported from early adulthood (Salthouse, 2009; Singh-Manoux et al., 2012; Zimprich & Mascherek, 2010). Brain changes associated with cognitive ageing also emerge in early adulthood (Bartzokis et al., 2007; Raz et al., 2005). Hence, interventions targeting the initial trajectory of age-associated decline may be the most effective in slowing ageing (Salthouse, 2009), as opposed to trying to reverse the symptoms once decline is evident.

1.2 Apolipoprotein E4

Apolipoprotein E (*APOE*), a single nucleotide polymorphism found on chromosome 19, is the strongest genetic factor influencing LOAD, and also impacts age-associated cognitive decline in the absence of neurodegenerative disease (Corder et al., 1993; Farrer et al., 1997). Of the three allelic variants coded by *APOE*, epsilon-2, epsilon-3, epsilon-4 (henceforth ε2, ε3, ε4), the ε4 allele is focused on here due to its disadvantageous effects on later-life cognition. In contrast, the less frequently studied ε2 allele is premised to exert protective effects on

cognition and neurological function in later life (Corder, Saunders, Risch, Strittmatterl, & Schmechel, 1994; Suri, Heise, Trachtenberg, & Mackay, 2013).

Carrying a copy of the *APOE* ε4 variant increases risk of AD in a gene dose dependent manner; risk of diagnosis increases 2-3 fold in heterogeneous ε4 carriers and 12-fold in homozygous ε4 carriers (Corder et al., 1993). Additionally, possession of ε4 allele is associated with an earlier age of symptom onset (Corder et al, 1993; Sweet et al., 2012), and a more rapid rate of cognitive decline in clinical groups (e.g. Cosentino et al., 2008; Craft et al., 1998; Hirono, Hashimoto, Yasuda, Kazui, & Mori, 2003). Crucially, disadvantageous effects of the ε4 allele are also observed in healthy cognitive ageing (for reviews see Rusted & Carare, 2015; Small, Rosnick, Fratiglioni, & Bäckman, 2004; Wisdom, Callahan, & Hawkins, 2011), hence the relationship between *APOE* and age more generally should be explored.

APOE is implicated in multiple physiological functions, including in the metabolism and transport of cholesterol, and neuronal repair (Bu, 2009; Mahley, Weisgraber, & Huang, 2006). Both pathological and non-pathological mechanisms underpin the association between *APOE* ε4 and cognitive ageing, further supporting the need to consider age-related change across a continuum. ApoE ε4 is associated with increased accumulation and reduced clearance of amyloid in the brain (Mahley et al., 2006)), a key determinant in the cascade of change associated with AD. In addition, the ε4 variant is associated with a general loss of neurological function, including reduced neuronal repair, reduced synaptic plasticity, mitochondrial dysfunction, neuroinflammation and altered neurovascular functions (Liu, Kanekiyo, Xu, & Bu, 2013).

1.3 *APOE* ε4 and Late-life Cognition: Neuropsychological Assessment Measures

The bulk of existing research has utilised neuropsychological assessment tools, designed for use in clinical settings, to explore *APOE* ε4 effects on late-life cognition. These measures provide a quick-to-administer assessment of performance on select domains, making them suitable for profiling cognition in larger groups. Next, we present an overview of the differential profile of *APOE* ε4 effects across cognitive domains, assessed using neuropsychological measures, for LOAD and healthy cognitive ageing.

1.3.1 Pathological Ageing

In LOAD, detrimental effects of *APOE* ε4 are predominantly reported for episodic memory, although not consistently (for a review see Haj et al, 2016). Small sample sizes, and hence

low statistical power, are suggested to account for variation in the reporting of ε4 effects in episodic memory (Haj et al., 2016). In addition, carrying an ε4 allele is associated with longitudinal increases in episodic memory decline (Hirono et al., 2003; Wilson, Bienias, Berry-Kravis, Evans, & Bennett, 2002; Wolk & Dickerson, 2010). The same trajectory of accelerated decline was not reported for working memory (WM), semantic memory, language, processing speed or visuospatial ability (Wilson et al., 2002). Interestingly, EF measures do not appear sensitive to *APOE* ε4 effects in LOAD (van der Vlies et al., 2007; Wolk & Dickerson, 2010). Furthermore, increased atrophy of medial temporal lobe regions in ε4 carriers is associated with episodic memory disadvantages in this group. A differential profile of LOAD-related degradation is reported in non-ε4 carriers, predominantly affecting frontal-parietal networks, consistent with the behavioural profile observed (Geroldi et al., 1999; Wolk & Dickerson, 2010).

Mild cognitive impairment (MCI) represents the transitional stage between healthy cognitive ageing and dementia, characterised by objective impairment in at least one cognitive domain alongside normal day-to-day functioning (Albert et al., 2011a; Mariani, Monastero, & Mecocci, 2007b; R. C. Petersen, 2004). On neuropsychological assessment measures, ε4 status in individuals diagnosed with MCI is associated with increased impairment in episodic memory, fluency and processing speed, and EF measures (Risacher et al., 2013; Whitehair et al., 2010). Furthermore, ε4 status is associated with an accelerated trajectory of decline on measures of global cognition, WM, memory, fluency and language (Whitehair et al., 2010). *APOE* differences on neuropsychological measures in MCI patients has been linked to structural changes in the brain (Farlow et al., 2004), and differences in the deposition of amyloid (Risacher et al., 2013).

1.3.2 Healthy ageing

Systematic reviews of *APOE* ε4 genotype effects in healthy older adulthood report an association between ε4 status and cognitive disadvantages (Small et al., 2004; Wisdom et al., 2011), however, detrimental effects of the variant are not consistently found in the literature (Bunce et al., 2014; Bunce, Kivipelto, & Wahlin, 2004; Caselli et al., 2014). Importantly, meta-analytic reviews confirm the profile of ε4 effects is not uniform across cognitive domains, with the greatest disadvantages seen for episodic memory, global cognition, EF and processing speed, while effects appear non-significant for attention, verbal abilities and visuospatial abilities (Wisdom et al., 2011). Several studies report effects of ε4 on episodic memory (e.g. Caselli et al., 1999; O'Hara et al., 1998; Packard et al., 2007; Staehelin, Perrig-Chiello, Mitrache, Miserez, & Perrig, 1999). Effects outside of this domain are also reported

including on spatial processing (Berteau-Pavy, Park, & Raber, 2007) and WM (Reinvang, Winjevoll, Rootwelt, & Espeseth, 2010). Age appears an important determinant in the emergence of *APOE* ε4 effects (Wisdom et al., 2011), with the detrimental effect of ε4 on memory (Jochemsen, Muller, van der Graaf, & Geerlings, 2012; Laukka et al., 2013; Schiepers et al., 2012), as well as processing speed and global cognition measures increasing with age (Laukka et al., 2013).

1.4 *APOE* ε4 and Late-life Cognition: Behavioural paradigms

1.4.1 Sensitivity of cognitive assessment

One issue with the reliance on neuropsychological assessment measures for detecting genotype differences in healthy cognitive ageing is the sensitivity of these tools for detecting differences within the bounds of normal cognitive performance. These tools also provide assessment at the level of a cognitive domain. Hence, to detect *APOE* ε4 differences in healthy ageing, paradigms capable of sensitively isolating individual cognitive processes may be needed to provide a more nuanced understanding. Several studies have used process-specific paradigms to explore *APOE* differences in attentional control. These will now be reviewed, prefaced by a brief outline of attentional control and associated theoretical models.

1.4.2 Attentional control

'Attentional control' or the 'executive control of attention' describes goal directed attention, for which 'top-down' control mechanisms must be exerted (Petersen & Posner, 2012; Treisman & Gelade, 1980). This cognitive ability, importantly, incorporates several distinct but interactive sub-processes, for example selective attention, attentional updating, set shifting, and response inhibition. Of note, selective attention, WM capacity and goal maintenance are viewed as interdependent constructs, involving heightened processing of task-relevant information (Kane, Bleckley, Conway & Engle, 2001; Awh, Vogel, & Oh, 2006; Chun, 2011; Cowan, 1999; Gazzaley & Nobre, 2012). The neural basis of these attentional control mechanisms includes prefrontal, cingulate and parietal regions (e.g. Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Hampshire & Owen, 2006; Hopfinger, Buonocore, & Mangun, 2000; Osaka et al., 2004; for review see Kane, 2002; Yuan & Raz, 2014). These regions are vulnerable to age-related change in neural structure and functional activity (George Bartzokis et al., 2007; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Raz, 2000; Rowe et al., 2007; Villemagne et al., 2011).

In understanding how attentional control is impacted by age, whilst some theories suggest decline is observed as a result of a general slowing of processing ability (Salthouse, 1996), others emphasise an additional need to consider age-related change within individual sub-processes (Verhaeghen & Cerella, 2002). There are several theoretical models of the interdependence of attentional control processes. Kane and Engle's model of executive attention comprises two hierarchical processes. The first actively maintains information as short-term memory representations (Simple WM span). The second process combines the concepts of executive processing with complex WM span, entailing the controlled processing of information in an active state, often in the context of additional task demands. It includes inhibition and attentional set-shifting (Engle & Kane, 2002; Kane, 2002). Similarly, Faust & Balota (2007) propose an attentional control framework driven by central attentional set maintenance, upon which attentional control acts to enhance or inhibit response pathways. The widely cited 'Unity/Diversity framework' (Friedman & Miyake, 2015) suggests that there is a common executive ability relating to the active maintenance of information within attention, which supports additional elements of executive attention including response inhibition, updating and attentional-set shifting. A hierarchical account of executive attention has recently been proposed (Tiego, Testa, Bellgrove, Pantelis, & Whittle, 2017). This model suggests selective attention and inhibition are independent processes dependent on a higher-order WM construct, with functions analogous to the central executive (reduced interference, divided attention, set-shifting and links to long-term memory) (Baddeley, 2012).

1.4.3 Selective attention

Selective or focused attention is often analogized to a 'spotlight' mechanism, with a gradient of heightened attentional processing surrounding a point of fixation (Posner, 1980). This 'spotlight' of focused attention is needed to maximize the processing of goal relevant information whilst minimising interference from the processing of irrelevant information. Previous research has found LOAD and healthy cognitive ageing to be associated with declines in this attentional process (Cansino, Guzzon, Martinelli, Barollo, & Casco, 2011; Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Hasher & Zacks, 1988; S. Kim, Hasher, & Zacks, 2007; Perry & Hodges, 1999). In healthy ageing, this manifests as a deficit in exclusively processing goal-relevant information in the presence of distractors.

In older adulthood, carriers of an *APOE* ε4 variant demonstrate performance differences on visual search and spatial WM tasks consistent with accelerated or premature age-related impairment. During visual search, the use of spatial cues to actively adjust the breadth of selective attention, and hence minimise the processing of irrelevant information, is referred to

as attentional scaling (Greenwood & Parasuraman, 2004). Independent of genotype, ageing is associated first with an increase in dependence on top-down information to guide attentional scaling, followed by a decrease in the ability to use top-down information to more efficiently search (Parasuraman, Greenwood, & Alexander, 2000). *APOE* ε4 carriers in late-mid adulthood (aged 50 years and older) demonstrate reduced utilisation of attentional scaling consistent with a profile of premature ageing (Greenwood, P M, Sunderland, T., Friz, J., & Parasuraman, 2000). In addition, homozygous ε4 carriers showed a longitudinal reduction in attentional scaling across three years, which was absent in heterozygous ε4 carriers and non-ε4 carriers (Greenwood, Sunderland, Putnam, Levy, & Parasuraman, 2005).

On a simple spatial WM task requiring no active manipulation of stored information, older ε4 carriers demonstrate poorer retrieval accuracy on trials with the highest discrimination difficulty (Greenwood, Espeseth, Lin, Reinvang, & Parasuraman, 2014). A smaller sample was followed longitudinally over 3 years; ε4 carriers demonstrated significant decline in performance, relative to non-ε4 carriers, consistent with a profile of accelerated ageing (Greenwood et al., 2014). Furthermore, Espeseth and colleagues (2008) report *APOE* genotype differences in older adults on a visual discrimination task (Parasuraman, Greenwood, Haxby, & Grady, 1992). The task required participants to search for a target stimulus amid an array of distractors, with a neutral, valid, invalid or no cue presented to aid performance. *APOE* ε4 status was associated with longer RTs for invalid cues, associated with reduced white matter volume. Follow-up research using a selective attention 'odd-ball' task reported lower accuracy in ε4 carriers (Thomas Espeseth et al., 2012).

1.4.4. Attentional maintenance, shifting and inhibition

The behavioural phenotype of LOAD is characterised by deficits in more complex attentional processes including the division of attention between multiple task goals and set shifting (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Perry & Hodges, 1999; Sebastian, Menor, & Elosua, 2006). In addition, these processes are vulnerable to age-related change (e.g. Milham et al., 2002; Rodríguez-Aranda & Sundet, 2006; Wasylyshyn & Sliwinski, 2011). Performance on a Stroop-switch paradigm targeting goal maintenance, shifting and inhibition was found to be a reliable marker of LOAD diagnosis (Hutchison, Balota, & Ducheck, 2010), and had predictive utility for the subsequent development of the disease (Balota et al., 2010).

Wetter et al., (2005) reported an effect of *APOE* ε4 on Stroop-switch performance in older adulthood. Participants completed a computerised Stroop paradigm including distinct inhibition (incongruent trials) and inhibition plus switching (incongruent trials plus rule

switch) conditions. Relative to their ε3 peers, ε4 carriers selectively demonstrated greater errors for the condition with combined inhibition and switching demands, indicative of deficits in attentional set shifting. Furthermore, on a speeded category decision task assumed to load on attentional control processes, amyloid deposition was reported to mediate the relationship between *APOE* ε4 and errors (Aschenbrenner et al., 2015). E4 carriers (aged 50-79 years) demonstrate poorer performance on an Operation Span task (Turner & Engle, 1989), a measure of WM requiring divided attention, and hence executive control.

1.4.4.1 Prospective memory

Prospective memory (PM), pervasive in day-to-day life, is the timely retrieval of an earlier-formed intention whilst engaged in ongoing cognitive activity. Non-focal PM, when retrieval of the intention involves processing distinct from ongoing cognitive activity, is a demonstration of attentional control in an everyday context. Executive processes are required to maintain multiple goals at the forefront of attention and actively monitor for the PM cue (Einstein et al., 2005; McDaniel, Umanath, Einstein, & Waldum, 2015; Scullin, McDaniel, Shelton, & Lee, 2010). Non-focal retrieval is mediated by the available executive resource, and supported by frontal, parietal and cingulate regions of the brain (Cona, Bisiacchi, Sartori, & Scarpazza, 2016; Cona, Scarpazza, Sartori, Moscovitch, & Bisiacchi, 2015; McDaniel, LaMontagne, Beck, Scullin, & Braver, 2013). Focal PM, or retrieval of a PM intention processed as an integral part of the ongoing cognitive activity, relies on 'bottom-up' attention and associative memory processes, mediated by mediated by occipital, parietal (Cona et al., 2016) and temporal lobe regions (McDaniel et al., 2013).

Healthy ageing is associated with select impairment in non-focal PM (for reviews see Henry, MacLeod, Phillips, & Crawford, 2004; Kliegel, Jäger, & Phillips, 2008), whereas individuals with MCI or in the early stages of LOAD demonstrate an additional impairment in focal PM (Blanco-Campal, Coen, Lawlor, Walsh, & Burke, 2009; Costa, Caltagirone, & Carlesimo, 2011; Duchek, Balota, & Cortese, 2006; McDaniel, Shelton, & Breneiser, 2012). Thus far, research exploring *APOE* genotype effects on PM across the lifespan are mixed. In mild LOAD ε4 carriers demonstrate significant impairment on a focal PM task consistent with this variant exaggerating the impairment seen in LOAD (Duchek et al., 2006), however null effects of genotype were reported in a sample of healthy older adults (McDaniel et al., 2012).

1.5 *APOE* ε4 earlier in the lifespan

The effects of *APOE* on cognition are not restricted to later life. Indeed, there is some support for ε4 carriers showing cognitive advantages in youth, supported by naturalistic studies reporting higher IQ and greater educational achievement in this group (Hubacek et al., 2001; Yu, Lin, Chen, Hong, & Tsai, 2000). Reports of beneficial effects in youth are inconsistent with the negative effects of *APOE* ε4 in later life, suggesting a change in the expression of this gene across the lifespan. This emphasizes the need to consider the cumulative impact of the ε4 allele across the lifespan (Rusted & Carare, 2015).

Reviewing laboratory studies of *APOE* genotype effects on cognition in youth provides mixed evidence in favor of ε4 advantages. Several studies report equivalent performance across *APOE* genotype groups in children on measures of IQ and academic ability (Acevedo, Piper, Craytor, Benice, & Raber, 2010; Bloss, Delis, Salmon, & Bondi, 2010; Ruiz et al., 2010; Turic, Fisher, Plomin, & Owen, 2001). An Age x *APOE* interaction, however, was reported on a neuropsychological test battery; specifically homozygous ε4 carriers aged 8 years and younger were disadvantaged on EF and WM measures, whilst performance was equivalent or better in this group over the age of 8 years (Chang et al., 2016). This highlights the need for longitudinal assessment of how *APOE* effects change developmentally.

In young adults, ε4 advantages are consistently reported on verbal fluency measures (Alexander et al., 2007; Han et al., 2007; Marchant, King, Tabet, & Rusted, 2010a; Puttonen, Elovainio, Kivimäki, Lehtimäki, & Keltikangas-Järvinen, 2003). Several other studies report null effects of the variant across a wider range of measures (Bunce et al., 2014; Dennis et al., 2010; Jorm et al., 2007; Reiman et al., 2004; Taylor et al., 2011). Indeed, an earlier meta-analytic review of the literature reported limited evidence for ε4 advantages prior to 35 years of age (Ihle, Bunce, & Kliegel, 2012), with the null effect size consistent across tasks categorized as both low and high executive demand.

One issue consistently arising across the *APOE* literature is the validity of using neuropsychological assessment tools to detect subtle differences in healthy individuals. Behavioural paradigms designed to provide a nuanced measure of individual cognitive processes, as opposed to domains, in healthy adults are sensitive to ε4 advantages in youth. For example, ε4 carriers (mean age 23 years) demonstrate subtle advantages on a delayed episodic memory task probing face-profession associations, however, no differences were seen on a measure of WM (Mondadori et al., 2007). Further research, however, provides no support for *APOE* ε4 differences on episodic memory paradigms in youth (Filippini et al., 2009; Suri et al., 2015). Support for ε4 advantages in spatial processing, reliant on hippocampal functioning, is also mixed. While no ε4 differences were recorded on word-list

learning (an index of episodic memory), ε4 carriers demonstrated spatial memory advantages on tasks including a virtual water maze, mental rotation task and object location task in adults aged 19-35 years (Stening et al., 2016). On an object location virtual arena memory task, young ε4 carriers demonstrated altered navigational strategies in association with disrupted functioning of grid-cell representations in the entorhinal cortex (Kunz et al., 2015).

1.5.1 Young ε4 carriers and attentional control

Focusing on attentional control, there has been some evidence for ε4 advantages in youth when probed with more nuanced behavioural measures. A rapid visual information processing task (RVIP), loading on attentional updating, demonstrated an ε4 advantage in target detection (Rusted et al., 2013). In addition, young ε4 carriers showed reduced cost of invalid spatial cues on a measure of covert attention (Rusted et al., 2013). Hence, it seems ε4 advantages are present when using more nuanced measures of cognitive performance, with differences demonstrated in both memory and attention (executive and perceptual). In a slightly older sample (aged 20-40 years), ε4 status was associated with select disadvantages in episodic memory and attentional shifting (indexed using a More-Odd shifting task) (Nao et al., 2017). Genotype differences in WM and inhibition were non-significant.

APOE ε4 genotype differences in PM in youth have been explored in association with the cholinergic agonist nicotine; a neurotransmitter system affected by the gene (Poirier et al., 1995). On a card-sort measure of non-focal PM, demanding of attentional control, ε4 carriers demonstrated greater retrieval accuracy following nicotine administration (Marchant et al., 2010a). Follow up research, again probing the effect of nicotine on PM performance, did not find overall ε4 advantages on the task. Selectively for PM retrieval trials, however, nicotine advantaged ε4 response times (RTs), associated with increased extrastriate blood-oxygen-level-dependent (BOLD) activations suggestive of increased bottom-up processing (Evans et al., 2013). Performance on a focal measure of PM, distinguished by a reliance on automatic, associative memory processes, was insensitive to genotype difference in youth (Duchek et al., 2006).

1.6 Theoretical accounts for the role of *APOE* ε4 in cognitive ageing

Multiple theories have been proposed to account for the influence of *APOE* on cognition in the absence of LOAD. One option is that *APOE* ε4 represents a LOAD prodrome, with this genetic factor predisposing carriers to develop the disease (Smith et al., 1998). Hence, individuals with preclinical LOAD pathology and neurodegeneration may skew the effects of

APOE ε4 observed in older adulthood. The prodrome of LOAD typically begins 6-7 years prior to clinical symptoms, with the mean age of LOAD diagnosis currently 77.4 years old (Wilson et al., 2011), and so this explanation struggles to deal with cognitive differences in ε4 carriers earlier in the lifespan, as well as effects reported in the absence of LOAD pathology. Furthermore, although evidence for ε4 advantages in youth is inconsistent, these do not align with the prodrome account.

An alternative explanation is that *APOE* ε4 is linked to a cognitive phenotype (Greenwood, Lambert, Sunderland, Parasuraman, 2005; Negash et al., 2009), defined by a profile of behavioural symptoms independent of LOAD pathology. A general mechanism for *APOE* effects across the lifespan is required, hypothesised to stem from the physiological role of apoE in cholesterol and neuronal repair (Mahley et al., 2006). Carrying an ε4 variant is associated with an accelerated trajectory of de-myelination from the 5th decade (Bartzokis, 2007), leaving individuals vulnerable to cognitive insult, and hence this would explain effects of ε4 from mid-adulthood. Advantages in youth may be explained by some form of early compensatory strategy that cannot be maintained across the lifespan (Greenwood et al., 2014). Furthermore, not necessarily exclusive of the cognitive phenotype account, *APOE* ε4 carriers may undergo premature or accelerated ageing. In support, BOLD activations reported in youth and mid-adulthood are consistent with an early compensatory shift similar to those seen in older-adulthood (Evans et al., 2014; Rusted et al., 2013). In addition, the differential effects of ε4 status on selective attention in mid-adulthood are comparable to those seen in older adults (Greenwood, Sunderland, Putnam, Levy, & Parasuraman, 2005). Whilst ε4 carriers are reported to show greater decline in structural and cognitive measures (e.g. Cohen, Small, Lalonde, Friz, & Sunderland, 2001; Espeseth et al., 2008; Moffat, Szekely, Zonderman, Kabani, & Resnick, 2000), longitudinal research is needed to establish a profile of accelerated ageing across the lifespan.

The changes associated with advantaged performance in youth may also be important for establishing a mechanism for emergent disadvantageous effects. For example, although Mondadori et al. (2007) reported decreased hippocampal activation across learning runs in ε4 carriers, consistent with increased neural efficiency, several studies have reported greater activations in the absence of behavioural effects (Dennis et al., 2010; Filippini et al., 2009; Rusted et al. 2013). Although difficult to interpret in the absence of a cognitive difference, it may be that ε4 carriers are over-activating from youth. In addition, ε4 carriers have demonstrated medial temporal lobe recruitment, unrelated to task demands, indicative of unspecialized compensatory recruitment (Rusted et al., 2013). Hence, the functional

activation differences reported in young ε4 carriers are not inconsistent with carriers demonstrating premature ageing.

An additional account of *APOE* ε4 in cognitive ageing is that this gene represents an example of antagonistic pleiotropy, according to which the effects of ε4 transition from advantageous to disadvantageous across the lifespan (Han & Bondi, 2008). Longitudinal lifespan research is needed to firmly establish this theory. In addition, cognitive advantages in youth are not yet well established.

1.7 Mid-adulthood: a critical window for *APOE* effects?

Mid-adulthood is a critical window for understanding cognitive ageing, as individual differences in early cognitive decline may first be detectable at this point. In the adult lifespan, vulnerability triggered by the influence of genetic factors, the environment and vascular ageing may alter the pathway of both neurological and cognitive decline (Finch, 2009; Herrup, 2010).To date, the influence of *APOE* at this stage of the lifespan is not clearly established. This thesis investigates how *APOE* genotype influences early cognitive ageing, to establish if cognition is sensitive to *APOE* ε4 genotype in mid-adulthood. In relation to the cognitive advantages reported in attention and memory in youth, ε4 differences may manifest as advantages in select cognitive processes only. By mid-adulthood, however, subtle disadvantages in ε4 carriers may emerge, supporting a profile of premature and/or accelerated cognitive ageing. Additional risk factors for cognitive decline, including vascular ageing, begin to impact cognitive from the 5th decade (Waldstein et al. 2008; Pace et al, 2010; Debette et al, 2011; Mitchell et al, 2011), which may further moderate the presence of ε4 effects in mid-adulthood.

1.8 Research questions and article outline

The present thesis explores two key questions: 1) Does *APOE* genotype differentially impact cognitive ageing from mid-adulthood? Included articles predominantly focus on the ε4 differences apparent by mid-adulthood, a crucial window of the lifespan when impairment may first be detectable. In addition, there will be some consideration of the protective ε2 allele to further understanding of how *APOE* variants independently contribute to behavioural change. 2) Does the *APOE* ε4 variant selectively impact specific cognitive processes? Focus will be on attentional control processes, and to the impact of change on everyday functioning in individuals experiencing mild cognitive deficits. The thesis also explores how additional factors mitigating cognitive ageing might moderate *APOE* effects early in the lifespan.

Article 1 provides a systematic and meta-analytic review of the literature to date, investigating the effects of *APOE* ε4 on cognition in mid-adulthood. The review collectively considers ε4 performance differences on both established neuropsychological assessment measures and computerised cognitive paradigms, as well as the influence of this variant on longitudinal cognitive change. The principle aims of this review are to establish: a) Is cognition sensitive to *APOE* ε4 effects in mid-life, b) Is there a differential profile of sensitivity across cognitive domains? In addition, this article highlights methodological shortcomings in the existing literature, important in shaping the subsequent empirical work of this thesis.

Previous research using sensitive behavioural paradigms identified attentional control as sensitive to *APOE* ε4 effects in youth and middle age. Articles 2 and 3 report the use of six behavioural paradigms exploring *APOE* genotype differences in selective attention and more executive attention respectively. In light of the methodological limitations identified in Article 1, these articles independently compare all three variants of the *APOE* gene (ε2, ε3, and ε4) in volunteers, aged 45-55 years. Importantly, whilst ε2 genotype differences were reported in measures of visual search and sustained attention, performance of ε4 carriers was equivalent aside from on two tasks: a non-focal PM task and a Stroop-switch task. Together, this was interpreted as ε4 carriers showing a subtle disadvantage on the ability to maintain multiple goals at the forefront of attention. Following this, the thesis directly pursues *APOE* differences in tasks loading on this element of executive attention.

One of the challenging issues in ageing research is the complexity of additional factors impacting cognitive decline. Article 4 presents an exploratory analysis of how lifestyle factors such as occupational complexity and leisure activities, physical activity and vascular health moderate the emergence of *APOE* genotype effects on executive attention in mid-adulthood. In line with predictions, cognitive reserve proxies are reported to benefit ε4 carriers goal maintenance abilities to a greater extent than their ε3 peers in mid-adulthood, demonstrating the importance of this factor in individual differences from early in the ageing trajectory. Non-significant effects of physical activity and physiological health are reported.

Article 5 uses the distinction between non-focal and focal PM to explore age-related cognitive change in *APOE* ε4 carriers. PM paradigms provide an interesting framework for exploring genotype effects in mid-adulthood due to the distinct profile of impairment associated with healthy and pathological ageing. Specifically, Article 5 asks is ε4 associated with a cognitive phenotype of premature ageing or vulnerability consistent with the preclinical stages of

LOAD. The study includes a cross-sectional comparison of young and mid-age adults to infer the extent of age-related change. In addition, the study includes a manipulation of WM load to examine if increasing the burden on attentional control exaggerates ε4 differences in mid-adulthood. Results indicate equivalent performance on PM retrieval accuracy between groups, however, the interference costs of carrying both a focal and non-focal PM intention were greater in mid-age ε4 carriers, consistent with the profile seen in pathological cognitive ageing. This suggests early vulnerability in ε4 carriers to change in processes that are also vulnerable to LOAD.

Through several studies in this thesis, non-focal PM consistently demonstrated sensitivity to the effects of *APOE* ε4 in mid-adulthood. The final article (Article 6) explores whether performance differences on a non-focal PM paradigm are also seen in an 'at-risk' group of individuals, defined as those visiting a memory assessment clinician to report symptoms of mild cognitive decline, and the impact of *APOE* genotype differences in this group. There are numerous examples of PM in everyday functioning, and so as an additional goal, this research explores how non-focal performance correlates with subjective reports of cognitive failings in daily activity. There were no significant performance differences on a non-focal PM measure in this 'at-risk' group, however, in line with predictions, PM retrieval accuracy correlated with reports of attentional control in daily life. *APOE* genotype did not moderate performance differences at this later stage of the lifespan.

2. Article 1

The elusive nature of *APOE* ε4 in mid-adulthood: understanding the cognitive profile

Article 1 is published in the Journal of the International Neuropsychological Society as:

> Lancaster, C., Tabet, N., & Rusted, J. (2017). The elusive nature of APOE ε4 in mid-adulthood: understanding the cognitive profile. *Journal of the International Neuropsychological Society*, *23*(3), 239-253.

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2. 1 Abstract

Objective: The *APOE* ε4 allele is an established risk factor for dementia, yet this genetic variant is associated with a mixed cognitive profile across the lifespan. This paper undertakes both a systematic and meta-analytic review of research investigating *APOE*-related differences in cognition in mid-adulthood, when detrimental effects of the allele may first be detectable.
Method: 36 papers investigating the behavioural effects of *APOE* ε4 at mid-age (defined as a mean sample age between 35-60 years) were reviewed. In addition, the effect of carrying an ε4 allele on individual cognitive domains was assessed in separate meta-analyses.
Results: The average effect size of *APOE* ε4 status was non-significant across cognitive domains. Further consideration of genotype effects indicates preclinical effects of *APOE* ε4 may be observable in memory and executive functioning.
Conclusions: The cognitive profile of *APOE* ε4 carriers at mid-age remains elusive. Whilst there is support for maintained ε4 performance until the 5th decade, studies administering sensitive cognitive paradigms indicate a more nuanced profile of cognitive differences. Methodological issues in this field preclude strong conclusions, which future research must address, as well as considering the influence of further vulnerability factors on genotype effects.

Keywords: *Cognitive Ageing, Middle-aged, Neuroimageing, Alzheimer Disease, Memory, Executive Function*

2.2 Introduction

Pathological cognitive ageing is an increasing problem worldwide, with 850,000 cases of Alzheimer's disease (AD) at present in the UK alone. With prevalence expected to double within the next 20 years (Alzheimer's society, 2016), understanding the risk factors associated with dementia is crucial. The Apolipoprotein E (*APOE*) epsilon 4 (ε4) allele is the leading genetic risk factor for late-onset Alzheimer's disease (Corder et al., 1993; Farrer et al., 1997). This variant of the *APOE* gene constitutes one of the three *APOE* alleles (ε2, ε3 and ε4), present in approximately 25% of the population (Mahley, 1988).

Systematic reviews of studies including healthy older adults support an association between possession of an ε4 allele and cognitive impairment in ageing more generally (Small et al., 2004; Wisdom et al., 2011), although not all studies are consistent in reporting this effect (Bunce et al., 2014; Bunce, Kivipelto, & Wahlin, 2004; Caselli et al., 2014). The association between ε4 and healthy cognitive ageing suggests the effects of this variant are not solely linked to neuropathology, and so a dimensional approach is needed to consider the overlap between healthy and pathological ageing (Walhovd et al., 2014). Potentially accounting for inconsistency within the older-adult literature, meta-analyses of study effect sizes suggest *APOE*-related differences are small and limited to certain classes of cognitive task, including global cognition, episodic memory, perceptual speed and executive function (EF) (Small et al., 2004; Wisdom et al., 2011). Age and gene-dose are also implicated as important moderators of ε4 effects (Small et al., 2004). These factors are important for how we approach understanding *APOE* genotype differences.

Curiously, the detrimental effects of *APOE* ε4 are not consistent across the lifespan, muddying attempts to explain the causality of this risk factor for decline. In naturalistic research, ε4 carriers (henceforth ε4+) were reported to have higher IQ and greater educational achievement than ε4 non-carriers (henceforth ε4-) (Hubacek et al., 2001; Yu, Lin, Chen, Hong, & Tsai, 2000). This led to the hypothesis that ε4+ may show cognitive advantages earlier in life, with performance advantages similarly being demonstrated in some (Alexander et al., 2007; Han et al., 2007; Schultz et al., 2008), although not all (Bunce et al., 2014a; Bunce, Anstey, Burns, Christensen, & Easteal, 2011; Jorm et al., 2007) studies assessing genotype differences with neuropsychological batteries. Importantly, no steps have been taken to explore the potential moderating effects of early-life IQ and education on the trajectory of cognitive ageing in ε4+ through longitudinal research.

A meta-analytic review found no conclusive support for an ε4 advantage in younger years (Ihle, Bunce, & Kliegel, 2012); however, the authors acknowledge conclusions may stem

from the predominant inclusion of studies using quick to administer behavioural assessments. Such assessments are typically used for detecting clinically relevant cognitive differences rather than the subtle changes expected in young healthy adults. When considering evidence from research paradigms designed to sensitively index select cognitive processes, ε4+ advantages have been reported. Young ε4+ showed behavioural advantages compared to ε4- on a delayed episodic memory measure (Mondadori et al., 2007). Furthermore, Marchant, King, Tabet, & Rusted (2010) demonstrated an ε4 advantage in 18-30 year olds across a number of domains including prospective memory, decision-making and sustained attention. Advantages in sustained attention were replicated in a further study (Rusted et al., 2013), which also reported ε4 advantages in covert attention (Rusted et al., 2013). In addition, ε4+ show EF advantages up until age 50 (Taylor et al., 2016). While carrying an ε4 allele might promote cognitive advantages in youth, it is important to understand how early differences cumulatively impact on the ageing trajectory of ε4+.

This review attempts to unravel the development of *APOE* ε4 cognitive effects by considering studies recruiting healthy mid-age volunteers. Mid-adulthood, as well as being influenced by the cumulative impact of *APOE* ε4 in younger years, may represent a stage when the detrimental effects of carrying this gene are first appearing. Additionally, mid-adulthood represents a period of emergence for further risk factors for dementia (e.g. vascular health), which may modulate the trajectory of cognitive ageing. By studying the impact of risk factors for cognitive decline during mid-adulthood, there is the potential to facilitate the early identification and prevention of cognitive decline. In combination, these motivations emphasise the theoretical interest of studying the effects of *APOE* ε4 at mid-age.

Here, we present a systematic review of research investigating *APOE* differences in mid-adulthood, including studies administering neuropsychological assessment measures, process-specific paradigms, and those assessing change in cognition over time. In addition, ε4 differences in individual cognitive domains are subject to a meta-analytic review.

2.3 Methods

2.3.1 Selection of studies

This review was conducted in accordance with the Helsinki declaration. A literature search of 3 databases (PsychInfo, Web of Science and Scopus) was conducted, using search

terms including '*APOE*', 'Apolipoprotein', 'cognitive', 'cognition', and 'performance' [1]. The search was limited to articles published post-1993 as this was when the link between *APOE* and detrimental cognitive ageing was first identified (Corder et al., 1993). Articles referenced by included papers were also considered if they aligned with the search criteria of this review. The last update for the search was conducted in July 2016. An overview of the search procedure is given in Figure 2.1.

2.3.2 Eligibility criteria

Studies were included in the review if they met the following criteria: (1) The study included volunteers grouped by *APOE* genotype, enabling the comparison of ε4+ to an ε4- group. (2) The mean age of volunteers in the study falls between 35-60 years. If no mean was available, the entire age range included must fall within 35-60 years. (3) The study included cognitively healthy adult volunteers. Studies including clinical groups, for example diagnosed with dementia, neural trauma or a psychiatric condition were excluded. (4) At least one objective measure of cognition must be included. (5) The study was published in English. In some cases, studies overlapped in reporting cognitive performance of the same sample, and so some papers were omitted from the review (e.g. Caselli, Chen, Lee, Alexander, & Reiman, 2008; Zuelsdorff et al., 2013).

Papers were included in the meta-analytic review if sufficient statistical data was provided for calculating the standardised effect size of carrying an ε4 allele on cognitive performance (mean, standard deviation (sd)) compared to an ε4- group. Study outcomes were included if task performance could be summarised by a measure of accuracy. Authors were contacted where insufficient data was provided.

[1] The exact search terms were as follows: (Apolipoprotein E OR apoe OR Apoliopoprotein-E) AND (Cognition OR Behaviour OR Memory OR Performance OR Executive OR Attention OR Mid-age OR Adult OR Mid-adulthood). These key words must be found in the title or abstract of identified papers.

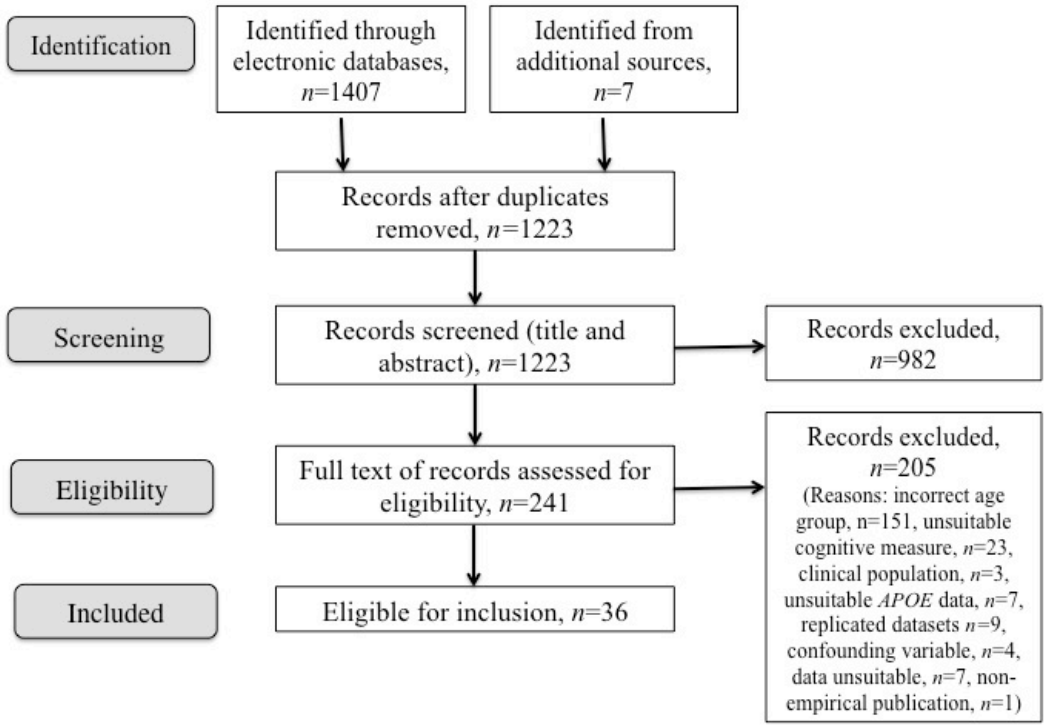


Figure 2.1. Flow chart of study selection process for review of APOE effects in mid-adulthood.

2.3.3 Organisation of studies

36 studies met criteria for being included in this review, 23 of which were included in the meta-analysis. Separate meta-analyses were completed for performance in 7 cognitive domains (global cognition, memory, executive abilities, verbal fluency, language, visuospatial processing and processing speed). For the narrative review, studies were considered more broadly as those using neuropsychological assessment measures, those that administered more detailed research paradigms and longitudinal assessments.

2.3.4 Statistical analysis

For the outcome of each task included in the meta-analytic review, Hedge's *g* was calculated as the difference in mean performance between ε4+ and ε4-, divided by the pooled sd. The unbiased estimate (Hedge's *d*) was used in the analysis, with a positive effect size indicating stronger performance by the ε4+ group. In studies reporting multiple performance outcomes per cognitive domain, effect sizes were averaged across tasks (Borenstein, Hedges, Higgins, & Rothstein, 2009; De Costa, 2009) to prevent the average effect size being over-biased by one sample. Multiple effect sizes were included when studies included more than one

sample of ε4 + and non-ε4 + grouped by another variable such as ethnicity or age (e.g (Blair et al., 2005; Shin et al., 2014). For each domain, a random-effects meta-analysis was completed. Tests of homogeneity were completed for each domain (Q_T, and I^2) to check the validity of the model. A significant Q statistic indicates a non-homogenous distribution of effect sizes. The I^2 was used to further validate this statistic, as it is not dependent on the number of studies included. Where heterogeneity was detected, data was screened for outliers based on the standardised weight of residuals and the difference excluding a study made to heterogeneity.

Results

Table 2.1 presents a summary of cross-sectional studies included in this review, including details of the sample demographics and cognitive tasks administered. A further summary of the studies included in each meta-analysis and the associated effect sizes are shown in Table 2.2

2.4.1 Meta-analyses

A summary of the results from each meta-analytic model is provided in Table 2.3. Forest plots demonstrating the distribution of effect sizes per domain are shown in Figure 2.2.

2.4.1.1 Global

A meta-analysis of effect sizes from 9 studies assessing global cognition found carrying an ε4 allele had a non-significant effect on performance, d=.03, p>.05. Tests for homogeneity indicated moderate heterogeneity in the individual studies' effect sizes, $Q(8)$=15.88, p=.044, I^2=48.36%. Data was screened for outliers, with a sample aged 55-64 years (Shin et al., 2014) identified as substantially increasing heterogeneity. With this effect size removed, carrying an ε4 allele had a positive effect on global cognitive performance in mid-adulthood, with the effect size approaching significance, d=.09, p=.066 ($Q(7)$=5.20, p>.05, I^2=0%).

2.4.1.2 Memory

Effect sizes from 20 studies were included in a meta-analysis of *APOE* ε4 effects on memory; ε4 status had a non-significant effect on performance (d=-.01, p>.05). Again, there was moderate heterogeneity in the sample of effect sizes, $Q(19)$=48.38, p<.001, I^2=10%. After screening for outliers the effect size from Levy et al., (2004) was removed, but the average effect size remained non-significant (d=-.01, p>.05)($Q(18)$=17.40, p>.05, I^2=0%).

2.4.1.3 Executive abilities

Effect sizes from 12 studies were included in a meta-analysis of *APOE* ε4 effects on executive skills. ε4 status did not significantly influence performance (d=-.03, p>.05). There was no significant heterogeneity in this collection of effect sizes, $Q(11)$=8.60, p>.05, I^2=0%.

2.4.1.4 Verbal fluency

10 studies contributed effect sizes to a meta-analysis of ε4 effects on fluency performance. The average effect of *APOE* genotype was non-significant (d=.02, p>.05). There was no significant heterogeneity in this sample of effect sizes, $Q(9)$=8.17, p>.05, I^2=21.25%.

2.4.1.5 Language

Effect sizes from 8 studies were included in a meta-analysis which found no significant effect of carrying an ε4 allele on language performance (d=.00, p>.05). There was no significant heterogeneity in this sample of effect sizes, $Q(7)$=6.81, p>.05, I^2=26.65%.

2.4.1.6 Visuospatial

Effect sizes from 5 studies were included in the meta-analysis. There was no significant effect of carrying an ε4 allele on visuospatial performance (d=-.01, p>.05), with non-significant heterogeneity reported in the sample of effect sizes, $Q(4)$=2.78, p>.05, I^2=11.96%.

Table 2.1. *Overview of cross-sectional studies investigating APOE genotype differences in mid-adulthood.*

First Author (year)	*n*	Age: mean (range)	Gender (% M)	Ethnicity	Cognitive domains	Neuropsychological tasks	Zygosity
Bender (2012)	72	50 (19-77)	-	74% Caucasion, 26% other.	G, EM, EA, PS	MMSE, Word recognition task (individual, paired association), Size judgement span, Spatial recall, Listening span, n-back; Letter same-different (PS), Pattern same-different (PS)	ε4- vs. ε4+ (ε3/ε3, vs. ε3/ε4, ε4/ε4)
Blair (2005)	6810	56 (45-64)	51 38	6202 Caucasian 1693 African-American	EM, EA, VF	DWR, DSS, VF	**1.** ε2+ vs. ε3 vs. ε4 He vs. ε4 Ho (ε2/ε2; ε2/ε3 vs. ε3/ε3 vs. ε2/ε4, ε3/ε4 vs. ε4/ε4) **2.** ε4- vs. ε4+
Caselli (1999)	100	56 (49-69)	28	-	EM, EA, VF, L, VS	AVLT, WAIS DS, WAIS Mental arithmetic, COWAT, WAIS Similarities, BNT, CFT, WAIS Block design	ε4- vs. ε4+ (ε3/ε3, vs. ε3/ε4, ε4/ε4)
Caselli (2011)	621	59 (21+)	30	-	EM, EA, VF, PS	AVLT, COWAT, DSS, PASAT, WCST	ε4- vs. ε4+ (ε3/ε3, vs. ε3/ε4, ε4/ε4)
Chen (2013)	18	42 (-)	44	-	G, EA	MMSE, *n*-back	ε4- vs. ε4 He (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε3/ε4)
Deeny (2008)	54	60 (50-70)	56	-	EA	Sternberg WM task	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3, vs. ε3/ε4, ε4/ε4)
Donix (2010)	28	55.3 (38-63)	~23	-	G, EM, EA,VF, L, VS	MMSE, WMS (logical memory-delayed, verbal paired associates), Buschke selective reminding test, DS (forward, backward), Stroop interference, WCST, TMT-B, VF, BNT, CFT	ε4- vs. ε4+ (ε2/ε3, ε3/ε3, vs. ε3/ε4, ε4/ε4)
Evans (2013; 2014)	40	50 (43-58)	42	-	EM, EA	Immediate recall, PM hits, Covert attention task, RVIP	ε3 vs. ε4 (ε3/ε3 vs. ε3/ε4, ε4/ε4)
Flory (2000)	220	47 (24-60)	51	-	EM, EA	Verbal learning, Verbal delayed recall, Figure delayed recall, DS (forward, backward), Recurring word test	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3, vs. ε2/ε4, ε3/ε4, ε4/ε4)

Goveas (2013)	46	54 (44-65)	33	-	EM, EA, PS	AVLT, TMT-A & B, DS	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3, vs. ε2/ε4, ε3/ε4, ε4/ε4)
Greenwood (2000)	97	59 (50+)	39	-	EM, EA	WMS General, WMS Delayed, Buschke selective reminding test, Cued letter discrimination task, Vigilance task, Dynamic scaling	ε2+ vs. ε3 vs. ε4+ (ε2/ε2; ε2/ε3 vs. ε3/ε3 vs. ε2/ε4, ε3/ε4, ε4/ε4)
Greenwood (2005a)	177	59 (41-85)	41	-	EA	Cued letter discrimination task, Spatial WM task, Attention/WM task	ε4- vs. ε4 He vs. ε4 Ho (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε2/ε4, ε3/ε4 vs. ε4/ε4
Greenwood (2014)	591	50 (40-59)	-	92% Caucasian	EA	MMSE, WAIS logical memory, WAIS letter-number sequencing, Delayed match-sample task	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3, vs. ε2/ε4, ε3/ε4, ε4/ε4)
Jorm (2007)	2176	- (40-44)	47	-	EM, EA, L, PS	CVLT, DS (backward), Spot-the-word, DSS	ε4- vs. ε4 He vs. ε4 Ho (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε2/ε4, ε3/ε4 vs. ε4/ε4
Langbaum (2010)	27	55 (47-68)	19	Latino	G, EM, EA, VF, L, VS	MMSE, WAIS, AVLT, COWAT, BNT, CFT	ε4- vs. ε4+ (ε2/ε3, ε3/ε3, vs. ε2/ε4, ε3/ε4, ε4/ε4)
Levy (2004)	176	59 (42-86)	36	-	EM, VF, VS, L, PS	WMS Logical Memory I & II, Buschke Selective Reminding Test, WMS Verbal Paired Associations I & II, WMS Visual Reproduction I & II, Verbal fluency (letter, category), BNT, CFT, Block design, DSS	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3, vs. ε2/ε4, ε3/ε4, ε4/ε4)
Marioni (2016)	12 472	42 (19-59)	41	-	EM, VF, L, PS	WAIS Logical memory, VF, Mill Hill Vocabulary scale, DSS	ε2/ε2 vs. ε2/ε3 vs. ε2/ε4 vs. ε3/ε3 vs. ε3/ε4 vs. ε4/ε4
Nichols (2012)	133	36 (19-77)	44	Caucasian	G, EM	WAIS, Recognition memory task	ε2/ε3 vs. ε3/ε3 vs. ε3/ε4
Oberlin (2015)	975	45 (30-54)	49	Caucasian	EM, EA	WMS Logical memory, WMS Visual reproduction, TMT-A & B	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3, vs. ε2/ε4, ε3/ε4, ε4/ε4)
Panizzon (2014)	717	56 (51-60)	100	89.7% Caucasian	EM	CVLT, WMS Story recall, WMS Figure recall	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3, vs. ε2/ε4, ε3/ε4, ε4/ε4)
Patel (2013)	36	45 (-)	42	72% Caucasian, 19% Afro-American, 9% Other	G, EM, EA, VF, PS	IQ, WRAT, BVMT (delayed recall, recognition), DS, VF, Groove-pegboard task, Letter-number sequencing, Symbol search, TMT A & B	ε4- vs. ε4+ (ε2/ε3, ε3/ε3, vs. ε3/ε4, ε4/ε4)

Protas (2013)	149	56 (47-68)	36	-	G, EM, VF, VS, L	MMSE, WAIS, AVLT, CFT, COWAT, BNT	ε4- vs. ε4 He vs. ε4 Ho (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε2/ε4, ε3/ε4 vs. ε4/ε4
Ready (2011)	23	56 (46-66)	39	-	EM, EA, VF	Memory composite (WMS Logical, CVLT, WMS Visual Reproduction), Trail-making composite, Colour-word composite, VF composite (letter, category)	ε4- vs. ε4+ (ε2/ε3, ε3/ε3 vs. ε3/ε4)
Sager (2005)	452	53 (40-65)	29	-	EM, EA, VF, L, VS	AVLT, Faces I and II, Stroop-colour, TMT-B, WCST, WAIS WM index, VF, WAIS Vocabulary, Similarities, Word-reading, BNT, WAIS Block design, Matrix reasoning, Line orientation judgment	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3, vs. ε2/ε4, ε3/ε4, ε4/ε4)
Schultz (2008)	626	55 (50-59)	100	-	EM	WMS Logical Memory, WMS Visual Reproduction	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε2/ε4, ε3/ε4, ε4/ε4)
Shin (2014)	2401	45-54	36	-	G	Korean MMSE	ε4- vs. ε4 He vs. ε4 Ho (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε2/ε4, ε3/ε4 vs. ε4/ε4)
	3919	55-64	39	-			
Sunderland (2004)	142	59 (-)	37	-	G	MMSE, BNT	ε4- vs. ε4+ (ε2/ε3, ε3/ε3 vs. ε2/ε4, ε3/ε4, ε4/ε4)
Trachtenberg (2012)	72	46 (30-55)	48	-	EM, EA	Episodic retrieval-pictures; Counting Stroop task	ε2 vs. ε3. ε4 He vs. ε4Ho (ε2/ε3 vs. ε3/ε3 vs. ε3/ε4 vs. ε4/ε4)
Velichkovsky (2015)	35	50 (-)	26	-	EM, EA	AVLT, WMS Visual reproduction, Anti-saccade task, Switching task, *n*-back task, Operation span	ε3 Ho vs. ε4 Hz (ε3/ε3 vs. ε3/ε4)
Xu (2009)	74	59 (50-65)	27	-	EM	Recognition memory task	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3, vs. ε2/ε4, ε3/ε4, ε4/ε4)
	43	58 (50-65)	30	-	EM, EA, L, VF	AVLT, TMT-A & B, COWAT, BNT	

Abbreviations*:* Domains: Global (G), Memory (M), Executive abilities (EA), Verbal Fluency (VF), Language (L), Visuospatial processing (VS), Processing Speed (PS). Tasks: Mini-mental State Examination (MMSE), Wide Range Achievement Test (WRAT), Delayed Word Recall (DWR), Brief Visuospatial Memory test (BVMT), Rey's Auditory verbal learning task (AVLT), Californian verbal learning test (CVLT), Digit span (DS), Paced Auditory Serial Attention task (PASAT), Prospective memory (PM), Rapid Visual Information Processing task (RVIP), Trails-making test (TMT), Wisconsin Card Sort task (WCST), Complex figure test (CFT), Controlled oral association task (COWAT), Boston Naming Task (BNT), Digit-symbol Substitution (DSS). Zygosity: Heterozyous (He), Homozygous (Ho)

Table 2.2. *Average effect size per study organised by cognitive domain, where a positive effect size represents better performance by the ε4+ group*

Domain	Authors (year)	Group n			
		Age (M)	ε4+	ε4-	Hedge's *d*
Global	Bender (2012)	50	20	52	0.45
	Donix (2010)	55	12	16	-0.02
	Langbaum (2010)	55	11	16	0.00
	Nichols (2012)	36	35	81	-0.21
	Patel (2013)	45	14	22	0.21
	Protas (2013)	56	73	76	0.00
	Shin (2014) (45-54)	-	380	1967	0.09
	Shin (2014) (55-64)	-	679	3240	-0.12
	Sunderland (2004)	59	57	85	0.22
Memory	Blair (2005) (C)	56	1720	3648	0.00
	Blair (2005) (A)	56	698	744	0.00
	Caselli (2011)	59	265	356	-0.03
	Caselli (1999)	56	50	50	-0.13
	Donix (2010)	59	12	16	0.03
	Evans (2013; 2014)	50	19	21	-0.45
	Flory (2000)	47	61	159	-0.27
	Greenwood (2000)	59	38	48	-0.26
	Goveas (2013)	54	20	26	-0.48
	Jorm (2007)	-	611	1571	0.01
	Langbaum (2010)	55	11	16	0.08
	Levy (2004)	59	61	115	-1.94
	Marioni (2016)	42	3807	8665	-0.01
	Nichols (2012)	36	35	81	-0.18
	Patel (2013)	45	14	22	-0.28
	Protas (2013)	56	73	76	0.09
	Sager (2005)	53	204	248	0.05
	Trachtenberg (2012)	46	33	20	-0.16
	Velichkovsky (2015)	50	13	22	-0.23
	Xu (2009)	58	18	25	0.35
Executive abilities	Caselli (1999)	56	50	50	0.06
	Caselli (2011)	59	265	356	0.05
	Chen (2013)	42	9	9	0.20
	Donix (2010)	59	12	16	-0.01
	Evans (2013; 2014)	50	19	21	0.36
	Flory (2000)	47	61	159	-0.09
	Goveas (2013)	54	20	26	-0.54
	Jorm (2010)	-	611	1571	-0.06
	Langbaum (2010)	55	11	16	0.26
	Sager (2005)	53	204	248	-0.06

	Trachtenberg (2012)	46	33	20	-0.17
	Velichkovsky (2015)	50	13	22	-0.15
Verbal Fluency	Blair (2005) (C)	56	1720	3648	0.00
	Blair (2005) (A)	56	698	744	-0.06
	Caselli (2011)	59	265	356	0.01
	Donix (2010)	55	12	16	-0.02
	Langbaum (2010)	55	11	16	0.34
	Levy (2004)	59	61	115	0.05
	Marioni (2016)	42	3807	8665	0.06
	Protas (2013)	56	73	76	0.18
	Sager (200)	53	204	248	0.05
	Xu (2009)	58	18	25	-0.24
Language	Donix (2010)	59	12	16	0.07
	Jorm (2007)	-	611	1571	-0.02
	Langbaum (2010)	55	11	16	-0.29
	Levy (2004)	59	61	115	0.10
	Marioni (2016)	42	3807	8665	0.05
	Protas (2013)	56	73	76	-0.14
	Sager (2005)	53	204	248	-0.12
	Xu (2009)	58	18	25	-0.18
Visuospatial	Casell (2011)	59	50	50	0.12
	Langbaum (2010)	55	11	16	-0.04
	Levy (2004)	59	61	115	0.04
	Protas (2013)	56	73	76	0.12
	Sager (2005)	53	204	248	-0.10
Processing speed	Blair (2005)	56	1720	3648	0.01
	Blair (2005)	56	698	744	-0.13
	Goveas (2013)	54	20	26	0.08
	Jorm (2007)	-	611	1571	0.01
	Levy (2004)	59	61	115	-0.11
	Marioni (2016)	42	3807	8665	-0.01
	Patel (2013)	45	14	22	0.33

Notes: Caucasians (C), Afro-Americans (A)

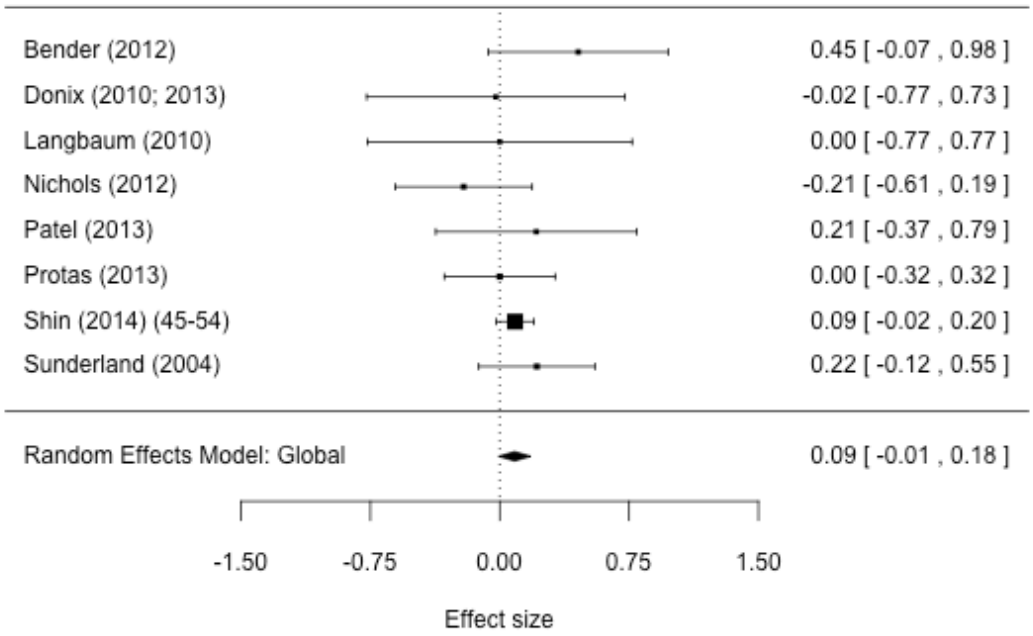
2.4.1.7 Processing speed

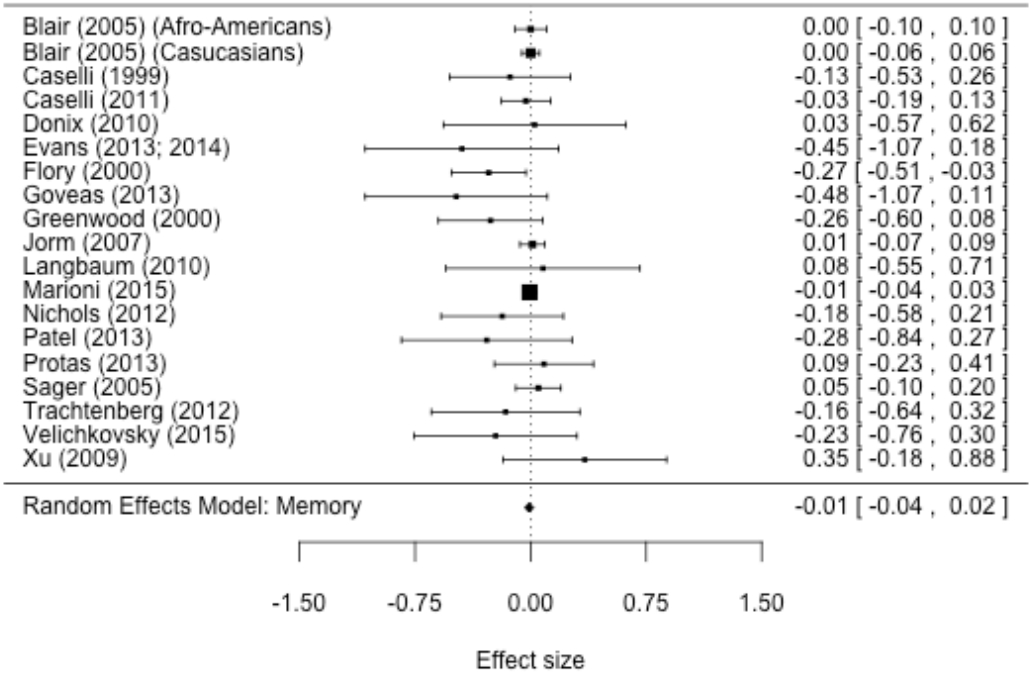
7 studies contributed effect sizes to a meta-analysis of genotype differences in processing speed. The average effect of carrying an ε4 allele was non-significant (*d*=-.01, *p*>.05). There was no significant heterogeneity in this sample of effect sizes, $Q(6)=7.15$, *p*>.05, $I^2=0\%$.

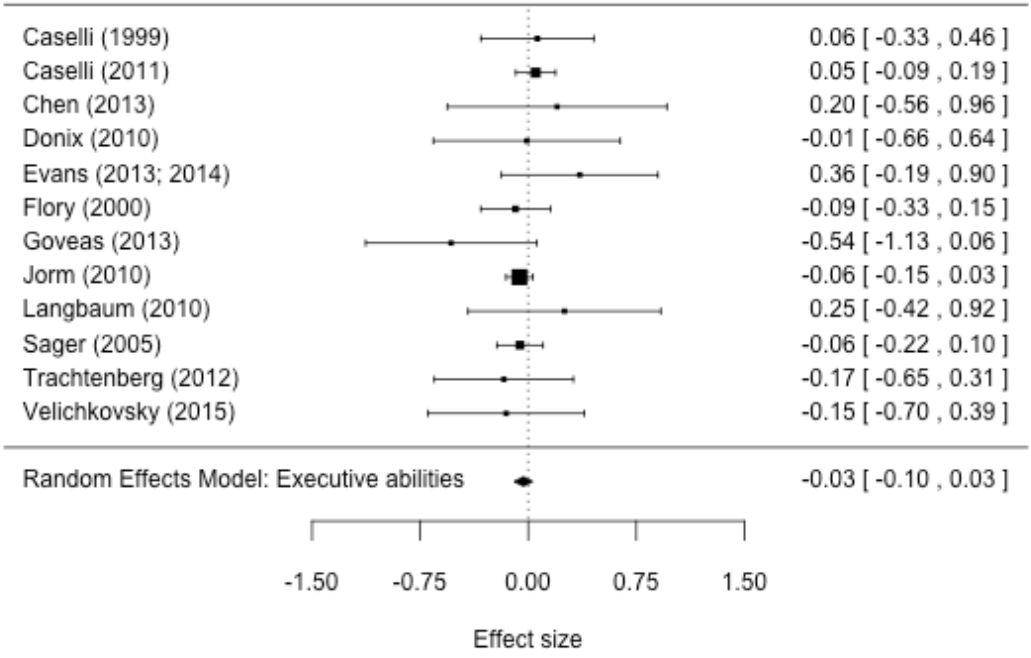
Table 2.3. *A summary of findings for the meta-analysis within each cognitive domain.*

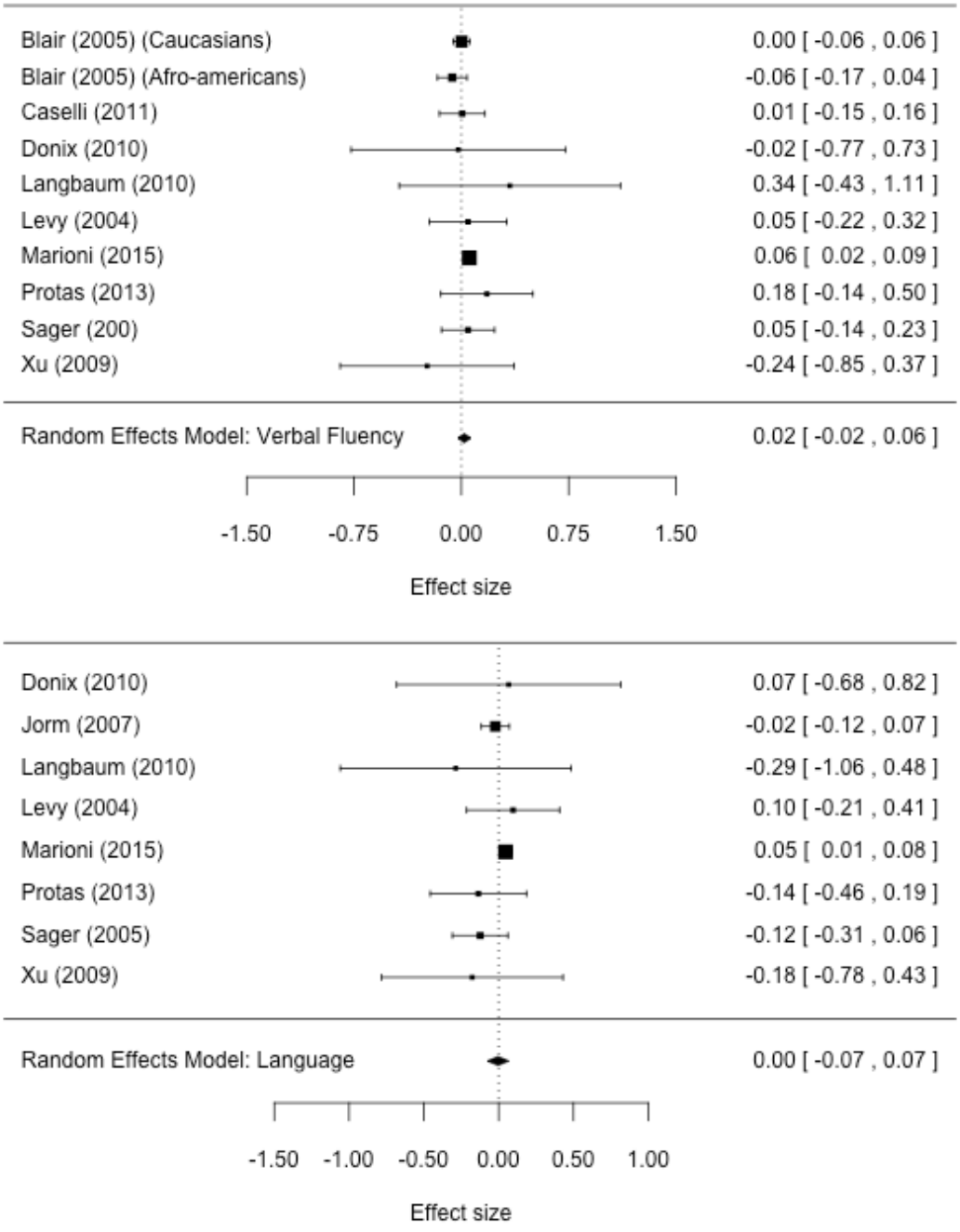
Domain	**Studies (*k*)**	**ε4+ (*n*)**	**ε4- (*n*)**	***d***	**95% CI**	***Q***
Global	8	602	2315	0.09	-.01, .18	5.20
Memory	19	7702	15814	-0.01	-.04, .02	17.40
EA	12	2045	3615	-0.03	-.10, .03	8.60
VF	10	6869	13909	0.02	-.02, .06	8.17
Language	8	4797	10732	0	-.07, .07	6.81
Visuospatial	5	399	505	-0.01	-.14, .12	2.78
PS	7	6931	14791	-0.01	-.04, .02	7.15

Notes: * *p*<.01, ***p*<.05




Blair (2005) (Afro-Americans) 0.00 [-0.10 , 0.10]
Blair (2005) (Casucasians) 0.00 [-0.06 , 0.06]
Caselli (1999) -0.13 [-0.53 , 0.26]
Caselli (2011) -0.03 [-0.19 , 0.13]
Donix (2010) 0.03 [-0.57 , 0.62]
Evans (2013; 2014) -0.45 [-1.07 , 0.18]
Flory (2000) -0.27 [-0.51 , -0.03]
Goveas (2013) -0.48 [-1.07 , 0.11]
Greenwood (2000) -0.26 [-0.60 , 0.08]
Jorm (2007) 0.01 [-0.07 , 0.09]
Langbaum (2010) 0.08 [-0.55 , 0.71]
Marioni (2015) -0.01 [-0.04 , 0.03]
Nichols (2012) -0.18 [-0.58 , 0.21]
Patel (2013) -0.28 [-0.84 , 0.27]
Protas (2013) 0.09 [-0.23 , 0.41]
Sager (2005) 0.05 [-0.10 , 0.20]
Trachtenberg (2012) -0.16 [-0.64 , 0.32]
Velichkovsky (2015) -0.23 [-0.76 , 0.30]
Xu (2009) 0.35 [-0.18 , 0.88]
Random Effects Model: Memory -0.01 [-0.04 , 0.02]
-1.50
-0.75
0.00
0.75
1.50
Effect size


Caselli (1999) 0.06 [-0.33 , 0.46]
Caselli (2011) 0.05 [-0.09 , 0.19]
Chen (2013) 0.20 [-0.56 , 0.96]
Donix (2010) -0.01 [-0.66 , 0.64]
Evans (2013; 2014) 0.36 [-0.19 , 0.90]
Flory (2000) -0.09 [-0.33 , 0.15]
Goveas (2013) -0.54 [-1.13 , 0.06]
Jorm (2010) -0.06 [-0.15 , 0.03]
Langbaum (2010) 0.25 [-0.42 , 0.92]
Sager (2005) -0.06 [-0.22 , 0.10]
Trachtenberg (2012) -0.17 [-0.65 , 0.31]
Velichkovsky (2015) -0.15 [-0.70 , 0.39]
Random Effects Model: Executive abilities -0.03 [-0.10 , 0.03]
-1.50
-0.75
0.00
0.75
1.50
Effect size


Blair (2005) (Caucasians) 0.00 [-0.06 , 0.06]
Blair (2005) (Afro-americans) -0.06 [-0.17 , 0.04]
Caselli (2011) 0.01 [-0.15 , 0.16]
Donix (2010) -0.02 [-0.77 , 0.73]
Langbaum (2010) 0.34 [-0.43 , 1.11]
Levy (2004) 0.05 [-0.22 , 0.32]
Marioni (2015) 0.06 [0.02 , 0.09]
Protas (2013) 0.18 [-0.14 , 0.50]
Sager (200) 0.05 [-0.14 , 0.23]
Xu (2009) -0.24 [-0.85 , 0.37]
Random Effects Model: Verbal Fluency 0.02 [-0.02 , 0.06]
-1.50 -0.75 0.00 0.75 1.50
Effect size
Donix (2010) 0.07 [-0.68 , 0.82]
Jorm (2007) -0.02 [-0.12 , 0.07]
Langbaum (2010) -0.29 [-1.06 , 0.48]
Levy (2004) 0.10 [-0.21 , 0.41]
Marioni (2015) 0.05 [0.01 , 0.08]
Protas (2013) -0.14 [-0.46 , 0.19]
Sager (2005) -0.12 [-0.31 , 0.06]
Xu (2009) -0.18 [-0.78 , 0.43]
Random Effects Model: Language 0.00 [-0.07 , 0.07]
-1.50 -1.00 -0.50 0.00 0.50 1.00
Effect size

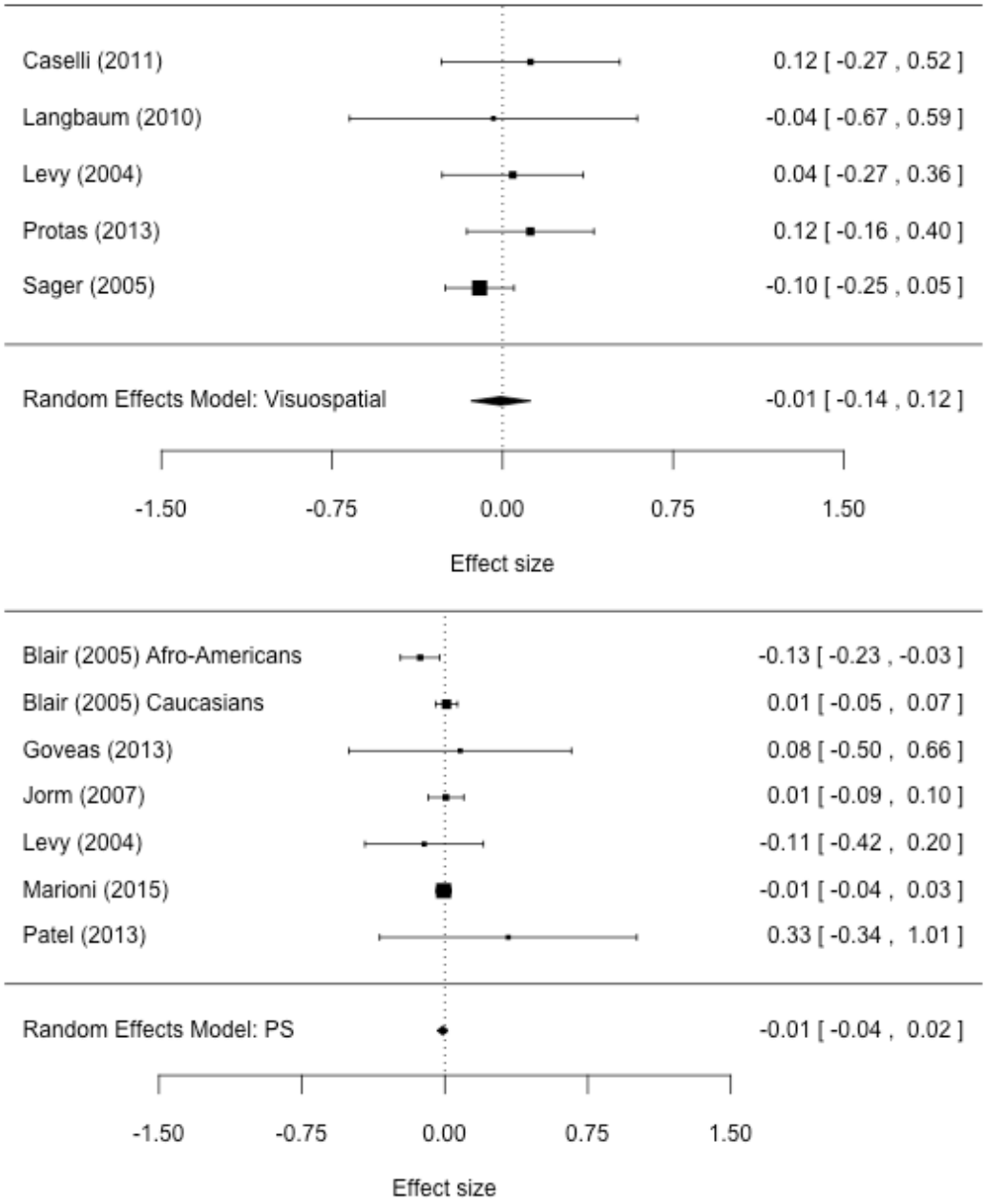


Figure 2.2 Forest plots of weighted effect sizes by cognitive domain. For each study, effect size is reported as Hedge's d [95% CI], where a positive effect size represents greater performance by the ε4+ group.

2.4.2 Systematic review

2.4.2.1 Neuropsychological Assessment

The majority of studies examining the effect of *APOE* ε4 in mid-adulthood have chosen to administer a compilation of neuropsychological assessment measures. These studies report

limited effects of *APOE* ε4 in mid-adulthood (e.g. Jorm et al., 2007; Marioni et al., 2016; Sager, Hermann, & La Rue, 2005; Shin et al., 2014; Zhao et al., 2005). Indeed, in a large community-based sample, the effect of *APOE* status was non-significant in both mid-adulthood (40-44 years), as well as groups aged 20-24 years and 60-64 years (Jorm et al., 2007), leading authors to conclude there are no preclinical effects of *APOE* genotype on cognition. Of interest, however, other studies suggest sample age is a key determinant in the expression of preclinical *APOE* ε4 effects. Age x *APOE* interactions were found both for scores on the Korean MMSE (Shin et al., 2014), and performance on measures of declarative memory and processing speed (Marioni et al., 2015). In both studies, detrimental effects of ε4 status emerged when analyses isolated volunteers aged in the latter half of the 5th decade (55+ years and 60+ years respectively).

Mid-age studies investigating *APOE* differences across a broad range of neuropsychological measures typically observe ε4 effects, when present, within a select domain. For example, in the research of Sager et al. (2005) ε4+ selectively show worse performance on visuospatial processing tasks, driven by decrements on block design performance. In contrast, detrimental effects of ε4 status were limited to female participants on tasks probing memory and semantic fluency (Zhao et al., 2005), whereas ε4 advantages were reported in verbal fluency and language across the adult lifespan by Marioni et al., (2016). While the selectivity of effects agrees with reports of genotype effects in older adulthood (Small et al., 2004; Wisdom et al., 2011), failure to identify a consistent pattern of ε4 effects within a cognitive domain in mid-adulthood makes interpretation difficult.

Results within the domain of memory offer the clearest profile of cognitive differences in ε4+, with several studies associating possession of an ε4 allele with poorer memory performance (Caselli et al., 1999; Flory, Manuck, Ferrell, Ryan, & Muldoon, 2000; Goveas et al., 2013; Levy et al., 2004; Schultz et al., 2008). Attempts have been made to link differential memory performance with neural differences. In adults aged 44-65, ε4+ showed a trend of worse performance on the Rey Auditory Verbal Learning Test (AVLT) (Goveas et al., 2013). Performance on this task correlated with observed reductions in the functional connectivity of medial temporal lobe (MTL) circuits, as well as differential connectivity of the default mode network (Li et al., 2014; Goveas et al., 2013), offering a possible neurobiological basis of genotype differences. In addition, two studies report an altered BOLD response in ε4+ during episodic memory tasks, despite no detectable genotype difference in behavioural performance (Trachtenberg, Filippini, Cheeseman, et al., 2012; Xu et al., 2009). Although this raises the question of how neural activations relate to cognition, identifying the neural basis of *APOE* differences will further mechanistic explanations of how *APOE* ε4 influences cognitive ageing.

Research has started to explore how carrying an *APOE* ε4 allele interacts with environmental factors in influencing performance on neuropsychological measures. Education was found to interact with *APOE* status in a cohort of adults aged 45-54 years, in that only ε4+ with no formal education showed cognitive advantages on a measure of global cognition compared to their ε4- peers (Shin et al., 2014). In contrast, *APOE,* education and socio-economic status were reported to independently affect cognition (Zhao et al., 2005).

Considering cardiovascular health factors, an *APOE* x Blood Pressure interaction has been reported for cognition in mid-adulthood. Although there was no main effect of *APOE* status or systolic blood pressure on performance across 3 cognitive domains; episodic memory, visual memory or EF, in ε4+ only, high blood pressure was associated with worse episodic memory performance (Oberlin et al., 2015). High blood pressure was also found to enhance the negative association of *APOE* ε4 with processing speed and working memory (WM), as well as reduced white matter integrity in frontal regions (Bender & Raz, 2012). In both studies, the relationship between *APOE,* blood pressure and cognition was absent in the ε4- group, suggesting cardiovascular health factors may exaggerate cognitive effects in ε4+.

2.4.2.2 Behavioural paradigms

Paradigms designed to detect subtle differences in cognition have predominantly been used to explore the sensitivity of executive abilities, including WM and attention, to *APOE* effects in mid-adulthood.

On a measure of covert attention, there was a non-significant effect of *APOE* genotype on overall performance, and on the ability to benefit from valid cues in mid-adulthood (Greenwood, Sunderland, Friz, & Parasuraman, 2000). ε4+, however, showed increased response time costs following an invalid cue, relative to ε4- peers, interpreted as a deficit in attentional disengagement. In contrast, a more recent study reported equivalent performance between genotype groups on this task (Evans et al., 2013; Evans, Dowell, Tabet, Tofts, King & Rusted, 2014). Control of visual attention was explored in an attentional scaling task (Greenwood et al., 2000; Greenwood, Lambert, Sunderland & Parasuraman, 2005a). The dynamic scaling task measures the ability to constrict one's attentional spotlight in response to top-down information cueing the spatial location of a target stimulus. ε4+ did not show the same benefit as their ε4- peers in response times following more precise cues.

Executive attention was explored in a cross-sectional comparison of mid-age (aged 43-58) and young adults (aged 18-30) (Evans et al., 2013; 2014). On a measure of sustained attention, a trend of higher accuracy, coupled with slower reaction times, was found in mid-age ε4+ relative to their ε4- peers. When compared to the data from the young group, the mid-age ε4+ group showed exaggerated age-related slowing. In comparison, a second study found no effect of *APOE* genotype on a similar task in adults aged 50+ (M=59 years) (Greenwood et al., 2000). A comparable pattern of results was seen on a prospective memory task, probing attentional monitoring and switching between goals. ε4+ demonstrated greater accuracy but slower response times on the prospective memory paradigm, suggestive of a speed-accuracy trade-off (Evans et al., 2013; 2014). Corresponding functional activations during this task indicated greater recruitment of frontal regions, but reduced recruitment of parietal and extrastriate visual regions in ε4+ relative to their ε4- peers. Specifically, left inferior frontal gyrus activity correlated with prospective memory accuracy in ε4+ only, consistent with an early compensatory shift towards reliance on more frontal systems.

Genotype effects were explored using a selection of cognitive paradigms designed to probe the 3 components of executive function identified by Miyake et al. (2000): inhibition, switching and updating in WM (Velichkovsky, Roschina, & Selezneva, 2015). No genotype differences were recorded on either an anti-saccade inhibition measure, or two WM paradigms (*n*-back test, the operation span task). A non-significant effect of *APOE* ε4 status on *n*-back performance has previously been reported in middle-aged adults (Chen et al., 2013; Yan, Wu, Chao, Chen, & Tseng, 2015). Both studies reported a differential pattern of neural change in ε4+, with this group showing an absence of neural activation increases in correspondence to greater WM load (Chen et al., 2013; Yan et al., 2015). This was interpreted as ε4+ maximally recruiting processing resources at a lower level of load, which cannot be further increased under greater demands. Hence, it may be that on more demanding tasks, significant effects of carrying an ε4 allele may be observable. On the switching paradigm administered by Velichovsky et al., (2015), ε4+ showed significantly larger switching costs than their ε4- counterparts.

Greenwood et al., (2005a) assessed spatial WM in adults, aged 41-85. Relative to ε4-, only homozygous ε4+ displayed a disadvantage on spatial WM tasks, driven by performance on trials placing the greatest load on spatial WM. In a further study of spatial WM, no genotype difference was seen in mid-age adults (Greenwood, Espeseth, Lin, Reinvang, & Parasuraman, 2014)

2.4.2.3 Longitudinal assessments

Several studies have explored how cognition changes longitudinally as a function of *APOE* genotype (Table 2.4). Schultz et al. (2008) compared the cognitive test performance of army cadets in the 6th decade of life, to their scores on the same measure at age 20, and found ε4+ showed greater decline. Across a period of 6 years, relatively limited effects of *APOE* genotype were reported across a selection of cognitive domains (Zhao et al., 2005), with only semantic fluency being negatively associated with ε4 status in females aged 40-49; this study reported no genotype differences in a slightly older sample (aged 50-59).

The dominant focus of longitudinal research has been establishing if ε4+ show a differential rate of memory change over time. Several studies suggest that ε4+ show significantly greater memory decline from mid-adulthood (Caselli et al., 2009; Kozauer, Mielke, Chan, Rebok, & Lyketsos, 2008), with this effect isolated to delayed memory in two studies (Greenwood, Sunderland, Putnam, Levy, & Parasuraman, 2005b; Greenwood et al., 2014). Performance change across an average of 3.8 years was investigated for measures of memory (Jochemsen et al., 2012), with participants stratified by age. Of interest, it was found ε4+ aged 47-57 years showed improvements in recall performance, whilst ε4+ aged 58-67 years showed significant decline by the follow-up assessment. How change in memory is influenced by the interaction between *APOE* genotype, ethnicity and cardiovascular health has also been explored over a 6 year interval (Blair et al., 2005). Negative associations between ε4+ and memory change were small and limited to Caucasian adults. There was no interaction between cardiovascular health factors (diabetes, hypercholesterolemia, hypertension), *APOE* genotype and memory change.

Two papers found a non-significant effect of *APOE* genotype on change in executive abilities over time (Greenwood et al., 2014; Jochemsen et al., 2012). There is support, however, for the ε4 allele being associated with greater decline in processing speed (Blair et al., 2005; Caselli et al., 2011). In a group of Caucasian adults, ε4+ also diagnosed with hypercholesterolemia or diabetes showed increased decline on the digit-symbol substitution measure of processing speed (Blair et al., 2005). No *APOE* x Hypertension interaction was found for change in processing speed. Verbal fluency scores were maintained in both the Caucasian and Afro-American groups included in Blair et al. (2005).

Table 2.4. *A summary of longitudinal studies investigating APOE differences in mid-adulthood*

First Author (year)	*n*	Age: M (range)	Gender (% M)	Ethnicity	Cognitive domain	Neuropsychological tasks	Follow-up	Attrition	Genotype comparison
Blair (2005)	6810	56 (45-64)	51 38	6202 Caucasian 1693 African-American	M, EA, VF	DWR, DSS, VF	6 yrs (2-yr intervals)	24%	**1.** ε2+ vs. ε3 vs. ε4 He vs. ε4 Ho (ε2/ε2; ε2/ε3 vs. ε3/ε3 vs. ε2/ε4, ε3/ε4 vs. ε4/ε4) **2.** ε4- vs. ε4+
Caselli (2009)	815	60 (21-97)	31	85% Caucasian, 12 % Latino, 3% Other,	G, M, VF, VS	MMSE, AVLT, COWAT, JLO	5 yrs (1-2 yr intervals	-	ε4- vs. ε4+ (ε3/ε3, vs. ε3/ε4, ε4/ε4)
Caselli (2011)	621	57 (21-97)	30	-	M, EA, VF	AVLT, COWAT, PASAT, DSS, WCST, Iowa Gambling task	6.3 yrs (2-yr intervals)	23%	ε4- vs. ε4+ (ε3/ε3, vs. ε3/ε4, ε4/ε4)
Greenwood et al (2005b)	139	60 (33-85)	31	-	M, EA	WMS-G, WMS-D, Cued Visual Search task	3 yrs (1-yr intervals)		ε4- vs. ε4 He vs. ε4 Ho (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε2/ε4, ε3/ε4 vs. ε4/ε4)
Greenwood (2014)	249	- (40-59)	-	97% White	G, M EA	MMSE, WAIS logical memory,WAIS letter-number sequencing, Delayed match-sample task	3 yrs (1-yr intervals)	-	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε2/ε4, ε3/ε4, ε4/ε4)
Jochemsen (2012)	188	57 (27-79)	80	-	G, M, EA, VF	RAVLT, ROCF, Elevator task, Brixton spatial task, MMSE, VF	3.8 yrs	44%	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε3/ε4, ε4/ε4)
Kozauer (2008)	492	53 (18-65)	-	-	G, M	MMSE, Immediate recall, Delayed recall, Recognition	22 yrs (3 follow-ups_	-	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε2/ε4, ε3/ε4, ε4/ε4)
Schultz (2008)	626	55 (50-59)	100	95.5% Caucasian, 3.8% African-American, 0.3% Hispanic, 0.3% "other."	G	AFQT	35 yrs	-	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε2/ε4, ε3/ε4, ε4/ε4)
Zhao (2005)	1128	- (40-49)	77	European descent	G, M, VF, L	Verbal memory, AH4-1, MHV, VF (letter,	6 yrs	-	ε4- vs. ε4+ (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε2/ε4, ε3/ε4,

2601	- (50-59)	74	European descent	category)	6 yrs	-	ε4/ε4)

Abbreviations: Domain- Global (G), Memory (M), Executive ability (EA), Verbal Fluency (VF), Language (L) Visuospatial (VS). Tasks-Mini-Mental State Examination (MMSE), Weschler Adult Intelligence Scale (WAIS), Weschler Memory Scale (WMS), Delayed Word Recall (DWR), Rey's Auditory Verbal Learning Task (AVLT), Controlled Oral Association Task (COWAT), Digit-symbol Substitution (DSS), Paced auditory serial attention task (PASAT), Wisconsin Card-sort task (WCST), Armed Forces Qualification task (AFQT), Rey-Osterrich Complex figure (ROCF), Judgement of Line Orientation (JLO), Mill Hill Vocabulary test (MHV). Zygosity: Heterozygous (He), Homozygous (Ho).

Longitudinal measures (Greenwood et al., 2014) revealed no genotype difference across trials with relatively low WM demand. On trials incorporating a mismatch between encoded and target stimuli, and hence placing greater demand on WM resources, however, performance of ε4+ improved over 3 years, whilst performance of the ε4- group remained stable. The observed practice effects in ε4+ were interpreted by the authors to represent compensatory mechanisms during mid-adulthood, and as a result of the increased cognitive effort in this group, some ε4 benefits were still observed.

2.5 Discussion

This review highlights the inconsistencies reported for *APOE* ε4 effects on cognition in mid-adulthood. Synthesising the results through meta-analyses, the effect of carrying an ε4 allele was non-significant across the 7 cognitive domains examined (global cognition, memory, executive ability, verbal fluency, language, visuospatial processing, and processing speed). Closer inspection of individual studies, however, indicates ε4 effects may emerge under certain conditions, and when probed with measures designed to maximise sensitivity.

The results of the meta-analyses offer limited support for ε4+ showing cognitive differences in mid-adulthood; ε4+ show relatively sustained performance until the end of the 5th decade. This is not inconsistent with the antagonistic pleiotropy position whereby the ε4 allele has opposing effects on fitness across the lifespan (Han & Bondi, 2008), with mid-adulthood as a transition point between ε4 behavioural advantages in youth switching to disadvantages in older adulthood.

When considering individual studies in more detail, the age range of participants is a likely factor in the inconsistency between study outcomes. Critically, existing research lacks a precise and consistent definition of mid-adulthood, reflected in the diverse and often broad age ranges of volunteers participating in the research reviewed here (see Table 1). For example, mid-adulthood was defined as 24-69 years in one study (Flory et al., 2000) and 41-85 years in another (Greenwood et al., 2005a). To draw conclusions of genotype effects at any precise window of the lifespan is difficult with such large age inclusion criteria, and the disparity in age groups may relate to the inconsistency of results presented. In cases where samples were stratified by age, Age x APOE interactions were reported, indicating emergence of the detrimental effects of *APOE* ε4 in the latter half of the 5th decade (Jochemsen et al., 2012; Marioni et al., 2016; Shin et al., 2014). This highlights the importance of controlling for age.

Age was not included as a moderator in the current meta-analyses due to the small number of studies in each domain, but this is certainly an important avenue for future research.

A key question for this review was whether process-specific cognitive measures show increased sensitivity to *APOE* genotype effects in mid-adulthood. Although the results of the meta-analyses failed to report a robust effect of ε4 status on memory, looking across studies there is a relatively consistent pattern of emerging detriments in ε4+ performance (11/20 studies). Detrimental effects of ε4 status on memory were also supported by longitudinal studies, suggesting this genotype group shows an accelerated trajectory of memory decline (Caselli et al., 2009; Greenwood et al., 2005; Greenwood et al., 2014; Kozauer et al., 2008). The sensitivity of memory to the effects of *APOE* ε4 from mid-adulthood is further supported by imageing evidence of genotype differences in MTL regions, implicating this region as a neural basis for behavioural changes (Goveas et al., 2013; Li et al., 2014). Memory is over-represented in studies probing the effects of *APOE,* and with more careful consideration of other cognitive domains, effects may emerge.

It is important to consider that many of the study outcomes included in the meta-analyses were based on neuropsychological assessment performance. It may be that the preclinical effects of *APOE* ε4 are too subtle for detection with neuropsychological measures, more commonly used for clinical assessment. In support of this, studies using computerized paradigms designed to target specific cognitive processes, report *APOE* ε4 differences in mid-adulthood within the domains of EF, attention and WM (Evans et al., 2013, 2014; Greenwood et al.,, 2000; 2005; 2014; Velichkovsky et al., 2015). These domains have also been linked to cognitive advantages in early adulthood (Marchant et al., 2010b; Rusted et al., 2013; Taylor et al., 2016), and so may show early sensitivity to genotype effects. Future research should focus on specific cognitive processes in order to establish the pattern of age-related change more clearly. Identifying replicable cognitive markers of those at heightened risk of poor cognitive ageing would make a substantial contribution to the development of early intervention strategies, independently and in association with the study of biomarkers and additional risk factors for dementia.

An additional methodological issue is the role of individual differences in moderating the effects of *APOE*. Several studies attempt to control for differences in ethnicity, education, socio-economic status (SES), and health factors; however, these factors are not uniformly included. Investigation of how these factors interact with *APOE* ε4 to alter the initial stages of ageing is limited to date. Although methodological shortcomings contribute to the inconsistency of findings, it is important to recognise that mid-age itself will play an important role. Mid-age

brings with it other risk factors for poor cognitive ageing (e.g. hypertension, cholesterol and diabetes (Atzmon et al., 2002; Köhler et al., 2014; van Exel et al., 2002; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005), and interactions between vascular health, APOE and cognition are reported (de Frias, Schaie, & Willis, 2014; Peila et al., 2001; Puttonen, Elovainio, Kivimäki, Lehtimäki, & Keltikangas-Järvinen, 2003; Zade et al., 2010). Current behavioural research is neither considering the potential modifying effects of wider risk factors nor adequately controlling for them, though they undoubtedly contribute to the cognitive ageing trajectory (Herrup, 2010). One account for the role of *APOE* ε4 in cognitive ageing is that this allele represents a genetic susceptibility, increasing vulnerability to both detrimental and protective factors in cognitive ageing (Wirth, Villeneuve, La Joie, Marks, & Jagust, 2014). Mid-adulthood represents a period of the lifespan where ε4+ are particularly susceptible to cognitive insults and benefits, and this underlines the need to consider the cognitive profile of ε4+ in relation to other potential modulators for cognitive health when establishing the preclinical effects of this gene.

2.6 Conclusions

It remains difficult to untangle the effects of *APOE* ε4 on cognition in mid-adulthood; methodological issues including imprecise criteria for age of volunteers and differential sensitivity of the measures used make it hard to form concrete conclusions. Results reviewed here, however, suggest ε4+ show relatively sustained performance in mid-adulthood, with subtle differences apparent in memory and executive abilities. Future research should focus on administering cognitive paradigms specifically chosen for their ability to sensitively measure the more nuanced processes of a particular domain, rather than relying on assessment measures more traditional of clinical settings. Since mid-age is a time when the trajectory of cognitive ageing will be influenced by multiple factors, these must also be incorporated into any lifespan model of the effects of this gene. Through the consideration of these factors in future study design; reliable cognitive markers of those showing accelerated cognitive ageing may be developed in mid-adulthood.

3. Article 2

Putting attention in the spotlight: The influence of *APOE* genotype on visual search in mid adulthood

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3.1 Abstract

The Apolipoprotein E ε4 allele is associated with greater cognitive decline with age, yet effects of this gene are also observed earlier in the lifespan. This research explores genotype differences (ε2, ε3, ε4) in the allocation of visuospatial attention in mid-adulthood. Sixty-six volunteers, aged 45-55 years, completed two paradigms probing the active selection of information at the focus of attention (a dynamic scaling task) and perceptual capacity differences. Two methods of statistical comparison (parametric statistics, Bayesian inference) found no significant difference between ε4 carriers and the homozygous ε3 group on either the dynamic scaling or perceptual load task. E2 carriers, however, demonstrated less efficient visual search performance on the dynamic scaling task. The lack of an ε4 difference in visuospatial attention, despite previous suggestion in the literature of genotype effects, indicates that select attentional processes are intact in ε4 carriers in mid-adulthood. The association of ε2 genotype with slower visual search performance complicates the premised protective effects of this allele in cognitive ageing.

Keywords: *APOE,* Cognitive Ageing, Alzheimer's disease, Attention, Visuospatial, Mid-adulthood

3.2 Introduction

The Apolipoprotein E *(APOE)*[2] gene is associated with individual differences in cognitive ageing. The three allelic variants (ε2, ε3, and ε4) differ in prevalence, estimated at 12%, 60% and 23% of Caucasian populations respectively (Raber, Huang, & Ashford, 2004). While homozygous ε3 carriers are considered the population norm, possession of an ε4 allele increases risk of Alzheimer's disease (AD) (Corder et al., 1993; Farrer et al., 1997). In addition, negative effects of carrying an ε4 allele are reported in a number of domains in healthy ageing (65 years and older), including global cognition, episodic memory, attention, and executive function (Berteau-Pavy, Park, & Raber, 2007; Espeseth et al., 2006; Marioni et al., 2015; Packard et al., 2007; Reinvang, Winjevoll, Rootwelt, & Espeseth, 2010; Staehelin, Perrig-Chiello, Mitrache, Miserez, & Perrig, 1999; for reviews see: Small, Rosnick, Fratiglioni, & Bäckman, 2004, Wisdom, Callahan, & Hawkins, 2011). Of interest, the ε2 variant is suggested to offer some protection against pathological ageing (Farrer et al., 1997; Lippa et al., 1997; Wilson, Bienias, Barry-Kravis, Evans & Bennett, 2002), but fewer studies have considered the effects of this allele in healthy cognitive ageing, with reported effects limited to tasks engageing memory (Helkala et al., 1996; McFall et al., 2015; Wilson et al., 2002).

Carriers of the ε4 allele demonstrate subtle cognitive differences earlier in the lifespan, but at present genotype differences observed prior to 65 years of age lack consistency (for reviews see: Ihle, Bunce, & Kliegel, 2012; Lancaster, Tabet, & Rusted, 2017; Rusted & Carare, 2015; Salvato, 2015). A likely factor in this inconsistency is the cognitive process under study, with the strength of genotype effects premised to vary by cognitive domain. To date, many studies have explored the association between *APOE* and episodic memory, in line with the prevalence of memory loss in dementia. A meta-analysis, however, found attention differences to be a more reliable marker of preclinical dementia than measures of delayed recall (Twamley, Ropacki, & Bondi, 2006). Hence, we predict attention may be a more sensitive marker than episodic memory of cognitive decline from mid-adulthood, facilitating the early identification of those shifting to a disadvantageous trajectory of cognitive ageing.

Here we explore *APOE* genotype differences in visual search, defined as the efficient deployment of selective attention to a relevant target within the visual scene (Awh et al., 2006). Selective attention is often analogised to a 'spotlight', conceptualised as a gradient of

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[2] **Abbreviations:** Analysis of variance (ANOVA), Apolipoprotein E (*APOE*), Alzheimer's Diseases (AD), Bayes factor (*B*), Blood pressure (BP), Body mass index (BMI), Independent variables (IV), Irrelevant distractor (ID), National Adult Reading Test (NART), No distractor (ND), Response time (RT), Simple response time (SRT), Standard deviation (SD).

heightened processing surrounding a central fixation; with individuals able to shift this spotlight across the visual scene (Posner, 1980). Greenwood & Parasuraman (2004) argue selective attention is characterised by an additional ability to scale the breadth of this attentional 'spotlight' on the basis of top-down information. Selective attention and working memory are sometimes viewed as overlapping constructs, with working memory acting as an interface for the active maintenance and manipulation of information at the forefront of attention (Awh et al., 2006; Chun, 2011b; Cowan, 1999; Gazzaley & Nobre, 2012). Hence, early genotype differences should be considered in the context of the expected pattern of age-related decline in both of these processes.

The dynamic scaling paradigm (Greenwood & Parasuraman, 1999) probes individual differences in the ability to adjust the breadth of attentional 'spotlight' during visual search. Participants' attention is guided to a region of the visual scene by a spatial cue presented before the search array. This cue facilitates visual search by indicating where the target stimulus will appear, if present, hence promoting greater perceptual processing at this location (Hawkins, Goyal, & Sergio, 2015). The size of the cue varies across trials, with smaller cues (encompassing fewer stimuli from the visual array) providing more localised target information. Decreasing cue size is associated with shorter search response times (RTs), indexing the benefit of dynamically restricting attentional focus on the basis of this top-down information. The greatest benefit of spatial cueing is observed on conjunction search trials, characterised by a target letter being distinct in a combination of features, as opposed to feature or 'pop-out' trials where the target is identifiable by one feature (i.e. colour) (Parasuraman, Greenwood, & Alexander, 2000).

Performance on the dynamic scaling paradigm shows sensitivity to both age-related change, and pathological change associated with AD (Parasuraman et al., 2000). In adults aged 65-74 years, more localised spatial cues clearly benefit the efficiency of visual search, however, this effect is reduced in a sample of healthy older adults, aged 75-85 years, and is present only following the most localised spatial cue for a group with AD (Parasuraman et al., 2000). Hence it is interpreted that the spatial flexibility of attentional focus is sensitive to age-related decline.

The dynamic scaling task has also been used to explore *APOE* genotype effects in late-mid adulthood. In comparison to both a homozygous ε3 group and an ε2 group, ε4 carriers aged 50 years and older demonstrated reduced benefit of smaller, more localised spatial cues (Greenwood, Sunderland, Friz & Parasuraman, 2000). Additionally, in a population of healthy adults (mean age 60 years), homozygous ε4 carriers showed significant declines in the use of spatial cueing across three years (Greenwood et al., 2005). This pattern was not seen in

heterozygous ε4 carriers, or non-carriers. These results suggest that ε4 carriers demonstrate a profile of accelerated ageing, with comparable reductions in the spatial flexibility of attentional focus seen in this group and adults aged 75 years and older. Therefore, reduced visuospatial attentional scaling may be a sensitive marker for those in the initial stages of cognitive decline.

APOE genotype differences have also been reported using variants of the Posner spatial cueing task (Posner, 1980). While visual search paradigms probe the selection of information within attentional focus, this task provides an index of both the efficiency of attentional shifts across the visual field and the ability to process information at the periphery of the attentional 'spotlight'. On trials of the Posner spatial cueing task, a directional spatial cue is presented prior to target onset, which guides attention to one half of the visual scene. The majority of cues are valid, leading to more efficient perceptual processing of the visual target. Some trials however, contain invalid cues; these trials are associated with a cost to the speed of target identification as following target onset in the periphery, attentional focus must be disengaged from the incorrect location and shifted across the visual scene (Pesce & Bösel, 2001; Posner & Petersen, 1989).

In agreement with ε4 carriers demonstrating a profile of accelerated ageing in visuospatial attention, ε4 carriers aged 41-85 years, and 50 years and older respectively, showed greater cost of invalid cueing to target item location (Greenwood et al., 2000; Greenwood et al., 2005). This was interpreted by the authors as representing deficits in the reorientation of attentional focus across the visual scene, similar to the behavioural profile shown by those in the early stages of AD on this task (Parasuraman, Greenwood, Haxby & Grady, 1992). In a group of middle-aged adults, aged 43-58 years, however, no genotype differences in attentional shifting were observed (Evans et al., 2014), questioning at what point in the lifespan ε4 detriments in visuospatial attention emerge. Indeed, in a sample of young adults, aged 18-30 years, ε4 carriers showed reduced cost of invalid cueing compared to homozygous ε3 carriers, suggesting this group are less disadvantaged by directing their attention to an incorrect region of the visual scene (Rusted et al., 2013). This may represent ε4 carriers approaching the task with a larger 'spotlight' of perceptual attention, allowing for greater processing of targets in the periphery. Of note, reports of differential *APOE* genotype effects across age-groups may reflect changing gene expression over the lifespan, rather than contradictions across research reports (Han & Bondi, 2008).

The overarching aim of this research is to establish if there are *APOE* genotype differences in the allocation of selective attention during visual search in mid-adulthood. The study administers two complementary tasks; the dynamic scaling paradigm (Greenwood & Parasuraman, 1999) (used previously), and a perceptual load task (Forster & Lavie, 2007).

Whilst the dynamic scaling task probes the active selection of information at the locus of attention, the perceptual load task explores another important determinant of selective attention: perceptual capacity. Together these tasks provide a broad investigation of differences in attentional 'spotlight' processes during visual search.

Over the past two decades a large body of evidence supporting Load Theory has highlighted that the involuntary allocation of attention to irrelevant information depends on the availability of perceptual capacity (Lavie, Hirst, de Fockert, & Viding, 2004; Lavie, 1995; for review see: Lavie, 2005; 2010). Load Theory accommodates both early and late selection accounts of attention, with selection at the stage of perception defined as early and post-perceptual selection as late (Benoni & Tsal, 2013; Lavie et al., 2004). Load theory suggests that information will be attentionally processed until our fixed perceptual capacity limit is reached, after which point task-irrelevant information will be passively filtered out (early selection). When the limit of perceptual capacity has not been reached, attentional control mechanisms are applied to bias processing of goal-relevant stimuli in cases where the distractor has reached attentional awareness (late selection). This theory has been supported by measures of distractor processing in healthy adults (Forster & Lavie, 2007, 2008). A consistent cost of peripheral distractor presence has been found in visual search trials of low perceptual load. This cost is eliminated in trials of high perceptual load, as there is no capacity left to process the distractor. The level of load in which the cost disappears is indicative of the perceptual attentional capacity.

Recruiting individuals from a narrow age-range (45-55 years) we sought to avoid any potential influence of preclinical pathological change. The study explores two possibilities: whether visuospatial attention is sensitive to accelerated ageing in ε4 carriers, indicated by either a reduction in perceptual capacity or in the spatial flexibility of 'spotlight' mechanisms; or alternatively, whether, as in early adulthood, ε4 carriers differentially approach visual search with a broader 'spotlight' of perceptual attention that persists into mid-adulthood.

In line with previous research using the same dynamic scaling paradigm (Greenwood et al., 2000; Greenwood et al., 2005), ε4 carriers are expected to show less efficient attentional scaling on this task, consistent with reduced spatial flexibility of attentional 'spotlight' mechanisms. Carriers of the ε3 and ε2 alleles are expected to show equal benefit of increasingly localised spatial cues on the dynamic scaling paradigm, indicative of an efficient use of attentional scaling. Detrimental effects of ε4 status may be absent, however, due to the younger group included here compared with previous research (Greenwood et al., 2000, 2005).

Like dynamic scaling, the perceptual load task has demonstrated sensitivity to cognitive ageing. In healthy older adults (aged 65-79 years), distractor compatibility effects were significantly reduced between low (set size: one stimulus) and mid (set size: four stimuli) levels of perceptual load. By contrast, distractor effects were still present on trials of mid perceptual load in young adults, although both age groups showed an elimination of distractor effects on trials with high perceptual load (set size: six stimuli) (Maylor & Lavie, 1998). The elimination of distractor processing at a lower level of perceptual load is consistent with an age-related reduction in perceptual capacity. If ε4 carriers were demonstrating a profile of accelerated ageing on this task, by mid-adulthood this group may show no distractor effects on mid-perceptual load trials (i.e. showing the reduced capacity found in older adults in Maylor & Lavie's (1998) study). If, however, the widened attentional 'spotlight' suggested by performance on the Posner spatial cueing task in younger adults (Rusted et al., 2013) persists into mid-adulthood, distractor cost may persist on trials of higher perceptual load in ε4 carriers. As the effect of ε2 status is less commonly studied, no predictions are made for this genotype group.

3.3. Method

3.3.1 Participants.

One hundred and sixty-five healthy adult volunteers (aged 45-55 years), recruited through advertisement at local universities, clubs and community centres, completed the initial screening phase of the study. Volunteers were required to be non-smokers and fluent in English. Furthermore, volunteers were screened for a history of vascular health problems, untreated high blood pressure (BP), psychoactive medication use, or recorded neurological/psychiatric condition within the past 5 years.

The initial screening allowed for prior collection of a genotype sample from each volunteer. Screening procedures followed Human Tissue Authority (HTA) procedures, and the full study followed a protocol approved by the research ethics committee of the school of Psychology and Life Sciences, University of Sussex. All procedures were in accordance with the Helsinki declaration. Volunteers first provided written informed consent, including acknowledgment that the results of the genotype analysis would not be made available to them, before DNA was collected by buccal swab. Genotyping followed triangulated anonymization procedures, with two anonymized codes used per sample. Samples were analysed to determine *APOE* gene variant by LGC Genomics (Hertfordshire, www.lgcgroup.com/genomics). A fluorescence-based competitive allele-specific polymerase chain reaction determined the combination of three

major *APOE* alleles (ε2, ε3, and ε4) based on two *APOE* single nucleotide polymorphisms (rs429358, rs7412).

Sixty-six volunteers completed the experimental phase of the research. Post-screening, invitation to participate was pseudo-random to ensure a suitable sample size in each genotype group, rather than selection being representative of the expected frequencies of each allele within the population. The distribution of genotypes within the sample was as follows: 16 ε2 carriers (1 ε2/ε2; 15 ε2/ε3), 26 homozygote ε3 carriers, and 25 ε4 carriers (17 ε3/ε4; 7 ε4/ε4). Throughout the study both the participant and the experimenter were kept blind to genotype information. Characteristics of the final sample are shown in Table 3.1.

3.3.2 Materials.

3.3.2.1 *Demographics and baseline cognitive measures.*

Medical history, medication use and general state of health were assessed using a shortened version of the Nuffield Medical History Questionnaire. Additionally, baseline measures of IQ (National Adult Reading Test (NART)(Nelson & Willison, 1991)), working memory (backwards digit-span), and simple response time (SRT) were obtained. To index response time (RT), participants were required to make a keyboard response as soon as possible following presentation of a stimulus on screen. Response time was averaged over 48 trials, excluding RTs more than 3 standard deviation (SD) away from the mean.

3.3.2.2 *The dynamic scaling task.*

The dynamic scaling task (Greenwood & Parasuraman, 2004) required participants to search for a pink T within a 15 letter array (5 across x 3 down*),* and make a speeded response as to whether the target letter is present (‘2’ keyboard response) or absent (‘6’ keyboard response). Before each array is presented, a black box cues where the target may or may not appear.

In total, the task consisted of 240 trials split randomly into 3 blocks. In each trial, a central fixation cross was presented for 1000ms, followed by a cue for 500ms prior to the onset of the letter array. The letter array and the cue were then presented simultaneously until a response was detected. The array could appear on either the right (120 trials) or left (120 trials) of the fixation cross, and consisted of the characters T, G, and N presented in either pink, blue or

green. Letter-colour combinations of non-target items in the array were generated randomly, following constraints of the search type (conjunction, feature) for that trial.

The task had 3 IVs integrated into its design: search type, cue size and cue validity. Search trials were split into feature search (120 trials), where the target letter in the only pink letter in the display, and conjunction search (120 trials), where the participant searched for the pink 'T' among an array of letters of the same type ('T') and colour (pink). Physical cue size varied across trials, encompassing either 1, 3, 9, or 15 letters from the search array, with 60 trials at each size of cue. Cues were classed as valid (200 trials) or invalid (40 trials) depending on whether the target letter was enclosed within. An example trial of the dynamic scaling task is presented in Figure 3.1.

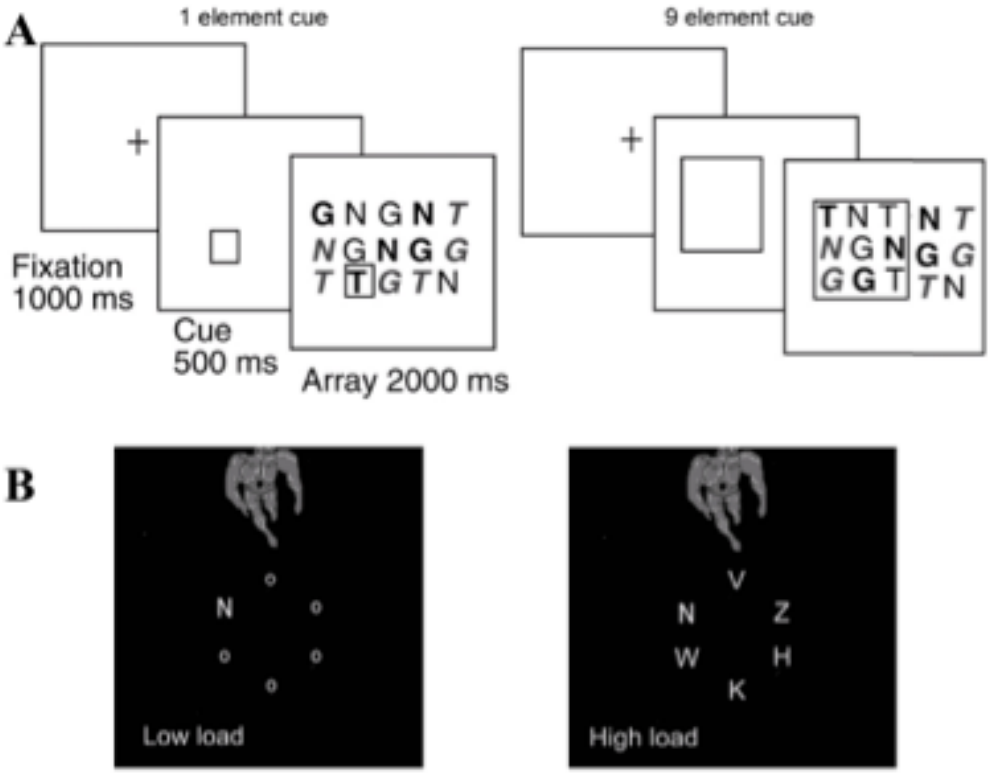

Figure 3.1. A representation of experimental tasks: A) The dynamic scaling task showing two conjunction search trials with spatial cues encompassing 1 and 9 search array stimuli respectively, B) The perceptual load task with example low and high load distractor trials. Note- the distractor is an example rather than the actual cartoon stimuli used in task.

3.3.2.3 *The perceptual load task.*

The perceptual load task (Forster & Lavie, 2007; 2008) is a visual search paradigm including two independent variables (IVs): perceptual load (low, high and medium) and distractor presence (blank, capture).

Participants were required to indicate the presence of either an 'X' or an 'N' target letter in each trial, by making a '0' key press response for X and '2' key press response for N. Each trial initiated with the presentation of a central fixation cross for 500ms, followed by the presentation of a stimuli display for 200ms. Each stimuli display consisted of 6 white letters, one of which was always a target letter, arranged circularly on a black background. Identity of target letter and position of target within circle was counterbalanced across trials. Participants were requested to respond as quickly and accurately as possible. An auditory tone was used to provide feedback for incorrect responses or if no response was made within 2000ms.

Perceptual load was manipulated across trials. In trials of low perceptual load (set size 1), non-target letters in the stimulus display consisted of small 'O's. In trials of medium perceptual load (set size 4) there was 1 target letter, 3 non-target letters and 2 small 'O's in the stimulus display. In trials of high perceptual load (set size 6), in addition to the target, there were 5 non-target letters in the display. Non-target letters consisted of 'H', 'K', 'Z', 'M', 'W'; chosen to be similar to target letters in angular shape. 720 trials were presented in 12 blocks of 60, with each block containing trials of a single level of perceptual load. Each participant completed 4 repetitions of a counterbalanced perceptual load sequence. In addition, participants completed a practice block for each level of perceptual load, with feedback on performance accuracy provided. An accuracy level of 65% was required for participants to proceed to experimental trials to ensure each participant was able to perform the task above chance level (50%).

Trials were classified according to whether a task-irrelevant distractor image (Spongebob, Spiderman, Superman, "Pokemon", Donald duck and Mickey) was presented in the periphery of the screen. 10% of trials featured a distractor image and were hence considered 'capture' trials, whilst 90% of trials had no distractor, and so were considered 'blank'. An example of distractor trial can be seen in Figure 1. Participants were instructed to ignore the distractors, as these would impede their performance.

3.3.3 Procedure

Volunteers selected from the screening phase took part in a single study session. First, demographic and health measures including age, family history of dementia, height, weight, and BP were collected. A measure of systolic and diastolic blood pressure was collected whilst seated, using an automatic arm-cuff machine on the right arm. Participants then completed a selection of experimental tasks and questionnaires in a fixed order.

3.3.4 Analysis

Differences in demographics and baseline cognitive performance were analysed between genotype groups (ε2, ε3 and ε4) using a series of one-way analysis of variances (ANOVAs) for continuous variables, and chi-squared tests for categorical measures (gender, family history).

For each experimental task data was first analysed using parametric statistics, then using Bayesian statistics. All three genotype groups were compared using parametric statistics; following this, if there was suggestion of a genotype difference, separate analyses were run comparing ε4 carriers and ε2 carriers individually to the ε3 group. Bayesian statistics independently compared ε2 and ε4 genotype groups to homozygote ε3 carriers.

Bayesian statistics were included to establish the strength of evidence for either the null (H0) or alternative hypothesis (H1). A Bayes factor (*B*) of > 3 indicates substantial evidence for H1, whereas a *B* of $< 1/3$ indicates substantial evidence for H0. A *B* in the range 1/3 – 3 indicates the data may be insensitive for distinguishing between the two hypothesis (Dienes, 2014). *Bs* were modelled from 3 distributions in the current analysis. Directional predictions were modelled from a half-normal distribution ($B_{H(0, x)}$), with x representing the prior estimate of effect size. Non-directional predictions were modelled from a normal distribution ($B_{N(0, x)}$), with x representing half the prior effect size. In addition, when all effects in a specified range were equally likely *Bs* were modelled as a uniform distribution ($B_{U(0, x)}$), with x representing the maximum expected effect.

3.3.4.1 The dynamic scaling task.

3.3.4.1.1 Overall task performance.

Accuracy and median RTs for each search type (feature, conjunction) and cue size (1, 3, 9, 15 letter stimuli) were analysed for valid trials. Across all volunteers, a repeated measures ANOVA (search type x cue size) was completed for search RTs. The slope of attentional scaling (an index of RT change with decreasing cue size) was used to probe this interaction

further using Bayesian inference, with a greater scaling slope predicted for conjunction trials compared to feature search trials. The prior effect size was based on the feature and conjunction scaling slopes reported in a late-mid age homozygous ε3 group (Greenwood et al., 2000).

3.3.4.1.2 Genotype effects.

To explore genotype differences in RT a mixed ANOVA with cue size (1, 3, 9, and 15 letter stimuli) as the within-subject factor and genotype (ε2, ε3, ε4) as the between-subject factor was conducted for both feature and conjunction search trials. Individual Bonferroni-adjusted *t*-tests were used to probe significant effects of genotype where present, comparing ε4 and ε2 carriers to the ε3 group. A *B* for the Genotype x Cue Size interaction was modelled from the current data for both feature and conjunction search trials (see Dienes (2014) for further explanation of using Bayesian statistics to explore interactions). The population interaction effect (effect of cue size in group 1- effect of cue size in group 2) was modelled as a uniform distribution for each search type, varying from 0 (i.e. when both groups show an equivalent effect of cue size) and the maximum effect of cue size reported for the two groups (i.e. when one group demonstrates an effect of cue size, and one group demonstrates no effect). In addition, following a significant Genotype x Cue Size interaction (indicated by parametric statistics), *B*s were computed for each post-hoc comparison. Prior effect sizes were based on previously reported genotype differences (Greenwood et al., 2000). It was predicted that ε4 and ε2 carriers would demonstrate greater search RTs at cue size 3 and 1. All other predictions were non-directional.

The scaling slope for conjunction search trials was compared between genotype groups using a one-way ANOVA. Again, individual Bonferroni adjusted *t*-tests were used to probe significant effects of genotype where present, comparing ε4 and ε2 carriers to the ε3 group. For the Bayesian analysis of scaling slope on conjunction search trials, no directional prediction was made for an ε2 difference, however, ε4 carriers were predicted to show a reduced slope compared to the ε3 group. Prior effect sizes were estimated from the genotype differences in slope reported in Greenwood et al., (2000).

A one-way ANOVA was used to test genotype differences in accuracy. There was no directional prediction for a genotype difference in accuracy, hence *B*s were modelled from a normal distribution. The prior effect size was based on the maximum difference in accuracy previously reported (Greenwood et al., 2000).

3.3.4.1 The perceptual load task.

RTs less than 100ms or more than 3000ms were removed prior to analysis. Mean RT for correct trials and accuracy were considered separately. Mixed 3 x 3 x 2 ANOVAs were performed on both RTs and accuracy, with genotype (ε2, ε3, ε4) as the between-subjects factor, and perceptual load (low, mid, high) and distractor (blank, capture) as the within-subjects factors. Interactions were probed using Bonferroni-adjusted *t*-tests.

3.3.4.1.2 Bayesian analysis

Bayesian analysis of the main effect of perceptual load followed the same approach for RTs and accuracy. For blank trials, a *B* for each pairwise comparison of perceptual load was modelled from a half normal distribution, based on the prediction that RTs would increase and accuracy decrease with increasing perceptual load. The neutral distractor condition in young adults[3] (set size 1, 4 and 6) was used for prior effect sizes (Maylor & Lavie, 1998).

The Load x Distractor interaction was analysed by calculating a *B* for the difference in distractor cost, defined as the difference between blank and capture trials, for all pairwise comparisons of perceptual load. For RTs, the prior effect size was based on the difference in irrelevant distractor cost between trials of low (set size 1) and high (set size 6) perceptual load (Experiment 2b: Forster & Lavie, 2008). In addition, the presence of RT distractor costs at each level of perceptual load was probed, modelled as a half normal distribution with a prior effect size based on the maximum distractor cost reported in Experiment 2b; Forster & Lavie (2008). Perceptual load differences in distractor cost for task accuracy were modelled from a full-normal distribution, as load was not predicted to modulate distractor effects.

Multiple *Bs* for the Load x Distractor x Genotype interaction were computed to assess the strength of evidence for distractor costs at each level of perceptual load in each genotype group. For both RTs and accuracy, prior effect sizes were again based on Experiment 2b, Forster & Lavie (2008).

[3] The effect of perceptual load in our dataset, both for RT and accuracy, more closely resembled the effect reported in young adults than the older group included in Maylor and Lavie (1998). Hence this group was used for the prior. Recalculating the *Bs* with prior effect sizes based on the older population did not change the results.

3.4 Results

3.4.1 Demographics & baseline cognitive measures.

No genotype difference was found across demographic measures (p>.05). Furthermore, no group differences were found in WM span, or SRT (p>.05). The demographic and baseline characteristics of each genotype group are shown in Table 3.1.

Table 3.1. *Demographics and performance on baseline cognitive measures*

	Genotype Group		
Measure	**ε2**	**ε3**	**ε4**
n	16	26	24
Age	50.44 (3.58)	49.04 (2.68)	49.17 (3.07)
Gender (% female)	75	73	63
Family History (%Yes)	25	35	54
Education	17.22 (3.24)	17.23 (3.13)	17.85 (4.32)
NART	119.06 (2.84)	118.56 (2.93)	116.87 (4.62)
BMI	24.02 (3.44)	26.24 (4.37)	25.15 (3.78)
Systolic BP	115.63 (7.55)	118.23 (8.47)	115.00 (8.76)
Diastolic BP	77.31 (9.99)	81.77 (10.63)	79.13 (7.77)
SRT (ms)	272.24 (44.15)	265.24 (32.39)	266.90 (27.84)
Digit-span	4.31 (1.30)	4.19 (1.50)	4.00 (1.65)

Notes: Mean (SD). Body mass index (BMI)

3.4.2 Dynamic scaling task.

3.4.2.1 *Overall task performance*.

Accuracy on task was consistently high, with scores ranging from 84% to 100% (Mean=97%) correct across valid trials. Accuracy of one volunteer was below chance (43%) on this task, and so their data was removed prior to analysis.

Across participants, median RTs were significantly longer for conjunction search trials than feature search trials, $F(1,63)=458.19$, $p<.001$, $\eta^2_\rho=.879$. A significant effect of cue size, F (1.99, 125.65)=202.53, $p<.001$, $\eta^2_\rho=.763$, was also found, with RTs decreasing as a function of smaller cue. There was a Search type x Cue size interaction, $F(1.99, 125.65)=115.73$, $p<.001$, $\eta^2_\rho=.648$, shown in Figure 3.2. This was driven by a greater slope of RT decrease with reducing cue size for conjunction search trials (b=15.44) than feature search trials (b=3.98), $t(64)=-14.83$, $p<.001$, $B_H(0, 7.5) = 8.09374E+46$.

3.4.2.2 *Genotype differences.*

No significant genotype difference was found for accuracy across valid trials, $F(2, 61)=.979$, $p=.381$. Both the ε2 to ε3 comparison ($B_N(0, 2.35)=.97$) and the ε4 to ε3 comparison ($B_N(0, 2.35)=.95$) are insensitive for determining a genotype difference in accuracy.

For feature search trials, there was a significant main effect of cue size on RT, $F(2.26, 137.82)=50.81$, $p<.001$, $\eta^2_\varrho=.454$, but the main effect of genotype ($p=.243$) and the interaction between genotype and cue size ($p=.290$) were both non-significant. Bayesian analysis of the Genotype (ε2, ε3) x Cue Size (1, 3, 9, 15 letters) interaction provides anecdotal support for H0: $F(3, 117)=.56$, $p=.646$, $\eta^2_\varrho=.014$, $B_U(0, 56.80)=.57$. Data was insensitive for determining a Genotype (ε4, ε3) x Cue size (1, 3, 9, 15 letters) interaction, $F(3, 141)1.98$, $p=.120$, $\eta^2_\varrho=.040$, $B_U(0, 74.13)=.1.58$.

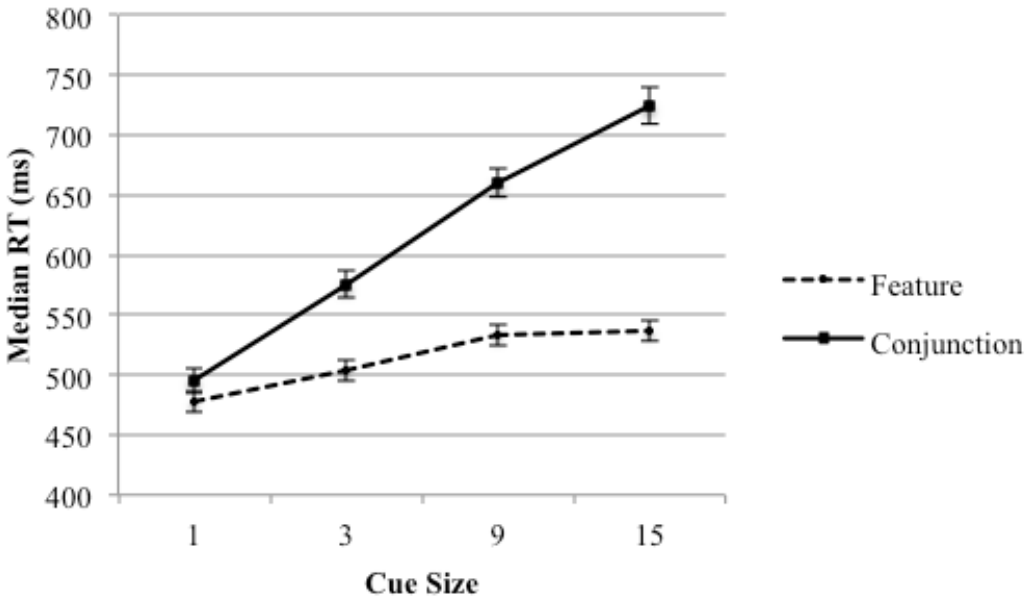

Figure 3.2. Median response time for each cue size presented by search type.

Search RTs and the slope of attentional scaling on conjunction search trials are shown in Table 3.2. There was a significant main effect of both cue size, $F(2.04 , 124.50)=213.26$, $p<.001$, $\eta^2_\varrho=.778$, and genotype, $F(2, 61)=3.69$, $p=.031$, $\eta^2_\varrho=.108$, on conjunction search RTs. The effect of genotype was driven by ε2 carriers responding significantly slower than the ε3 group ($p=.042$). In addition, there was a significant Genotype x Cue Size interaction, $F(4.08, 124.50)=2.53$, $p=.043$, $\eta^2_\varrho=.077$. The comparison of ε2 and ε3 genotype groups provide sensitive support for a Genotype x Cue Size interaction, $F(3, 117)=4.53$, $p=.005$, $\eta^2_\varrho=.104$,

$B_U(0, 279.67)=4.33$. The comparison of ε4 and ε3 genotype groups provide sensitive support for no Genotype x Cue Size interaction, $F(3, 141)=.239$, $p=.869$, $\eta^2_\varrho=.005$, $B_U(0, 221.70)=.26$.

Results of the post-hoc analysis of genotype differences at each cue size on conjunction search trials are shown in Table 3.3 (Bonferroni corrected α=.006). E2 carriers demonstrated significantly longer RTs than the ε3 group at cue size 15 ($p=.004$, $B_N(0, 30)=4.32$). There was also support for this group showing significantly longer RTs at cue size 1 ($p=.068$, $B_H(0, 60)=.3.47$). E4 carriers did not significantly differ in search RTs from the ε3 group at any cue size ($p>.006$) however; data appears insensitive for supporting either the null or alternative hypothesis.

To further probe the interaction between genotype group and cue size on conjunction trials, the slope of change in RT with reducing cue size was considered. At trend level there was an effect of genotype, $F(2, 63)=2.66$, $p=0.78$, driven by the difference between the ε3 and ε2 groups ($p=.035$; $B_N(0, .1)=1$). The genotype difference between ε3 and ε4 carriers was non-significant, ($p=.525$; $B_N(0, 1.75)=1.07$). Genotype differences in slope are also shown in Figure 3.3

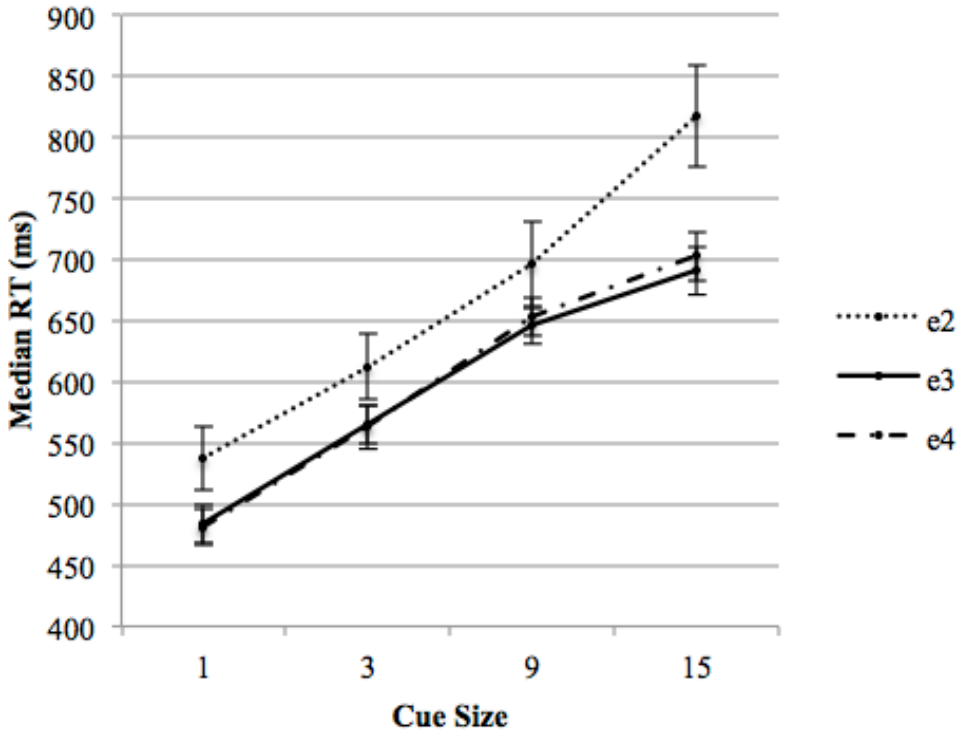

Figure 3.3 Benefit of reducing cue size on RT for conjunction search trials by genotype group.

Table 3.2. *For each genotype group, RT (ms)(SD) to detect target presence and the slope of attentional scaling is shown.*

	Cue size				Slope
Genotype	**1**	**3**	**9**	**15**	***B***
ε2	537 (73)	612 (74)	696 (80)	817 (85)	18.80
ε3	484 (73)	565 (75)	646 (80)	691 (85)	13.83
ε4	481 (73)	563 (75)	654 (80)	703 (85)	14.93

Note: Cue size represents the number of letter stimuli encompassed within each spatial cue

Table 3.3. *p values and Bs for the post hoc comparisons of the Genotype x Cue Size interaction for conjunction search trials*

Genotype group comparison		**Cue Size**			
		1	**3**	**9**	**15**
ε2 and ε3	*p*	.068	.114	.156	.004
	B	$B_H(0, 60)$=.3.47	$B_H(0, 65)$=2.27	$B_N(0, 22.5)$=1.14	$B_N(0, 30)$=4.32
ε3 and ε4	*p*	.899	.932	.748	.687
	B	$B_H(0, 45)$=.39	$B_H(0, 35)$=.53	$B_N(0, 2)$=1	$B_N(0, 2.5)$=1

Note: Bonferonni corrected alpha=.006. *B*'s <1/3 or >3 or sensitive.

3.4.3 The perceptual load task.

Performance on this task is shown according to genotype group in Table 3.4.

3.4.3.1 *RT*.

Assumptions of sphericity were violated so a Greenhouse-Geisser correction was applied for the main effect of perceptual load. With increasing perceptual load, RTs significantly increased, $F(1.27, 78.62)=352.16$, $p<.001$, $\eta^2_\varrho=.850$. The Bayes analysis supports a sensitive increase in RT with increasing perceptual load (low to mid : $B_H(0, 118)$= 9.80017E+90; low to high: $B_H(0, 230)$= 1.54409E+92; mid-high: $B_H(0, 52)$= 2.93020E+22).

The main effect of distractor was significant, $F(1, 62)=17.81$, $p<.001$, $\eta^2_\varrho=.223$, with RTs longer for capture trials than blank trials. Sphericity was again violated for the interaction between perceptual load and distractor presence, so degrees of freedom were corrected using a Huynh-Feldt correction (ε=.92). A significant interaction between perceptual load and distractor presence was found, $F(1.84, 113.98)=8.55$, $\eta^2_\varrho=.223$. This interaction is shown in Figure 3.4., and was driven by there only being a main effect of distractor presence at low-load, Bonferroni corrected $\alpha = .017$, $t(64)=-8.87$, $p<.001$, $B_H(0, 61)$= 1.03191E+16. At mid and high perceptual load the effect of the distractor was eliminated ($p>.017$; mid: $B_H(0, 61)$= .29; high: $B_H(0, 61)$=

.16). Distractor cost was reduced at both mid (B_H (0, 50)= 573.01), and high levels of perceptual load (B_H (0, 50)= 292.22) compared to low perceptual load. There was no difference between the distractor cost at mid and high perceptual load (B_H (0, 50)= .23).

The main effect of genotype was non-significant (p=.262) as were all interactions between genotype, perceptual load and distractor (p>.05). All 3 genotype groups show a sensitive distractor cost on trials of low perceptual load (ε2: B_H (0, 61)= 86169, ε3: B_H (0, 61)= 356206, ε4: B_H (0, 61)= 43112), however, there suggestion of no distractor cost at mid (ε2: B_H (0, 61)= .74, ε3: B_H (0, 61)= .50, ε4: B_H (0, 61)=.14) and high levels (ε2: B_H (0, 61)=.97, ε3: B_H (0, 61)=.39, ε4: B_H (0, 61)=.17) of perceptual load, with sensitive nulls reported in the ε4 group.

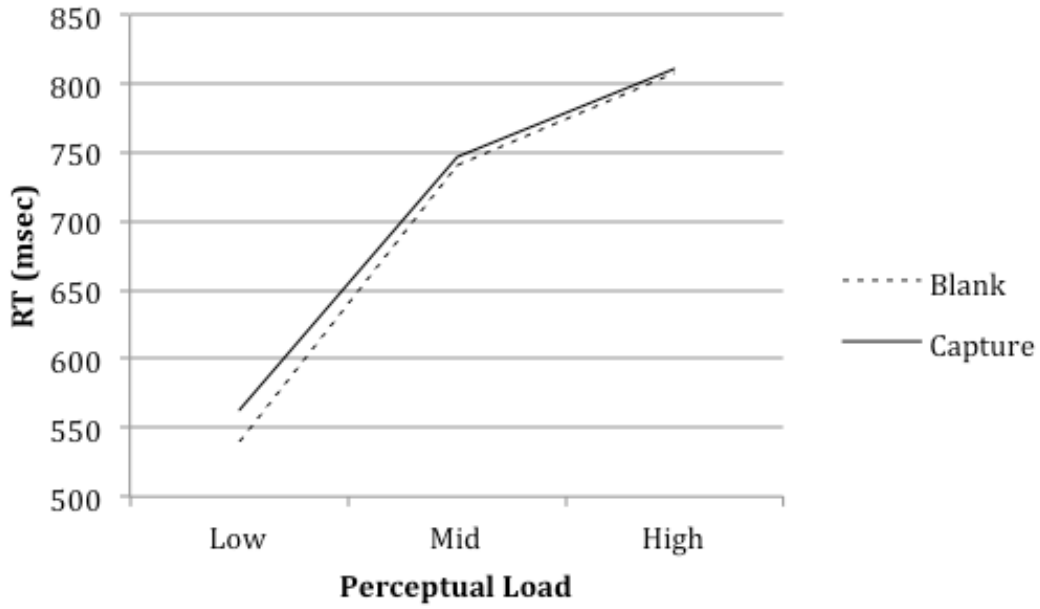

Figure 3.4. The interaction between perceptual load and distractor presence on RTs.

3.4.3.1 *Accuracy*.

Perceptual load again violated assumptions of sphericity, so a Greenhouse-Geisser correction was applied. Accuracy significantly decreased as perceptual load increased, F(1.46, 91.08)=71.62, p<.001, η^2_g=.536. The Bayes analysis supports a sensitive decrease in accuracy with increasing perceptual load (low to mid: B_H (0, .05)=157.06; low to high: B_H (0, .01)=1.86562E+22; mid-high: B_H (0, .07)=1.60033E+21).

The main effects of distractor and genotype on task accuracy were both non-significant, as were all interaction terms (p>.05). Bayesian analysis indicated data was insensitive for detecting a

change in distractor cost on accuracy with increasing perceptual load ($B_N(0, .03) < 1/3$ and > 3). The perceptual load x distractor x genotype interaction approached significance, $F(4, 124)=2.11$, $p=.084$, $\eta^2_Q=.064$, but further examination using pairwise comparisons revealed no significant differences ($p>.05$). Data was insensitive for detecting a distractor cost in task accuracy at each level of load when separately considered between genotype groups ($B_N(0, .03) < 1/3$ and > 3)

Table 3.4. Mean RT (ms) and accuracy (proportion of trials correct) on the perceptual load task, presented by genotype group, with SD shown in brackets.

Genotype	Load		ND	ID	Cost
ε2	Low	RT	552 (48)	579 (63)	27 (21)
		Accuracy	.93 (.04)	.94 (.05)	
	Mid	RT	770 (69)	780 (69)	10 (40)
		Accuracy	.89 (.07)	.89 (.07)	
	High	RT	827 (81)	829 (81)	2 (48)
		Accuracy	.82 (.09)	.79 (.12)	
ε3	Low	RT	524 (42)	542 (42)	19 (18)
		Accuracy	.93 (.05)	.92 (.07)	
	Mid	RT	716 (100)	724 (101)	8 (27)
		Accuracy	.90 (.07)	.91 (.07)	
	High	RT	780 (132)	788 (134)	8 (34)
		Accuracy	.83 (.11)	.82 (.11)	
ε4	Low	RT	549 (85)	573 (90)	24 (23)
		Accuracy	.94 (.04)	.94 (.05)	
	Mid	RT	750 (121)	749 (126)	-1 (38)
		Accuracy	.90 (.07)	.88 (.12)	
	High	RT	825 (156)	826 (160)	1 (28)
		Accuracy	.83 (.10)	.82 (.13)	

Notes: ND= no distractor, ID= irrelevant distractor, Cost = ID-ND

3.5. Discussion

This study sought to explore how *APOE* genotype influences performance on visuospatial search paradigms in mid-adulthood. Both of the experimental tasks administered here sensitively demonstrated the variation in cognitive performance appropriate to within-task manipulations, supporting the theoretical underpinnings of these paradigms. Of interest, distractor effects were eliminated at both mid and high levels of perceptual load, supporting a reduction in perceptual capacity in a mid-age cohort, an age-range that has not previously been tested (Maylor & Lavie, 1998).

The two tasks included here were selected to investigate if ε4 carriers show attentional 'spotlight' differences during visual search in mid-adulthood. E4 carriers, however, demonstrated comparable performance to the homozygous ε3 group on both the dynamic scaling task and the perceptual load task. This provides no support for the risk factor being associated with either a less responsive 'spotlight' mechanism in mid-adulthood, or a widened perceptual window of attention. Carriers of the less commonly studied ε2 allele, however, did show performance disadvantages. This group were slower overall to detect the target on conjunction search trials in the dynamic scaling task, with sensitive differences confirmed on trials including both the maximum and minimum size of spatial cue. These results are not consistent with the simple view that ε2 status is protective against cognitive ageing, whilst ε4 status is disadvantageous.

In contrast to Greenwood and colleagues' (2000, 2005) findings, our mid-age ε4 carriers showed no difference in the ability to modify attentional 'spotlight' in light of top-down information. This does not support a trajectory of accelerated ageing being present by mid-adulthood. Failure to replicate this earlier finding may in part be accounted for by differences in sample selection, highlighting a methodological concern in the existing mid-age *APOE* literature (Lancaster et al., 2017). The age-range of participants' included in Greenwood et al.'s (2000) study was wider, and as a consequence of including older individuals, later-life ε4 disadvantages may have impacted overall group differences. The narrow age range included here (aged 45-55 years) importantly, precludes the potential confound of preclinical pathological change. Furthermore, while Greenwood et al. (2000) selected individuals on the basis of an immediate family history of AD, family history of AD was not a selection criterion of the current study meaning the sample may be more representative of a healthy ageing population. In addition, the tightly controlled age-range included here acknowledges the expectation that expression of *APOE* genotype effects is not constant across the lifespan.

Performance on the perceptual load task was equivalent between *APOE* genotype groups, supporting intact perceptual attention in mid-age ε4 carriers. Distractor effects were absent in all three genotype groups on trials of both mid and high perceptual load, suggesting reductions in perceptual capacity, comparable to those seen in an older group (aged 65-79 years) (Maylor & Lavie, 1998), occur by mid-adulthood regardless of genotype. Future research could apply the present perceptual load paradigm to test whether young ε4 carriers might show this reduction at an earlier point. Previous research reported ε4 genotype differences on the Posner spatial cueing task in both young (Rusted et al., 2013) and older adults (Greenwood et al., 2000; Greenwood et al., 2005), perhaps indicating a difference in the breadth of attentional 'spotlight'. No genotype differences on this task, however, were found in a group of similar age (43-58 years) to the

current participant sample (Evans et al., 2014). This may suggest that in mid-adulthood at least, there is little effect of *APOE* genotype on breadth of perceptual attention. One explanation for why no genotype differences in perceptual threshold were seen could be that task sensitivity was poor - load increased in jumps of one item, four items, and six items; a more gradual increase in load may have improved sensitivity to any subtle genotype differences.

Overall, the present results suggest that relative to the ε3 population 'norm', ε4 carriers show equivalent attentional scaling and perceptual capacity in mid-adulthood, countering the argument that the ε4 genotype represents a detrimental cognitive phenotype right across the lifespan. There is some support in the literature for an age x *APOE* interaction, with several studies identifying the end of the 5th decade as a point when detrimental performance effects of *APOE* ε4 emerge (Caselli et al., 2009; Jochemsen, Muller, van der Graaf, & Geerlings, 2012; Marioni et al., 2015; Shin et al., 2014). It would seem behavioural performance is preserved in ε4 carriers up until 5th decade despite evidence for structural and functional changes prior to this (e.g Dowell et al. 2016; Trachtenberg et al., 2012a; 2012b). Given the reported attentional detriments in a late-mid age sample (Greenwood et al., 2000; 2005a; 2005b), research probing additional factors that may mediate the emergence of decline in this genotype, is important. In respect of the antagonistic pleiotropy position (Han & Bondi, 2008), if the effects of this gene are transitioning from advantages in young adulthood, to disadvantages in later life, the absence of genotype differences recorded here are consistent with a transitioning stage in which the allele is exerting neither a positive nor a negative effect of cognition. Stronger evidence of dissociative effects with longitudinal data across the age span is needed, however, to substantiate this model.

Contrary to expectations, the current study reported performance disadvantages in carriers of the premised 'protective' ε2 allele. Although cognitive effects of ε2 in mid-adulthood have not been well characterised to date, Greenwood and colleagues (2000; 2005) included an ε2 group, and found no performance differences on the dynamic scaling task. Again, our results may differ due to discrepancy in population selection. Our results suggest that ε2 carriers are approaching the visual search paradigms differently, showing less efficient visual search strategies.

In line with the differential performance of ε2 carriers seen in this task, neural data has suggested both ε2 and ε4 carriers show corresponding differences in function BOLD response compared homozygous ε3 carriers (Trachtenberg et al., 2012a; 2012b). Despite equivalent performance on both an episodic memory and Stroop task, both ε2 and ε4 groups showed overlapping profiles of over-activation in a mid-age group (Trachtenberg et al., 2012a), and similar profiles in a resting-state connectivity analysis (Trachtenberg et al., 2012b). These

results, again, confuse the clear dichotomy between cognitive risk and variants of the *APOE* gene, and support the need for further profiling that directly compares all three variants across a wider age span.

There are limitations in the current study. The sample size of each genotype group, in particular the number of ε2 carriers, completing the behavioural paradigms was relatively small. However, Bayesian analysis was used to confirm the sensitivity of both ε4 equivalence and ε2 differences in cognitive performance. Further, although overall group performance on the perceptual load task replicated those suggested by perceptual load theory, standard deviations were large, and this may have reduced sensitivity of the task for detecting genotype differences.

3.6. Conclusions

The results suggest that in healthy mid-age individuals, carrying the ε4 variant of *APOE* is not associated with disadvantaged performance on dynamic scaling and perceptual load measures of visuospatial attention, despite the established detrimental effects of this gene in older adults. Attentional 'spotlight' differences did not emerge as a potential marker of cognitive decline in this 'at-risk' group. Carriers of the ε2 allele showed performance disadvantages on the measures tested here, stressing the need to consider all three variants of *APOE* individually when assessing its impact on cognition. The distinction between 'protective' ε2 and 'detrimental' ε4 status is not as clear-cut as supposed, and longitudinal studies of how both of these variants impact the trajectory of cognitive ageing is a vital next step.

4. Article 3

The *APOE* paradox: how do attentional control differences in mid-adulthood reflect risk of late-life cognitive decline.

Article 3 is published in Neurobiology of Ageing as:

Lancaster, C., Tabet, N., & Rusted, J. (2016). Neurobiology of Ageing The APOE paradox : do attentional control differences in mid-adulthood reflect risk of late-life cognitive decline. *Neurobiology of Ageing*, *48*, 114–121. http://doi.org/10.1016/j.neurobiolageing.2016.08.015

4.1. Abstract

Possession of an *APOE* ε4 allele is an established risk factor for Alzheimer's disease, while the less commonly studied ε2 variant is premised to offer some protection. This research explores the purported deleterious-protective dichotomy of *APOE* variants on attentional control in mid-adulthood. 66 volunteers, aged 45-55 years, completed three tasks that provided complementary measures of attentional control: prospective memory, sustained attention and inhibition. Performance was compared between ε2 carriers, ε4 carriers and ε3 homozygotes (the population norm). Carriers of the ε4 allele showed subtle disadvantages, compared to the ε3 group, in accuracy of Stroop task and prospective memory performance. Contrary to expectations, ε2 carriers showed performance disadvantages in sustained attention. The finding of detrimental effects in attentional control for both ε4 and ε2 complicates the current model that proposes opposing effects of these variants on later-life cognition. Future research is needed to understand how cognitive differences develop with increasing age, and the physiological mechanisms that underpin these changes.

Keywords: *APOE,* Cognitive Ageing*,* Alzheimer's disease, Attention, Executive Function, Mid-adulthood

4.2. Introduction

Cognitive ageing is differentially associated with the three variants (ε2, ε3, and ε4) of the Apolipoprotein E (*APOE*) gene, a single nucleotide polymorphism. The ε4 allele, present in approximately 25% of the population, is associated with increased risk of Alzheimer's disease (AD) (Corder et al., 1993). While the ε3 allele is positioned as the population norm, possession of an ε2 allele, prevalent in ~15% of the population (Raber et al., 2004) is hypothesised to be protective against AD risk (e.g. Farrer et al., 1997; Lippa et al., 1997; Wilson et al., 2002).

In addition, carrying at least one copy of the *APOE* ε4 allele has been associated with poorer cognition in healthy older adults, with effects most commonly reported in episodic memory (e.g. Caselli et al., 1999; O'Hara et al., 1998; Staehelin et al., 1999; Packard et al., 2007), but not isolated to this domain (e.g. Berteau-Pavy et al., 2007; Reinvang et al., 2010; Small et al., 2004; Wisdom et al., 2011). Not all studies have been consistent in reporting an effect of *APOE* ε4 in older adulthood, however (e.g. Bunce et al., 2014; Bunce et al., 2004; Juva et al., 2000; Kim et al., 2002; Salo et al., 2001).

Significantly, effects of carrying an *APOE* ε4 allele are not isolated to ageing populations, with reports of subtle cognitive differences in ε4 carriers from childhood (Acevedo et al., 2010; Bloss et al., 2008). Evidence for cognitive advantages in young ε4 carriers has been reported within the domains of episodic memory, executive function (EF) and attention (Marchant et al., 2010; Mondadori et al., 2007; Rusted et al., 2013; Taylor et al., 2016), contrasting with the detrimental associations of *APOE* ε4 in later adulthood. As effects of ε4 are detectable in youth, however, this highlights the need to consider *APOE* genotype earlier in the ageing trajectory.

The cognitive effects of *APOE* in mid-adulthood are of crucial interest as this may be when the ε4 allele is first exerting detrimental effects on the ageing trajectory. To date, reported effects of *APOE* ε4 in mid-adulthood are inconsistent (for review; Lancaster et al., 2017; Rusted & Carare, 2015; Salvato, 2015), with many studies reporting null effects. The exceptions are studies within the domain of memory, where detrimental effects are reported from the end of the fifth decade (Caselli et al., 2004; Jochemsen et al., 2012; Schultz et al., 2008). The inconsistency of reported findings is likely to stem from several methodological issues, including variation in age group included, control of potential moderators and sensitivity of cognitive tasks used. Moreover, as the effect of *APOE* ε4 is non-uniform across cognition, the domain under study represents another factor in the inconsistency.

Aside from memory, attentional control, necessary to complete any goal-driven behaviour, may show sensitivity to *APOE* status in mid-adulthood. Both attentional control mechanisms and EF deficits have been associated with the preclinical stages of dementia (Carlson et al., 2009; Harrington et al., 2013; Twamley et al., 2006). Frontal regions, the predominant neural focus of executive attention, are vulnerable early in the ageing trajectory to both a loss of neural integrity and the deposition of amyloid, with this pattern reported in both healthy and pathological ageing (Bartzokis et al., 2003; Raz, 2000; Rowe et al., 2007; Villemagne et al., 2011). Further supporting the sensitivity of attentional control to ageing processes, amongst a battery of neuropsychological measures, the profile of errors and response time (RT) on a computerized Stroop-switch paradigm, an established measure of attentional selection and distractor inhibition, was found to best distinguish the cognitive profile of mild AD (Hutchison et al., 2010). In addition, performance on this task predicted the subsequent development of AD in a sample of older adults (Balota et al., 2010).

Neuropsychological assessments have not consistently found an effect of *APOE* ε4 on attention or EF in mid-adulthood (Flory et al., 2000; Jochemsen et al., 2012; Sager et al., 2005), although genotype differences have been found using computerized research paradigms developed for maximum sensitivity. On a measure of sustained attention, ε4 carriers (aged 45-55 years) demonstrated greater accuracy for detecting target strings, but slower RTs relative to a homozygous ε3 group (Evans et al, 2014). This pattern of performance was replicated on a prospective memory (PM) measure in the same cohort, with ε4 carriers demonstrating more accurate retrieval of PM intentions, but slower RTs on the ongoing task. Imaging data collected during the PM task found that in ε4 carriers only, left inferior frontal gyrus activity correlated with retrieval accuracy. This was interpreted as evidence of a compensatory response within top-down attentional control mechanisms.

Failure to account for the effect of *APOE* ε2 is likely a key factor in the reported inconsistency of *APOE*-related cognitive change in the literature to date. Predominantly, research either excludes ε2 carriers, or considers ε2 and ε3 variants collectively as a non-ε4 group, despite purported protective effects. In light of the opposing effects of *APOE* variants on dementia risk, intuitively differences are expected in the cognitive profile of ε4 and ε2 carriers. Recent research, however, has found overlapping patterns of task-related functional activity in mid-age ε2 and ε4 carriers, compared to an ε3 group, during both a Stroop task, and an episodic memory task (Trachtenberg et al., 2012a). Both genotype groups also showed differences in resting-state activity compared to an ε3 group (Trachtenberg et al., 2012b). This calls into question how the assumed dichotomy in *APOE* associated cognitive ageing manifests, and highlights *APOE* ε2 as a crucial area for future research.

The current study provided a detailed investigation into the association between *APOE* and attentional control in mid-adulthood. The study aimed to extend previous findings of genotype differences within this domain (Evans at al., 2014) by administering a broader range of attentional tasks, allowing for a more in-depth exploration of the specific cognitive processes showing genotype sensitivity. The research also provided novel investigation into the hypothesised 'protective' ε2 allele.

The behavioural session administered a rapid visual information processing task (RVIP; Wesnes & Warburton, 1983) and a PM measure (Rusted & Trawley, 2006), to establish if a speed-accuracy trade-off in ε4 carriers is reliably observed. Specifically, the research expected to replicate the ε4 advantage in PM retrieval, and target detection on the RVIP, in comparison to the population norm (ε3 homozygotes), at the cost of response latency in this group. The processes targeted by these tasks include goal maintenance, switching, monitoring and updating, all of which burden executive attention and load on frontal lobes (Cona et al., 2015; Coull et al., 1996). In addition, a computerized Stroop-switch task (Hutchison et al., 2010) was used to explore if errors on this task differentiate carriers of a genetic risk for AD as early as mid-adulthood. As this task has previously been shown to distinguish older adults at heightened risk of developing Alzheimer's disease (Balota et al., 2010), by mid-age ε4 carriers may show similar costs of incongruency on the proportion of errors made. Differences in task accuracy are linked to the ability to hold relevant information at the forefront of attention, and resist interference.

Despite reported protective effects of carrying an *APOE* ε2 allele on longevity (Blanché et al., 2001; Frisoni et al., 2001) and cognition in older adulthood (Helkala et al., 1996; Wilson et al., 2002), understanding of how this variant affects cognition is limited at present. In light of recent research (Trachtenberg et al., 2012a; Trachtenberg et al., 2012b), it is unclear whether ε2 carriers will show equal or advantaged performance compared to homozygous ε3 carriers. This study took an exploratory look at the ε2 effects on attentional control mechanisms, to provide the foundation for future work establishing the profile of this genotype in mid-adulthood.

Furthermore, the study addresses many of the methodological shortcomings within existing mid-age literature. The tasks record trial-by-trial response time data, as well as accuracy, to allow detailed analysis of performance on task. Additionally, the study recruits individuals from a narrow range of the lifespan (aged 45-55 years), and measures participant variables including education and cardiovascular health, which may moderate the influence of *APOE* on cognition.

4.3. Methods

4.3.1. Participants

165 healthy volunteers were recruited for the initial screening phase of this study, through advertisement at local universities, clubs, and community centers. For inclusion, volunteers were required to be aged 45-55 years, a non-smoker and using English as their daily-language. Exclusion criteria consisted of: a history of vascular health problems, untreated high blood pressure, psychoactive medication use, or a history of neurological trauma or psychiatric condition within the past 5 years.

The initial screening phase followed Human Tissue Authority (HTA) procedures, and the research ethics committee of the school of Psychology and Life Sciences, University of Sussex approved the full study. In line with ethical guidelines, volunteers first provided written informed consent, including acknowledgment that the results of the genotype analysis would not be made available to them. DNA was collected with a buccal swab, using an Isohelix SK1 kit. Genotyping followed triangulated anonymisation procedures, with two anonymised codes used per sample. Samples were analysed to determine *APOE* gene variant by LGC Genomics (Hertfordshire, www.lgcgroup.com/genomics). A fluorescence-based competitive allele-specific polymerase chain reaction determined the presence of three major *APOE* alleles (ε2, ε3, and ε4) based on two *APOE* single nucleotide polymorphisms (SNPs) (rs429358, rd7412).

66 volunteers were invited to complete the behavioural session. Selection was made pseudo-randomly, in that efforts were made to ensure an approximately even numbers of participants in each genotype group (ε2, ε3, ε4). Double-blind procedures were followed in that both the experimenter and participants remained blind to genotype. Distribution within genotype groups was as follows: 16 ε2 carriers (2 ε2/ε2, 14 ε2/ε3), 26 ε3 homozygotes, and 24 ε4 carriers (17 ε3/ε4, 7 ε4/ε4). Volunteer characteristics are shown in Table 4.1.

4.3.2. Materials

4.3.2.1. Demographics and Baseline Cognitive Measures

A shortened version of the Nuffield Medical History Questionnaire assessed general state of health, recent medical history, medication use, and alcohol consumption. Additionally, the

National Adult Reading Test (NART) (Nelson & Willison, 1991), a backward digit-span task and a visual simple response time task (SRT) were administered to provide baseline cognitive characteristics. For the SRT, participants were required to make a keyboard response ('space bar') as quickly as possible when presented with a visual target stimulus. The task consisted of 48 trials, with a mask of varying length (300ms-1000ms) present between each target stimulus. RTs greater or less than 3 standard deviation (SD) from a participant's mean RT were removed prior to analysis.

4.3.2.2. RVIP task

The RVIP task (Wesnes & Warburton, 1983) was administered for 4 minutes. A continuous stream of digits was presented to participants at a rate of 80 per minute, centrally on a computer monitor. Participants were required to monitor the digits, and respond when either 3 odd or 3 even digits appeared consecutively. Per each minute of the task, there were 8 target strings. Correct detections were recorded up to 1500ms after presentation of the third digit in the target string. Measures of response accuracy, response latency and number of false alarms (FA) (pressing when no target occurred) were recorded. Responses greater or less than 3 SD from each participant's mean RT were removed prior to analysis.

4.3.2.3. Card-sort PM task

The card-sort task (Rusted, Sawyer, Jones, Trawley, & Marchant, 2009)required participants to respond to a succession of playing card stimuli, displayed in a pseudo-random order on screen. In each trial, a card back was displayed for a variable duration (100-1000ms), followed by a card face, which was displayed for 1000ms. The on-going component of the task required participants to sort cards according to suit, pressing '1' for a spade and '3' for a hearts, as quickly and accurately as possible. Participants were asked to give no response if presented with a diamond or a club. Participants initially sorted one deck of 52 cards (26 sort trials, 26 non-sort trials) to provide a baseline measure of decision-making performance. Participants then received the PM instruction to press 'space' in response to the presentation of a specific target card, which was any card with the number '7'. Participants were asked to repeat this instruction back to the experimenter in their own words to check understanding. They then completed 2 further decks of the on-going task with the additional PM instruction, containing 48 sort trials, 48 non-sort trials, and 8 PM trials.

Sort accuracy and RT was recorded for the baseline deck, and the 2 decks following the introduction of the PM instruction. For each volunteer, RTs more than 3 SD from their own

mean were removed. Comparison of performance between these 2 conditions provides a measure of the cost of carrying a PM intention on ongoing sort performance. Accuracy of PM retrieval was also recorded.

4.3.2.4. Stroop-switch task

A computerised version of the Stroop-switch task was administered (Hutchison et al., 2010). Stimuli were presented on a black background and consisted of 4 colour words (blue, green, red and yellow) and 4 neutral words (bad, deep, legal, and poor) written in either blue, green, red or yellow font. Participants were required either to name the font colour or to read the word aloud. The naming rule (colour, word) switched throughout the task after every 2 trials. Trials were classified as either neutral (40 trials), when a neutral word appeared in any of the 4 font colours or incongruent (48 trials), when a colour word appeared in a non-matching font colour.

Participants completed 24 practice trials and 88 experimental trials. For each trial, a precue of 'word' or 'colour' in white font was presented for 1500ms, followed by a wait of 200ms, followed by the stimuli. Participants made a verbal response, with latency recorded using a microphone-connected serial response box. Stimuli remained on screen until a response was detected or 8000ms had elapsed. Accuracy of response was coded by the experimenter for each trial as correct, self-corrected error (e.g. 'bl..green') or intrusion error (i.e. if the participant says incongruent response). For each volunteer, only RTs for correct trials, and within 3 SD of their personal mean were considered for analysis.

4.3.3. Procedure

Volunteers selected from the screening phase took part in a single study session lasting 90 minutes. First, demographic and health measures including age, family history of dementia, height, weight, and blood pressure were collected. A measure of systolic and diastolic blood pressure was collected whilst seated, using an automatic arm-cuff machine on the right arm. Participants then completed a selection of experimental tasks and questionnaires in a fixed order (see Figure 4.1).

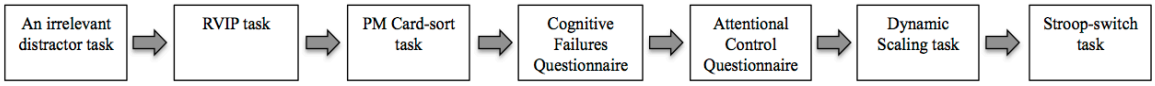

Figure 4.1. A timeline of the experimental tasks included in the behavioural session. The results of several experimental tasks administered in the session fell outside the scope of this paper and will be reported separately.

4.3.4. Design

Differences in the demographic and health characteristics of the genotype groups (ε2, ε3, ε4) were analysed using a series of one-way analysis of variances (ANOVAs) for continuous variables, and chi-squared tests for categorical measures (gender, family history).

Across experimental tasks, analyses were first run to compare performance across all 3 genotype groups. All analyses were two-tailed. Gender was also included in parametric analyses to explore possible *APOE* X Gender interactions: as no interactions were found the effect of gender is not reported in the main body of results (main effects of gender are included as footnotes). For non-parametric analyses, data was screened for any differences by gender.

Secondary analyses were run selectively comparing ε2 carriers and ε4 carriers independently to the population norm (homozygous ε3 carriers) where a main effect of genotype or genotype interaction term were significant or at trend level, or where specific predictions were made based on previous findings. The decision to run these secondary analyses were based on recent suggestions of similarity in the profile of ε2 and ε4 carriers, so separately comparing both groups to the population norm is needed for more detailed exploration.

4.3.4.1 Card-sort task

All volunteers retrieved at least 1 PM intention, taken as an indication that they had encoded and retained the PM intention, and so no volunteers were excluded from the analysis. Sort accuracy and RTs for correct sort responses were analysed, as well as accuracy of PM retrieval. A one-way ANOVA was used to assess group differences in baseline sort RT and accuracy, followed up by Bonferroni corrected independent *t*-tests to assess pair-wise genotype differences. A mixed ANOVA was conducted with deck (baseline, PM) as the within-subjects factor, and genotype group as the between-subjects factor, for both sort RT and accuracy, to

assess performance change following introduction of the PM intention. Non-parametric tests were used to assess genotype differences in PM retrieval as the data violated assumptions of normality. A Kruskal-Wallis analysis was used to assess differences between all 3 genotype groups, followed by two separate Mann-Whitney U tests to compare both ε4 and ε2 variants to the ε3 group, with a conservative alpha (α=. 025) applied.

4.3.4.2 RVIP

Number of target hits, hit latency, and number of FAs were analysed using separate ANOVAs, with time on task as the within-groups factor (time bins: minute 1-4) and genotype group (ε2, ε3, ε4) as the between-groups factor. Separate analyses for both ε2 and ε4 were then completed to explore any suggested genotype effects.

4.3.4.3. Stroop-switch task

The distribution of RTs for Stroop-switch trials deviated from normality and hence a log transformation was applied to this variable prior to analysis. Initially, data was checked to search for an effect of rule switching (switch prior to trial, no switch prior to trial) on RTs and errors. There was no significant effect of switching, and switching did not interact with stimuli type, congruency or genotype (p>.05), and so these trials were considered collectively. For both RTs (correct trials) and proportion of errors, a mixed ANOVA was run with rule (colour, word) and congruency (incongruent, neutral) as the within-subjects factors, and genotype (ε2, ε3, ε4) as the between-subject factor. Where present, interactions were probed with Bonferroni corrected t-tests. Separate analyses were then run comparing ε2 and ε4 variants to the ε3 population norm to further explore suggested genotype effects.

4.4. Results

4.4.1. Demographics & Baseline Cognitive Measures

There were no significant genotype differences across the demographic measures (p>.05). Furthermore, no group differences were found in working memory (WM) span, or SRT (p>.05).

Table 4.1. *Demographics and baseline cognitive performance presented by genotype group.*

	Genotype Group		
Measure	**ε2**	**ε3**	**ε4**
n	16	26	24
Age	50.44 (3.58)	49.04 (2.68)	49.17 (3.07)
Gender (% female)	75	73	63
Family History (%Yes)	25	35	54
Education	17.22 (3.24)	17.23 (3.13)	17.85 (4.32)
NART	119.06 (2.84)	118.56 (2.93)	116.87 (4.62)
BMI	24.02 (3.44)	26.24 (4.37)	25.15 (3.78)
Systolic BP	115.63 (7.55)	118.23 (8.47)	115.00 (8.76)
Diastolic BP	77.31 (9.99)	81.77 (10.63)	79.13 (7.77)
SRT (ms)	272 (44)	265 (32)	266 (27)
Digit-span	4.31 (1.30)	4.19 (1.50)	4.00 (1.65)

Note: Mean (sd)

4.4.2. Card-sort task

For a summary of performance on this task by each genotype group see Table 4.2.

4.4.2.1. Baseline decision-making

Across participants, accuracy on the control 'decision-making' deck was at ceiling, with scores ranging from 50-52 correct (M=51.65) out of a maximum score of 52, with no significant difference between groups (p>.05). The genotype difference in decision-making RT approached significance, $F(2, 62)=2.92$, p=.061, n^2_p=.086. The ε2 group trended towards being slower than the ε3 comparison group (p=.072), whereas the ε4 and ε3 groups did not differ in RT (p>.05).

4.4.2.2. PM performance

Introducing the PM intention was associated with a significant slowing of RTs on card-sort trials, $F(1, 62)=107.77$, p<.001, n^2_p=.635. The main effect of genotype and the interaction between deck and genotype group were non-significant, (p>.05). For sort accuracy, again introducing the PM intention was associated with a significant drop in accuracy, $F(1,62)=37.94$, p<.001, n^2_p=.380. The effect of genotype and the interaction between genotype and deck were both non-significant, (p>.05).

Across the 3 genotype groups there was no significant difference in retrieval of the PM targets (p>.05), although secondary analyses indicated ε4 carriers (M=6.75, mean rank=21.46) retrieved fewer PM intentions than the ε3 group (M=7.31; mean rank=29.23), and this difference approached significance, U=215, p=.040. There was no significant difference in the PM

retrieval accuracy of ε2 carriers (*M*=7.13, mean rank=20.62) compared to the ε3 group (mean rank=22.04), *U*=222, *p*>.05.

Table 4.2. *Performance on the Card-sort task displayed by genotype group.*

Genotype	**Control deck**		**PM decks**		
	RT (ms) ±sd	**Accuracy/52**	**RT (ms)±sd**	**Accuracy/96**	**PM retrieval/8**
ε2	606 ± 67	51.8	736 ± 64	93.00	7.13
ε3	560 ± 77	51.5	710 ± 85	92.35	7.31
ε4	590 ± 38	51.7	710 ± 69	93.13	6.75

4.4.3 RVIP

The data of 4 volunteers was removed prior to analysis due to comparable levels of hits and FAs, or a FA rate greater than 2 sd above the norm. For a summary of performance on this task by genotype group see Table 4.3.

Table 4.3. *Overall performance on RVIP task by genotype, sd shown in brackets.*

Genotype	**Mean hit detection/ 32**	**Mean hit latency (ms)**	**Mean false alarms**
ε2	19.29 (6.28)	558 (69)	1.14 (1.41)
ε3	23.52 (4.88)	510 (72)	2.09 (0.42)
ε4	21.18 (7.20)	514 (77)	1.65 (0.35)

4.4.3.1. Hits

Accuracy decreased with time on task, $F(3, 171)=5.09$, $p=.002$, $n^2_p=.082$. Both the main effect of genotype, $F(2, 57)=2.72$, $p=.087$, $n^2_p=.087$, and the Time on task x Genotype interaction approached significance for number of hits, $F(6, 171)=5.09$, $p=.074$, $n^2_p=.064$.[4] The interaction between time on task and genotype is shown in Figure 4.2.

Secondary analysis found the effect of genotype was driven by ε2 carriers making significantly less hits than the ε3 group, $F(1, 36)=5.51$, $p=.024$, $n^2_p=.133$. There was no significant difference between ε4 carriers and ε3 carriers ($p>.05$).

Further probing of the Time x Genotype interaction found ε2 carriers made fewer hits than the ε3 group only in minute 1, and this difference approached significance, $t(17.7)=-2.72$, $p=.014$. E4 carriers did not significantly differ from ε3 carriers at any minute of the task.

[4] The effect of gender on RVIP hit performance approached significance, $F(1, 57)=3.71$, $p=.059$, $n^2_p=.061$: males (mean=23.68) made more correct hits than females (mean=20.81).

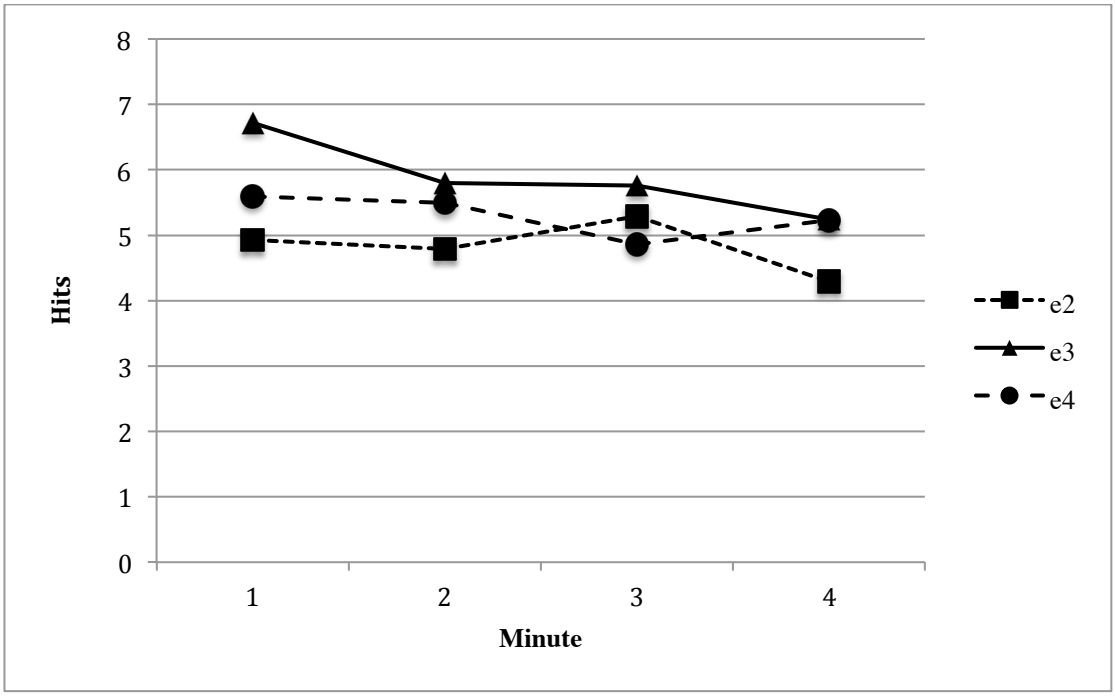

Figure 4.2. The Genotype x Time on task interaction for RVIP hit performance.

4.4.3.2. Hit Latency

With all 3 genotype groups included in the model, the effect of time on task on hit latency was non-significant (p>.05). The main effect of genotype and the Genotype x Time interaction were both non-significant (p>.05).

4.4.3.3. False Alarms

Both the main effects of time on task and genotype, and the interaction between Time x Genotype were non-significant (p>.05).

4.4.4. Stroop

4.4.4.1 Overall task performance

4.4.4.1.1. RTs

RTs were significantly slower for colour naming than word naming, $F(1, 60)=11.10$, $p=.001$, $n^2_p=.156$. Incongruency also led to significantly slower naming, $F(1, 60)=34.65$, $p<.001$,

n^2_p=.366, and this effect was larger for colour naming than word naming, $F(1, 60)=7.78$, p=.007, n^2_p=.115.[5]

4.4.4.1.2 Errors

There was no significant difference in the number of errors made for colour vs. word stimuli (p>.05). At trend level, more errors were made for incongruent stimuli than neutral stimuli, $F(1, 60)=3.10$, p=.089, n^2_p=.049. Again, there was a significant Rule x Congruency interaction, $F(1, 60)=12.17$, p=.001, n^2_p=.169. More errors were made for incongruent colour naming trials (M=.067) than neutral colour naming (M=.018), $t(63)=5.13$, p<.001. For word naming, more errors were made for neutral trials (M=.038) than incongruent trials (M=.017), $t(63)=-2.98$, p=.004 (Bonferroni corrected α=.013). [6]

4.4.4.2. Genotype effects

Performance on the Stroop-switch task is summarised by genotype group in Table 4.4.

4.4.4.2.1. RTs

There were no genotype differences in RT (p>.05), and genotype status did not interact with either rule or congruency in affecting RT (p>.05).

4.4.4.2.2. Errors

The effect of genotype was non-significant (p >.05), as was the Congruency x Genotype interaction, $F(2, 60)=2.32$, p=.107, n^2_p=.072. The Genotype x Rule interaction, and the 3-way Genotype x Rule x Congruency interaction were both non-significant (p>.05).

The Congruency x Genotype interaction, displayed in Figure 4.3., was probed in secondary analysis comparing ε2 and ε4 groups to the homozygous ε3 group in separate models due to an a priori hypotheses of a genotype difference. There was no significant difference in the overall number of errors between the ε3 group and ε4 carriers (p>.05), but there was a significant Genotype x Congruency interaction, $F(1, 46)=4.27$, p=.044, n^2_p=.085, further explored with Bonferroni corrected t-tests (α=.013). There was no significant difference between errors on incongruent stimuli (M=.038) and neutral stimuli (M=.037) for ε3 carriers (p>.0125), but ε4 carriers made significantly more errors for incongruent (M=.052) than neutral stimuli (M=.022),

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[5] A main effect of gender on Stroop RTs was found with males slower in all trials, $F(1, 60)=5.90$, p=.029, n^2_p=.077. The effect of gender was more pronounced for trials with the rule 'word', than trials with the rule 'colour', $F(1, 60)=5.79$, p=.019, n^2_p=.088.

[6] There was a significant effect of gender on the proportion of errors made on the Stroop task, $F(1, 60)=9.64$, p=.003, n^2_p=.138, with males consistently making more errors.

t(22)=2.73, *p*=.012. There was no significant difference between ε4 carriers and the ε3 group in the proportion of errors made for neutral trials, or incongruent trials (*p*>.0125).

ε2 carriers did not significantly differ from the ε3 groups in the number of errors made (*p*>.05), and the Genotype x Congruency interaction was non-significant (*p*>.05). Additionally, ε2 carriers did not show a significant cost of congruency on number of errors made (*p*>.05).

Table 4.4. *Mean naming RT and the proportion of errors recorded, shown by condition and genotype for performance on the computerized Stroop task.*

			Genotype		
Stimuli	**Congruency**		**ε2**	**ε3**	**ε4**
Colour					
	Neutral	RT (ms)	729 (126)	669 (123)	708 (107)
		Errors	.01	.02	.02
	Incongruent	RT (ms)	815 (131)	800 (177)	818 (128)
		Errors	.06	.06	.08
Word					
	Neutral	RT (ms)	683 (130)	623 (144)	662 (135)
		Errors	.03	.05	.03
	Incongruent	RT (ms)	715 (144)	662 (246)	674 (167)
		Errors	.01	.02	.02

Note: RTs shown as mean (sd)

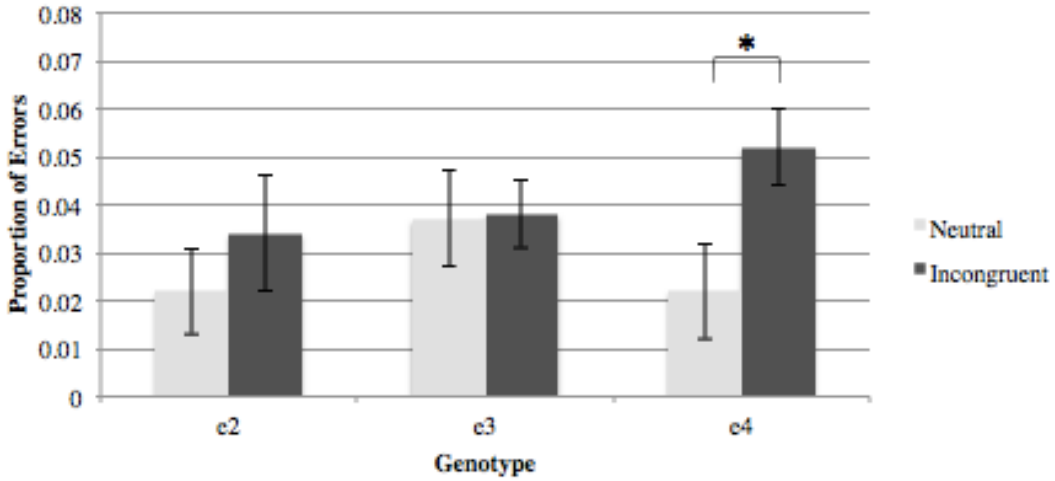

Figure 4.3. The proportion of errors made for congruent and incongruent stimuli shown by genotype group.

4.5. Discussion

The aim of current study was to establish whether *APOE* genotype is associated with differences in attentional control in mid-adulthood. By including all three genotype groups, results provide a novel exploration into the opposing effects of *APOE* status on cognitive ageing.

The current findings suggest deficits in attentional control are detectable by mid-adulthood in ε4 carriers, however, effects were not uniform across cognitive measures. Carriers of this allele demonstrated a larger effect of incongruency on errors during a computerized Stroop-switch task. Similarly, there was a trend for ε4 carriers to show reduced accuracy of PM retrieval in comparison to the population norm (ε3 homozygotes). Despite the expectation that ε2 carriers would show cognitive advantages in mid-adulthood, in line with the suggested protective effects of this allele, results did not consistently support performance advantages. On the RVIP measure of sustained attention, compared to both homozygous ε3 carriers and the ε4 group, ε2 carriers detected fewer target strings. On the control deck of the PM task ε2 carriers trended to sort cards with slower RTs. These differences were found despite there being no genotype differences in simple RTs, suggesting differences specifically relate to decision-making RT.

The study administered versions of the RVIP and card-sort PM tasks comparable to those previously reported to show a speed-accuracy trade-off in mid-age ε4 carriers (Evans et al, 2014). Our results did not replicate this pattern, and this is unlikely to be a factor of the subtle differences in paradigms used. Although the Evans study used a 6-minute version of the task, the reported genotype differences were observed in the first 3 minutes, so this should have been replicable in the 4-minute version. Across these tasks, with the exception of PM retrieval, ε4 carriers showed equivalent performance to the ε3 group. This could be interpreted as ε4 carriers having relatively sustained cognitive performance in mid-adulthood. This over-arching pattern is not inconsistent with the antagonistic pleiotropy hypothesis (Han & Bondi, 2008), that the ε4 variant transitions from having advantageous to disadvantageous consequences in mid-adulthood.

Importantly, ε4 carriers did show subtle deficits within select processes, prominently a marked congruency effect in the number of errors made on the Stroop task. Similarly, a marked increase in errors for incongruent trials was found to both predict and characterize AD (Balota et al., 2010; Hutchison et al., 2010). These parallel results indicate that performance on this task is an important early identifier of cognitive decline, with the task showing sensitivity by mid-adulthood. Although previous research has reported no effect of *APOE* ε4 on Stroop-task

performance in mid-age (Sager et al., 2005; Trachtenberg, Filippini, Cheeseman, et al., 2012), the paradigm used here collected data on a trial-by-trial basis, providing a more sensitive measure.

In terms of specific cognitive processes, the computerized Stroop task requires both goal maintenance and response inhibition. Previous research suggests that RT distributions on this task are linked to detriments in inhibitory control, whereas errors represent failures to maintain task goals (Kane & Engle, 2003). Accordingly, ε4 carriers showed decrements in the executive attention required for active goal maintenance. Notably, they also showed deficits in PM retrieval, in which both active maintenance of the PM intention, and monitoring of the environment for the opportunity to act are required, consistent with detriments in sustaining information at the forefront of attention.

Attentional control, as indexed by Stroop errors and PM performance, has been linked to WM span (Kane & Engle, 2003). Likewise, active updating and monitoring, the component of EF most closely assessed by the three paradigms administered in the current study, is described as being closely associated with WM (Miyake et al., 2000). In this study however, no genotype difference was found on a backward digit-span measure. It may be that future study, including a more detailed exploration of WM ability, would demonstrate sensitivity to *APOE* effects in mid-adulthood, for example the Operation Span task (Turner & Engle, 1989). In a slightly older sample (50-79 years), ε4 carriers showed deficits on this task (Rosen et al., 2002). An important avenue for future research is establishing a reproducible effect of *APOE* ε4 genotype on the active processing of information in attention, and the neural basis of this difference.

Results from previous fMRI research suggest reported correlations between advantaged PM retrieval in ε4 carriers and heightened inferior frontal gyrus activity might represent an early compensatory frontal shift (Evans et al., 2014). As activity of the inferior frontal gyrus has previously been associated with detection of salient stimuli (Hampshire et al., 2010), increased activity in this area fits with heightened PM accuracy. No evidence was provided in this study for ε4 carriers showing any advantages in performance measures, however.

An important avenue for future research is to establish the mechanisms behind the *APOE* ε4 effects on attentional control. *APOE* ε4 is known to influence the profile of amyloid deposition in the brain (Morris et al., 2010; Villemagne et al., 2011). The detrimental effect of *APOE* ε4 on executive attention in older adulthood and the very early stages of AD is likely mediated in part by amyloid deposition in regions including the prefrontal cortex (Aschenbrenner et al., 2014). Research probing the relationship between *APOE* ε4 and amyloid across the lifespan found that

despite no episodic memory performance difference, ε4 carriers showed accelerated deposition of amyloid, with 10% of the population defined as amyloid positive by halfway through the fifth decade (Jack et al., 2015). This may also be the route by which *APOE* ε4 impacts functional connectivity (Sheline et al., 2010), demonstrated in the earlier research of Trachtenberg et al (2012a; 2012b). These changes may be particularly relevant for executive attention, which requires communication between multiple processing regions. Imaging techniques should be used to explore which neural mechanisms are most relevant for the initial stages of cognitive ageing in ε4 carriers.

At present, there is insufficient research on the cognitive profile of healthy ε2 carriers. The current results, however, contrast with past research suggesting ε2 is protective (Chiang et al., 2010; Farrer et al., 1997; Helkala et al., 1996; Lippa et al., 1997; Wilson et al., 2002). The results reported here are based on a small sample of ε2 carriers, but contribute to the small number of studies that have explored ε2 effects on cognition prior to older-adulthood (Alexander et al., 2007; Alexopoulos et al., 2011). Recent papers have reported differential spatial navigation strategies in ε2 carriers in youth (Konishi et al., 2016), as well as altered memory function in individuals diagnosed with post-traumatic stress disorder (Freeman et al., 2005; Johnson et al., 2015; Kim et al., 2013). Therefore, although it may be possible to detect ε2 differences earlier in the lifespan, the link between *APOE* ε2 and executive attention is also relatively unexplored.

Recent research, however, reported overlap in the functional activation patterns of ε2 and ε4 carriers compared to ε3 carriers, despite no behavioural differences (Trachtenberg et al., 2012a; Trachtenberg et al., 2012b). Whereas, the behavioural profile of ε2 carriers and ε4 in the current study did not overlap, both groups showed some disadvantage in attentional control. This encourages a closer examination of the hypothesised polarity in *APOE* effects. Our behavioural results suggest late-life dementia risk might not equate with cognitive performance in mid-adulthood, with both ε2 and ε4 carriers showing process-specific detriments. It may be that ε4 carriers show increased vulnerability to cognitive insult (Wirth et al., 2014), whereas ε2 carriers are better able to employ protective mechanisms. In support of a compensatory mechanism in ε2 carriers, in adults aged 90+ years, carriers of this variant were significantly less likely to meet clinical criteria for AD diagnoses, despite similar levels of AD neuropathology between ε2 and ε4 genotypes at autopsy (Berlau et al, 2009). Reports have also been made, however, that ε2 is protective against amyloid deposition in later life (Morris et al., 2010), and in AD (Nagy et al., 1995).

Several limitations of the current study must be acknowledged. First, the number of participants within each genotype group was relatively small, meaning analysis may have lacked statistical power. This also limited exploration of gene dose effects. Effects of ε4 gene dose (i.e. increased impact with 0, 1, and 2 ε4 alleles) have been reported (Farrer et al., 1997; Raber et al., 2004; Wilson et al, 2011), however, the effects of ε2 zygosity are less clearly demonstrated (Farrer et al., 1997). An additional analysis to the results reported here found no differences by *APOE* haplotype, but this would need to be further determined in future research. In addition, performance on the PM task was close to ceiling, and so the task may have lacked sensitivity for discriminating between genotype groups. Future research would benefit from increasing the demands placed on the attentional control system, for example by increasing the resource needs of the ongoing task.

4.6 Conclusions

In this study, both those carrying detrimental and protective variants of *APOE* showed decrements in executive attention by mid-adulthood. In ε4 carriers, subtle disadvantages on a Stroop task and in PM retrieval were apparent, suggestive of deficits in goal-maintenance in the face of irrelevant information processing. This indicates that through the application of sensitive research paradigms, it is possible to identify those at genetic risk of cognitive decline from mid-adulthood. Surprisingly, behavioural disadvantages were identified in ε2 carriers, despite the premised benefits of carrying this allele for cognitive health in older adulthood. Of critical importance, results illustrate the importance of including ε2 carriers as an independent group, and the need to establish both how this variant influences cognition and neural function across the lifespan, and how it interacts with environmental factors to promote protection against age-related cognitive decline.

APOE genotype, cognitive reserve and physical fitness in mid-adulthood: moderation of early executive attention differences

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5.1 Abstract

Objective: To investigate how environmental factors impact age-related cognitive deficits by mid-adulthood, both independently and in interaction with *APOE* genotype.
Method: Cognitive data from 66 adults (aged 45-55 years), representing executive attentional processes (goal maintenance, updating, and inhibition) and subjective reports of cognitive failures, were included in multiple regression analyses. Genotype (ε2, ε3, ε4), cognitive reserve (education, occupation and leisure activities, estimated IQ), self-reported physical activity, and metabolic and cardiovascular health (body mass index, mean arterial blood pressure) were included as predictors.
Results: In ε4 carriers, protective effects of cognitive reserve were selectively observed for goal maintenance abilities. In ε2 carriers, counter-intuitively, increased cognitive reserve was associated with greater self-report of cognitive errors.
Conclusions: Cognitive reserve appears to protect against the emergence of early goal maintenance impairments in ε4 carriers. Across objective cognitive measures, ε2 carriers appear less sensitive to the protective effects of cognitive reserve. We conclude that ε4 carriers may show greater plasticity to factors modifying age-related cognitive deficits in mid-adulthood, highlighting the importance of taking preventative steps against cognitive decline earlier in the lifespan.

Key words: *APOE,* Cognitive Ageing, Executive function, Cognitive Reserve, Mid-adulthood

5.2 Public Significance Statement

The study revealed a protective effect of cognitive reserve in mid-age adults carrying a genetic risk for dementia, indicating this group may show increased plasticity to the modifying effects of environmental factors that mitigate against age-associated deficits. Environmental factors with the potential to modify genetic susceptibility to age-related cognitive decline advance our understanding of protective strategies. In addition, by demonstrating effects in mid-adulthood, the results emphasize the importance of implementing potential interventions early.

5.3 Introduction

Apolipoprotein E (*APOE*) is a single nucleotide polymorphism with six possible genotypes determined by the combination of three alleles: ε2, ε3 and ε4. Possession of the ε4 allele is a well-established risk factor for late onset Alzheimer's disease (LOAD) (Corder et al., 1993; Farrer et al., 1997). The prevalence of the ε4 allele, carried by ~ 23% of Caucasian individuals (Raber et al., 2004), makes this variant an important target for interventions that help prevent cognitive decline. By contrast, the ε2 allele is held to offer protection against LOAD (Farrer et al., 1997; Lippa et al., 1997; Wilson et al., 2002).

Opposing influences of the ε4 and ε2 variants are also reported in healthy cognitive ageing. The ε4 allele is associated with cognitive deficits across various domains in older adulthood, including global cognition, episodic memory, attention, and executive function (e.g. Berteau-Pavy, Park, & Raber, 2007; Espeseth et al., 2006; Marioni et al., 2015; Packard et al., 2007; Reinvang, Winjevoll, Rootwelt, & Espeseth, 2010; Staehelin, Perrig-Chiello, Mitrache, Miserez, & Perrig, 1999; for reviews see: Small, Rosnick, Fratiglioni, & Bäckman, 2004, Wisdom, Callahan, & Hawkins, 2011). Although less frequently studied, possession of an ε2 allele is associated with benefits to memory and executive function in older adulthood (Bonner-Jackson, Okonkwo, & Tremont, 2012; Deary et al., 2004; Helkala et al., 1996), coupled with reduced longitudinal cognitive decline (Blair et al., 2005).

The opposing effects of *APOE* variants in later life highlight the possibility that the ε2 and ε4 alleles differ in their behavioural and neural effects across the lifespan, and in their respective trajectories of cognitive ageing. To date, the bulk of research focuses on isolating the effects of the ε4 allele, whilst collectively considering carriers of the ε2 and ε3 alleles as a low risk group, or excluding ε2 carriers from the sample. Previous research comparing all *APOE* variants, surprisingly reports similar patterns of brain activation in ε2 and ε4 carriers from mid-adulthood. In adults aged 32-55 years, both genotype groups displayed increased task-unrelated neural activity during executive attention and episodic memory tasks, compared to an ε3 group, despite no performance differences (Trachtenberg et al., 2012a). Likewise, comparable differences in resting-state activity are reported in mid-age ε2 and ε4 carriers (Trachtenberg et al., 2012b). In an older sample (aged 54-80 years), groups of ε2 and ε4 carriers both show diminished functional connectivity in the default mode network, that correlated with measures of processing speed (Shu et al., 2016). Importantly, cross-sectional comparisons across the age-range suggest the genotype groups are associated with opposing trajectories of change in functional connectivity, with increasing connectivity in ε2 carriers and decreasing connectivity in ε4 carriers observed with age. These results call into question the assumption made by many

studies, that the ε2 and ε4 alleles have differential effects across the lifespan, and hence a key question for future research is how these opposing late-life effects develop.

Although ε4 and ε2 alleles may independently confer a differential vulnerability for cognitive decline, interactions between *APOE* genotype and additional mitigating factors are important to consider. Variants of the *APOE* gene may differ in their susceptibility to the influence of factors associated with age-related cognitive decline. In addition, the strength of genotype effects on cognition may be influenced by an individual's brain reserve (e.g., Bunce, Kivipelto, & Wahlin, 2004; Lindenberger, 2008), and hence factors that modify brain reserve may modulate the influence of *APOE* variants on the early ageing trajectory. In the present study we present an exploratory analysis of the effects of cognitive engagement, physical activity, and indices of cardiovascular and metabolic health (arterial pressure and body mass index (BMI)) on *APOE* genotype differences in mid-adulthood.

5.3.1 *APOE* and Cognitive Reserve

Cognitive reserve suggests that the threshold at which cognitive deficits emerge as a function of age-related neural decline is actively modified through lifetime cognitive engagement (for review see Barulli & Stern, 2013; Scarmeas & Stern, 2003; Stern, 2002). Education and IQ, as well as occupation and ongoing leisure activities, have been used as proxies of cognitive reserve (Barnes & Yaffe, 2011; Cheng, 2016). *APOE* ε4 carriers are reported to show increased benefit of high cognitive reserve on later-life cognition (Brewster et al., 2014; Bunce, Kivipelto, et al., 2004; Carlsson, Gleason, Hess, & Moreland, 2008; Forstmeier et al., 2012; Vemuri et al., 2014; Wirth et al., 2014). Furthermore, young and mid-life cognitive activity has been associated with biomarkers of Alzheimer's disease pathology (amyloidosis, brain metabolism) in *APOE* ε4 carriers (Vemuri et al., 2016; Wirth et al., 2014). Research exploring how cognitive reserve impacts *APOE* ε4 behavioural differences earlier in the lifespan, however, is limited.

To date, there has been minimal research exploring the interaction between *APOE* ε2 and cognitive reserve. One longitudinal study (mean follow-up 9.2 years) found enhanced benefits of cognitive reserve, indexed through years of education, vocabulary and reading level, on the emergence of pathological cognitive change in ε2 carriers (Soldan et al., 2013). This research found independent associations of ε4 status and cognitive reserve on later-life risk, but contrary to previous research, found no interaction between the two factors. Variation in the method of assessing cognitive reserve and which epoch of the lifespan is targeted could account for inconsistency in the reported relationship between cognitive reserve and *APOE* ε4. The

question of whether ε4 and ε2 carriers show similar benefits of cognitive reserve, and the age at which these effects emerge, however, remains unclear.

5.3.2. *APOE* and Physical Activity

E4 carriers demonstrate greater vulnerability to the adverse effects of low physical activity, here collectively referring to both purposeful exercise and active leisure time (e.g., gardening, housework). Several studies report greater benefits of physical activity on the cognitive performance of older ε4 carriers compared to their non-ε4 peers (Etnier et al., 2007; Woodard et al., 2012; Niti, Yap, Kua, Tan, & Ng, 2008; Schuit, Feskens, Launer, & Kromhout, 2001). Inactivity in ε4 carriers is associated with longitudinal declines in hippocampal volume, (Smith et al., 2014). Importantly, from mid-adulthood a sedentary lifestyle has been linked to increased amyloid deposition in ε4 carriers (Smith, Nielson, Woodard, Seidenberg, & Rao, 2013; Head et al, 2012), providing a potential mechanism for the relationship between *APOE* ε4, physical activity and cognitive decline. Physical activity in mid-adulthood exerted the greatest protective effect in ε4 carriers on cognitive ageing 21 years later (Rovio et al., 2005), highlighting the importance of physical fitness earlier in the lifespan. As yet, the link between *APOE* ε2 and physical activity is not well established.

5.3.3. *APOE,* cardiovascular health and metabolic function

Cardiovascular factors, including hypertension, hypercholesterolemia, and obesity, are risk factors for cognitive decline (Anstey, Cherbuin, Budge, & Young, 2011; Atzmon et al., 2002; Köhler et al., 2014; van Exel et al., 2002; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). E4 carriers are predisposed to poorer cardiovascular health (Bennet et al., 2007; de Frias et al., 2007; Haan & Mayeda, 2010). In turn, the relationship between vascular heath and cognitive decline appears more marked in older ε4 carriers (e.g. de Frias et al., 2007; Zade et al., 2010).

Importantly, blood pressure differentially impacts the relationship between *APOE* genotype and cognition from mid-life. Systolic blood pressure moderates the association between ε4 and cognitive performance in mid-adulthood (Bender & Raz, 2012; Oberlin et al., 2015). High pulse pressure negatively impacted longitudinal change in episodic memory in ε4 carriers and homozygous ε3 carriers aged 53 years and older, but not in ε2s (McFall et al., 2015). This supports greater vulnerability in ε4 carriers to cognitive insult from mid-adulthood, whilst ε2 carriers appear to show reduced sensitivity.

Body mass index (BMI) is a marker of health status, with high BMI associated with increased risk of vascular-related disease (Kivipelto & Solomon, 2008; Qiu, Kivipelto, & Von Strauss, 2009). In a cross-sectional study, high BMI was associated with lower cognitive performance (Corley, Gow, Starr, & Deary, 2010; Nilsson & Nilsson, 2009), as well as greater decline in cognition from 40 years of age (Dahl et al., 2013; Dahl, Hassing, Fransson, & Pedersen, 2010). How BMI interacts with *APOE* status is less well established; in older adults (aged 65 plus), the negative effects of ε4 status increase with lower BMI (Rajan, Skarupski, Rasmussen, & Evans, 2014; Sachs-Ericsson, Sawyer, Corsentino, Collins, & Blazer, 2010). Low BMI in later life, however, is associated with increased illness (Newman et al., 2005), which may contribute to exaggerated ε4 effects in older-adulthood. In a mid-age sample, however, the relationship between BMI, *APOE* ε4 and cognition may be reversed.

5.3.4. Current aims and hypotheses

The present research explores the potential impact of APOE allelic variation on cognition in mid-adulthood, addressing previous shortcomings in considering how cognitive reserve, physical activity, cardiovascular and metabolic health moderate the effects of both ε4 and ε2 alleles. By focusing on mid-adulthood, the research aims to capture how key modifiers of cognitive ageing influence the emergence of early cognitive differences between *APOE* genotypes, progressing our understanding of what might protect or promote cognitive health in mid-age.

A series of hierarchical regression analyses explore the independent and interactive effects of these factors on components of executive attention, as well as subjective ratings of cognitive errors. Executive attention is a cognitive domain sensitive to *APOE* genotype effects in mid-adulthood (Chen et al., 2013; Evans et al 2013, 2014; Velichkovsky, Roschina, & Selezneva, 2015; Yan, Wu, Chao, Chen, & Tseng, 2015). It is also sensitive to both the effects of physical activity and cognitive reserve (Smith et al., 2011). Here we derive a composite index of executive attention from performance across three tasks (a prospective memory task, rapid visual information processing task (RVIP) and a Stroop-switch task). Following Miyake & Friedman (2012), these tasks combine online maintenance of goals, updating, shifting and inhibition, and have been shown to load on frontal lobe function (Cona, Bisiacchi, Sartori, & Scarpazza, 2016; Evans et al., 2014; Kane & Engle, 2003; Neale, Johnston, Hughes, & Scholey, 2015).

We predicted that carrying an ε4 allele would increase vulnerability to the impact of risk factors for cognitive decline, namely low physical activity, increased BMI and high blood pressure. In

addition, we expected that ε4 carriers would show enhanced protective effects of lifetime cognitive engagement. At present, there is little to guide our predictions of how these factors may modify cognition in ε2 carriers, but we anticipated differences in the sensitivity of the two groups, in line with the reported divergence of cognitive ageing trajectories between *APOE* genotypes.

5.4. Methods

5.4.1. Participants

165 volunteers were recruited for a mid-age *APOE* genotype database via advertisement at local universities, community centers and clubs. For participation, volunteers were required to be 45-55 years of age, non-smokers, fluent in English, and with no diagnosed history of vascular, psychiatric or neurological illness within the past 5 years. In addition, volunteers were screened for current medication use.

From this database, a smaller number of volunteers (n=66) participated in the cognitive test session. As the distribution of allelic variants in the *APOE*-screened database was heavily biased towards ε3 homozygotes (consistent with population norms (Raber et al., 2004)), a third party randomly selected approximately equal numbers of each genotype group, ε2 carrier (ε2/ε2, ε2/ε3), homozygous ε3, and ε4 carrier (ε3/ε4, ε4/ε4), for recall; ε2/ε4 carriers were excluded from participation as understanding of these variants in combination is limited. The study followed double-blind procedures in that both the participant and experimenter were blind to genotype information. Demographic information, including National Adult Reading Test (NART) (Nelson & Willison, 1991), is displayed in Table 5.1. The University of Sussex, School of Psychology and Life Sciences Research Ethics Committee approved the study, with procedures adhering to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

5.4.2. Materials

Physical measures were recorded for each volunteer including height and weight measurements, and seated systolic and diastolic blood pressure (using an upper-arm automatic monitor). In addition, physical activity was assessed using a scale taken from the Nurses Health Study (Colditz & Hankinson, 2005; Colditz, Manson, & Hankinson, 1997). Average frequency of 10 listed activities, over the past 6 months, was scored on a 10-point scale ranging from 0 minutes per week, to 11+ hours per week. A single score was derived for each participant by summing

responses for each ordinal scale with higher values representing greater engagement with physical activities.

The Cognitive Reserve Index quotient (CRIq) (Nucci, 2012), a 20-item questionnaire assessing education, occupational background and adult leisure activities, was administered. A score for each of these components, as well as an overall cognitive reserve score was produced. The education sub-score was based on the number of years in education and/or vocational training. Occupational background was measured as the number of years working (part-time, full-time) across 5 levels of employment, split as a function of presumed intellectual demand and personal responsibility (unskilled manual work, skilled manual work, skilled non-manual work, professional occupation or highly intellectual occupation). Examples of each were included. 16 items measuring leisure time activity were included, divided by frequency (weekly, monthly, annual). Frequency of each item was rated: never/rarely or often/always. If the activity was carried out 'often/always', participants were asked to provide an estimate of the number of years of activity since reaching adulthood. Number of children was also included in the leisure activity domain. Higher scores represented greater engagement with cognitively stimulating activities.

Table 5.1. Sample characteristics shown grouped by *APOE* status

	Genotype			
	ε2	**ε3**	**ε4**	***p***
n	16	26	24	
Age	50.4 (3.6)	49.0 (2.7)	49.2 (3.1)	.319
Gender (% f)	75	73	63	.624
Family History (%)	25	35	58	.077
NART	119.1 (2.8)	118.6 (2.9)	116.9 (4.6)	.258
Education (years)	17.2 (3.2)	17.2 (3.1)	17.9 (4.3)	.804
CRIq (total)	128.4 (8.6)	119.5 (9.7)	122 (12.0)	.030
BMI (kg/m$^{2)}$	24.0 (3.4)	26.2 (4.4)	25.2 (3.8)	.341
Systolic BP (mmHg)	115.6 (7.6)	118.2 (8.5)	115.0 (8.8)	.365
Diastolic BP (mmHG)	77.3 (10.0.)	81.8 (10.6)	79.1 (7.8)	.320
Physical activity (/90)	19.3 (6.4)	17.8 (9.0)	17.3 (10.6)	.785

Notes: Family history is coded as the number of volunteers with a first-degree relative diagnosed with dementia. Values represent mean (sd) unless otherwise stated. Abbreviations: National adult reading test (NART), Cognitive reserve quotient index (CRIq), body mass index (BMI), blood pressure (BP).

5.4.2.1. Composite predictors

The following variables were considered as moderators of the relationship between *APOE* genotype and cognition: estimated IQ (taken from NART), total CRIq, BMI, mean arterial pressure (MAP), and physical activity score. Note, arterial pressure was calculated using the

formula: diastolic pressure + ⅓ (systolic pressure – diastolic pressure) (e.g. Salvi, 2012; Tian et al., 2013; Zheng et al., 2008), and represents the steady component of blood pressure (Sesso et al., 2000).

Data for each potential moderator was screened for normality prior to analysis. Two scores on individual measures were identified as outliers (3 standard deviations (SD) or more away from the group mean). These scores were removed but the remaining data for these two participants were included in the analysis.

To assess the independent effects of physical activity this variable was treated as an individual predictor. The remaining moderator variables were submitted to principle components analysis (PCA) with varimax rotation; extraction was based on Eigenvalues greater than 1 (component loadings are shown in brackets). Estimated IQ (.71) and CRIq score (.85) significantly correlated ($r(63)=.26$, $p=.022$) and loaded on a single component, henceforth named 'Cognitive reserve'. MAP (.80) and BMI (.79) loaded onto the same component, henceforth called 'metabolic and vascular health', and were again, significantly correlated, $r(63)=.30$, $p=.010$.

All predictors were converted into standardized Z-scores, and the average of these standardized scores were used to form composites of 'cognitive reserve' and 'metabolic and vascular health'. For participants with incomplete data ($N=2$) (i.e. those identified as having an outlier), scores were created based on the remaining standardized variable.

5.4.2.2. Cognitive outcomes

The executive attention tasks used in the current analyses have previously been described in Lancaster, Tabet and Rusted (2016). Performance on a prospective memory task (PM) (with ongoing speeded decision-making component) (Rusted & Trawley, 2006), rapid visual-information processing (RVIP) task (Wesnes & Warburton, 1983), and Stroop-switch paradigm (Hutchison et al., 2010) were included.

In addition, volunteers were asked to complete 2 subjective measures of everyday cognition. The Cognitive Failures Questionnaire (CFq) (Broadbent, Cooper, FitzGerald, & Parkes, 1982) asks volunteers to rate how often they make 25 common 'cognitive failures', on a scale from 'Never' (0) to 'Very often' (5). Cognitive failures are premised to represent 4 subscales: memory, attention, perception and motor ability. A total score for each volunteer was produced, with higher scores representing greater reported failures. The Attentional Control scale (Derryberry & Reed, 2002) was also used, consisting of 20 items targeting 3 processes; mind

wandering, susceptibility to boredom and distractibility. Scores for each question were based on a 4-point Likert Scale from 'Almost never' (1) to 'Always' (4). Responses were scored so higher values represented worse attentional control. Internal consistency for both the CFq and Attentional Control scale in this group was high (CFq: Cronbach's $\alpha = .906$; Attentional Control scale: Cronbach's $\alpha = .833$).

5.4.2.3. Cognitive composites

Objective indices of executive attention (decision-making RT, PM retrieval, RVIP performance, Stroop effect (RT, errors)) were subject to a PCA with varimax rotation. Note, data for both target hits and latency on the RVIP task was combined into a single inverse efficiency score (Bruyer & Brysbaert, 2011; Townsend & Ashby, 1978). Performance on these measures was screened for outliers ($M \pm 3SD$) prior to inclusion in the analysis.

Components were extracted on the basis of Eigenvalues > 1 and the scree plot. The PCA of objective indices suggested 3 components accounting for 60.56% of the variance. Component 1 accounted for 21.36% of the variance with the following loadings: decision-making RT (.82), RVIP inverse efficiency score (.83). Component 2 comprised the Stroop effect (RT) for both colour naming trials (.86) and word naming trials (.81), and accounted for 20.83% of the variance. Component 3 accounted for 18.34% of the variance, with PM retrieval (.56) and Stroop errors for both colour (.46) and word rule trials (-.85) loading on this factor.

Theoretically these components were interpreted as representing 1) updating, 2) inhibition and 3) mental-set or goal maintenance, overlapping with the factors identified by (Miyake & Friedman, 2012). Performance on the components measures was standardized and averaged for variables loading on the same factor to form composite measures. All 3 composites were created so that a greater value represented worse performance.

Subjective cognitive indices (CFq, ACs) were considered separately. Scores on these measures were highly correlated, $r(65)=.470$, $p < .001$, and a PCA confirmed both scales loaded onto one factor accounting for 73.5% of the variance. A composite of standardized scores on these scales was created, with higher values representing worse ratings of cognition.

5.4.2.4. APOE genotyping

DNA samples, collected by a buccal swab of the inner-cheek, were used to screen for *APOE* genotype, in line with HTA procedures. Samples were analysed by LGC Genomics

(Hertfordshire, www.lgcgroup.com/genomics), using a fluorescence-based competitive allele-specific polymerase chain reaction. The presence of three major *APOE* alleles (ε2, ε3, and ε4) was determined using two *APOE* single nucleotide polymorphisms (SNPs) (rs429358, rd7412).

5.4.3. Statistical analyses

A series of 12 multiple regression models were used to explore the relationship between *APOE* status, each additional predictor of cognitive decline (cognitive reserve, physical activity, and cardiovascular and metabolic health), and cognitive performance. Separate regressions were used to explore performance on each of the 4 cognitive composites: (1) updating (2) goal maintenance (3) inhibition and, (4) subjective cognition.

APOE genotype was entered into the analysis as two dummy coded variables. The first variable coded ε4 carriers against ε4 non-carriers, while the second variable coded ε2 carriers against ε2 non-carriers, positioning homozygous ε3 carriers as the reference variable. For each cognitive outcome, each potential moderator was included in separate models, as well as their interaction terms with the two *APOE* dummy variables.

5.5 Results

Demographics are presented by genotype in Table 5.1. One-way Analyses of Variances (ANOVAs) or chi-squared (X^2) tests were used to check for genotype differences in demographic measures. The only significant genotype difference was in total CRIq score, $F(2, 62)=3.70$, $p=.030$, driven by ε2 carriers scoring higher on this measure than the ε3 group (Bonferroni corrected $p=.026$). In addition, the genotype difference in family history of dementia approached significance, $X^2(66)=5.11$, $p=.077$. Genotype differences in the standardized predictor and cognitive composites are shown in Table 5.2. The genotype difference in cognitive reserve composite approached significance, $F(2, 61)=2.47$, $p=.093$.

For each potential moderator (cognitive reserve, physical activity, cardiovascular and metabolic health), step 1 of the hierarchical regression included the primary effects of ε4 status, ε2 status and the moderator. Interaction terms were added in Step 2. At each step of the regression model, the significance of the change in explained variance (R^2) was tested using a F-ratio statistic. A significant change at step 2 indicated that the model including the interaction terms provided a better fit for the data. In addition, the significance of individual regression coefficients was considered. Changes in R^2 (ΔR^2) and the β values for each regression model are presented in Tables 5.3, 5.4, and 5.5. A conservative α of .01 was applied to correct for Type 1 error.

Table 5.2. Scores on standardized composite measures of cognition and lifestyle shown by genotype group.

		Genotype			
Composite		**ε2**	**ε3**	**ε4**	***p***
Cognitive	**GM**	-.05 (.59)	-.20 (.48)	.26 (.67)	.027
	Updating	.43 (.79)	-.31 (.83)	.07 (.80)	.022
	Inhibition	-.13 (.43)	.16 (1.19)	-.08 (.59)	.482
	Subjective	-.34 (.86)	-.02 (.72)	.26 (.94)	.095
Lifestyle	**CR**	.38 (.46)	-.10 (.56)	-.06 (.58)	.093
	PA	.15 (.71)	-.02 (1.00)	-.08 (1.18)	.785
	CMH	-.26 (.89)	.25 (.82)	-.04 (.77)	.149

Notes: Mean (sd). Abbreviations: Goal Maintenance (GM), Cognitive reserve (CR), Physical activity (PA), Cardiovascular and metabolic health (CMH).

5.5.1 Cognitive Reserve

In step 1, ε4 status significantly predicted lower performance on the goal maintenance composite (β=.39, p=.003). Possession of an ε2 allele was predictive of lower performance on the updating composite (β=.38, p=.010). In addition, primary effects of cognitive reserve were found on both the goal maintenance (β=-.36, p=.008) and subjective composites (β=-.39, p=.002), in that higher reserve was predictive of better performance.

At step 2, adding the *APOE* x Cognitive reserve interaction terms accounted for marginally more variance in predicting subjective ratings (p=.017). An ε2 x Cognitive reserve interaction suggested that subjective report of cognitive failures by ε2 carriers was predicted by higher cognitive reserve according to their subjective ratings of cognition (β=.44, p=.006).

There was a trend towards significantly greater variance in goal maintenance scores being accounted for in Step 2 of the model (p=.055), driven by a marginal ε4 x Cognitive reserve interaction (β=-.43, p=.019); high cognitive reserve was more positively associated with better goal maintenance in ε4 carriers relative to the ε3 reference group. This relationship is shown in Figure 5.1.

5.5.2. Physical activity

In step 1, ε4 status was marginally predictive of lower performance on the goal maintenance composite (β=.34, p=.014). Possession of an ε2 allele was predictive of lower performance on the updating composite (β=.36, p=.010). The primary effect of physical activity was non-

significant across the 4 domains of cognition (p>.01). Adding the interaction terms in step 2 of the models did not account for significantly more variance (p>.01).

5.5.3. Cardiovascular and Metabolic Health

Across cognitive outcomes, regression models including *APOE* genotype and the composite of cardiovascular and metabolic health did not account for significant variance (R^2) in performance (p>.01). Adding the interaction terms in step 2 of the models did not add significantly to the variance accounted for (p>.01).

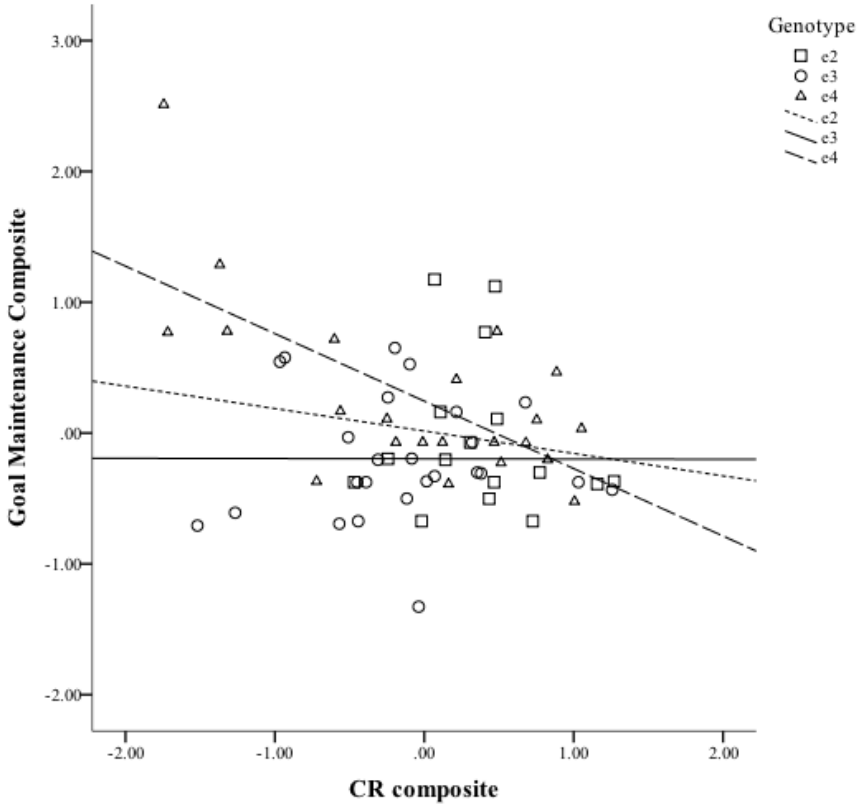

Figure 5.1. The interaction between *APOE* genotype and cognitive reserve in predicting goal maintenance performance

Table 5.3. Hierarchical Regression Analyses: Cognitive Performance regressed on *APOE* status, cognitive reserve and the interaction

	Goal Maintenance		**Updating**		**Inhibition**		**Subjective Cognition**	
Predictor	**β**	ΔR^2	**β**	ΔR^2	**β**	ΔR^2	**β**	ΔR^2
Step 1		.23*		.12		.03		.20*
ε4	.39*		.21		-.15		.13	.
ε2	.22		.38*		-.13		-.06	
Cognitive Reserve	-.36*		-.01		-.07		-.39*	
Step 2		.06		.04		.01		.11
ε4 x Cognitive Reserve	-.43		.25		.02		-.02	
ε2 x Cognitive Reserve	-.08		-.05		.17		.44*	

Notes: *p<.01. Step 1- df (3, 60), Step 2- df (2, 58)

Table 5.4. Hierarchical Regression Analyses: Cognitive Performance regressed on APOE status, physical activity (PA), and the interaction

	Goal Maintenance		Updating		Inhibition		Subjective Cognition	
Predictor	**β**	ΔR^2	**β**	ΔR^2	**β**	ΔR^2	**β**	ΔR^2
Step 1		.13		.16		.03		.12
ε4	.37*		.22		-.14		.15	
ε2	.10		.36*		-.16		-.14	
PA	.12		.19		.10		-.22	
Step 2		.09		.03		.02		.05
ε4 x PA	.37		-.27		.15		.08	
ε2 x PA	-.09		.-.11		-.05		-.22	

Notes: * p<.01. Step 1- df(3, 57), Step 2- df (2, 55)

Table 5.5. Hierarchical Regression Analyses: Cognitive Performance regressed on APOE status, cardiovascular and metabolic health, and the interaction

	Goal Maintenance		Updating		Inhibition		Subjective Cognition	
Predictor	**β**	ΔR^2	**β**	ΔR^2	**β**	ΔR^2	**β**	ΔR^2
Step 1		.12		.11		.03		.07
ε4	.34		.18		-.15		.16	
ε2	.06		.34		-.16		-.16	
CMH	-.14		-.08		-.05		-.03	
Step 2		.01		.00		.00		.03
ε4+ x CMH	-.02		.03		.02		.25	
ε2+ x CMH	-.14		.08		.02		.10	

Notes: * $p<.01$. Step 1- df(3, 57), Step 2- df (2, 55)

5.6 Discussion

The ε4 and ε2 variants of *APOE* have differential effects on cognitive fitness in later life (Corder, et al., 1994; Farrer et al., 1997), yet in this mid-aged sample, both ε4 and ε2 participants demonstrated subtle impairments on executive attention measures. The present research provides a preliminary exploration of how key factors implicated in cognitive ageing moderate the presence of *APOE* genotype effects in mid-adulthood.

The results support both independent and interactive effects of cognitive reserve on executive attention in mid-adulthood. Higher levels of cognitive reserve were associated with performance benefits in the 'online' maintenance of goals and fewer subjective reports of cognitive errors. After accounting for interactions with *APOE* genotype*,* cognitive reserve appears to exert a protective influence on goal maintenance abilities in ε4 carriers only. For subjective ratings of cognition, the positive effect of cognitive reserve for the ε3 control group remained significant, however the reverse was seen in ε2 carriers, in that higher levels of cognitive reserve were associated with more reported cognitive failings. In this sample of mid-age adults, neither physical activity nor indices of cardiovascular and metabolic health exerted independent or interactive effects on cognition.

Previous research has demonstrated an effect of mid-life cognitive reserve on later-life cognition and biomarkers of ageing (Tolppanen et al., 2015; Vemuri et al., 2014; Wirth et al., 2014). The present results, however, are important in suggesting cognitive reserve may influence the trajectory of cognitive ageing from at least the 5th decade. Support for a beneficial effect of cognitive reserve earlier in the lifespan indicates a potential neuroprotective role for factors, such as education, occupational complexity and cognitively engageing leisure activities, which increase reserve. This fits with recent evidence that cognitive reserve can both modulate the development of neuropathology across the lifespan and impede the behavioural manifestations of existing AD-related pathology (Arenaza-Urquijo, Wirth, & Chételat, 2015).

Of interest, the protective effect of cognitive reserve was selectively enhanced in ε4 carriers for performance on measures of active goal maintenance, an important result given that goal maintenance was sensitive to impairment in mid-age ε4 carriers. The observed interaction between *APOE* ε4 and cognitive reserve is in line with past research suggesting the protective effects of cognitive reserve are enhanced in ε4 carriers later in life (e.g Carlsson et al, 2008; Vemuri et al., 2014; Wirth et al, 2014, Brewster et al., 2014). A recent meta-analysis of fMRI studies including healthy older adults found increased cognitive reserve was associated with activation differences within bilateral frontoparietal regions, including the anterior cingulate,

precuneus and dorsolateral prefrontal cortex (Colangeli et al., 2016). These regions are implicated in executive control functions, and sensitive to ε4 differences in function prior to old age (Chen et al., 2016; Evans et al., 2014), aligning with the *APOE* ε4 x cognitive reserve interaction observed here in mid-adulthood. Importantly, this interaction at mid-adulthood suggests lifestyle cognitive enrichment may shift the emerging ageing trajectory of this group.

Links to the deposition of amyloid provides a potential mechanism for the protective effects of cognitive reserve in mid-age ε4 carriers. Cognitive reserve is reported to impact amyloid neuropathology (Jagust & Mormino, 2011; Landau et al., 2012; Rentz et al., 2010), with the relationship exaggerated in healthy older ε4 carriers (Schreiber et al., 2016; Wirth et al., 2014). Relative to ε3 carriers, a higher percentage of ε4 carriers show significant amyloid build-up by the 5th decade (Jack et al., 2015; Morishima-Kawashima et al., 2000). In addition, frontal regions (which support goal maintenance) show loss of neural integrity and amyloid build up early in the ageing process (Bartzokis et al., 2003; Raz, 2000; Villemagne et al., 2011) . The directional nature of these relationships need to be established, however.

In contrast to the findings of Soldan et al. (2013), the current study did not demonstrate cognitive benefits of higher cognitive reserve in ε2 carriers. The discrepant results may reflect the younger age group in the present study, or the particular measure of cognitive reserve (estimated from occupation and leisure activities). Alternatively, the results may simply indicate that ε2 carriers are less sensitive to modulation by both detrimental and protective factors associated with cognitive decline (McFall et al., 2015). The findings reported here should be interpreted with caution, due to the small number of ε2 carriers in the present analysis. Surprisingly, cognitive reserve was associated with greater reported cognitive failings in the ε2 group, though they had a higher mean cognitive reserve score than the ε3 group. It may be that diminished gains are measurable in those with high baseline scores. Across the sample, cognitive reserve was generally high with all participants having a CRq score classed in the mid-band or above (mid: n=15, mid-high n=33, high: n=17), hence, the protective effects of cognitive reserve may be greater in a more diverse sample.

The majority of research has demonstrated increased vulnerability in older ε4 carriers to the detrimental effects of risk factors associated with cognitive decline (e.g. physical inactivity, hypertension) (e.g. Woodard et al., 2012, Schuit et al., 2001; Etnier et al., 2007; Bunce et al, 2004; de Frias et al., 2007; Zade et al., 2010). The current study explored those relationships in a mid-age cohort, anticipating that negative risk factors would exacerbate the detrimental effects of ε4 genotype on executive attention. It may be that the age-range included here was too young, and that the participants, being reasonably healthy and normotensive, did not generate

the spread of scores needed to see modulatory effects. In support, Oberlin et al (2015) only observed the negative association between ε4 status and cognition in prehypertensive or hypertensive mid-age adults (systolic blood pressure > 130mm hg).

Several limitations of the current study must be addressed when considering the implications of these results. The number of participants in each genotype group was relatively small, and hence the analysis may be underpowered for detecting subtle effects, particularly relating to differences within the normal range of physiological functioning. In addition, the study used a self-report scale of exercise frequency. Previous studies have considered exercise as a function of average metabolic expenditure rather than weekly duration (Head et al., 2012), or objectively measured fitness (Etnier et al., 2007), which may provide a more indepth measure of physical activity. Also caution must be taken with attempting to infer the long term moderation of genotype effects by additional factors when the data is cross-sectional. The findings from this study, however, provide motivation for larger studies exploring the moderation of *APOE* genotype effects in mid-adulthood.

5.7 Conclusions

In this study, increased cognitive reserve, indexed through education, occupation and engagement in leisure activities, protected ε4 carriers against subtle impairments in goal maintenance abilities. Although reported physical activity did not interact with *APOE* ε4 status in this mid-age group, the results are consistent with the suggestion that *APOE* ε4 represents a plasticity gene, such that carriers from mid-adulthood show increased sensitivity both to protective and risk factors for cognitive ageing. This highlights the potential importance of taking steps to prevent cognitive decline earlier in the lifespan for those at increased risk. In contrast, the relative lack of ε2 interactions with cognitive reserve or current reported physical activity may suggest this variant shows reduced susceptibility to both positive and adverse influences.

6. Article 5

Prospective Memory: Age related change is influenced by APOE genotype

Article 5 is submitted to Neurobiology of Ageing as:

Lancaster, C., McDaniel M., Tabet, N., & Rusted, J. (*under review*). Prospective Memory: Age related change is influenced by APOE genotype

6.1. Abstract

Non-focal prospective memory (PM) is sensitive to age-related decline; an additional impairment in focal PM is characteristic of Alzheimer's disease. This research explores if differences in the demands of focal and non-focal PM retrieval expose cognitive differences in carriers of an *APOE* ε4 allele, a genetic risk factor for Alzheimer's disease, by mid-adulthood. 33 young and 55 mid-age adults, differentiated by *APOE* genotype, completed a category-decision task with a concurrent focal or non-focal PM task. In addition, ongoing WM load was manipulated to investigate whether genotype differences were more likely to be observed under high cognitive demand. Only mid-age ε4 carriers show a cost of carrying a focal PM intention. All groups showed a significant cost of carrying a non-focal PM intention; however, mid-age ε4 carriers showed greater cost than both the young ε4 group and mid-age ε3 group, consistent with compromised processing in this group by mid-adulthood. The profile of cost differences is consistent with that observed in pathological ageing, indicative of early vulnerability in the ε4 group.

Keywords: *APOE,* Prospective memory, Cognitive Ageing, Alzheimer's disease, Mid-adulthood

6.2. Introduction[7]

Prospective memory (PM) refers to the timely recall of a previously formed intention whilst being engaged in ongoing cognitive activity. Importantly, what distinguishes PM from retrospective memory is that retrieval of the intention is self-initiated (McDaniel et al., 2015), and hence it relies on a somewhat different subset of cognitive processes. Each day includes numerous examples of PM, such as remembering to take medications on time or to pass on a message to a family member, and hence PM is important for maintaining independent living in older adulthood (Kliegel et al., 2016; McDaniel et al., 2008).

6.2.1. Age-related change in prospective memory

Healthy ageing is associated with decline in PM performance, with the greatest change seen in situations where carrying the PM intention burdens available cognitive processing resources (Henry et al., 2004; Kliegel et al., 2008). The cognitive demand of PM is, in part, dependent on how central the cue initiating PM retrieval is to the ongoing task (Scullin et al., 2010). The multi-process framework of PM (McDaniel & Einstein, 2000) argues that focal cues, defined as those that are processed directly as part of the ongoing task, activate spontaneous, relatively automatic retrieval processes. In contrast, features of non-focal PM cues are not processed as part of the ongoing task, and hence cognitive control is required to maintain the intention at the forefront of attention and actively monitor for its presence (Einstein et al., 2005; McDaniel et al., 2015; Scullin et al., 2010). As ageing is associated with reduced cognitive processing resources (Salthouse, 1991), non-focal PM is subject to substantially greater impairment than focal PM with increasing age. Aligned with this pattern, non-focal PM is supported by frontal regions of the brain (Cona et al., 2016; Cona et al., 2015; McDaniel et al., 2013), which show early sensitivity to age-related change (Bartzokis et al., 2003; Raz, 2000; Villemagne et al., 2011). Pathological cognitive ageing is distinguished by an additional impairment in focal PM (Blanco-Campal et al., 2009; Costa et al., 2011; Duchek et al., 2006; McDaniel et al. 2011). This may be due to greater reliance of retrieval on 'bottom-up' attention and associative memory processes, mediated by occipital, parietal (Cona et al., 2016) and temporal lobe regions (McDaniel et al., 2013).

[7] **Abbreviations:** Prospective Memory (PM), Apolipoprotein E (*APOE),* working memory (WM)

6.2.2. Does *APOE* influence age-related change in prospective memory?

The distinct profiles of PM impairment associated with healthy and pathological cognitive ageing provide an interesting framework for exploring the effects of Apolipoprotein E (*APOE*) ε4 across the lifespan. *APOE* ε4, one of the three variants of the *APOE* single nucleotide polymorphism (ε2, ε3, ε4), is a well established risk factor for Alzheimer's disease (AD) (Corder et al., 1993). In addition, carrying at least one copy of the ε4 allele is linked to poorer cognition in healthy older adults (e.g. Jack et al., 2015; Marioni et al., 2015; Reinvang et al., 2010; for reviews see: Small et al., 2004; Wisdom et al., 2011), although this result has not consistently been found (e.g. Bunce et al., 2014; Bunce et al., 2004; Salo et al., 2001). One reason behind this inconsistency may be the non-uniformity of ε4 effects across cognitive domains (Lancaster et al., 2017; Small et al., 2004; Wisdom et al., 2011).

Evidence for the sensitivity of PM to *APOE* genotype effects in later life is mixed. Whilst carrying an ε4 allele was associated with increased impairment on a focal PM task in adults with mild AD, healthy older ε4 carriers demonstrated performance advantages compared to their non-ε4 peers (Duchek et al., 2006). Other research however, reported a non-significant effect of *APOE* status in both focal and non-focal PM conditions in a group of healthy older adults (McDaniel et al., 2011).

Reports of an association between *APOE* genotype and cognition are not restricted to later life (for reviews see: Ihle et al., 2012; Lancaster et al., 2017; Rusted & Carare, 2015; Salvato, 2015). A cross-sectional comparison of mid-age (45-55 years) and young adults (18-30 years) suggested a speed-accuracy trade-off in mid-age ε4 carriers, with greater non-focal PM retrieval accuracy coupled with slower ongoing task response times (RTs) (Evans et al., 2014). In this study, task-related BOLD activity in the left inferior frontal gyrus correlated with PM accuracy in ε4 carriers, interpreted as a premature shift towards a reliance on frontal lobe activation to support cognitive performance.

Lancaster et al. (2016) reported that mid-age ε4 carriers showed subtle impairments in non-focal PM retrieval accuracy. In addition, ε4 carriers demonstrated reduced accuracy selectively for incongruent trials of a Stroop-switch paradigm. The updating of goals within executive attention has consistently been linked to successful non-focal PM retrieval (Schnitzspahn et al., 2013; Zuber et al., 2016). In addition the profile of errors on the Stroop task supported impairments in the flexible control of multiple goals at the forefront of attention (Conway & Kane, 2001; Kane & Engle, 2003). Hence, ε4 carriers may be showing early differences in this component of executive attention by mid-adulthood. This is an important avenue for future exploration, as by

identifying which cognitive processes differentiate those at heightened risk of cognitive decline in mid-adulthood, steps can be made towards developing early intervention strategies.

6.2.3. Aims and hypotheses

The principle aim of this study is to explore age-related *APOE* genotype differences in focal and non-focal PM to help illuminate which cognitive processes are potentially more sensitive to premature age-related change in those at heightened genetic risk of cognitive decline. The PM task (McDaniel et al., 2011) was embedded within an ongoing category decision task, and the type of PM cues (focal versus non-focal) were manipulated . Both PM retrieval accuracy and prospective interference (Marsh et al., 2003) or cost of carrying a PM intention on ongoing task performance, will be used in conjunction to index how well volunteers are completing the task. For both the 'at-risk' ε4 group and homozygous ε3 carriers (the population 'norm'), cross-sectional age-related differences in performance will be used to explore the prediction that ε4 carriers show a profile of accelerated ageing. In addition, in mid-adulthood, performance of ε4 carriers will be directly compared with their ε3 peers to address whether this group is demonstrating disadvantages by the 5th decade.

Following Henry et al. (2004) and Kliegel et al. (2008), we anticipated that mid-age adults would find the non-focal PM condition more challenging than younger adults due to the demand this places on executive attention resources. This may be reflected in increased interference for ongoing task performance or reduced PM retrieval accuracy. The effect of age on focal PM performance was predicted to be substantially smaller, in agreement with the suggestion that focal PM intentions can be successfully retrieved using automatic 'stimulus-driven' processes (Harrison & Einstein, 2010; Scullin et al., 2010).

Following Lancaster et al. (2016), we predicted that mid-age ε4 carriers' premature decline in executive attention would increase their age-related deficit in non-focal PM, while focal PM performance would be equivalent. As an additional measure, subjective indices of task demand and motivation were included as an exploratory means of assessing if *APOE* genotype differences can be accounted for by different approaches to performing the task.

A second goal of the study was to probe the effect of adding a working memory (WM) load within the ongoing task on PM performance. The WM load manipulation was designed to place an additional tax on executive functioning, and hence exaggerate any genotype differences present by mid-adulthood. WM and non-focal PM are hypothesized to draw on distinct yet overlapping frontal lobe systems (Basso et al., 2010, Reynolds et al., 2009) and hence tasks

loading on the central executive of WM disrupt PM performance (Marsh et al., 2002; West et al., 2006). With age-effects reported previously for PM under WM load (Bisiacchi et al., 2013), it was predicted WM load would exacerbate emerging non-focal PM impairments in the mid-age group.

6.3. Methods

6.3.1 Participants

Participants were recruited from an existing database of young and mid-age volunteers who had previously provided swabs for *APOE* genotyping, or via advertisement in the local community. An independent third party pseudo-randomly selected the participants from the database, to maintain the population bias towards homozygous ε3, while recruiting a suitable sample size of ε4 carriers. No genotype information was provided directly to the researcher; genotype was added to the anonymised dataset provided by the researcher at the end of the study. For inclusion, participants had to be aged 18-30 years or 45-56 years and using English as their daily language. Exclusion criteria were: a self-reported history of neurological or psychiatric illness within the past 5 years and self-reported psychoactive medication use.

All genotyping procedures followed UK Human Tissue Authority (HTA) guidelines, with ethical approval for the study granted by the Research Ethics committee of the School of Psychology and Life Sciences, University of Sussex. Volunteers were first asked to provide written informed consent, including acknowledgment that the results of the genotype analysis would not be made available to them. DNA was then collected with a buccal swab, using an Isohelix SK1 kit. Genotyping followed triangulated anonymisation procedures, with two anonymised codes used per sample. Samples were analysed to determine *APOE* gene variant by LGC Genomics (Hertfordshire, www.lgcgroup.com/genomics). A fluorescence-based competitive allele-specific polymerase chain reaction determined the presence of three major *APOE* alleles (ε2, ε3, and ε4) based on two *APOE* single nucleotide polymorphisms (SNPs) (rs429358, rs7412).

The final sample consisted of 37 young volunteers (2 ε2/ε3, 1 ε2/4, 16 ε3/ε3, 12 ε3/ε4, 5 ε4/ε4, 1 unknown), and 58 mid-age volunteers (3 ε2/ε2, 1 ε2/ε4, 36 ε3/ε3, 14 ε3/ε4, 4 ε4/ε4). Prior to analysis individuals with ε2/ε2 or ε2/ε3 genotypes were excluded. Volunteers with ε3/ε3 genotype, henceforth referred to as ε3 carriers, were treated as the control group, justified by this genotype being most prevalent in the population (Farrer et al., 1997). All volunteers

carrying an ε4 allele (ε2/ε4, ε3/ε4, ε4/ε4) were grouped together, henceforth referred to as ε4 carriers[8]. Volunteer characteristics for the analysed dataset are shown in Table 6.1.

Table 6.1. Demographic characteristics of participants

	Age	Gender (% F)	IQ
Youngs			
ε3 (*n*=16)	20.75 (1.81)	69	112.34 (6.07)
ε4 (*n*=18)	21.33 (2.61)	83	109.88 (6.14)
Mids			
ε3 (*n*=36)	50.22 (2.74)	69	122.03 (2.76)*
ε4 (*n*=19)	49.74 (3.53	68	119.44 (3.59)

* Denotes a significant genotype group difference (p>.05).

6.3.2 Materials

6.3.2.1. Demographics and baseline measures

A short demographic questionnaire was administered establishing age, gender, occupation and general health (smoking status, medication use, blood pressure). Blood pressure and pulse rate were measured using an automatic upper-arm cuff machine. The National Adult Reading test (Nelson & Willison, 1991) was administered to provide a baseline measure of IQ. In addition, the 12-item Grit Scale (Duckworth et al., 2007) was used to measure individual differences in trait-level perseverance and adherence to long-term goals.

6.3.2.2. Category decision PM task

Ongoing category decision trials consisted of on-screen item and category pairings, with participants required to indicate if the lowercase word on the left (e.g. dentist) belonged to the same category as the uppercase word on the right (e.g. PROFESSION). Participants pressed a 'y' button or 'n' button, representing 'yes' and 'no' respectively to make this judgment.

The task was divided into 3 blocks (control, focal PM and non-focal PM), counterbalanced across participants. In each block (control, focal PM and non-focal PM) there were 106 category decision-pairings (53 congruent, 53 incongruent) taken from Einstein et al. (2005). Three lists of category pairings were used across the 3 task blocks, with the order of lists counterbalanced across participants, independent of the order of PM conditions.

[8] Volunteers with ε2/ε4 genotype were retained in the present analysis, however, the effect of these two alleles in combination is not well established. The results of an additional analysis removing these two volunteers were not significantly different.

In the focal PM block participants were given an additional instruction to make a 'Q' keyboard press if a target word was presented as part of a category decision trials. The focal PM target was either: tortoise, raspberry or aluminum, counterbalanced across participants. The focal PM target was always presented 3 times, embedded in the 31st, 72nd and 102nd category decision trials. In the non-focal PM condition, participants were instructed to make a 'Q' keyboard press at any point during the category decision trials if a target syllable was presented: tor, ras, min. Again, the non-focal PM target was counterbalanced across participants to ensure no individual received the same target for both conditions (e.g. tortoise, tor). The non-focal PM cue was presented three times (tor: tortoise, history, motorcycle; ras: raspberry, harassment, grasshopper; min: aluminum, peppermint, minister), embedded in category decision trials 31, 72 and 102. In both focal and non-focal PM blocks, the PM cue was always presented on the left of the category decision pairing in lower case font. The addition of 3 PM trials led to a total of 109 trials in these two blocks. In the control condition participants were not given an additional PM instruction, and hence were only instructed to respond to the 106 category-decision pairings.

At the start of the task, participants were instructed to make their category decision judgments as quickly and as accurately as possible. There were 12 practice trials, including 6 trials providing feedback on response time and accuracy. Before each PM block (focal, non-focal) participants were given the PM instructions, with an additional point being that if they were unable to press the 'Q' key on the PM trial, they could make this response as soon as possible after the trial concluded. Participants were then asked to repeat these instructions back to the experimenter in their own words to ensure they had understood the task before being allowed to proceed. Between summarizing the PM instruction and beginning the PM block there was a 1-minute delay task to create a break between encoding and retrieval. Following this delay, participants were reminded of the ongoing category decision instructions but there was no mention of the PM instruction. Upon completion of each PM block, participants were told the PM cue would not appear again in the subsequent blocks.

6.3.2.2.1 WM manipulation

The full category decision task was administered a second time with an additional WM load. The task was presented in the format described previously, but each participant had a different counterbalanced order of blocks (control, focal and non-focal) and lists of category-decision pairings.

The WM task asked participants to monitor how many times the word 'fish' appeared as part of a category-decision pairings. 'Fish' could be presented as either the example (lowercase, left-hand side) or the category (uppercase, right-hand side). Participants were not allowed to make a record of targets, but were instructed to keep a count mentally. The number of WM targets (3, 4, 6) varied for each block, dependent on the counterbalanced order of category-decision lists presented. At the end of each block, participants were prompted to recall the number of targets.

6.3.2.3 The NASA task load index

Perceived workload was measured at the end of each version of the category decision task using a pen-and-paper version of the NASA task load index. This consists of 6 visual analogue scales measuring: mental demand, physical demand, temporal demand, performance, effort, and frustration. Participants were instructed to mark along the scale to indicate how they had experienced the category decision task (No load, WM load). Only data from two subscales: 1) mental demand, 2) effort were relevant to the current research questions.

6.3.4. Procedure

Volunteers took part in a single study session lasting 60 minutes, outlined in Figure 6.1. Mood, blood pressure and pulse were measured both before and after completing each version of the category decision task (no WM load, WM load). During the category decision task, a one-minute interval after receiving the instructions for each condition (control, focal and non-focal) was filled by a single verbal fluency trial in which volunteers were asked to generate as many words beginning with a select letter (F, A, S) as possible in 60 seconds (Strauss, Sherman, & Spreen, 2006). Participants were not reminded of the PM instruction before resuming the category-decision task. At the end of each version of the category decision task, participants were asked to complete a NASA task load index reflecting on all three conditions (control, focal and non-focal). Participants who were not recruited from the pre-genotyped *APOE* database provided a buccal swab at the end of the session.

6.3.5. Statistical Analysis

For each age group, genotype differences in demographic characteristics were screened using either an independent *t*-test (age, IQ) or a chi-squared test (gender).

6.3.5.1. Category decision PM task

Prior to analysis, category decision performance in each age group was screened for outliers, and RTs more than 3 standard deviation (SD) away from each individual's mean were removed. In the mid-age group, accuracy was above 85% and there were no consistent outliers across conditions for decision-making RT. In the young group one participant was removed, with their average accuracy falling below 80%, and their RTs classed as outliers in 5/6 conditions.

The between-subjects factors considered in the following analysis were Age (young, mid) and *APOE* genotype (ε3, ε4). Condition (control, focal, non-focal) and Load (no load, WM load) were considered as within-subject factors.

For PM retrieval accuracy, effects of Age and Genotype on focal and non-focal PM were analysed using a mixed 2 (Condition: focal, non-focal) x 2 (Age) x 2 (Genotype) ANOVA.

A preliminary analysis comparing category decision accuracy across conditions was completed using separate one-way ANOVAs for the no load and WM load versions of the task. RTs in the control condition (no PM intention, no WM load) of the category decision task were analysed using a 2 (Age) x 2 (Genotype) ANOVA.

The cost of carrying a PM intention for ongoing category decision performance was indexed by a significant difference between RT in the PM condition and the control condition, with separate analyses completed for focal and non-focal PM intentions. For category decision RTs, a 2 (Condition: control, PM condition) x 2 (Age) x 2 (Genotype) ANOVA was run to investigate group differences in the presence of PM interference costs. Following a significant Condition x Age x Genotype interaction, differences were probed using a single cost measure (PM condition–control condition), with a Bonferonni adjustment used to control for multiple comparisons.

The impact of adding a WM load to PM retrieval was analysed using a 2 (Load) x 2 (Condition: focal, non-focal) x 2 (Age) x 2 (Genotype) mixed ANOVA. Prospective interference following the addition of a WM load was analysed separately for focal and non-focal conditions, using a 2 (Condition: control, PM condition) x 2 (Age) x 2 (Genotype) ANOVA. Interactions were probed using a single cost measure, with a Bonferonni-adjusted alpha.

6.3.5.2. Motivational factors and perceived difficulty

Group differences in overall Grit score were analysed using a 2 (Age) x 2 (Genotype) between-subjects ANOVA. For each scale of the NASA, a mixed 2 x 2 x 2 ANOVA was completed,

with Load (no load, WM load) as the repeated-measures factor, and Age and Genotype as the between-subjects factor. Interactions were probed using Bonferroni-adjusted t-tests.

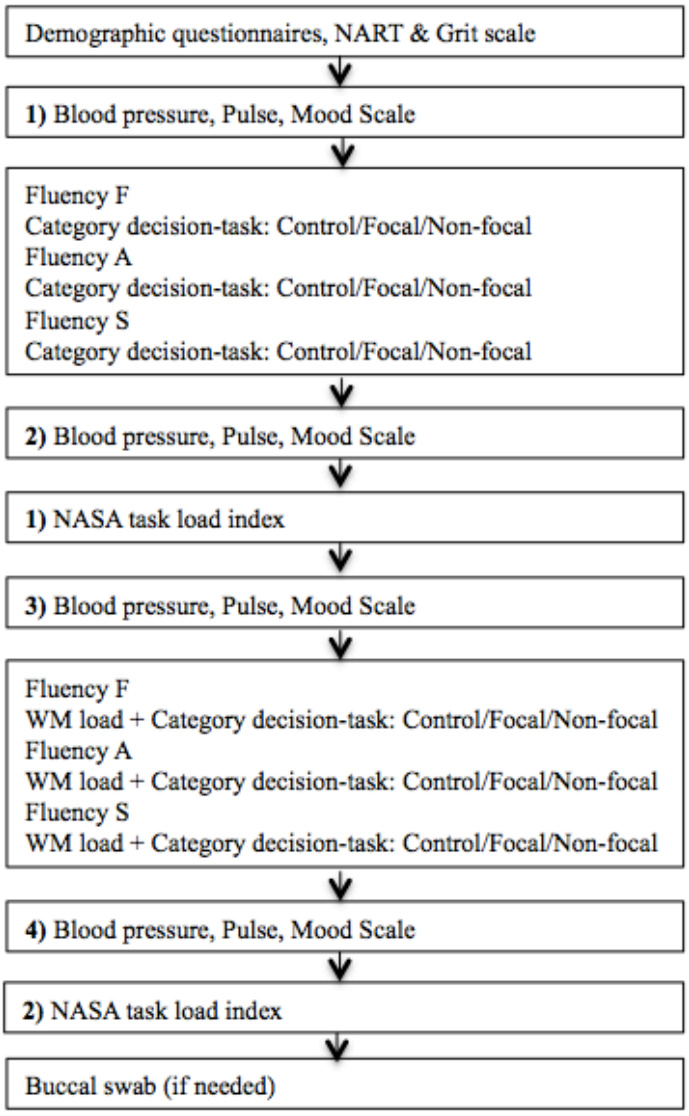

Figure 6.1. Timeline of experimental procedure

6.4. Results

6.4.1. Volunteer Characteristics

In the young group, there were no significant genotype differences in age, gender or IQ (p>.05). Mid-age adults did not significantly differ by genotype in age or gender (p>.05) however, mid-

age ε4 carriers had significantly lower estimated IQ scores than mid-age ε3 carriers, $t(53)=2.98$, $p=.004$.[9]

6.4.2. Category decision PM task

6.4.2.1. PM accuracy

Retrieval accuracy for focal PM was significantly higher than for non-focal PM, $F(1, 83)=28.48$, $p<.001$, $\eta^2_p=.244$. The main effects of Age and Genotype, as well as all interaction terms, were non-significant ($p>.05$). The mean proportion of focal and non-focal PM cues correctly retrieved for each volunteer group can be seen in Table 6.4.

6.4.2.2. Category decision performance

Accuracy was consistently high across conditions, ranging from 81% to 100%. In addition, the inclusion of a PM intention (focal or non-focal) did not significantly impact category decision accuracy, either under no load and WM load ($p>.05$). Hence all further considerations of category decision performance will be restricted to RTs. Table 6.2 shows mean accuracy for each group for each condition.

Young participants were significantly faster in the baseline category decision condition than the mid-age group, $F(1, 83)=9.38$, $p=.003$, η2 p=.102, but the main effect of genotype was non-significant ($p>.05$). There was no significant Genotype x Age interaction ($p>.05$).

Table 6.2. Mean accuracy on the category decision task shown by age and genotype group

		Young		Mid-age	
		ε3	**ε4**	**ε3**	**ε4**
Control	**No Load**	.93 (.03)	.91 (.03)	.96 (.03)	.96 (.03)
	WM Load	.93 (.03)	.94 (.03)	.96 (.02)	.96 (.03)
Focal	**No Load**	.92 (.03)	.92 (.03)	.96 (.03)	.96 (.03)
	WM Load	.93 (.02)	.93 (.03)	.96 (.02)	.96 (.03)
Non-focal	**No Load**	.92 (.03)	.93 (.03)	.96 (.03)	.97 (.03)
	WM Load	.94 (.03)	.93 (.03)	.96 (.03)	.95 (.03)

Notes: Values represent mean (SD)

[9] All main analyses were run including IQ estimate as a covariate. IQ did not significantly ($p>.05$) account for variance in category decision task performance and so is not commented on further.

6.4.2.3. PM interference cost

Mean RT on the category decision task across control, focal and non-focal conditions is summarised by group in Table 6.3.

6.4.2.3.1. Focal condition.

Category decision RTs were significantly longer in the focal PM condition (M=1166, SE=21) compared to the control condition (M=1097ms, SE=21ms)(standard error=SE), $F(1,83)=30.91$, $p<.001$, η2 p=.271. In addition, mid-age volunteers (M=1207, SE=26) were significantly slower than young volunteers (M=1097ms, SE=21ms), $F(1,83)=13.73$, $p<.001$, η2 p=.142. Importantly, there was a significant Condition x Age x Genotype interaction, $F(1,83)=4.50$, $p=.039$, η2 p=.051, shown in Figure 6.2.

Only mid-age ε4 carriers showed a significant cost of carrying a focal PM intention on category decision RTs ($p=.001$); the cost in all other groups was non-significant ($p>.006$). Moreover, the Age x Genotype interaction indicated that mid-age ε4 carriers demonstrated greater cost than both young ε4 carriers ($p=.016$) and mid-age ε3 carriers ($p=.029$), however, following adjustment for multiple comparisons (SME, Bonferroni-adjusted α = .006) these differences did not reach significance. There was no significant genotype difference in young volunteers ($p=.361$), and focal PM cost was equivalent between age-groups for ε3 carriers ($p=.680$).

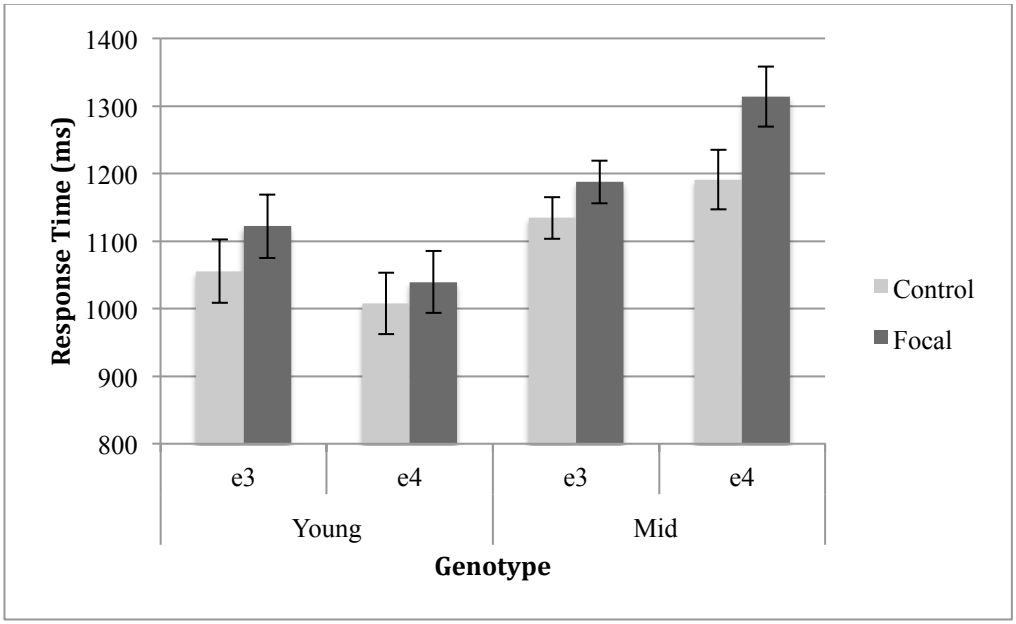

Figure 6.2. *Mean category decision RT shown for the control and focal condition.*

6.4.2.3.2. Non-focal condition

Category decision RTs were significantly longer in the non-focal PM condition (M=1486ms, SE=43ms) than the control condition (M=1097ms, SE=21ms), $F(1,83)=142.99$, $p<.001$, η2 p=.633. In addition, across conditions mid-age volunteers (M=1394ms, SE=38ms) were significantly slower than young volunteers (M=1189ms, SE=46ms), $F(1,83)=13.73$, $p<.001$, η2 p=.142. There was a significant Condition x Age x Genotype interaction, $F(1,83)=5.27$, $p=.024$, η2 p=.060, shown in Figure 6.3.

SME analysis (Bonferroni adjusted α of .006) of the Age x Genotype interaction for non-focal RT cost (entered as a single variable) revealed mid-age ε4 carriers demonstrated significantly greater cost than young ε4 carriers ($p=.003$), while there was a non-significant age-difference in the ε3 group ($p=.984$). In young volunteers, the genotype difference was non-significant ($p=.177$). At mid-age, there was a trend for ε4 carriers demonstrating greater cost than their ε3 counterparts ($p=.054$).

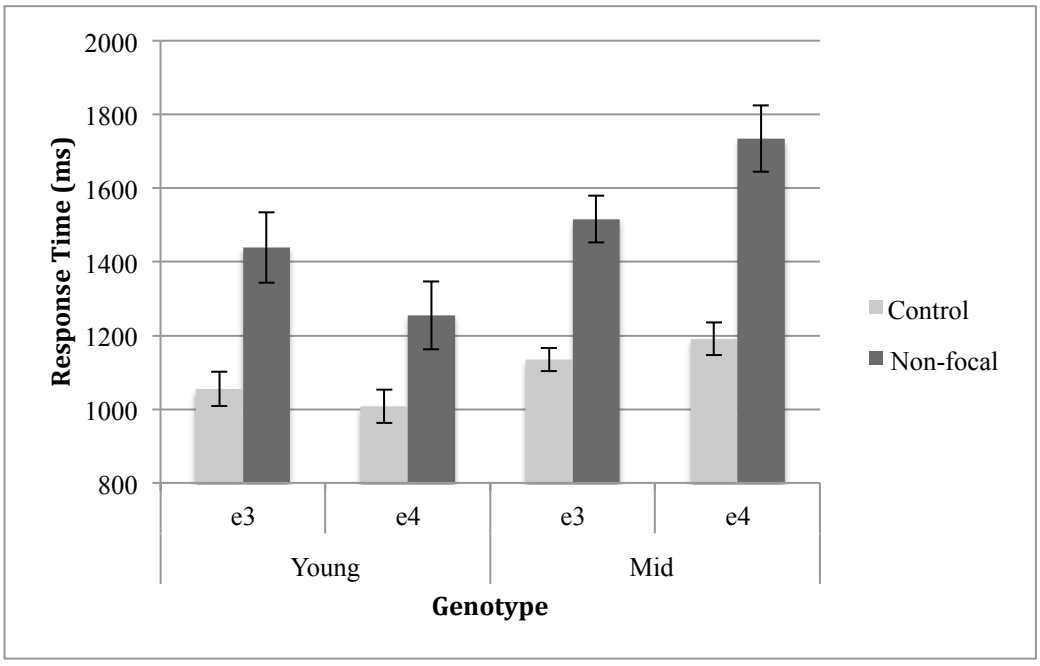

Figure 6.3. *Mean category decision RT shown for the control and non-focal condition.*

Table 6.3. Mean RT and PM cost shown for category decision performance under no load and WM load

			Young		Mid	
			ε3	**ε4**	**ε3**	**ε4**
Control	**No Load**	**RT**	1055 (129)	1008(142)	1134 (206)	1191 (223)
	WM Load		1048 (104)	1008 (147)	1117 (184)	1181 (202)
Focal	**No Load**	**RT**	1122 (163)	1039 (109)	1187 (219)	1314 (199)
		Cost	67 (77)	32 (72)	53 (120)	123 (136)
	WM Load	**RT**	1139 (117)	1078 (158)	1224 (203)	1306 (295)
		Cost	91 (73)	70 (79)	106 (77)	125 (152)
Non-Focal	**No Load**	**RT**	1439 (269)	1254 (218)	1516 (381)	1735 (556)
		Cost	383 (255)	247 (209)	382 (263)	544 (404)
	WM Load	**RT**	1327 (119)	1245 (212)	1458 (350)	1550 (418)
		Cost	279 (120)	237 (140)	340 (223)	369 (249)

Notes: Values represent Mean (SD)

6.4.2.4. The addition of a WM load

Group differences in WM retrieval accuracy are included in the Appendix.

6.4.2.4.1. PM retrieval

Across both focal and non-focal PM, WM did not significantly impact PM retrieval accuracy (p >.05), however, there was a significant Load x Age interaction, $F(1, 83)=4.33$, $p=.040$, $\eta 2$ $p=.050$. In the mid-age volunteers, PM retrieval was marginally less accurate under the WM load condition than in the no load condition ($p=.028$). Young volunteers did not show a significant difference in PM accuracy between no load and WM load ($p>.05$) (Bonferroni-corrected $\alpha=.025$). There were no genotype differences in PM accuracy under WM load, and no significant genotype interactions ($p>.05$). Accuracy of PM retrieval under WM load is shown in Table 6.4.

Table 6.4. The mean proportion of correct PM responses across conditions (Focal/Non-focal; No Load, WM Load)

		No Load		WM load	
		Focal	**Non-focal**	**Focal**	**Non-focal**
Young	**ε3**	.98 (.08)	.67 (.35)	.92 (.26)	.71 (.30)
	ε4	.82 (.34)	.65 (.36)	.96 (.16)	.67 (.37)

Mid	**ε3**	.94 (.21)	.70 (.35)	.89 (.26)	.68 (.34)
	ε4	.98 (.08)	.74 (.35)	.86 (.32)	.67 (.35)

6.4.2.4.2 Prospective interference under WM load

Mean RT on the category decision task under WM load is shown for control, focal and non-focal conditions in Table 6.3, summarised by group. Under WM load, category decision RTs were significantly longer in the focal PM condition (M=1186ms, SE=23ms) than the control condition (M=1089ms, SE=19ms), $F(1,83)=79.49$, $p<.001$, η2 p=.486; however, there were no significant effects of age or genotype ($p>.05$). All interaction terms were non-significant.

Under WM load, category decision RTs were significantly longer in the non-focal PM condition (M=1395ms, SE=35ms) compared to the control condition (M=1089ms, SE=19ms), $F(1,84)=79.49$, $p<.001$, η2 p=.687. Across conditions, there was a main effect of Age, $F(1,84)=10.50$, $p=.002$, η2 p=.111, and a significant Age x Condition interaction, $F(1,84)=4.57$, $p=.035$, η2 p=.052. This was driven by the mid-age group (M=350ms, SD=231ms) demonstrating greater cost than the young group (M=258ms, SD=231ms), $t(85.78)=-2.41$, $p=.018$. The effect of genotype was non-significant, as were all other interactions ($p>.05$).

6.4.3. Motivational factors and perceived difficulty

6.4.3.1. Grit Trait Score

There was a significant effect of age, $F(1, 84)=7.90$, $p=.006$, η2 p=.086, with mid-age adults (M=3.72, SD=.42) scoring higher on this questionnaire than young adults (M=3.42, SD=.45). There was a no main effect of Genotype, or Genotype x Age interaction ($p>.05$).

6.4.3.2. The NASA task-load index

Load ratings of the no load and WM load category decision task are shown in Table 6.5.

The no load category decision task (M=44.76, se=2.52) was associated with higher mental demand than the WM load category decision task, M=33.26, se=2.31), $F(1, 84)=23.85$, $p<.001$, η2 p=.221. Mid-age volunteers (M=43.44, se=2.73) reported significantly greater mental demand than young adults (M=34.89, se=3.29), $F(1, 84)=4.38$, p=.039, η2 p=.050. The main effect of genotype was non-significant ($p>.05$), but there was a significant Genotype x Load interaction, $F(1, 84)=6.77$, $p=.039$, η2 p=.075. SME (Bonferroni-adjusted α=.013) revealed ε4

carriers, but not ε3 carriers (p=.092), showed a significant drop in perceived demand under WM compared to the no load condition (p<.001). In the no load and in the WM load condition, genotype groups did not significantly differ in their mental demand ratings (p>.013).

Subjective estimates of effort were greater for the no load condition (M=47.94, SD=24.62) than the WM load condition (M=36.00, SD=20.44), F(1, 83)=3.29, p=.073, η2 p=.038. The main effects of both age and genotype were non-significant (p>.05), however, there was a significant Load x Age x Genotype interaction, F(1, 83)=10.69, p=.002, η2 p=.114. SME analysis found no significant age-difference in ε4s in the perceived effort completing the no load condition (p=.513), however, mid-age ε4s reported greater effort than young ε4s under WM load (p=.019). In the young group, but not the mid-age group, effort decreased from no load to WM load (p<.001) (Bonferroni corrected α=.013). The Load x Age interaction was non-significant in the ε3 group (p>.05).

Table 6.5. NASA scores of mental demand and effort for the no load and WM load version of the category decision task

		Young		**Mid**	
		ε3	**ε4**	**ε3**	**ε4**
No Load	**Demand**	37 (17)	46 (21)	43 (26)	54 (22)
	Effort	43 (28)	54 (27)	46 (27)	49 (23)
WM load	**Demand**	31 (18)	26 (19)	38 (24)	40 (18)
	Effort	36 (18)	29 (16)	34 (22)	45 (22)

6.5. Discussion

The present study addressed two research questions: 1) Do carriers of an *APOE* ε4 allele, a genetic risk factor for poor cognitive ageing, show a distinct profile of age-related change in focal versus non-focal PM retrieval accuracy or cost of carrying an intention? 2) Does adding a WM load to the ongoing task differentially impact PM performance according to age or genotype? In addition, the research included subjective indices of mental demand and effort to explore group differences in how the task was performed.

Irrespective of cue focality, the current findings do not support early life *APOE*-genotype differences in PM retrieval accuracy. PM interference, or the cost of carrying a PM intention on ongoing task performance, however, was sensitive to the detrimental effects of *APOE* ε4 by mid-adulthood. Carrying a focal PM intention selectively disadvantaged ongoing task performance in mid-age ε4 volunteers. For both focal and non-focal PM intentions, evidence for an age-associated increase in PM interference was limited to carriers of the disadvantageous ε4

allele. Furthermore, there was a trend of the mid-age ε4 group demonstrating greater non-focal cost than their age-equivalent ε3 counterparts. Including a concurrent WM load alongside ongoing category demands negatively impacted PM retrieval in the mid-age group only; however, inclusion of a WM load did exaggerate genotype differences in PM by mid-age.

Based on previous research (Lancaster et al., 2016), we anticipated that genotype differences would selectively be observed in non-focal PM retrieval, consistent with the enhanced vulnerability of frontal-based executive systems to *APOE* genotype effects from mid-adulthood. In this study, ε4 carriers, demonstrated equivalent PM retrieval accuracy for both focal and non-focal cues, but registered a cost in maintaining the PM intention. Past research measuring BOLD activity during non-focal PM retrieval suggested the employment of early compensatory strategies in mid-age ε4 carriers (Evans et al., 2014). Hence, it may be that ε4 carriers are employing attentional resources differently to support PM retrieval.

Genotype differences were reported in the cost of maintaining a PM intention on ongoing task performance, with mid-age ε4 carriers demonstrating increased cost of carrying both a focal and non-focal PM intention. The presence of both focal and non-focal disadvantages by mid-adulthood in this 'at-risk' group, importantly, is consistent with the profile of impairment observed in the very early stages of pathological memory decline (Duchek et al., 2006; McDaniel et al.2011). Focal PM retrieval is hypothesised to rely on spontaneous, associative memory processes, supported by the medial temporal lobe (MTL) (Atienza et al., 2011; McDaniel et al., 2013). Structural differences in MTL volume are associated with focal PM accuracy in both healthy older adults and adults in the early stages of dementia (Gordon, Shelton, Bugg, McDaniel, & Head, 2011). Hence, the presence of focal costs in ε4 carriers by mid-adulthood indicates compromised associative memory processes in this group. In support, other research has indicated MTL regions are sensitive to ε4 differences by mid-adulthood (Den Heijer et al., 2002; Shaw et al., 2007; Wishart et al., 2006), and these differences have been interpreted as early vulnerability in neural systems sensitive to the pathological change associated with AD.

In addition, ε4 carriers demonstrated increased interference of carrying a non-focal PM intention by mid-adulthood. One account of non-focal prospective interference costs is that individuals adjust the distribution of executive resources to the ongoing task based on their ability to cope with the demands of the PM (Boywitt & Rummel, 2012; Marsh et al., 2005). In support, increased variability of ongoing task RTs following the introduction of a non-focal PM correlated with successful PM retrieval (Loft et al., 2014), reflecting the necessary monitoring processes implemented to support retrieval. Our results suggest that by mid-adulthood, ε4

carriers may be committing a greater proportion of cognitive resources to support equivalent levels of PM retrieval compared to the ε3 group, and reduced ability to maintain and co-ordinate multiple goals at the forefront of attention (Lancaster et al, 2016), consistent with the speed-accuracy trade-off reported by Evans et al (2014). Sustained processing during non-focal PM is associated with BOLD activation in dorsal frontal-parietal regions and the precuneus (Cona et al., 2016). Sensitivity to *APOE* differences has previously been reported in these regions (Chen et al., 2016; Evans et al., 2014).

Mid-age ε4 carriers showed a greater age-related increase in ongoing task cost (relative to young ε4 carriers) than did mid-age ε3 carriers (relative to young ε3 carriers) for both focal and non-focal PM intentions. More broadly, this implies the *APOE* ε4 genotype represents a trajectory of accelerated ageing, with subtle impairments present from mid-adulthood. However, a recent investigation into the *APOE* differences in age-related cognitive change prior to age 50 reported smaller declines in a composite of executive functioning in ε4 carriers (Taylor et al., 2016). This composite consisted of a different set of executive processes (fluency, switching and inhibition) than those targeted in the present study, perhaps indicating non-uniform effects of *APOE* genotype across executive functions. Of interest, our data were in the direction of a smaller PM cost in young ε4 carriers compared to their ε3 counterparts. This aligns with previous reports of an ε4 advantage in executive attention in youth ((Marchant et al., 2010; Rusted et al., 2013).

An alternative account of the age-related increase in PM interference costs observed in ε4 carriers is that greater costs are associated with increased ongoing response hesitancy, resulting from the need to make a more complicated decision (i.e. both a category-decision and a PM decision) (Heathcote et al., 2015; Horn et al., 2013; Strickland et al., 2017). It may be that mid-age ε4 carriers are adopting a more conservative task strategy to support PM retrieval, driving the observed performance differences.

To increase the tax placed on executive resources, a concurrent WM load task was included alongside ongoing category decision-making. Independent of focality, the additional of a WM load negatively impacted PM retrieval in the mid-age group. This supports previous reports of an age-related difference in sensitivity to the effects of a secondary WM demand, with older adults demonstrating greater PM failings than young adults under load (Bisiacchi et al., 2013; Logie et al., 2004). In addition, the mid-age group recalled a smaller proportion of WM targets (see appendix), suggesting increased difficulty maintaining multiple task goals by mid-adulthood, or the ability to flexibly apply attention to these goals (Kane & Engle, 2003).

While we anticipated that adding a WM load to ongoing processing would further expose early PM decline in ε4 carriers, there was in fact, no *APOE*-genotype difference in PM retrieval accuracy, and counter intuitively, the Age x Genotype interaction for ongoing task cost disappeared under WM load, with mid-age ε4 carriers showing similar cost to their ε3 counterparts. Following the inclusion of a WM load, a cost of carrying a focal PM intention was observed irrespective of age or genotype, hence, increasing the cognitive load of ongoing activities may promote a shift in the strategy necessary to maintain multiple demands. The reduction in non-focal prospective interference cost observed in mid-age ε4 carriers under WM load did not negatively impact PM retrieval in this group. The WM load condition, however, was always completed second to the no load condition, hence, the absence of mid-age ε4 effects may represent a practice effect.

Subjective measures of task load were included in an attempt to interrogate group differences in perceived demand and motivation. Consistent with an age-related decline in executive attention, mid-age adults reported greater mental demand than young adults. In both age groups, however, ε4 carriers reported greater mental demand selectively for the no load condition. This may reflect greater focus on maintaining the PM intention, which may disappear when resources are stretched across two concurrent ongoing demands. Given the WM load task was always completed in the second half of the session, however, reduced ratings of mental demand may be a product of having plenty of experience completing the ongoing task. Mid-age ε4 carriers did not demonstrate the same reduction in task effort under WM load as the other groups, perhaps indicating they are working harder to maintain performance.

Finally, the absence of age-effects on PM retrieval accuracy is consistent with a previous study reporting comparable levels of PM accuracy in older (*M*=66.3 years), and mid-age *(M*=42.5 years) adults compared to young adults on an event-based PM task (Einstein et al., 1995, Experiment 3). The current study builds on these findings by including ongoing task interference as an additional metric, suggesting that early age-related change in PM performance manifests as cost. A second conclusion of the earlier paper (Einstein et al., 1995) is that age-associated change in PM retrieval accuracy depends on the degree of self-initiation required. Increasing the level of self-initiation required could be an interesting manipulation for future research exploring *APOE* genotype effects on PM.

One limitation of the current study is that the WM load embedded in the ongoing task may not have placed great enough demand on the central executive component of WM (see e.g., WM load effects on PM in young adults with a demanding central executive task; McDaniel & Scullin, 2010). Bisiacchi and colleagues (2013) included an additional WM load or an

additional monitoring load in the ongoing component of a PM task and found age-related declines in PM were selectively increased by the WM load (1-back, listening span), not the monitoring component. It is possible the load task included here did not place enough demand on manipulating information within attention. Finally, the sample size in each genotype group was relatively small.

6.6. Conclusions

Mid-age individuals carrying at least one copy of the *APOE* ε4 genetic variant, and hence at heightened risk of poor cognitive ageing, showed greater costs of maintaining a concurrent PM intention relative to their young adult counterparts. They did not, however, show select impairment in PM retrieval accuracy by mid-adulthood. This mid-age deficit in cost of carrying a PM intention was observed for both focal and non-focal PM cues, and selectively disadvantaged ongoing performance of ε4 carriers. This profile of impairment is consistent with the pattern of performance observed in individuals diagnosed with mild AD, and hence may represent early compromise to both MTL and frontal-based neural systems in carriers of this 'at-risk' allele. In conclusion, this research confirms subtle differences in the early ageing trajectory of ε4 carriers, perhaps indicative of a vulnerability consistent with the preclinical stages of AD. Further research is needed to interrogate the mechanisms of early change in ε4 carriers, focusing on the vulnerability of neural systems to change across the lifespan, and the effect of strategies on PM task performance.

7. Article 6-

Non-Focal Prospective Memory and Everyday Cognition in the Early Stages of Cognitive Decline

7.1. Abstract

Background: Non-focal prospective memory (PM) provides a proxy measure of attentional control in everyday life. Support for non-focal PM deficits in the early stages of cognitive impairment is mixed; in part this may stem from the heterogeneity of PM paradigms used. This study will explore if a card-sort measure of non-focal PM is sensitive to behavioural differences in individuals self-referring to a memory assessment service (MAS), and if performance correlates with cognitive errors in everyday life. Furthermore, the moderation of performance differences by genetic risk for late-life dementia is considered.

Methods: Forty-eight volunteers, recruited within nine months of their initial MAS appointment (35 mild cognitive impairment (MCI), 13 subjective cognitive dysfunction (SCD): hereafter referred to collectively as the 'MAS' group), and 52 healthy older adults completed the card-sort PM task. In addition, subjective ratings of cognitive errors in daily life and *APOE* genotype were considered as potential factors in performance differences.

Results: The MAS group showed poorer baseline card-sorting performance, as indexed by RT and accuracy; however, PM retrieval and PM cost did not distinguish individuals in the early stages of decline from their cognitively healthy peers. PM accuracy marginally correlated with ratings of attentional control in daily life, however, there was no association between PM cost and cognitive errors in everyday life. *APOE* ε4 genotype did not significantly impact PM performance or subjective complaints.

Discussion: Individuals in the early stages of cognitive decline showed comparable non-focal PM to a healthy older group, with no additional impairment shown beyond the typical profile of age-related decline. PM accuracy correlated with attentional control problems in everyday life, and hence this ability may be a good target for everyday interventions.

7.2. Introduction

With the proportion of adults aged 65 years and older in the population increasing, cases of Alzheimer's disease (AD) are expected to rise 35% by 2025 (Office for National Statistics, 2012; Prince, 2015). Age-associated cognitive decline significantly impacts everyday independence in older adulthood (Salthouse, 2012). Despite episodic memory loss being the hallmark of cognitive ageing (e.g. Caselli et al., 2014; Chen et al., 2001; for a review see Mortamais et al., 2016), reported errors in 'self-initiated' prospective memory (PM) are prevalent both in healthy older adults and individuals with AD (Smith, Del Sala, Logie, & Maylor, 2000). Defined as the retrieval of an earlier formed intention at the appropriate time whilst engaged in ongoing cognitive activity, there are numerous examples of PM in the context of everyday life. Examples include medication adherence and remembering to attend appointments, hence this ability is suggested to be particularly relevant for maintaining independence in later life (Kliegel et al., 2016; McDaniel et al., 2008).

This study considers if PM is a sensitive marker of individuals at heightened risk of converting to AD, including individuals with mild cognitive impairment (MCI) or subjective cognitive dysfunction (SCD) (Buckley et al., 2016; Hu et al., 2017; Mendonça, Alves, & Bugalho, 2016). MCI is characterised by marked impairment in one or more cognitive domains, however, the profile of cognitive deficits varies between individuals (Chertkow et al., 2007; Mariani, Monastero, & Mecocci, 2007a). The behavioural phenotype of SCD is less well characterised, and here refers to individuals who self-referred for a memory assessment and were not classified by the clinician to have MCI. Understanding the profile of cognition in these 'preclinical' stages is an important target for furthering both the timely identification of individuals at greater risk and early intervention strategies (Sperling et al., 2011).

7.2.1. Prospective memory in MCI and SCD

Existing reviews indicate PM performance is impaired in individuals with MCI compared to healthy age-matched peers (Costa et al., 2011; van den Berg, Kant, & Postma, 2012), however there are inconsistencies in reported effects, in part stemming from variation between PM paradigms. The presence of PM impairment in MCI is suggested to depend on the cognitive demand of the task. In existent literature, typically a distinction is made between two types of PM retrieval, with the attentional requirements varying according to the focality of the PM retrieval cue (McDaniel et al., 2015; Scullin, McDaniel, & Shelton, 2013). Focality is defined by the relationship of the PM cue to the ongoing task. Non-focal cues are not processed as part of the ongoing task and hence attentional control is required for the active maintenance and

monitoring of the PM intention (Einstein et al., 2005; McDaniel et al., 2015; Scullin, McDaniel, Shelton, et al., 2010). Focal cues, in contrast, are salient to the processing of the ongoing task, and hence facilitate PM retrieval through relatively automatic, associative memory processes (McDaniel et al., 2015).

Individuals with MCI demonstrate worse accuracy of non-focal PM retrieval compared to age-matched healthy peers, despite equivalent ratings of subjective effort (Tam & Schmitter-Edgecombe, 2013). In the context of a verbal working memory (WM) ongoing task, participants were instructed to carry out the PM intention when a stimulus was presented on the target background, requiring a large monitoring component. PM retrieval accuracy correlated with subjective reports of everyday memory failings in healthy older adults but not in individuals diagnosed with MCI. A further study directly manipulated the attentional demand of PM retrieval by varying the salience and specificity of cues on a 'Silly sentences' paradigm, requiring participants to make speeded judgements on the coherence of sentences (Blanco-Campal et al., 2009). Retrieval of non-specific, non-salient (i.e. non-focal) cues was a better discriminator of MCI than both retrospective memory measures and focal PM retrieval.

Several studies, however, report intact non-focal PM retrieval in MCI and in the very earliest stages of AD (McDaniel, Shelton, Breneiser, Moynan, & Balota, 2011; Niedźwieńska, Kvavilshvili, Ashaye, & Neckar, 2017). Alongside the same ongoing tasks (a category decision, and face-profession matching task respectively), focal PM retrieval was impaired in clinical groups compared to healthy older peers. This led to the suggestion that whilst non-focal PM is sensitive to typical age-related decline (e.g. Henry, MacLeod, Phillips, & Crawford, 2004; Kliegel, Jäger, & Phillips, 2008; Uttl, 2008), additional impairment in focal PM is a sensitive marker of early pathological cognitive decline. Further supporting this, Chi et al., (2014) found significant impairment in focal PM in an MCI group, but not in individuals experiencing SCD using the same paradigm as McDaniel et al., (2011). Non-focal PM impairment was found in individuals with MCI without marked memory impairment (naMCI), but not in individuals with amnestic MCI (aMCI) or SCD. On a 'Supermarket shop' experimental paradigm, individuals with SCD have also been reported to show intact focal and non-focal PM (Lee, Ong, Pike, & Kinsella, 2017). This supports the use of PM as a discriminator of the profile of early cognitive decline.

Methodological discrepancies may underpin inconsistent reports of differential non-focal PM performance in the early stages of cognitive decline. Firstly, several studies consider PM retrieval accuracy in isolation as a measure of how well individuals are able to maintain a prospective intention (e.g. Lee et al, 2017; Tam & Schmitter-Edgecombe, 2013). Prospective

interference or cost to ongoing performance is suggested to index the allocation of attention control for the active maintenance and monitoring of non-focal PM intentions (Marsh et al., 2003). Limited studies have considered this as a marker of PM performance in preclinical populations (McDaniel et al., 2011; Chi et al, 2014); however, less efficient attentional control may manifest in increased cost in preclinical groups. Furthermore, as PM targets are rare, there may be reduced sensitivity to detect performance differences (Costa et al., 2011; Uttl, 2008). A further issue concerns the suitability of computerised experimental paradigms for use in elderly populations. Many paradigms employ ongoing tasks removed from everyday life, for example lexical decision tasks. On more naturalistic measures of PM (i.e. when given a PM instruction to pass on a message at the appropriate moment), deficits in MCI and SCD individuals have been reported (Lee et al., 2017; Rabin et al., 2014).

7.2.2. Current aims and hypothesis

The current study explores if non-focal PM, a proxy measure for the everday application of attentional control, is sensitive to performance deficits in the earliest stages of cognitive impairment using a simple computerised card-sort measure of PM (Rusted, Sawyer, Jones, Trawley, & Marchant, 2009). In this paradigm, individuals are first asked to complete a baseline measure of the ongoing task: a speeded measure of card sorting according to suit. Following this they are provided with a non-focal PM instruction, asking them to make an additional response when they see a specific target card.

The decision to focus on non-focal PM in the present study is supported by reports that executive attention is consistently affected in the earliest preclinical stages of AD (Elias et al., 2000; Rajan, Wilson, Weuve, Barnes, & Evans, 2015; Twamley et al., 2006). Furthermore, this paradigm has been developed and used previously with older adults with memory impairment (Farina, Young, Tabet, & Rusted, 2013) and addresses some of the existing methodological concerns that may contribute to inconsistency in the literature. As participants complete a baseline sort task, the task provides a measure of both PM retrieval accuracy (of which there are 12 possible targets) and PM cost, maximising sensitivity. Furthermore, the use of playing card stimuli provides a computerized version of a real-life scenario, maximising the ease in which participants can process the rules of both the ongoing and PM instructions. This further supports the suitability of using this task with an older population.

The study recruits volunteers within nine months of their initial referral visit to a memory assessment clinic (MAS), including individuals experiencing the early stages of cognitive decline (MCI or SCD), in addition to a healthy control group. The MAS group are expected to

show marked impairment on the card-sort task, which may manifest as either reduced PM retrieval accuracy or increased cost of carrying a PM intention on ongoing sort performance. This aligns with previous reports of disadvantages in this group (Blanco-Campal et al., 2009; Costa et al., 2011; Tam & Schmitter-Edgecombe, 2013).

An additional aim of the current study is to explore whether Apolipoprotein E (*APOE*) genotype moderates non-focal PM performance on the card-sort task in this preclinical population. The *APOE* ε4 allele is the greatest risk factor for late-onset AD, as well as being associated with poorer cognition in healthy older adults (Corder et al., 1993; Farrer et al., 1997; Wisdom, Callahan, & Hawkins, 2011). Furthermore, carrying a copy of this allele is associated with greater impairment in MCI and increased risk of progression to AD (Albert et al., 2014; Whitehair et al., 2010). The card-sort paradigm demonstrates sensitivity to genetic risk from mid-adulthood (Evans et al., 2014; Lancaster, Tabet, & Rusted, 2016). Whilst disadvantages on the card-sort task have been seen as reduced PM retrieval accuracy (Lancaster et al., 2016), on a category decision PM task ε4 disadvantages manifest as increased PM cost (Lancaster, McDaniel, Tabet & Rusted, *in prep*). Given the pattern of performance in ε4 carriers on the card-sort task in mid-adulthood, the presence of the ε4 allele in the MAS group is expected to exaggerate performance disadvantages on the card-sort paradigm, indexed by either PM retrieval or cost.

Attentional control is necessary for activities of daily living, both in healthy and pathological ageing (Marshall et al., 2011); hence this research explores how performance in non-focal PM relates to reports of everyday cognition. Previous research reports PM is directly associated with everyday cognition in MCI (Schmitter-Edgecombe, Woo, & Greeley, 2009; Woods, Weinborn, Velnoweth, Rooney, & Bucks, 2012). As part of a preliminary phase, the current study collects subjective ratings of general cognitive functioning (the Cognitive Failures Questionnaire (CFq) (Broadbent et al., 1982)), and attentional control more specifically (the Attentional Control scale (ACs) (Derryberry & Reed, 2002)). Intuitively, individuals visiting the MAS are expected to report greater subjective problems with cognition in everyday life. As non-focal PM is supported by frontally-based executive resources (Cona et al., 2016; McDaniel et al., 2013), attentional control is expected to correlate with card-sort performance. In addition, due to the relevance of PM to everyday contexts, PM may correlate with errors more generally.

7.3. Methods

7.3.1. Participants

7.3.1.1. Preliminary questionnaire phase

87 MAS-users (59 MCI, 28 SCD) completed subjective ratings of cognition in everyday life. This 'preclinical group' was recruited following appointments with a memory clinician at the Sussex Partnership NHS Foundation Trust, or via advertisement on the Join Dementia Research database (restricted to Sussex-based volunteers). In addition, the partners or spouses of the MAS-users were asked to participate as healthy controls (n=55), given they reported no prior history of cognitive complaints.

7.3.1.2. Behavioural phase

All volunteers completing the questionnaire were invited to participate in the behavioural session. 48 MAS-users (35 MCI, 13 SCD) participated alongside 52 controls. Due to the smaller number of healthy older controls in the initial questionnaire sample, an additional subset of healthy older adults were recruited to participate via advertisement at local University of the Third Age groups (n=25), alongside 27 of the healthy partners/spouses from the questionnaire phase.

7.3.1.3. Inclusion criteria

All volunteers were required to be aged 55 years or older, and speaking English as their daily language. In addition, volunteers were asked to report if they had any history of head injury or trauma, treatment for depression or treatment for hypertension within the past 5 years, however, these were not used as criteria for exclusion.

In addition, the preclinical group was required to complete the study within 9 months of their initial MAS appointment, in which they received a diagnosis of MCI or no diagnosis but reported SCD. The criteria for a diagnosis of MCI was based on recommendations from the National Institute on Ageing and Alzheimer's Association (Albert et al., 2011) including: subjective concerns regarding change in cognition, impairment in one or more cognitive domains, preservation of independence, and not meeting the criteria for a dementia diagnosis. There was no threshold for those classed as SCD, however neuropsychological test results were available for 23/28 SCD volunteers. [10]

[10] The mini-mental state examination was the most common neuropsychological test administered, with scores in the range of 25-30.

7.3.1.4. *APOE* genotyping

Volunteers completing the behavioural phase were genotyped for *APOE* status following Human Tissue Authority guidelines, with all procedures approved by Health Research Authority NHS ethics and the Research Ethics Committee of the School of Psychology and Life Sciences, University of Sussex. Volunteers first provided written informed consent, including acknowledgement that the results of the genotype analysis would not be made available to them. DNA was collected with a buccal swab, using an Isohelix SK1 kit. A triangulated anonymisation procedure was used for each sample, with the researcher remaining blind to genotype throughout. Samples were analysed by LGC Genomics (Hertfordshire, www.lgcgroup.com/genomics). *APOE* genotype was determined using fluorescence-based competitive allele-specific polymerase chain reactions to determine the presence of ε2, ε3, and ε4 alleles based on two single nucleotide polymorphisms (rs429358, rs7412). The distribution of genotypes for the MAS patient group was as follows: 4 ε2 carriers (ε2/ε3), 24 homozygote ε3 carriers, 20 ε4 carriers (1 ε2/ε4, 15 ε3/ε4, 4 ε4/ε4). In the control group there were 6 ε2 carriers (1 ε2/ε2, 5 ε2/ε3), 33 homozygotes ε3 carriers and 13 ε4's (1 ε2/ε3, 11 ε3/ε4, 1 ε4/ε4). E2 carriers were excluded prior to analysis.

7.3.2. Materials

Demographic information, including age and years of education was collected using a short questionnaire. For individuals completing the behavioural session, the National Adult Level Reading test (NART) (Nelson & Willison, 1991) was used to provide an estimate of premorbid IQ. In addition, the Cognitive Reserve Index quotient (CRIq) (Nucci, Mapelli & Mondini, 2011), a 20-item questionnaire assessing education, occupational background and adult leisure activities, was administered orally as an index of cognitive engagement across adulthood.

7.3.2.1. Questionnaires: Everyday cognition

The CFq (Broadbent et al., 1982) asks volunteers to rate how often they make 25 common 'cognitive failures', on a scale from 'Never' (0) to 'Very often' (5). Cognitive failures are premised to represent 4 subscales: memory, distractibility, naming and blunders (Wallace, Kass, & Stanny, 2002). The ACs (Derryberry & Reed, 2002) consists of 20 items targeting 3 processes; mind wandering, susceptibility to boredom and distractibility. Previous exploratory factor analysis suggests questions cluster into two components; attentional focusing and shifting (Judah, Grant, Mills, & Lechner, 2014). Scores for each question were based on a 4-point Likert

Scale from ‘Almost never’ (1) to ‘Always’ (4). For both the CFq and ACs responses were scored so that higher values represent worse subjective cognition.

7.3.2.2. Card-sort PM task

The card-sort task (Rusted et al., 2009) presents participants with a sequence of playing card stimuli, displayed in a pseudorandom order. Each trial consists of a card back, presented for a variable duration (100-150ms), followed by a card face displayed for 1000ms. The ongoing task requires participants to respond to each card according to suit, making a ‘1’ keyboard response for a ‘spade’ and a ‘3’ keyboard response for a ‘heart’, as quickly and as accurately as possible. For cards belonging to ‘spades’ or ‘diamonds’, participants are required to provide no response.

Participants initially complete one deck (52 cards: 26 sort trials; 26 non-sort trials) of the ongoing task (the control deck) to provide a baseline measure of decision-making performance. Participants are then provided with an additional PM instruction to make an alternative keyboard response (‘space’) each time they see the target card, which is any card with the number ‘7’. To ensure the PM instruction has been correctly interpreted, volunteers are required to repeat the instructions back to the experimenter in their own words. Following this there is a 2-minute interval, before participants sort a further 3 decks of cards, containing 72 sort trials, 72 non-sort trials and 12 PM trials. At the end of the task participants are requested to summarise the task instructions, ensuring that they remembered the additional PM instruction.

Sort accuracy and RT are recorded for the control deck and the 3 decks following the introduction of the PM intention. For each participant, individual sort RTs were screened for outliers, defined as those more than 3 standard deviation (SD) away from the participant’s mean. In addition, accuracy of PM retrieval is also recorded.

7.3.2.3. NASA task load index

Perceived workload is measured for the control and PM decks of the card-sort PM task using a pen-and-paper version of the NASA task load index. This consists of 6 visual analogue scales measuring: mental demand, physical demand, temporal demand, performance, effort, and frustration. Participants are instructed to mark along the scale to rate how they experienced each section (baseline deck, PM decks of the card-sort task). Greater values represent increased ratings.

7.3.3. Procedure

For the initial questionnaire phase, volunteers were asked to complete a demographic questionnaire and the two questionnaires of cognition in everyday life (the CFq, the ACs) in their own time and return them to the experimenter by post.

For volunteers accepting the invitation to complete the behavioural session, individuals were first asked to complete the NART before beginning the card-sort PM task. Following completing the control sort-deck and receiving the PM instruction, there was a two-minute interval where volunteers were orally asked questions from the CRIq, prior to resuming the task. Any remaining questions from the CRIq were asked following completion of the card-sort PM task. Measures of task load were completed following the initial control card-sort deck (time point 1), and again following the three PM decks (time point 2). Finally participants were asked to provide a buccal swab for *APOE* genotype analysis. The session lasted a maximum of 60 minutes.

7.3.4. Design

Prior to analysis, data from nine individuals was excluded, as they were aged 54 years or younger (Questionnaire phase n=7; Behavioural phase n=2). Adults recruited from the MAS clinic, including both individuals diagnosed with MCI and experiencing SCD, were collectively analysed in comparison with a healthy older-adult group. For all genotype comparisons, ε4 carriers (ε2/ε4, ε3/ε4, ε4/ε4) were compared to a homozygous ε3 group (the population norm). Group differences in demographic characteristics were screened prior to analysis using either a between-groups t-test for continuous variables, or a χ^2 test for categorical variables.

7.3.4.1. Card-sort PM task

Prior to analysis, mean sort RTs and accuracy were screened for outliers based on the overall sample. Group differences in baseline card-sort performance (mean RT, accuracy) was analysed using a 2 (Group: MAS, healthy) x 2 (Genotype: ε3, ε4) ANOVA, with age and years of education included as covariates.

For analysis of subsequent PM performance, data from individuals unable to recall the PM instruction were excluded (n=6). Accuracy of PM retrieval (/12) was analysed using a 2 (Group: MAS, healthy) x 2 (Genotype: ε3, ε4) ANOVA.

To establish if introducing a PM intention led to significant interference for ongoing sort performance, separate paired *t*-tests were used to compare card-sort RT and accuracy on the control deck and for each of the 3 subsequent PM decks (Bonferroni-corrected α=.017). Interference was probed further, where significant, using a single measure of cost for each deck (the difference between baseline sort performance and sort performance with the additional PM instruction). Separate ANOVAS with Deck as a within-subjects factor, Group and Genotype as between-subjects factors were completed for cost to sort RT and accuracy. Again, age and years of education were included as covariates. [11]

7.3.4.2. NASA task-load

The impact of introducing a PM intention on the six indices of task load was analysed using repeated-measures t-tests comparing ratings of the baseline and PM condition (Bonferonni corrected α=.008). To screen for group differences in physical ability to complete the card-sort measure, 2 x 2 x 2 mixed ANOVA was completed with Group (MAS, healthy), Genotype (ε3, ε4) as the between-subjects factors and Condition (baseline, PM) as the repeated measures factor. In addition, group differences in perceived mental demand and effort were analysed (Group x Genotype x Condition mixed ANOVAs).

7.3.4.3 Questionnaires: Cognitive errors in daily life

Prior to analysis, responses to both the CFq and the ACs were screened for missing data. For participants with up to four blank responses per questionnaire, missing responses were estimated as the average score for that participant in order to ensure comparable scores. Questionnaire data for participants with over four missing responses were removed (CFq *n*=1; ACs *n*=1).

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[11] To assess the profile of age-related change in performance on the card-sort paradigm, PM retrieval accuracy (/8) and PM cost was compared for the first 2 PM decks in the current study, with existing data from a mid-age sample (45-55 years) (Lancaster et al., 2016). Both measures of performance were compared in separate one-way ANOVAs comparing mid-age, healthy older-adults and MAS-users. PM retrieval accuracy was significantly higher in mid-age adults (*M*=7.03, SE=.27) compared to healthy older adults (*p*<.001) (*M*=5.20, SE=.32) and MAS users (*p*<.001)(*M*=4.75, SE=..31), *F*(2, 126)=18.21, *p*<.001, n2p=.224. Healthy older adults and MAS users did not significantly differ (*p*=.312). There was no significant difference in PM cost (*p*>.05).

The total score on each questionnaire was compared between-groups (MAS, healthy) using a between-groups t-test. In addition, scores on the individual factors of each questionnaire were compared (CFq: Memory, Distractibility, Blunders, Naming (Wallace et al., 2002); ACs: Focusing, Shifting (Judah et al, 2013)), using Bonferonni-corrected t-tests (CFq α=.010, ACs α=.017). Furthermore, for the preclinical group with known genotype, a 2 (Group: MAS, healthy) x 2 (Genotype: ε3, ε4) between-subjects ANOVA was run. Genotype differences in the control group were not analysed due to a small sample size (ε3 *n*=16, ε4 *n*=3).

Pearson's correlation coefficients were calculated between total scores on the CFq and ACs and measures of PM accuracy and interference.

7.4. Results

7.4.1. Demographics

7.4.1.1. Preliminary questionnaire phase

Demographic measures for the questionnaire phase are shown in Table 7.1. Between groups, the distribution of gender was not equivalent, with a higher proportion of males in the MAS group than the healthy group, χ^2 (135)=7.21, *p*=.007. All other group differences were non-significant.

Table 7.1. The demographic characteristics of volunteers completing the questionnaire phase shown according to group

	Controls	**MAS**
n	48	86
Age	72.65 (7.67)	75.44 (8.89)
Gender (% M)	33*	57*
Education (years)	13.74 (3.30)	13.46 (3.60)
Smokers (n)	0	4
Hypertensive (%)	17	25

* $p < .05$

7.4.1.2. Behavioural phase

Table 7.2 shows the demographic characteristics of volunteers completing the behavioural phase. The healthy group had significantly more years of education than the MAS group, *F*(1, 85)=4.35, *p*=.040, n2p=.049, however, there was no significant difference in years of education between genotype groups (*p*>.05). No other group differences were significant (*p*>.05).

Table 7.2. Demographic characteristics of volunteers participating in the behavioural phase, shown according to group and *APOE* genotype

	Controls		**MAS**	
	ε3	**ε4**	**ε3**	**ε4**
n	33	12	24	20
Age	71.49 (6.86)	71.15 (11.42)	73.88 (17.62)	71.25 (18.81)
Gender (% M)	63	40	30	31
IQ	117.97 (3.56)	117.37 (8.26)	118.96 (6.19)	118.84 (2.48)
Education*	15.82 (4.60)	15.46 (5.19)	13.38 (4.30)	13.63 (4.37)
CRq	135.30 (20.85)	129.39 (21.36)	130.58 (20.19)	129.40 (19.78)

* $p < .05$

7.4.2. Card-sort PM task

For a summary of performance on this task by each group, see Table 7.3.

7.4.2.1. Baseline decision-making

MAS users (M=758.27ms, SD=177.20ms) were significantly slower to perform the card-sort in comparison to the healthy older adults, (M=625.63ms, SD=115.92ms), $F(1, 82)=12.54$, $p=.001$, n2p=.133. Age accounted for significant variance in sort RTs, $F(1, 82)=5.92$, $p=.017$, n2p=.067, with larger RTs recorded with increasing age ($B=3.23$). The effects of genotype, year of education and all interaction terms were non-significant ($p>.05$).

Across participants, accuracy on the baseline card-sort measure ranged from 56% to 100%. MAS users (M=90.83, SD=11.82) made significantly more errors than healthy older adults (M=96.51, SD=4.69), $F(1, 79)=5.95$, $p=.017$, n2p=.070. The effect of genotype, age, years of education and all interaction terms were non-significant ($p>.05$).

7.4.2.2. PM retrieval accuracy

There was no difference in PM retrieval accuracy (/12) between MAS users and healthy older adults ($p>.05$). The effect of genotype was also non-significant, as was the Group x Genotype interaction ($p>.05$). Age did not account for significant variation in PM retrieval accuracy, however, years of education was associated with increasing PM retrieval accuracy, $F(1, 78)=5.14$, $p=.026$, n2p=.062, $B=.181$.

7.4.2.3. PM interference

Compared to the baseline deck, introducing the PM intention was associated with a significant slowing of card-sort RTs on all 3 subsequent decks (p<.001). Cost to sort RTs did not significantly change across decks (p>.05). There was no significant difference according to Group or Genotype (p>.05). In addition, age and years of education did not account for significant variation, and there were no significant interactions (p>.05).

Carrying the PM intention was only associated with a significant cost in sort accuracy for the first deck following the introduction of the additional PM intention, $t(81)=3.15$, p=.002. The cost for the subsequent 2 decks was non-significant (p>.05). Cost to sort accuracy for this initial PM deck did not differ by Group or Genotype, and the Group x Genotype interaction term was also non-significant (p>.05). In addition, age and years of education did not account for significant variation (p>.05).

7.4.2.5. Task-load ratings

Subjective ratings of task load are shown in Table 7.4. Across participants, introducing the PM intention increased subjective ratings across 5 measures of task load (Mental demand: $F(1, 80)=66.67$, p<.001, n2p=.455, Temporal demand: $F(1, 80)=56.93$, p<.001, n2p=.416, Physical demand: $F(1, 80)=40.60$, p<.001, n2p=.342, Effort: $F(1, 80)=67.88$, p<.001, n2p=.459, Frustration: $F(1, 80)=21.28$, p<.001, n2p=.210). In addition, perceived performance was lower in the PM condition, $F(1, 80)=41.611$, p<.001, n2p=.342.

The group difference in perceived physical demand of the card-sort task was non-significant (p>.05), as were differences in subjective mental demand (p>.05). There was a marginal Group x Genotype interaction for perceived effort, $F(1, 80)=3.70$, p=.058, n2p=.044. In the healthy older group, ε4s reported significantly greater effort than the ε3 group (p=.012), but there was no genotype difference in MAS-users (p=.815). Split by genotype, there was no difference between groups (MAS, healthy older adults in perceived effort (p>.013) (Bonferonni corrected α=.013).

Table 7.3. Group differences on the card-sort task shown for the baseline condition, and as an average across the 3 PM decks.

		Baseline Deck		PM decks			
Group		RT (ms)	Accuracy (%)	RT (ms)	Accuracy (%)	PM retrieval/ 12	RT cost (ms)
	ε3	636 (115)	96.84 (5.04)	721 (112)	95.81 (4.40)	8.97	129 (58)
Controls	ε4	600 (119)	95.69 (3.72)	670 (115)	94.33 (3.73)	7.69	109 (84)
	ε3	784 (178)	93.77 (8.98)	859 (179)	90.27 (11.61)	7.14	113 (97)
MAS	ε4	727 (175)	89.10 (12.52)	791 (167)	85.44 (14.96)	8.18	126 (65)

Table 7.4. Subjective ratings of task-load following the control card-sort deck (Time point 1) and the PM decks (Time point 2), shown as mean (SD)

		Controls		MAS	
	Time point	**ε3**	**ε4**	**ε3**	**ε4**
Mental demand	**1**	3.12 (2.44)	4.96 (2.49)	4.84 (2.36)	4.14 (3.42)
	2	6.43 (2.64)	6.51 (2.54)	6.62 (2.77)	5.88 (2.65)
Physical demand	**1**	1.78 (2.38)	3.62 (2.41)	2.83 (2.20)	2.36 (2.85)
	2	3.76 (3.03)	6.32 (2.10)	4.20 (2.76)	3.77 (2.66)
Temporal demand	**1**	4.48 (2.82)	5.66 (2.20)	5.01 (2.86)	4.97 (3.06)
	2	5.99 (2.79)	7.26 (2.24)	7.01 (2.12)	6.47 (2.22)
Effort	**1**	3.82 (2.54)	5.74 (2.45)	5.28 (2.59)	4.79 (2.64)
	2	6.04 (2.70)	7.69 (1.89)	6.94 (2.07)	7.09 (2.03)
Performance	**1**	7.44 (2.36)	6.52 (2.46)	6.16 (2.81)	3.93 (3.61)
	2	4.86 (2.33)	4.94 (2.45)	3.66 (2.93)	3.55 (2.63)
Frustration	**1**	2.86 (2.86)	4.57 (2.98)	3.10 (2.41)	4.01 (3.47)
	2	4.65 (3.03)	6.08 (2.11)	5.04 (2.50)	5.94 (3.09)

7.4.3. Questionnaires: Cognitive errors in daily life

Average scores on both questionnaires of cognition in everyday life (the CFq, the ACs) are summarised by group in Table 7.5. The MAS group (M=50.27, SD=14.13) reported a significantly higher numbers of cognitive failures in daily life than healthy older adults (M=34.33, SD=11.85), $F(1, 124)=36.55$, $p<.001$, $\eta^2_\rho=.233$. Age and years of education did not account for significant variance in scores ($p>.05$). This difference was consistent across each of the four factors (memory, distractibility, blunders, naming) ($p<.001$). In the MAS group, ε4 carriers (M=48.93, SD=15.88) did not significantly differ in total CFq compared to homozygous ε3 carriers (M=49.10, SD=12.50) ($p>.010$). In addition, the genotype difference was non-significant across all four individual factors ($p>.010$).

In addition, the MAS group reported significantly worse attentional control in daily life than the control group, $F(1, 119)=29.26$, $p<.001$, $\eta^2_\rho=.197$, indexed using the ACs. Age did not account

for significant variance in scores (p>.05), however, there was a marginal effect of education (β=-.40, p=.055). The effect of group was consistent across questions targeting attentional focus (p<.001) and shifting (p=.006). Education did not account for significant variance when considering these individual factors (p>.05). In the MAS group, ε3 carriers (M=49.07, SD=5.75) reported significantly worse attentional control than ε4 carriers (M=42.93, SD=9.24), $t(41)=7.04$, p=.011, η^2_ρ=.153. Following correction for multiple comparisons, when interrogating this difference for individual factors, the genotype difference in MAS users was marginal for both attentional focusing, $t(41)=4.85$, p=.034, η^2_ρ=.111, and shifting, $t(41)=3.32$, p=.076, η^2_ρ=.078.

The correlation between ACs score and PM retrieval accuracy approached significance, $r(73)=-.211$, p=.074, however, the relationship between CFq and PM retrieval was non-significant (p=.215). In addition, PM interference on ongoing task performance did not significantly correlate with subjective scores on either questionnaire (p>.05).

Table 7.5. Subjective ratings of cognition in everyday life shown by group (control, preclinical) and genotype (ε3, ε4)

	Control	**MAS**		
			ε3	**ε4**
CFq	34.96 (11.96)	50.27 (14.13)	49.10 (12.50)	48.93 (15.88)
Acs	39.79 (6.85)	47.87 (8.24)	49.07 (5.75)	42.93 (9.24)

7.5. Discussion

The present study addressed the following research questions: 1) is performance on a card-sort measure of non-focal PM impaired in individuals self-referring to memory assessment clinics with mild cognitive complaints? 2) Does non-focal PM correlate with subjective reports of everyday cognitive impairment? 3) Does carrying the *APOE* ε4 allele further moderate differences in executive control?

The current findings suggest non-focal PM performance is intact in individuals in the early stages of cognitive decline; both PM retrieval and PM interference costs were equivalent compared to cognitively healthy older adults. The MAS group, however, demonstrated poorer performance (both accuracy and RTs) in the baseline card-sort condition, suggestive of some reduction of attentional resource in this group. As expected, reports of cognitive errors in daily life were greater in the MAS group, with PM retrieval accuracy correlating with reports of poorer attentional control, but not with cognitive failures more broadly. *APOE* ε4 genotype did not moderate PM performance in either the clinical group, or healthy older controls.

The card-sort paradigm indexes both the accuracy of PM retrieval and the cost of carrying a PM intention on ongoing performance, providing a sensitive measure of attentional control in prospective remembering. Equivalent performance on this paradigm in individuals experiencing the early stages of preclinical cognitive decline is inconsistent with reports of impaired non-focal PM in MCI (Blanco-Campal et al., 2009; Tam & Schmitter-Edgecombe, 2013), and deficits in executive attention more broadly (Rajan et al., 2015; Twamley et al., 2006). As the behavioural profile of SCD is less defined (Stewart et al, 2012), an additional analysis confirmed intact non-focal PM performance in individuals diagnosed with MCI as an independent group. The current findings align with the theory that non-focal PM is generally sensitive to age-related decline (for reviews see Henry et al., 2004; Kliegel et al., 2008; Uttl, 2008), but additional impairment in focal PM differentiates individuals in the preclinical stages of cognitive impairment (Chi et al., 2014; McDaniel et al., 2011; Niedźwieńska et al, 2017). Consistent with a profile of age-related decline, an informal comparison of performance levels in the current sample compared to existing mid-age data (Lancaster et al., 2016), suggested PM retrieval accuracy was poorer in both healthy older adults and the MAS group. This is in line with frontal regions being impacted early in the ageing trajectory (Bartzokis et al., 2003; Raz et al., 2005). AD-related pathology initially impacts medial temporal regions (Braak & Braak, 1991). Hence focal PM, reliant on associative memory processes, may be a more sensitive marker of a divergent trajectory of cognitive ageing.

Intact non-focal PM in the early stages of cognitive decline, as indicated in this study, contradicts reports of impaired attentional control in both MCI and SCD on neuropsychological assessment measures (Amariglio et al., 2012; Crowell, Luis, Vanderploeg, Schinka, & Mullan, 2002; Traykov et al., 2007). Executive attention comprises multiple separable processes (e.g. Engle & Kane, 2002; Friedman & Miyake, 2015), which likely differ in their sensitivity to cognitive decline. The current results suggest that goal maintenance and monitoring abilities are preserved in the preclinical stages of AD. Differences may emerge in PM tasks placing greater demand on the active manipulation of information within WM, predictive of decline in MCI (Belleville, Chertkow, & Gauthier, 2007). In healthy older adults, increasing the monitoring load of a PM task did not impact performance, however, including a WM task requiring active updating significantly increased age-related PM deficits (Bisiacchi et al., 2013a). Hence, non-focal PM deficits in the early stages of cognitive impairment may emerge in tasks with more attentionally demanding ongoing components.

Non-focal PM may be sustained in the early stages of cognitive decline through compensatory mechanisms. In individuals reporting SCD, equivalent episodic memory performance is

associated with compensation-like increases in frontal activations (Erk, 2011). Although compensatory recruitment has not been demonstrated during non-focal PM performance, individuals in the early stages of cognitive decline may be recruiting additional neural resources to support performance. Cognitive strategies, both external (e.g. reminders in the physical environment) and internal (e.g. checking behaviours), can be used to support PM performance in naturalistic environments (Aronov et al., 2015). The use of internal cognitive strategies is linked to both executive function and general intelligence (Bouazzaoui et al., 2010); as the current study population is relatively well-educated, perhaps individuals in the MAS group are able to effectively employ strategies to sustain equivalent performance. Furthermore, individuals were recruited within nine months of their initial referral appointment; a slightly more progressed group may experience a breakdown of compensatory ability.

PM was expected to correlate with reports of cognitive decline in everyday functioning; specifically due to the demand placed on executive attention by non-focal PM, a stronger relationship was predicted for indices of attentional control. The correlation between PM retrieval and attentional control in daily life was marginal, aligning with both measures being supported by frontal, executive abilities. Cognitive failures more generally did not correlate with measures of PM retrieval or cost, contradicting previous reports that PM is central to everyday functioning (Schmitter-Edgecombe et al., 2009; Woods et al., 2012). Recent research in individuals reporting SCD found that although there was a non-significant negative correlation between PM retrieval and functioning in daily life, the relationship between Stroop and memory for temporal order, and everyday cognition was significant (McAlister & Schmitter-Edgecombe, 2016). Everyday cognition is likely supported by a wider constellation of abilities, of which attentional control is an important factor.

As a secondary aim of the study, the impact of *APOE* genotype on non-focal PM was explored. Despite evidence for differential performance on the card-sort task in *APOE* ε4 carriers by mid-adulthood (Evans et al., 2014; Lancaster et al., 2016), carrying an ε4 allele did not negatively impact PM performance in the current study. In mild AD, *APOE* ε4 is associated with disadvantages on focal PM (Duchek et al., 2006), but not non-focal PM impairment (McDaniel et al., 2011). In MCI, *APOE* ε4 has been linked to impaired declarative memory performance but intact executive functions (van der Vlies et al., 2007; Wolk & Dickerson, 2010). Corresponding to these changes, ε4 carriers demonstrate greater atrophy of MTL regions, whilst frontal regions are more sensitive to deterioration in ε4 non-carriers (Wolk & Dickerson, 2010). Hence, in preclinical populations, ε4 may primarily impact on memory processes supported by MTL regions. Further research is needed to establish how, or whether, *APOE* ε4 effects differentiate between healthy and pathological ageing. Subjective indices of task effort

indicated healthy ε4 carriers were working harder to maintain performance. Although based on a small sample, it may be that ε4 carriers are showing increased compensation to maintain performance (Filbey, Chen, Sunderland, & Cohen, 2010; Scheller et al., 2017; Wishart et al., 2006).

The initial cognitive complaints reported in the MAS group were not well defined. Due to the heterogeneity of cognitive deficits associated with MCI, two subtypes are proposed (amnestic MCI (aMCI), non-amnestic MCI (naMCI))(Petersen & Morris, 2005), and these have previously been linked to differential profiles of PM impairment. While individuals with both aMCI and naMCI demonstrate focal impairment, disadvantaged interference of carrying a non-focal PM intention has previously been reported selectively in individuals with naMCI (Costa et al., 2010). This could be further explored in future studies. One limitation of the current study is the sample size of each *APOE* genotype group (ε3, ε4). The study employed an opportunistic sample, and while group sizes for ε4 carriers and ε3 homozygotes was relatively equal for the preclinical group, the healthy older adults group was biased towards homozygous ε3 carriers (as expected)

7.6 Conclusions

Performance was equivalent in adults experiencing the early stages of cognitive impairment on a card-sort measure of non-focal PM, selected for its sensitivity and suitability for administration in older populations, suggesting attentional control in an everyday context is not impacted in the preclinical stages of AD. These results indicate non-focal PM is not impaired beyond the trajectory of change expected in healthy ageing; however, there are inconsistencies across the literature and perhaps subtle effects emerge under more taxing executive conditions. Focal PM may be a more sensitive marker of preclinical change, and could be a useful addition to clinical assessments (Lee et al., 2016). Future research should interrogate the distinction between focal and non-focal PM using more ecologically relevant paradigms. PM is associated with attentional control in daily life, supporting the development of interventions to strategically improve this ability as a route to maintain functional independence in older adulthood.

8. General Discussion

Carrying a copy of the *APOE* ε4 variant is associated with poorer cognitive ageing, however, the presence of behavioural differences in early adulthood highlights the importance of understanding the expression of *APOE* effects across the lifespan. The current thesis considered the following research questions: 1) Does *APOE* genotype impact cognition in mid-adulthood? 2) Are individual attentional control processes differentially impacted by *APOE* variants? Focus was placed on the ε4 risk variant; however, effects of the protective ε2 variant were also considered to understand how allelic versions of *APOE* differentially contribute to cognitive ageing. Furthermore, the thesis began to explore if additional factors in age-related decline influence the presence of *APOE* effects in early cognitive ageing.

This general discussion will collectively consider the empirical results included in this thesis and how the provided evidence speaks to those questions. In addition, as Articles 2 and 3 investigated the independent effects of *APOE* ε2 on attentional control, the effects of this allele are considered as they relate to the reported late-life protective effects of this allele. Following this, theoretical accounts of *APOE* ε4 and individual differences in cognitive ageing will be discussed in relation to attentional control. Finally, the relevance of this research to clinical practice and our understanding of cognitive impairment in everyday life will be considered, followed by a short discussion of the present work's limitations and future directions.

8.1 *APOE* in mid-adulthood

Article 1 systematically reviewed existing reports of *APOE* ε4 genotype differences in healthy middle-aged adults, and concluded that support for a differential profile of cognition in ε4 carriers was limited before the end of the 5th decade. Closer interrogation of individual studies, however, suggested ε4 differences are present by mid-adulthood when administering behavioural paradigms sensitive to small effects. This highlighted a key methodological concern with the *APOE* literature to-date, motivating the careful selection of sensitive cognitive paradigms in subsequent experiments.

Results from Articles 2, 3 and 5 are consistent with the conclusions of the mid-age review (Article 1): ε4 differences are not consistently present in adults aged 45-55 years, however, subtle disadvantages are detectable on select behavioural indices. Collectively, these results imply that performance of ε4 carriers is relatively intact until the end of the 5th decade within the domain of executive attention, with some evidence for deficits apparent on individual

cognitive processes. Whilst existing meta-analyses of ε4 effects in young and healthy older adulthood support a heterogeneous profile of effects across cognitive domains (Ihle et al., 2012; Wisdom et al., 2011), this research suggests effects may be nuanced at the level of individual cognitive processes.

8.1.1 *APOE* ε4 and attentional control

This thesis considered *APOE* genotype effects in 'attentional control' or 'executive attention' as this constellation of cognitive processes, in addition to showing marked age-related decline (e.g. Hasher & Zacks, 1988; Milham et al., 2002; Wasylyshyn & Sliwinski, 2011), is associated with ε4 differences in youth (e.g. Marchant, King, Tabet, & Rusted, 2010; Rusted et al., 2013; Taylor et al., 2016). Furthermore, behavioural paradigms targeting attentional control report ε4 genotype effects in mid-adulthood, but not consistently so (e.g. Evans et al., 2014; Evans et al., 2013; Greenwood, Lambert, Sunderland, Parasuraman, 2005; Greenwood, Sunderland, Friz, & Parasuraman, 2000; Velichkovsky, Roschina, & Selezneva, 2015) (see Article 1).

The experiments completed in this thesis report equivalent visual search performance in mid-age ε4 carriers on both the dynamic scaling task and the perceptual load task (Article 2). These tasks measure selective visual attention on trials requiring the heightened processing of a target location whilst preventing interference from distractor items. Selective attention, or simple WM capacity (Awh et al., 2006; Chun, 2011a), therefore, does not appear sensitive to the disadvantageous effects of ε4 until later in the lifespan, when carriers are suggested to show a profile of accelerated ageing (Espeseth et al., 2012; Greenwood et al., 2000; Greenwood, Espeseth, Lin, Reinvang, & Parasuraman, 2014).

Higher-order, executive attention shows a differential profile of ε4 effects in mid-adulthood (Article 3). The rapid visual information processing (RVIP) task (Wesnes & Warburton, 1983) provides a measure of sustained attentional focus and the ability to continuously update 'online' information. Previous research reports mid-age ε4 carriers are slower, but more accurate in detecting target strings on this task (Evans et al., 2014), however, Article 3 suggested performance was comparable between mid-age ε4 carriers and ε3 homozygotes. On a Stroop-switch task, however, mid-age ε4 carriers demonstrated a greater congruency effect for errors. In addition, ε4 disadvantages in non-focal PM manifested as either decreased PM retrieval accuracy on the card-sort paradigm (Article 3) or increased interference to ongoing task performance on the category decision task (Article 5). Previous studies of non-focal PM in mid-age ε4 carriers, again, reported a speed-accuracy trade off on PM trials in association with

heightened frontal fMRI BOLD activations (Evans et al., 2014). This study, however, did not include an index of PM interference to provide a complete consideration of genotype effects.

The profile of attentional control differences in mid-age ε4 carriers (Articles 2, 3 and 5) is suggestive of an early vulnerability in carriers of this variant in the ability to process multiple attentional sets, a central component of existing theoretical models of attentional control (Faust & Balota, 2007; Friedman & Miyake, 2015; Kane & Engle, 2003; Tiego et al., 2017). During non-focal PM individuals must process the ongoing task whilst maintaining and monitoring for the PM intention. Likewise, on the Stroop-switch paradigm, individuals must maintain multiple task rules (word naming, colour naming). Models of attentional control, importantly, indicate this complex goal maintenance ability is the overarching construct of executive attention, supporting additional processing such as inhibition and set shifting, and hence it may be this central ability that is most vulnerable to early ε4 deficits (Friedman & Miyake, 2015; Tiego et al., 2017). Article 5 explored how increasing the complexity of executive demand differentially impacted ε4 carriers in mid-adulthood by including a third WM component within a PM paradigm. The results were equivocal, however, and further interrogation of genotype differences in the ability to multi-task between several attentionally demanding tasks is needed. Furthermore, although the current study included a Stroop-switch paradigm, as the switches were regular and bi-trial (as opposed to random and unpredictable), the cost of attentional switching did not emerge as a sensitive index. To gain a more complete understanding of *APOE* genotype across individual processes of executive attention a more challenging switch task could be included in future research, with ε4 disadvantages predicted based on existing research (Velichkovsky et al., 2015).

The presence of specific cognitive deficits in ε4 carriers by mid-adulthood can be used to infer which neural regions are vulnerable to early ε4 effects. Non-focal PM is supported by dorsal frontal-parietal regions, cingulate regions and the precuneus (Cona et al., 2016, 2015; McDaniel et al., 2013), aligning with reports of genotype differences within these regions prior to the 6th decade (e.g. Chen et al., 2016; Evans et al., 2014). As change in frontal regions are reported in the initial stages of cognitive ageing (Bartzokis et al., 2003; Raz, 2000; Villemagne et al., 2011), perhaps ε4 are showing a premature decline in these regions.

Aside from attentional control, Article 5 also reports ε4 differences in focal PM by mid-adulthood, which were absent in youth. This suggests associative memory processes show early vulnerability to ε4 effects, reliant on medial temporal lobe function (Cona et al., 2016; Gordon et al., 2011; McDaniel et al., 2013). E4 differences in medial temporal lobe regions have

previously been reported in mid-adulthood (Den Heijer et al., 2002; Shaw et al., 2007; Wishart et al., 2006).

8.1.2 *APOE* ε2 and attentional control

The *APOE* ε2 variant is purported to have protective effects against LOAD (Corder, Saunders, Risch, Strittmatterl & Schmechel, 1994; Chiang et al, 2010) and the associated neuropathology (Grothe, Villeneuve, Dyrba, & Bartrés-faz, 2017; Nagy et al., 1995; Serrano-Pozo, Qian, Monsell, Betensky, & Hyman, 2015; Tiraboschi et al., 2004; for review see: Suri, Heise, Trachtenberg, & Mackay, 2013). Although infrequently studied, carrying an ε2 allele is linked to cognitive advantages in older adulthood (Bonner-Jackson et al., 2012; Deary et al., 2004; Helkala et al., 1996), as well as youth (Alexander et al., 2007; Alexopoulos et al., 2011; Konishi et al., 2016; Mondadori et al., 2007), although the data are less than consistent (Yasen, Raber, Miller, & Piper, 2015). Despite this, existing literature predominantly considers ε2 carriers collectively with homozygous ε3 carriers as a 'non-ε4' group, potentially biasing results, or excludes ε2 carriers from the sample altogether. This thesis independently considered the effects of this variant, as understanding the effects of all three alleles is essential for a complete understanding of how *APOE* genotype effects develop across the lifespan.

Given the purported protective role of *APOE* ε2, carriers of this genotype were expected to show cognitive advantages in mid-adulthood. Articles 2 & 3, however, report ε2 disadvantages, relative to their ε3 peers, on measures of selective attention and sustained attentional updating (Articles 2 & 3). The presence of both ε4 and ε2 disadvantages in this thesis aligns with reports of comparable fMRI BOLD activations in task-unrelated regions in mid-age ε2 and ε4 carriers (Trachtenberg, Filippini, Cheeseman, et al., 2012), potentially representing similar levels of neural network dedifferentiation between these variants. Furthermore, mid-age ε4 and ε2 carriers demonstrate similar profiles of resting-state BOLD activity (Trachtenberg, Filippini, Ebmeier, et al., 2012b). The presence of ε2 disadvantages earlier in the lifespan raises the question of how the opposing effects of ε4 and ε2 alleles develop in older adulthood. More recent research suggests that whilst ε2 and ε4 carriers both show diminished functional connectivity within the default mode network in older adulthood (aged 54-80 years), cross-sectional comparisons indicate a differential trajectory of age-related change between these variants (Shu et al., 2016). Understanding the mechanisms for why the effects of these alleles diverge in cognitive ageing is an important future step.

8.2 Theoretical accounts for the role of *APOE* ε4 in cognitive ageing

8.2.1 Mid-adulthood as a transitional stage in ε4 effects

Overall, the results from the studies reported here suggest carriers of an ε4 genotype show relatively preserved attentional control until the end of the 5th decade, with subtle deficits detectable on individual behavioural parameters. Although only one cognitive domain was considered in the current thesis, broadly intact performance is not inconsistent with the antagonistic pleiotropy hypothesis (Han & Bondi, 2008). It may be that mid-adulthood represents a transitional stage, with the expression of ε4 effects shifting from being cognitively advantageous (e.g. Marchant et al., 2010; Mondadori et al., 2007; Rusted et al., 2013; Stening et al., 2016) to detrimental in later life (Wisdom et al., 2011). To allow for a cross-sectional comparison between young and mid-age ε4 carriers, adults aged 18-30 years were included in Article 5. Considering this age group independently, evidence for ε4 advantages on measures of focal and non-focal PM was non-significant in youth, out of line with the predictions of antagonistic pleiotropy. Longitudinal research, however, is needed to establish lifespan developmental effects of the ε4 allele.

ε4 cognitive advantages in youth have been attributed to early compensatory strategies, supported by reports of increased fMRI BOLD activations, comparable to those seen in healthy ageing (e.g. Evans et al., 2014; Rusted et al., 2013). Continuation of compensatory strategies may in part be responsible for executive attention being largely intact in mid-age ε4 carriers; however, processes may be breaking down in line with small disadvantages appearing. In support, one study has reported that mid-age ε4 carriers show heightened fMRI BOLD activation at low levels of WM load, with no further increase in activation recorded under more challenging conditions as reported in their non-ε4 peers (Chen et al., 2013). This was interpreted as ε4 carriers utilising compensatory strategies to sustain performance under low demand, and hence being unable to further recruit additional support under more taxing conditions. Evidence for compensation is limited, however, in the absence of an association between neural activations and behaviour (Cabeza & Dennis, 2012).

Developing the idea that ε4 carriers may be approaching cognitive tasks differently, this thesis explored subjective cognitive effort and task load. Across Articles 5 and 6, healthy ε4 carriers across a range of age groups (young, mid, older) report greater perceived effort in completion of a PM task. Furthermore, in Article 5, the presumed practice-related decrease in effort on the second session of the category-decision PM task (under WM load) was absent in mid-age ε4 carriers only, suggestive of persistently high workload in this group. Hence ε4 carriers may consciously be exerting greater cognitive resource to maintain comparable levels of performance. These results are not inconsistent with the speed-accuracy trade-off reported in

Evans et al. (2014). Whilst using subjective reports to probe task load may not be the most accurate gauge of cognitive demand, further research exploring ε4 differences on physiological indices of response to task could be worthwhile.

8.2.2 Premature Ageing in Mid-age *APOE* ε4 Carriers

The presence of ε4 disadvantages on select processes implicated in attentional control supports early vulnerability in this group by mid-adulthood, with the uneven profile of impairment mirroring the non-uniform decline typical of healthy cognitive ageing. The pattern of impairment reported in ε4 carriers aged 45-55 years (Articles 3 and 5) is comparable with the profile of decline reported in older adulthood (Bélanger, Belleville, & Gauthier, 2010; Henry, MacLeod, Phillips, & Crawford, 2004; Kliegel, Jäger, & Phillips, 2008), suggestive that *APOE* ε4 is associated with an early loss of frontal-based cognitive resource. In addition, Article 5 included a cross-sectional comparison between young (18-30 years) and mid-age ε4 carriers. Compared to the young group, ε4 carriers demonstrated a greater age-related increase in prospective interference compared to their ε3 counterparts, consistent with enhanced cognitive ageing in this group.

Mid-age participants in this thesis were recruited from the age-range 45-55 years to minimise bias from individuals in the 'preclinical' stage of LOAD and the associated pathology (Sliwinski & Buschke, 1999; Sperling et al., 2011). Hence, the behavioural results consistent with premature ageing in mid-age ε4 carriers can be considered to result from a non-pathological physiological mechanism, consistent with *APOE* ε4 representing a cognitive phenotype (Greenwood, Lambert, Sunderland, Parasuraman, 2005; Negash et al., 2009). Considering existing literature, one potential mechanism for differential ε4 impairment in mid-adulthood may be altered cortical connectivity, linked to *APOE* ε4's role in the synthesis and transport of cholesterol, and as a result, myelination and the efficiency of neuronal communication (Liu et al., 2013). In late mid-adulthood, APOE ε4 is associated with disrupted functional connectivity within the default mode, executive control and salience networks (Goveas et al., 2013b), including in individuals demonstrating no significant amyloid accumulation (Sheline et al., 2010). Importantly, demyelination accelerates in ε4 carriers from the 5th decade (Bartzokis, 2007) supporting this as a potential mechanism for decline from mid-adulthood. Higher-order cognitive processes requiring the integration of processing across multiple neural regions may be more significantly impacted by disrupted connectivity.

Of interest, the attentional disadvantages reported in mid-age ε4 carriers overlap with the profile of cognitive impairment distinguishing individuals in the preclinical or early stages of LOAD

from age-matched healthy controls. Specifically, an effect of congruency on errors on the Stroop-switch task in mid-age ε4 carriers is comparable with behavioural deficits predictive of future LOAD onset in a group of healthy older adults (Balota et al., 2010)(Article 3). Whilst healthy cognitive ageing is associated with selective decline in non-focal PM, pathological ageing is distinguished by an additional impairment in focal PM (Chi et al., 2014; McDaniel, Shelton, Breneiser, Moynan, & Balota, 2011; Niedźwieńska, Kvailashvili, Ashaye, & Neckar, 2017). By mid-adulthood ε4 carriers show significant impairment in both focal and non-focal PM, consistent with the profile characteristic of LOAD. Hence, a second possibility is that ε4 carriers show early vulnerability to LOAD-related processes, driving increased age-related decline.

Early vulnerability to pathological ageing may result from a differential trajectory of amyloid deposition in ε4 carriers. One influential model argues that the accumulation of β amyloid acts as the initial insult within the cascade of neurodegenerative processes (Selkoe & Hardy, 2016), and hence may be expected to influence individual differences in early cognitive ageing. Further supporting amyloid as a probable mechanism of LOAD-type vulnerability, carrying a copy of the ε4 variant directly impacts the accumulation and clearance of amyloid in the brain (Mahley et al., 2006). Although this thesis included adults aged 45-55 years, *APOE* ε4 is seen to accelerate the accumulation of amyloid earlier in the lifespan. For example, a higher proportion of ε4 carriers are reported to show build up of Aβ42 by their 40s (Morishima-Kawashima et al., 2000). In addition, 10% of ε4 carriers show clinically significant levels of amyloid by the 5th decade (Jack et al., 2015). Below the threshold for clinically significant amyloid accumulation, the initial build up of this protein may impact early *APOE* genotype differences in cognitive ageing. Increased neural activation is hypothesised to accelerate amyloid deposition (Jagust & Mormino, 2011); hence increased frontal and medial temporal lobe BOLD activations in young ε4 carriers (e.g. Filippini et al., 2009; Rusted et al., 2013; Trachtenberg, Filippini, Cheeseman, et al., 2012) may indicate early vulnerability, stressing the need to consider the cumulative impact.

In line with frontal regions being preferentially impacted by the neural deposition of amyloid (Rowe et al., 2007; Villemagne et al., 2011), several studies have investigated the relationship between *APOE,* executive attention, and amyloid in late-mid adulthood. The presence of amyloid is reported to accelerate decline in mid-age ε4 carriers (mean age 53.6 years) on neuropsychological assessment measures of inhibition, switching and processing speed (Clark et al., 2016). In further support, although no independent effect of ε4 was reported on cognition in adults aged 50-69 years, the presence of amyloid was associated with poorer executive attention in ε4 carriers (Mielke et al., 2015). On a behavioural paradigm of attentional control, a

speeded category-decision task, ε4 differences were mediated by the presence of Aβ42, specifically in regions including the prefrontal cortex, precuneus and temporal regions (Aschenbrenner et al., 2015). Therefore, there is support for both non-pathological and LOAD-related mechanisms of premature ageing in ε4 carriers, supporting the need to take a dimensional approach to understanding cognitive ageing (Herrup, 2010; Sheline et al., 2010; Verghese, Castellano, & Holtzman, 2011).

8.2.3 *APOE* ε4: a genetic vulnerability factor?

Herrup (2010) suggested age-related processes are central to cognitive decline; however, the presence of neural insult is necessary to trigger an enhanced profile of deterioration. In addition to allowing for the role of *APOE* in the pathological accumulation of amyloid, this model suggests carrying an ε4 allele creates a general propensity for decline. Although *APOE* ε4 may reduce the reserve of the brain to cope with insult via multiple LOAD independent mechanisms, including neuroinflammation and mitochondrial dysfunction (Liu et al., 2013), a susceptibility to vascular damage is identified as the key factor in this model. In line with the methodological comments outlined in Article 1, this motivated an exploratory examination of the moderation of *APOE* effects by additional factors influencing cognitive ageing, including vascular health (Article 4).

In line with previous research (Bender & Raz, 2012; Oberlin et al., 2015; McFall et al., 2015), *APOE* ε4 status was predicted to interact with poor vascular health to exaggerate cognitive deficits from mid-adulthood. Specifically, systolic blood pressure and ε4 in combination associate with decreased white matter volume and executive decline (Bender & Raz, 2012), supporting disruption in neural connectivity as a general mechanism for ε4 effects. This thesis did not find an association between vascular health and *APOE* genotype on measures of executive attention, however, this may stem from methodological limitations (detailed in the discussion of Article 4). The current studies report attentional disadvantages in both ε4 and ε2 carriers in mid-adulthood (Articles 2, 3, 5), yet one possibility is that the opposing influence of these variants in later life stem from differential vulnerability to cognitive insult (McFall et al., 2015). In youth, cerebrovascular reactivity and thus resistance to vascular insult increases in a stepwise manner across genotypes ε4, ε3, ε2 (Suri et al., 2015a). This fits with the suggestion that whilst the trajectory of ε4 carriers is more flexible, the ε2 allele may be more resistant to modification by external factors. Furthermore, beneficial effects of cognitive reserve were enhanced in ε4 carriers (Article 4), supporting the hypothesis that ε4 represents a plasticity gene (Belsky et al., 2015).

8.3 Limitations

Each Article includes an independent discussion of potential shortcomings; here, common limitations across the studies are considered. A principle concern is the relatively small sample size of each genotype group across experimental studies. In particular, the study reported in Article 6 recruited participants opportunistically, either from the MAS clinics or local community groups, leading to an unequal distribution of *APOE* genotype groups. Small group sizes may result in underpowered statistical analysis, leading to under- or overestimated effect sizes (Button et al., 2013). In support, smaller effect sizes of *APOE* ε4 genotype are reported in studies with larger group sizes (e.g. Jorm et al., 2007; Marioni et al., 2015; Shin et al., 2014), as evidenced in the meta-analytic review of *APOE* ε4 effects in mid-adulthood (Article 1), and the meta-analysis of ε4 effects in youth (Ihle et al., 2012). Although effects of *APOE* ε4 on attentional control in mid-adulthood were consistent across studies in this thesis, research should focus on the reproducibility of *APOE* ε4 behavioural effects with larger sample sizes, to strengthen conclusions.

The field of cognitive ageing is rapidly moving towards a reliance on large cohort studies, such as 'Generation Scotland' (Marioni et al., 2015a), the Arizona *APOE* cohort (Richard J Caselli et al., 2009) and the 'Atherosclerosis Risk in Communities Study' (Blair et al., 2005). Whilst these are invaluable for gathering cognitive data representative of the general population, cohort studies typically rely on quick-to-administer generic neuropsychological test batteries. The use of sensitive and process-specific cognitive paradigms is generally more time consuming, hence limiting study sample size. Future research could consider using remote computerised tasks to sensitively measure cognition in larger groups.

Sample size further limited our consideration of *APOE* gene dose, with a small number of homozygotes in each study. The impact of ε4 reportedly increases with 0, 1 and 2 copies of the gene (Farrer et al., 1997; Raber et al., 2004; Wisdom et al., 2011). The effects of *APOE* ε4 are reported to differ on measures of attention and general processing speed in mid-life according to zygosity (Blair et al., 2005; Greenwood, Lambert, Sunderland, Parasuraman, 2005), but not consistently (Trachtenberg, Filippini, Cheeseman, et al., 2012). The additive effects of carrying two copies of the ε4 allele could be explored in future research, with a necessity for large sample sizes due to the low frequency of homozygous ε4 carriers in the population (~2% (Raber et al., 2004)).

A further limitation of the thesis is that the participating mid-age volunteers were generally high functioning, with many of them recruited from a university background and mean premorbid IQ

between 117- 119 for Articles 2, 3, 4 and 5. This makes it difficult to draw strong conclusions about how *APOE* ε4 effects generalise to a broader general population. Article 4 investigated the moderation of *APOE* genotype effects under varying environmental conditions, including past cognitive engagement, vascular and metabolic health, and physical activity. Again, low variability in participants along these variables limit exploration of *APOE* x Environment interactions.

Finally one of the reasons for considering *APOE* genotype effects in mid-adulthood is that the presence of genotype effects at this stage of the lifespan will further understanding of how gene expression changes across the lifespan. It is difficult to draw conclusions of genetic differences in the trajectory of cognitive ageing, however, from taking snapshots of ε4 effects at any one window of the lifespan. Future longitudinal research is needed to validate lifespan models of *APOE* ε4 effects.

8.4 Applications and Future Directions

Clear evidence for subtle behavioural impairment in ε4 carriers by mid-adulthood has important applications for future research. The results of Articles 2-5 suggest individual processes within the framework of attentional control are differentially sensitive to the effects of the ε4 variant, however, this thesis did not administer paradigms sensitive to attentional set-shifting. Furthermore, although the profile of impairment reported in mid-age ε4 is consistent with deficits in the maintenance of multiple goals within attention, it may be differences emerge under conditions more taxing to the integration of multiple attentional processes. To explore *APOE* differences in a more ecologically valid context of attentional control, paradigms assessing multi-tasking may be explored in future research. This will allow more careful interrogation of *APOE* differences in frontally based processing. In addition, the focus of this thesis was investigating ε4 differences within the domain of attentional control. In line with the conclusions of Article 1, sensitive behavioural paradigms should be used to explore early genotype differences across a range of cognitive domains.

An important next step for future research is to explore the biological basis of premature ageing in ε4 carriers, focusing on directly correlating changes in the behavioural phenotype with genotype differences in the brain. In addition to focusing on region-of-interest BOLD activations, studies considering the integration of cortical activity across brain regions are important. Further understanding the neural basis of ε4 effects has important applications for timely interventions against cognitive decline.

Reports of ε4 effects on attentional control by mid-adulthood (Articles 2-5) has wider relevance for understanding cognitive impairment in older adulthood. Whilst changes in episodic memory are considered the hallmark of cognitive ageing (e.g. Caselli et al., 2014; Chen et al., 2001; for review see Mortamais et al., 2016), changes in attentional control may be responsible for lapses in everyday function. The current thesis consistently demonstrated effects of *APOE* ε4 on PM in mid-adulthood (Articles 3 and 5), considered the archetypical form of 'everyday' memory. In light of this, the relationship between non-focal PM and cognitive errors in everyday life was explored in individuals self-referring to the MAS (Article 6). Although PM was not differentially impacted in this 'at-risk' group, the correlation between performance and subjective reports of lapses in attentional control encourages interventions targeting PM for the maintenance of independence in everyday life.

The crucial conclusion of this thesis is that mid-adulthood represents a critical window when individual differences in the trajectory of cognitive decline may first be apparent. The demonstration of ε4 disadvantages at the end of the 5th decade presents the opportunity for early risk assessment and more timely intervention strategies. To build on the presence of existing ε4 differences on measures of attentional control, future research should explore if the combination of *APOE* genotype with inter-individual differences in these parameters is predictive of a more detrimental trajectory of cognitive ageing. Furthermore, mid-adulthood is a key stage of the lifespan when additional factors in age-related decline, including vascular health and cognitive reserve may become more prominent in their effects (Ritchie, Ritchie, Yaffe, Skoog, & Scarmeas, 2015), and hence *APOE* ε4 should not be considered in isolation. Future research should explore environmental factors in depth to see if interventions can reverse early genotype differences in mid-adulthood. There is the potential to use *APOE* genotype in personalized medicine (Villeneuve, Brisson, Marchant, & Gaudet, 2014), referring to the tailoring of medical advice based on individual characteristics including genotype, family history and additional risk factors (Offit, 2011). If ε4 carriers show greater plasticity in their trajectory of cognitive decline, and increased vulnerability to cardiovascular risk mechanisms, *APOE* status could directly be used to implicate the most effective preventative steps. There are considerable ethical implications, however, for both the collection and disclosure of genotype information at the level of the individual.

8.6 Conclusions

Carrying a copy of the *APOE* ε4 risk variant is associated with disadvantages in executive attention by mid-adulthood. Importantly, an uneven profile of impairment was reported across attentional processes, with tasks requiring the maintenance of multiple goals within attention

most consistently affected. This suggests rather than ε4 being uniformly disadvantageous, distinct elements of attentional control are vulnerable to the negative effects of this allele. Overlap in the cognitive profile of ε4 carriers and the distinguishing behavioural impairments of LOAD is suggestive of *APOE* ε4 acting via both general ageing mechanisms and LOAD-related pathology, emphasising the need to adopt a dimensional approach to cognitive ageing. Cognitive reserve moderated ε4 effects in mid-adulthood, with differential sensitivity of this group positioning ε4 as a vulnerability gene. Furthermore, the mitigation of ε4 affects effects in mid-adulthood highlights the importance of focusing preventative steps earlier in the lifespan. Future research should focus on linking these early cognitive differences to their biological basis, and importantly on whether the influence of ε4 can be minimised at this formative stage through the interplay of this allele with additional factors.

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Appendix:

In addition, group differences (Age, Genotype) in the proportion of WM targets identified in each condition (control, focal, non-focal) was probed using a 3 (Condition) x 2 (Age) x 2 (Genotype) mixed ANOVA.

The proportion of WM targets recalled in each PM condition is shown in Table 5. At trend level, young adults (M=.91, SD=.18) recalled a higher proportion of WM targets than mid-age adults (M=.84, SD=.19), $F(1, 84)=3.16$, $p=.079$, $n2p=.036$. The main effect of focality was non-significant ($p>.05$), however there was a significant Focality x Age x Genotype interaction, $F(1.79, 150.13)=3.18$, $p=.050$, n2p=.036. In ε3 carriers, there was a significant Age x Focality interaction, $F(2, 100)=3.17$, $p=.046$, $n2p=.060$. SME analysis identified a trend of mid-age volunteers retrieving a smaller proportion of WM targets than young volunteers selectively in the non-focal condition ($p=.039$) (Bonferroni-corrected $\alpha=.013$). In ε4s the Age x Focality interaction was non-significant ($p>.05$).

Table A. The proportion of WM targets reported in each focality condition.

		Control	**Focal**	**Non-focal**
Young	**ε3**	.81 (.27)	.87 (.30)	.95 (.17)
	ε4	1.01 (.16)	.94 (.23)	.88 (.28)
Mid	**ε3**	.87 (.24)	.87 (.25)	.78 (.30)
	ε4	.85 (.19)	.80 (.31)	.86 (.38)