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Review

APOE genotype and cognition in healthy individuals at risk of Alzheimer's disease: A review[☆]

M. Clare O'Donoghue^a, Susannah E. Murphy^{b,c}, Giovanna Zamboni^d, Anna C. Nobre^{a,e} and Clare E. Mackay^{a,*}

^a Oxford Centre for Human Brain Activity, Wellcome Centre for Integrative Neuroimaging, Department of Psychiatry, University of Oxford, UK

^b Department of Psychiatry, University of Oxford, UK

^c Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

^d Wellcome Centre for Integrative Neuroimaging, FMRIB, Nuffield Department for Clinical Neurosciences, John Radcliffe Hospital, Oxford, UK

^e Department of Experimental Psychology, University of Oxford, UK

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ABSTRACT

APOE- ϵ 4 is best known as a risk factor for Alzheimer's disease (AD). Consequently, there is considerable research interest in understanding whether APOE- ϵ 4 influences cognition in healthy adults. Despite a substantial literature reporting effects of APOE genotype on cognition, findings are inconsistent. In particular, it is challenging to separate whether cognitive deficits in APOE- ϵ 4 carriers reflect the influence of prodromal dementia pathology ("prodromal hypothesis"), or a direct contribution of APOE genotype to individual differences ("phenotype hypothesis"). Variable methodology across studies further complicates the issue. These challenges have limited what can be learnt about the processes underlying cognitive ageing and dementia by studying the influence of APOE genotype on cognition. In this review, we focus on the two compatible neurobiological mechanisms by which APOE genotype may influence cognition in healthy adults (prodromal and phenotype). We summarise the behavioural evidence for the influence of APOE on cognition in non-demented adults and explore key methodological challenges for disentangling the cognitive effects of different neurobiological mechanisms of APOE. Evidence suggests that at least some APOE- ϵ 4 cognitive deficits are due to early AD pathology, whilst sensitive measures of cognition are beginning to reveal subtle cognitive differences between APOE genotypes in mid-adulthood, prior to the onset of the AD prodromal period. We conclude

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* Corresponding author. Oxford Centre for Human Brain Activity, Warneford Hospital, Warneford Lane, Oxford, OX3 7JX, UK.

E-mail addresses: clare.odonoghue@psych.ox.ac.uk (M.C. O'Donoghue), susannah.murphy@psych.ox.ac.uk (S.E. Murphy), giovanna.zamboni@ndcn.ox.ac.uk (G. Zamboni), kia.nobre@psy.ox.ac.uk (A.C. Nobre), clare.mackay@ohba.ox.ac.uk (C.E. Mackay).

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with recommendations for future research to investigate the cognitive consequences of neurobiological processes affected by APOE and maximise the translational potential of this research.

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1. Introduction

Since the discovery of apolipoprotein-E (APOE) $\epsilon 4$ as a genetic risk factor for Alzheimer's disease (AD; Corder et al., 1993; Saunders et al., 1993), researchers have investigated whether healthy $\epsilon 4$ -carriers show impaired cognition or more rapid cognitive decline compared to non-carriers, as an early sign of impending dementia (e.g., Bondi et al., 1995; Staehelin, Perrig-Chiello, Mitrache, Miserez, & Perrig, 1999; Wetter et al., 2005), or source of variability in healthy cognitive ageing (e.g., Deary et al., 2003, 2002; Greenwood & Parasuraman, 2003; Greenwood, Lambert, Sunderland, & Parasuraman, 2005; Helkala et al., 1996). Understanding the association between APOE genotype and cognition in healthy adults can aid development of preclinical biomarkers for AD, increase knowledge of the mechanisms by which APOE- $\epsilon 4$ increases AD risk, and inform interventions to boost cognition in older adults. However, the reported effects of APOE on cognition are highly inconsistent, and interpretation of these mixed findings is complicated by conceptual and methodological challenges.

A major challenge in understanding the association between APOE and cognition is the difficulty disentangling direct influences of APOE genotype on a 'cognitive phenotype' (Greenwood & Parasuraman, 2003; Greenwood, Lambert, et al., 2005) from the influence of greater prodromal AD pathology in the at-risk group (Smith et al., 1998). In part, this stems from a conceptual challenge where the two possibilities have been framed as competing 'hypotheses' to explain the effect of APOE on cognition (Bunce et al., 2014; Foster et al., 2013; Greenwood & Parasuraman, 2003; Greenwood, Espeseth, Lin, Reinvang, & Parasuraman, 2014; Greenwood, Sunderland, Putnam, Levy, & Parasuraman, 2005; Hofer et al., 2002; Negash et al., 2009; Parasuraman, Greenwood, & Sunderland, 2002), with evidence supporting one 'hypothesis' interpreted as evidence against the other (e.g., Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Foster et al., 2013; Small, Basun, & Backman, 1998; Smith et al., 1998). Unquestionably, the proposed direct versus pathology-mediated cognitive effects related to APOE genotype are underpinned by different neurobiological mechanisms, but these need not be mutually exclusive. Dissecting the relative influence of each neurobiological mechanism on cognitive performance will ultimately elucidate their roles in cognitive ageing and Alzheimer's disease.

In this review, we outline two compatible neurobiological mechanisms by which APOE genotype may influence cognition, and highlight the individual and interacting methodological challenges for separating the cognitive consequences of each mechanism. The main objective is to demonstrate that

APOE genotype may affect cognition via multiple neurobiological mechanisms, each with the potential to provide insight into different aspects of cognitive ageing and Alzheimer's disease. We conclude with recommendations for future studies to facilitate interpretation of APOE-related effects and increase the translational value of these findings.

2. Neural mechanisms of APOE genotype influence on cognition

The APOE gene has three major allelic variants – $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$. Individuals possess two APOE alleles, one inherited for each parent, resulting in three homozygous genotypes – $\epsilon 2\epsilon 2$, $\epsilon 3\epsilon 3$, $\epsilon 4\epsilon 4$ - and 3 heterozygous genotypes – $\epsilon 2\epsilon 3$, $\epsilon 2\epsilon 4$, $\epsilon 3\epsilon 4$. APOE- $\epsilon 3$ is the most common allele, estimated to be present in 68–86% of the Caucasian population, compared to 10–23% and 4–14% for the $\epsilon 4$ and $\epsilon 2$ alleles, respectively (Davignon, Gregg, & Sing, 1988; Gerdes, Klausen, Sihm, & Faergeman, 1992; Myers et al., 1996; Singh, Singh, & Mastana, 2006).

The APOE gene codes for the apolipoprotein-E lipid-transport protein (ApoE). ApoE mediates the movement of cholesterol between cells (Mahley, 1988), and provides essential lipids for central nervous system (CNS) functions such as neuronal growth, synaptic plasticity, and neuronal maintenance and repair (Liu, Kanekiyo, Xu, & Bu, 2013). Structural differences in ApoE proteins, which result from allelic variation in APOE genotype, are associated with isoform-specific alterations of these CNS functions. For example, ApoE4 is less efficient at transporting brain cholesterol compared to ApoE3 (Rapp, Gmeiner, & Hüttinger, 2006), which may disrupt the supply of lipids needed for maintenance of synaptic integrity and plasticity (Liu et al., 2013). Consistent with this, animal models suggest APOE- $\epsilon 4$ genotype is associated with delayed neuronal development (Nwabuisi-Heath, Rebeck, Ladu, & Yu, 2014), lower dendritic spine density (Dumanis et al., 2009), and reduced long-term potentiation (Trommer et al., 2004), whilst human $\epsilon 4$ -carriers show reduced synaptic plasticity (Arendt et al., 1997), altered myelin formation (Dean et al., 2014), and poorer outcomes following traumatic brain injury (TBI; Zhou et al., 2008) and subarachnoid haemorrhage (Martínez-González & Sudlow, 2006; for a review of the role of APOE genotype in a range of neurological disorders, see Verghese, Castellano, & Holtzman, 2011).

The APOE- $\epsilon 4$ allele is the best known genetic risk factor for sporadic Alzheimer's disease (Corder et al., 1993; Rocchi, Pellegrini, Siciliano, & Murri, 2003). Carriers of the $\epsilon 4$ allele show increased risk and earlier age of onset of AD, compared to non-carriers (Borgaonkar et al., 1997; Corder et al., 1993; Sando et al., 2008). $\epsilon 4$ -related AD risk is conferred in a dose-dependent manner, with greater risk and earlier age of onset

in $\epsilon 4$ -homozygotes compared to $\epsilon 4$ -heterozygotes (Blacker et al., 1997; Liu et al., 2013). In contrast, possession of an $\epsilon 2$ allele may provide protection against AD diagnosis (for a review of APOE- $\epsilon 2$, see Suri, Heise, Trachtenberg, & Mackay, 2013). The mechanisms by which APOE- $\epsilon 4$ increases AD risk are not fully understood, but a role of ApoE4 in greater deposition and/or reduced clearance of amyloid- β , resulting in increased aggregation of this hallmark pathological feature of AD, has been proposed (Huang, Weisgraber, Mucke, & Mahley, 2004). Isoform-specific effects on neuroinflammation, neurogenesis, and neuronal toxicity may also contribute to increased risk of AD in $\epsilon 4$ -carriers (for a review of APOE mechanisms and AD risk, see Liu et al., 2013). Possession of an APOE- $\epsilon 4$ allele is neither necessary nor sufficient for development of AD (Henderson et al., 1995; Hyman et al., 1996); however, approximately half of $\epsilon 4$ -homozygotes will develop AD by age 85, compared to only 10% of non-carriers (Genin et al., 2011).

2.1. Prodrome

APOE genotype may influence cognition in currently healthy adults indirectly via an increased presence of early AD pathology in APOE- $\epsilon 4$ carriers. Whilst AD is typically diagnosed after age 65 (McKhann, Drachman, Folstein, & Katzman, 1984), the accumulation of pathology begins years prior to the onset of clinical symptoms (Ohm, Müller, Braak, & Bohl, 1995; Tondelli et al., 2012). Progressive cognitive impairment, particularly in episodic memory (Bondi et al., 2008; Weintraub, Wicklund, & Salmon, 2012), is also detectable years before a diagnosis is made (Amieva et al., 2005; Wilson, Leurgans, Boyle, & Bennett, 2011). A proportion of any sample of currently healthy older adults will be in the prodromal stage that precedes clinical diagnosis of AD (Sliwinski, Lipton, Buschke, & Stewart, 1996). The increased risk and earlier age of onset of AD in APOE- $\epsilon 4$ carriers (Blacker et al., 1997; Corder et al., 1993; Sando et al., 2008) means the proportion of prodromal individuals will be greater in this at-risk group, compared to non-carriers.

According to the ‘prodromal hypothesis’ (Foster et al., 2013; Smith et al., 1998), cognitive deficits in healthy APOE- $\epsilon 4$ carriers, particularly in samples aged over 60 years, reflect the indirect effect of prodromal AD pathology in a subset of $\epsilon 4$ -carriers who will go on to be diagnosed with AD. Some researchers argue APOE genotype itself has no direct influence on cognition, but rather observed $\epsilon 4$ -related cognitive deficits result entirely as a consequence of prodromal AD. In support of this, a number of studies reported elimination of $\epsilon 4$ -related deficits after exclusion of incident AD cases (Bondi et al., 1999; Hayden et al., 2009; Hofer et al., 2002; Knight et al., 2014; Praetorius, Thorvaldsson, Hassing, & Johansson, 2013; Winnock et al., 2002), and significantly faster cognitive decline in $\epsilon 4$ -carriers in domains affected in early AD (Bretsky, Guralnik, Launer, Albert, & Seeman, 2003; Caselli, Dueck, Locke, Hoffman-Snyder, et al., 2011; Haan, Shemanski, Jagust, Manolio, & Kuller, 1999; Helkala et al., 1996; Hofer et al., 2002; Hyman et al., 1996; Mayeux, Small, Tang, Tycko, & Stern, 2001; Packard et al., 2007; Riley et al., 2000; Schiepers et al., 2012; Small et al., 1998; Yaffe, Cauley, Sands, & Browner, 1997), as well as mediation of cognitive deficits in $\epsilon 4$ -carriers by the

presence of mild cognitive impairment (MCI) rather than APOE genotype itself (Foster et al., 2013).

2.2. Phenotype

In contrast to a strong prodromal view, other researchers consider that APOE genotype may exert a direct effect on cognition, independent of future AD diagnosis, via genotype-specific influences on neurobiological processes that affect cognition (Greenwood & Parasuraman, 2003; Parasuraman & Greenwood, 2004). Genetics are an important determinant of cognitive ability (Plomin, DeFries, McClearn, & McGuffin, 2001), and normal allelic variation may contribute to individual differences in cognitive abilities throughout life. This *cognitive neurogenetic* approach (Greenwood & Parasuraman, 2003; Parasuraman & Greenwood, 2004) proposes a cascade of events linking genotype to cognitive phenotype (also see Deary, Penke, & Johnson, 2010; Meyer-Lindenberg & Weinberger, 2006; Reinvang, Deary, et al., 2010). As the isoform structure of a protein depends on the specific genotype of the coding gene, this will result in isoform-specific alteration of *neurobiological endophenotypes*, ultimately producing variable *cognitive phenotypes*.

According to the ‘phenotype hypothesis’ (Greenwood & Parasuraman, 2003; Greenwood, Lambert, et al., 2005; Parasuraman et al., 2002), the putative roles of ApoE in CNS functions, such as synaptic plasticity and repair, provide an altered neural endophenotype by which APOE genotype may result in a ‘cognitive phenotype’. According to this hypothesis, cognitive differences in $\epsilon 4$ -carriers are not confined to older adults and are independent of subsequent AD diagnosis (Greenwood, Lambert, et al., 2005). Neuroimaging studies in younger adults (under 60 years) provide corroborative results that suggest APOE- $\epsilon 4$ is associated with differences in the brain prior to the onset of AD pathology, in a manner independent of future AD. Similar patterns have been observed in at-risk $\epsilon 4$ -carriers and low-risk $\epsilon 2$ -carriers, compared to $\epsilon 3$ -carriers, in task and resting-state functional MRI, as well as white matter (WM) integrity (e.g., Trachtenberg, Filippini, Cheeseman, et al., 2012; Trachtenberg, Filippini, Ebmeier, et al., 2012; Westlye, Reinvang, Rootwelt, & Espeseth, 2012; for reviews of APOE genotype effects on MRI measures in healthy adults, see Fouquet, Besson, Gonneaud, La Joie, & Chételat, 2014; Trachtenberg, Filippini, & Mackay, 2012).

Whilst the association between APOE and Alzheimer's disease is unusually strong for an individual susceptibility gene–disease association (Genin et al., 2011), a direct effect of APOE on a cognitive phenotype is likely to be subtle. Cognitive ability is influenced by multiple genes, environmental factors, and complex gene–environment interactions, so any single gene will exert only a small effect on a cognitive phenotype (Marian, 2012). However, the phenotypic influence of APOE on cognition may be particularly observable in later life. The influence of genetics on cognition is thought to increase with age (e.g., McClearn et al., 1997; McGue & Christensen, 2002), possibly due to neuronal and neurochemical losses with age that highlight genetic influences on cognition (Lindenberg et al., 2008). Normal allelic variation may therefore particularly contribute to increased variability in cognitive

performance in older adults (e.g., Christensen et al., 1999; Wilson, Beckett, et al., 2002).

3. Literature search

For this comprehensive review of APOE and cognition studies in healthy adults, online searches were performed in PubMed using combinations of the following search terms: 'APOE', 'apolipoprotein', 'cognition', 'cognitive', 'performance', 'cognitive ability', and 'cognitive abilities'. Only studies published from 1993, when APOE genotype was identified as a risk factor for AD (Corder et al., 1993), were considered.

Studies that used neuropsychological measures, forming the majority of the literature, were considered for inclusion in Tables 1 and 2. Participants were required to be cognitively healthy and grouped by APOE genotype. Any studies that included individuals with objective cognitive impairment or clinical diagnoses at baseline were not included, unless results were separately reported for non-demented participants. Studies with highly selected samples, e.g., women on hormone replacement therapy, were also not included. Studies that focused on APOE genotype interactions with other variables, including MRI metrics, were not included. Age of the sample (range or mean) and follow-up duration, where applicable, were required to be reported for inclusion. Only studies published in English were considered. As detailed discussion of neuroimaging findings is beyond the scope of this review, functional MRI studies were not included and are reviewed elsewhere (see Trachtenberg et al., 2012). Studies with overlapping samples were not excluded (e.g., Bunce, Anstey, Burns, Christensen, & Eastaale, 2011; Jorm et al., 2007).

4. Summary of research findings

In the last twenty years, many studies have investigated the influence of APOE genotype on cognition in the absence of diagnosed dementia. A large proportion of these studies compared the performance of older adults on neuropsychological tests between APOE- $\epsilon 4$ carriers and non-carriers, particularly on measures of episodic memory (Small, Rosnick, Fratiglioni, & Bäckman, 2004; Wisdom, Callahan, & Hawkins, 2011). The effect of APOE on cognition has also been investigated across the lifespan, from children to the oldest-old, using cross-sectional and longitudinal cognitive measures spanning a range of cognitive domains, including semantic memory, working memory, executive function, processing speed, attention, visuospatial processing, language, intelligence, and tests of global cognition, as well as a smaller selection of experimental cognitive tasks.

Despite this breadth of investigation, a consistent pattern of results has failed to emerge. Whilst many cross-sectional studies have reported significant cognitive deficits in APOE- $\epsilon 4$ carriers compared to non-carriers across a range of cognitive domains (Bondi et al., 1995; Bondi et al., 1999; Caselli et al., 2001; Chey, Kim, & Cho, 2000; Deary et al., 2004, 2002; Flory, Manuck, Ferrell, Ryan, & Muldoon, 2000; Houston et al., 2005; Izaks et al., 2011; Jacobson, Delis, Lansing, et al., 2005; Jacobson, Delis, Bondi, & Salmon, 2005; Laukka et al., 2013;

Levy et al., 2004; Liu et al., 2010; Luciano, Gow, Harris, et al., 2009; Luck et al., 2015; Nao et al., 2017; O'Hara et al., 2008; Reed et al., 1994; Rosen, Bergeson, Putnam, Harwell, & Sunderland, 2002; Rosen et al., 2005; Sager, Hermann, & La Rue, 2005; Schmidt et al., 1996; Schultz et al., 2008; Striepens et al., 2011; Welsh-Bohmer et al., 2009; Wetter et al., 2005), other studies have found no significant effect of APOE genotype on cognition (Bathum et al., 2006; Berteau-Pavy, Park, & Raber, 2007; Bunce et al., 2011; Caselli et al., 1999; Caselli et al., 2002; Chen et al., 2002; Driscoll, McDaniel, & Guynn, 2005; Duchek, Balota, & Cortese, 2006; Foster et al., 2013; Greenwood, Sunderland, Friz, & Parasuraman, 2000; Jorm et al., 2007; Kim et al., 2002; Liu et al., 2010; Luciano, Gow, Taylor, et al., 2009; Payton et al., 2006; Quintas et al., 2014; Reiman et al., 1996; Richter-Schmidinger et al., 2011; Salo et al., 2001; Small et al., 2000; Ward et al., 2014; Wetter et al., 2006; Ystad et al., 2009; Zhang, Ren, et al., 2015; Zhang, Chen, et al., 2015). Table 1 summarises the reported effects of APOE on cross-sectional neuropsychological measures of cognition, including the cognitive domains tested in each case (definition of cognitive domains is detailed in the Supplementary Table). A small number of studies reported superior performance in $\epsilon 4$ -carriers, although such findings are typically restricted to young (e.g., under 30 years; Mondadori et al., 2007; Schultz et al., 2008) or very old (e.g., over 80 years; Carrión-Baralt et al., 2009; Smith et al., 1998) samples.

Table 2 summarises the reported APOE effects from longitudinal studies, including sample age at baseline, length of follow-up period, and screening at baseline and follow-up(s). Many such studies have reported more rapid cognitive decline in APOE- $\epsilon 4$ carriers (Andrews, Das, Cherbuin, Anstey, & Eastaale, 2016; Baxter, Caselli, Johnson, Reiman, & Osborne, 2003; Bretsky et al., 2003; Carmelli et al., 2000; Caselli et al., 2004; Caselli et al., 2009; Caselli, Dueck, Locke, Hoffman-Snyder, et al., 2011; Christensen et al., 2008; Donix et al., 2012; Greenwood et al., 2014; Helkala et al., 1996; Hofer et al., 2002; Jochemsen, Muller, Graaf, & Geerlings, 2012; Jonker et al., 1998; Mayeux et al., 2001; Praetorius et al., 2013; Riley et al., 2000; Schiepers et al., 2012; Shadlen et al., 2005; Small et al., 1998; Tupler et al., 2007; Wilson, Bienias, Berry-Kravis, Evans, & Bennett, 2002), with some also reporting baseline $\epsilon 4$ -related deficits (Barnes et al., 2013; Blair et al., 2005; Lavretsky et al., 2003; Packard et al., 2007; Sapkota, Bäckman, & Dixon, 2017; Yaffe et al., 1997; Zehnder et al., 2009). However, other longitudinal studies observed no difference in rate of cognitive decline between APOE genotype groups (Batterham, Bunce, Cherbuin, & Christensen, 2013; Bunce, Fratiglioni, Small, Winblad, & Bäckman, 2004; Bunce et al., 2014; Cohen, Small, Lalonde, Friz, & Sunderland, 2001; Deary et al., 2003; Dik et al., 2000; Jarvik et al., 2005; Juva et al., 2000a; Knight et al., 2014; Mortensen & Høgh, 2001).

As illustrated in Tables 1 and 2, many studies have investigated the effect of APOE genotype on not only one cognitive test, but on extensive cognitive batteries assessing multiple cognitive domains in the same sample (e.g., Caselli et al., 2001; Duchek et al., 2006; Foster et al., 2013; Levy et al., 2004). In these studies, $\epsilon 4$ -related deficits have often been reported in some, but not all, domains, suggesting a domain-specific effect of APOE- $\epsilon 4$ on cognition, with episodic memory particularly affected. However, the pattern of spared

Author (Year)	Age (M)	N	Legend	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Domain 7	Domain 8	Domain 9	Domain 10	Domain 11	Domain 12	Domain 13	Domain 14	Domain 15
Chen et al. (2002)	66.7	153	●															
Striepens et al. (2011)	67.2	72	●															
Bondi et al. (1999)	69.2	133	●															
Luciano, Gow, Harris, et al. (2009)	69.6	1013	●															
Luciano, Gow, Taylor, et al. (2009)	69.6	1013	●															
Kim et al. (2002)	70.0	466	●															
Foster et al. (2013)	70.5	764	●															
Luck et al. (2015)	70.9	202	●															
Bondi et al. (1995)	71.8	52	●															
Duchek et al. (2006)	72.5	20	●															
Laukka et al. (2013)	72.8	2694	●															
Quintas et al. (2014)	72.9	213	●															
Helkala et al. (1995)	73.8	912	●															
Jacobson, Delis, Bondi et al. (2005)	74.0	42	●															
O'Hara et al. (2008)	74.8	51	●															
Wetter et al. (2006)	74.8	28	●															
Small et al. (2000)	74-85	211	●															
Jacobson, Delis, Lansing, et al. (2005)	76.2	40	●															
Houston et al. (2005)	76.2	52	●															
Wetter et al. (2005)	76.3	51	●															
Driscoll et al. (2005)	78.0	32	●															
Deary et al. (2004)	79.1	462	●															
Welsh-Bohmer et al. (2009)	79.8	507	●															
Smith et al. (1998)	79.9	341	●															
Deary et al. (2002)	80.0	466	●															
Berteau-Pavy et al. (2007)	81.6	115	●															
Duchek et al. (2006)	86.8	13	●															
Salo et al. (2001)	88.8	46	●															
Carrion-Baralt et al. (2009)	92.9	87	●															
Bathum et al. (2006)	93.1	1551	●															

No APOE effect

Significant deficit in APOE-ε4 carriers

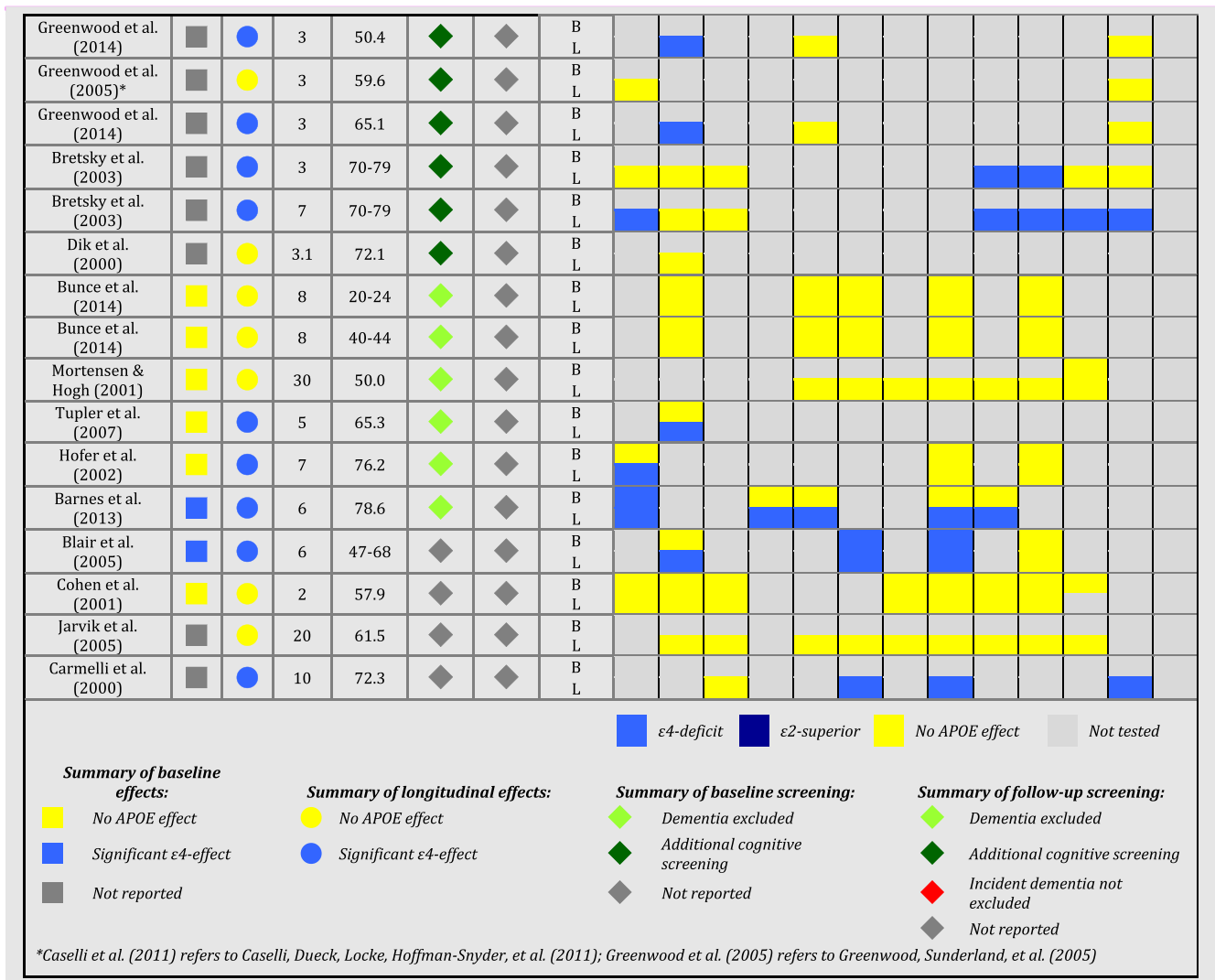
Superior performance in APOE-ε4 carriers

Other significant APOE group difference

Domain not tested

versus impaired performance across cognitive domains is inconsistent across studies. Whilst many studies have reported an ε4-related deficit in at least one cognitive domain, the majority of comparisons have resulted in non-significant effects (see Tables 1 and 2). Meta-analyses addressing the domain specificity of APOE effects on cognition, primarily in

older samples (over 60 years), suggest APOE-ε4 carriers are specifically impaired on measures of episodic memory, executive function, global cognition, and possibly perceptual speed, but there is no genotype effect on verbal ability, attention, visuospatial function, and primary memory (Small et al., 2004; Wisdom et al., 2011).



Interpretation of these heterogeneous findings is challenging. Methodological factors such as age of sample, sample size, and cognitive measures vary substantially among studies, making cross-study comparisons difficult. Inconsistent reporting of the substantial number of potential modifying variables limits the value of meta-analysis to shed light on the sources of heterogeneity in this literature (Small et al., 2004; Wisdom et al., 2011). Additionally, since the majority of research in this field is conducted in older samples, it is often unclear whether observed ε4-deficits relate to a direct effect of APOE on cognition or the presence of prodromal AD. In many cases, it is also difficult to resolve whether the absence of significant APOE effects on cognition reflects a genuine lack of genetic effect, or rather a lack of statistical power or insensitive cognitive measures. For example, several studies that reported null effects had large samples (N > 1000) and therefore high statistical power (Bathum et al., 2006; Bunce et al., 2011; Jorm et al., 2007; Liu et al., 2010; Luciano, Gow, Taylor, et al., 2009), but some had young and mid-adulthood samples, so the cognitive measures used may not have been sensitive to an APOE

effect in this age group (see 5. Methodological challenges for further discussion). Other studies with similarly large samples, all with older adults, observed significant cognitive deficits in ε4-carriers (Izaks et al., 2011; Laukka et al., 2013; Liu et al., 2010; Luciano, Gow, Harris, et al., 2009).

Disentangling the cognitive consequences of the neurobiological mechanisms by which APOE may influence cognition requires methodology that is optimised to address specific research questions. Multiple methodological factors must be optimised in concert to improve the ability to interpret findings. Consideration of ‘prodromal’ and ‘phenotypic’ as distinct but compatible neurobiological mechanisms, rather than competing hypotheses, will aid the separation of direct and prodromal effects of APOE on cognition. Fig. 1 highlights the importance of separating these cognitive effects of APOE, as they can provide insight into separate neurobiological processes, with applications to distinct aspects of cognitive ageing and Alzheimer’s disease. In the next sections, we highlight key methodological challenges for investigating the cognitive effects of different underlying neurobiology of APOE, and make recommendations for future studies.

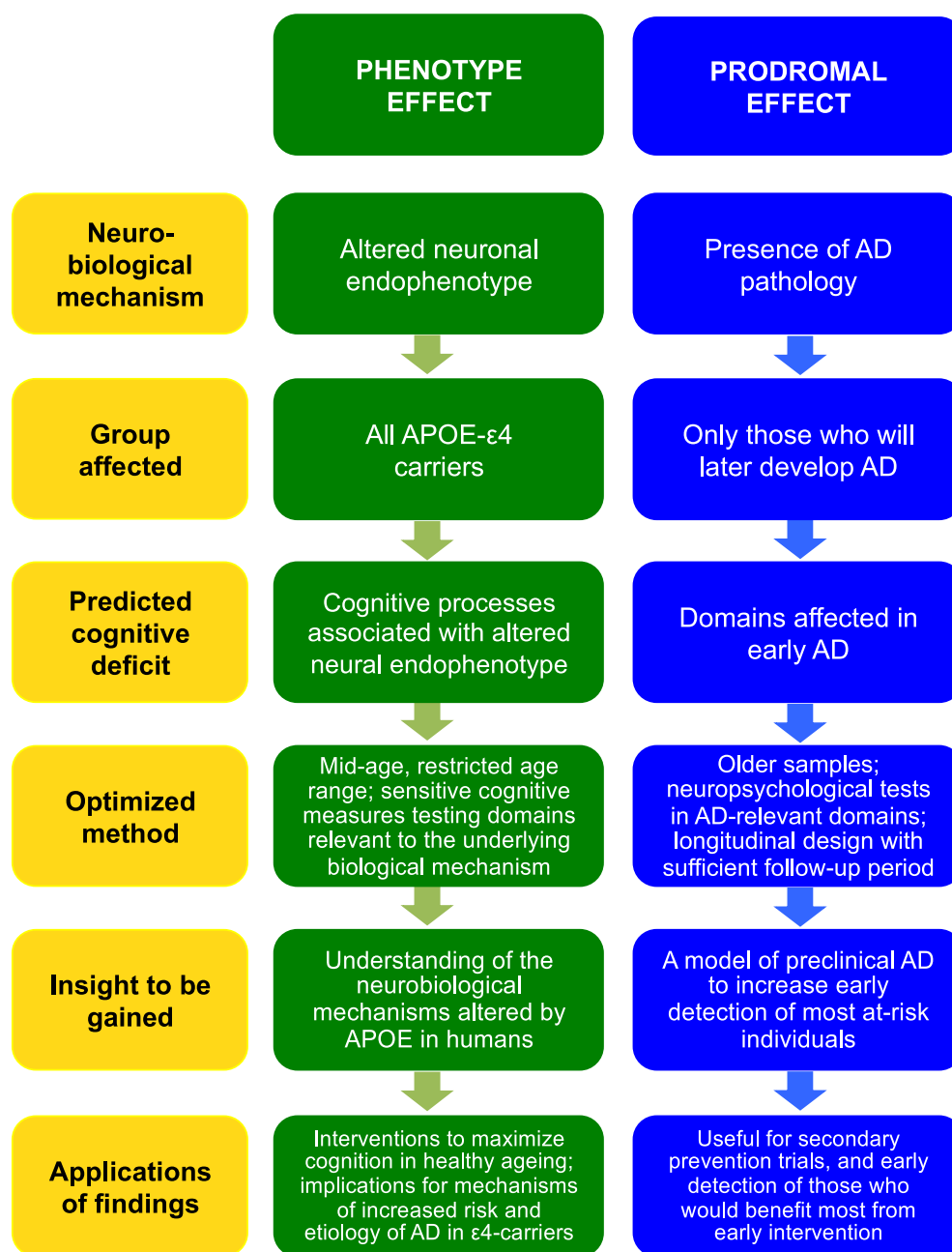


Fig. 1 – An overview of the possible phenotype and prodrome effects of APOE on cognition, and potential insights to be gained from increased understanding of each mechanism.

5. Methodological challenges

5.1. Age

Age is a major methodological challenge for separating direct effects of APOE on cognition from the cognitive consequence of early AD pathology, as sample age determines the mechanism that can be studied. The long prodromal period of AD makes it difficult to rule out the influence of AD pathology in elderly samples, particularly given the earlier age of AD onset in APOE-ε4 carriers. Significant interactions between age and APOE genotype in older samples (over 60 years), representing

an increasing negative influence of APOE-ε4 genotype on cognition with age (e.g., [Baxter et al., 2003](#); [Caselli et al., 1999](#); [Laukka et al., 2013](#); [Wisdom et al., 2011](#)), may reflect an increasing presence of AD pathology with age, although other studies have found no significant interaction of age and genotype ([Bunce et al., 2011, 2014](#); [Jorm et al., 2007](#); [Small et al., 2000, 2004](#)). Cross-sectional findings in [Table 1](#) are ranked by mean age of sample, but a clear pattern does not emerge. Variable and often broad age ranges between studies make comparison of findings challenging.

To minimise inclusion of prodromal AD, most studies use cognitive screening in older samples. However, the method of

cognitive screening used varies greatly between studies (see Table 2), including a single clinician or consensus panel decision, use of clinical diagnostic tools such as the Cambridge Mental Disorders of the Elderly Examination (CAMDEX; Roth et al., 1986) or the Clinical Dementia Rating tool (CDR; Morris, 1993), and varying thresholds of the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), whilst other studies report no details of the cognitive screening used, if any. A stringent cognitive screening approach used in a small number of studies is retrospective exclusion of individuals diagnosed with AD during a follow-up period from the cross-sectional analysis of baseline data. Studies using this approach found significant baseline $\epsilon 4$ -related deficits in episodic memory, executive function, attention, semantic memory, processing speed, language, and global cognition were no longer significant after incident AD cases were excluded (Bondi et al., 1999; Hayden et al., 2009; Hofer et al., 2002; Knight et al., 2014; Laukka et al., 2013; Praetorius et al., 2013; also see Batterham et al., 2013; Jorm et al., 2007; Schiepers et al., 2012), suggesting the initial $\epsilon 4$ -deficits were due to prodromal AD (also see 5.3. *Sample size and longitudinal design*). However, in some studies, significant $\epsilon 4$ -deficits in memory, perceptual speed, and global cognition remained after exclusion of incident AD cases (Hofer et al., 2002; Jonker et al., 1998; Laukka et al., 2013; Praetorius et al., 2013; Winnock et al., 2002; also see Bäckman et al., 2004; Riley et al., 2000). Even with stringent methods, the possible influence of prodromal AD in older samples is difficult to rule out.

Several observations indicate that the association between APOE genotype and cognition also changes across the lifespan. Children and young adults (under 30 years) who possess an APOE- $\epsilon 4$ allele have demonstrated superior cognitive performance (e.g., Bloss, Delis, Salmon, & Bondi, 2010; Mondadori et al., 2007; Schultz et al., 2008; Wright et al., 2003; although see Bunce et al., 2011, 2014; Ihle, Bunce, & Kliegel, 2012). This effect is proposed to reflect ‘antagonistic pleiotropy’, where the influence of a gene changes across the lifespan, being evolutionarily advantageous in early life, but exerting a negative effect later in life (Han & Bondi, 2008; Tuminello & Han, 2011; Williams, 1957). Some researchers have argued that ApoE4 has a possible protective role in development (e.g., Alexander et al., 2007), but this is controversial (e.g., Dumanis et al., 2009; Klein, Mace, Moore, & Sullivan, 2010; Shaw et al., 2007). Furthermore, a meta-analysis found no evidence for an APOE- $\epsilon 4$ related cognitive benefit in young people (Ihle et al., 2012).

At the other end of the lifespan, superior cognitive performance has been reported in the oldest $\epsilon 4$ -carriers (over 80 years), compared to non-carriers (Carrión-Baralt et al., 2009; Duchek et al., 2006), as well as attenuation of $\epsilon 4$ -deficits observed in young-old carriers (Negash et al., 2009; Riley et al., 2000; Smith et al., 1998). These cognitive effects correspond with reported attenuation of the association between APOE- $\epsilon 4$ and Alzheimer’s disease risk in the oldest-old (Blacker et al., 1997; Breitner et al., 1999; Corrada, Paganini-Hill, Berlau, & Kawas, 2013; Farrer et al., 1997; Juva et al., 2000a; Valerio et al., 2014; also see Kozauer, Mielke, Chan, Rebok, & Lyketsos, 2008). The oldest-old non-demented APOE- $\epsilon 4$ carriers have been proposed to represent ‘selective

survivors’ (Duchek et al., 2006), resilient to the negative influences of APOE- $\epsilon 4$ on development of AD (Rebeck et al., 1994) or cardiovascular disease (Stengård, Pekkanen, Ehnholm, Nissinen, & Sing, 1996) earlier in life. This may reflect the influence of additional protective factors (Carrión-Baralt et al., 2009) or absence of other AD risk factors (Tuminello & Han, 2011). However, the attenuation of associations between APOE- $\epsilon 4$ and cognition or AD risk in the oldest-old has not been consistently reported (Geßner, Reischies, Kage, Geiselmann, & Borchelt, 1997; Nilsson et al., 2006; Rebeck et al., 1994), and some studies have found no APOE effects (Bathum et al., 2006; Berteau-Pavy et al., 2007; Juva et al., 2000b; Riley et al., 2000; Salo et al., 2001; Small et al., 1998) or $\epsilon 4$ -related cognitive deficits in the oldest-old (Praetorius et al., 2013; Riley et al., 2000; Small et al., 1998; Welsh-Bohmer et al., 2009).

To investigate genetic effects in the absence of prodromal AD pathology, studies have more recently moved to investigate the effect of APOE on cognition in mid-adulthood (30–60 years) samples, before AD pathology is likely to accumulate. Possible antagonistic pleiotropic effects in early life may also be avoided in mid-adulthood samples. Due to the long period of accumulation of AD pathology before symptom onset, individuals in their late 50s may already fall into the prodromal AD pre-dementia stage, meaning that a more restricted age range (e.g., 30–50 years) may be optimal. Without very large samples, the inclusion of participants with a wide age range (Caselli, Dueck, Locke, Hoffman-Snyder, et al., 2011; Wishart et al., 2006) is unlikely to provide clear results.

5.2. Cognitive measures

Cognitive measures are key to unpicking the cognitive effects of the prodromal and direct neurobiological mechanisms of APOE. The neuropsychological measures used in most studies, whilst well-validated and quick to administer, typically lack the sensitivity to detect subtle variation in cognition (Houx et al., 2002; Jorm et al., 2007) and lack the specificity to measure variation in isolated cognitive processes (Greenwood et al., 2000; Greenwood, Lambert, et al., 2005; Wisdom et al., 2011). Neuropsychological tests therefore have limited use for investigating the direct effect of APOE on a cognitive phenotype in mid-adulthood samples, and a recent meta-analysis found no evidence for an APOE genotype effect on midlife neuropsychological performance (Lancaster, Tabet, & Rusted, 2017).

More sensitive ‘cognitive assays’ that target specific cognitive processes are required to detect subtle direct cognitive effects of APOE genotype (Greenwood, Lambert, et al., 2005). Several studies in older adults have reported selective $\epsilon 4$ -related deficits on sensitive cognitive neuroscience-based measures of prospective memory, implicit learning, spatial navigation and working memory (Berteau-Pavy et al., 2007; Driscoll et al., 2005; Duchek et al., 2006; Negash et al., 2007; Reinvang, Winjevoll, Rootwelt, & Espeseth, 2010; Rosen et al., 2002). However, in older samples, such sensitive measures again face the challenge of isolating direct effects of APOE from the potential influence of incipient AD. In a study by Negash et al., 2007, older APOE- $\epsilon 4$ carriers demonstrated deficits in contextual cueing, but no APOE-related effect on

serial reaction time performance was observed, interpreted as a selective effect of APOE- ϵ 4 on medial temporal function, but spared frontal function. However, the same pattern of spared and impaired performance was also observed using the same measures in a sample diagnosed with MCI, regardless of APOE status (Negash et al., 2007).

Sensitive cognitive measures have only been used in a small number of studies to investigate APOE-related effects in mid-adulthood samples, although this number is increasing. Many such studies come from Greenwood and colleagues, who, based on observed cognitive deficits in AD patients (Parasuraman et al., 2002), have investigated whether ϵ 4-carriers show selective deficits in attentional processes in mid-adulthood. In a series of experiments, mid-adulthood APOE- ϵ 4 carriers demonstrated intact sustained attention, but impaired attentional disengagement in a cued discrimination task, and impaired scaling of attention during a visual search task (Espeseth et al., 2006; Greenwood, Lambert, et al., 2005, Greenwood, Sunderland, et al., 2005, Greenwood et al., 2000; Negash et al., 2009; although see Lancaster, Forster, Tabet, & Rusted, 2017). Longitudinally, APOE- ϵ 4 homozygotes showed increasingly impaired attentional scaling during visual search, whilst non-carriers improved over 3 years (Greenwood, Sunderland, et al., 2005). Additionally, mid-adulthood ϵ 4-carriers showed cross-sectional selective deficits in retaining visuospatial information in working memory (Greenwood, Lambert, et al., 2005; although see Greenwood et al., 2014). Surprisingly, Greenwood et al., 2014 reported a significant improvement in working memory performance in mid-adulthood ϵ 4-carriers when retested after 3 years, whilst non-carriers showed longitudinal decreases in performance, interpreted by the authors as possible cognitive compensation in APOE- ϵ 4 carriers.

More recently, other researchers have expanded the investigation of APOE effects on mid-adulthood cognition to other cognitive domains. A study by Salvato, Patai, McCloud, & Nobre, 2016 investigated the effect of APOE genotype on long-term memory-guided attention in a mid-adulthood sample (mean age 45.7 years). Whilst APOE genotype had no significant effect on explicit memory or memory-guided attention, ϵ 4-homozygotes showed an impaired correlation between memory and attention, indicating the memories guiding attentional orienting in ϵ 4-homozygotes were not explicitly available (Salvato et al., 2016). The authors suggested these cognitive results might reflect changes in brain regions that underpin long-term memory-guided attention, e.g., medial temporal, parietal and frontal regions, which are also compromised in AD (Salvato et al., 2016). In another study, adults aged 40–51 completed a short-term memory paradigm where participants were required to hold multiple fractals in memory, and after a short delay identify which of 2 fractals had previously been presented, as well as the location in which it was shown (Zokaei et al., 2017). This task was previously shown to be sensitive to memory deficits in patients with medial temporal lobe (MTL) damage (Pertzov et al., 2013). Intriguingly, this paradigm revealed a behavioural advantage in male APOE- ϵ 4 carriers, with less mislocalisation of the remembered item to the location of another item held in memory, interpreted as a possible example of antagonistic pleiotropy in midlife (Zokaei et al., 2017).

The breadth of domains studied with sensitive cognitive assays remains relatively limited to those impaired in patients with AD/MTL damage. Investigation of further neurobiologically relevant domains is warranted. To robustly investigate the direct effect of a gene on behaviour, the measured phenotype should reflect the likely altered neurobiological endophenotype, to provide a plausible and mechanistic association between genotype and phenotype (Goldberg & Weinberger, 2004). Additional cognitive processes that are biologically related to the proposed influence of APOE genotype on CNS function, e.g., synaptic plasticity and neuronal repair (Liu et al., 2013), should therefore be explored. Tasks that assess long-term learning may be particularly sensitive to such effects of APOE genotype on CNS functions (see 6.1. Recommendations for phenotype effect of APOE on cognition).

Characterisation of the APOE- ϵ 4 cognitive effects related to prodromal AD may also benefit from a more selective focus on measures relevant to the underlying neurobiology. Numerous studies have assessed the effect of APOE genotype on extensive neuropsychological batteries, regardless of the association of each measure with cognitive impairments in early AD. The resulting multiple comparisons problem is inconsistently and sometimes insufficiently controlled for. A more selective assessment of cognitive domains may be advantageous, for example those recommended in a recent consensus statement on cognitive outcomes in preclinical AD based on cognitive correlates of preclinical brain changes, including verbal episodic memory, working memory, and navigation in egocentric space (Ritchie et al., 2017).

5.3. Sample size and longitudinal design

The lower frequency of APOE- ϵ 4 in the population, compared to APOE- ϵ 3, has resulted in consistently smaller APOE- ϵ 4 samples in most studies, unless specifically matched between groups (e.g., Caselli et al., 2001, 1999; Salvato et al., 2016; Zokaei et al., 2017). There are also relatively few investigations of the specific effect of APOE- ϵ 2 on cognition, due to the low occurrence of the ϵ 2 allele in the population (although see Bartrés-Faz et al., 1999; Batterham et al., 2013; Blair et al., 2005; Bloss et al., 2010; Bunce et al., 2014; Chey et al., 2000; Chiang, Raptentsetsang, & Jack, 2010; Greenwood et al., 2000; Helkala et al., 1995, 1996; Hofer et al., 2002; Marioni et al., 2016; Pendleton et al., 2002; Quintas et al., 2014; Salo et al., 2001; Staehelin et al., 1999; Ward et al., 2014; Wilson, Bienias, et al., 2002; Lancaster, Forster, et al., 2017). Table 1 also illustrates the variability in sample size across studies.

The required sample size may depend on the neurobiological mechanism of APOE under investigation. Longitudinal studies are required to investigate prodromal APOE- ϵ 4 cognitive effects in relation to clinical outcomes, e.g., for biomarker development. Therefore, a large initial sample is required, as cognitive effects will be driven by only a subsample with early AD, and some participants may be lost to follow-up. Sufficient sample size is particularly important if incident AD cases will be retrospectively excluded from baseline analysis, as these cases are more likely to be excluded from the already smaller APOE- ϵ 4 group (e.g., Batterham et al., 2013). Elimination of initially significant baseline APOE effects after exclusion of

incident AD (e.g., Bondi et al., 1999; Hayden et al., 2009; Hofer et al., 2002; Knight et al., 2014; Praetorius et al., 2013) may have resulted from degraded statistical power in some cases. In contrast, a subtle APOE-related cognitive phenotype should be present in all $\epsilon 4$ -carriers, therefore smaller samples may be sufficient, as long as the cognitive measures used test appropriate domains and are sufficiently sensitive.

6. Recommendations for future research

In the previous sections, we have outlined the mixed reported effects of APOE on cognition, and discussed how key methodological factors complicate the interpretation of these findings. Some studies have attempted to facilitate interpretation by addressing individual methodological challenges (e.g., larger sample size or under-studied cognitive domain). However, the interactive nature of these methodological factors requires multiple aspects of methodology to be optimised simultaneously to aid the interpretation of APOE and cognition results. Future studies can add to our understanding of the prodromal and direct routes of APOE influence on cognition by employing methodology targeted at specific neurobiological mechanisms, to simplify the interpretation of results. Here we make recommendations for future studies (summarised in Fig. 1).

6.1. Recommendations for phenotype effect of APOE on cognition

As evidence for APOE-related alterations of CNS functions has primarily come from animal literature, evidence of an APOE cognitive phenotype would provide support for an altered neural endophenotype in humans. The applications of this knowledge are two-fold: firstly, to provide greater understanding of the neurobiological processes altered by APOE genotype, and secondly, to inform how genetic variability contributes to individual differences in cognition, providing targets for interventions to maximise cognition in non-neuropathological ageing. The amyloid-independent mechanism(s) that directly influence cognition in $\epsilon 4$ -carriers may also reflect a ‘susceptibility’ factor that contributes to increased risk of AD (Greenwood, Lambert, et al., 2005), and may interact with amyloid-dependent pathways by promoting amyloid deposition (Verghese et al., 2011), or exacerbating the impact of amyloid deposition, possibly via pro-inflammatory responses (Liu et al., 2013). Greater understanding of the direct effect of APOE genotype on a cognitive phenotype may therefore inform interventions to ameliorate increased risk of AD in $\epsilon 4$ -carriers.

Whilst future studies may avoid the influence of prodromal AD when investigating an APOE cognitive phenotype by excluding volunteers positive for preclinical AD biomarkers, e.g., increased amyloid or reduced glucose metabolism on PET imaging, or reduced CSF amyloid (Sperling et al., 2011), limited resources and invasiveness of procedures means such screening is not always feasible. Instead, the use of mid-adulthood samples (30–50 years) is optimal to investigate a cognitive phenotype prior to the development of AD pathology, whilst also avoiding possible antagonistic pleiotropic

effects of APOE on cognition earlier in life. Future research should also examine cognitive domains relevant to the putative neurobiological mechanisms affected by APOE- $\epsilon 4$ using sensitive and specific cognitive measures. A promising initial target is the effect of APOE genotype on long-term learning over days or weeks, e.g., learning a new skill (Scholz, Klein, Behrens, & Johansen-Berg, 2009), rather than minutes or hours tested in neuropsychological assessments, to reflect the effect of disrupted lipid provision on synaptic plasticity. Alternatively, the detrimental effect of APOE- $\epsilon 4$ on response to neuronal injury, via neuronal repair, neuroinflammatory, or neurotoxicity mechanisms (Liu et al., 2013; Verghese et al., 2011), may be associated with more diffuse cognitive deficits, depending on the nature and location of injury (Greenwood, Lambert, et al., 2005).

Furthermore, if APOE- $\epsilon 4$ has a cognitive phenotype independent of future AD diagnosis, APOE- $\epsilon 2$ genotype may also be associated with its own cognitive phenotype, although the supporting neurobiological mechanism is not clear. Amyloid aggregation is an unlikely candidate, as the oldest-old $\epsilon 2$ -carriers have a similar presence of amyloid pathology compared to $\epsilon 4$ -carriers, despite reduced risk of dementia (Berlau, Corrada, Head, & Kawas, 2009). Instead, APOE- $\epsilon 2$ may promote synaptic integrity, suggested by greater dendritic arborisation observed in APOE- $\epsilon 2$ transgenic mice, versus $\epsilon 3$ and $\epsilon 4$ (Dumanis et al., 2009), or facilitate anti-inflammatory processes, as ApoE2 appears to be more effective at protecting cells from oxidative stress-induced cell death compared to ApoE3 and ApoE4 (Miyata & Smith, 1996; see Suri et al., 2013).

Although not the subject of this review, neuroimaging provides system-level evidence for the neurobiological mechanisms underpinning an APOE cognitive phenotype. Altered brain structure and function in young $\epsilon 4$ -carriers supports APOE-related alteration in CNS function(s) prior to the onset of AD pathology (e.g., Evans et al., 2017; Rusted et al., 2013; Shine, Hodgetts, Postans, Lawrence, & Graham, 2015; Suri et al., 2015). Neuroimaging findings may even inform targets for investigation of APOE cognitive effects, e.g., cognitive processes associated with altered WM integrity (Heise, Filippini, Ebmeier, & Mackay, 2011; Westlye et al., 2012, c.f. Nyberg & Salami, 2014) or altered hippocampal connectivity (Harrison, Burggren, Small, & Bookheimer, 2017; Heise et al., 2014).

6.2. Recommendations for prodromal effect of APOE on cognition

A growing body of work suggests that at least some cognitive deficits in currently healthy older APOE- $\epsilon 4$ carriers are due to prodromal AD. These findings do not rule out the possibility of additional mechanisms of direct APOE influence on cognition, and are important in demonstrating that cognitive deficits relating to future diagnosis of AD can be detected early, in adults currently considered to be healthy. APOE- $\epsilon 4$ genotype alone provides limited prognostic information about whether a person will be diagnosed with AD (Bookheimer & Burggren, 2009), so prodromal AD-related $\epsilon 4$ cognitive effects can be utilised in future studies to develop preclinical cognitive biomarkers to more precisely identify who is most at-risk. Secondary prevention clinical trials enriched with those most at-

risk of AD will reduce the sample size and longitudinal period required to assess treatment efficacy (Holland, McEvoy, Desikan, & Dale, 2012). Cognition can provide cheap, quick and non-invasive preclinical biomarkers to be used alone, or in combination with other biomarkers, such as CSF, PET or MRI metrics, to identify those who will benefit most from treatment and track early treatment efficacy.

Future studies aimed at utilising APOE genotype to characterise the cognitive markers of prodromal AD pathology in $\epsilon 4$ -carriers require participants in whom prodromal AD is likely to be present (i.e., over 60s), as well as longitudinal designs to measure clinical outcomes, with sufficient follow-up period to allow for conversion to AD. The cognitive domains tested should be focused on those affected in early AD to minimise multiple comparisons. Such studies may be able to utilise existing data, for example through initiatives such as the MRC Dementias Platform UK (DPUK; www.dementiasplatform.uk), European Medical Information Framework – Alzheimer's Disease (EMIF; <http://www.emif.eu/about/emif-ad>) and Alzheimer's Disease Neuroimaging Initiative (ADNI, <http://adni.loni.usc.edu/>), which pool data from many existing ageing cohorts both locally and internationally.

7. Conclusions and future directions

APOE genotype is the strongest genetic risk factor for AD, yet the influence of APOE on cognition in healthy adults remains controversial. Some evidence suggests that at least some APOE- $\epsilon 4$ cognitive deficits are due to early AD pathology, whilst sensitive measures of cognition are beginning to reveal subtle cognitive effects of APOE genotype in mid-adulthood, prior to the onset of the AD prodromal period. To unpick the direct and prodromal cognitive consequences of APOE genotype, future studies need to address specific research questions with methodology that is appropriate to the neurobiological mechanism being investigated. Combining an optimised cognitive approach with other biomarkers, e.g., neuroimaging, will provide additional evidence to make the study of APOE and cognition useful for understanding cognitive ageing and dementia.

Once we have a clearer understanding of the direct and prodrome-mediated effect of APOE on cognition, further investigations of the cognitive consequences of interactions of APOE genotype with other factors, e.g., cardiovascular health (Caselli, Dueck, Locke, Sabbagh, et al., 2011; de Frias et al., 2007; de Frias, Schaie, & Willis, 2014; Liu et al., 2010; McFall, Sapkota, McDermott, & Dixon, 2016; West et al., 2008), hormones (Burkhardt et al., 2004, 2006; Fiocco, Poirier, Joobar, Nair, & Lupien, 2008; Gerritsen, Comijs, Deeg, Penninx, & Geerlings, 2011; Panizzon et al., 2014), physical activity (e.g., Deeny et al., 2008; Etnier et al., 2007) and gender (e.g., Lehmann et al., 2006; Swan, Lessov-Schlaggar, Carmelli, Schellenberg, & La Rue, 2005; Zokaei et al., 2017), as well as other genes, e.g., TOMM40 (Ferencz, Laukka, Lövdén, Kalpouzos, & Keller, 2013; Schiepers et al., 2012), CHRNA4 (Espeseth et al., 2006; Reinvang, Lundervold, Wehling, Rootwelt, & Espeseth, 2010), BDNF (Sapkota et al., 2017; Tsai et al., 2008; Ward et al., 2014) and COMT (Sapkota et al., 2017), is warranted. Increased use of

technology, e.g., remote-monitoring devices, and big data initiatives, such as UK Biobank (<http://www.ukbiobank.ac.uk/>), will provide increasingly novel and rich information about the effect of APOE on cognition.

Conflicts of interest

None.

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Supplementary data

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