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Structural neuroimaging in preclinical dementia: from microstructural deficits and grey matter atrophy to macroscale connectomic changes

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Highlights

- We reviewed the literature of structural imaging changes in preclinical dementia.
- There was a high overlap of brain regions implicated in both preclinical and sporadic AD.
- The imaging literature in relation to AD risk factors was highly discrepant.
- More research and validation studies of structural imaging techniques are needed.

ABSTRACT

The last decade has witnessed a proliferation of neuroimaging studies characterising brain changes associated with Alzheimer's disease (AD), where both widespread atrophy and 'signature' brain regions have been implicated. In parallel, a prolonged latency period has been established in AD, with abnormal cerebral changes beginning many years before symptom onset. This raises the possibility of early therapeutic intervention, even before symptoms, when treatments could have the greatest effect on disease-course modification. Two important prerequisites of this endeavour are (1) accurate characterisation or risk stratification and (2) monitoring of progression using neuroimaging outcomes as a surrogate biomarker in those without symptoms but who will develop AD, here referred to as preclinical AD. Structural neuroimaging modalities have been used to identify brain changes related to risk factors for AD, such as familial genetic mutations, risk genes (for example apolipoprotein epsilon-4 allele), and/or family history. In this review, we summarise structural imaging findings in preclinical AD. Overall, the literature suggests early vulnerability in characteristic regions, such as the medial temporal lobe structures and the precuneus, as well as white matter tracts in the fornix, cingulum and corpus callosum. We conclude that while structural markers are promising, more research and validation studies are needed before future secondary prevention trials can adopt structural imaging biomarkers as either stratification or surrogate biomarkers.

Search terms: Alzheimer's disease, neurodegeneration, preclinical dementia, magnetic resonance imaging, diffusion weighted imaging, neuroimaging, cognitive impairment

1. INTRODUCTION

There are now 30 million people living with dementia, and the number is expected to rise to 115 million in 2050 (World Alzheimer Report 2010, www.alz.org). Current treatments are symptomatic and limited to Alzheimer's disease (AD). It is assumed that functional decline and dementia will be a relatively late feature in the pathophysiology of AD, with increasing evidence of an insidious latency period, with pathological changes beginning decades before symptom onset (Trojanowski et al., 2010). The 'amyloid cascade hypothesis' posits an initiating event of amyloidosis, with subsequent tau pathology and other downstream processes involving neurotoxicity and progressive cerebral atrophy (Hardy and Selkoe, 2002). This self-perpetuating mechanism of neurodegeneration is difficult to slow once established, and may partly account for the spate of notable clinical trial failures, particularly anti-amyloid therapy (Doody et al., 2014). Thus, recent proposals are urging the need to shift the focus to presymptomatic interventional trials in individuals at elevated risk for AD (Caselli and Reiman, 2013; Ritchie et al., 2015).

To facilitate this endeavour, biomarkers are mandatory prerequisites (a) to aid in the early pre-symptomatic detection of AD for recruitment to clinical trials and (b) to serve as surrogate markers for disease progression and to be used therein as intermediary phenotypes to assess the efficacy of potential disease-modifying treatments. In clinical trials of presymptomatic dementia, any disease-related changes would likely be subtle and therein lays the challenge of establishing the means to assess outcomes in clinical trials. Ideally, a biomarker should sensitively and specifically reflect the underlying pathology (i.e. amyloid / tau deposition, grey matter volume loss, etc.), be easily reproducible and accessible (i.e. available in standard clinical settings), and be non-invasive. In this regard, structural neuroimaging techniques – T1-MRI and diffusion

weighted imaging (DTI) – that enable assessment of grey matter volume loss, cortical thinning, or white matter microstructural changes have contributed to the characterisation of disease-related changes in neurodegenerative conditions, such as AD (Braskie and Thompson, 2014), dementia with Lewy bodies (Mak et al., 2014a), and Parkinson's disease (Mak et al., 2015a). Similarly, evidence from structural neuroimaging studies have begun to reveal characteristic patterns of grey matter atrophy and white matter abnormalities in preclinical dementia, particularly involving individuals possessing (a) familial AD (FAD) genetic mutations (Ginestroni et al., 2009; Li et al., 2015; Quiroz et al., 2013; Reiman et al., 2012; Ridha et al., 2006; Ringman et al., 2007; Schott et al., 2003; Thordardottir et al., 2015), (b) one or two copies of the apolipoprotein epsilon-4 allele (ApoE4) (Burggren et al., 2008; Cherbuin et al., 2008; den Heijer et al., 2002; Desikan et al., 2013; Fan et al., 2010; Hashimoto et al., 2009; Lemaître et al., 2005; Shaw et al., 2007; Smith et al., 2010; Wishart et al., 2006), (c) a family history of AD (Berti et al., 2011; Fox et al., 1999; Honea et al., 2011, 2010; Mosconi et al., 2014).

The purpose of this review is to provide an exhaustive summary of the literature concerning grey and white matter abnormalities in presymptomatic individuals at high-risk of dementia: individuals with familial AD genetic mutations, carriers of ApoE4 and those with a positive family history of dementia. We first begin with a brief description of each risk factor before reviewing the literature of structural neuroimaging in preclinical AD: (a) macroscopic grey matter atrophy and cortical thinning, (b) hippocampal and other subcortical atrophy, (c) microstructural properties as measured by DTI, and (d) macroscale changes in the connectome. The potential influence of age on some of these risk factors will be discussed. Lastly, we

conclude with future directions and provide a summary of structural neuroimaging in preclinical AD.

2. RISK FACTORS IN ALZHEIMER'S DISEASE

Genetic mutations

FAD is a rare and inheritable form of AD and it is typically associated with an early onset before the age of 65 (Ringman, 2005). Causative factors of FAD include autosomal-dominant inheritable mutations in the genes of presenilin 1 (PSEN1), presenilin 2 (PSEN2) and amyloid precursor protein (APP). Their effects are fully penetrant, implying a near certainty of developing AD in carriers, often at an earlier age (~ 30 – 50 years) as well as exhibiting a more aggressive disease course and shorter relative survival time compared to typical AD (Rossor et al., 2010; Seltzer, 2016).

Although FAD only accounts for 1% of all AD cases, presymptomatic FAD mutation carriers offer an opportunity to investigate the earliest clinical and biomarker substrates of the prodromal dementia stage. For instance, it is possible to estimate the age of onset in FAD mutation carriers, allowing enrolment into therapeutic trials years and even decades before the emergence of cognitive decline. Because the clinical (i.e. insidious onset of amnestic symptoms and progression of decline in multiple cognitive domains) and pathological features (i.e. neuronal loss, amyloid plaques and neurofibrillary tangles) of FAD are similar to sporadic AD, putative drugs that demonstrate high efficacy in the prevention or delay of dementia in FAD trials are likely to inform other disease modification trials in sporadic AD. The notion for FAD as a model to investigate the pathogenesis of sporadic AD has also received support from spatial

overlapping of brain regions that are commonly implicated in sporadic AD (will be discussed in more detail later).

Apolipoprotein epsilon-4

While autosomal dominant mutations exist in AD, they are exceedingly rare as the majority of AD cases most likely involve a multifaceted interplay of genetic and environmental risk factors. Investigating the imaging characteristics of genotypes offers another opportunity to investigate morphological aberrations in the brain during preclinical AD. The ApoE gene exists as three polymorphic alleles – E2, E3, and E4 – which have a worldwide frequency of 8.4%, 77.9% and 13.7% respectively (Farrer, 1997). Inheritance of ApoE4 is established as the greatest genetic risk factor associated with AD with dose-dependent effects (Harold et al., 2009). The mechanisms by which ApoE4 influences the risk, onset and progression of neurodegeneration have been the subject of intense research (Farrer, 1997), revealing a range of influences including beta-amyloid metabolism, impaired clearance of beta-amyloid across the blood brain barrier, and increased oligomerization of beta-amyloid in the brain (Liu et al., 2013).

Family history

AD is highly heritable. Even in those without FAD, a family history of dementia is another significant risk factor for AD particularly of the late-onset type (LOAD). The risk for developing LOAD is 4-10 fold higher in first-degree relatives of LOAD patients, and is highest in children of parents affected by LOAD (Farrer, 1997; Fratiglioni et al., 1993). However, its association with AD appears to be less certain compared to FAD mutations and ApoE4 carriage, as several studies have not reported an association between family history of dementia and elevated risk of

AD (Lindsay et al., 2002; Tyas et al., 2001). The link between family history and AD is most likely mediated at least in part by ApoE4 carriage. A 6-year follow-up study in the Kungsholmen Project Cohort showed that family history of dementia conferred an increased risk of dementia only among ApoE4 carriers (Huang et al., 2004). This finding has been corroborated by other evidence showing an additive effect of both ApoE4 and family history on of age of onset and cognitive decline (Duara et al., 1996; Hayden et al., 2010; Jarvik et al., 1996). There is also evidence from imaging (will be discussed in greater detail) and CSF studies suggesting a stronger maternal contribution to dementia compared to paternal dementia (Edland et al., 1996; Honea et al., 2012). In light of these findings, others have implicated the mitochondrial DNA in the genetic transmission of AD (Mosconi et al., 2011; Swerdlow et al., 2010).

Translocase of outer mitochondrial membrane 40

In light of previous evidence showing a stronger AD risk from maternal dementia, others have implicated the mitochondrial DNA in the genetic transmission and pathogenesis of AD (Mosconi et al., 2011; Swerdlow et al., 2010). Accordingly, the translocase of outer mitochondrial membrane 40 (TOMM40) has emerged as a potential candidate gene for AD. Variable poly-T length polymorphism at rs10524523, within intron 6 of TOMM40 gene, has been shown to influence the risk and age of onset in AD (Roses et al., 2010). Specifically, the long allele was associated with a 7-year earlier age of onset of AD in a relatively small sample of ApoE4 heterozygotes. However, these findings have not been consistently replicated in substantially larger samples (Cruchaga et al., 2011; Jun et al., 2012), and the influence of the TOMM40 gene in preclinical AD remains unclear.

Brain derived neurotrophic factor

Finally, some of the remaining variance in dementia risk could be accounted for by neurotrophins as they are influenced by a myriad of factors including caloric intake (Araya et al., 2008) and physical activity (Neeper et al., 1995). The brain-derived neurotrophic factor (BDNF) is essential for neuronal survival and synaptic function, particularly in the hippocampus (Tapia-Arancibia et al., 2008). Histopathological and CSF studies have consistently documented reductions in BDNF expression among AD patients (Laske et al., 2007; Phillips et al., 1991), as well as correlations with episodic memory and progression from MCI to AD (Forlenza et al., 2015).

3. METHODS

Literature searches were performed to review structural brain changes in preclinical dementia. Two reviewers (EM and SG) searched PubMed for articles published from Jan 1990 till present. We identified relevant papers using the keywords: 'structural magnetic resonance imaging', 'diffusion tensor imaging', 'Alzheimer's disease'. Further, we searched for 'amyloid, 'family history', 'ApoE4', 'PSEN' and 'APP'. Articles included were only human studies in the English language. Studies were considered for inclusion if structural neuroimaging modalities (T1 MRI and diffusion-weighted MRI) were used to investigate brain changes related to risk factors of AD, such as familial APP/PSEN gene mutations, the presence of ApoE4 and/or family history of AD. No further attempts were made to extract quantitative data for meta-analysis.

4. RESULTS

This database search resulted in 606 studies. Full-text articles were obtained to assess further eligibility, resulting in the exclusion of articles based on methodological consideration or sample characteristics, and the inclusion of additional studies from the references of these individual articles. After detailed evaluation, 95 key papers published between 1996 and 2016 were included in the systematic review. A summary of principal findings from highlighted studies (i.e. large cohort studies with longitudinal follow-up) is described in Table 1 and 2.

5. CORTICAL GREY MATTER CHANGES

In general, structural imaging studies across preclinical groups have converged to reveal an atrophic cortical pattern that is characteristic of AD (Quiroz et al., 2013), such as increased longitudinal whole brain atrophy rates (Chen et al., 2007; Fox et al., 1999; Ridha et al., 2008; Schott et al., 2010), parahippocampal atrophy (Hashimoto et al., 2009), and atrophy / cortical thinning in frontal, temporal and parietal cortices as well as the precuneus (Berti et al., 2011; Burggren et al., 2008; Chen et al., 2007; Ginestroni et al., 2009; Mosconi et al., 2014; Schott et al., 2003). It is noteworthy that atrophy or cortical thinning in temporo-parietal cortices has been consistently predictive of conversion from mild cognitive impairment (MCI) to AD in longitudinal studies (Chételat et al., 2005; Risacher et al., 2010), while the precuneus has also been shown to be an early site of preferential amyloid uptake in positron emission tomography (PET) studies (Villemagne et al., 2009), supporting the notion that these cortical changes are potential harbingers of progressive atrophy in the earliest stages of AD. We now discuss these findings in greater depth, organised into sections pertaining to the type of risk factor.

Familial AD

In general, the prevailing evidence points to temporo-parietal atrophy in presymptomatic FAD mutation carriers, although non-significant and increased volumes have also been reported (Table 1). APP and PSEN1 mutation carriers (n = 13, age = 43) from four Swedish families showed reductions of cortical volumes in temporal and precuneus regions, even after correcting for gender and ApoE genotype (Thordardottir et al., 2015). These findings are congruent with an earlier longitudinal study of an aged-matched (n = 9, age = 44) sample of APP and PSEN1 mutation carriers who expressed an accelerated course of thinning in similar regions such as the entorhinal cortex, parahippocampal gyrus, posterior cingulate cortex and the precuneus. In particular, cortical thinning in the posterior cingulate cortex and the precuneus were found 1.8 and 4.1 years prior to diagnosis in mutation carriers (Knight et al., 2011). The effects of PSEN1 mutations on early structural aberrations have been investigated in the Colombian Alzheimer's Prevention Initiative Registry, which includes more than 1500 living members from the largest known autosomal-dominant AD kindred, 30% of whom are carriers of the PSEN1 *E280A* mutation (Lopera et al., 1997). Carriers from this kindred have an estimated median age of 44 years at onset of MCI and 49 years at onset of AD (Acosta-Baena et al., 2011). Echoing the aforementioned studies (Knight et al., 2011; Thordardottir et al., 2015), structural imaging analyses from this cohort have revealed an 'AD signature' of cortical thinning in both mid-life (age = 38) (Quiroz et al., 2013), most prominently in parietal cortices and precuneus. In addition, Quiroz and colleagues reported that these cortical changes occurred 6 years before symptom onset and 11 years prior to AD diagnosis (Quiroz et al., 2013). Notably, the parietal predilection was similarly found in a Voxel Based Morphology (VBM) analysis of younger PSEN1 mutation carriers (n = 20; age = 22) (Reiman et al., 2012).

However, the literature on presymptoamatic FAD mutation carriers remains mixed with negative findings (Apostolova et al., 2011) as well as reports of cortical thickening in the precuneus and temporo-parietal cortices (Fortea et al., 2010). Interestingly, Fortea and colleagues showed that these regions exhibited an inverse pattern of cortical thinning in symptomatic carriers, possibly reflecting a compensatory process that could not be sustained as the disease progressed (Fortea et al., 2010).

The cortical expressions of FAD mutations also appear to be complex in the youngest populations. Unlike the atrophic cortical profile expressed in older aged carriers (Quiroz et al., 2013; Reiman et al., 2012), children (9 – 7 years old) with PSEN1 mutation carriers had larger grey matter volumes in temporo-parietal regions, particularly in the parahippocampal gyrus and temporal pole (Quiroz et al., 2015). Interestingly, an opposite effect of thinner entorhinal cortex was found in children and adolescent ApoE4 carriers (age = 18) (Shaw et al., 2007). Shaw and colleagues also reported a stepwise increase in cortical thickness in the entorhinal cortex: from the thinnest cortex in ApoE4 carriers, through an intermediate thickness in ApoE3 carriers, to the thickest cortex in carriers of the ApoE2 allele (Shaw et al., 2007). At an even younger age, ApoE4 infant carriers (6 – 22 months old) also showed a combination of greater volumes in frontal regions and decreased volumes in the precuneus, cingulate, and temporal regions (Dean et al., 2014). These studies suggest potentially differential effects of PSEN1 and ApoE4, which could in turn be modulated by age. Future studies are needed to clarify the role of PSEN1 and ApoE4 in neurodevelopmental processes and how alterations in these processes (i.e. synaptic pruning and cortical gyrification) may be relevant to the future development of AD.

Apolipoprotein E4

Imaging studies in preclinical AD have attempted to characterise ApoE4-related cortical changes in preclinical AD, although the literature is fragmented with highly discrepant findings (Table 2). Generalised volumetric loss and cortical thinning in ApoE4 carriers have been reported in several studies (Crivello et al., 2010; Fan et al., 2010; Hashimoto et al., 2009; Lemaître et al., 2005), even in younger groups below 60 (Burggren et al., 2008; Wishart et al., 2006). More specifically, entorhinal thinning and medial temporal lobe volume loss have been observed in heterozygous ApoE4 carriers relative to non-carriers (Burggren et al., 2008; Fan et al., 2010; Wishart et al., 2006), and others have demonstrated congruent findings showing a steeper trajectory of age-related thinning of widespread cortical thinning in individuals with at least one ApoE4 allele (Espeseth et al., 2008).

However, these findings are in contrast with studies reporting no structural difference in heterozygous ApoE4 carriers compared to non-carriers (Cherbuin et al., 2008; Crivello et al., 2010; Heise et al., 2011; Lemaître et al., 2005) (Age range: 69 – 75). The disparity of findings has prompted debate about the existence of a gene-dose effect of ApoE4 on cortical atrophy, particularly in light of other studies demonstrating medial temporal lobe atrophy and accelerated cortical atrophy only in homozygous ApoE4 carriers of comparable age (Chen et al., 2007; Crivello et al., 2010; Lemaître et al., 2005) (Age range: 55 – 75).

Family history

Some studies have compared the presymptomatic imaging endophenotypes of maternal family history (FHm) against paternal family history (FHp) in AD (Berti et al., 2011; Honea et al., 2011,

2010; Mosconi et al., 2014). Using VBM approaches, these studies have converged to reveal a more severe extent of cortical atrophy in FHm compared to controls and FHp (Berti et al., 2011; Honea et al., 2010). Conversely, no structural differences were found between FHp and controls (Berti et al., 2011), although Honea and colleagues (Honea et al., 2010) reported additional frontal lobe and precuneus atrophy in the FHp group compared to the controls. A subsequent 2-year duration longitudinal VBM study showed progressive atrophy in the precuneus and parahippocampal cortex of FHm individuals compared to both FHp and controls (Honea et al., 2011). Another VBM study identified a 'parent-dose effect' where individuals (age = 56) with both FHm and FHp showed the most severe atrophy in the temporal cortex, while additional parietal atrophy was found in the FHm group compared to FHp (Mosconi et al., 2014). Overall, these observations of greater atrophy in individuals with FHm are in agreement with evidence that maternal transmission of AD is associated with more severe hypometabolism (Mosconi et al., 2009) and memory impairment (Debette et al., 2009). However, other VBM studies have not found a parent-of-origin effect on cortical atrophy in middle-aged groups (age range: 53 - 57) (Okonkwo et al., 2012; Ten Kate et al., 2016). For instance, both FHm and FHp groups showed precuneus atrophy compared to individuals without a family history (Ten Kate et al., 2016).

Interactions between apolipoprotein E4 and family history

The potential interactions between ApoE4 carriage and family history on structural morphology have also been a topic of investigation. In the Framingham Offspring study, a higher rate of global brain atrophy over 6 years was only found in ApoE4 carriers with a positive family history of AD (Debette et al., 2009). Through an exploratory VBM analysis that is unrestricted by an AD-ROI mask, another study found differential effects of ApoE4 and family history on

regional atrophy in a relatively younger sample. ApoE4 carriage (age = 61) was associated with striatal atrophy whereas family history (age =57) was associated with atrophy in the precuneus (Ten Kate et al., 2016). Individuals characterised by an extreme phenotype of "double risk" (i.e. positive family history and ApoE4) also demonstrated bilateral insular atrophy compared. This finding is particularly noteworthy as that it has not been reported in the literature of preclinical dementia (Ten Kate et al., 2016)., even though it has been implicated in mild cognitive impairment with PD and AD (Mak et al., 2014b; Sluimer et al., 2009).

TOMM40 gene

Few studies have characterised the effect of TOMM40 poly-T length on cortical changes in cognitively healthy individuals (Johnson et al., 2011). In a search-restricted VBM study focussing on homozygotic ApoE3 middle-aged adults, a dose-dependent increase in the Very-Long (VL) TOMM40 polymorphism was associated with atrophy in the precuneus and posterior cingulate (no VL alleles < Short/VL heterozygotes < VL/VL homozygotes) after adjusting for age and total intracranial volumes. It is worth mentioning that the precuneus and posterior cingulate cortex have repeatedly been implicated in this article as well as other studies in AD (i.e. hypometabolism, decreased white matter integrity and macroscopic atrophy). A network perspective (discussed in greater detail later) could offer some insights into the preferential vulnerability of these regions across the spectrum of dementia. The precuneus and posterior cingulate cortex are heavily involved in the default mode network. Interestingly, network analyses have consistently identified these regions as hubs with dense anatomical connections occupying a central position in the topology of brain networks (van den Heuvel and Sporns, 2013). However, a centrality confers a high biological cost (i.e. increased metabolic demands)

and renders these regions susceptible to disease-related processes (Crossley et al., 2014). At present, further studies, are warranted to investigate the link between TOMM40 variations and imaging changes at the cross- and longitudinal levels.

Brain-derived neurotrophic factor gene

Considering its critical role in neuroplasticity underlying learning and memory in the hippocampus, the brain-derived neurotrophic factor (BDNF) gene represents another potential risk factor for AD, although its influence on brain morphology is relatively understudied in the context of preclinical AD. A single nucleotide polymorphism in the BDNF gene produces a valine to methionine (Val66Met) amino acid substitution that affects intracellular packaging and activity-dependent secretion of the BDNF, in turn affecting human memory function (Chen, 2004; Egan et al., 2003) and hippocampal morphology (Bueller et al., 2006). In a retrospective longitudinal study over 3 years, Hashimoto and colleagues were the first to report a significant effect of the Val66MET polymorphism in preclinical AD, showing accelerated atrophy in the precuneus and cingulate regions in MET-BDNF carriers compared to VAL-BDNF carriers (Hashimoto et al., 2009).

6. SUBCORTICAL ATROPHY

Hippocampus

Hippocampal volumetry is one of the most validated, accessible and widely used biomarkers in AD. The hippocampus is an early preferential target of neurofibrillary tangles (Braak and Braak, 1991), and is markedly atrophied at the time of AD diagnosis, with a meta-analysis reporting approximately 25% smaller volumes compared to age-matched controls (Shi et al., 2009).

Similarly, the neuroimaging literature suggests a predilection of hippocampal atrophy in presymptomatic individuals, although evidence regarding the effects of ApoE4 remains inconclusive. Cross-sectionally, studies have reported significant hippocampal atrophy in ApoE4 carriers (den Heijer et al., 2002; Honea et al., 2009; Lemaître et al., 2005; Lind et al., 2006; Tohgi et al., 1997), as well as younger FAD mutation carriers (age range: 21-45) (Bateman et al., 2012; Fleisher et al., 2015; Ridha et al., 2006). However, there are just as many notable exceptions of negative findings in cross-sectional comparisons (Apostolova et al., 2011; Cherbuin et al., 2008; Gold et al., 2010; Lupton et al., 2016; Lyall et al., 2013; Protas et al., 2013). Indeed, one of the primary limitations of cross-sectional designs concerns the inter-individual variability of brain structures within a study sample. Longitudinal imaging studies wherein the same individuals are tracked over time may be more sensitive to subtle atrophy, particularly during the preclinical phase of AD. Lending support to this notion is the homogeneity of findings across longitudinal studies. For instance, increased rates of hippocampal atrophy were found in ApoE4 carriers (Cohen et al., 2001; Moffat et al., 2000) and individuals with family history (Okonkwo et al., 2012) over time, despite showing relative preservation at baseline. In addition to the independent effect of family history on hippocampal volumes, there is also increasing evidence that family history can interact with ApoE4. In the longitudinal study from the Wisconsin Registry for Alzheimer's Prevention (WRAP), Okonkwo and colleagues demonstrated that the effect of family history on hippocampal atrophy was more pronounced in non-carriers of ApoE4 (Okonkwo et al., 2012). These findings are consistent with other longitudinal studies of homozygous ApoE4 carriers (Crivello et al., 2010), younger FAD genetic mutation carriers (age < 60) (Fox et al., 1996; Ridha et al., 2006; Schott et al., 2003).

Fewer studies have addressed the effect of ApoE4 on the hippocampus in healthy younger adults (age < 30). The small but growing literature has yielded equivocal findings, where both atrophy (Alexopoulos et al., 2011; O'Dwyer et al., 2012) and preservation (Khan et al., 2014; Mondadori et al., 2007; Richter-Schmidinger et al., 2011) have been reported. In a large cohort of more than 1400 adolescents (age = 14), Khan and colleagues did not demonstrate any hippocampal volume (automatically segmented and normalised for ICV) differences between ApoE4 carriers and non-carriers (Khan et al., 2014). This is consistent with other studies of similarly aged samples (Heise et al., 2011; Mondadori et al., 2007; Richter-Schmidinger et al., 2011). Intriguingly, Mondadori and colleagues have also reported an association of ApoE4 with better episodic memory compared to ApoE2 and ApoE3 in a sample of 340 young adults (age = 22) (Mondadori et al., 2007). Considered in tandem with previous evidence where ApoE4 has been associated with higher IQ scores in younger adults (Yu et al., 2000) and enhancement of hippocampal long-term potentiation (Kitamura et al., 2004), it could be hypothesised that ApoE4 mediates neurodevelopmental resilience (Oría et al., 2005) (Brazil study) and enhanced intellectual function in children and young adults. It is thus possible that, through an interaction with age, the effect of ApoE4 transitions from a quiescent or even neuroprotective role from childhood to young adulthood before exerting a deleterious effect on cognition (Lothian Birth Cohort 1921) (Schiepers et al., 2012) and brain morphology in later life. Key to our ability to understand this would be studies that can provide regular follow up of participants from before, during and after this transition point.

Amygdala and striatal structures

Several post-mortem studies have also reported AD neuropathology in the amygdala (Arriagada et al., 1992; Tsuchiya and Kosaka, 1990), although its vulnerability in preclinical AD remains to be established. Amygdala atrophy has been reported in presymptomatic ApoE4 carriers (den Heijer et al., 2002; Honea et al., 2009) with potential dose-dependent effects of ApoE4 (den Heijer et al., 2002). However, negative findings have been reported from other studies employing manual tracing (Cherbuin et al., 2008) and automated segmentation approaches (Lupton et al., 2016).

Other subcortical regions including the thalamus, caudate and putamen have been implicated in presymptomatic FAD mutation carriers (Cash et al., 2013; Lee et al., 2012; Ryan et al., 2013). These findings run counter to a previous study in which presymptomatic FAD mutation carriers expressed an unexpected larger caudate whereas symptomatic carriers demonstrated an expected caudate atrophy relative to controls (Fortea et al., 2010). Given that the carriers were on average 9.9 years from expected age at onset, Fortea and colleagues interpreted their findings to reflect a possible reactive neuronal hypertrophy and/or neuroinflammation early in the presymptomatic stage that could explain the initial increase in the volume of these structures, which then undergo progressive atrophy as the disease progresses. Consistent with their interpretations, we have recently shown that proinflammatory processes could be observed up to 10 years before diagnosis (Ritchie et al., 2016). Thus, these findings argue that structural imaging findings of presymptomatic familial AD should be interpreted in light of the temporal proximity to expected age of symptom onset.

7. MICROSTRUCTURAL CHANGES IN PRECLINICAL DEMENTIA

Over the last decade, there has been exponential progress in the development and application of diffusion tensor imaging (DTI) (Le Bihan, 2006) to study both grey and white matter brain structure during neurodevelopment and neurodegeneration. The breakdown of microstructural barriers (i.e. myelin) that normally constrain the Brownian motion of water molecules results in a quantifiable difference in the diffusion of water along white matter tracts that could be indexed by various DTI metrics. Fractional anisotropy (FA) reflects the directional constraint (tendency for water diffusion to occur in a single direction) of the water diffusion along axons, and lower FA is commonly interpreted as disrupted microstructural integrity. Mean diffusivity (MD) is a measure of the average rate of diffusion in all directions and generally increases with axonal degeneration and demyelination. Such DTI changes are not visible on conventional structural MRI sequences, and previous evidence suggests that they could precede grey matter atrophy (Kantarci et al., 2005) and the appearance of amyloid and tau pathology (Desai et al., 2009).

DTI has been increasingly applied to investigate early microstructural deficits in FAD genetic mutation carriers (Li et al., 2015; Ringman et al., 2007; Ryan et al., 2013; Sánchez-Valle et al., 2016), cognitively normal ApoE4 carriers (Adluru et al., 2014; Bendlin et al., 2010; Heise et al., 2011; Honea et al., 2009; Kim et al., 2015; Lyall et al., 2014; Nierenberg et al., 2005; Persson et al., 2006; Ryan et al., 2011; Smith et al., 2010), and individuals with family history of AD (Hawkins et al., 2015; Kim et al., 2015; Smith et al., 2010).

Familial AD

Global FA was reduced in preclinical FAD mutation carriers (age = 35), and this effect was most pronounced in the fornix and white matter tracts of the orbitofrontal region during the

presymptomatic stage (Ringman et al., 2007). Li and colleagues reported that, in the absence of grey matter atrophy, presymptomatic FAD mutation carriers (age = 43) expressed higher MD but not FA in the longitudinal fasciculus and cingulum (Li et al., 2015). In contrast, other studies have not found significant changes in DTI metrics in similarly aged presymptomatic FAD mutation carriers (Parra et al., 2015; Sánchez-Valle et al., 2016), although significant FA decrease and MD increase were found in the corona radiata and corpus callosum in the symptomatic group (Sánchez-Valle et al., 2016). Interestingly, one study reported that presymptomatic carriers (age = 38) showed significantly decreased MD in the right hippocampus and the cingulum, as well as increased FA in the bilateral thalamus and left caudate (Ryan et al., 2013). The authors speculated that these seemingly paradoxical findings could reflect earlier axonal insults in the pathway towards subsequent neurodegeneration, such as initial microglial activation/accumulation and swelling of neurones and glial, which could, in turn, lead to a greater restriction on the Brownian motion of water molecules.

Apolipoprotein E4 and family history

Healthy individuals with ApoE4 are characterised by less white matter volume (Ready et al., 2011) (age = 53) and a higher rate of myelin breakdown in an older sample (Bartzokis et al., 2006) (age = 66). Furthermore, ApoE4 carriers have also showed decreased FA in widespread white matter tracts associated with temporal lobe structures, including the cingulum (Smith et al., 2010) (age = 58), corpus callosum, and longitudinal fasciculus (Heise et al., 2011; Lyall et al., 2014). In addition, the microstructural integrity of the medial temporal lobe could be highly susceptible to the earliest pathology in preclinical AD. Other studies have found convergent ApoE4-related FA decreases in parahippocampal gyrus white matter (Honea et al., 2009;

Nierenberg et al., 2005) and left hippocampus (Persson et al., 2006) in older cognitively normal individuals (age > 60). Considering the accumulating evidence of medial temporal lobe atrophy in presymptomatic ApoE4 carriers as described earlier (Section 4), it could be a case where white matter integrity is compromised through Wallerian degeneration. However, this argument is increasingly challenged by other multi-modal (DTI and T1) studies showing that presymptomatic individuals had decreased microstructural integrity of widespread regions – including the medial temporal fibre tracts – without total grey matter or hippocampal atrophy (Gold et al., 2010; Heise et al., 2011). Thus, further longitudinal studies are needed to elucidate the temporal sequence of microstructural and grey matter changes.

Other studies have investigated the relative contributions of parental family history and ApoE4 carriage to microstructural changes in presymptomatic individuals (Adluru et al., 2014; Bendlin et al., 2010; Gold et al., 2010) (age = 60). Individuals possessing both positive family history and ApoE4 showed the lowest FA in characteristic AD regions, such as the corpus callosum, cingulum, and medial temporal grey and white matter connections (Bendlin et al., 2010; Gold et al., 2010). However, these findings are also in contrast to another study, which did not show any ApoE4-related white matter changes, although individuals with a positive family history showed an unexpected FA increase in the corpus callosum and the superior longitudinal fasciculus (Adluru et al., 2014). In order to move beyond speculative interpretations of such DTI changes, the field needs more concerted attempts to validate FA or MD changes with histological data. In parallel, more longitudinal studies are needed to characterise the course of microstructural brain changes that occur at presymptomatic disease stage, and to investigate their associations with cognitive decline over time.

8. THE PRECLINICAL CONNECTOME

Graph theoretical approach in brain networks

While the studies reviewed in this paper have identified characteristic patterns of atrophy and microstructural deficits in the preclinical stages of AD, questions about their macro-level impact on the brain organisational properties remain unresolved. Increasing attention on these questions has coincided with the ascendancy of connectomics – an attempt to map the multitude of neuronal connections in the brain – and graph theory as a joint-approach to quantify the large-scale topological properties of the brain networks in neurodegenerative diseases (Alexander-Bloch et al., 2013; Bullmore and Sporns, 2009). The field of connectomics also represents a paradigm shift away from the conventional segregated region-based approach towards an integrative perspective that considers the topological organization of the entire human cortex. Network-based analyses may be sensitive to aberrations not evident in brain structure because they take into account multivariate interactions and co-dependencies between brain regions as well as the integration of each region in the overall network architecture.

Construction and statistical comparisons of structural networks

The structural network could be derived from the structural covariance approach (i.e. inter-regional correlations of cortical thickness) at the group level (Alexander-Bloch et al., 2013; Bernhardt et al., 2011; Mak et al., 2016) as well as similarity-based grey matter networks in individual subjects (Tijms et al., 2012). In addition, white matter tracts constituting the macroscale connectome can be constructed using diffusion tractography pipelines (Hagmann et al., 2008). Subsequently, network properties such as path length and clustering are quantified

from these networks using graph theoretical concepts and subsequently normalised against benchmark (i.e. random) networks. Statistical comparisons are highly dependent on the nature of the networks. For instance, metrics from single-subject DTI and GM networks are typically compared using independent Student T-tests or ANOVA to correct for covariates (Tijms et al., 2013a), while comparisons of group-level cortical thickness connectomes would necessitate non-parametric permutation testing or bootstrapping simulations across network densities (5 – 40%) (Bernhardt et al., 2011; Mak et al., 2016).

Summary of connectomic changes in mild cognitive impairment and Alzheimer's disease

A consistent finding across the literature indicates the brain networks are organised with an efficient 'small-world' topology, reflecting an optimal balance of (a) short characteristic path length (CPL), facilitating efficient integration of information from multiple brain regions using a relatively short distance; and (b) high clustering coefficient (CC), resulting in dense inter-connections between adjacent brain regions (Rubinov and Sporns, 2010). Recent studies have characterised the structural brain networks in AD and MCI (see (Tijms et al., 2013b) for a review), and while there is a general agreement that AD and MCI are associated with changes in network properties, there is a worrying lack of consensus about the directionality and interpretation of these changes. For instance, AD has been characterised with a pairing of increased CPL and CC compared to controls (Lo et al., 2010). This increased CPL might reflect an abnormal loss of circuit 'short-cuts', resulting in increased local segregation of information transfer at the expense of global integration. In contrast, others have reported decrease clustering in AD (Tijms et al., 2013a). With regards to the potential utility of graph theory as a biomarker for subsequent disease progression, the Randić index – the degree to which highly connected

nodes are also connected to other highly connected nodes (i.e. a rich club) – obtained at baseline could distinguish MCI subjects who remained stable over 3 years from those who converted to AD (Phillips et al., 2015).

Topology of brain networks in preclinical AD

We have identified only two previous studies investigating the macroscale impact of focal brain changes in preclinical AD (age range: 61 - 67). Using DTI tractography, Brown and colleagues (Brown et al., 2011) reported that cognitively normal ApoE4 carriers showed a significant decrease of small-worldness with age that was largely driven by the loss of local clustering. Interestingly, key brain regions in the default mode network also showed less interconnectivity (Brown et al., 2011). Chen and colleagues (Chen et al., 2015) reported a modulating effect of the rs405509 genotype – a newly recognised AD-related polymorphism located in the ApoE promoter region (Lambert et al., 2002) – on structural covariance networks in cognitively normal elderly subjects. Only the non-risk group (rs405509 G-allele carriers) expressed cortical thickness covariance between the left parahippocampal gyrus and left medial cortex. At present, the biological mechanisms that subserve structural covariance remains a contentious topic, although inter-regional correlations of cortical thickness have been found to partly overlap with underlying white matter connections (Gong et al., 2012). Future studies could use diffusion tractography to assess the microstructural integrity of the white matter tracts in question.

9. PRECLINICAL DEMENTIA AND NORMAL AGEING

It is now well established that the normal process of ageing is intrinsically related to progressive impairment of neural mechanisms and neurotransmitters (Mora et al., 2007), changes in

cognition and behaviour, as well as morphological changes over time (Fjell et al., 2009). Unlike the stereotypical localisations of temporo-parietal susceptibility in preclinical dementia, brain changes associated with normal aging appear to follow a non-linear trend (Ziegler et al., 2012) with strong effects in frontal cortices (Fjell et al., 2009). However, previous studies have also demonstrated thinning in regions that are known to be vulnerable to AD, such as age-related acceleration of entorhinal thinning (Fjell et al., 2014). In summary, the literature suggests that brain changes in preclinical dementia are superimposed on normal ageing, albeit with greater magnitude conferred by pathological amyloid and/or tau. Thus, the co-localisations of atrophy in normal and preclinical dementia underscore the importance to adjust for age as a covariate in all imaging comparisons.

10. FUTURE DIRECTIONS

Need for more longitudinal studies

Most of the studies investigating the effects of AD risk factors on brain structure often employed a cross-sectional design in which brain structure was compared between carriers and non-carriers. While convenient, this design precludes the evaluation of the effects of AD risk factors on intra-individual progression of atrophy. Longitudinal studies including serial scans provide an assessment of individual trajectories of brain changes and give insight into the variability of brain changes between different persons. Future prospective studies over longer time periods are required to determine the predictive utility of various biomarkers for transitioning to AD and elucidate within-individual trajectories of the biomarkers. It is encouraging that multiple longitudinal preclinical cohorts are pursuing these endeavours. Notably, the WRAP project presently has 7 – 10 years worth of multimodal imaging data in a late middle-age cohort. The

PREVENT study (Ritchie et al., 2013), which is an on-going study from our group, is also collecting large amounts of imaging data (including MRI, DTI, MRS and fMRI) from people aged 40 to 59 at baseline, as well as detailed neuropsychological assessment using the COGNITIO test battery (Ritchie et al., 2014) designed for pre-clinical cognitive assessment as well as genetic analyses. In the context of autosomal dominant AD and individuals in the earliest stages of the disease, ongoing longitudinal analyses of imaging data from the Dominantly Inherited Alzheimer Network (DIAN) (Cash et al., 2013), the Alzheimer's Prevention Initiative's Columbia Registry (Lopera et al., 2013) and others (Yau et al., 2015) will clarify not only the spatial extent but the trajectory of preclinical brain changes with respect to estimated age of onset AD. These collective efforts will also facilitate important studies to investigate the generalisability of imaging findings in FAD to sporadic AD.

Investigating hippocampal subfields

The hippocampus is one of the most heavily implicated regions in this review, suggesting preferential predilection even at the earliest stages of AD. However, the influence of certain risk factors, such as ApoE4, on hippocampal volumetry remains highly controversial with inconclusive findings. Apart from some of the common culprits such as sample heterogeneity and adjusted covariates, these divergent findings could also be attributed to non-uniform effects of the E4 allele across the histologically and functionally distinct subfields of the hippocampus. Consequently, treating the hippocampus as a unitary structure would have obscured these subtle changes. Local analyses of the hippocampus are increasingly recognised as a viable method to characterise the involvement of cytoarchitectonic regions in the pathology of neurodegenerative diseases (de Flores et al., 2015; Mak et al., 2015b). Based on a probabilistic Bayesian approach,

automated techniques for the segmentation of hippocampal subfields based on *ex vivo* training data have been improved and are publicly available (Iglesias et al., 2015) for the analyses of large datasets. We envisage that this will become a promising research area that is capable of detangling the differential effects of preclinical AD risk factors on specific sub-regions.

Multi-modal imaging

More studies are needed to investigate the potential influence of amyloid burden (PET imaging and CSF amyloid levels) in the context of the structural brain changes reviewed in this paper. Characteristic AD patterns of cortical thinning in temporal regions have been reported in cognitively normal AB+ individuals (Dickerson et al., 2009). Longitudinal studies have found that cognitively normal individuals with high amyloid deposition showed accelerated cortical atrophy in other susceptible regions of the brain, including the precuneus, medial temporal lobe, and other temporo-occipital cortices (Chetelat et al., 2012; Ewers et al., 2012). Several studies have also considered the interaction of amyloid with tau in cortical changes, with two longitudinal studies indicating that amyloid-associated thinning in the entorhinal cortex occurred only in the presence of elevated CSF phospho-tau (Desikan et al., 2013, 2011). For a thorough review of amyloid imaging in cognitively normal individuals within at-risk populations, the reader is referred to Chételat et al (Chetelat et al., 2013). Beyond this, a combination of in *vivo* multi-modal biomarkers is also expected to provide additive information to quantify AD pathology in the preclinical phase. This approach is advocated based on an updated proposal of the pathophysiological trajectory in AD (Jack et al., 2013). For instance, a plateauing effect has been demonstrated in amyloid deposition during the later stages of AD. In contrast, neurodegeneration and tau pathology appear to worsen in close synchrony with cognitive decline

(Jack et al., 2013). As a corollary, it follows that combining amyloid pathology and structural imaging may allow a finer characterization of preclinical staging (Jack et al., 2016; Sperling et al., 2011). In addition, the recent advent of *in vivo* tau imaging represents an exciting frontier to establish the relation of tau accumulation to downstream atrophy and perform. Ideally, these models would also eventually include relevant comorbid pathological events such as cerebrovascular changes and inflammation.

11. CONCLUSION

The use of structural neuroimaging techniques to study presymptomatic individuals offers a valuable time window to identify cerebral abnormalities of AD during the preclinical phase of the disease, with changes predating the onset of symptoms as early as up to a decade. Ultimately, clinical trials of interventions aimed at preclinical AD will likely hinge on two parallel endeavours: (a) fuller understanding of the complex effects of classical risk factors on both clinical and imaging characteristic in preclinical AD (i.e. is there a non-linear effect of ApoE4 and FAD mutations through ageing); and (b) identification of reliable and sensitive outcome measures (or combinations of outcome measures) that are capable of tracking disease progression in the absence of cognitive impairment at an individual level.

In the context of structural markers, this review has provided a comprehensive summary of preclinical structural disruptions occurring across different scales, from microstructural deficits in white matter tracts, volumetric loss in subcortical structures and cortical thinning, to network effects in the connectome. Overall, the literature reveals a preferential vulnerability of highly select brain regions that overlap with structures that are noted to be affected in prodromal AD

and sporadic AD itself. They include the medial temporal lobe and its connected white matter tracts, temporo-parietal cortices, hippocampus, precuneus, as well as the cingulum bundle and the corpus callosum.

Yet, the literature of structural changes in relation to risk factors was highly fragmented – particularly in ApoE4 carriers – with many discrepant findings of structural preservation and even hypertrophy in a small number of studies. Two caveats should be considered during the interpretation and comparison of imaging findings in preclinical AD. Firstly, AD has a multifaceted aetiology that is set against a convoluted polygenic background. Secondly, genetic risk factors such as ApoE4 could exert deleterious effects via multiple mechanisms with potentially differential effects across different stages of the lifespan (Liu et al., 2013). Therefore, the heterogeneous findings could be attributed to a range of factors: (a) single-modality imaging studies being unable to accurately characterise the full spectrum of ApoE4 effects; (b) variability in the demographics, both within and across studies, (c) variable length of time prior to onset of symptoms and (d) methodological differences in acquisition parameters, quantification methods (e.g. cortical thickness, voxel-based morphometry, region-of-interest approaches). Finally, there are also suggestions from the literature that ApoE4 and family history could interact to affect both grey and white matter, even at the asymptomatic stages.

We conclude that while structural imaging measurement is promising, more research and validation studies are needed before neuroimaging research can inform decisions regarding the adoption of structural measures in future treatment and prevention trials. In particular, there

needs to be an incorporation of age or distance from dementia diagnosis as an interactive term in any modelling work which would benefit in particular from frequent longitudinal follow up.

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Table 1. Asymptomatic changes in FAD mutation carriers

Study	Definition of preclinical dementia	Imaging modality and acquisition	Design and analyses	Sample (Mean age ± SD)	Main findings
Cash et al. (2013) * DIAN	FAD mutation carriers: Mostly PSEN1	3T T1 MRI	Cross-sectional: VBM in SPM8 GM WM	Non-carriers: *n* = 73 (40.6 ± 8.9) Presymptomatic carriers: *n* = 69 (34.1 ± 8.9)	NS, trend for decreased thalamus GM for carriers closer to EYO
Bateman et al. (2012) * DIAN	FAD mutation carriers: PSEN1 and APP	3T T1 MRI	Cross-sectional: Hippocampus from Freesurfer	Non-carriers: n = 40 (39.5 ± 8.9) Mixed Carriers: n = 88 (39.1 ± 10.3)	Hippocampal atrophy
Fleisher et al. (2015) * API Columbian kindred	FAD mutation: PSEN1	1.5T MRI	Cross-sectional: Hippocampus from Freesurfer	Non-carriers: *n* = 22 (33 ± 9) Carriers: *n* = 20 (32 ± 9)	Hippocampal atrophy
Quiroz et al. (2013) * API Columbian kindred	FAD mutation: PSEN1	1.5T T1 MRI	Cross-sectional: CTh thickness in AD-signature ROIs from Freesurfer	Non-carriers: *n* = 22 (39.5 ± 6.2) Carriers: *n* = 18 (38.2 ± 4.5)	Thinner cortex in AD-signature ROI
Quiroz et al. (2015) * API Columbian kindred	FAD mutation: PSEN1	1.5T T1 MRI	Cross-sectional: VBM	Non-carriers: *n* = 19 (13 ± 3) Carriers: *n* = 18 (13 ± 2)	Increased GM volume in temporal regions
Reiman et al. (2012) * API Columbian kindred	PSEN1	1.5T T1 MRI	Cross-sectional: Restricted VBM based on findings in AD	Non carriers: *n* = 24 (22 ± 2) Carriers: *n* = 20 (22 ± 3)	Reduced GM volume in parietal regions
Parra et al.	PSEN1	1.5T	Cross-	Non carriers: *n* = 21	NS

(2015) * API Columbian kindred	DTI	sectional: FA and MD from FSL; ROI	(39.3 ± 83) Carriers: *n* = 18 (35.1 ± 5.5)

Notes: This abbreviated table contains highlighted studies in FAD that have more than 15 subjects per group, and extra attention was afforded to longitudinal studies. Abbreviations: NS = No significant findings; APP = Amyloid precursor protein; PSEN1 = Presenilin 1; EYO = Estimated Year to Onset; ApoE4 = Apolipoprotein E4; DIAN = Dominantly Inherited Alzheimer Network; WRAP = Wisconsin Registry for Alzheimer Prevention; FH = family history; FA = Fractional anisotropy, MD = Mean diffusivity, ROI = Regions of Interest; CTh = Cortical thickness, GM = Grey matter; WM = White matter; AAL = Automated Anatomical Labeling, VBM = Voxel based morphometry, SPM = Statistical Parametric Mapping.

TABLE 2. Asymptomatic changes related to ApoE4 carriage and family history

Study	Definition of preclinical dementia	Imaging modality and acquisition	Design and analyses	Sample (Mean age ± SD)	Main findings
Dean et al. (2014)	ApoE4	3T T1 and T2	Cross-sectional: VBM in SPM MWF	Carriers: n = 60 (391 ± 196) days Non-carriers: n = 102 (366 ± 181) days	Widespread reductions in MWF and GM. Greater MWF and GM volume in frontal regions.
Espeseth et al. (2008)	ApoE4	1.5T T1	Cross-sectional: CTh from Freesurfer	Carriers *n* = 37 (63.9 ± 7.9) Non-carriers: *n* = 59 (64.9 ± 7.7)	Cortical thickening in frontal and temporal regions. Steeper age-related cortical thinning.
Khan et al. (2014) * European IMAGEN project	ApoE4	3T T1 MRI	Cross-sectional: Hippocampus from Freesurfer	Carriers: *n* = 343 (14.44 ± 0.40) ApoE4-: *n* = 1069 (14.45 ± 0.41)	NS
Lind et at. (2006)	ApoE4	1.5T T1 MRI	Cross-sectional: Hippocampus from manual tracing	Carriers *n* = 30 (65.3 ± 7.9) Carriers: *n* = 30 (66.6 ± 8.3)	Right hippocampal atrophy
Lupton et al. (2016) * Multi-cohort project	ApoE4	Field strength not reported MRI	Cross-sectional: Hippocampus and amygdala from Freesurfer and FSL	Healthy young: *n* = 467 (22.9 ± 3.3) Healthy older: *n* = 746	No association of ApoE4 with hippocampal and amygdala volumes in healthy adults.

				(75.3 ± 5.9)	
Lyall et al. (2013) * Lothian Birth Cohort 1936	ApoE4 TOMM40	1.5T T1 MRI	Cross-sectional: Hippocampus from FSL	Total *n* = 655 (72.7 ± 0.7) Subgroups based on ApoE4 and TOMM40	NS
Protas et al. (2013)	ApoE4	MRI	Cross-sectional: Hippocampus from a semi-automated technique	Homozygotic carriers: *n* = 31 (55.5 ± 5.1) Heterozygotic carriers: *n* = 42 (55.9 ± 4.0) Non-carriers: *n* = 76 (56.5 ± 4.7)	NS
Richter-Schmidinger et al. (2011)	ApoE4 BDNF-Met66	1.5T T1 MRI	Cross-sectional: Hippocampus from manual tracing	Non-carriers: *n* = 117 (24.6 ± 3.1) Carriers *n* = 18 (24.1 ± 3.8) BDNF Met66-: *n* = 84 (24.9 ± 3.6) BDNF Met66+: *n* = 51 (23.9 ± 2.3)	NS
Ten Kate et al. (2016) * Gipuzkoa Alzheimer Project	ApoE4 and FH	3T T1 MRI	Cross-sectional: VBM in SPM	FH-ApoE4-: *n* = 55 (58.4 ± 7.0) FH-ApoE4+: *n* = 12 (61.1 ± 9.9) FH+ApoE4-: *n* = 166 (56.5 ± 6.6) FH+ApoE4+: *n* = 62 (54.9 ± 6.0)	Relative to controls, ApoE4 carriers showed reduce striatal volumes while FH+ had right precuneus atrophy. Similar atrophy patterns in maternal and

					paternal FH.
Cherbuin et al. (2008)	ApoE4	1.5T T1 MRI	Cross-sectional: VBM, Hippocampus and amygdala from manual tracing	Carriers: *n* = 89 (62.4 ± 1.5) Non-carriers: *n* = 242 (62.7 ± 1.4)	NS
Crivello et al. (2010)	ApoE4	1.5T T1 MRI	Longitudinal: Hippocampus from AAL	ApoE4+/+: *n* = 14 (71.0 ± 2.3) ApoE4+/-: *n* = 239 (72.0 ± 3.9) ApoE4-/-: *n* = 933 (72.4 ± 4.0)	Higher rate of hippocampal atrophy in ApoE4 homozygotes relative to heterozygotes and non-carriers.
den Heijer et al. (2002)	ApoE4	1.5T T1 MRI	Cross-sectional: Hippocampus and amygdala from manual tracing, global brain atrophy from visual rating	ApoE2: *n* = 120 (72 ± 7) ApoE3/E3: *n* = 568 (73 ± 7) ApoE4: *n* = 261 (71 ± 7)	ApoE4 carriers showed more hippocampal and amygdala atrophy compared to ApoE3 carriers. No difference in whole brain measurements.
Honea et al. (2011) *KU Brain Aging project	ApoE4 and FH	3T T1 MRI	Longitudinal: Whole brain atrophy rate VBM	FH maternal: *n* = 11 (69 ± 6) FH paternal: *n* = 10 (75 ± 8) FH-: *n* = 23 (74 ± 7)	Combined FH+ showed increased whole brain atrophy compared to FH-. Only FHm showed longitudinal brain atrophy in precuneus and hippocampal regions compared to FH- and FHp. ApoE4 carriers showed more

					frontal atrophy compared to non-carriers.
Okonkwo et al. (2012) * WRAP	ApoE4 and FH	3T T1 MRI	Longitudinal: VBM restricted to search volume encompassing AD regions	FH+ApoE4-: *n* = 27 (52.78 ± 6.77) FH+ApoE4+: *n* = 33 (53.91 ± 5.83) FH-ApoE4-: *n* = 40 (55.48 ± 5.99) FH-ApoE4+: *n* = 8 (48.13 ± 5.94)	Those with FH and ApoE4 showed significant atrophy in posterior hippocampus. No effects of FH or ApoE4 on GM volumes at baseline.
Shaw et al. (2007)	ApoE4	1.5T T1 MRI	Longitudinal: CTh from manual tracing of ROI	ApoE4+: *n* = 65 (18.0 ± 2.3) ApoE2: *n* = 29 (18.9 ± 1.3) ApoE3: *n* = 145 (16.0 ± 4.0)	Reduced entorhinal thickness in ApoE4 carriers. No evidence of accelerated cortical thinning in ApoE4 carriers.
Debette et al. (2009) * Framingham Offspring Study	ApoE4 and FH	1/1.5T T2 MRI	Longitudinal: Global brain volume Hippocampus from manual tracing	FH: *n* = 285 (62.7 ± 8.4) FH-: *n* = 432 (57.0 ± 7.6)	Only individuals with FH and ApoE4 showed higher rate of global brain atrophy.
Adluru et al. (2014) * WRAP	ApoE4 and FH	3T DTI	Cross-sectional: AD ROIs	Total *n* = 358 FH+: (60.29 ± 6.89) FH-: (62.96 ± 5.84) ApoE4+: (60.12 ± 6.81) ApoE4-: (61.54 ± 6.63)	FH+ showed higher FA in the corpus callosum and superior longitudinal fasciculus. No main effect of ApoE4 on DTI measures.

					FH+ApoE4- showed lower, whereas FH+ApoE4+ showed higher AD in the uncinate fasciculus.
Bendlin et al. (2010) * WRAP	ApoE4 and FH	3T DTI	Cross-sectional: TBSS in FSL	FH+ApoE4+: *n* = 35 (57.5 ± 5.7) FH+ApoE4-: *n* = 38 (57.4 ± 5.4) FH-ApoE4+: *n* = 21 (55.4 ± 5.7) FH-ApoE4-: *n* = 42 (58.4 ± 4.2)	No effect of ApoE4 on DTI measures. FH was associated with decreased FA in widespread AD regions. Additive effects of ApoE4 and FH resulting in lowest FA in widespread regions including the hippocampus.
Kim et al. (2015) * WRAP	ApoE4 and FH	3T DTI	Cross-sectional: Graph theory analyses from tractography	FH+: *n* = 93 (62.96 ± 5.84) FH-: *n* = 250 (60.29 ± 6.89)	FH+ showed altered connectivity in the precuneus.
Lyall et al. (2014) * Lothian Birth Cohort 1936	ApoE4 TOMM40	1.5T DTI	Cross-sectional: Tractography in FSL	Total *n* = 640-650 (72.70 ± 0.74) Subgroups based on ApoE and TOMM40	ApoE4 carriers showed mildly reductions of FA in ventral cingulum and the inferior longitudinal fasciculus.

Notes: This abbreviated table contains highlighted studies that have more than 30 subjects per group, and extra attention was afforded to longitudinal studies. Abbreviations: NS = No significant findings; MWF = white matter myelin water fraction; ApoE4 = Apolipoprotein E4; WRAP = Wisconsin Registry for Alzheimer Prevention; FH = family history; FA = Fractional anisotropy, MD = Mean diffusivity, ROI = Regions of Interest; CTh = Cortical thickness, GM =

Grey matter; WM = White matter; AAL = Automated Anatomical Labeling, VBM = Voxel based morphometry, SPM = Statistical Parametric Mapping.

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