REVIEW

Structural brain volume differences between cognitively intact ApoE4 carriers and non-carriers across the lifespan

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Abstract
Apolipoprotein E4 (ApoE4) is a prominent genetic risk factor for Alzheimer's disease. The purpose of this review is to explore differences in structural brain volume detected by magnetic resonance imaging between cognitively intact ApoE4 carriers and non-carriers across the lifespan (i.e., older adults, middle-aged adults, young adults, children and adolescents, and neonates). Consistent findings are found throughout various developmental stages. This area of research may elucidate the mechanisms by which ApoE4 influences risk of developing Alzheimer's disease. It could also inform potential treatment strategies and interventions for carriers of the ApoE4 allele.

Key Words: *MRI; healthy aging; genetic risk factor; biomarker; Alzheimer's disease*

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Introduction
Apolipoprotein E4 (ApoE4) is a prominent genetic risk factor for Alzheimer's disease (AD). An individual can be a carrier of one or two ApoE4 alleles, or a non-carrier. The risk of developing AD increases exponentially as the number of alleles increases. One study reported that the lifetime risk of AD is between 51% and 60% for men and women who are carriers of two ApoE4 alleles and between 23% and 30% for men and women who are carriers of one ApoE4 allele (Genin et al., 2011). Apolipoprotein E2 (ApoE2) and apolipoprotein E3 (ApoE3) alleles also exist, and ApoE2 has been shown to have a neuroprotective effect (Wu and Zhao, 2016).

The purpose of this review is to explore structural brain volume differences between cognitively intact ApoE4 carriers and non-carriers. What this review contributes to the literature is an examination of structural differences across the lifespan. As such, the review is broken into various developmental stages. Given the strong association between ApoE4 and AD, it is expected that structural differences exist in areas commonly targeted by AD, most notably medial temporal structures such as the hippocampus and entorhinal cortex. This area of research may elucidate the mechanisms by which ApoE4 influences risk of developing AD. It could also inform potential treatment strategies and interventions for carriers of the ApoE4 allele.

ApoE4 and Magnetic Resonance Imaging (MRI) Findings in Healthy Individuals
Older adults
Honea et al. (2009) investigated the impact of ApoE status on structural brain volume in cognitively healthy older adults over the age of 60 years (mean age = 73.4 years, SD = 6.3). Participants were grouped by genotype: ApoE4 carriers (4/4, 4/3) and ApoE4 non-carriers. MRI was used to assess structural brain volume differences between the groups. The areas of interest included the hippocampus, amygdala, precuneus, inferior parietal cortex, superior frontal cortex, and angular/supramarginal gyrus. The results showed significantly less hippocampal and amygdala volume in ApoE4 carriers relative to non-carriers. This finding is significant because the hippocampus and amygdala (both part of the medial temporal cortex) are brain regions known to undergo accelerated atrophy in mild cognitive impairment (MCI) and AD (Basso et al., 2006; Schuff et al., 2009).

Middle-aged adults
Burggren et al. (2008) examined ApoE status and its association with structural brain volume and cortical thickness in cognitively healthy middle-aged adults. Participants were grouped by genotype: ApoE4 carriers (all 4/3) and ApoE4 non-carriers (all 3/3). Using MRI, they measured several subregions of the medial

temporal lobe, specifically the hippocampus, dentate gyrus, entorhinal cortex, subiculum, perirhinal cortex, parahippocampal cortex, and fusiform gyrus. It was found that ApoE4 carriers had significantly less cortical thickness in the entorhinal cortex and the subiculum as compared to non-carriers. The entorhinal cortex (which was not examined in Honea et al., 2009) is associated with neuropathology and volume loss in early AD (Braak and Braak, 1991; Bobinski et al., 1999). Contrary to the results of Honea et al. (2009), Burggren et al. did not find significant differences in hippocampal volume. This study strengthens the findings of Honea et al. because ApoE4 status was found to influence differences in cortical thickness in subregions of the medial temporal lobe (an area associated with significant morphological change in MCI and AD) in cognitively healthy, middle-aged adults.

Young adults

O'Dwyer et al. (2012) studied whether young adult ApoE4 carriers and non-carriers differ in terms of brain volume. Participants between 20 and 38 years of age (mean = 26.8, SD = 4.6) were grouped by genotype: ApoE4 carriers (4/4, 4/3) and ApoE4 non-carriers (3/3). The areas of interest included the nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, thalamus, and brain stem. O'Dwyer et al. reported significantly less right hippocampal volume in ApoE4 carriers compared to non-carriers. Furthermore, they found a borderline significant reduction in left hippocampal volume in ApoE4 carriers compared to non-carriers. Surprisingly, no significant differences were observed in other brain areas, including the amygdala. This study is consistent with Honea et al. (2009), and contrasts with Burggren et al. (2008) in terms of the differences in hippocampal volume observed between ApoE groups. However, this study conflicts with Honea et al. in that they did not find differences in amygdala volume between groups.

Similar to Honea et al., O'Dwyer et al. combined 4/4 and 4/3 participants to create an ApoE4 carrier group. The inclusion of the ApoE4 carrier group could possibly explain the significant result for hippocampal volume in both studies. Interestingly, O'Dwyer et al. only found significantly less right hippocampal volume, suggesting that the right hippocampus is more susceptible to atrophy than the left hippocampus in ApoE4 carriers. Future studies should examine whether cognitive deficits are present in these individuals, and if so, elucidate whether less right hippocampal volume is associated with the same degree of cognitive decline as in ApoE4 carriers with less total hippocampal volume (Honea et al., 2009). O'Dwyer et al. provides further evidence of the influence of ApoE4 on the volume of medial temporal lobe subregions in cognitively healthy individuals.

Children and adolescents

Shaw et al. (2007) investigated the impact of ApoE status on cortical morphology in children and adolescents. Participants were grouped by genotype: ApoE4 carriers (4/4, 4/3) and ApoE4 non-carriers (2/3, 3/3). The researchers examined structural differences between groups with respect to a number of areas, including the entorhinal cortex, medial temporal cortex, and orbitofrontal cortex. Shaw et al. found that compared to non-carriers, ApoE4 carriers showed significantly thinner cortical thickness of the left entorhinal cortex. Although nonsignificant, ApoE4 carriers had thinner cortical thickness of the right entorhinal cortex as well. Furthermore, in the left entorhinal cortex, medial temporal cortex, and orbitofrontal cortex, the researchers observed that ApoE2 (2/3) carriers had the greatest cortical thickness, followed by ApoE3 homozygotes, while ApoE4 carriers had the thinnest cortical volume. The increased cortical thickness observed in ApoE2 carriers is a possible explanation for ApoE2's suggested neuroprotective properties. Significant group differences were not found in other brain areas, including the frontal, parietal, occipital, and lateral temporal cortex. In sum, Shaw et al. demonstrated that significant ApoE allele-specific structural brain differences can be observed as early as childhood. Consistent with Burggren et al. (2008) findings, Shaw et al. found differences in the entorhinal cortex, a brain region associated with neuropathology and volume loss in early AD (Braak and Braak, 1991; Bobinski et al., 1999). Furthermore, consistent with all studies presented thus far, they found evidence of the influence of ApoE4 on the volume of medial temporal lobe subregions in cognitively healthy individuals.

Neonates

Knickmeyer et al. (2014) examined the impact of ApoE status on structural brain volume in neonates. Neonates were grouped by genotype: ApoE4 carriers (4/3) and ApoE4 non-carriers (3/3). Brain areas examined include temporal, frontal, and parietal lobes, and their subregions. Knickmeyer et al. (2014) found that ApoE4 carriers had less volume in multiple brain ar-

Table 1 Structural brain volume differences between cognitively intact ApoE4 carriers and non-carriers across the lifespan

Study	Population	Design	Findings
Knickmeyer et al. (2014)	Neonates	Cross-sectional	ApoE4 carriers had significantly less volume in multiple brain areas, including temporal, frontal, and parietal lobes. ApoE4 carriers had significantly less volume in temporal subregions including bilateral hippocampus, parahippocampus, fusiform, and middle and inferior temporal gyri.
O'Dwyer et al. (2012)	Young adults	Cross-sectional	ApoE4 carriers had significantly less right hippocampal volume compared to non-carriers.
Lu et al. (2011)	Older adults	Longitudinal	ApoE4 carriers had more extensive annual atrophy rates of temporal lobe and hippocampal region compared to non-carriers. More extensive annual atrophy rates were found specifically in the right hippocampus.
Honea et al. (2009)	Older adults	Cross-sectional	ApoE4 carriers had significantly less hippocampal and amygdala volume compared to non-carriers.
Burggren et al. (2008)	Middle-aged adults	Cross-sectional	ApoE4 carriers had significantly less cortical thickness in the entorhinal cortex and subiculum compared to non-carriers.
Shaw et al. (2007)	Children and adolescents	Cross-sectional	ApoE4 carriers had significantly less cortical thickness of the left entorhinal cortex compared to non-carriers.

eas, including the temporal, frontal, and parietal lobes. The researchers also observed less volume in temporal subregions for ApoE4 carriers, including the bilateral hippocampus, parahippocampus, fusiform, and middle and inferior temporal gyri. The differences found in hippocampal volume are consistent with Honea et al. (2009) and O'Dwyer et al. (2012). This study demonstrated that ApoE status-dependent morphological brain differences can be observed in individuals shortly after birth.

Longitudinal examination

A limitation of all the preceding studies is their cross-sectional design. Longitudinal studies may further elucidate the influence of ApoE4 on structural morphological changes in healthy individuals because such studies allow researchers examine how these changes progress over time.

In one longitudinal study, Lu et al. (2011) investigated differences in atrophy rates for ApoE4 carriers (all 4/3) and non-carriers (2/3). Healthy older adults between the ages of 55 and 75 were grouped by genotype: ApoE4 carriers (all 4/3) and ApoE4 non-carriers (all 2/3). They examined frontal, temporal, parietal, occipital lobes, and the hippocampus. Participants completed baseline and 5-year follow-up MRI assessments. Lu et al. found more extensive annual atrophy rates of temporal lobe and hippocampal region in ApoE4 carriers compared to non-carriers. Furthermore, more extensive annual atrophy rates were found specifically in the right hippocampus. No significant differences in annual atrophy rates were observed in the left hippocampus. This result is consistent with O'Dwyer et al. (2012). In sum, this study highlighted the importance of studying longitudinal change in right hippocampus volume in ApoE4 carriers as a potential preclinical biomarker of AD.

Discussion

ApoE4 and structural MRI findings in healthy individuals have been studied in older adults, middle-aged adults, young adults, children and adolescents, and neonates. Convincing evidence exists which suggests regionally specific effects of the ApoE4 allele on structural brain morphology, specifically the medial temporal cortex and its subregions (the hippocampus, amygdala, entorhinal cortex, and subiculum; see **Table 1**).

There are a number of limitations of the current literature. Several of the articles (Burggren et al. 2008; Honea et al., 2009; O'Dwyer et al., 2012) provided incomplete demographic information (*e.g.*, race/ethnicity) for the sample, making it difficult to determine the generalizability of the results. Furthermore, Knickmeyer et al. (2014) involved an all-white sample. As a result, it cannot be concluded that the influence of ApoE4 on brain morphology is generalizable to other racial and ethnic groups. Future research should recruit participants from a diverse range of multicultural backgrounds.

When conducting research on cognitively intact individuals, researchers must ensure that the participants are, in fact, cognitively healthy. Using a Clinical Dementia Rating (CDR) score alone to determine whether older adults are cognitively intact (Honea et al., 2009) may not be sufficient. The use of multiple measures (Burggren et al., 2008; Lu et al., 2011) makes for a far more valid assessment of cognitive health. Also, consistent with the literature, there are limitations to

the validity of self-report measures because of their inherent subjectivity (Robinson and Clore, 2002).

Several studies grouped subjects into ApoE4 carriers and non-carriers (Shaw et al., 2007; Honea et al., 2009; O'Dwyer et al., 2012). That is, some combination of 4/4, 4/3, and 4/2 made up carriers, while some combination of 3/3, 2/3, 2/2 made up non-carriers. These grouping strategies make it difficult to determine the unique contribution of homozygote ApoE4 (genetic risk factor for of AD) and homozygote ApoE2 (neuroprotective). Future research should investigate 4/4, 4/3, 4/2, 3/3/, 2/3, and 2/2 groups independently, as seen in Burggren et al. (2008), Lu et al. (2011), and Knickmeyer et al. (2014).

In closing, most of the existing literature on ApoE4 and structural MRI findings in healthy individuals involves cross-sectional examination (Shaw et al., 2007; Burggren et al., 2008; Honea et al., 2009; O'Dwyer et al., 2012; Knickmeyer et al., 2014). Therefore, it is not possible to confirm whether these morphological brain changes are, in fact, preclinical markers of AD. Longitudinal studies that track participants throughout the lifespan are needed; especially ones that monitor how these morphological brain changes relate to cognitive performance (Wolf, 2012). If conclusive evidence emerges that these ApoE status-dependent structural brain differences – which can be detected shortly after birth (Knickmeyer et al., 2014) – do represent risk factors for later cognitive decline and AD, they provide particularly promising targets for treatment strategies and interventions.

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