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Apolipoprotein E, Gender, and Alzheimer's Disease: An Overlooked, but Potent and Promising Interaction

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Abstract

Alzheimer's disease (AD) is an increasingly prevalent, fatal neurodegenerative disease that has proven resistant, thus far, to all attempts to prevent it, forestall it, or slow its progression. The ε4 allele of the Apolipoprotein E gene (APOE4) is a potent genetic risk factor for sporadic and late-onset familial AD. While the link between APOE4 and AD is strong, many expected effects, like increasing the risk of conversion from MCI to AD, have not been widely replicable. One critical, and commonly overlooked, feature of the APOE4 link to AD is that several lines of evidence suggest it is far more pronounced in women than in men. Here we review previous literature on the APOE4 by gender interaction with a particular focus on imaging-related studies.

1. Introduction

Alzheimer's disease (AD) is an increasingly prevalent, ultimately fatal neurodegenerative disorder for which there are no disease-modifying treatments. In the wake of several large, costly, and negative phase III studies of antibodies against beta-amyloid, there is a critical need for novel approaches to understanding AD and developing alternative targets for treatment. The ε4 allele of the Apolipoprotein E gene (APOE4) is a potent genetic risk factor for sporadic and late-onset familial AD(Corder et al., 1993; Saunders et al., 1993; Strittmatter et al., 1993). While estimates vary across studies and ethnic backgrounds, the APOE4 allele is typically present in more than 50% of AD patients but is found only in about 15% of healthy older controls(Ward et al., 2012). Basic science research has suggested several roles that the ε4 isoform of apolipoprotein E (ApoE4) may play in augmenting the development of AD. Cell culture and animal models have identified potential pathogenic mechanisms related to beta-amyloid clearance, tau hyperphosphorylation, and synaptic function, among others(Brecht et al., 2004; Castellano et al., 2011; Dumanis et al., 2009). In the clinical realm, several drug trials have suggested that efficacy and side effect profiles may differ between APOE4 carriers and non-carriers though the findings have not always been replicated(Farlow, 2010; Petersen et al., 2005; Risner et al., 2006; Salloway et al., 2009). Some, but not all, imaging and cerebrospinal fluid (CSF) biomarker studies have shown early AD-like findings in healthy older APOE4 carriers(Machulda et al., 2011; Peskind et al., 2006; Reiman et al., 2001; Shaw et al., 2009; Sheline et al., 2010; Sunderland et al., 2004; Westlye, Lundervold, Rootwelt, Lundervold, & Westlye, 2011). Some, but not all, longitudinal studies suggest that among patients with mild cognitive impairment (MCI) APOE4 carriers are more likely to convert to AD (Devanand et al., 2005; Landau et al., 2010; Petersen et al., 1995; Tierney et al., 1996).

Thus, while the link between APOE4 and AD is strong, many expected effects, like increasing the risk of conversion from MCI to AD, have not been widely replicable. One critical, and commonly overlooked, feature of the APOE4 link to AD is that several lines of evidence suggest it is far more pronounced in women than in men. Shortly after the initial linkage studies, a prominent interaction between APOE and gender was reported(Payami et al., 1994). The first large meta-analysis of APOE4 studies found that women in their sixties with one APOE4 allele had a 4-fold increased risk whereas male APOE4 heterozygotes did not bump their risk much, if at all(Farrer et al., 1997). Among APOE4 homozygotes, men and women both showed a pronounced increase in risk compared to homozygous carriers of the risk-neutral ε3 allele (APOE3). Even among the APOE4 homozygotes, however, there appeared to be a gender interaction in that female APOE4 homozygotes' risk peaked around 12-fold compared to 10-fold in the male APOE4 homozygotes. This finding has been replicated several times and yet is almost never considered or investigated in clinical AD research where male and female APOE4 carriers are generally viewed as having equal risk(Bretsky et al., 1999; Payami et al., 1996). In the few recent studies that have examined this interaction between APOE4 and gender, female, but not male, APOE4 carriers have shown more pronounced AD-like changes in neuroimaging, neuropathological, and neuropsychological measures when compared to their APOE3 homozygous peers(Corder et al., 2004; Damoiseaux, Seeley, et al., 2012; Fleisher et al., 2005; Lehmann et al., 2006). In mouse models designed for AD research, the same interaction between APOE and gender was identified years ago, so that today many studies only carry out experiments in female mice(Andrews-Zwilling et al., 2010; Raber, Bongers, LeFevour, Buttini, & Mucke, 2002; Raber et al., 1998).

Here we review previous literature on the APOE4 by gender interaction with a particular focus on imaging-related studies.

2.1 Genetics of Alzheimer's Disease

There are genes besides ApoE that have been linked to increased AD frequency, but compared to ApoE, they occur either rarely or their effects are less potent. On one hand autosomal dominant AD—linked to mutations in presenilin-1 (PS1), presenilin-2 (PS2), or the amyloid precursor protein (APP)— is caused by genes that are fully penetrant, but their occurrence is rare; they are thought to account for less than 5% of AD cases(Bertram & Tanzi, 2012). In contrast, a slew of recent genome-wide association studies (GWAS) have identified polymorphisms that are more common, but the risk conferred by any one of these genes has been marginal (Guerreiro & Hardy, 2011). The more potent genes reported in GWAS publications typically result in a roughly 0.1 to 0.15-fold change in risk compared to the 4-fold increased risk associated with APOE4(Bertram, Lill, & Tanzi, 2010).

In contrast, APOE4 is found in more than half of AD patients across most studies and in closer to 65% of patients of Northern European descent(Ward et al., 2012). The reports linking late-onset familial and sporadic AD to APOE4 provided a compelling new inroad into AD pathogenesis(Corder et al., 1993; Saunders et al., 1993; Strittmatter et al., 1993). The main findings—APOE4 increases AD risk 2–3 fold in heterozygotes and 10-fold in homozygotes while moving the age of onset earlier—have been replicated numerous times

across a variety of ethnic groups(Farrer et al., 1997; Ward et al., 2012). It has also been shown that the less common ε2 allele (APOE2) is protective against AD(Corder et al., 1994; Talbot et al., 1994). Briefly, the product of the APOE gene is the 299 amino acid long apoE protein. The three major isoforms (ε2, ε3, and ε4) differ only in two single nucleotide polymorphisms leading to changes in the encoded amino acids at positions 112 and 158, respectively. The consequence is that at the protein level, the ε4 isoform is more prone than the ε2 or ε3 isoforms to an interaction between the N-terminal and C-terminal domains, resulting in a pronounced conformational change that is presumed to underlie the functional differences(Zhong & Weisgraber, 2009). In mouse models combining APP mutations with either APOE3 or APOE4 mutations, the APOE4 mice showed increased deposition of beta-amyloid plaques(Bales et al., 2009). Subsequent work suggests that the increased beta-amyloid deposition is due to reduced clearance in the APP/APOE4 mice(Castellano et al., 2011). Several monogenic APOE mouse models have been created and show a variety of beta-amyloid independent, but AD-relevant changes including impaired learning and memory, impaired synaptogenesis, and tau hyperphosphorylation(Huang, 2010). Though the predictive power of the APOE4 allele is less than that of a PS1 mutation, it is sufficiently high to merit the consideration of presymptomatic trials in older APOE4 homozygotes(Reiman et al., 2011).

2.2. APOE Effects on the Clinical Course of Healthy Aging, MCI and AD

In addition to increasing the risk of developing AD, APOE4 tends to move the age of onset 5–15 years earlier(Corder et al., 1993; Gomez-Tortosa et al., 2007). In studies with long-lived subjects, the APOE4 effect is detectable in age of onset but is diminished in terms of overall risk, such that beyond age 80 there is little additional risk attributable to APOE4(Blacker et al., 1997; Dickson et al., 2008; Farrer et al., 1997; Khachaturian, Corcoran, Mayer, Zandi, & Breitner, 2004). Whether or not APOE4 speeds the clinical course of AD is less clear. Several studies have suggested that patients with APOE4 have a shorter survival after diagnosis than their APOE3 counterparts(Dal Forno et al., 2002; Tilvis, Strandberg, & Juva, 1998). A number of other studies, however, have failed to replicate this effect(Corder et al., 1995; Slooter et al., 1999; van Duijn et al., 1995). Studies are similarly split as to whether cognitive and behavioral scores decline more quickly in APOE4 carriers. Some studies suggest APOE4 speeds cognitive decline, some studies suggest no effect, and some studies suggest APOE4 slows cognitive decline(Craft et al., 1998; Hirono, Hashimoto, Yasuda, Kazui, & Mori, 2003; Kleiman et al., 2006; Stern et al., 1997). The data are no clearer on the question of whether APOE4 increases the risk or rate of conversion from MCI to AD. The first study to examine this question found that APOE4-carrying MCI patients had a 4-fold increased risk of converting to AD over 5 years compared to non-carriers(Petersen et al., 1995). The following year it was reported that APOE4, in isolation, was not predictive of conversion from MCI to AD but was predictive when used in combination with measures of memory performance(Tierney et al., 1996). Subsequent studies have suggested that, in isolation, APOE4 status is not a reliable predictor of conversion from MCI to AD(Devanand et al., 2005; Landau et al., 2010). Most recently, APOE4 has been shown to be a strong predictor of conversion from MCI to AD (and even from healthy aging to AD) in a large sample of Chinese patients(P. N. Wang, Hong, Lin,

Liu, & Chen, 2011). Regarding cognitive decline in healthy aging, there are, again, studies supporting both possibilities: APOE4 carriers decline more rapidly and APOE4 carriers do not decline more rapidly(Anstey & Christensen, 2000; Beaudreau, Kaci Fairchild, Spira, Lazzeroni, & O'Hara, 2012; Caselli et al., 2009; Jorm et al., 2007; Mayeux, Small, Tang, Tycko, & Stern, 2001; Van Gerven, Van Boxtel, Ausems, Bekers, & Jolles, 2012). Overall, therefore, the literature is decidedly mixed on the issue of APOE4 hastening the progression of disease, whether measured as decline in healthy aging, conversion from MCI to AD, progression of cognitive decline in AD, or survival in AD.

2.3. APOE Effects on AD Biomarkers

Clinical data are noisy, a fact which could account for the lack of consensus on whether APOE4 speeds cognitive and functional decline along the AD spectrum. Endophenotypes or biomarkers are meant to reduce noise in clinical research by providing a biological measure that tracks closely with disease status but is more reliably measured(Meyer-Lindenberg & Weinberger, 2006). In AD research, the field has adopted several imaging and CSF protein biomarkers that can be used alone, or in conjunction with clinical information, to guide research and improve diagnostic accuracy(Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). These biomarkers are also now being routinely used in clinical trials in the hopes that they may provide an early signal predictive of later clinical response(Aisen, 2011; Cummings, 2010).

In the imaging domain most research has focused on three measures: hippocampal volume measured on T1-weighted structural MRI, glucose metabolism measured with fluorodeoxyglucose positron emission tomography (FDG PET), and amyloid plaque burden measured with Pittsburgh compound B (PIB) PET or one of the F-18 amyloid agents such as florbetapir (AV45 PET)(Jack, 2012). Resting-state functional MRI (fMRI) is a fourth candidate biomarker, which is also gaining some traction in the field and has recently been added to the Alzheimer's Disease Neuroimaging Initiative (ADNI, discussed below) (Greicius, Srivastava, Reiss, & Menon, 2004; Jack et al., 2010). CSF biomarkers include levels of beta-amyloid, tau, and phosphorylated tau(p-tau)(Trojanowski et al., 2010). As a general summary across measures, AD patients show reduced hippocampal volumes; reduced glucose metabolism in the posterior cingulate cortex (PCC) and temporoparietal cortex; increased PIB signal (plaque deposition) in the PCC, medial prefrontal cortex, and temporoparietal cortex; reduced functional connectivity between the PCC, temporoparietal cortex, and hippocampus; reduced CSF levels of beta-amyloid; and increased CSF levels of tau and p-tau(Jack, 2012; Trojanowski et al., 2010). Remarkably, most of these biomarkers have shown similar AD-like patterns in MCI patients and even in presymptomatic carriers of genetic mutations causing autosomal dominant AD(Bateman et al., 2012; Damoiseaux, Seeley, et al., 2012; Drago et al., 2011; Sorg et al., 2007).

Following this pattern, one would then expect to see similar AD-like biomarker patterns when studying healthy older APOE4 carriers. As described above with the clinical progression literature, however, the biomarker studies in healthy older APOE4 carriers are also somewhat mixed. Structural MRI studies of healthy older controls are fairly evenly split between those that show an effect of APOE4 on hippocampal volume and those that do

not(den Heijer et al., 2002; Lu et al., 2011; Moffat, Szekely, Zonderman, Kabani, & Resnick, 2000; Reiman et al., 1998; Tohgi et al., 1997; Tupler et al., 2007). Some studies of healthy older controls have shown an effect of APOE4 on hippocampal volume loss over time but no effect on baseline hippocampal volume(Jak, Houston, Nagel, Corey-Bloom, & Bondi, 2007; Moffat et al., 2000). Other studies of older controls have found no effect of APOE4 on hippocampal volume loss over time(Du et al., 2006). In two of the larger studies, Mazoyer and colleagues have found that APOE4 homozygotes have reduced baseline hippocampal volumes and show more volume loss over time whereas APOE4 heterozygotes do not differ from non-carriers in baseline hippocampal volume or volume loss over time(Crivello et al., 2010; Lemaitre et al., 2005).

While we do not intend to do an exhaustive review of the task-based fMRI findings in healthy APOE4 carriers, suffice to say that a similar pattern of mixed results can be found in this domain as well. The first study of task-based activation during memory encoding found that older E4 carriers (aged 47 to 82) showed increased activation in the hippocampus (Bookheimer et al., 2000). A subsequent study of healthy E4 carriers with a mean age of 60 also showed increased hippocampal activation in the E4 carriers (Kukolja, Thiel, Eggermann, Zerres, & Fink, 2010). Two more recent studies, however, reported reduced hippocampal activation in older APOE4 carriers (mean age around 64 in both studies) (Adamson, Hutchinson, Shelton, Wagner, & Taylor, 2011; Filippini et al., 2011). In younger APOE4 carriers, there are fewer studies but the results are more consistent, suggesting that E4 carriers have increased hippocampal activation during memory encoding (Dennis et al., 2010; Filippini et al., 2009).

The resting state fMRI studies related to APOE4 are as mixed as the task-based memory studies. Previous resting state fMRI studies have shown that functional connectivity changes in the default mode network (DMN) in MCI (Sorg et al., 2007) and AD (Greicius et al., 2004; K. Wang et al., 2007; Zhang et al., 2009) and that this default mode functional connectivity deteriorates as the disease progresses (Bai et al., 2011; Damoiseaux, Prater, Miller, & Greicius, 2012). Recent resting state fMRI studies have investigated whether we can detect similar changes in brain functional connectivity in healthy older APOE4 carriers (Machulda et al., 2011; Sheline et al., 2010; Trachtenberg et al., 2012; Westlye et al., 2011). Trachtenberg et al. (2012) found no APOE-related differences in DMN connectivity. The other three studies show significant DMN connectivity differences between APOE4 carriers and APOE3 homozygotes, although there is substantial variability in their results. Sheline et al. (2010) found increases and decreases in DMN connectivity in e4 carriers, Machulda et al. (2011) only found decreases, Westlye et al. (2011) only found increases, and Trachtenberg et al. (2012) found no differences in the DMN but reported differences in two hippocampal networks. None of these fMRI studies of APOE, task-based or resting state, examined whether the observed default mode functional connectivity differences varied by gender.

The imaging literature has numerous examples of healthy older APOE4 carriers with AD-like changes in glucose metabolism(Reiman et al., 1996; Small et al., 2000; Small et al., 1995). An early study by Reiman and colleagues reported that, in the 50–65 age range, APOE4 homozygotes showed reduced glucose metabolism in several regions typically targeted in AD, including the PCC and lateral parietal cortex(Reiman et al., 1996).

Intriguingly, Figure 2 in that study also demonstrates hypometabolism in the APOE4 carriers in many additional regions not typically affected by AD. A subsequent study by the same group reported similar findings for a much younger group of healthy APOE4 heterozygotes(Reiman et al., 2004). Here again, AD-targeted regions showed hypometabolism but many additional regions (gray-green clusters in Figure 1 of that study) also showed reduced metabolism in the APOE4 carriers. These studies suggest a non-specific effect of APOE4, involving regions typically affected by AD as well as regions commonly spared in AD. More recent work, using large sample sizes and subject-specific control databases, has found that glucose metabolism in AD-relevant regions did not differ between healthy older APOE4 carriers and non-carriers(Samuraki et al., 2012). The literature is, thus far, more consistent when it comes to amyloid imaging in older APOE4 carriers. Several studies have reported that healthy older APOE4 carriers are more likely to harbor amyloid plaques on imaging either with PIB or AV45(Aizenstein et al., 2008; Drzezga et al., 2009; Morris et al., 2010; Reiman et al., 2009; Rodrigue et al., 2012).

The CSF protein studies are also fairly consistent when it comes to beta-amyloid levels. Two large studies have both reported reduced beta-amyloid levels in healthy older APOE4 carriers compared to non-carriers(Morris et al., 2010; Shaw et al., 2009). Importantly, neither study found a significant effect of APOE4 on total tau levels in the CSF. In ADNI MCI patients it has been reported that APOE4 carriers have lower beta-amyloid and higher tau levels than non-carriers, though it is not clear that the model used controlled for potential cognitive differences in APOE4 carriers(Shaw et al., 2009). One study, reporting on CSF data in ADNI, found that APOE status had no effect on annual change in beta-amyloid or total tau levels in healthy controls, MCI patients, or AD patients(Vemuri et al., 2010).

In sum, APOE4 has a pronounced and widely-replicated effect on AD risk. Convergent evidence from amyloid imaging and CSF studies suggests that APOE4 drives beta-amyloid plaque deposition. Despite the strength of these findings, the numerous additional predicted effects of APOE4—hastening decline in healthy aging, speeding conversion from MCI to AD, increasing CSF tau levels in healthy controls, reducing glucose metabolism in healthy controls and several others described above—have not been consistently demonstrated. We hypothesize that this marked lack of replicability in many predicted effects of APOE4 is due to the fact that most researchers overlook, or are unaware of, the potent interaction between APOE and gender. Given that the amyloid findings are among the most consistent, it is possible that the APOE4 effect on amyloid processing is equivalent in the two genders but that downstream effects are still more prominent in women.

3.0 APOE and Gender: Historically

The discovery of the interaction between APOE and gender dates to just after the discovery of the effect of APOE on AD. Just one year following the initial studies linking APOE4 to AD risk, it was shown that, for APOE4 heterozygotes, the risk was mainly seen in women(Payami et al., 1994). Initially, this finding was viewed as controversial, with some studies attributing the increased prevalence of APOE4 alleles in AD women to the longer survival of AD women carriers.(Corder et al., 1995) However, the significance of the interaction, even accounting for survival, was replicated in a larger sample size in 1996, and

in 1997 Farrer et al. reported their results from a large meta-analysis of over 5000 patients and 8000 controls(Farrer et al., 1997; Payami et al., 1996). Figure 1, adapted from Farrer et al., makes a compelling case for the interaction between APOE and gender. Two additional studies of AD risk conducted later confirmed the increased AD risk in female compared to male APOE4 carriers. One study used a logistic regression model to show that the significance of a term for an interaction between sex and APOE4 carrier status (sex-by-E4 interaction) was preserved both including and excluding female E4/E4 homozygotes, (Bretsky et al., 1999). The second study found, even more provocatively, that the main effect of sex on AD vanished when accounting for the sex-by-E4 interaction, with the association between female sex and AD applying exclusively to female E4 carriers(Breitner et al., 1999). Moreover, these data suggest that males with one copy of the APOE4 allele have little to no increased risk compared to male APOE3 homozygotes. Even among APOE4 homozygotes, it appears that women are at increased risk compared to men.

Despite being potent and widely-replicated, however, the interaction between APOE and gender is almost never considered either in the clinical or research setting. Below we present the available research on this interaction, organized by modality.

3.1 APOE and Gender: Animal Models and Pathophysiology

The neurobiological relevance of this interaction is supported by the fact that it is also manifested in mouse models of APOE(Raber et al., 1998). The original study of transgenic APOE4 mice demonstrated this interaction, finding that female but not male transgenic APOE4 mice show impairments in memory and learning in special tasks (Raber et al., 1998). In a subsequent study the same group found that the effects of androgen treatment depended on the mice's APOE4 carrier status and gender (Raber et al., 2002). Further studies found that E4 leads to an age related decline in spatial memory tasks in female but not male mice (Bour et al., 2008; Raber et al., 2000; Reverte, Klein, Ratner, Domingo, & Colomina, 2012). Even more recently, a study suggested a neuropathological correlate of these behavioral findings, demonstrating that female but not male E4 mice have decreased presynaptic density in the their hippocampi (Rijpma et al., 2013). As the interaction became widely replicated and recognized within the APOE mouse model research field, some subsequent studies restricted experiments to female mice, conceding that male mice are typically less affected by the APOE genotype (Andrews-Zwilling et al., 2010; van Meer, Acevedo, & Raber, 2007).

3.2 APOE and Gender: Clinical Outcomes in Healthy Aging and MCI

Though more commonly addressed in the APOE mouse model literature, some human APOE studies have pursued the APOE by gender interaction. These studies can be separated, broadly speaking, into two categories by focusing on their patient population of interest, with the first group of studies examining cognitive performance or clinical conversion in healthy aging and the second examining cognitive performance or clinical conversion in MCI. We will consider a selection of these studies below.

Even in healthy aging, it appears that female E4 carriers have worse cognitive performance, especially in memory tasks. One study of 189 Danish subjects ages 50–80, who did not have

dementia, showed that APOE4 was associated with a rapid cognitive decline (performance IQ and verbal IQ) in women after the age of 70, but not in men (Mortensen & Hogh, 2001). Another larger study of episodic memory, including 2181 Norwegian healthy elderly patients aged 70–74, reproduced this finding, evincing that episodic memory was more impaired in heterozygote E4 carrying women than in heterozygote E4 carrying men. Among homozygotes, however, the effect was stronger in men, thus representing one of the few studies showing a worse phenotype in E4 carrying men (Lehmann et al., 2006). Additionally, Reinvang et al. found that the interaction effects not only episodic memory, but working memory as well (Reinvang, Winjevoll, Rootwelt, & Espeseth, 2010). Finally, Swan et al. showed, more generally, that APOE4 is associated with cognitive decline differently in men than in women across a number of tasks. This study measured cognitive performance in men and women with average ages of 79 and 75 respectively at study onset, and again in those same men and women after four years. (Note the older age of these subjects than those in many other studies, and that the men in this study were significantly older than women.) Initially, the expected interaction was demonstrated, with female E4 carriers performing more poorly on short delay cued recall than women without E4. Longitudinally, however, the results were more complex and task dependent, with E4 men demonstrating a greater decline in executive function and verbal memory tasks compared to men without an E4 allele, whereas women with an E4 allele exhibited a greater decline in the Trail Making test compared to women without an E4 allele (Swan, Lessov-Schlaggar, Carmelli, Schellenberg, & La Rue, 2005).

Two recent, prospective studies have examined the interactive effect of APOE and gender on clinical conversion from healthy aging to MCI or AD. Beydoun et al. found a main effect of APOE on conversion from healthy aging to AD (Beydoun et al., 2012). Though the effect was numerically greater in women than men, the formal interaction was not significant. The authors pointed out that they may have been underpowered to detect the interaction. Note that this paper is also informative in that it includes a brief review of the extensive list of studies on APOE and cognitive decline (both with and without an APOE-by-gender interaction term). In a larger prospective study, Altmann et al. found a significant interaction, with female APOE4 carriers more likely to convert from healthy aging to MCI or AD over a mean interval of about 4 years (Altmann, Tian, Henderson, & Greicius, 2013).

In MCI, we were only able to find one study that examined the effect of the APOE by gender interaction on cognition. In a study of 193 subjects with MCI, Fleisher et al. demonstrated that APOE4 genotype status has a greater deleterious effect on memory performance in women than men (Fleisher et al., 2005). In terms of prospective studies of conversion from MCI to AD, we are only aware of one study that explicitly modeled the interaction. In the prospective study by Altmann et al., there was a main effect of APOE4 in increasing the risk of conversion from MCI to AD. The interaction term showed a substantial trend, with a p-value < 0.06 suggesting a greater risk of converting from MCI to AD in female APOE4 carriers (Altmann et al., 2013).

3.3 APOE and Gender: AD pathological and CSF biomarkers

Compared to the ample research on the interaction in animal models and clinical outcomes, the literature on the interaction on AD biomarkers is relatively sparse. With a few prominent exceptions in the AD biomarker domain, the interaction has been overlooked or neglected entirely. Those exceptions are notable, however. In terms of pathological biomarkers, a large autopsy series found that female APOE4 carriers had greater amyloid plaque and neurofibrillary tangle pathology (Corder et al., 2004). A smaller autopsy series evinced a similar but subtler result, showing an interaction between APOE4 and gender on senile plaques in women between the ages 60–79 but not in women older than 80, but an association between APOE4 and increased senile plaques across men of all ages. (Ghebremedhin et al., 2001) Intriguingly, this demonstration that age may modify the interaction of APOE and gender on senile plaque formation echoes a similar modification by age of the APOE by gender interaction on cognitive tasks in Swan et al. 2005, mentioned in section 3.2, suggesting that age may be a modifying factor vis-a-vis the APOE-by-gender interaction generally. In terms of CSF biomarkers, Damoiseaux et al. recently demonstrated that there are higher spinal fluid levels of Tau in female APOE4 carriers, and the difference between female APOEE4 carriers and female APOE3 heterozygotes was significant, whereas the same comparison in men showed no significant differences between male APOE4 carriers and male homozygotes.(Damoiseaux, Seeley, et al., 2012)

3.4 APOE and Gender: Neuroimaging biomarkers

Neuroimaging biomarker research on the interaction is also quite sparse but telling nonetheless. In terms of structural neuroimaging, in MCI subjects, it has been shown that female, but not male, APOE4 heterozygotes have smaller hippocampal volumes when compared to non-carriers(Fleisher et al., 2005). In terms of functional neuroimaging, Damoiseaux et al also recently showed that healthy older female, but not male, APOE4 carriers have reduced functional connectivity in the PCC, a key hub in the brain's default-mode network which is targeted early in the course of AD(Damoiseaux, Seeley, et al., 2012; Greicius et al., 2004) (see figure 2). For the most part, however, this potent interaction between APOE and gender has been overlooked in neuroimaging research, particularly taking into consideration the vast array of studies that have examined the effect of APOE4 on AD biomarkers more generally (as in section 2.3). Clearly, neuroimaging biomarkers have a lot to tell us about the effects of APOE and we hope that this review will encourage imaging researchers to include an APOE by gender interaction term in subsequent analyses.

4.0 Implications and Future Research

In the fourth and final part of this review, we consider the explanations for and implications of this interaction, with a view towards pathophysiology, diagnosis, and treatment.

4.1 Mysterious Mechanism: Sex-hormone mediated?

Despite the importance of the interaction, and its having been replicated time-and-time-again in multiple and sundry contexts, the underlying mechanisms remain a mystery. The most obvious pathophysiology would be, in some way, sex-hormone mediated. There is a

wide literature exploring the relationship between estrogen and cognitive decline (Henderson, 2009). The results, however, are mixed. The Women's Health Initiative Memory famously determined that hormone replacement therapy (HRT), at least when initiated post-menopause, is associated with increased, not decreased, rates of dementia (Coker et al., 2010). However, the study did not explicitly examine the interaction's relationship with hormone replacement therapy, and the studies that have examined that interaction complicate the picture. Yaffe et al. for instance found that estrogen use is associated with less cognitive decline in APOE4 negative healthy older women than in women who are APOE4 carriers (Yaffe, Haan, Byers, Tangen, & Kuller, 2000). Subsequently, Kang et al, in a large and longitudinal study of 16,514 nurses, showed similarly that the fastest rates of cognitive decline were registered by APOE4 carriers who were HRT users (Kang & Grodstein, 2012). These studies together suggest that the jury is still out on the relationship between HRT and cognitive decline, that this relationship may be more subtle than initially suggested, and that the interaction of APOE4 and AD may be crucial to understanding it.

4.2 Implications for diagnosis of APOE4 carriers

The advent of direct-to-consumer (DTC) genetic testing means that more healthy individuals will be "diagnosed" as APOE4 carriers(Messner, 2011). Even outside of research settings, clinical testing for APOE is common enough that guidelines have been developed for genetic counseling(Goldman et al., 2011). Indeed, so serious is the "diagnosis" of APOE4 carrier, or at least its perception, that when James Watson released his sequenced genome, the only part of it he had redacted was his APOE status (Nyholt, Yu, & Visscher, 2008). But what exactly it means, clinically, to be an APOE4 carrier depends, as we have discussed, on a patient's gender. Elucidating the APOE by gender interaction, then, will help mitigate some of the uncertainty related to both clinical and DTC genetic testing.

4.3 Implications for treatment

Regarding treatment, a better understanding of the APOE by gender interaction could have two important kinds of benefits. First, male and female APOE4 carriers could differ in their response to current and future therapeutics, and understanding how they differ could lead to personalized therapeutic regimens. Indeed, at least two studies have already uncovered such a difference: a placebo-controlled, double-blind study of tacrine (an early acetocholinesterase-inhibitor) evinced a different response in APOE4 women as opposed to men, such that tacrine was less effective in APOE4 carrying women than in non APOE4 carrying women, but equally effective in men across genotypes (Farlow et al., 1998). In contrast, a smaller study of tacrine and galantamine (also an acetylcholinesterase-inhibitor) found the opposite, that APOE4 women carriers were more likely to benefit from acetylcholinesterase-inhibitor therapy (MacGowan, Wilcock, & Scott, 1998). Despite these intriguing early finding, most subsequent studies of AD or MCI treatments did not explore the possible effect of the APOE by gender interaction on treatment response(Petersen et al., 2005; Raskind, Peskind, Wessel, & Yuan, 2000) (Rogers, Farlow, Doody, Mohs, & Friedhoff, 1998; Rosler et al., 1999; Wilcock, Lilienfeld, & Gaens, 2000). One subsequent study of donepezil's efficacy in AD did formally explore the interaction and though it did

not reach significance, it reported a p-value of 0.09 (with an N of only 117), although tantalizingly that study did not report in which direction their results were trending (Rigaud et al., 2002). In any case, an understanding of the importance of the interaction vis-à-vis existing therapies could lead to more effective, personalized therapeutic regimens, even involving current medications.

Second, from a basic science perspective, dissecting the mechanisms behind this interaction should provide novel insights into AD pathogenesis and suggest novel approaches to treatment. AD is a progressive, neurodegenerative disorder that gradually, sequentially robs a patient of their memory, language, personality, and mobility, ultimately resulting in death. The course is typically prolonged, lasting on the order of ten years, so that in addition to the patient's suffering, there is a considerable emotional, physical, and financial toll paid by family members. From a societal perspective, AD represents a massive threat to the stability of the health care system. With the aging population, it is estimated that between 11 and 16 million Americans will have AD by mid-century. Direct health-care costs for AD patients in the U.S. were estimated at $210 billion in 2012. This figure does not account for the lost wages of the estimated 15 million family members and friends who provided unpaid care to patients in 2011("2012 Alzheimer's disease facts and figures," 2012). The prevalence estimates assume the continued absence of a preventative or curative intervention for AD. Even without being curative, an intervention that delayed disease onset would result in a substantial reduction of the prevalence of AD and, in turn, a substantial cost-savings for the healthcare system(Sloane et al., 2002). Unfortunately, despite decades of research and development, we have no disease-modifying medications available. Novel insights into AD pathogenesis, of just the kind that a fuller understanding of the interaction between APOE and gender will yield, are desperately needed.

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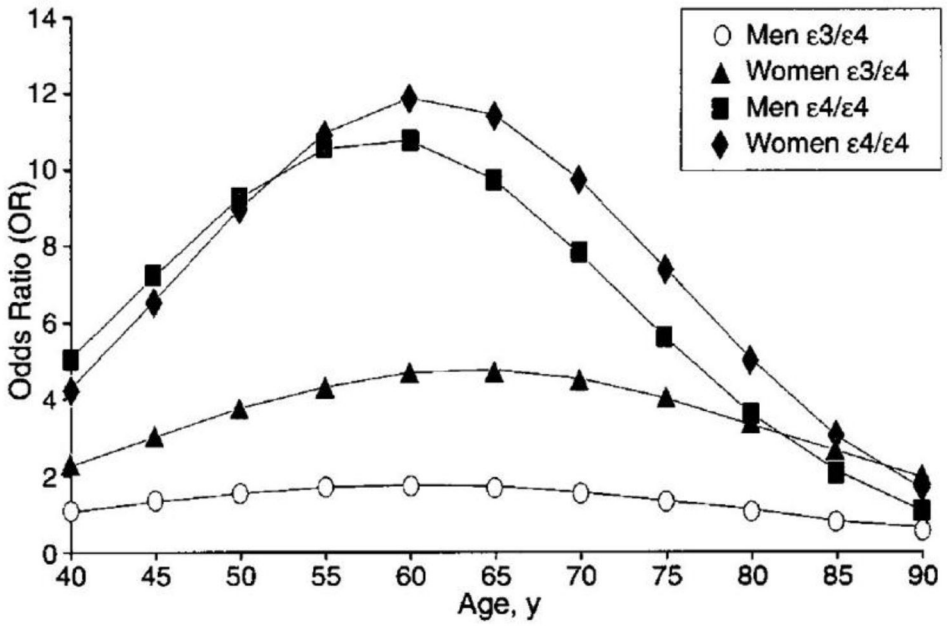

Figure 1. APOE4 risk is greater in women

Compared to background risk in APOE3 homozygotes, female APOE3/4 heterozygotes' odds ratio peaks near 4 whereas the odds ratio in male APOE3/4 heterozygotes barely exceeds 1. The odds ratio for both men and women APOE4 homozygotes peaks near 10 though remains somewhat higher in women. (This is adapted from Figure 2 in the meta-analysis by Farrer and colleagues).

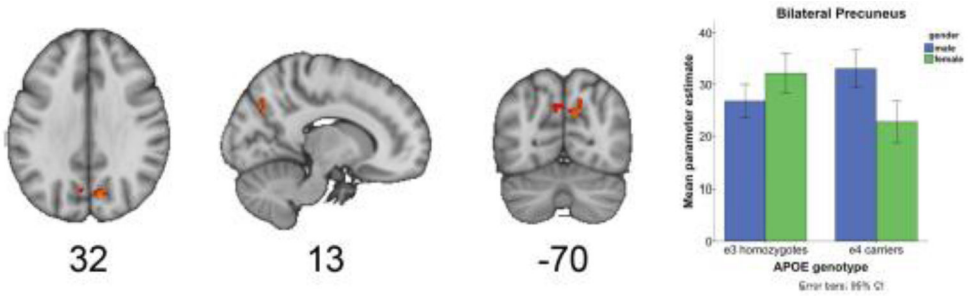

Figure 2.

Gender modulates the APOE effect on default mode network connectivity. An ApoE by gender interaction was found in the precuneus region of the default mode network. The bar graph shows the mean parameter estimates for this cluster, for male and female E3 homozygotes and male and female E4 carriers. The greatest reduction was observed in the female 4 carriers. (This is adapted from Figure 3 of Damoiseaux et al.)