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EFFECT OF APOE ε4 VARIANT ON PROGRESSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER’S DISEASE

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MENTOR: JOHN KRANTZ

Abstract

Alzheimer’s disease is a very prevalent and fatal disorder in older adults, and Mild Cognitive Impairment is often seen as a precursor to Alzheimer’s disease. Alzheimer’s disease is a form of Dementia that is characterized by loss of cognitive abilities while aging. It is ultimately fatal. Mild Cognitive Impairment is more of an intermediate stage between normal mental decline with aging and the more serious decline of dementia. The APOE ε4 gene has been shown to be highly correlated with a greater likelihood of acquiring late-onset Alzheimer’s disease. This study looked to see the effect that the APOE ε4 gene has on the rate of brain volume loss (specifically in the hippocampus, entorhinal cortex, and cerebral cortex) in patients who transition from Mild Cognitive Impairment to Alzheimer’s disease. This was done by comparing people, gathered from the Alzheimer’s Disease Neuroimaging Initiative, with Mild Cognitive Impairment who test positive for the ε4 allele vs. those with Mild Cognitive Impairment who test negative for the ε4 allele, to see which group has a faster loss of brain volume to Alzheimer’s disease. My study found that testing positive for the ε4 allele led to faster neurodegeneration in both people with Mild Cognitive Impairment who converted to Alzheimer’s and even those who did not convert to Alzheimer’s. This study is beneficial because it could provide further insight into the potential genetic cause of Alzheimer’s disease, especially if the study is replicable. It is unique from other studies of this nature because it involves a new cohort.

1 The researcher would like to express the deepest gratitude to the following two people; without their help, this project would not be possible:
First, to Dr. John Krantz, who advised me through this entire process and continues to be a great mentor to this day.
Second, to Dr. Shannon Risacher, who helped teach me about neuroimaging and running statistical procedures to understand brain atrophy.
Introduction

Dementia is an umbrella term used to describe a group of illnesses that occur in the aging process and are associated with the loss of cognitive abilities, including memory. The diseases that fall under the category of dementia are characterized by the fact that the loss of cognitive abilities is such that it interferes significantly with one’s daily life (National Institutes of Health, 2013). Dementia is life-altering and has major effects on the patient’s health, his or her family, and society as a whole.

Dementia was not always the major health problem it is today. In recent times, people are living significantly longer than they ever did in the past (Verbrugge, 1984). A lot of this is because of recent medical advancements and increased knowledge of the benefits of diet and exercise. In the past, people had the genetic code that would make them more prone to acquiring dementia later in life; however, they never acquired the disease because they died at an earlier age, likely from another illness that recent medical advancements have cured. It is important to note this because it means dementia has not been studied as much as some other diseases that have been a problem in the past. As future generations continue to live longer and longer, dementia will similarly continue to increase in prevalence (Ferri et al., 2005). Therefore, it is absolutely vital that researchers look into further understanding these diseases.

Alzheimer’s disease (AD) is one of the many forms of dementia and is characterized by the significant loss of cognitive abilities, primarily memory, that it makes one unable to go about one’s daily life. According to the Alzheimer’s Association (2014), it is estimated that 5.2 million Americans currently have AD. AD has no cure and is 100% fatal. The disease is first characterized by short-term memory loss, but progresses to confusion, language difficulties, long-term memory loss, and even mood swings. It also causes a significant and gradual loss of brain volume (Braak & Braak, 1998). Alzheimer’s disease is truly horrifying for the patient and the family and friends of the patient who must now witness him or her completely regress mentally, forget the past, and basically disappear before their very eyes. An example of AD may be someone who seems to lack continuity of conversation. The patient may forget a story he just told you merely an hour before and proceed to retell the story in its entirety again. This person has experienced such a significant degree of memory loss that they can no longer function properly in society. However, it should be noted that AD does not strike
completely out of the blue; there is thought to be a prodromal stage called Mild Cognitive Impairment (MCI).

Often times, MCI is seen as a precursor or a warning sign that AD is to come (Friedrich, 1999). MCI should best be thought of as an intermediate stage between the normal, slight cognitive declines associated with healthy aging and the drastic cognitive declines of AD (Petersen, 2009). It is the moderate slope of decline that occurs before a sharp drop-off to an AD diagnosis. While MCI is a diagnosis of its own and sometimes shows with no progression to AD, the majority of patients with MCI slowly progress to AD, and for purposes of this study, it is best to think of it as a step on the path to AD. When a patient starts to exhibit symptoms of MCI, usually the patient, close family, and friends will begin to notice a decline in mental abilities, usually memory. An example of someone with MCI may be someone who loses their keys on a more frequent basis, such that it moderately, not significantly like it does in AD, interferes with daily life. This person is still able to function as a part of society. He or she can still get up, get dressed, and go to work like before. However, there is a noticeable impairment. Not everyone with MCI progresses to AD, but it means one’s chances of progressing to Alzheimer’s disease are significantly higher (Boyle, Wilson, Aggarwal, Tang, & Bennett, 2006). This begs the question: how are MCI and AD diagnosed?

These diseases are diagnosed often by neuropsychological tests, which are tests of cognitive abilities and basic motor skills (Khachaturian, 1985). These include things like basic memory tasks and walking tests, for example. Clinical neuropsychologists look for declines in scores from one time to another. Participants may come in with different baseline scores, as a result of having a more intellectual background, for example, and this is why future tests are needed to see if the scores decline. However, most people do not just have neuropsychological tests on file. That is why input from family members or close friends is often used to first see if a neuropsychological test should be administered. For example, a close friend may notice that the patient has been forgetting their car keys more frequently than usual and may refer him or her to a Clinical neuropsychologist for a test. More recently, brain imaging is starting to be used as a means of diagnosis (Chetelat & Baron, 2003). Scans from two different times are beneficial to see if neurodegeneration, or loss of brain volume, is taking place. The regions primarily affected, and the regions I will be focusing on in this study, are the hippocampus and entorhinal cortex (due to their roles in memory) and the cerebral cortex (due to its density of grey matter, which is where the neurons are) (Du et al.,
Based on previous research, there appears to be a gene that may explain why greater neurodegeneration, and risk of AD, happens in some people than others.

ApoE is short for Apolipoprotein E. An apolipoprotein is a protein that binds lipids to form lipoproteins. It has a role in the central nervous system (the brain and spinal cord) to transport cholesterol to neurons via ApoE receptors (Yao, 2002). The gene that codes for ApoE is APOE and is mapped on chromosome 19 (Olaisen, Teisberg, & Gedde-Dahl, 1982). It has three major alleles, which is just an alternate form of the same gene (Corbo, Scacchi, 1994). A specific allele (ε4) of this gene (APOE) has been found to be strongly correlated with AD. If one has this specific allele (14% do), one’s chances of eventually being diagnosed with AD are much higher than if one is without this specific allele of the APOE gene (Corder et al., 1993). Of course, there are other factors that contribute to progression to AD: fitness, education level, degree of sustained-thinking throughout one’s life, and even personality traits (The Search, 2014). All of these traits can improve one’s chances of not acquiring AD or at least delay the onset of AD. However, that is solely focusing on the nurture side of things. My study, on the other hand, will be focusing solely on the potential genetic effect of a specific gene (APOE). There has been research already conducted on the effect of having the APOE ε4 allele on likelihood of acquiring AD, but the effect of having an APOE ε4 allele on neurodegeneration and conversion from MCI to AD as compared to people without an APOE ε4 allele (they have combinations of the two other variants (ε2 or ε3)) is significantly less-studied.

The following research questions are then posed: (1) Does being APOE ε4 positive lead to greater change in brain volume in people with MCI who either did or did not convert to AD as compared to those who are APOE ε4 negative? Prior research from Dr. Risacher of the Department of Radiology and Imaging Sciences at the Indiana University School of Medicine and other researchers would suggest that this is likely (Risacher 2009, Risacher 2010). Therefore, our hypothesis follows that APOE ε4 positive MCI patients will exhibit faster change in brain volume than the APOE ε4 negative patients regardless of conversion status and that APOE ε4 group status will be significantly correlated with conversion status, potentially in addition to (and independent from) the effect ongoing neurodegeneration of crucial brain regions.
Methods

PARTICIPANTS
This is an archival study. The participants come from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California-San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. Further information can be found at http://www.adni-info.org/ and http://adni.loni.usc.edu.

Data about longitudinal clinical diagnosis (cognitively normal, MCI, or AD) and conversion, APOE genotype data, and structural MRI scans were downloaded from the ADNI data repository (http://adni.loni.usc.edu). The database has longitudinal brain scans, so we compare one person’s brain scans over time and watch how they worsen as the person progresses from MCI to AD. There were 454 original patients with MCI who converted to AD at some point over a two-year span. 234 of them were APOE ε4 positive, and the other 220 participants were either APOE ε4 negative. Subjects ranged between 47 and 91 years of age, with the average age being 73.3 years old.
PROCEDURE

Brain scans are gathered by using MRI machines. These work by the fact that atoms are spinning in random motion in their own magnetic fields (Berger, 2002). When a magnetic field is applied, most atoms either point north or south, but some do no line up either way. When a radio frequency pulse is applied, these atoms that are not lined up either way, spin the opposite direction. When that radio frequency is turned off, the atoms that are not lined up return to their original position. This emits energy, which is sent to a computer, and that computer converts the signal into an image (i.e. a brain scan). These brain scans are completed on all participants and archived for analysis in ADNI.

After obtaining the brain scans of people from the ADNI, the brains of patients with the APOE ε4 allele will be compared against patients without the APOE ε4 allele to see if the APOE ε4 allele leads to greater neurodegeneration in MCI patients, and increased rate of conversion from MCI to late-onset AD.

MEASURES

Freesurfer (version 5.1) is a software program that takes the brain image and divides it up into the anatomical sub-regions. For regions like the hippocampus, the program essentially traces a 3D line around where it thinks this structure is based on previous knowledge of structure location and landmarks identified in the image. Then it gives you the total volume of the structure. For the cortical surface, it estimates the thickness of the grey matter across the entire cortex. Then it slices the brain up into different anatomical cortical regions and reports the average thickness of the cortex across that part of the grey matter. Figure 1 shows a pictorial representation of Freesurfer (Desikan et al., 2006; Freesurfer (n.d.)).

STATISTICS

Three separate ANCOVA models were used to compare differences in annualized percent change (APC) in three brain areas (hippocampal volume, entorhinal cortex thickness, and cerebral cortex volume) as a function of APOE ε4 carrier status (positive or negative) and two-year conversion status (convert to AD or stable at MCI), covaried for age, gender, education, and handedness between groups. A logistic regression model was used to assess
the effect of APOE ε4 carrier status on likelihood of conversion from MCI to AD over two years, covaried for age, education, gender, MCI type (early or late), and handedness. A second logistic regression model was estimated to determine the independent effects of hippocampal atrophy rate and APOE ε4 carrier status on clinical conversion from MCI to AD over and above age, gender, MCI type (early or late), education, and handedness. This second logistic regression model was run again for both entorhinal cortex thickness atrophy rate and cerebral cortex atrophy rate.

**Figure 1.** This image demonstrates how Freesurfer represents different brain regions.
Results

The overall model evaluating the effect of conversion and APOE ε4 carrier status on Annual Percent Change (APC) in hippocampal volume that included conversion status, APOE ε4 carrier status, and the interaction between conversion and APOE ε4 group, as well as age, handedness, education, and gender was significant ($F (7, 447) = 9.636, p < 0.001$). Specifically, significant independent main effects of both conversion status ($p = 0.003$) and APOE ε4 group ($p = 0.002$) were observed, but the interaction of APOE ε4 group status by conversion status was non-significant ($p>0.05$). A similar effect was seen on APC in entorhinal cortex thickness, with the overall model significant ($F(7, 447)=14.428, p<0.001$), and significant main effects of conversion status ($p=0.001$) and APOE ε4 group ($p=0.002$), but no interaction ($p>0.05$). Finally, the same pattern was observed when evaluating APC in cerebral cortex volume. The overall model was significant ($F(7, 447) = 9.478, p < 0.001$), with significant main effects of both conversion
status ($p = 0.007$) and APOE $\varepsilon 4$ group ($p = 0.008$), but no interaction ($p > 0.05$).

To see if APOE $\varepsilon 4$ carrier status was associated with conversion status independent of the APC in hippocampal volume, a logistic regression, covaried for education, handedness, baseline diagnostic group, age, and gender, was run. APOE $\varepsilon 4$ carrier group status was significantly associated with conversion status independent of the APC in hippocampal volume ($p = 0.007$, odds ratio (OR) = 1.926). The APC in hippocampal volume was also significantly associated with conversion status independent of the APOE $\varepsilon 4$ carrier status ($p < 0.001$, OR = 0.844). Similar analyses were run for the impact of APOE $\varepsilon 4$ carrier status and APC in entorhinal cortex and cerebral cortex volume. APOE $\varepsilon 4$ carrier status was significantly correlated with conversion status independent of the APC of entorhinal cortex thickness ($p = 0.028$, OR = 1.730). The APC in entorhinal cortex thickness was also significantly correlated with conversion status independent of the APOE $\varepsilon 4$ carrier status ($p < 0.001$, OR = 0.795). Finally, APOE $\varepsilon 4$ carrier status was significantly associated with conversion status independent of APC in

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{The effect of APOE $\varepsilon 4$ carrier status and Conversion on the Mean Thickness (in mm) Atrophy Rate of the Entorhinal Cortex.}
\end{figure}
The APC in cerebral cortex volume was also significantly correlated with conversion status independent of the APOE ε4 group status ($p < 0.001$, OR = 0.767).

Figure 2 shows that APOE ε4 positive participants have a greater loss of hippocampal volume than APOE ε4 negative participants, whether or not one converted to AD from MCI or not. In both conversion conditions (yes and no) the APOE ε4 positive patients had significantly more loss of hippocampal volume than the APOE ε4 negative patients. There was even a trend for slightly more loss of hippocampal volume in the APOE ε4 group positive patients who did not convert to AD than those who converted to AD but were not APOE ε4 carriers.

Figure 3 shows APOE ε4 positive participant have a more significant loss of entorhinal cortex thickness than those negative for an APOE ε4 allele in either of the conversion conditions. These results are even more pronounced than the ones seen for the hippocampus, with the differences between the APOE ε4 conditions being even larger. Again, the patients who
tested positive for the APOE ε4 group allele, and who did not convert to AD, still had a trend for slightly greater entorhinal cortex thickness atrophy rate than those who actually did convert to AD but who were APOE ε4 negative.

**Figure 4** shows again APOE ε4 positive participants show more significant loss of cerebral cortex volume than those APOE ε4 negative participants. Again, the APOE ε4 positive patients who did not convert to AD had a trend for slightly more loss of cerebral cortex volume than the APOE ε4 negative patients who did actually convert to AD.

**Discussion & Conclusion**

My hypothesis that APOE ε4 positive MCI patients would exhibit greater atrophy in brain volume (hippocampus, cerebral cortex, and entorhinal cortex) regardless of conversion status was confirmed. There is greater neurodegeneration in both APOE ε4 positive patients who acquire AD and APOE ε4 positive patients who do not acquire AD than APOE ε4 negative patients in either group. Further, my hypothesis that APOE ε4 status was significantly associated with conversion status independent of neurodegeneration of brain regions was also confirmed. In fact, carrying an APOE ε4 allele made you approximately two or more times more likely to convert to AD, independent of the significant effect of increased atrophy rate on conversion (more atrophy = greater rate of conversion). Overall, these findings are a prime example of the importance and, in this case, sad role that genetics plays in our health.

However, even though I have shown that carrying the APOE ε4 allele does lead to greater neurodegeneration, the results do not tell us about the effects of non-genetic factors such as physical and mental exercise. Physical Exercise has already been shown to reduce one’s likelihood of acquiring MCI (Geda et al., 2010). Mental Exercise has also been shown to improve the episodic memory of MCI subjects (Belleville, Gilbert, Fontaine, Gagnon, Ménard, & Gauthier, 2006). However, there have not been many studies done on the potential varying levels of effects of physical and mental exercise on people who test positive for the APOE ε4 allele versus those who test negative for it. Future studies could look to see if there is a greater decrease in brain atrophy with the physical and mental exercise intervention in those without the APOE ε4 allele versus those who test positive for it.

This study was potentially limited by the fact that all the data came from people in the United States and Canada. A hot-button issue in modern
psychology is the fact that a lot of our data comes from WEIRD (Western, Educated people from Industrialized, Rich, and Democratic countries) populations. Whereas, a huge chunk of the world’s population is not “WEIRD” (Henrich, Heine, & Norenzayan, 2010). Different cultures would likely vary with regard to non-genetic factors like levels of exercise, education, and general lifestyle. Due to the expensive nature of MRI machines, it makes sense that most people who have been tested come from wealthy countries. It would be interesting to see how these studies differ in potentially different populations.

These results also beg the question of whether or not MCI should be its own diagnosis or seen only as a precursor to AD. Prior literature lists MCI as both a syndrome, in and of itself, and also as a risk state for dementia (Gauthier et al., 2006). I believe that these results are supportive of prior literature in the sense that MCI can be both its own stand-alone diagnosis and a risk state for dementia. Also, the fact that researchers are attempting to keep people at MCI and not allow it to progress to AD only reinforces the fact that people can stay at MCI. These diseases are certainly interconnected, but one should remain hesitant to claim that MCI is definitely going to result in AD until further research is done.

In sum, APOE ε4 positive MCI patients showed greater rates of neurodegeneration regardless of conversion status. Further, APOE ε4 positive MCI participants showed an approximately two-fold increased risk of conversion to AD over two years, independent from the effect of atrophy rate on conversion.

Works Cited


