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Apolipoprotein E ε4 influences on episodic recall and brain structures in aging pilots

Maheen M. Adamson[a,b,*], **Kelly M. Landy**[b], **Susan Duong**[c,d], **Sabrina Fox-Bosetti**[c,d], **J. Wesson Ashford**[a,b], **Greer M. Murphy**[b], **Michael Weiner**[c,d], and **Joy L. Taylor**[a,b]

[a] Department of Veterans Affairs and Sierra-Pacific MIRECC, Palo Alto, CA, United States

[b] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

[c] Department of Veterans Affairs, San Francisco, CA, United States

[d] University of California, San Francisco, CA, United States

Abstract

The apolipoprotein (APOE) ε4 allele is associated with cognitive deficits and hippocampal atrophy in nondemented middle-aged and older adults. It is not known to what extent this genetic risk factor for Alzheimer's disease (AD) impacts performance in late middle-aged and older workers in cognitively demanding occupations. This cross-sectional analysis examines brain–cognitive–genetic relationships in actively flying general aviation pilots, half of whom are APOE ε4 carriers. Fifty pilots were studied with structural MRI and memory tasks. Average visual paired associate memory recall performance was lower in APOE ε4 carriers than non-carriers. Memory performance correlated positively with hippocampal volume, but no structural differences were found in hippocampal or frontal volumes with respect to APOE ε4 allele. These results were evident in healthy professionals without any presenting memory problems and without selection for a family history of AD. These findings point to basic memory testing as a sensitive tool for detecting APOE ε4 -related influences on memory in aging workers.

Keywords

Episodic memory; Hippocampus; Frontal lobe; APOE ε4; Cognitive aging; Volumetric MRI; Dementia; Alzheimer's disease

1. Introduction

The apolipoprotein (APOE) ε4 allele is a major genetic risk factor for Alzheimer's disease (AD; Corder et al., 1993), accelerating the age of symptom onset (Khachaturian et al., 2004). The APOE ε4 allele has frequently been examined as a correlate or predictor of cognitive impairment in nondemented populations to facilitate early detection of AD. However, the results reported in these studies are not only inconsistent (Small et al., 2004), little is known about the impact of APOE ε4 on middle-aged and older workers in cognitively demanding occupations. For instance, recent cross-sectional studies report lower

* Corresponding author at: Stanford/VA Aging Clinical Research Center, 3801 Miranda Avenue (151Y), Palo Alto, CA 94304, United States. Tel.: +1 650 493 5000x62179; fax: +1 650 852 3297. E-mail address: madamson@stanford.edu (M.M. Adamson).

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performance during memory tasks in APOE ε4 carriers compared to non-carriers (mean age < 70 years) (Caselli et al., 2001; Chey et al., 2000; Flory et al., 2000; Levy et al., 2004; Lind et al., 2006), but several other studies do not (Jorm et al., 2007; Moffat et al., 2000; Nilsson et al., 2006; Romero et al., 2002; Sager et al., 2005). The impact of APOE ε4 on memory has been more consistent in longitudinal studies (Anstey and Christensen, 2000; Blair et al., 2005; Caselli et al., 2004; Kozauer et al., 2008; Reynolds et al., 2006; Tupler et al., 2006). A few cross-sectional MRI studies report smaller hippocampal volumes in APOE ε4 carriers than in non-carriers (mean age < 70 years) (den Heijer et al., 2002; Lind et al., 2006; Plassman et al., 1997; Tohgi et al., 1997) but many do not (Cohen et al., 2001; Lemaitre et al., 2005; Moffat et al., 2000; Reiman et al., 1998; Schmidt et al., 1996; Tupler et al., 2006). As in the case of memory performance, the impact of APOE ε4 on hippocampal volume in cognitively normal adults appears larger and more consistent in longitudinal studies (Cohen et al., 2001; Moffat et al., 2000).

Studies using the frontal lobe as an anatomical measure usually report its reduction with age (Raz et al., 2005) and/or its association with working memory/attention-demanding tasks (Gunning-Dixon and Raz, 2003). The ability to fly an airplane provides an ideal platform to study aging workers (Taylor et al., 2007), especially those at risk for AD, as this skill involves working memory and attentional networks (Taylor et al., 2005). Below, we report the baseline results from an ongoing longitudinal MRI study where actively flying, FAA medically certified pilots aged 50–76 years undergo structural MRIs and neuropsychological testing every 2 years.

2. Methods

2.1. Participants

A total of 50 general aviation pilots were selectively recruited (50% APOE ε3/4 or 4/4 and 50% ε3/3) from the ongoing longitudinal Stanford/VA aviation study (see Table 1 for participant characteristics and brief description of measures). Written informed consents were obtained from all participants.

2.2. MR Image acquisition and analysis

MRI data were acquired with a 1.5-T (GE Medical Systems, Milwaukee, WI) scanner using the following sequences: (a) a T2-weighted spin-echo MRI, TR/TE1/TE2 = 5000/30/80 ms, 51 oblique axial 3 mm slices angulated parallel to the long axis of the hippocampus (1.00 mm × 1.00 mm in plane resolution); b) 3D spoiled GRASS MRI of entire brain, TR/TE=9/2 ms, 15° flip angle, perpendicular to the long axis of the hippocampi (1.00 mm × 1.00 mm in plane resolution, 1.5 mm coronal slices, no skip).

3. Results

3.1. Effects of APOE ε4 and age on episodic memory

There were no significant differences between ε4 carriers and non-carriers with regards to age and education, p's > 0.15. The visual paired associate (VPA) average recall score was significantly lower for APOE ε4 carriers (mean % correct = 70 ± 19.33) than non-carriers (mean % correct = 84.5 ± 16.47); $F(1,49) = 8.80$ $p < 0.01$, effect size (ES) = −0.42. No main effect of age or Age × APOE interaction was observed (F's < 1). The effect size decreased slightly from −0.42 to −0.37 when the two homozygous APOE ε4 carriers were removed and from −0.42 to −0.34 when women were removed. The APOE ε4 effect however remained significant ($F(1,41) = 4.76$, $p < 0.05$). In addition, VPA coding throughput (number of correct responses per minute) was lower among APOE ε4 carriers compared to non-carriers ($p = 0.047$, ES = −0.29) and showed a strong decline with age ($p < 0.001$, ES =

−0.55) with no Age × APOE ε4 interaction. No effect of APOE ε4, age or interaction was seen on the Rey auditory verbal learning test (AVLT) composite *z*-score.

3.2. Effects of APOE ε4 and age on hippocampal and frontal lobe volume

As shown in Table 1, there were no significant differences between *APOE* ε4 groups in normalized hippocampal ($F(1,46) = 0.28$, $p > 0.1$) or frontal lobe volume ($F < 1$). There was no significant main effect of age on hippocampal volume ($F(1,46) = 2.47$, $p > 0.10$). There was a main effect of age on frontal lobe ($F(1,44) = 8.44$, $p < 0.01$). Age × APOE interactions were not significant. We note that hippocampal volume correlated with VPA average recall ($r = 0.45$) and Rey AVLT composite ($r = 0.47$) scores.

4. Discussion

APOE ε4 carriers had lower memory performance, as measured by a VPA task assessing both immediate and delayed recall. This APOE ε4-related difference remained significant after potential sampling biases (gender imbalance) and APOE ε4 homozygosity were addressed. VPA recall, which is seldom assessed after symbol-digit coding in neuropsychological testing, proved to be more useful than the Rey AVLT in detecting an APOE ε4 influence on episodic memory in this sample. VPA coding throughput was lower in ε4 carriers than non-carriers on average. VPA coding throughput is similar to the number completed score of the symbol-digit modalities test (SDMT), a paper-and-pencil analogue of VPA coding portion of the task. SDMT was recently shown to be one of the best predictors, along with 10-item delayed word recall, for progression from amnestic MCI to AD (Fleisher et al., 2007). Thus, symbol-digit coding tests including a recall component appear to be a promising means of rapidly assessing persons at increased risk for AD.

Analogous to Schmidt et al. (1996) we did not observe hippocampal volume differences between APOE ε4 carriers and non-carriers in our cross-sectional study, despite an APOE ε4 effect on memory recall. Normal older adults clearly have larger hippocampi on average than age-matched AD individuals (Kramer et al., 2005), but the structural changes within the hippocampi are not well understood in nondemented APOE ε4 carriers. As addressed in the introduction, only 4/10 cross-sectional studies reported a significant decrease in hippocampal volume in APOE ε4 carriers compared to non-carriers. In contrast, two longitudinal studies to date reported APOE ε4-related hippocampal atrophy (Cohen et al., 2001; Moffat et al., 2000).

Our cohort selection criteria targets healthy middle-aged and older individuals and is less likely to include memory impaired individuals usually found in cohorts of participants older than 75. Our cohort has an average education level of 17 years, and more years of education may reduce the degree of APOE ε4-related memory decline (Mayeux et al., 2001). Additionally, unlike studies where recruitment is based on a family history of AD (Caselli et al., 2004; Sager et al., 2005; Tupler et al., 2006) none of our participants were recruited on this basis. Finally, as our participants are actively flying pilots, they employ visuo-spatial attention and navigation techniques in familiar and unfamiliar environments. Several human studies show that frontal and medial temporal lobe are involved in spatial attention and navigation (Maguire et al., 2006). Interestingly, an APOE ε4-related difference was observed in a visuo-spatial processing test which requires scanning, sequencing and learning strategies—cognitive skills pilots routinely use in flying. Our results suggest that healthy and actively flying middle-aged to older pilots who are genetically at risk for AD may be vulnerable to an earlier decline in episodic recall of items requiring visuo-spatial attention during learning. These changes are not yet evident in the hippocampus or frontal lobes (as quantified by MRI). Future studies combining genetic information, innovative memory

testing, and various imaging techniques are more likely to capture alterations in cognitive performance of at-risk professional individuals.

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Table 1

Characteristics (mean ±S.D.) of the 50 participants

	APOE $\varepsilon 4$[a] carriers $n = 24$	APOE $\varepsilon 4$ non-carriers $n = 26$
Age, year, mean ± S.D.	60.50 ± 6.8 (age range = 50–76)	61.39 ± 6.7 (age range = 51–74)
Education, year, mean ± S.D.	17.7 ± 2.8	17.0 ± 1.9
Number White, non-Hispanic	23	23
Number men	22	19
Number statin use ever	5	4
Number hypertension medication use ever	5	8
Number family history of dementia (yes/no/not sure)	8/15/1	4/19/3
Number FAA proficiency rating (VFR/IFR/CFII-ATP)[b]	7/10/7	6/13/7
Number FAA medical class I, II or III[c]	1/7/16	2/7/17
Total flight time, h, median ± S.D.	1656 ± 1199	2567 ± 2328
VPA[d] average recall (% correct)[e]**	70 ± 19.33	84.5 ± 16.47
VPA coding throughput[f]*	25.61 ± 5.19	28.7 ± 8.45
VPA coding accuracy rate[g]	99.23 ± 1.72	98.65 ± 1.54
Rey AVLT[h] composite[i] z-score	−0.17 ± 0.93	0.16 ± 0.94
Total hippocampal/TIV volume[j]	0.00373 ± 0.00038	0.00376 ± 0.00034
Total frontal lobe/TIV volume[k]	0.344 ± 0.014	0.344 ± 0.017

* $p < 0.05$;

** $p < 0.01$.

[a] APOE genotyping is based on genomic DNA extracted from frozen blood/buccal mucosa/saliva samples based on Murphy et al. (1997). All participants agreed to have the results of APOE genotyping withheld from them.

[b] VFR: visual flight rules are a set of aviation regulations under which a pilot can operate the aircraft by visual reference to the environment outside the cockpit. IFR: instrument flight rules allow a pilot to fly in poorer visibility conditions using navigational instruments. CFII: certified flight instructor of pilots in training for IFR. ATP: certified to fly air-transport planes. The basic rating is VFR and the most advanced is ATP (see Taylor et al., 2007 for more detail).

[c] Pilots are required to pass periodic medical examinations in order to fly. Class I is the most stringent and Class III is the least.

[d] Visual paired associate (VPA) recall was assessed with the symbol digit coding (SDC) test available in CogScreen–AE (Kay, 1995), a computerized aviator assessment battery administered as part of the Stanford/VA aviation study's annual testing.

[e] VPA average recall is the average of the immediate and delayed recall scores from the SDC task in Cogscreen AE.

[f] VPA coding throughput is the number of correct responses per minute derived from the number of correct responses made during the 90-s trial of SDC.

[g] VPA coding accuracy is the % of correct responses during the 90-s trial of SDC.

[h] Verbal episodic memory was assessed with the Rey AVLT.

[i] Composite score is the average of immediate and delayed z-scores.

[j] Hippocampal volume for $n = 47$ participants; semi-automated volumetry (Hsu et al., 2002). No APOE $\varepsilon 4$-related differences in left and right hippocampal volumes were found.

[k] Frontal lobe volume for $n = 45$ participants; tissue segmentation and semi-automated lobar voluming method based on Van Leemput et al. (1999).