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Influences of APOE ϵ 4 and Expertise on Performance of Older Pilots

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Abstract

Little is known about how APOE ϵ 4-related differences in cognitive performance translate to real-life performance, where training and experience may help to sustain performance. We investigated the influences of APOE ϵ 4 status, expertise (FAA pilot proficiency ratings), and their interaction on longitudinal flight simulator performance. Over a 2-year period, 139 pilots aged 42–69 years were tested annually. APOE ϵ 4 carriers had lower memory performance than noncarriers ($p = .019$). APOE interacted with Expertise ($p = .036$), such that the beneficial influence of expertise ($p = .013$) on longitudinal flight simulator performance was more pronounced for ϵ 4 carriers. Results suggest that relevant training and activity may help sustain middle-aged and older adults' real-world performance, especially among APOE ϵ 4 carriers.

Keywords

cognitive aging; Apolipoprotein E; gene-environment interaction; dementia; Alzheimer's disease

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APOE ϵ 4-related differences in cognitive performance are detectable before age 65 (Adamson et al., 2010; Blair et al., 2005; Caselli et al., 2009; Kozauer et al., 2008). Little is known about how such differences translate to real-life measures of performance, where training and experience may help to sustain performance in a given skill domain despite advancing age or APOE ϵ 4 status. Education, good health, and specific types of training or expert knowledge may moderate APOE ϵ 4-related risk for cognitive decline. For example, APOE ϵ 4-related decline in cognitive performance has been found to be reduced as a function of additional years of education (Mayeux, Small, Tang, Tycko, & Stern, 2001) and better physical health, in particular, an absence of significant cardiovascular disease or diabetes (Bunce, 2006; Haan et al., 1999). In this paper, we examine the interplay between expertise and APOE ϵ 4 status as they relate to performance of a skilled real-world task.

Pilots over the age of 40 who differed in their level of aviation expertise—as indexed by previously acquired FAA pilot proficiency ratings—were tested annually using a flight simulator over a two-year period. The flight simulator assessment involves executing air-traffic controller communications, avoiding traffic conflicts, scanning cockpit instruments and executing an approach to landing. It is sensitive to pilot differences in aviation expertise, age, and cognitive ability (Taylor, Kennedy, Noda, & Yesavage, 2007; Taylor et al., 2005; Taylor, O'Hara, Mumenthaler, & Yesavage, 2000; Yesavage et al., 1999). We hypothesized that APOE ϵ 4 status would interact with expertise, such that any negative impact of APOE ϵ 4 on longitudinal simulator performance would decrease as level of expertise increased. A computerized symbol-digit coding task served to characterize participants' cognitive processing speed and memory.

Method

Participants

Selection criteria—Participants were 139 pilots who completed three annual visits as part of the ongoing longitudinal Stanford/VA Aviation Study. Enrollment criteria were age between 40 and 69 years, current FAA medical certificate, 300 to 15,000 hours of total flight time, and currently flying. At entry, each participant was classified into one of three ordinal levels of expertise based on previously attained FAA proficiency ratings: (1) least expertise: VFR (rated for flying under visual flight rules only); (2) moderate expertise: IFR (also rated for flying under instrument flight rules); and (3) most expertise: CFII or ATP (certified flight instructor of IFR students or rated for flying air-transport planes). VFR pilots fly recreationally. In contrast, approximately one half of the CFII/ATP participants in this study were employed as air transport pilots, flight instructors, or their job duties included aircraft piloting. (See Taylor et al. 2007, for additional details.) Each proficiency rating requires progressively more advanced training (as well as a minimum amount of flight hours). Therefore, we feel that pilot proficiency ratings are a more direct indicator of 'deliberate practice' to improve skills (Ericsson & Lehmann, 1996) than total flight hours.

Retention and temporal spacing—The 139 longitudinally followed participants were part of an original pool of 205 participants that completed a baseline visit by April 2005; 171/205 provided a DNA sample (83%); 167 had a known APOE genotype; 139/167 (83%) completed 3 annual follow-up assessments. The average span of follow-up in years was 2.1 years ($SD = 0.3$, range = 1.8 to 3.3). The desired time window for annual assessments was ± 1 month from the anniversary month of the baseline visit. The desired 11- to 13-month temporal spacing was achieved for 101/139 participants (73%). Thus, 101 participants had the desired time span of 22 to 26 months between the baseline and third assessment. Twenty-nine participants had spans of 27 to 30 months, and the remaining 9 had spans of 31 to 39 months. Differences among participants in span of follow-up were not related to

APOE, expertise, or the APOE $\times$ Expertise interaction, F 's < 1 . There were no differences in longitudinal flight simulator performance between the 139 participants with APOE genotypes and those who were not genotyped, $t < 1$.

Demographic characteristics—Of the 139 longitudinal participants, 39 (28%) were APOE $\epsilon 4$ carriers and 100 were noncarriers. The distribution of specific genotypes was: $\epsilon 2/2 = 3$ (2.2%); $\epsilon 2/3 = 26$ (18.7%); $\epsilon 3/3 = 71$ (51.1%); $\epsilon 2/4 = 1$ (0.7%); $\epsilon 3/4 = 34$ (24.5%); and $\epsilon 4/4 = 4$ (2.9%). This distribution is comparable to those reported in population-based studies of middle-aged and young-old adults (Blair et al., 2005; Pendleton et al., 2002), and older nondemented Caucasian populations (Farrer et al., 1997). As can be seen in Table 1, APOE $\epsilon 4$ carriers and noncarriers were demographically similar, p 's $> .10$. Both groups are well educated and healthy.

In terms of flight experience, participants with more advanced proficiency ratings had more total hours of flight time ($p < .0001$), and more flying hours in the month prior to the baseline visit ($p = .004$) than pilot participants with less advanced ratings (Table 2). Older age was associated with more total flight time ($p = .0001$). This is typical for aviation. There were no significant main effects of APOE or APOE $\times$ Expertise interactions on total or recent flight time (p 's $> .15$). During the two-year period of annual testing, differences in hours of flight experience reported at baseline by VFR, IFR and CFII/ATP pilots progressively widened ($p < .0001$). VFR pilots accumulated an average of 59.6 ± 53.0 hours per year, IFR pilots an average of 86.9 ± 67.7 hours per year, and CFII/ATP pilots an average of 212.9 ± 188.3 hours. The gain in flight hours that varied by level of expertise was evident in both APOE groups. Interestingly, there was nonsignificant trend for an APOE $\times$ Expertise interaction ($p = .051$). As can be seen in Table 2, at the basic VFR level, APOE $\epsilon 4$ pilots accumulated 77 hours per year on average, whereas noncarriers accumulated 49 hours per year. At the highest level (CFII/ATP), APOE $\epsilon 4$ pilots accumulated 124 hours per year on average; noncarriers accumulated 260 hours per year. The role of accumulated flight hours in relation to longitudinal flight simulator performance was addressed in supplementary analyses (reported in Results).

Equipment

Pilots “flew” a Frasca 141 flight simulator (Urbana, IL). The simulator was linked to a computer specialized for graphics (Silicon Graphics, Mountain View, CA) that generated a “through-the-window” visual environment and continuously collected data concerning the aircraft’s position and communication frequencies. This system simulated flying a small single-engine aircraft above flat terrain with surrounding mountains and clear skies. A cockpit speaker system was used to present pre-recorded messages that simulated air-traffic control (ATC).

Procedure

Prior to annual testing, participants had six practice flights to gain familiarity with the flight scenario used throughout the study. Participants typically completed their practice flights during a 1- to 3-week period, after which they had a 3-week break before returning for the first annual visit. At each of the 3 annual 6-hour-long study visits, participants flew a morning and an afternoon flight. During each 75-minute flight, pilots heard 16 ATC messages, presented at the rate of one message every 3 minutes. Each message directed the pilot to fly a new heading and a new altitude, thus directing the pilot to begin a new segment, or ‘leg’ of the flight. Each message also contained a new radio frequency for contacting ATC; 8 of the ATC messages contained a second communication frequency (a transponder code). To further increase workload, pilots were confronted with randomly presented emergency situations: engine malfunctions (carburetor icing, drop of engine oil

pressure; 8/16 legs), and/or suddenly approaching air traffic (10/16 legs). Pilots were to report engine malfunctions immediately and to avoid air traffic by veering quickly yet safely in the direction diagonal to the path of the oncoming plane. Pilots flew in severe turbulence throughout the flight, and also encountered a 15-knot crosswind during approach and landing. Multiple versions of this flight scenario were presented to reduce learning of specific maneuvers and ATC messages. Each flight was followed by a 40- to 60-minute battery of cognitive tests, including CogScreen-AE (Kay, 1995).

Measures

Flight simulator—The scoring system of the flight simulator-computer system produces 23 variables that measure reaction time or deviations from ideal positions or assigned values (e.g., altitude in feet, heading in degrees) (Yesavage et al., 1999). Because these individual variables have different units of measurement, standardized *z*-scores were computed using the cohort's baseline *M* and *SD*. On the basis of previous principal component analyses, we aggregated the individual *z*-scores into four component measures: (1) accuracy of executing ATC communications; (2) traffic avoidance; (3) time to detect engine emergencies; and (4) executing a visual approach to landing. The correlations among the four components ranged between .12 and .53 (lowest between traffic avoidance and time to detect engine emergencies; highest between executing ATC communications and approach to landing). This study focuses on the flight summary score (the average of the four components).

Cognitive measures—CogScreen-AE (Kay, 1995) is a computerized battery designed for screening and monitoring of cognitive abilities relevant to flying. Two CogScreen-AE scores characterized participants' processing speed and episodic memory: 1) Symbol Digit Coding ThruPut, which is the number of correct responses made per minute during this touch-screen analogue of the Symbol Digit Modalities Test; 2) Symbol Digit Coding Recall, which assesses memory for the six symbol-digit pairings. Memory for the pairs was assessed immediately after the participant completed 90 seconds of symbol-digit coding, and then again after an approximate 25-minute delay. Each time, the participant was asked to indicate the digit that corresponded to each symbol (displayed one at a time in random order). The immediate and delayed recall scores were averaged.

Genotyping—APOE genotyping was performed as previously described (Murphy, Taylor, Kraemer, Yesavage, & Tinklenberg, 1997) using restriction isotyping (Hixson & Vernier, 1990) on genomic DNA extracted from samples of frozen whole blood, buccal mucosa, or saliva. Laboratory staff were blind to participants' performance data; clinical staff were blind to genotypes.

Statistical analyses—The primary longitudinal outcome was average rate of change per year in overall flight simulator performance. As in our previous work (Taylor et al., 2007), average rate of change was a "slope" score. Slope scores were computed separately for each participant by regressing the three flight summary scores on the subject's age at each annual test. For secondary analyses of longitudinal performance, we computed slopes for the four flight components and for processing speed. Median scores for both immediate and delayed recall reached a ceiling level of performance (100% correct) by the second visit. Preliminary analyses of slope scores assessing change in memory did not differ significantly by APOE $\epsilon 4$, expertise, or age, p 's > .12, consistent with limited between-subject variance due to a ceiling effect. To more reliably characterize memory performance as measured by this 6-item test, we averaged each participant's memory scores from the 3 annual tests. Multiple regression modeling (Proc GLM; SAS Version 9.1.3, Cary, NC) was used to examine main effects of APOE $\epsilon 4$ (carrier vs. noncarrier), level of aviation expertise (ordinal grouping = VFR, IFR, or CFII/ATP), the APOE $\times$ Expertise interaction, and age at entry (continuous

covariate) on the primary longitudinal outcome and secondary measures. Each predictor variable was centered (Kraemer & Blasey, 2004).

Results

APOE, Aviation Expertise, and Memory Performance

APOE $\epsilon 4$ carriers had a lower level of memory performance, in that they recalled fewer symbol-digit pairs than noncarriers ($b_1 = -6.98$; $SE = 2.95$; $p = .019$; APOE $\epsilon 4$ $M = 76.5 \pm 16.5\%$ correct, averaged across time; noncarrier $M = 84.3 \pm 15.9\%$). Surprisingly, aviation expertise was associated with better recall ($b_2 = 5.02$; $SE = 1.98$; $p = .013$), such that the CFII/ATP pilots' average memory score was 89.5% correct, IFR pilots was 79.9%, and VFR pilots 80.0%. APOE $\epsilon 4$ status and expertise did not interact, $p > .50$. Older age was associated with a lower level of memory performance, $p = .011$. Processing speed scores at the first annual visit were associated with age ($p < .0001$), but not with APOE, expertise, or their interaction. Speed scores improved over time ($p < .0001$); however, the rate of improvement did not depend on APOE, expertise, APOE $\times$ Expertise, or age (p 's $> .07$).

APOE, Aviation Expertise, and Flight Simulator Performance

APOE $\epsilon 4$ carriers and noncarriers had similar flight summary z -scores at the first annual visit (APOE $\epsilon 4$ $M = 0.064 \pm 0.403$; noncarriers $M = 0.049 \pm 0.516$; $p = .536$). Aviation expertise was associated with superior flight summary z -scores (Table 2). Supplementary analyses of the four flight component measures revealed that the expertise advantage was most evident in the accuracy of executing air-traffic controller communications from memory ($p = .001$) and in avoiding conflicting air traffic ($p = .005$; component scores are not shown).

Flight summary scores declined over time, such that the average rate of change was -0.059 z -score units per year (i.e., parameter estimate $b_0 = -0.059$; $SE = 0.015$; $p = .0001$). The APOE $\epsilon 4$ group did not show steeper rates of decline ($b_1 = -0.001$, $SE = 0.03$, $P = .981$; APOE $\epsilon 4$ mean rate $= -0.062 \pm 0.193$; noncarrier mean rate $= -0.060 \pm 0.151$). On the other hand, aviation expertise was associated with less decline in flight summary scores on average, as indicated by a positive parameter estimate ($b_2 = 0.051$, $SE = 0.020$, $p = .013$). The scores of the most expert (CFII/ATP-rated) pilots declined the least (mean rate of change per year $= -0.02 \pm 0.13$). IFR-rated pilots had an intermediate rate of change ($M = -0.06 \pm 0.15$). VFR-rated pilots had the steepest rate of decline in flight summary scores ($M = -0.10 \pm 0.21$).

As predicted, APOE $\epsilon 4$ status interacted with aviation expertise ($b_3 = 0.086$, $SE = 0.041$, $p = .036$; effect size (ES) = 0.18), such that pilots at the lowest level of aviation expertise (VFR-rated pilots) who possessed an APOE $\epsilon 4$ allele experienced the steepest rate of decline in flight summary scores. At the component level, nonsignificant trends for the APOE $\times$ Expertise interaction were observed in the slope scores assessing rate of change in the communication and traffic avoidance components (p 's $= .09$). The parameter estimates for the communication ($b_3 = 0.103$, $SE = 0.060$), and traffic avoidance ($b_3 = 0.118$, $SE = 0.070$) components were in the same direction as that observed in the primary longitudinal outcome measure reported above. Figure 1 depicts the longitudinal trajectories for the different expertise $\times$ APOE group. Plotted in the figure are mean flight summary scores at baseline, along with time-trend lines, based on the slope scores that were computed for each participant. Table 2 lists means $\pm SD$ for the baseline and slope scores. Analyses of the influence of aviation expertise, performed separately for each APOE $\epsilon 4$ group, revealed that the beneficial influence of expertise on longitudinal performance was significant for the APOE $\epsilon 4$ carriers only ($b_2 = 0.094$; $SE = 0.037$; $p = .017$), and not for noncarriers ($b_2 =$

0.007; $SE = 0.023$; $p > .50$). In summary, aviation expertise may be a protective factor against decline in flight simulator performance over time, particularly for APOE $\epsilon 4$ carriers.

Because memory performance was influenced by expertise and APOE status, it is important to consider whether memory potentially mediated the effect of aviation expertise or the APOE $\times$ Expertise interaction on rate of change in flight simulator performance. Memory performance was not associated with rate of change in flight simulator performance ($b = -0.0014$; $SE = 0.0009$; $p = .10$). Correlation coefficients between memory and the slope measure assessing rate of change in flight summary scores, when computed separately for VFR, IFR, and CFII/ATP groups, were modest and not significant (Spearman rho's were $-.11$, $-.16$, and $-.27$ respectively. The influences of age and expertise on memory were partialled out for these within-group analyses). Because aviation expertise was associated with more hours of flying during the course of longitudinal follow-up, it is also important to ask whether flight activity could account for the expertise effect and the APOE $\times$ Expertise interaction on rate of change in flight simulator performance. Therefore, we recomputed the model of change in flight summary scores in which we replaced pilot proficiency ratings with accumulation of flight hours. (Note: ranked hours were used because flight hours had a skewed distribution.) Accumulation of flight hours during the 2-year period of testing did not predict change in flight simulator performance ($b_2 = 0.0006$; $SE = 0.0004$; $p = .17$). Nor did APOE $\epsilon 4$ status interact with accumulated flight hours ($b_3 = 0.0013$; $SE = 0.0009$; $p = .13$). The pattern of results was essentially identical when the variable 'accumulated flight hours' was used as a covariate along with the main effect of expertise, when 'total flight hours' was used, and when stepwise variable selection was used. Taken together, these results support the interpretation that the beneficial influence of expertise on longitudinal flight simulator performance, particularly for APOE $\epsilon 4$ carriers, is best explained by advanced aviation training, as opposed to hours of flying activity or memory ability.

Discussion

During this 2-year longitudinal study, pilots carrying an APOE $\epsilon 4$ allele had a lower level of memory performance than noncarriers, as assessed by recall of symbol-digit pairs (immediate and delayed recall combined and averaged across the three annual time points). The magnitude of the difference in memory performance between carriers and noncarriers was approximately 0.5 standard deviations. These results concur with the APOE $\epsilon 4$ -related differences in memory reported in our recent neuroimaging paper involving 50 Stanford/VA Aviation Study participants (Adamson et al., 2010). They also are consistent with a meta-analysis of the influence of APOE $\epsilon 4$ on cognitive performance in healthy adults in which the APOE $\epsilon 4$ effect in cross-sectional analyses is small, but statistically significant (Small, Rosnick, Fratiglioni, & Backman, 2004).

In contrast to the observed APOE $\epsilon 4$ -related differences in episodic memory, there was no significant main effect of APOE $\epsilon 4$ on flight simulator performance. There was no main effect of $\epsilon 4$ longitudinally in part because of the marked variability of change within the group of 39 APOE $\epsilon 4$ -positive pilots. Yet, the most expert pilots that were APOE $\epsilon 4$ -positive showed the least decline, while those with the least expertise showed the most decline. In a simple-effects analysis to pull apart the APOE $\times$ Expertise interaction, we found that the influence of expertise was significant for $\epsilon 4$ carriers only, and failed to reach significance for noncarriers, despite a smaller number of $\epsilon 4$ participants. In other words, aviation training and experience mattered more to individuals who were APOE $\epsilon 4$ positive.

Future research may shed light on how prior training in a skill interacts with APOE $\epsilon 4$ effects on memory and cognitive performance. The prevailing theoretical view is that expertise in a particular skill domain (such as music, athletics, or chess) is the result of years

of deliberate, well-structured practice leading to long-term procedural memories and “crystallized” knowledge that are relatively well preserved into old age (Krampe, 2002; Krampe & Ericsson, 1996; Masunaga & Horn, 2001). Such long-term procedural memories and “crystallized” knowledge might be especially important for persons experiencing mild decline in episodic memory. Multiple mechanisms may be needed to explain how procedural memory and knowledge acquired in midlife could aid APOE $\epsilon 4$ carriers in later life. Regarding the longitudinal study of aviators, we have speculated (Taylor, et al., 2007) that pilots may have learned test-taking strategies during the practice flights preceding the yearly test days. Decline in flight simulator performance across the three annual visits may be due to the collective influences of aging, APOE genotype, and diminishing episodic memory for the simulator scenario. Recollection of the flight scenario (relatively recent and brief episodes encountered in later life) may be less consequential for APOE $\epsilon 4$ -positive pilots who undertook advanced flight training (typically during mid-life) compared to APOE $\epsilon 4$ -positive pilots who ceased flight training at the basic proficiency level. A pilot with advanced flight training should have a more elaborate base of long-term procedural and declarative memories related to flying. Second, between the annual tests, pilots with advanced training and proficiency ratings may engage in certain flight activities (e.g., flight instructing or instrument flying to maintain close altitudes and precision runway approaches) that require continual access of knowledge and practice of skills, which may help maintain flight simulator performance over the course of annual testing. Advanced ratings require flying precise altitudes and headings. Precision flying is advantageous because the simulator’s flight quantification software assesses approach, communications regarding course, and traffic avoidance performance in terms of closeness to ideal spatial coordinates. VFR-rated pilots are less likely to be engaged in such precise flying between annual tests. This account of long-term procedural memories and “crystallized” knowledge compensating for APOE $\epsilon 4$ -related influences on episodic memory should ultimately be substantiated by more direct evidence of APOE $\epsilon 4$ -related decline, such as medial temporal lobe atrophy. The pilots in this study will be followed to assess medial temporal lobe atrophy.

Two observational studies of APOE $\epsilon 4$ status and longitudinal cognitive function of non-demented older adults have reported gene-environment interactions analogous to the present study. In these studies, more education and greater time spent in leisure activities mattered more to APOE $\epsilon 4$ carriers. First, a one-year prospective study of leisure activities and change in MMSE scores in nondemented adults aged 55 and older found that, not only was increased leisure activity associated with less risk of declining by one or more points on the MMSE, but APOE $\epsilon 4$ carriers were more sensitive to effects of low-to-high levels of leisure activities (Niti, Yap, Kua, Tan, & Ng, 2008). The least active APOE $\epsilon 4$ carriers were at highest risk for cognitive decline and the most active APOE $\epsilon 4$ carriers were at lowest risk. A seven-year prospective analysis of education in relation to APOE in healthy nondemented adults over age 65 found that APOE $\epsilon 4$ was associated with more rapid memory decline in persons with less than 10 years of education, but not significantly so in persons with more years of education (Mayeux, et al., 2001). These observational studies point to a need for controlled trials of cognitive enrichment that incorporate APOE $\epsilon 4$ allele status into the study design. Evidence-based training of cognitive skills and similar cognitive enrichment programs may help sustain middle-aged and older adults’ everyday cognition performance. These enrichments could be particularly relevant for APOE $\epsilon 4$ -positive individuals. In light of autopsy studies that suggest the presence of early AD-like neuropathology by late middle-age (Arai et al., 1999; Ghebremedhin, Schultz, Braak, & Braak, 1998; Warzok et al., 1998), there is a clear need for interventions that slow neurodegenerative processes of AD or delay the age of symptom onset.

Limitations of the present study include modest sample size, modest representation of women, limited neurobiological markers related to APOE $\epsilon 4$ status, and limited duration of

follow-up. More participants, especially at the lowest and highest expertise levels, would increase statistical power to test the influence of APOE $\epsilon 4$ within each expertise level. Preliminarily, the effect size of the standardized mean difference in rate of decline in flight simulator performance between APOE $\epsilon 4+$ and $\epsilon 4-$ VFR pilots is -0.30 , based on the data of the 35 VFR-rated pilots. Longer follow-up of the aviator participants will be needed to assess the magnitude of an APOE $\epsilon 4$ influence on basic cognitive abilities more conclusively.

Additionally, as noted by a reviewer, our analyses taking accumulated flight hours into account as a potential moderator of decline in flight simulator performance is limited in its implications by the sample size, and by the fact that our measure of flying activity was generic and restricted to the 2-year period of longitudinal follow-up. In their study on older expert musicians' retrospective reports of hours spent in deliberate practice, Krampe and Ericsson (1996) found that amount of "maintenance" practice during the last ten years (but not current levels of practice) moderated the maintenance of expert performance in older pianists. From this standpoint, the issue whether "crystallized" knowledge and long-term procedural memories, or "maintenance" practice, or both, account for the effect in our study remains an open issue.

Several other longitudinal studies of clinically normal middle-aged and young-old adults have reported a significant effect of APOE $\epsilon 4$ on annual decline in cognitive performance, especially memory. These other studies differ from the present one in that they achieved longer follow-up (Blair et al., 2005; Carmelli et al., 1998; Caselli et al., 2009; Kozauer et al., 2008; Mortensen & Høgh, 2001; Nilsson et al., 2006; Reynolds et al., 2006; Tupler et al., 2007), tested large epidemiological cohorts (Dik et al., 2000; Kozauer et al., 2008; Nilsson et al., 2006; Slooter et al., 1998; Tervo et al., 2004), detected more decline only for $\epsilon 4$ homozygous participants (Greenwood, Sunderland, Putnam, Levy, & Parasuraman, 2005; Lemaitre et al., 2005), or achieved large numbers of APOE $\epsilon 4$ positive participants by recruiting individuals who had a family history of AD (Caselli et al., 2004; Greenwood, et al., 2005; Tupler, et al., 2007). Studies with nonsignificant differences tend to have sample sizes smaller than 30 or follow-up spans shorter than 5 years, as in the present analysis (Cohen, Small, Lalonde, Friz, & Sunderland, 2001; Moffat, Szekely, Zonderman, Kabani, & Resnick, 2000).

In summary, benefits associated with prior aviation training were more pronounced for APOE $\epsilon 4$ carriers. Indeed, expert pilots performed well in the flight simulator over time, despite an APOE $\epsilon 4$ -related effect on memory. These results point to the importance of investigating the circumstances under which training moderates the relationships between genetic markers and measures of real-world performance.

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Figure 1.

Patterns of longitudinal change in flight simulator performance by APOE $\epsilon 4$ carrier and expertise group. Plotted in the figure are the mean baseline flight summary z-scores and mean slopes for each group. “Year 0” values are the means at baseline, which differed by level of expertise (Table 2). The “Year 2” values depict the average rate of change from baseline to 2 years later (baseline + slope). We note that the number of APOE $\epsilon 4$ carriers within each level of expertise was modest (n’s ranging from 11 to 15).

Table 1

Baseline demographic characteristics of the 139 longitudinally followed participants, grouped according to APOE ε4 carrier status

Characteristic	<i>APOE</i> ε4 carriers	<i>APOE</i> ε4 noncarriers
	<i>n</i> = 39	<i>n</i> = 100
Age, <i>M</i> ± <i>SD</i> (range in years)	57.5 ± 6.5 (45 – 68)	56.4 ± 6.4 (42 – 69)
Years of education, <i>M</i> ± <i>SD</i>	17.3 ± 1.9	16.7 ± 1.9
Women, <i>n</i> (%)	5 (13%)	17 (17%)
% Aviation expertise rating: VFR/IFR/CFII-ATP ^a	33/39/28%	22/57/21%
% Medical Class I, II, or III ^b	8/31/61%	9/34/57%
% Medical Waivers ^c	3%	8%
% Self-rated health “excellent/good/fair”	64/36/0%	60/39/1%
% Cholesterol-lowering medications	18%	9%
% Anti-hypertensive medications	15%	14%
% Family history of dementia: “yes/no/not sure”	25/75/0%	12/85/3%

^a VFR: rated for flying under visual conditions, which restricts a pilot to flying only in good visibility conditions, is the rating given to pilots when they first obtain a license. IFR: instrument rated, which allows a pilot to fly in poorer visibility conditions using navigational instruments. An IFR rating requires at least 40 hours of instrument time, where pilots learn how to use instruments and radar information to achieve precise navigation and maneuvering and learn more about Air Traffic Control instructions and procedures. CFII/ATP: certified flight instructor of pilots in training for IFR and/or certified to fly air-transport planes. Major airline captains and other professional pilots have the ATP rating.

^b Pilots are required to pass periodic medical examinations in order to fly. A Class I medical certificate indicates passing a medical examination within the past 6 months; a Class II medical certificate indicates passage within the past 1 year; a Class III medical certificate is within the past 2 years. Class I and II medical certificates have higher standards for vision than Class III; a Class I certificate requires an ECG at age 35 and annually after age 40, but Class II and III do not routinely require them.

^c A few participants (9/139) had an FAA medical waiver, which allows a pilot to have a valid FAA medical certificate despite having an otherwise disqualifying medical condition, such as Type II diabetes.

Table 2

Age and flight time at study entry; accumulation of flight time during longitudinal follow-up; baseline and longitudinal flight simulator performance (means $\pm$ SD), by APOE $\epsilon 4$ status and level of aviation expertise

Measure	APOE ε4 Carriers				Noncarriers				p values [*]	A × E
	Aviation Expertise (Least to Most)		Aviation Expertise (Least to Most)		Aviation Expertise (Least to Most)		CFII/ATP	CFII/ATP		
	VFR n=13	IFR n=15	CFII/ATP n=11	VFR n=22	IFR n=57	n=21				
Age at study entry	57.2 ± 7.7	58.4 ± 5.6	56.4 ± 6.6	53.5 ± 5.8	58.0 ± 6.1	54.8 ± 6.3	.38	.81	.53	
Total flight hrs ^a	681 ± 473	1196 ± 647	4167 ± 2829	961 ± 1638	1662 ± 1618	6042 ± 3618	.25	.0001	.54	
Flight hrs in past month ^b	4.9 ± 4.4	7.9 ± 6.1	10.4 ± 13.0	5.1 ± 8.1	6.3 ± 5.3	19.2 ± 21.9	.66	.004	.19	
Accumulated flight hrs ^c	77 ± 54	83 ± 56	124 ± 86	49 ± 51	88 ± 71	260 ± 211	.54	.0001	.051	
Flight summary z-score at baseline ^d	−.046 ± .427	.025 ± .388	.247 ± .364	−.147 ± .499	.018 ± .522	.337 ± .400	.54	.0005	.26	
Flight summary z-score rate of change (slope) ^e	−.144 ± .233	−.069 ± .166	.045 ± .130	−.080 ± .197	−.051 ± .145	−.060 ± .111	.98	.013	.036	

* p values for main effects of APOE carrier status and aviation expertise, and APOE $\times$ Expertise interactions (SAS Proc GLM). Age was a significant covariate with respect to baseline flight summary z-scores ($b = -.028$; $SE = 0.006$; $p < .0001$) and total flight time ($b = 1.48$; $SE = 0.375$; $p = .0001$).

^a At study entry, the CFII/ATP group had significantly more total flight hours than the IFR group, and the IFR group had significantly more total flight hours than the VFR group ($p < .05$; analysis performed on ranked hours due to skewed distributions).

^b At study entry, the CFII/ATP and IFR groups had significantly more recent flight hours than the VFR group ($p < .05$; analysis performed on ranked hours due to skewed distributions).

^c 'Accumulated flight hrs' is the average yearly increase in flight hours during the course of follow-up. At each annual follow-up, the number of flight hours since the previous visit were recorded, based on self-report and by verification of the pilot's log book whenever possible. The CFII/ATP group accrued significantly more flight hours than the IFR and VFR groups ($p < .05$; analysis performed on ranked hours due to skewed distributions).

^d Higher scores indicate better performance.

^e More negative values indicate steeper decline in performance over time.

Age was not a significant covariate with respect to longitudinal change in flight summary z-scores ($b = 0.003$; $SE = 0.002$; $p = .18$). It should be noted that we previously reported that older pilots showed less decline over 3 years in flight summary z-scores than younger pilots (although older pilots' baseline performance was lower than younger pilots) (Taylor et al., 2007). The major difference in the present data set, compared to that of the previous paper, is the inclusion of more recent enrollees and consequently shorter follow-up duration. The previous report localized this longitudinal age difference to the traffic avoidance component. In the present analysis, the same pattern (between age and traffic avoidance) was replicated, $p = .048$.