ties in our cohort may be due to the high proportion of CT in irradiated patients.

Furthermore, modest significant associations were found between the extent of radiologic cerebral abnormalities and cognitive performance. Apparently, not only white matter abnormalities[7] but also cerebral atrophy relate to some extent with cognitive performance.

The current study has its limitations. The number of patients in this study was relatively small, which precluded an analysis of the correlation between neuropsychological data and exact tumor location (e.g., frontal vs parietal location), or extent of residual tumor. Furthermore, the large nationwide study will ultimately yield data on the effects of the brain tumor itself and its treatment on cognitive performance.[8]

Based on our findings, it may be tentatively concluded that long-term cognitive performance and radiation-induced radiologic cerebral abnormalities are correlated in patients with LGG.

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Donepezil and flight simulator performance: Effects on retention of complex skills

Abstract—We report a randomized, double-blind, parallel group, placebo-controlled study to test the effects of the acetylcholinesterase inhibitor, donepezil (5 mg/d for 30 days), on aircraft pilot performance in 18 licensed pilots with mean age of 52 years. After 30 days of treatment, the donepezil group showed greater ability to retain the capacity to perform a set of complex simulator tasks than the placebo group, $p < 0.05$. Donepezil appears to have beneficial effects on retention of training on complex aviation tasks in nondemented older adults.

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For more than 20 years giving acetylcholinesterase inhibitors to older adults has improved performance on long-term and recent memory as well as working memory and recognition tasks.[1,2] This pharmacologic work along with extensive neurochemical, neuropathologic, and animal data has led to the "cholinergic hypothesis," which proposes that part of age-related cognitive decline is caused by reduced cerebral cholinergic function.[3]

Piloting an aircraft requires a range of cognitive and psychomotor skills, many of which are affected by aging.[4] We hypothesized that an acetylcholinesterase inhibitor would affect simulated flight performance. There are several advantages of studying drug effects on flying as a complex task. First, flight simulators allow for the collection of reliable, highly quantified data. Second, the testing "scenario" in the simulator can be designed to highlight tasks emphasizing cognitive areas where drug effects are expected, such as sustained attention, working memory, or psychomotor speed. Third, the task has high "face validity" that goes beyond mere laboratory measures of cogni-

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tion. Fourth, the ability of older pilots to fly complex aircraft has been highly controversial and has led to mandatory retirement rules such as the United States' "Age-60 Rule" that prohibits pilots from flying for scheduled carriers when they reach age 60. Thus, there is considerable interest in this issue and much data has already been generated about the performance of older pilots.[4] Fifth, the flight simulator in this study has been used to document subtle effects of drugs such as nicotine and alcohol, which may provide useful comparisons.[5,6]

Methods. *Subjects.* In a randomized, double-blind, parallel group, placebo-controlled study, we investigated the influence of taking 5 mg donepezil for 30 days on skills associated with aviation performance in 18 licensed pilots between 30 and 70 years of age, with a mean age of 52 years (figure). The protocol was approved by the Human Subject Committee of Stanford University and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. All subjects gave written informed consent to participate and could withdraw at any time. Subjects held at least a private pilot's license and current FAA medical certificate. They were excluded if they were taking psychotropic medications or medications with arousal or sedative effects. At baseline, there were no significant differences between donepezil and placebo groups with respect to age, height, weight, overall simulator performance, total flight hours, or percent of pilots instrument rated (table).

Treatments and design. Before receiving treatments, pilots performed seven 75-minute practice flights (including baseline) in the simulator to train them to perform a complex series of specific Air Traffic Control instructions. At the end of the baseline flight (day 0), each subject was given an identical bottle with 30 identical capsules either containing drug or placebo. The matching capsules of drug and placebo were prepared and randomized at the University of California San Francisco using medication obtained from samples and lactose powder. All subjects and all individuals who had contact with the subjects were blind to the treatment. Subjects were given instructions to take one capsule at noon every day for 30 days. On day 30, the subjects returned to the laboratory and flew 2 post-treatment flights. As described below, change on the flight summary score (i.e., day 30 minus day 0) was the primary outcome measure.

Equipment and measures. We used a Frasca 141 flight simulator (Urbana, IL) linked to a specialized computer (Silicon Graphics, Mountain View, CA) that generated realistic "through-the-window" graphics of the environment in which the pilots flew, and collected data concerning the aircraft's flight conditions. The instrumentation and flight characteristics simulate a small single-engine aircraft similar to the common Cessna 172. A cockpit speaker system was connected to a tape recorder, through which the pilot received Air Traffic Control messages in accordance with FAA standards (FAA Order 7110.650).

Each Air Traffic Control script contained take-off clearance, 16 critical en route messages, and instructions for approach and landing. Each flight was 75 minutes in duration. After receiving take-off clearance, pilots were given a new Air Traffic Control command every 3 minutes with a new heading, altitude, radio frequency, and on 50% of the legs, a new transponder (identification) code that they had to remember and dial into the cockpit panel. To increase the pilots' workload, we confronted them with three different, randomly occurring, emergency situations (carburetor icing, drop of engine oil pressure, or suddenly approaching air traffic) that demanded quick, appropriate reactions.

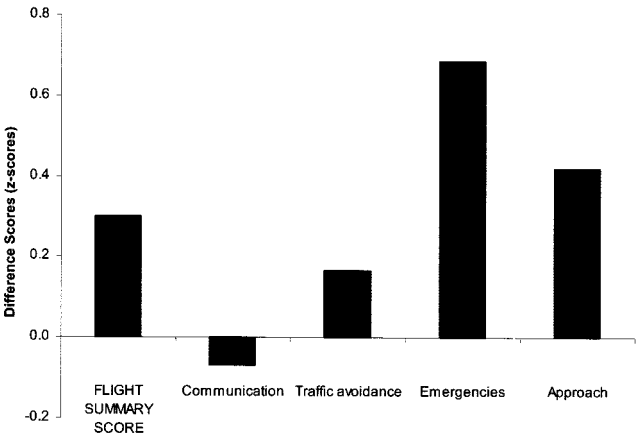

Figure. Flight components difference scores.

The scoring system of the flight simulator-computer unit produced 23 flight-performance variables.[4] The values of these variables were scores derived from errors or deviations from ideal or assigned positions or values (e.g., altitude in feet, heading in degrees, airspeed in knots), or reaction time in seconds. Because these individual variables had different units of measurement, it was necessary to standardize the scores for each variable to a common scale such as z-scores. We used the sample mean and SD for each individual variable at the first baseline flight as the basis for the z-scores. The standardized variables were aggregated into flight component scores: communication, traffic avoidance, emergency scanning, and approach to landing. Finally, a flight summary score was computed for each flight as the mean of the z-standardized flight component scores of the communication, traffic avoidance, emergency scanning, and approach to landing scores. In several previous studies, our instrumentation has proven to be sensitive to the effects of age and drugs (nicotine, alcohol, marijuana) on flight performance as measured by this flight summary score.[5,6]

Results. All subjects enrolled into the clinical trial at day 0 completed the study. No adverse experiences were reported. After 30 days of treatment, there was a significant difference between the donepezil group (n = 9, mean

Table *Demographics*

Characteristics	Donepezil, mean (SD)	Placebo, mean (SD)
Age, y	51.2 (6.6)	53.1 (10.6)
Height, cm	179.5 (9.0)	177.8 (4.9)
Weight, kg	87.0 (17.8)	86.7 (10.0)
Total flight time, h	732 (549)	1033 (812)
Percent instrument rated	50.0	66.6

age = 51.2 years) and the placebo group (n = 9, mean age = 53.1 years) in flight performance change ($F = 6.1$, $p < 0.05$, effect size = 0.58). Overall, flight performance of the pilots in the donepezil group changed little from performance after initial training to 30-day post-treatment (+0.06 z-score units; SD = 0.31), whereas it declined in pilots in the placebo group (−0.24 z-score units; SD = 0.19). To help focus discussion of the likely locus of drug effects, post hoc analyses of flight component difference scores were computed. These scores reflect differences in performance between treatments over the course of treatment. Examination of the figure suggests the largest effects of donepezil were on the emergency scanning (effect size = 0.56) and the approach to landing scores (effect size = 0.52).

Discussion. Given the extensive literature on the effects of acetylcholinesterase inhibitors on memory, we were not surprised to find some effects of the drug on ability to retain a practiced skill in pilots. It should be emphasized that because of the need to avoid "ceiling effects," the flight tasks learned in this experiment are more difficult than those experienced in routine flight operations. Thus, the applicability of these results to aviation issues such as the "Age 60 Rule" may be limited. Furthermore, these results should not be interpreted to advocate widespread use of donepezil in nondemented populations. Side effects such as sleep disturbance might become more apparent in larger populations, especially if higher doses such as the 10 mg commonly administered to patients with AD were used.

Nonetheless, these results are consistent with previous studies in nondemented adults that have reported that cholinesterase inhibitors improve cognitive performance.[1,7] Recently, a cerebral blood flow study with healthy human volunteers (age range 22 to 68 years) found administration of the cholinesterase inhibitor physostigmine to be associated with improved working memory efficiency, as indicated by faster reaction times and by reduced activation of cortical regions associated with working memory.[1,2] A further investigation using functional MRI, found physostigmine enhanced neural processing in visual cortical areas during a visual working memory task, particularly during encoding.[8] The authors suggest that augmenting cholinergic function may improve working memory by enhancing the selectivity of perceptual processing during encoding. The association of cholinergic drugs with better attention has led investigators to suggest that part of the benefit of cholinergic drugs on memory performance may be mediated through attentional components involved in working memory.[7-9] This suggestion is supported by the current data that show the strongest drug effects on emergency tasks and the approach to landing. The emergency tasks involve visually scanning the instrument panel for aberrant readings. The approach to landing requires sustained divided attention to maintain proper altitude, speed, and heading. Although these findings may support interpretations of the effects of cholinergic augmentation on cognitive processing, the precise neurochemical mechanisms of action remain to be fully delineated.

Even though our results need to be replicated in larger samples, if cognitive enhancement becomes possible in intellectually intact individuals, significant legal, regulatory, and ethical questions will emerge.[10] To date, cholinesterase inhibitors have been used primarily for the treatment of AD. Recently, they have been considered as palliative approaches for individuals at risk for AD, such as those with mild cognitive impairment. However, many older adults, who will never have AD, have cognitive impairments that impact their day-to-day functioning, and there is an increasing demand for therapeutic interventions to remediate such deficits. How should one pay for such interventions? Will we further worsen the divisions between the "have" and "have-nots" when the rich are cognitively enhanced not only through better education but also through drugs or other technologies? Finally, how should one regulate the use of such agents in settings and populations beyond aviation and normal aging, such as chess matches or test taking among college students?

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