

# Effects of a 14-Day Healthy Longevity Lifestyle Program on Cognition and Brain Function

*Gary W. Small, M.D., Daniel H. S. Silverman, M.D., Ph.D.,  
Prabha Siddarth, Ph.D., Linda M. Ercoli, Ph.D.,  
Karen J. Miller, Ph.D., Helen Lavretsky, M.D.,  
Benjamin C. Wright, M.D., Susan Y. Bookheimer, Ph.D.,  
Jorge R. Barrio, Ph.D., Michael E. Phelps, Ph.D.*

---

**Objective:** *The objective of this study was to determine the effects of a 14-day healthy longevity lifestyle program on cognition and cerebral metabolism in people with mild age-related memory complaints. **Methods:** Seventeen nondemented subjects, aged 35–69 years (mean: 53 years, standard deviation: 10) with mild self-reported memory complaints but normal baseline memory performance scores were randomly assigned to 1) the intervention group (N = 8): a program combining a brain healthy diet plan, relaxation exercises, cardiovascular conditioning, and mental exercise (brain teasers and verbal memory training techniques); or 2) the control group (N = 9): usual lifestyle routine. Pre- and postintervention measures included self-assessments of memory ability, objective tests of cognitive performance, and determinations of regional cerebral metabolism during mental rest with [fluorine-18]fluorodeoxyglucose (FDG) positron emission tomography (PET). **Results:** Subjects in the intervention group objectively demonstrated greater word fluency. Concomitantly, their FDG-PET scans identified a 5% decrease in activity in the left dorsolateral prefrontal cortex. The control group showed no significant change in any of the measures. **Conclusions:** A short-term healthy lifestyle program combining mental and physical exercise, stress reduction, and healthy diet was associated with significant effects on cognitive function and brain metabolism. Reduced resting activity in left dorsolateral prefrontal cortex may reflect greater cognitive efficiency of a brain region involved in working memory. (Am J Geriatr Psychiatry 2006; 14:538–545)*

**Key Words:** Positron emission tomography, age-related memory complaints, cognitive measures, healthy longevity lifestyle

---

---

Received December 17, 2005; revised February 27, 2006; accepted March 3, 2006. From the Department of Psychiatry and Biobehavioral Sciences and Semel Institute for Neuroscience and Human Behavior (GWS, PS, LME, KJM, HL, BCW, SYB), Department of Molecular and Medical Pharmacology (DHSS, MEP, JRB), Brain Mapping Center (SYB), Alzheimer's Disease Center (GWS), and Center on Aging (GWS), University of California, Los Angeles. Send correspondence and reprint requests to Dr. Gary W. Small, Semel Institute, Suite 88-201, 760 Westwood Plaza, Los Angeles, CA 90024. e-mail: gsmall@mednet.ucla.edu

© 2006 American Association for Geriatric Psychiatry

As people age, their risk for cognitive decline increases. An estimated 40% of people 65 years and older have age-associated memory impairment characterized by self-perception of memory loss and a standardized memory test score demonstrating lower objective memory performance compared with young adults.<sup>1,2</sup> Such mild age-related memory changes are often relatively stable over time. By contrast, patients with mild cognitive impairment, characterized by greater cognitive decline without impairment of activities of daily living, are at risk for progressing to Alzheimer disease at a rate approximating 15% each year.<sup>3</sup>

The MacArthur study of successful aging<sup>4</sup> found that certain lifestyle habits are associated with health and vitality as people age and, for the average individual, such nongenetic influences can account for a higher proportion of cognitive and physical health than genetic factors. Epidemiologic, laboratory, and clinical evidence point to several lifestyle behaviors that may maintain brain health and lower the risk for dementia, including mental and physical activity, diet, and response to stressful stimuli.<sup>5-7</sup> These and other lifestyle habits are not only associated with better health status, but also to increased longevity.<sup>4,8</sup>

Studies of rodents in enriched environments have found more neurons in their hippocampal memory centers compared with rodents living in ordinary laboratory cages.<sup>9</sup> Research in humans has shown that the risk for developing Alzheimer disease is lower in people who have been mentally active.<sup>10</sup> People with advanced educational and professional accomplishments tend to have greater density of neuronal connections in brain areas involved in complex reasoning.<sup>11</sup> Other studies of specific memory techniques, including visualization, elaboration, and association, have been shown to improve objective memory performance scores.<sup>12</sup> These discoveries support the conclusion that mental stimulation and cognitive training may not only improve memory performance, but may stave off future cognitive decline.

When laboratory animals exercise regularly, they develop new neurons in the hippocampus, whereas inactive animals do not.<sup>13</sup> The physical exercise may increase cerebral blood flow, which in turn promotes neural growth. Studies of physically active people show that they have a lower risk for Alzheimer dis-

ease compared with inactive individuals.<sup>14</sup> A study of healthy older adults found that mental tasks involving executive control improved in a group prescribed a cardiovascular conditioning program but not in a control group prescribed only stretching and toning.<sup>15</sup>

Excess body fat increases an individual's risk for such illnesses as diabetes and hypertension, which can increase the risk for dementia, cerebrovascular disease, and cognitive decline.<sup>16</sup> Epidemiologic studies have found lower rates of dementia in geographic areas where populations eat diets low in animal fats.<sup>17</sup> Diets high in omega-3 fats from olive oil or fish,<sup>18</sup> as well as those rich in antioxidant fruits and vegetables,<sup>19</sup> are associated with less age-related cognitive decline. In addition, diets that avoid processed and refined foods and emphasize low glycemic index carbohydrates may reduce the risk for type 2 diabetes, stroke, and vascular dementia.<sup>20,21</sup>

Studies of laboratory animals show that prolonged exposure to stress hormones has an adverse effect on the hippocampus, a brain region involved in memory and learning.<sup>22</sup> Human investigations<sup>23</sup> indicate that several days of exposure to high levels of the stress hormone cortisol can impair memory. Prone-ness to psychologic distress also is associated with an increased risk for Alzheimer disease.<sup>24</sup>

Data from controlled clinical trials on the short-term benefits of many of these lifestyle strategies are limited. Moreover, cognitive and brain function effects of combining several strategies together are not known. To this end, we studied a 14-day program that combined healthy lifestyle behaviors associated with a lower risk for dementia—mental and physical exercises, healthy diet, and stress reduction techniques—on cognitive ability and brain function.

---

## METHODS

### Subjects and Clinical Assessments

We studied 17 righthanded white adults who were selected from a pool of 344 potential volunteers recruited through advertisements, media coverage, and referrals from physicians and families. After telephone screening, 49 individuals were seen for clinical evaluation. We excluded volunteers who had

major medical or neuropsychiatric illnesses that could affect cognitive status as well as those who were unwilling to make a commitment to undergo the study procedures as described. To be included in the study, volunteers needed to have objective cognitive performance scores that were normal for their age group. All subjects had mild age-related memory complaints, which is present in nearly half of individuals age 50 and older.<sup>2</sup>

All subjects had neurologic and psychiatric evaluations, routine screening laboratory tests, and magnetic resonance imaging scans to rule out reversible causes of cognitive impairment,<sup>25</sup> and volunteers meeting diagnostic criteria for dementia<sup>26</sup> or mild cognitive impairment<sup>3</sup> were excluded. All subjects were given a Mini-Mental State Examination<sup>27</sup> and Hamilton Rating Scale for Depression.<sup>28</sup> Volunteers were excluded if they were taking drugs that could influence cognition (e.g., cholinesterase inhibitors, sedative-hypnotics) or supplements (e.g., phosphatidyl serine, ginkgo biloba) that could have such effects. Volunteers with a history of excessive alcohol, caffeine, or tobacco use were also excluded from participation.

At baseline and follow up (within one week after completing the 14-day program), subjects received objective cognitive assessments, including a multi-trial verbal learning and memory test<sup>29</sup> and a word-generation (letter-fluency) test.<sup>30</sup> Subjects also completed a standardized measure of self-awareness of memory ability, the Memory Functioning Questionnaire (MFQ).<sup>31</sup> The MFQ is a 64-item instrument that provides four-unit weight factor scores measuring frequency of forgetting, seriousness of forgetting, retrospective functioning (changes in current memory ability relative to earlier life), and mnemonics use. Higher scores indicate higher levels of perceived memory functioning (e.g., fewer forgetting incidents, less frequent mnemonic use). For a sample of 639 adults aged 16–89 years, Cronbach alpha internal consistency alphas ranged from 0.82–0.93 for different scales on the MFQ, and test-retest reliabilities, over a three-year period, ranged from 0.22–0.64.<sup>32</sup>

All scanning procedures were performed within two weeks of clinical assessments. Informed consent was obtained in accordance with the recommendations and requirements of the Radiation Safety Committee and the Institutional Review Board of the University of California, Los Angeles.

### **Healthy Lifestyle Program**

After baseline assessments and scanning procedures were completed, each subject in the intervention group received a notebook with the 14-day healthy longevity lifestyle program, which is detailed elsewhere.<sup>33</sup> The program provides simple instructions so that subjects were able to readily follow several healthy lifestyle strategies—memory training, physical conditioning, relaxation techniques, and diet—that are associated with a lower risk for dementia.<sup>7–10,12,14–21,23,24</sup> The conceptual basis of the program involved developing a usable guide to initiating lifestyle and behavior strategies associated with improved cognitive abilities and a lower risk for cognitive decline. The exercises build gradually over a 14-day period so they are readily learned and integrated into the volunteer's daily schedule. In addition to brain teasers and mental puzzles, the program provides daily exercises that teach memory techniques to help focus attention and improve visualization and association skills for better retention and recall. These memory techniques begin at a basic level and increase in complexity over the two-week period. For example, the first day, subjects are given an exercise to focus attention to improve learning and concentration (e.g., subjects are instructed to concentrate on two random details of the clothing or accessories on a family member). After attention skills improve the first few days, exercises are introduced to improve visualization and association skills for better mnemonic techniques.

Cardiovascular conditioning exercises such as brisk walks are recommended each day. Daily, brief relaxation exercises are designed to lower stress and help subjects to focus their attention. Suggested shopping lists and menus guide subjects to follow a healthy diet plan, including five daily meals emphasizing antioxidant fruits and vegetables, omega-3 fats, and low glycemic index carbohydrates.

The brief 14-day period was chosen so that volunteers would not be daunted by a requirement for an extensive commitment. Moreover, it was predicted that the time period would be adequate for participants to adapt to and feel comfortable with the lifestyle changes so they would continue them beyond the initial two-week period. Exercises and suggested menus are described in simple terms and the amount

of time needed to follow the exercises totals from 30–45 minutes each day.

Before initiating the program, a research nurse reviewed the daily instructions with each subject. The research nurse monitored self-reports of compliance through participants' daily notes and posttreatment interviews to ensure that volunteers were able to follow the recommended program exercises and diet. The volunteers in the control group were instructed to continue their usual lifestyle habits during the two-week period between clinical and brain imaging procedures.

### Scanning Procedures

At baseline and after completing the program or the control condition (usual lifestyle habits) for two weeks, subjects underwent positron emission tomography (PET) imaging. Intravenous lines were placed 10–15 minutes before tracer injection. [Fluorine-18]fluorodeoxyglucose (FDG) was used to assess regional cerebral metabolism during mental rest as previously described.<sup>34,35</sup> Subjects were scanned in the supine position 40 minutes after injection of 370 MBq FDG in a dimly lit room having low ambient noise with eyes and ears unoccluded. PET was performed with 3-D acquisitions collecting 63 contiguous data planes parallel to the canthomeatal line in a  $128 \times 128$  image matrix using a CTI HR + scanner (CTI, Knoxville, TN). Transmission scans obtained with a positron-emitting source were used for attenuation correction. Six 5-minute frames were acquired, and summed-frame images were produced after excluding frames for patient motion, if necessary.

Anatomic brain magnetic resonance imaging (MRI) scans were obtained using either a 1.5-Tesla or a 3-Tesla magnet (General Electric-Signa, Milwaukee, WI) scanner. Fifty-four transverse planes were collected throughout the brain, superior to the cerebellum, using a double-echo, fast-spin echo series with a 24-cm field of view and  $256 \times 256$  matrix with 3 mm/0 gap (TR = 6000 [3T] and 2000 [1.5T]; TE = 17/85 [3T] and 30/90 [1.5T]). An intermodality image coregistration program<sup>36</sup> that preprocesses image segmentation and simulation was used to coregister PET and MRI scans of each subject.

### Image Analysis

For comparisons between the intervention and the control groups at baseline and follow up, PET data were subjected to statistical parametric mapping analysis. Briefly, images were coregistered and reoriented into a standardized coordinate system<sup>37</sup> using the nonlinear spatial transformation package in SPM2<sup>38</sup> spatially smoothed with a three-dimensional Gaussian smoothing filter having a full-width half-maximum of 16 mm and normalized to mean global activity before carrying out analyses. The pooled data were then assessed on a voxel-by-voxel basis to identify the profile of voxels that differed within each treatment condition between those scans obtained at baseline and the scans acquired after the 14-day control or intervention condition had concluded, as well as directly assessing the profile of voxels in which that change significantly differed according to the therapy arm.

### General Statistical Analysis

The intervention and control groups were compared on baseline demographic and clinical characteristics with chi-square statistics for categorical measures and Wilcoxon Mann-Whitney tests for continuous measures. Changes in objective (verbal fluency and verbal recall) and subjective (seriousness of forgetting, retrospective functioning, and mnemonics use from the MFQ) cognitive measures were compared across groups using Wilcoxon Mann-Whitney tests. In addition, significance of changes in these measures within each group was assessed using Wilcoxon signed-ranks test. All statistical analyses were for two-tailed tests, and exact p values were computed using StatXact because sample sizes were small.

---

## RESULTS

Subjects were on average middle-aged (overall mean age: 53 years; standard deviation [SD]: 10; range: 35–69 years) and college-educated, and did not have evidence of cognitive impairment or depression (Table 1). The intervention and control groups did not differ significantly in mean age or years of educational achievement; proportion of females; or in



**TABLE 1. Subject Group Demographic and Clinical Characteristics<sup>a</sup>**

Characteristic	Intervention (N = 8)	Control (N = 9)
Age (yrs)	54 ± 12	53 ± 10
Education (yrs)	18 ± 3	17 ± 4
Female—no. (%)	5 (63)	6 (67)
Mini-Mental State Examination	29.6 ± 0.5	29.2 ± 0.7
Hamilton Rating Scale for Depression	3.7 ± 3.4	2.8 ± 2.4

<sup>a</sup>Values are means ± standard deviations.

mean baseline scores on the Mini-Mental State Examination and Hamilton Rating Scale for Depression (Table 1).

Mean baseline subjective and objective cognitive measures did not differ significantly between the intervention and control groups (Table 2). Changes in cognitive measures were not significantly different between the intervention and control groups. However, for the objective measures, the intervention group improved significantly in verbal fluency (mean change: 10.3; SD: 7.5, Wilcoxon signed rank statistic: 35, exact  $p = 0.015$ ), whereas the control group did not (mean change: 3.3; SD: 7.0; Wilcoxon signed rank statistic: 27, exact  $p = 0.25$ ).

Subjects in the intervention group showed a 5%

**TABLE 2. Baseline and Follow-Up Results of Objective and Subjective Cognitive Measures<sup>a</sup>**

Measure	Time Point	Intervention (N = 8)	Control (N = 9)
<i>Subjective measures</i>			
Seriousness of forgetting	Baseline	75.8 ± 31.6	79.4 ± 32.0
	Follow up	92.1 ± 37.6 <sup>b</sup>	83.7 ± 21.8
Retrospective functioning	Baseline	14.0 ± 2.2	14.4 ± 3.3
	Follow up	15.3 ± 2.7	16.3 ± 3.9
Mnemonic use	Baseline	19.0 ± 8.2	19.1 ± 8.3
	Follow up	17.8 ± 7.7	20.0 ± 5.9
<i>Objective measures</i>			
Verbal learning and memory	Baseline	116.9 ± 10.3	114.3 ± 18.5
	Follow up	123.3 ± 7.8	119.1 ± 15.1
Verbal fluency	Baseline	42.1 ± 5.0	43.2 ± 12.2
	Follow up	52.4 ± 7.7 <sup>c</sup>	46.6 ± 13.4

<sup>a</sup>Values are means ± standard deviations.

<sup>b</sup>Follow-up - baseline change:  $p = 0.06$ .

<sup>c</sup>Follow-up - baseline change significant:  $p = 0.015$ .

Subjective memory was measured using the MFQ.<sup>30</sup>

Verbal learning and memory = Buschke-Fuld Selective Reminding Test<sup>28</sup>; verbal fluency = Controlled Oral Word Association Test.<sup>29</sup>

For standardized rating scales and memory tests, lower scores reflect poorer performance.

decrease in left dorsolateral prefrontal activity compared with baseline ( $Z = 3.30$ ,  $p < 0.001$ ) (Fig. 1). The control group showed no significant change in brain metabolism, and direct statistical comparison of the two therapy arms demonstrated that the decline in this region, involving a stretch of prefrontal cortex in the vicinity of Brodmann's areas 8,9, and 10, was significantly greater in the intervention group relative to the control group ( $Z = 3.82$ ,  $p < 0.001$ ).

## DISCUSSION

To our knowledge, this is the first study to show that combining several healthy lifestyle strategies will change measures of cognitive and brain function in a relatively brief time period. The results suggest that a program combining mental and physical exercise, stress reduction, and healthy diet can have significant short-term effects on brain metabolism and cognitive performance.

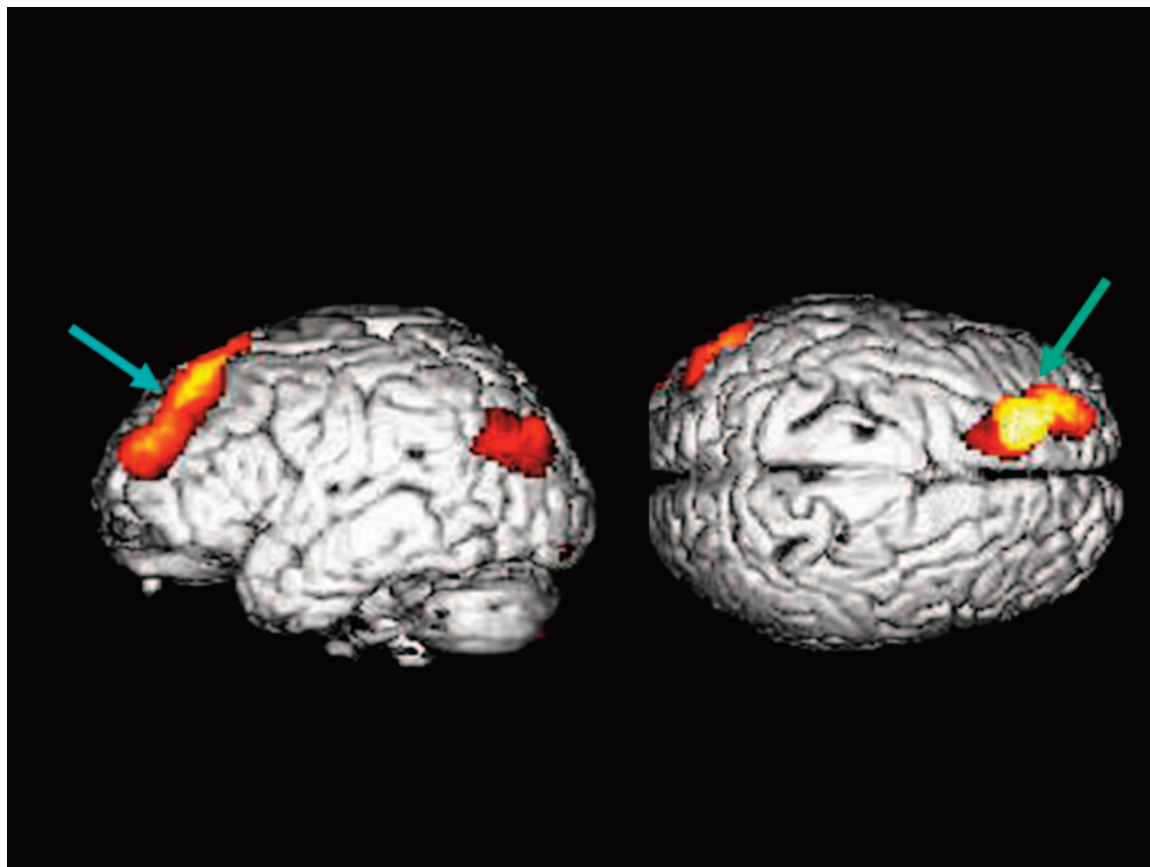
The SPM analysis identified a change in cerebral activity in the intervention group in a brain region that modulates several mental functions relevant to the lifestyle intervention. Previous studies have demonstrated that working memory, the ability to retain information for brief periods, requires an intact dorsolateral prefrontal cortex.<sup>39</sup> A study using functional MRI found that semantic organizational strategies engage this same region.<sup>40</sup> The dorsolateral prefrontal cortex also mediates anxiety symptoms, and this regional metabolic reduction may in part have resulted from the intervention's relaxation exercises.<sup>41</sup> The significant change observed in the left hemisphere also is consistent with the verbal emphasis in the program's memory training exercises. Moreover, the observations that the intervention group experienced both improved objective verbal fluency and significant change in left dorsolateral prefrontal metabolism are consistent with previous work showing that verbal fluency is associated with activation in this same brain region.<sup>45</sup> Future studies will determine specific effects of individual components of the program and whether a combination of healthy lifestyle strategies produces a greater effect than individual strategies.

The finding that the intervention reduced regional cerebral metabolic rates could correspond to subjects

---

**FIGURE 1. Statistical Parametric Mapping of FDG-PET Images Comparing Changes in Intervention and Control Subject Groups**


---




---

*Note:* A 5% decrease in activity was identified in the left dorsolateral prefrontal cortex of subjects in the intervention group but not the control group. The color scale highlights the location of all cortical voxels in which significantly greater decreases ( $p < 0.01$ ) occurred in the intervention group than the control group. The affected region involved a stretch of cortex in Brodmann's areas 8, 9, 10, shown in the left image from the left lateral viewpoint, and in the right image from the top of the brain. The arrows point to the voxels of peak significance ( $Z = 3.82$ ,  $p < 0.001$ ).

---

developing greater cognitive efficiency during mental rest, and previous studies are consistent with this hypothesis. PET scans of volunteers playing a computer game for the first time show high cerebral glucose metabolic rates, but after several months of practice, when the volunteers become proficient at the game, their scans display significantly lower rates of glucose metabolism.<sup>42</sup> This lower brain activity with improved mental performance suggests that with time, practice, and familiarity, our brains can essentially adapt themselves to achieve comparable performance levels with less work. The present study suggests that such an improvement in brain efficiency may occur over relatively brief periods of intervention.

In a previous functional MRI study,<sup>43</sup> our group found that middle-aged and older adults with a genetic risk for Alzheimer disease had greater MR signal activity in the dorsolateral prefrontal cortex during a memory task compared with those without such a genetic risk. Moreover, higher MR signals at baseline correlated with lower verbal memory scores 2 years later. Future studies may determine whether such apparent neural compensatory responses to genetic risk would change after a lifestyle intervention such as the one used in the present study.

We did not find significant changes in subjective cognitive measures in the intervention group, which could reflect the small sample size as well as the insensitivity of the MFQ to measure short-term

changes in memory self-awareness (several MFQ items focus on longer-term memory abilities). Self-awareness of cognitive improvement is helpful in encouraging individuals to continue a healthy lifestyle beyond a two-week period. By contrast, worry and concern about memory performance has been associated with worse objective memory performance scores.<sup>44</sup>

The current study combined several different lifestyle approaches together. Previous research indicates that combining different kinds of interventions can augment the overall effect on age-related health outcomes. For example, investigators have combined a healthy diet with regular physical exercise to reduce the risk for developing type 2 diabetes.<sup>46</sup> A strategy combining stress reduction with physical activity has been found to lower the risk for ischemic chest pain in cardiac patients compared with exercise alone.<sup>47</sup>

Several methodological issues deserve comment. The small sample size and relatively brief intervention period limits how much any conclusions from these results can be generalized. Because volunteers were living in the community and not strictly monitored on how closely they followed the healthy lifestyle program, compliance would be expected to be lower than in a closely monitored, residential intervention program. Moreover, without objective measures of physical activity, dietary intake, or degree of compliance with memory and relaxation exercises, the actual lifestyle behavior changes in the intervention group are not known. The research nurse monitored activity self-reports, but recall bias could have influenced these reports. Thus, the observed changes in outcome measures may have reflected nonspecific or placebo effects of being given a program that participants were only claiming to have followed. The nature of the cerebral metabolic results, however, would argue against such a possibility, because

the brain region showing highly significant results was not a random region, but rather one that controls brain functions that were specific targets of the program (e.g., working memory, verbal fluency). Although we recruited a convenience sample of volunteers who may have already been following a healthy lifestyle regimen, such a convenience sample would be expected to reduce any differences between groups rather than exaggerate them. Our significant findings, despite such methodological limitations, suggest that people may be able to enjoy the benefits of healthy lifestyle programs when they follow them on their own without the assistance of a professional staff.

In summary, a 14-day healthy lifestyle program improved measures of verbal fluency and reduced left dorsolateral prefrontal cortical metabolism, suggesting that such a program may result in greater cognitive efficiency of a brain region involved in working memory functions. Future longitudinal studies will determine the long-term effects of such combined interventions and whether they eventually lower the risk for developing dementia.

*This study was supported by the Department of Energy (DOE contract DE-FC03-87-ER60615), General Clinical Research Centers Program M01-RR00865, the Fran and Ray Stark Foundation Fund for Alzheimer's Disease Research, and the Judith Olenick Elgart Fund for Research on Brain Aging.*

*Presented in part at the International Conference on Alzheimer's Disease and Related Disorders (July 2004) and the Annual Meeting of the American College of Neuropsychopharmacology (December 2005).*

*The authors thank Ms. Andrea Kaplan, Ms. Debbie Dorsey, Ms. Gwendolyn Byrd, and Ms. Teresann Crowe-Lear for help in subject recruitment, data management, and study coordination.*

## References

1. Crook T, Bartus RT, Ferris SH, et al: Age-associated memory impairment: proposed diagnostic criteria and measures of clinical change—Report of a National Institute of Mental Health Work Group. *Dev Neuropsychol* 1986; 2:261-276
2. Larrabee GJ, Crook TH: Estimated prevalence of age-associated memory impairment derived from standardized tests of memory function. *Int Psychogeriatr* 1994; 6:95-104
3. Petersen RC, Stevens JC, Ganguli M, et al: Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001; 56:1133-1142
4. Kahn RL, Rowe JW: *Successful Aging*. New York, Pantheon, 1998
5. Mattson MP: Existing data suggest that Alzheimer's disease is preventable. *Ann N Y Acad Sci* 2000; 924:153-159
6. Fillit HM, Butler RN, O'Connell AW, et al: Achieving and maintaining cognitive vitality with aging. *Mayo Clin Proc* 2002; 77: 681-696

7. Small GW: What we need to know about age related memory loss. *BMJ* 2002; 324:1502-1505
8. Small G, Vorgan G: *The Longevity Bible*. New York, Hyperion, 2006
9. Van Praag H, Kempermann G, Gage FH: Neural consequences of environmental enrichment. *Nat Rev Neurosci* 2000; 1:191-198
10. Fritsch T, Smyth KA, Debanne SM, et al: Participation in novelty-seeking leisure activities and Alzheimer's disease. *J Geriatr Psychiatry Neurol* 2005; 18:134-141
11. Del Ser T, Hachinski V, Merskey H, et al: An autopsy-verified study of the effect of education on degenerative dementia. *Brain* 1999; 122:2309-2319
12. Ball K, Berch DB, Helmers KF, et al: Effects of cognitive training interventions with older adults. A randomized controlled trial. *JAMA* 2002; 288:2271-2281
13. Gage FH: Neurogenesis in the adult brain. *J Neurosci* 2002; 22:612-613
14. Friedland RP, Fritsch T, Smyth KA, et al: Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Proc Natl Acad Sci U S A* 2001; 98:3440-3445
15. Kramer AF, Hahn S, McAuley E, et al: Exercise, aging and cognition: healthy body, healthy mind? In: Fisk AD, Rogers W, eds. *Human Factors Interventions for the Health Care of Older Adults*. Hillsdale, NJ, Erlbaum, 2001
16. Luchsinger JA, Tang MX, Shea S, et al: Caloric intake and the risk of Alzheimer disease. *Arch Neurol* 2002; 59:1258-1263
17. Hendrie HC, Ogunniyi A, Hall KS, et al: Incidence of dementia and Alzheimer disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Ind. *JAMA* 2001; 285:739-747
18. Solfrizzi V, Panza F, Torres F, et al: High monounsaturated fatty acids intake protects against age-related cognitive decline. *Neurology* 1999; 52:1563-1569
19. Engelhart MJ, Geerlings MI, Ruitenberg A, et al: Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA* 2002; 287:3223-3229
20. Willett W, Manson J, Liu S: Glycemic index, glycemic load, and risk of type 2 diabetes. *Am J Clin Nutr* 2002; 76:274S-278S
21. Oh K, Hu FB, Cho E, et al: Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. *Am J Epidemiol* 2005; 161:161-169
22. Sapolsky RM: Glucocorticoids, stress, and their adverse neurological effects: relevance to aging. *Exp Gerontol* 1999; 34:721-732
23. Newcomer JW, Selke G, Melson AK, et al: Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Arch Gen Psychiatry* 1999; 56:527-533
24. Wilson RS, Evans DA, Bienias JL, et al: Proneness to psychological distress is associated with risk of Alzheimer's disease. *Neurology* 2003; 61:1479-1485
25. Small GW, Rabins PV, Barry PP, et al: Diagnosis and treatment of Alzheimer disease and related disorders: consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. *JAMA* 1997; 278:1363-1371
26. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR* (text revision). Washington, DC, American Psychiatric Association, 2000
27. Folstein M, Folstein S, McHugh P: 'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189-198
28. Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56-62
29. Buschke H, Fuld PA: Evaluating storage, retention and retrieval in disordered memory and learning. *Neurology* 1974; 24:1019-1025
30. Benton AL, Hamsher K: *Multilingual Aphasia Examination*. Iowa City, University of Iowa, 1976 (revised, 1978)
31. Gilewski MR, Zelinski EM: Memory Functioning Questionnaire (MFQ). *Psychopharmacol Bull* 1988; 24:665-670
32. Gilewski MJ, Zelinski EM: Questionnaire assessment of memory complaints. In: Poon LW, ed. *Handbook for Clinical Memory Assessment of Older Adults*. Washington, DC, American Psychological Association, 1986: 93-107
33. Small G, Vorgan G: *The Memory Prescription*. New York, Hyperion, 2004
34. Small GW, Ercoli LM, Silverman DHS, et al: Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. *Proc Natl Acad Sci U S A* 2000; 97:6037-6042
35. Silverman DHS, Truong CT, Kim SK, et al: Prognostic value of regional cerebral metabolism in patients undergoing dementia evaluation: comparison to a quantifying parameter of subsequent cognitive performance and to prognostic assessment without PET. *Mol Genet Metab* 2003; 80:350-355
36. Lin KP, Huang SC, Baxter L, et al: A general technique for inter-study registration of multi-function and multimodality images. *IEEE Trans Nucl Sci* 1994; 41:2850-2855
37. Talairach J, Tournoux P: *Co-planar Stereotaxic Atlas of the Human Brain. 3-Dimensional Proportional System: An Approach to Cerebral Imaging*. New York, Thieme Medical, Inc, 1988
38. Friston K, Ashburner J, Heather J, et al: *Statistical Parametric Mapping (SPM2)*. Available at: [www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm). London, The Wellcome Department of Cognitive Neurology, University College London, 2003
39. Funahashi S, Takeda K, Watanabe Y: Neural mechanisms of spatial working memory: contributions of the dorsolateral prefrontal cortex and the thalamic mediodorsal nucleus. *Cogn Affect Behav Neurosci* 2004; 4:409-420
40. Miotto EC, Savage CR, Evans JJ, et al: Bilateral activation of the prefrontal cortex after strategic semantic cognitive training. *Hum Brain Mapp*. Published online August 4, 2005
41. Mathew SJ, Mao X, Coplan JD, et al: Dorsolateral prefrontal cortical pathology in generalized anxiety disorder: a proton magnetic resonance spectroscopic imaging study. *Am J Psychiatry* 2004; 161:1119-1121
42. Haier RJ, Siegel BV, MacLachlan A, et al: Regional glucose metabolic changes after learning a complex visuospatial/motor task: a positron emission tomographic study. *Brain Res* 1992; 570:134-143
43. Bookheimer SY, Strojwas MH, Cohen MS, et al: Brain activation in people at genetic risk for Alzheimer's disease. *N Engl J Med* 2000; 343:450-456
44. Podewils LJ, McLay RN, Rebok GW, et al: Relationship of self-perceptions of memory and worry to objective measures of memory and cognition in the general population. *Psychosomatics* 2003; 44:461-470
45. Ravnkilde B, Videbech P, Rosenberg R, et al: Putative tests of frontal lobe function: a PET-study of brain activation during Stroop's Test and verbal fluency. *J Clin Exp Neuropsychol* 2002; 24:534-547
46. Knowler WC, Barrett-Connor E, Fowler SE, et al: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346:393-403
47. Blumenthal JA, Babyak M, Wei J, et al: Usefulness of psychosocial treatment of mental stress-induced myocardial ischemia in men. *Am J Cardiol* 2002; 89:164-168