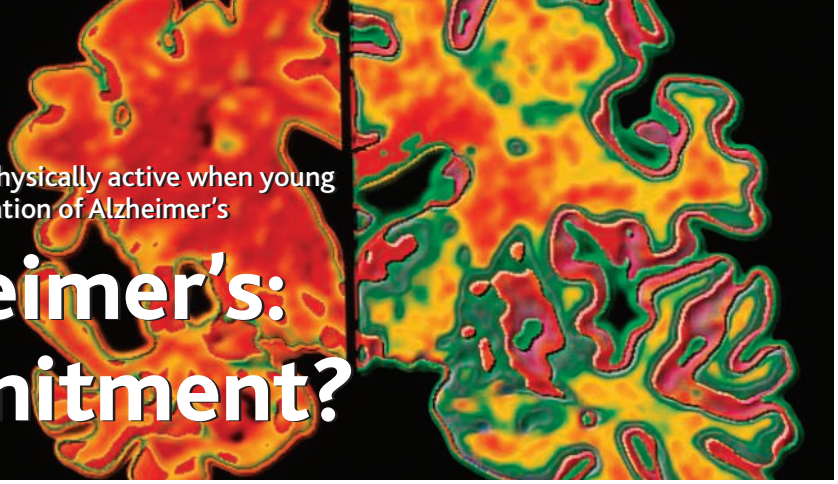

Recent research suggests that keeping mentally and physically active when young and middle-aged can help stave off the brain degeneration of Alzheimer's

Preventing Alzheimer's: A Lifelong Commitment?

A sweating man feverishly pumping an exercise bicycle may not seem to have much in common with a chess player coolly contemplating her next move. Yet both may be protecting their brains from the ravages of Alzheimer's disease. Recent results, some from epidemiological studies and others from investigations of animal models of Alzheimer's disease, suggest that exercise—both physical and mental—can help the brain combat the pathological changes that cause the illness.

If so, then people who engage in physical exercise and intellectual activities such as reading, solving crossword puzzles, and playing cards or chess may be able to slow down the development of Alzheimer's disease, perhaps delaying it long enough that incapacitating symptoms won't appear during a person's lifetime. "The brain is an organ that, like any other organ, ages depending on how it's used," says neurologist Robert Friedland of Case Western Reserve University School of Medicine in Cleveland, Ohio.

Yet parts of the story may not be that simple. Researchers are debating, for example, whether intellectual activities are actually protective or whether people who participate in them are more resistant to Alzheimer's disease, possibly because of the way their brains developed.

Building a cognitive reserve

Parents who warn their children that they will regret not going to college could be correct—but in an unexpected way. Over the years, several studies have shown that formal education seems to protect against Alzheimer's disease. For example, a 1997 study of 642 elderly people, conducted by Denis Evans of Rush Presbyterian–St. Luke's Medical Center in Chicago and his colleagues, found that each year of education reduces a person's risk of Alzheimer's disease by 17%.

As suggested in the late 1980s by Robert Katzman of the University of California, San Diego (UCSD), education might protect against Alzheimer's disease by increasing the number and strength of neuronal connections in the brain, thus improving an individual's so-called cognitive reserve. According to this theory, later in life when Alzheimer's pathology begins to eat away at the brain's neurons, people with larger reserves would be better able to cope with the onslaught.

One recent study supporting Katzman's idea came 2 years ago from a Rush Presbyterian–St. Luke's team led by David Bennett and Robert Wilson. Since the mid-1990s, these researchers have been following a group of older Catholic priests, nuns, and brothers who had agreed to donate their brains after they died.

Healthy bodies, healthy minds? Some studies show that exercise can slow cognitive decline.

Analysis of the brains available in 2003, 130 in all, showed no correlation between education and the formation of plaques and tangles, the abnormal brain deposits that characterize Alzheimer's disease. But a battery of 19 tests performed periodically in the years before the donors died revealed that people with high levels of education better maintained their cognitive abilities. Wilson says that the highly educated participants didn't develop Alzheimer's disease until they had about five times as many plaques and tangles as the less educated participants. "This suggests that education or cognitive activities achieve their effects by helping the brain tolerate the pathology," he says.

Not everyone finds support for the cognitive reserve theory, however. The so-called Nun Study points to a different conclusion: Early variations in how the brain develops makes some brains more resistant to developing Alzheimer's pathology than others.

David Snowdon started the Nun Study more than 15 years ago, when he was at the University of Minnesota, St. Paul. It originally included 678 members of the School Sisters of Notre Dame, all of whom were born before 1917. Snowdon, now at the University of Kentucky in Lexington, reasoned that studying nuns would help him identify factors that influence Alzheimer's development because they all have similar lifestyles and medical care. This eliminates some variables, such as smoking, that might skew the results.

As in other studies, Snowdon and his colleagues found that high education levels seem to protect against Alzheimer's disease. The researchers originally thought that this supported the idea that more education leads to a higher cognitive reserve. But analysis of biographical essays the sisters had written when they entered the convent, usually in their early 20s, pointed in a different direction. The early writings, Snowdon says, were an even better predictor of who would get Alzheimer's disease than education level. "Those who had the lowest linguistic skills at age 22 had a very high risk of Alzheimer's," Snowdon says. Indeed, most of the cases occurred in the nuns whose essays put them in the bottom third on the linguistic ability scale.

When Snowdon, neuropathologist William Markesbery, also at the University of Kentucky, and their colleagues examined the brains of nuns who had died, they found that those of lower linguistic ability were also much more likely to have signs of Alzheimer's disease such as brain shrinkage and tangles, although not plaques. That finding

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took Snowdon by surprise. He points out that if the lower risk of Alzheimer's disease in the high-linguistic-ability group was solely due to their having a better cognitive reserve, the pathology ought to be similar in all the nuns. Instead, it appeared as if the brains of the sisters with higher linguistic ability were somehow more resistant to developing the pathology in the first place. This, Snowdon suggests, might reflect differences in how the brain develops before birth and in early life. "Ultimately, it gets down to brain wiring and the biological mechanisms that defend the brain from disease," he says.

That doesn't mean, however, that there's nothing we can do to decrease our likelihood of getting Alzheimer's disease. "Genes are the driving force, but it's highly likely that diet and lifestyle influence Alzheimer's risk," Snowdon says. One indication of this comes from Margaret Gatz of the University of Southern California in Los Angeles.

In work she described at the International Conference on Prevention of Dementia held 2 months ago in Washington, D.C., she and her colleagues identified 109 pairs of identical twins in the Swedish Twin Registry in which one had been diagnosed with dementia and the other had not. "We do find that there is a difference in education. The twin with dementia had significantly less," Gatz says. So even in these genetically identical individuals, education apparently pays off in lowered Alzheimer's risk.

Several additional studies by teams including Friedland's, the Rush Presbyterian group, and Herman Buschke and his colleagues at the Albert Einstein College of Medicine in New York City suggest that a lifelong commitment to intellectual activities may aid in—indeed, may even be necessary for—maintaining any protection against Alzheimer's disease accrued in early life. "All forms of leisure activities requiring mental activity—reading, puzzles, cards, board games, crafts—are protective," Friedland says. "I believe they all involve learning in some way."

Conversely, Friedland and his colleagues found that one leisure activity that is arguably not intellectually demanding—watching television—was associated with an increased likelihood of developing Alzheimer's disease. Using questionnaires, they surveyed 331 normal controls and also the close associates, primarily spouses and children, of 135 Alzheimer's patients to find out what activities they participated in during midlife. As reported in the July issue of *Brain and Cognition*, the patients had watched more television; each additional hour of watching per day increased the Alzheimer's risk by a factor of 1.3. That doesn't necessarily mean that heavy television watching rots the brain. Rather, Friedland says, it may be a marker for an intellectually inactive lifestyle.

These epidemiological studies all suffer from the same complicating factor, however: Much evidence—including the Nun Study and a meta-analysis of 47 studies reported in the 31 July issue of *Neuropsychology* by a team led by Lars Bäckman of the Karolinska Institute in Stockholm, Sweden—indicates that Alzheimer's disease develops slowly over many years before failing memory and other symptoms become apparent. Although researchers have conducted long-term prospective studies that try to exclude people already showing Alzheimer's symptoms, it is hard to eliminate the possibility that low participation in cognitively demanding activities may be an early symptom of the disease rather than a cause.

Mind matters. A study of nuns suggests that high linguistic ability early in life correlates with lower Alzheimer's risk; engaging in lifelong mental activities, including crafts, may also help stave off the disease.

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More reason to exercise

Pursuing an intellectual life may not be the only tack that people can take to ward off Alzheimer's disease. Some recent research indicates that physical exercise can be as good for the mind as for the body, although the literature on this issue has been mixed, with not every study showing a benefit.

A few years ago, Arthur Kramer of the University of Illinois, Urbana-Champaign (UIUC), and his colleagues performed a meta-analysis of 18 trials involving adults between the ages of 55 and 80 that explored the effects of physical exercise on performance of various cognitive tasks. They concluded that the answer to the question, "Does aerobic exercise enhance cognition?" was an "unequivocal yes."

Since then, additional studies have borne out that conclusion. These include two large prospective epidemiological studies that focused on women. In one, Kristine Yaffe and her colleagues at UC San Francisco, followed for 6 to 8 years nearly 6000 women over age 65 who did not show signs of Alzheimer's disease at the time they were recruited into the trial. The other trial comes from Francine Grodstine of the Harvard School of Public Health and her colleagues, whose study group included 18,766 women aged 70 to 81 from the Nurses' Health Study. Both studies reached the same conclusion: Women who got the most exercise, mainly walking, showed less cognitive decline over the years than women at the low end of the activity scale.

Varying one's exercise routine may also have mental benefits beyond relieving boredom. Constantine Lyketsos of the Johns Hopkins Medical Institutions in Baltimore, Maryland, and his colleagues have looked at the effects of physical activity on mental abilities in more than 3000 men and women in the Cardiovascular Health Cognition Study. "What mattered wasn't the absolute energy expenditure but the number of activities," Lyketsos says.

As reported in the April issue of the *American Journal of Epidemiology*, study members who engaged in four or more physical activities, which could be anything from gardening to jogging or biking, had about half the risk of dementia as that of participants who engaged in one or none. The effect was primarily seen, however, in persons who did not carry a gene variant called *ApoE4* that's

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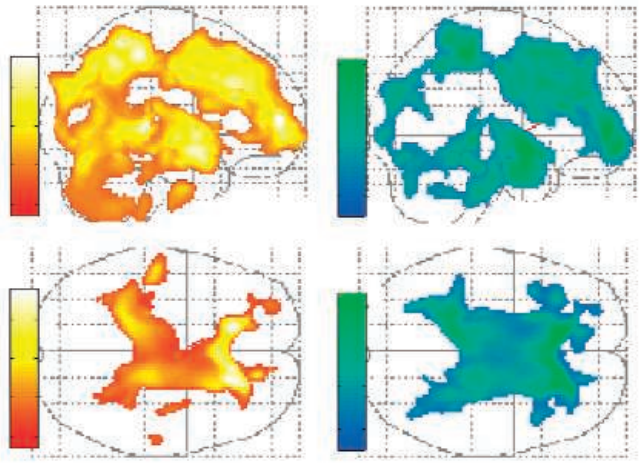
known to increase Alzheimer's risk. In the *ApoE4*-endowed population at least, genetics seems to trump activity.

The exercise studies all have the same potential downfall as the ones focusing on education and mental activities: the possibility that low activity levels are an early sign of Alzheimer's disease rather than a cause. But the exercise conclusions receive additional support both from imaging studies of human brains and from investigation of animal models of Alzheimer's disease.

Neurobiologists have known for some time that the human brain shrinks with age. Between ages 30 and 90, the losses range from 15% to 25% of brain matter, with the shrinkage particularly severe in areas such as the frontal and temporal cortex that are involved in memory and learning. About 2 years ago, Kramer and his colleagues confirmed such cortical shrinkage by using magnetic resonance imaging (MRI) to observe the brains of 55 older adults. But they also found that those losses were much reduced in the most physically fit individuals (assessed by performance on a treadmill).

In a second set of experiments, Kramer and his colleagues used functional MRI to assess brain activity in subjects performing a cognitive task. The more physically fit individuals not only performed better on the task than the less fit participants, but their brains also showed higher activity in the areas associated with the task. "Fitness training improves neuronal efficiency and performance," Kramer says. "Older brains are a lot more flexible and plastic than we have been led to believe."



Brain preservation. The brain images at left show the areas of gray matter (*top*) and white matter (*bottom*) that shrink with age. As indicated by the images at right, cardiovascular fitness can help preserve those brain regions.

Lessons from rodents

How physical exercise enhances brain maintenance and function is unclear, but work with rodents points to several possibilities. One is that it improves cerebral blood flow, thus providing better nourishment to the neurons. For example, William Greenough and colleagues at UIUC have shown that exercise increases blood flow to rat brains, at least partly by stimulating the growth of the capillary vessels feeding the cortex.

Another possibility is that exercise turns up production of proteins that stimulate neuronal growth. About 10 years ago, Carl Cotman's team at UC Irvine, found that the brains of rats who ran voluntarily on a wheel show increases in one such factor, BDNF (for brain-derived neurotrophic factor). The increase was particularly strong in the hippocampus, an area involved in learning and memory that's hard-hit by Alzheimer's disease.

Consistent with that finding, researchers including Greenough and Fred Gage at UCSD, have shown that exercise or so-called enriched environments in which animals live in cages equipped with exercise wheels and other toys can increase formation of brain neurons and lead to other changes that should strengthen neuronal connections.

For example, the numbers of dendrites, the tiny projections of nerve cells that receive incoming signals, normally decline with age. But Greenough's team found that keeping rats in an enriched environment could counteract that decline. All but the oldest animals kept in such an environment showed increases in dendrite numbers, and even those very old rats maintained their dendrites better than control rats kept in standard lab cages equipped with nothing more than food, water, and bedding. "At the younger ages, use it [the brain] and gain," Greenough says. "And at the older ages, use it or lose it."

Exercise may even prevent formation of the amyloid typical of Alzheimer's disease, although the evidence, derived from animal models, is far from clear. Sam Sisodia's team at the University of Chicago in Illinois has been studying mice genetically modified to overproduce a protein called β amyloid, a major plaque constituent. As the researchers report in the 11 March issue of *Cell*, mice kept in an enriched environment produced much less of the protein and had fewer plaques than did animals kept in standard cages (also see *Science*, 11 March, p. 1547). The effect was especially pronounced in those animals who spent the most time on the running wheels, Sisodia says.

The Sisodia team didn't determine whether the enriched environment improved the animals' learning abilities, but in a similar experiment, Cotman and his colleagues did. The Irvine group found that voluntary exercise, again running on a wheel, not only decreased the number of plaques in the hippocampus and cortex of mouse brains but also improved a rodent's performance on a cognitive task, learning to find a hidden platform in a water maze. (The results appeared in the 4 May *Journal of Neuroscience*.)

But not everyone has found that an enriched environment results in decreased plaque formation in Alzheimer's mice. In 2003, Joanna Jankowsky of the California Institute of Technology in Pasadena, David Borchelt of Johns Hopkins University School of Medicine in Baltimore, and their colleagues reported just the opposite: that it can lead to increased plaque formation. That experiment has been criticized on the basis that the animals were under stress. Jankowsky disputes that, noting that her team has since done additional experiments with a different genetically altered mouse strain. Again, they found that β-amyloid and plaque deposition increased when compared to control animals kept in standard cages. "Not only have we found the same result, but we found it in another strain of mice," Jankowsky says.

Even so, the experiment sounds a hopeful note about the effects of enrichment. All the animals kept in the enriched environment showed improved performance on three different cognitive tests, although the mice with high β-amyloid production fared less well than animals with lower levels.

The reason for the discrepancy between the various groups' plaque findings are unclear, although it might be due to differences in the strains of mice used. Still, Cotman describes the recent results as "cool." He points out that, taken together, they indicate that it may be possible to prevent or slow the mental decline of Alzheimer's disease with or without decreases in plaque formation.

Researchers warn, though, that people need to act before they get old. "If you're going to do something to ward off Alzheimer's, you have to do it before memory problems develop," Snowdon says. On the bright side, the interventions to prevent Alzheimer's disease are looking pretty much like the same ones recommended to prevent obesity and cardiovascular disease. Yaffe, who runs a memory clinic, notes that she tells her patients that exercise is "inexpensive, has very few side effects, and if worst comes to worst, it's good for your body."

—JEAN MARX

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