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Buff and Brainy

Exercising the body can benefit the mind

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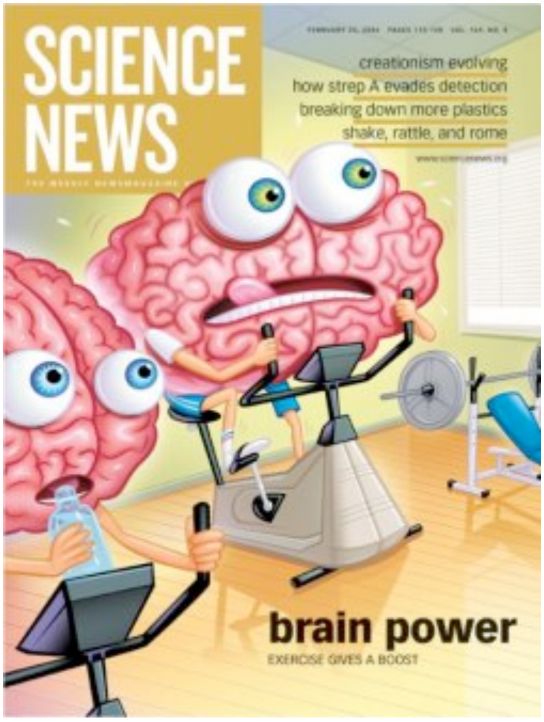
This is part one of a two-part series on lifestyle and brain fitness. Part II: "Eat Smart," is available at http://www.sciencenews.org/articles/20060304/bob8.asp.

Anyone who frequents the local gym has probably noticed a cyclical pattern to attendance. Workout kings and queens exercise religiously throughout the year, but as swimsuit season approaches, a rash of new faces flocks to the facility. Every treadmill is taken, each elliptical machine is engaged, and without fail, there's a waiting line for a weight machine.



Just as physical exercise primes the body, researchers are finding that it also primes the mind. Exercise prompts brain cells to multiply, strengthens their connections, and boosts their resilience against damage and disease.
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While exercise may be the path to looking great in a two-piece, everyone knows that it's also healthy for the body. It strengthens the heart and lungs, shores up thinning bones, and wards off a host of evils, including diabetes, heart disease, and stroke.

But what these newly inaugurated gym rats probably don't know is that besides buffing up their bodies for summer, they're also buffing up their brains. New research suggests that physical exercise encourages healthy brains to function at their optimum levels. Fitness prompts nerve cells to multiply, strengthens their connections, and protects them from harm. Benefits seem to extend to brains and nerves that are diseased or damaged. These findings could suggest new treatments for people with Alzheimer's disease, Parkinson's disease, and spinal cord injuries.

Sweating to the oldies

The cliché about a healthy mind residing in a healthy body has ancient roots. The famous quote of the same meaning, *"mens sana in corpore sano"* came from the Roman writer Juvenal in the early 100s A.D. And a century earlier, the philosopher Seneca was prescribing exercise as a way to achieve both physical and mental health.

But it wasn't until the early 1950s that reports that exercise conveys neurological benefits appeared in the scientific literature. These articles usually described what doctors had witnessed in their own practices, says neurobiologist Fernando Gómez-Pinilla of the University of California, Los Angeles. "This clinical literature described that exercise could be good for many different things," he says. The studies cited benefits ranging from alleviating depression and pain to regaining mobility in paralyzed limbs to maintaining good memory in old age.

However, for scientists who research how nerve cells work at a molecular level, such reports raise a bevy of questions. Gómez-Pinilla and other neurobiologists have aimed to fill this information gap by working with lab animals such as mice and rats—creatures that can be easily manipulated to sort out each one of an experiment's variables and that, unlike people, can be dissected in the end to get an insider's view of the brain.

By the mid-1990s, researchers began to get answers. Preliminary studies indicated that when lab animals exercise, their nerve cells release chemicals called neurotrophic factors. These proteins buffer nerve cells against illness or injury, prompt them to grow and multiply, and strengthen each neuron's connection with other nerve cells.

Out of the variety of neurotrophic factors released during exercise, however, scientists found that one in particular stood out: brain-derived neurotrophic factor, or BDNF. This protein seems to act as a ringleader, both prompting brain benefits on its own and triggering a cascade of other neural health–promoting chemicals to spring into action.

"I think of BDNF as brain fertilizer. It's thrilling to see what it does to cells in culture," says Carl Cotman, a neuroscientist at the University of California, Irvine. Sprinkling a dilute solution of BDNF onto neurons in a lab dish makes the cells "grow like crazy," he adds. The cells sprout branches prolifically and extend them rapidly.

Let's get physical

Knowing what BDNF can do to neurons in the lab, researchers wondered whether the BDNF that exercising animals produce has similar effects on neurons in their brains. If so, could these physical effects translate into behavioral ones, making the animals learn quicker and better?

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In 1999, Fred H. Gage of the Salk Institute in La Jolla, Calif., and his colleagues, including Salk's Henriette Van Praag, began exploring these questions. They studied two groups of healthy mice housed individually in cages that were identical except for one detail: One group of mice had running wheels.

"The mice just love [the wheel]. They run on it as soon as you put it in their cages," says Van Praag. "If you let them run as much as they want, they run all night long."

Over the next several weeks, the researchers kept track as the runners voluntarily racked up an average of 4 to 5 kilometers on their wheels every night. The scientists then tested whether the groups differed in how quickly each mouse solved a popular learning test known as the Morris water maze.

Although both groups of mice swam at about the same speed, Gage and his colleagues noticed that the runners learned the location of a platform hidden under the maze's opaque water significantly sooner than their less-fit counterparts did.

Dissections showed that the runners had about twice as many new brain neurons as the sedentary mice did.

When the researchers tested individual neurons isolated from both groups, they discovered that neurons taken from the runners showed greater signs of strengthened connections and cellular learning.

In a related study published in 2004, Gage's team teased out the molecular factors responsible for the behavioral effects that come with exercise. The researchers provided a group of rats with running wheels and compared them with rats without access to the wheels. On average, the runners voluntarily racked up an astounding 48 km per day over the next several weeks.

When they dissected the rats' brains, Gage's team found changes similar to those that they'd seen in the previous study's mice: The runners had more new neurons and stronger connectivity, which is evidence of learning, than did the rats that didn't have running wheels. After examining the messenger RNA of both groups, an indicator of gene expression, the researchers found that the running rats had consistently higher activity in the gene that codes for BDNF than the nonrunners did.

Gómez-Pinilla and his colleagues added more evidence that BDNF is a primary source for the behavioral benefits of exercise. Like Gage's group, Gómez-Pinilla's team worked with rats that were either sedentary or had access to a running wheel. After a week, some members of each group began receiving daily injections of a drug that blocked the action of BDNF. The rest of the animals were injected daily for several days with a chemical called cytochrome-C, which isn't known to cause any physical or behavioral effects.

The researchers then tested all the animals on the Morris water maze. While runners receiving cytochrome-C excelled at the test, runners that received the chemical that blocked BDNF performed only as well as the sedentary mice did. Performance by the nonrunners was about the same, regardless of which injection they received. "If we block the action of BDNF, we block learning and memory," concludes Gómez-Pinilla.

Keep on moving

With mounting evidence of what exercise and its associated BDNF can do for healthy animals, researchers speculated that a similar mechanism could benefit animals and people stricken with neurological disease or injury. For example, in the April 27, 2005 *Journal of Neuroscience*, Cotman and his colleagues suggested that exercise could slow the progression of Alzheimer's disease.

In the study, Cotman's team worked with mice that were genetically predisposed to develop an Alzheimer's-like disease. When they're a few weeks old—that's young adulthood in mice—the rodents' brains start accumulating a protein known as beta-amyloid. In the brains of people with Alzheimer's, this protein surges to form thick plaques that are one of the hallmarks of the disease.

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As in other exercise-related studies, Cotman housed Alzheimer's-prone mice individually in cages, some of which were equipped with running wheels. At the start of the experiment, the animals were around 1 month old. Alzheimer's-like symptoms "had barely started by then," says Cotman.

After 5 months, the researchers tested the animals in the Morris water maze. As in the earlier studies, the exercisers fared significantly better on that memory test than the sedimentary mice did.

However, in the "really exciting" part of the study, says Cotman, he and his colleagues dissected the animals' brains at 6 months of age to measure the beta-amyloid. They were surprised to find about half as much accumulation of the substance in the runners as in the nonrunners.

Cotman says that his team hasn't figured out how exercise reduces the buildup of amyloid-beta. But regardless of the mechanism, he notes that his results suggest that physical activity could eventually fight early Alzheimer's disease.

Exercise also shows promise in preventing Parkinson's-like symptoms from developing in animal models of that disease.

Surveys of lifestyle and health have suggested that people who exercise moderately, such as walking an hour each day, are less likely than others to develop Parkinson's disease. For the past 5 years, Michael Zigmond of the University of Pittsburgh and his colleagues have been experimenting with rats to explain this preventive effect.

In one study, the researchers forced healthy rats to exercise on a treadmill daily for a week. They then injected the animals with a chemical called 6-hydroxydopamine, which selectively kills dopamine-producing neurons. These cells also die in Parkinson's disease patients.

After several days, Zigmond's team examined the animals' brains. Compared with rats that received 6-hydroxydopamine but hadn't worked out on the treadmill, the exercisers lost fewer dopamine-producing neurons. Earlier studies had suggested that a protein called glial cell–derived neurotrophic factor (GDNF) protects dopamine-producing neurons in patients with Parkinson's disease and that neurons produce GDNF, just as they do BDNF, in response to exercise. So, Zigmond proposes that GDNF protected brain cells in the rats that exercised. He described his team's findings at the Society for Neuroscience meeting in October 2005 in Washington, D.C.

Researchers are also exploring physical activity as a way to treat neurological injuries, such as spinal cord damage. Although physical therapists have long helped patients regain some function by moving individual limbs affected by neurological damage, they have typically considered a patient with paralysis from the waist or neck down too damaged to rehabilitate.

"When you're told to go home and sit in a chair, your body doesn't get the feedback that comes from physical activity," says John McDonald, director of the International Center for Spinal Cord Injury at the Kennedy Krieger Institute in Baltimore. He developed exercise programs for Christopher Reeve as part of the late actor's therapy after his paralysis.

Without the neurotrophic factors produced in response to physical activity, McDonald hypothesizes, the nervous system fails to establish connections between damaged neurons and grow new ones.

To alleviate this problem, McDonald and his colleagues came up with a way for people with extensive paralysis to exercise. The researchers started with exercise bikes that had been equipped with electrodes that stimulate a patient's muscles to pedal. Heavy versions of these electrical-stimulation bikes had been used in physical therapy years ago, but their expense and inconvenience had made them fall out of favor. McDonald worked with the bikes' manufacturer to design models light enough for patients to use at home.

In a recent study, 24 people who had been paralyzed for an average of 5 years used the special bikes three times a week. Another 24 participants only stretched. After 2 years, 40 percent of the exercisers had regained some motor function, compared with only 4 percent of the other patients.

More research could eventually boost the bikes and similar assisted-movement equipment to become standard therapy for spinal cord injuries, says McDonald.

Long may you run

While evidence is soaring for exercise's brain benefits, physical fitness in the United States is plummeting. According to a report issued recently by the Centers for Disease Control and Prevention, almost one-fifth of people 18 and over exercise for less than 10 minutes a week. Only 46 percent of adults performed the recommended 30 minutes or more of brisk walking or other moderate exercise 5 days a week.

Whereas public health experts worry about the effects of a sedentary lifestyle on rates of heart disease, diabetes, and other health problems, Gómez-Pinilla is concerned that a lack of physical exercise could also foretell a wave of decreasing brain health for the United States.

"Locomotion played a very important role in evolution. Animals had to move to find food and run away from predators. Exercise had a direct action on brain regions related to cognition," he says. "Normally, when two functions evolve in this way, you can't separate them."

But it's never too late to pick up an exercise program, according to psychologist David Albeck of the University of Colorado at Denver. Sedentary middle-aged and elderly rats placed on a walking program showed improvements in learning and memory, compared with sedentary rats of the same age, Albeck's team reported at the 2005 Society for

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Neuroscience meeting.

Furthermore, memory tests given to 1,740 people over 65 during a 6-year project have linked moderate exercise to reduced risk of dementia. These results were published in the Jan. 17 *Annals of Internal Medicine* by a Seattle research team.

That's yet another piece of good news for the pre-swimsuit season rush of exercisers that will appear, like clockwork, at gyms across the country. For these new gym rats, starting to exercise is a smart move, says Zigmond, but the smartest move will be to stick with exercising for years to come.

"If somebody were to stop me in the street and ask me what to do, I wouldn't have any problem telling them to exercise," he says. "There are lots of reasons to exercise, and virtually no reason not to."

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