

# THE ELASTIC BRAIN

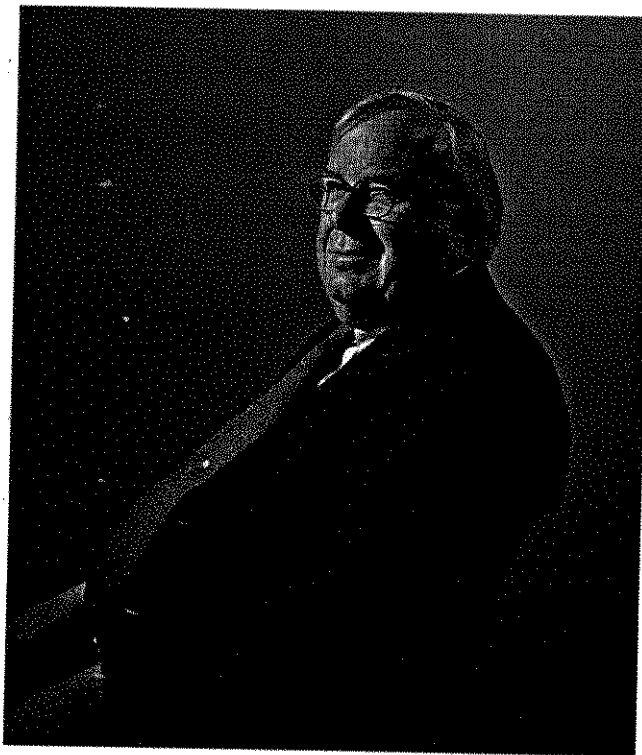
Michael Merzenich believes you can tone your mind and stave off memory loss. All it takes is time in his mental gym

BY KATHERINE ELLISON

In his twenties, Mike Merzenich dreamed of mapping the neurobiology of the soul. "I was interested in the genesis of the self," he says. "It's the kind of thing you think about when you're young and dumb." Four decades later, he has scaled back his ambitions. Now a graying 64, he hopes merely to reverse the toll of aging on the brain and cure schizophrenia. Without surgery or drugs.

Merzenich, a neuroscience professor at the University of California at San Francisco, aspires to "fix" brains with a series of innovative computer programs that he and his colleagues have designed, most notably his new Brain Fitness Program to help buff up gray matter that has turned flabby with age. The technique relies on a process called plasticity—the brain's innate capacity to reshape itself and even increase its complexity throughout a lifetime, depending on experience. Merzenich's faith in harnessing plasticity could change the way we think about mental health.

"We're going to revolutionize the way an older person looks at the end of life," he vows.



The concept of brain plasticity first came into vogue in the 1960s and 1970s. Back then, it referred mainly to the major developmental leaps seen in very young brains. Scientists assumed that adult brains were entrenched in their operating modes. Over the past two decades, however, a wave of studies—including Merzenich's own seminal research on monkeys—has shown that adult brains can also significantly change, producing new and modified inter-neuronal connections and even a limited number of new neurons. Although these changes are far less striking than those in young brains, the potential has inspired a burst of optimism about the human condition and launched a new era of neuroscience.

The genial, stocky Merzenich is this era's foremost apostle. "He's the father of neuroplasticity research," says UCLA research psychiatrist Jeffrey Schwartz, who has written widely on the topic. Merzenich may also be its most prolific entrepreneur, as he shuttles between his university lab and the two companies he has cofounded: the Scientific Learning Corporation in Oakland and Posit Science in San

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Francisco. His sometimes awkward straddling of the corporate and nonprofit worlds has placed him squarely in the middle of a heated debate over the issue of conflict of interest in the research world. Some colleagues, even while lauding his seminal early work in brain plasticity, charge that he cannot be objective about his research while promoting the fruits of it. The counterargument is that research advances do not matter unless they reach the people they are supposed to help, and Merzenich has been extraordinarily successful at making that happen.

The first of his companies—the Scientific Learning Corporation, launched in 1996—markets Fast ForWord, a much-publicized computer regimen for children with learning disabilities. Merzenich coinvented Fast ForWord with Rutgers University neuroscience professor Paula Tallal and her university colleagues. The original software and its sequels have since been used by more than 800,000 children in 22 countries, bringing Scientific Learning some \$40 million in revenue in 2005.

But Merzenich's greatest commercial hit could come with a \$395 treatment called the Brain Fitness Program, marketed by Posit Science, in which he has a minority interest. If clinical tests currently under way confirm his predictions, the treatment could become a must-have for many of the 77 million baby boomers in the United States alone, who are already on Orange Alert for any minor memory lapse that might foreshadow cognitive breakdown. The first of these boomers turned 60 last year. Many of them have already watched their parents decline and are eager to do whatever they can to avoid joining the more than 50 percent of Americans who end up with significant cognitive impairment, including full-blown dementia, by age 85.

Merzenich says that some 80-year-olds who have used his program have shown gains that bring their performance into the realm of someone decades younger. "Pre- and post-testing documented a significant improvement in memory within the training group" as

opposed to a control group, he reported in an August 2006 paper in *Proceedings of the National Academy of Sciences*. This finding has yet to be independently confirmed in a peer-reviewed journal. But in recent, as-yet-unpublished research, MIT neuroscientist John Gabrieli has discovered an exciting, plausible explanation for the improvement Merzenich reported. In a controlled, double-blind study sponsored by Posit Science, Gabrieli subjected 12 patients with mild cognitive impairment to fMRI brain scans. Half of the group's members had used the Brain Fitness Program as prescribed, and the other half had not. Gabrieli found that the group who had used the program showed greater blood flow in the hippocampal region, important in memory, compared with controls. Posit Science is now planning a larger study.

Merzenich says his program works by reversing what he calls the "negative plasticity" of aging. "Older people tend to want an easy life," he says. "They don't realize how bad that is for them." Normal wear and tear gets compounded by sloth and pessimism in this

scenario: As people age, the brain starts to shrink, and the cerebral cortex thins. There is a drop in the chemical neuromodulators that speed information across the synapses, and even in the elaboration of dendrites and axonal arbors, the

neuronal architecture that supports learning. An older person suffers what Merzenich calls "noisy processing": bad signal reception, like a radio tuned between channels. Pretty soon, Grandpa finds it increasingly difficult to understand Junior's rapid speech and in frustration begins to avoid the kid completely. His confidence ebbing, he ducks other kinds of challenges, and his skills slowly erode from disuse—unless he does something to build them back up.

This, of course, is the goal of the Brain Fitness training, which begins with a series of fine-tuning exercises, targeting the rudimentary workings of the auditory system. The intensive and highly repetitive practice—a much more targeted and disciplined exercise than, say, doing crossword puzzles—is meant to overhaul the way the brain receives and interprets information, which Merzenich contends ultimately helps improve the efficiency of how that information is stored. His suggestion is that it is like cleaning the portals of perception, making subtle adjustments that sharpen attention to small or rapid details, building more clarity and focus.

The first exercise plays one of two swooping bird whistles—whooEE! or WHEEoo!—after which the user must mouse-click to indicate whether the sound is moving from low to high or high to low. Next comes another simple test called Tell Us Apart, which requires the user to distinguish between sounds that are closer to human language, like "bo" and "do." The exercises start out quite easy, growing in difficulty over time. They eventually include drills geared toward improving sustained attention and memory by requiring users to remember the details of long stories.

Success is lavishly reinforced during the training process. A cheery bell rings with each correct answer, while a garbage-can plunk notes mistakes. The program also features two cartoon scientists in lab coats who call out at frequent intervals: "Good job!" "Fantastic!" "Excellent!" and "Now you're cooking!" Merzenich insisted on these coaches, but after many people found them intolerable, he grudgingly included a feature to mute them. His theory is that

are also recommended to keep the connections between neurons toned.) "As it stands, this is a barrier," acknowledges Avram Miller, a financial guru and adviser to Posit Science. "But I think the time it takes could be reduced significantly."

Hearing this, Merzenich frowns and shakes his head. Cutting back on the hours is not in his plans. "It takes time to change the brain," he says. "You've got to think of it like going to a regular gym."

**Merzenich's brilliance inspires many of his colleagues, but there** are still questions about how far he can take his ideas. Harvard neurobiology professor John Maunsell, who has studied plasticity in the visual cortex, says he has not found the same degree of change as Merzenich has reported in the somatosensory and auditory systems. The discrepancy could be due to differences in how his team carried out its research, even the different species of monkeys involved, he says, but "there's a question here that needs to be answered."

Maunsell credits Merzenich as a pioneer in brain plasticity, yet adds: "The scientist is supposed to be this model of objectivity and completely disinterested in the outcome. You can't do that when you're promoting a product, so he has to sort of walk a line. And there are going to be compromises on both sides."

Merzenich dismisses the rap with a smile. "I don't give a shit if the academic community criticizes this," he says. "My feeling is simple. If you have something that can impact tens of millions of people, it's a responsibility to deliver it. And the only way you can effectively deliver it is in the real world. The simple fact is that if things don't work in the real world, ultimately they don't go very far. In the real world, people commonly measure things. If they don't work, they don't buy them and don't use them. That's really what matters to me."

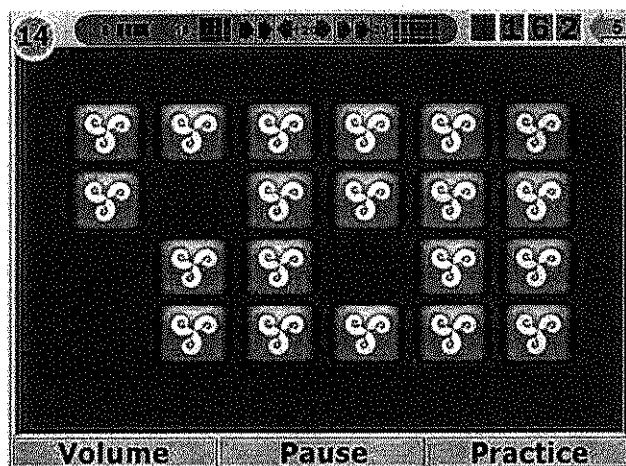
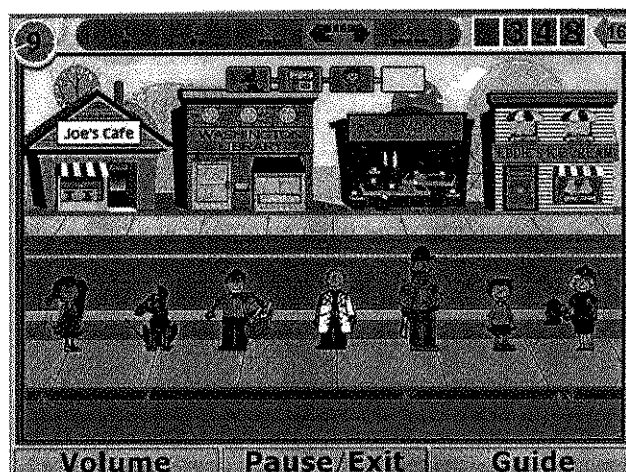
To be sure, this perspective raises some questions about the enduring popularity of wrinkle creams and diet supplements. Still, there is no lack of real-world endorsements for Merzenich's training programs. When it comes to Fast ForWord, Randy Poe, deputy superintendent of schools in Boone County, Kentucky, says, "We've had some testimonials from different parents that would make you cry." The program, he says, has delivered "significant gains in 7 out of 10 students."

The Brain Fitness software is collecting similar praise at the residential homes where Posit Science has been testing it. At the Redwoods, in Mill Valley, California, Cora Parick, a lively 92-year-old with a perfect white bouffant hairdo, says the course has improved her performance at the nightly domino games—"I can count better and remember the tiles"—and her ability to recall telephone numbers. When I asked if she thought any part of the improvement might be due to a placebo effect, or the considerable stimulation of learning to interact with a computer, she replies, "Who cares, if it works?"

Is plasticity as powerful as Merzenich believes? I am taken aback, in one phone conversation, when he casually says: "If you give me someone for three months, I could do anything to them. I could turn a Republican into a Democrat."

When asked about the comment several weeks later, Merzenich says that he was joking. In any case, the size of his vision has become his personal trademark. "The first time I had my interview with him, I'd read up on all his papers and felt I could handle whatever he threw at me," says Dan Polley, a former student, now an assistant professor at Vanderbilt Medical School. "But his first question was, 'What's it all about?'"

Merzenich spends about 40 hours a week in his UCSF lab, where he has been pursuing basic research on cognition and perception



The Brain Fitness Program developed by Michael Merzenich and his colleagues at Posit Science involves solving tasks displayed on a computer. For example, the top image relates to recalling a list of errands by the different people shown on the street. The bottom image concerns a task that involves comparing sounds and identifying the ones that are similar.

as well as collaborating on behavioral therapy for a condition known as focal dystonia, the loss of control of one or more fingers, also known as occupational hand cramp. At Posit Science, meanwhile, "there are about a billion other things we're interested in," Merzenich says. High on the list are programs to cope with the cognitive losses suffered by brain-injured people and chemotherapy and heart-surgery patients. Merzenich is also interested in testing the program on people with autism and bipolar disorder to see if their cognitive function could be improved.

With all this going on, Merzenich still manages to follow his own advice about living a life that is good for your brain. He exercises and does *The New York Times* crossword puzzle regularly and recently celebrated 40 years of marriage to his high school sweetheart, Diane Merzenich. He travels abroad often and comes home to tend a beehive, a garden, an orchard, and a vineyard at his Sonoma wine-country second home. And of course, he loves his work.

"If UC decided to cut my salary in half, I would not quit," he says. "I get up every day and don't know what I'm going to do, but I know it'll be good. What a life!" ■

the benefit of all this practice and encouragement can be seen inside the user's skull. The user's brain is engaged, and his neuronal connections strengthened, while the novelty and reward inherent in the program improve the release of neurotransmitters like dopamine, serotonin, and norepinephrine, which enable plasticity. His signal-to-noise ratio improves. Maybe he finds he is actually interested in what Junior is saying.

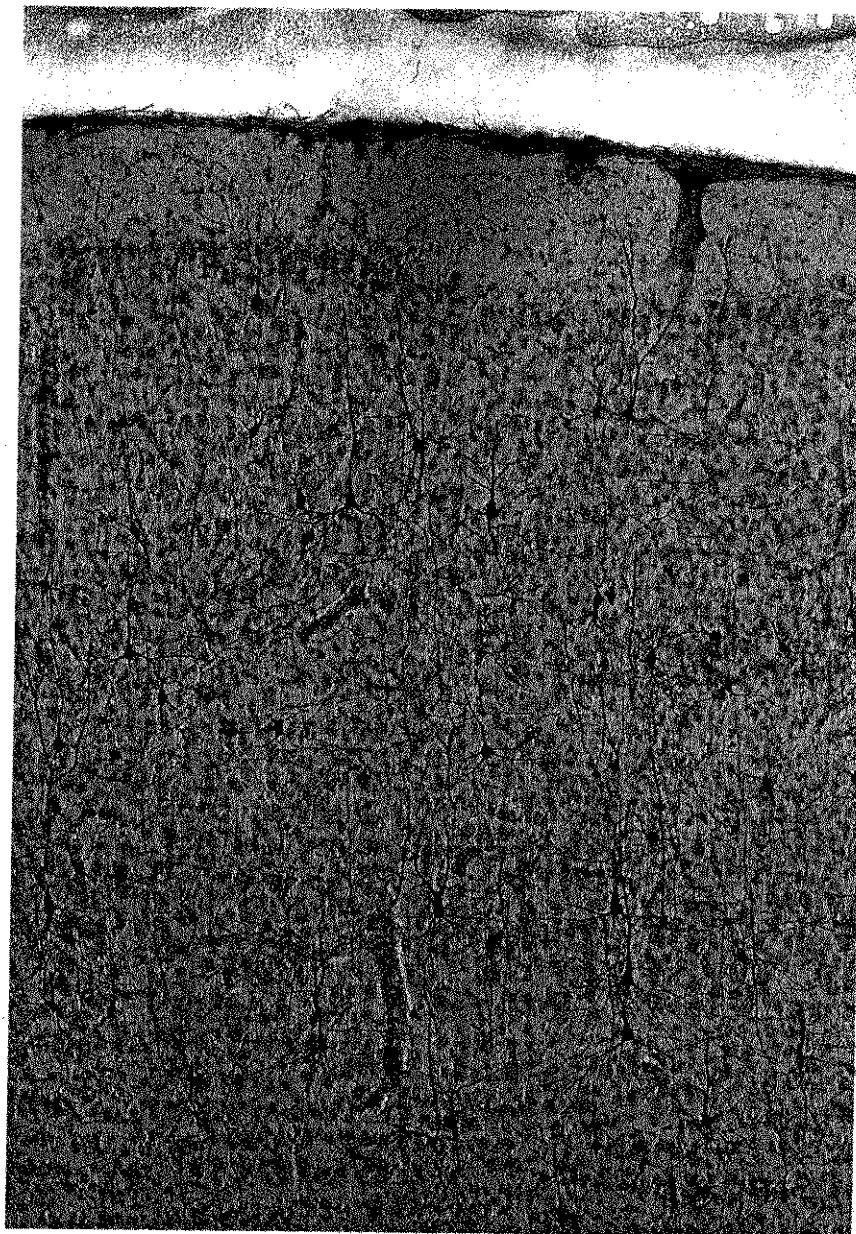
A dozen or more companies are promoting methods of memory-saving stimulation. Few have the stature of Merzenich, though.

**Spend any amount of time with Merzenich and you start to see reflections of his worldview in his software, which goads users to spare no effort in reaching for their maximum cerebral potential. Even the progressively quicker pace, as users acquire deeper skills, recalls Merzenich's teaching style. He is famous among his students for a one-word motivational speech: "Faster!"**

When I visit Posit Science's headquarters, which occupies most of two floors in a high-rise in the heart of San Francisco's financial district, the inventor in chief is in typical form. Roving through the company's computer-filled incubator, he spurs along a small group of twenty- and thirty-something engineers. He had put them to work on a program called Hawkeye, a series of exercises designed to pump up visual-processing capacity, much as the Brain Fitness Program works on the auditory system. "I want this accelerated," he tells them. "Getting it to a commercial form is not that far away."

The work ethic comes naturally to Merzenich, the third of six children of a foreman at a lumber mill in the small town of Lebanon, Oregon. His grandfather immigrated to America from a hilly region near Cologne, Germany. As Merzenich recalls in his self-published memoir, *A Childhood in the Sticks*, his parents raised their children with the expectation that they would all do something for the greater good. In high school, Merzenich was a voracious reader and the kind of tinkerer who built his own radio. He was also an energetic social networker: president of the science club and leader of the concert and dance bands. "I was a nerd for sure, but was successful at it and had good nerd connections," he writes.

Merzenich has long been as interested in engineering and the physical sciences as he is in basic biology and neuroscience. As an undergrad at the University of Portland, he impressed John Brookhart, the distinguished neuroscientist who would become one of his first mentors, with his efforts to record the electrical output of the nervous system of an insect. But it was Merzenich's groundbreaking experiments with owl monkeys, in the 1980s and 1990s, that cemented his reputation in the emerging field of plasticity. In a series of studies, he and his collaborators demonstrated dramatic changes in the adult monkeys' somatosensory cortex (the part of the brain that responds to sensory information) as a product of vary-



Neurons in the brain, including the large pyramidal cells (shown here as black spots), develop connections that change depending on experience—part of what makes learning possible.

ing kinds of input. In one famous experiment, researchers severed a nerve responsible for bringing information from a part of the hand to a specific area of the cortex. They found that once that nerve's input stopped, that same patch of real estate in the brain somehow began responding to other parts of the hand.

Yet while Merzenich continued this basic research, his own career was reorganized by his decision, made several years earlier, to collaborate on the development of one of the world's first cochlear implants—a medical device that has helped thousands of deaf people hear. Rather than amplifying sound as a hearing aid does, a cochlear implant electrically stimulates the auditory nerve, sending signals to the brain, which recognizes those artificial signals as sound. This alternate way of hearing takes time to learn, but eventually the brain is able to interpret this totally novel type of signal. For Merzenich, watching his patients adjust amounted to yet another impressive demonstration of plasticity, this time in humans.



## During his career Merzenich has explored one of the most stunning propositions of our time: We create ourselves, from the inside out, each day of our lives

The neuroscientist Vernon Mountcastle, Merzenich's grad school mentor at Johns Hopkins University, warned him not to join the world of business. Yet Merzenich's experience convinced him of the power of commerce to speed the availability of scientifically inspired products that can reduce human suffering. Conveniently for him and for UCSF, an amendment to U.S. patent law called the Bayh-Dole Act, passed in 1980, allows universities to license inventions without jeopardizing their federal research grants.

Merzenich proceeded to craft a career that has kept him exploring, and exploiting, the potential of one of the most stunning propositions of our time: We create ourselves, from the inside out, each day of our lives. The idea has echoes in existentialism, with its emphasis on freedom and responsibility, and in Buddhism, which teaches that willed attention can improve concentration and general mental health. But for Merzenich it is a rigorous piece of scientific insight.

**One of the newest and most surprising investigations at Posit Science** involves treating people suffering from schizophrenia with exercises similar to those already in use for learning-disabled children and the elderly. Merzenich is developing a 120-hour regimen that starts with the same training of the auditory system used in the Brain Fitness Program, adds the Hawkeye visual-processing component, and ramps up to more complex tests of information processing in a segment christened Aristotle.

Merzenich's work with schizophrenia may at first seem like a surprising detour. It is one thing to imagine that repetitive computer exercise might help restore brain "muscles" that have atrophied with age; it is something else entirely to speculate that such training could help people suffering delusions and hallucinations. Yet even though schizophrenia is popularly seen largely as an emotional illness, it is primarily about disordered thought. Merzenich says he was thinking about treating schizophrenia with cognitive training years before he came up with the Brain Fitness Program.

Today he has increasing reasons for optimism. Psychiatry professors Bruce Wexler, at Yale University, and Sophia Vinogradov, at UCSF, have independently found in randomized, controlled trials that people with schizophrenia have shown marked improvement after intensive and progressive cognitive training. Wexler's studies, begun in the mid-1990s, have shown the improvements to be lasting—up to 12 months—and capable of affecting real-life work performance. Patients with schizophrenia have long been known to have major problems with auditory processing, working memory, and language, similar in some ways to what happens to a brain ravaged by age, Wexler explains. Just like an elderly person who learns bad habits while attempting to cope with a decline in ability, a person with schizophrenia frequently slides from bad to worse. A potentially aggravating factor is that the severe memory problems accompanying the disorder mean that much of what happens to a person with schizophrenia seems surprising. A constant state of surprise triggers surges of the neurotransmitters dopamine and norepinephrine, which gradually poison the brain, according to Merzenich.

Merzenich is currently supervising clinical trials of his program for schizophrenia, conducted by Vinogradov and Wexler at UCSF and Yale. Pending the results, he plans to apply for approval of this use

from the Food and Drug Administration. Merzenich is hopeful that the right kind of training could ultimately free people with schizophrenia from drugs. Although Wexler suspects that this goal is overly ambitious, he does believe the training could greatly improve patients' lives. Scientists who specialize in schizophrenia also agree that Merzenich's regimen could have a great impact on prodromals, high-risk adolescents who have yet to have a psychotic break. Vinogradov has been awarded a grant by the Stanley Foundation to test Merzenich's programs on young people at this stage. The hope is that such intervention could prevent the first psychotic episode.

For now, the Brain Fitness Program remains Posit Science's main and most profitable focus. It got a major vote of confidence last summer, when Humana, the big insurance company, made it available either for no cost or for a reduced price to its Medicare-eligible plan members. Yet despite the enthusiastic testimony I heard from senior citizens who have tried the program, there are no formal studies published in peer-reviewed journals that demonstrate the program's effects. In their report in *Proceedings of the National Academy of Sciences*, Merzenich and his coauthors say Brain Fitness Program users in controlled studies showed an average improvement roughly equal to 10 years of memory performance, as assessed with a standardized test for memory and cognition known as RBANS (Repeatable Battery for the Assessment of Neuropsychological Status).

Posit Science is now sponsoring additional evaluations by outsiders, including a team at the Mayo Clinic. Glenn Smith, the principal investigator on that project, declined to comment on the work. But one of Smith's colleagues, Ron Petersen, director of the clinic's Alzheimer's Disease Research Center, called Merzenich's theory "enticing," then added: "Would I bet the farm on it? Not right now." Among a list of caveats, Petersen questioned the suitability of the control method in Posit Science's study, in which a group of age-matched subjects watched educational DVDs on computers. That relatively passive activity, he pointed out, matches up poorly with the interactive program, which would be much more stimulating, especially for someone without a lot of computer experience. "Why didn't they at least play *Donkey Kong* for eight weeks?" he asked.

Merzenich counters that Posit Science tested subjects in an unpublished study with video games that he says would be a more useful comparison than *Donkey Kong*. He says those subjects saw no improvement.

Petersen also questioned whether the RBANS test represents a meaningful improvement in real-world functioning and noted that the Posit Science team had not tested the longevity of the improvements past three months. "Cautious optimism is probably appropriate," he said. "But I'd bet they're being a lot more enthusiastic than that in their marketing materials." He is right about that. Posit Science's Web site last fall featured a photo of an attractive, smiling, white-haired couple on a motorcycle and enjoined visitors to "Be sharp. Stay sharp. For a vibrant life."

A second considerable hurdle for the Brain Fitness Program is the time and devotion it demands: an hour a day, five days a week, for eight weeks, of often tedious, repetitive drills. (Booster sessions