

Can Our Brain Repair Itself Through Exercise?

Animals Provide Insights for UPMC Research Team

By Frank Catanzano

Dr. Michael Zigmond pointed to his laptop resting on a conference table at the University of Pittsburgh's Center of Excellence in Parkinson's Disease Research. "Keep your eyes on the way each of these monkeys moves about the cage," he said, as he started the video.



Dr. Michael Zigmond

According to Dr. Zigmond, both primates had been administered a neurotoxin that selectively destroyed dopamine containing neurons in their brains' substantia nigra, effectively causing the motor symptoms of Parkinson's disease. One of the two Rhesus monkeys undertook a vigorous exercise program on a treadmill, while the other remained sedentary.

The difference in the way the animals each moved was startling. The Rhesus that exercised climbed easily about the cage, using both arms to navigate the bars, while the other monkey had difficulty moving about, keeping his left arm stiff and immobile, as would a human suffering from Parkinson's.

"Now take a look at their PET scans," as he pressed a button revealing images of the monkey's brains. The inactive Rhesus' dopamine neurons, colored purple, were dramatically reduced, while the exercised monkey's brain showed many more of the dopamine neurons that contributed to his ability to maintain motor skills.

Dr. Michael J. Zigmond, Professor of neurology and psychiatry at the University of Pittsburgh School of Medicine, is the Program Director of a National Institute of Neurological Disorders and Stroke-spon-

sored Center of Research focused on parkinsonism. He also has been the recipient of many other grants, including a MERIT award from the National Institute of Mental Health for his work on the neurochemical effects of acute and chronic stress.

Recent research at the Center involved a collaboration of an international team of researchers, which includes Dr. Judy Cameron, also at the University of Pittsburgh, as well as investigators at several other institutions in the United States and abroad, and is focused on the development of interventions that can slow down the development of Parkinson's disease. Special attention is being given to the effects of physical exercise and its ability to block the degeneration of the dopamine neurons that are normally lost in the disease.

Causes of PD

The paramount question is what causes roughly one person out of 100 over the age of 60 to exhibit the signs of Parkinson's disease (although it's estimated that 5 to 10 percent of those diagnosed are under the age of 40)? Researchers speculate it can be due to a combination of factors, such as environment, genetics, sex, age, head injury or exposure to toxic chemicals like pesticides.

People with Parkinson's experience difficulties transmitting neurological impulses, in some ways similar to a telephone switchboard with some of the lines crossed. Parkinson's symptoms can also be compared to surfing the internet with a slow speed dial up connection including the pauses, delays and even disconnects. A normal nervous system transmits neurological impulses instantly, more like an information super highway. Dopamine can be thought of as the lubricant that permits the super highway speeds.

"Brains can become damaged," said Dr.

Zigmond. "When that happens some of the capacity we had during brain development to make the right neurological connections would come in quite handy. The question we are trying to answer is, 'Does that capacity still exist in the adult and, if so, can it be triggered by exercise?'"

Dr. Zigmond and his research team have focused their studies of cellular and animal models to examine Parkinson's disease, which they believe is a multi-factorial disorder. The team is examining the role of what is technically called "intracellular signaling cascades" in determining the viability of dopamine neurons. These signaling cascades are essential in determining whether a neuron functions properly and even whether it lives or dies.

They hypothesize that exercise can stimulate the formation of "neurotrophic factors" such as Glial cell Derived Neurotrophic Factor (also known as GDNF), which is a molecule that helps the dopamine neurons survive by stimulating the intracellular survival cascades and thus protect the neurons from environmental toxins. If this is correct, it may provide important insights into new treatment regimes for PD.

Capacity for Self-Repair

A body of evidence is growing that suggests that our brain has a considerable capacity for self-repair. In a paper presented by Dr. Zigmond and associate Amanda D. Smith (Can the brain be protected through exercise? *Lessons from an animal model of Parkinson* *Experimental Neurology* 184 (2003) 31-39), explain that for the past 40 years animal studies have provided critical information on areas such as dopamine deficiency in Parkinson's and the effectiveness of the drug L-DOPA.

In earlier studies, the team used adult male mice and rats to test their hypothesis that intensive exercise of limbs affected by the degeneration of neurons will have a positive effect. It only recently was granted permission by the university's ethics board to use a small number of Rhesus monkeys in their experiments, which more closely emulated human

motor function.

"These results are extremely encouraging," Dr. Zigmond said. "While existing drug treatments for Parkinson's disease help supply dopamine to the brain and thus reduce the symptoms of the disease, they don't address its progressive nature, which will continue to advance." He hopes research into the effects of exercise on the brain will give PD patients an adjunctive therapy in addition to drugs that will work in harmony to delay the disease's progression.

Next Step: Humans

Dr. Zigmond believes that the next step is a comprehensive study of the effect of exercise on humans with Parkinson's. "It remains to be seen in clinical trials whether rigorous exercise can impact affected motor systems in people," he said. "We believe it does, based upon what we have learned from animal models thus far."

Dr. Anthony Delitto, Chair of the University of Pittsburgh Physical Therapy Department, and his team are currently exploring whether physical training will reduce the degeneration of dopamine neurons in humans.

"If these subsequent studies are successful, this also raises the interesting prospect that exercise will protect against a variety of other neurodegenerative conditions," Dr. Zigmond added. "But these next studies will take financial resources that have been dwindling. In light of the millions of people suffering from Parkinson's disease, it's critical that we and others continue our work. People must contact their legislators and push for more funding for research. In the last 8 years, real dollars for research has actually decreased. Opportunities for significant advances are being lost - we must reverse this trend!"



Exercising Down Under Keeps Him On Top of His PD

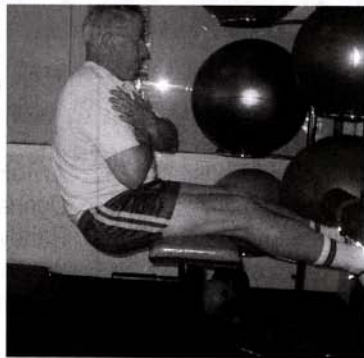
Neil Sligar is a 61-year-old Australian man who has exercised vigorously for nearly eight years despite having Parkinson's disease. His exercise regime is not alternative medicine. According to Neil, in a 2007 article that appeared in Shake, Rattle and Roll newsletter, he visits a neurologist and takes the medication he recommends.

"Getting PD had been beyond my control," he said. "Succumbing to heart disease or stroke was largely within my control. For the latter conditions, we know we should eat less, lower the proportion of fats in our diet, and devote regular time to physical activity. I know that Parkinson's disease was as yet incurable but wondered whether anything I could do might delay its symptoms."

In January 2000 Neil's lifestyle changed. He located a gym and worked with the gym manager to map out a program based on improved flexibility, improved stamina, and improved strength.

"My routine was, and remains, based on improving flexibility, stamina, and strength. I speculated that

stretching should ameliorate the rigidity of PD, running or riding would maintain my heart and lungs, and strengthening my body may delay a stooped posture. Regardless of its impact on PD, exercise could only be good for my general health.



Neil Sligar Exercising

"Whatever activity you choose, it has to be something you'll enjoy. We're not talking of a 10 week weight loss program or a 10 week program to make you look great in swimming attire. We're talking of a lifetime habit that's as normal as a daily shower. I go to a gym. You might prefer walking long distances, swimming, dancing, or something else. Just do it as vigorously as you can."

See inside for latest on UPMC research team and exercise...