The following are Alison Williams' notes on these topics, augmented by her comments on two lectures on the same themes. For the original lectures go to:

https://events.qwikcast.tv/public/QwikCast/QwikCastEvent?eventKey=1a1dbe73-e2f2-4945-9470-143f3f641805

1. **Gizelle Petzinger, based in University of Southern California, USA**

Petzinger is examining neuroplasticity – how the brain can make new connections.

NOTES: We already know that physical exercise protects the brain and increases its resilience; this research looks at how exercising affects the brain circuitry, especially the neurotransmitters. It has shown that (in Parkinsonian mice):

- Exercise modulates dopamine reception
- Exercise impacts glutamate neurotransmitters – it normalisises its reception

This is important because PD is a condition in which there is a physical loss of synapses (brain connections). Petzinger is proposing that if exercise can make changes in the morphology of the basal ganglia area of the brain in mice, then it should make changes in human brains.

What it means for PWPs

There are two types of exercise that are important for PWPs – aerobic and skills-based (goal-directed).

- **Aerobic exercise** increases blood flow to the brain and creates beneficial changes in the overall brain environment
- **Skills-based exercise** (goal-directed motor learning) repairs the brain circuitry, improving our synaptic connections so that we use the dopamine we have, more effectively. Petzinger said that skills-based exercise includes **Tai Chi, Dance, Yoga**.

She concludes by saying that **in managing Parkinson's, 50% is drug treatment, and**

50% IS LIFE STYLE

"Intensive exercise can help people with PD walk and move more normally, and research is beginning to reveal how it reconditions the underlying brain circuits."

There is a full article about this at the end of this note, and at:
http://www.pdf.org/en/fall09_exercise_parkinsons

2. **Gammon Earhart, based in Arcadia University, USA**

NOTES: Earhart is looking at the impact of different kinds of exercise on PD, and on how to maintain motivation and consistent practice. She concludes that:

- Individual working with a physical therapist maintains highest levels of improvement
- Group working with physical therapist is good
- Individuals working on their own at home find it difficult to maintain motivation and keep doing the exercises

And:

- The earlier after diagnosis the exercise starts, the better
- Aerobic exercise is important
- Strengthening exercise is important

There is a full article about this – and more – at the end of this note, and at http://www.pdf.org/en/research_earhart

Does Exercise Impact Parkinson's?

By Giselle M. Petzinger, M.D.

We all know that exercise is helpful to good health. We also know it is good for the heart and the muscles. But can it change the brain, and might these changes make an impact on Parkinson's disease (PD) symptoms?

The answer to both of these questions is yes.

Can the Brain Change?

We know that in PD, neurons — the brain cells that produce the chemical transmitter dopamine — are damaged and lost. We also know that there is a lag between the time when the loss of neurons begins and the time when Parkinson's motor symptoms start to show. In fact, by the time most people are diagnosed, nearly 80 percent of their dopamine neurons are already gone.

During this lag time, the brain is actually changing, compensating for the loss of dopamine neurons that occurs during the process of neurodegeneration. In fact, the brain reshapes itself throughout life in response to experience. As children learn motor skills, their brain cells are making connections and this process continues through adulthood.

Scientists call this ability to change and compensate, exercise-dependent neuroplasticity. Exercise may have an effect on the brain by driving this compensation. On a day-to-day basis, people with PD who exercise can move more normally than those who do not. We believe that exercise may be contributing to neuroplasticity — helping the brain to maintain old connections, form new ones and restore lost ones. This may actually outweigh the effects of neurodegeneration.

But what has been proven? There is compelling scientific evidence in animal models of PD that intensive exercise can alter the way the brain works and promote recovery. Research in my lab and those of my colleagues at the University of Southern California (USC), is showing how exercise improves walking and other motor skills in people with PD. It is also shedding light on how exercise influences neuroplasticity at the molecular level.

Exercise for Improved Walking and Balance in PD

Scientists who study stroke and traumatic brain injury have identified four features of exercise that drive neuroplasticity: intensity, specificity, difficulty and complexity.

To explore whether these findings apply to PD, we investigated the effect of exercise in two ways. One study was in mice that had been made Parkinsonian. The other study, conducted in collaboration with Beth Fisher, Ph.D., P.T., at USC, was in people who had been diagnosed with PD for less than three years. The human participants were divided into three groups to compare the effects of different levels of exercise. People in the high-intensity group exercised three times a week, an hour each time, on a body-weight supported treadmill — that is, a treadmill that supported them with a harness so that they didn't have to worry about falling. The second group did low-intensity balance and stretching exercises, which is what most previous studies of exercise in people with PD have evaluated. The third group did no organized exercise at all.

The body-weight supported treadmill combines all the features of exercise that we think are important for driving changes in the brain. The exercise is intense, meaning it moves fast and with high repetition. It is also complex. People are getting feedback from a trainer while they run, so they are simultaneously listening, processing the instructions and adjusting their pace. Exercising on the treadmill is also very task-specific: it addresses walking, a functional task that we need in our daily lives.

Over the course of 24 sessions, those in the high-intensity group walked and ran faster than those in the other groups, working up to speeds of five to eight miles an hour. They also took longer strides, and had better posture and bigger arm swings. And as they practiced on the treadmill three times a week, for an hour each time, every characteristic of their walking began to look more normal.

We also tested their balance. Though the participants were newly diagnosed and had not yet reported balance problems, we found — before they exercised — that already their balance was not normal. That is to say, when walking, they made very tight turns and they took small constrained steps. After several weeks of treadmill exercise, however, their turns became more stable. Balance, as well as gait, had improved.

How Exercise Changes the Brain

What happens in the brain to produce these visible benefits? To find out, we looked at the brains of the mice that had exercised under conditions parallel to the human study.

We found that exercising changed neither the amount of dopamine nor the amount of neurons in the animals' brains. But in the ones that had exercised, the brain cells were using dopamine more efficiently. We found that exercise improves that efficiency by modifying the areas of the brain where dopamine signals are received — the substantia nigra and basal ganglia.

At the molecular level, at least two things are happening to make dopamine use more efficient. Dopamine travels across a space between two adjacent brain cells called a synapse. This process is called signaling and it is essential for normal functioning. To end the signal, a protein complex called the dopamine transporter normally retrieves dopamine from the synapse. The first thing we found is that animals that had exercised possessed less of the dopamine transporter, meaning that dopamine stayed in their synapses longer, and their dopamine signals lasted longer. Secondly, we found that the cells receiving the dopamine signal had more places for the dopamine to bind in animals that exercised, and so could receive a stronger signal. This binding site is called the D2 receptor. We also studied the D2 receptor in a subset of our human subjects who were within one year of diagnosis and not on any medications, using the imaging technique known as positron emission tomography (PET). We found that in humans, too, exercise increased the number of D2 receptors.

Lastly, animal studies have shown that intensive exercise may also play a role in controlling glutamate, another molecule that signals between brain cells. Dopamine is responsible for holding glutamate in check, so when dopamine levels drop in PD, a chain of events is set off that leads to a build-up of glutamate signaling. The resulting surplus of glutamate damages the cells that control body movements. But animal studies show that exercise may play a role in normalizing glutamate signaling, thereby helping the brain to function normally and to promote recovery of the ability to move.

Conclusions

More research is needed to understand which aspects of exercise are most important, whether the benefits are long-lasting and whether drug and other therapies influence its effects. In studying the underlying molecular mechanisms, we may find new targets for drug therapies. In the meantime, we know the following: intensive exercise can help people with PD walk and move more normally, and research is beginning to reveal how it reconditions the underlying brain circuits.

Dr. Petzinger is Assistant Professor in the Department of Neurology, Movement Disorders Division at USC. Previously, Dr. Petzinger occupied a PDF-funded fellowship in Movement Disorders at Columbia University. This article was adapted from her presentation at a PDF webcast. To watch her presentation, please review ***PDF's Past Online Educational Events.***

Gammon M. Earhart, P.T., Ph.D.

In 2005, Gammon M. Earhart, P.T., Ph.D., was a new faculty member at Washington University School of Medicine in St. Louis, MO, studying differences in movement patterns between people with Parkinson's disease (PD) and healthy people. She was interested in why, when some people with Parkinson's disease turn around, they experience "freezing," the sudden inability to move. Then she learned of a study in which elderly people who were at high risk for falls improved their balance simply by learning how to dance the Argentine Tango.

For Dr. Earhart, it was an "Aha!" moment that opened a new direction for her research. Is it possible, she wondered, that dance lessons may also help improve balance among people with PD, whose risk of falls is high?

"Tango incorporates many of the movements that people with Parkinson's have difficulty with, including turning," explains Dr. Earhart. "The more I thought about it, the more it made sense. For example, falls often occur when people with PD try to step backward. If you are dancing Tango as the follower, you are dancing backward and learn a strategy for doing it. Also, there are many ways to turn in Tango, and there's lots of starting and stopping. Learning to execute and manage these movements could be valuable to people with PD."

So, Dr. Earhart began studying the Tango for Parkinson's disease. In 2010, PDF selected her for a research award through its International Research Grants Program, to test the idea for a year. (In 2011, she applied for and received a second year of funding.) International research grants are designed to support researchers who are trying out daring new ideas. The grants enable them to gather the preliminary data they need to make their case for additional funding from major agencies such as the National Institutes of Health.

Dr. Earhart's study included 52 volunteers who were living with Parkinson's disease and who were experiencing common problems with movement and balance. At the beginning of the study, they were performing similar levels of physical activity. About one half of the volunteers were assigned to take Tango lessons for a year, under the supervision of Dr. Earhart and her colleagues; the other half maintained their normal routines. It turned out that many of the Tango students experienced improvement in their Parkinson's disease symptoms. They were also able to walk farther and faster, and their balance improved. Among the non-Tango group, movement symptoms worsened or held steady.

Researchers also found that, over the course of a year, the people with PD who had learned Tango increased their participation in such activity areas as shopping and household tasks; leisure pursuits, including watching movies and gardening; and social activities such as eating out and spending time with friends. In many cases, they were resuming activities that they had put aside when they were diagnosed with PD. In the non-Tango group, no such changes were observed.

As with all forms of exercise, the benefits of Tango diminished when people stopped doing it. But Dr. Earhart thinks that people may find it easier to keep up the Tango than it is to keep up with traditional exercise programs. "People are more likely to continue doing it just because they enjoy it!" she says.

Dr. Earhart, along with her colleague, Ryan P. Duncan, D.P.T., published these findings in two medical journals. Now she is in pursuit of the answer to her next scientific question, namely: can exercise, including dance, slow or stop the changes in the brain that occur in PD? Having gathered initial data with PDF's support, she is investigating this bigger question with support from the NIH in the form of an R01 grant. She is studying brain activity before and after volunteers learn Tango, using functional magnetic resonance imaging (fMRI).

Says Dr. Earhart, "Without our initial Tango study, and funding from PDF, we simply wouldn't have been able to gather the preliminary data necessary to secure funding for a larger project."

Dr. Earhart's research was funded through PDF's International Research Grants Program. In FY2013, PDF is supporting the program with $1.16 million.