The Science Behind Exercise and Improved Motor Function in Parkinson’s Disease

The Impact of Grant Support from Team Parkinson/Parkinson Alliance on Parkinson’s Disease Research at the University of Southern California

From The Laboratories of:
Giselle M. Petzinger, MD (Department of Neurology)
Michael W. Jakowec, PhD (Department of Neurology)
John P. Walsh, PhD (Andrus School of Gerontology)
Garnik Akopian, MD (Andrus School of Gerontology)
Beth Fisher, PT/PhD (Division of Biokinesiology and Physical Therapy)
Brett Lund, PhD (Department of Neurology)
Daniel Holschneider, MD (Department of Psychiatry)
Ruth I. Wood, PhD (Department of Cell and Neurobiology)

Summary Points:
• Epidemiological Studies show that strenuous exercise over the lifetime of an individual reduces the risk for Parkinson’s Disease (PD).
• Clinical trials show that exercise improves motor performance in individuals with PD and in aged subjects, as well as improves memory, learning, and thinking.
• The adult brain possesses a tremendous capacity to learn, repair and compensate after injury, which can be “harnessed” through exercise.
• Animal models of PD are essential for understanding how exercise “repairs” areas of the brain affected by the loss of dopamine.
• Exercise is beneficial and should be routinely prescribed in the management of PD.
• Exercise should include gait and balance training since these are important in daily function and are commonly impaired in PD.
• Studies are needed to define the beneficial parameters of exercise including the role of skill training, degree of aerobic, duration, intensity, and frequency.
• Ongoing studies understanding the mechanisms of the benefits of exercise are necessary to find novel targets for developing new drugs to treat PD.
• The ultimate goal is to determine if exercise can in fact modify disease progression and thus increase the quality of life for patients.

INTRODUCTION

Epidemiological and clinical studies have shown that exercise is beneficial for patients with Parkinson’s disease. Through research using animal models of Parkinson’s disease and clinical studies, neuroscientists at the University of Southern California have begun to understand how exercise can help different areas of the brain affected by the loss of dopamine. This exercise effect on the brain that induces change and possibly repair is called “experience-dependent neuroplasticity”. Exercise enhances how effectively neurotransmitters (the chemicals that help convey information from one neuron to another) function more effectively and promotes neurons to make stronger and more healthy connections (termed synapses). Studies at USC are beginning to identify molecules and signaling pathways within the brain that are regulated by exercise and are important in driving protective and reparative changes involved in brain cell communication and thus the way information is stored. In parallel, recent exercise studies in patients with Parkinson’s disease have been important in validating findings in the basic research labs. In addition, clinical trials are helpful in determining the parameters of exercise that may promote brain repair and thus disease modification (slowing of disease progression).

EXERCISE AND PARKINSON’S DISEASE

Individuals who participate in activities such as exercise and who have a high degree of intellectual engagement live longer and healthier lives. For example,
reading, writing, and mental challenges such as crossword puzzles can provide protection from the onset of Alzheimer's disease, which targets cognitive functions in the cortex (thinking and information storage part) of the brain. Epidemiological studies and antitodal reports have also suggested that exercise is beneficial in patients with Parkinson's disease. Specifically, analogous to protecting the thinking regions of the brain through mental exercise, physical exercise may additionally provide protection to the motor regions of the brain, though practice and learning of motor tasks. Research at USC is attempting to address the following important questions: Can exercise be used to reverse deficits in movements such as walking, balance, and writing impairments? Can exercise in fact modify disease progression and slow its course? And ultimately, can the reparative effects of exercise on the brain, and understanding the mechanisms involved, provide clues towards new interventions and a potential cure?

THE EFFECT OF EXERCISE ON DOPAMINE IN ANIMAL MODELS OF PARKINSON'S DISEASE

Studies from our labs have shown that intensive exercise in the form of treadmill running can improve motor behaviors in rodent models of Parkinson's disease. Exercise also improves the animal's ability to learn other motor tasks, such as balancing on a rotating balance bean. This initial report was published in the Journal of Neuroscience Research in 2004. This was one of several reports indicating that exercise, either on a motorized treadmill (our work) or voluntary running wheels (colleague's work) resulted in improved motor performance and reduced parkinsonian features in rodent models of Parkinson's disease. While colleagues in the field reported that exercise could protect from loss of substantia nigra neurons and the development of Parkinson's disease, at USC we were interested in examining whether exercise could mitigate or repair brain function in animals that had already developed Parkinson's disease. Specifically we were interested in examining whether exercise could help the parkinsonian brain regain function despite the fact that neurons within the substantia nigra were already diminished.

Given that individuals with PD have dopamine loss and reduced dopamine signaling within the motor part of the brain, called the basal ganglia, we initiated our studies to examine the effects of exercise on dopamine levels and handling. Handling included features of dopamine that are related to how it is being released from nerve endings, called terminals, as well as how long it is made available to bind to its target within the basal ganglia. To our surprise we observed that the beneficial effects of exercise were not accompanied by an increase in the total amount of dopamine. Rather we determined that exercise facilitated the release of dopamine from its storage site within the nerve terminals and helped maintain its stability out in the synapse, or space where dopamine is able to work on its contacts or receptors for initiating signaling within the motor circuitry of the basal ganglia. In other words, exercise improved the handling of dopamine from a "storage mode" to a "use mode". In addition, exercise increased an important contact site (termed receptors) for dopamine within the basal ganglia. These receptors are called the dopamine D2 receptor. The dopamine D2 receptor is known to initiate an important signaling pathway within the basal ganglia that controls motor circuit connections and their function. These findings were reported in the Journal of Neuroscience in 2007. Because we were interested in understanding whether exercise could increase the dopamine D2 receptor (the contact and signaling pathway of dopamine) within individuals with PD, we initiated a study to use a non-invasive brain-imaging tool that would allow us to examine for changes in the receptor while keeping the animal alive. This study consisted of using an imaging technique called a PET (positron emission tomography) scan that allowed us to detect changes in the amount of the dopamine D2 receptor by using a radioactive label that would bind to the receptor and serve as a marker or indicator for the amount of receptor present before and after exercise. We imaged four groups of animals: (i) healthy animals; (ii) healthy animals after 28 days of intensive treadmill running; (iii) parkinsonian animals and (iv) parkinsonian animals after 28 days of intensive treadmill running. The animals were made parkinsonian through the administration of the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). After MPTP exposure, animals were given 5 days to develop parkinsonian features in the brain, due to the MPTP neurotoxin, before they started the exercise regimen. Exercise consisted of one hour of intensive treadmill running per day, 5 days per week, for 28 days of running. At the completion of the exercise program representative mice from all four groups were subjected to PET-imaging to determine the amount of expression of the dopamine D2 receptor within their basal ganglia. Our findings indicated that parkinsonian mice subjected to intensive treadmill running showed a dramatic increase in the amount of dopamine D2 receptors in their brains. These findings suggested that exercise could help remaining dopamine work more efficiently by increasing the “target” of dopamine, and thus help the basal...
EFFECTS OF EXERCISE ON OTHER NEUROTRANSMITTER SYSTEMS

An important role of dopamine and its receptors (e.g. D2) is to regulate circuits within the basal ganglia involved in movement. Circuits are regions of the brain that work together to coordinate an activity such as walking. These circuits are composed of brain cells that communicate with each other through contacts called synapses. Synapses contain a number of proteins on their surface that serve to (i) hold connections together and (ii) regulating the amount or attraction between two neurons. Although not fully understood, dopamine (thorough working at its receptor) appears to regulate both the (i) number of synaptic connections and (ii) attraction between connections within the basal ganglia. Given our observations that dopamine handling and it’s D2 receptor was increased after exercise, we asked whether this led to changes in the attraction or the number synaptic connections normally diminished in Parkinson’s disease. The first studies we undertook were examining molecules important in dictating the degree of attraction between synapses. One important “attraction” molecule is called glutamate and it works on receptors called glutamate receptors that are located on synapses. One very important glutamate receptor is termed the AMPA receptor. These receptors are important aspect of neuronal connections. Their amount or type can influence the attraction, and thus connections within a circuit. In the parkinsonian rodent model we observed an increase in the amount of the AMPA receptor molecule and a change in the type of AMPA receptor that was being expressed at the synapse. The AMPA receptor is composed of many potentially different subunits and their function is dependent on the subunit the express. We observed an increase in one subunit termed GluA1 type, which is known to play an important role in increasing the attraction or strength between synapses. This type of AMPA receptor is not expressed in the normal basal ganglia and may account for abnormalities within the basal ganglia circuitry that causes motor deficits in parkinsonian mice. Alternatively, at the completion of intensive treadmill training we observed a decrease in the GluA1 subunit but a return of the more common AMPA receptor subunit termed GluA2. These findings were determined using a number of molecular and physiological techniques that allowed us to specifically interrogate the synapses within the basal ganglia. Thus we observed that exercise could improve the type of attraction between connections or synapses within the parkinsonian brain. These data were published in 2010 in Journal of Neuroscience Research.

EFFECTS OF EXERCISE ON BRAIN CONNECTIVITY

Movement is orchestrated through circuits in the brain that store information and influence force, amplitude, and coordination of muscle groups. Important regions involved are the basal ganglia and the sensory-motor cortex, which relays information to one another regarding the coordination of movement. Dopamine plays an important role in modulating these connections called synapses, and with the loss of dopamine, as observed in PD, these circuits become physically disrupted so that there is a loss of connections in the basal ganglia. Many of these lost connections are coming from the cortex, and are responsible for normal movement. These synaptic connections occur on special “outcroppings’ of cells called spines. While dopamine loss is known to lead to a loss of spines (connections) work in our laboratories shows that intensive treadmill exercise causes a return in the number of spines. These results indicate that exercise in the parkinsonian mouse brain can in fact lead to dramatic changes in connections between neurons. These connections increase after exercise, despite the fact that there is no change in the number of substantia nigra neurons. Although, there is more work to do, our studies suggest that exercise can cause brain connections to occur even after a loss of dopamine. A paper with these findings is currently in review for publication.

EXERCISE STUDIES IN PATIENTS WITH PARKINSON’S DISEASE

While we are learning a great deal about the mechanisms of intensive exercise in the parkinsonian mouse model, a primary goal of our research program is to translate our findings from the laboratory to clinical studies and finally to patient care. To achieve this goal we first asked: can exercise in patients with Parkinson’s disease lead to improved motor performance? In other words, can any of the symptoms of Parkinson’s disease be influenced by exercise? Studies, led by Beth Fisher and Giselle Petzinger, enrolled early stage patients
(within three years of diagnosis with Parkinson’s disease) in an exercise program. Patients were recruited from the USC Movement Disorders Clinic. Patients were placed in one of three treatment arms including (i) educational classes on the role of diet and exercise in Parkinson’s disease; (ii) physical therapy involving stretching exercises, or (iii) high-intensity body-weight supported treadmill training. The exercise group underwent eight weeks of intensive treadmill running that included 3 sessions per week for a total of 24 sessions. Patients ran on body-weight supported treadmill. This treadmill is designed to ensure safety for the subject but also allows the subject to walk or run at speeds that they could not achieve on an ordinary treadmill. Also, each subject was under the supervision of trained physical therapists that provided feedback to the subject regarding form and features of their movements. This is important since we have found that feedback to the subject provides a form of learning, something that is critical in translating physical experiences into permanent connections in the brain through a process called synaptic plasticity. All subjects were evaluated at the beginning and at the end of the study in the biomechanics lab at the USC Division of Biokinesiology and Physical Therapy. The overall finding was that individuals with Parkinson’s disease who underwent intensive treadmill training exhibited a more normal gait pattern at the completion of the exercise regimen in comparison to individuals with Parkinson’s disease who had undergone stretching alone or education alone. The exercised patients had demonstrated that they had learned to execute a gait pattern that was consistent with that seen in normal unaffected individuals. Importantly, a subgroup of individuals from each of the three treatment arms participated in a transcranial magnetic stimulation (TMS) sub-study to further explore the effects of exercise on motor circuits. TMS is a non-invasive tool used for evaluating electrical activity in regions of the brain important in motor function and is known to be altered in Parkinson’s disease. Using TMS, researchers have reported an increase in neuronal excitability in the motor cortex, a region of the brain that controls movement. Symptomatic treatment of Parkinson’s disease, including either dopamine replacement therapy or deep brain stimulation (DBS), can reverse this state of excitability when symptoms are improved. Using TMS, we found that there was a consistent reversal of cortical hyper-excitability only observed in the intensive exercise treadmill group. These results are the first to demonstrate that exercise influences and normalizes the activity of brain circuitry involved in motor control in individuals with PD. These findings were published in the Archives of Physical Therapy and Rehabilitation in 2008.

EFFECTS OF EXERCISE ON DOPAMINE NEUROTRANSMISSION IN PATIENTS WITH PARKINSON’S DISEASE

A second approach we used to examine exercise-induced changes in the brain was through another non-invasive method called positron emission tomography (PET) imaging. Given the fact that our earlier work in animal models had demonstrated changes in dopamine D2 receptor expression using PET imaging we examined whether intensive exercise led to the same change in individuals with early stage Parkinson’s disease. For this study we recruited individuals who were within one year of diagnosis and were not yet on any treatment for their Parkinson’s symptoms. The intent of the study was to determine the effects of exercise on dopamine signaling without concern for medication-induced changes. We compared individuals who underwent 24 sessions of treadmill training to those who did not exercise at all. PET imaging was performed at the beginning and end of the study. We observed an 80-90 % increase in the dopamine D2 receptor in the treadmill exercise group. We imaged two healthy control individuals before and after exercise and observed only a small increase (less than 10%) of the dopamine D2 receptor. This study supports the potential for intensive exercise to facilitate dopamine signaling in individuals with Parkinson’s disease. These findings were recently submitted as a paper to the Movement Disorders Journal.

THE EFFECT OF EXERCISE ON THE IMMUNE SYSTEM

How does the brain receive information about its environment? How do experiences like physical exercise transmit their beneficial effects into the brain? We know that the brain is able to receive information from its environment in a number of different ways. The visual system receives light, the auditory system receives sound, and the olfactory system receives smell. What about the motor system? Through experiences like exercise activation of the motor system, either through the cerebral cortex or basal ganglia can begin to establish those connections necessary for newly learned skills like walking, running, balance, etc. Other cells, either neurons or non-neuronal cells called glia (astrocytes, oligodendrocytes, or microglia can make factors that help cement connections between neurons. This is one role of substances called neurotrophic factors. However, there may be other roles for non-neuronal cells. One set of studies underway is to determine the potential role of a class of non-neuronal cells called microglia (also called macrophages when they are not in the brain). In studies with Brett Lund in our group an interesting experiment may have revealed an important component of exercise in the parkinsonian brain in our mouse model. Brett was examining the activation of microglia in our model of
MPTP-lesioning just to characterize the immune response that may take place in the context of neurotoxic injury to the brain. As we were exercising parkinsonian mice he asked if he could examine the microglia profile of brains from these mice to see if exercise affected their numbers. To our surprise and that of his, he found a tremendous degree of activation of microglia in the brain of parkinsonian mice under going intensive treadmill exercise. This meant that cells usually a major component of the immune system were responding to exercise in the injured brain. This effect was much higher then seen in the brain of normal mice undergoing exercise. Just to add a more interesting twist to these studies he asked where were these cells coming from. Were they from the periphery (outside of the brain and coming in) or were they resident brain microglia now duplicating from active cell proliferation within the brain. Using a clever series of studies with a combination of transgenic mice in which the peripheral microglia are marked with a fluorescent tag and can be visualized with cell sorting Brett constructed a chimeric mouse in which the microglia of one mouse were eliminated and replaced with the tagged microglia of another mouse. Taking these mice, making them parkinsonian, and subjecting them to intensive treadmill exercise he has shown that peripheral microglia in fact get into the brain when parkinsonian mice exercise and not when they do not exercise. In addition to this finding he is beginning to dissect the precise molecular signals that are responsible for allowing activated microglia to enter the brain and go to specific sites of injury where they are able to generate their beneficial effects. He is also examining how they replicate, what factors they express, and what can we do to enhance this effect. These findings are very exciting because they have revealed a previously unknown role of the immune system. In fact, the immune response in exercise appears to be a good thing and may contribute important factors to mediate neuroplasticity and promote recovery of motor behavior.

EXERCISE AND ITS EFFECT ON BLOOD FLOW IN THE BRAIN

Exercise can change blood flow in the brain. Such changes in blood circuitry may be beneficial if they deliver factors important for brain repair and enhancing neuroplasticity. For example, increased blood flow to regions of injury in a brain may bring those components of the immune system needed for repair such as promoters of neuronal growth including neurotrophic factors. Increased blood flow may elevate the delivery of oxygen, removal of waste material, and support of increased metabolic demands in regions of the brain undergoing brain plasticity in response to new experiences such as exercise.

To address this issue, studies underway with Daniel Holschneider are designed to examine alterations in the blood flow map of the brain in parkinsonian rodents engaged in exercise. Comparing non-parkinsonian and parkinsonian rats with and without exercise Daniel is utilizing sophisticated image analysis techniques with specific tracers that indicate blood flow differences in the brains between these different groups. What he has found is that there are significant differences in a number of regions of the brain some expected and some unexpected. For example, parkinsonian rats show different blood flow patterns when compared to non-parkinsonian rats in response to exercise. In addition, blood flow increases in regions of the brain involved in response to motor behaviors including the cerebral cortex and basal ganglia. Other regions of the brain unexpectedly show elevation in blood flow such as the cerebellum and regions of the midbrain. There are a series of important questions under investigation to determine the significance of these findings. Are these changes in blood flow persistent or do they just occur early in exposure to exercise? Do all forms of exercise activate the same changes in blood flow map? What is the role of exercise intensity, duration, and complexity in changing blood flow? What are the factors that activate changes in blood flow in what is called angiogenesis? Ultimately similar studies examining changes in blood flow can be carried out in patients with Parkinson’s disease and maybe pharmacological agents can be administered to enhance angiogenesis to promote repair of the injured brain.

EXERCISE AND ITS EFFECT ON NONMOTOR BEHAVIORS

Up to this point we have been focusing the benefits of intensive exercise on the motor aspects altered in Parkinson’s disease. It is now clear that other behaviors are important in Parkinson’s disease that we term non-motor characteristics. These include a wide spectrum of behaviors including anxiety, depression, compulsions, and executive function; all of which are important in the quality of life of patients. Can exercise influence these non-motor behaviors? If so, what are the underlying mechanisms?

We all know exercise makes you feel good. After a good run, a brisk walk, or fast ride on the bike you feel relaxed, optimistic, and sometimes euphoric. These changes in mood are due to changes in the neurochemistry of the brain in a number of regions within and outside of the basal ganglia. Two regions that connect into the basal ganglia and influence these non-motor behaviors include projections from the amygdala and dorsal raphe. They involve other neurotransmitter systems in addition to dopamine and glutamate, especially the neurotransmitter serotonin. Ruth Wood is interested in knowing if exercise influences the serotonergic system, and if so, how are the benefits of exercise on non-motor behaviors mediated. She has examined a number of important features of exercise...
that may be playing a key role in this phenomenon. These features include the role of stress and hormones, the type of exercise comparing voluntary wheel running with forced treadmill running, and the influence of gender comparing benefits in males versus female mice. Behavioral studies have been carried out to examine the impact of these different parameters on mood, compulsions, and anxiety in parkinsonian mice under going exercise. While some of these studies are currently underway she is finding significant influence of exercise and its different forms on non-motor behaviors in the mouse model of Parkinson’s disease. We now want to know more about the underlying molecular mechanisms. Does the neurotransmitter serotonin change and in which anatomical regions of the brain. What are the receptor subtypes that are critical and how do they change? Do other neurons show evidence of neuroplasticity and how can this be influenced or enhanced? Overall these studies provide valuable insight into other characteristics of Parkinson’s disease and further highlight the beneficial impact of exercise for patients.

**IMPACT OF THESE STUDIES ON PATIENT CARE**

Will these studies impact patient care? The ultimate goal of our program is to improve patient care by finding new therapeutic treatments. Exercise appears to provide an important complementary non-pharmacological treatment for Parkinson’s disease. We believe that work from our group is also supporting the role of exercise in modifying Parkinson related injury within the brain, by changing and repairing connections within the brain. The next important step is to determine whether this is true in humans. To date, however, we can say that exercise plays an important role in helping individuals with PD function better, and in combination with medication can help patients perform better in their daily function and gait and balance. While the exact parameters of exercise that may be important for studying disease modification are still be determined, we believe our work does support the importance of intense, challenging and skill oriented types of exercise for influencing neuroplasticity and repair processes. We also believe that work investigating the role of exercise in repairing the brain provides valuable insight towards mechanisms involved in creating healthy synaptic connections along brain circuits. We are hopeful that these discoveries will lead to novel targeted interventions to enhance the function amongst circuits and their connections that are affected in PD.

**FUTURE DIRECTIONS**

Where do we go from here? There remains a tremendous amount of work to be done if we are to elucidate the underlying molecular mechanisms of exercise in the parkinsonian brain. What causes glutamate and dopamine receptors to change their amount, subunit composition, and electrophysiological properties in response to exercise? Why does the parkinsonian brain respond differently? How does exercise influence the number of connections, called spines, and what is the relationship between spine changes and the number and type of AMPA receptors? What is the precise role of the immune system, blood flow, and stress in these models? Are influences of exercise on motor and non-motor behavior due to similar or different mechanisms? What are the specific circuits in the brain altered by exercise and what is the role of changing morphology of synapses? What is the influence of current drug therapy including dopamine replacement therapy, dopamine agonists, and genetic background? Are the changes we observe permanent? How often do patients (and mice) have to exercise to maintain benefit? What are the parameters of exercise that are important in generating benefit including duration, intensity, complexity, challenge, and learning? And finally, while we translate our findings in the lab to clinical studies, at the same time we use our clinical studies and patient care to formulate key hypotheses and observations that we can take back to the lab to design new experiments that can lead to greater insight into exercise and the brain and ultimately change the way we treat and understand Parkinson’s disease.

**ACKNOWLEDGEMENTS**

We would like to express our gratitude to Team Parkinson and The Parkinson Alliance for their generous support in our research program. These research funds would not be possible without the support of many contributors and individuals including those who run in the LA Marathon and 5K. Funds raised by these organizations have been instrumental in the purchase of equipment used in our program for these studies including motorized treadmills, equipment to expand our TMS capability, new equipment for electrophysiological studies, and a new state-of-the-art imaging system including fluorescent confocal microscopy. Such funds have allowed us to generate meaningful data to support applications and obtain grants from other sources including the National institutes for Health, the US Army NETRP, USC CTSI, and Zumberge Foundation of USC, and the Parkinson’s Disease Foundation.

**REFERENCES FROM OUR LABS ON EXERCISE AND PARKINSON’S DISEASE**


