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**LAY SUMMARY**  
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Animal models of Parkinson's disease suggest that exercise is neuroprotective – that is, it may slow or halt the progression of a neurological disease. Regular exercise helps the brain produce its own neurochemicals (growth factors) that protect the dopamine cells from early death, which are the cells that die in Parkinson's disease. The idea that something as simple as exercise may be neuroprotective is a potential major breakthrough as exercise is immediately available, doesn't require FDA approval, and can be safely combined with other types of neuroprotective therapies for potentially additive effects. We have developed a novel rehabilitation approach (LearningBIG™) that when combined with medication therapy results in a significant decrease in neurological symptoms (impairments) and improvements in balance and quality of life over and beyond what medications offer alone. We propose that this exercise approach offers patients not only another potentially neuroprotective treatment, but also a treatment that may alleviate a major debilitating symptom (balance) that does not typically respond to traditional pharmaceutical approaches.

LearningBIG™ is a novel rehabilitation approach for people with Parkinson's disease. It targets a single goal: making big movements. For sixteen therapy sessions, people with Parkinson's are encouraged to take big steps, make big gestures, and make a big effort. The findings of researchers B.F. Farley, G. F. Koshland and M.M. Prior demonstrate that practicing big movements reduces bradykinesia; which is one of the most disabling symptoms of Parkinson's disease. Bradykinesia causes people to move slowly and to underestimate how much effort it will require to take a step. For example, a person with Parkinson's will believe he is expending enough effort to take a large step when in reality, it's only enough effort for a shuffle.

The scientific community has known that speed increases with distance. If you make a large gesture or take a large step, you move faster than when you make a smaller movement. This is the first time this phenomenon has been used as a rehabilitation strategy. When LearningBIG™ patients make high effort/large movements, increasing the drive to the muscles in their arms, legs, and trunk. When patients focus on sensory awareness of big movement, LearningBIG™ trains the sensory system to overcome the mismatch between the perceived movement and the actual movement. This is the first time Parkinson's-specific treatment concepts (increasing motor drive, retraining sensory perceptions) and motor learning principles (high effort/multiple repetitions, feedback) have been incorporated into a standardized rehabilitation protocol.

Traditional therapy for people with Parkinson's disease usually has multiple goals - flexibility, strength, balance - and requires patients to remember multiple instructions for each goal. LearningBIG™ patients simply focus on one goal: Think Big! As a result they learn to use more effort in everything they do - standing, dressing, getting out of a car, walking, cooking, cleaning. This makes it easier for people with neurological disorders who typically have difficulty with attention-demanding complex tasks. By restricting the cognitive load, the patient can focus on sensory feedback. Finally, when there is only one goal, patients can experience intensive, massed, repeated practice. Recent neuroimaging and motor learning studies suggest that this kind of intensive, high effort practice may be necessary to modify neural organization and effect recovery of functional motor skills.

While many types of external and attentional cueing strategies are advocated for people with Parkinson's disease, they are currently only being used as an adjunct to traditional physical therapy treatment and their effectiveness has not been tested in randomized controlled trials. The cueing strategy at the heart of LearningBIG™ (Think Big) can be generalized for all types of movements in any situation. In addition, LearningBIG™ represents a standardized protocol for teaching "Think Big" to patients and it is currently being tested in a randomized control trial. Even though LearningBIG™ is a strategy for focusing attention, patients were able to continue taking big steps even when they were asked to recite the days of the week backwards from an unpredictable starting point. This suggests that with practice, LearningBIG™ will become so automatic, it will not impose a conflict when patients are performing cognitive and motor tasks at the same time.

LearningBIG™ is based on a proven treatment for the speech motor system in people with Parkinson's disease, the Lee Silverman Voice Treatment (LSVT). Like LearningBIG™, LSVT has a simple focus: Think Loud. For the past 15 years research has shown that LSVT results in improvements in speech intelligibility and voice loudness. Speech studies have also show that treatment with a single focus such as "Think Loud" may generalize improvement to other systems such as speaking rate, swallowing, respiration, and may in fact result in changes in the way the neurons of the brain are organized. Thus one can predict that LearningBIG™ will not only result in being able to make bigger movements but will generalize to improvements in posture, respiration, handwriting and speech. This study is the first time well established treatment concepts from the speech motor system have been applied to the limb motor system.

In our first ongoing efficacy study, 43/50 subjects have been randomly assigned to participate in one of two different therapy approaches, Traditional or LearningBIG™ therapy. The frequency and duration of therapy in both groups is matched, with all subjects receiving individual therapy 4X/week for 4 weeks for a total of 16 sessions. Outcome measures are being collected the week before therapy starts, the week after therapy ends, and then again 3 months later. We are only reporting preliminary data on a subset of the data from the LearningBIG™ therapy (N=18). Pre-testing showed that subjects with Parkinson's disease increased speed with increased distance moved during multijoint reaching and gait, but at much reduced speeds compared to controls. Thus, the speed/distance relationship is intact in people with Parkinson's disease. After completing 16 sessions of LearningBIG™ therapy, subjects performed faster arm and leg movements during reaching and gait. Arm movements were most improved during horizontal reaching during as fast as possible conditions, especially for the larger distances. Leg movements during gait were faster and bigger for all speed conditions (preferred, preferred with a cognitive load, as fast as possible). While some subjects showed improvement in both reaching and gait, others showed improvement in only reaching or only gait. The lack of improvement in either reaching or gait velocity in some of the subjects may reflect disease severity and/or the distribution of motor impairments (gait-dominant vs. arm dominant). Thus, subjects with gait-dominant symptoms may only improve in gait and subjects with arm dominant may only improve in reaching. In addition to the ability to perform bigger and faster limb movements, subjects also showed improvements in trunk rotation, balance, quality of life, and decreased symptoms on a global neurological rating scale (UPDRS). Results to date suggest that subjects with Parkinson's disease can learn to use a simple attentional strategy (Think Big) to decrease bradykinesia in the limbs and axial (trunk) motor systems, and improvements may generalize to other systems (balance) and carryover to everyday functional tasks. In addition,

learning to “Think Big” may be a simple enough cue that it becomes internalized with intense practice, such that it does not interfere with the ability to perform complex dual tasks.

LearningBIG™ offers the field of rehabilitation a novel standardized behavioral intervention for the limb motor system that has the potential to generalize across motor systems (gait, reaching, respiration, balance, speech, handwriting) and to impart the capacity of the person with Parkinson’s disease to function optimally. Future studies will continue to investigate the short/long term effects of LearningBIG™ on impairments, function, and quality of life. We will develop new studies, collaborations and outcome measures to investigate transference to other systems to include respiration, speech, handwriting that may occur following the course of intensive therapeutic sessions. We will also continue to investigate the underlying mechanisms that may explain improvements such as neural reorganization (neuroimaging), increased muscle activation, and improved sensory functioning. To improve long-term retention (motor learning), we will develop feedback technology to deliver immediate feedback concerning actual movement bigness and that can be used in clinics to supplement LearningBIG™ therapy. Finally, we plan to develop training materials and protocols for physical and occupational therapists and begin the process of dissemination so that we can enhance the availability of LearningBIG™ around the world.