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Intensive Amplitude-specific Therapeutic Approaches for Parkinson's Disease

Toward a Neuroplasticity-principled Rehabilitation Model

Becky G. Farley, PT, PhD; Cynthia M. Fox, PhD, CCC-SLP; Lorraine O. Ramig, PhD, CCC-SLP; David H. McFarland, PhD, SLP

Recent scientific advances in animal models of Parkinson disease suggest exercise is a legitimate disease-modifying therapeutic option that contributes to behavioral recovery and neurochemical sparing. These data challenge current rehabilitative assumptions and emphasize the need for neuroplasticity-principled exercise-based approaches to challenge the impaired system. We suggest one novel solution—the intensive practice of amplitude—a global motor control parameter. Training a single focus (amplitude) across (1) disciplines (physical, occupational, speech therapy), (2) tasks (transfers, activities of daily living, recreation), and (3) motor systems (speech, locomotion, reaching) may provide the complexity, difficulty, and repetition necessary for disease-modification in human Parkinson disease. **Key words:** *amplitude*, *cross-system effects*, *cueing*, *exercise*, *motor training*, *neuroplasticity*, *rehabilitation*, *recovery*

From the Department of Physiology, AHSC, University of Arizona, Tucson (Dr Farley); National Center for Voice and Speech, Denver, Colo, and Department of Neurology, University of Arizona, Tucson (Dr Fox); Department of Speech, Language, Hearing Sciences, University of Colorado–Boulder; National Center for Voice and Speech, Denver Center for the Performing Arts, Denver, Colo; and Columbia University, New York City, New York (Dr Ramig); École d'orthophonie et d'audiologie et centre de recherche en sciences neurologiques, Faculté de médecine, Université de Montréal and School of Communication Sciences and Disorders and Center for Research on Language, Mind and the Brain, McGill University (Dr McFarland).

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Corresponding author: Becky G. Farley, PT, PhD, Department of Physiology, AHSC, University of Arizona, Tucson, AZ 85724 (e-mail: bfarley@u.arizona.edu).

ADVANCES in neuroscience reveal that exercise acts at the molecular level to inhibit cell death, increase synaptic efficiency, and promote behavioral recovery in animal models (rodents) of Parkinson's disease (PD).[1,2] Furthermore, research has identified fundamental principles of exercise that contribute to neuroplasticity in animal models of PD and in humans with stroke-related hemiparesis and spinal cord injury.[1,3–8] These data challenge the assumptions of current rehabilitative models that there is no potential for neuroplasticity or recovery in people with PD; therefore, current therapies primarily target compensatory behavioral interventions that bypass basal ganglia (BG) pathology.[9–15]

Instead, we propose to translate these data from animal models of PD and human stroke-related hemiparesis and spinal cord injury to a neuroplasticity-principled model of rehabilitation for the treatment of human PD. We will provide the theoretical foundation

for exercise-based programs that are immediately available at the time of early diagnosis, continuous, and that challenge the impaired system to optimize the potential for disease modification in PD. Toward that goal, we will introduce intensive amplitude-specific exercise-based therapeutic approaches that adhere to the principles of neuroplasticity, as one possible solution to improve rehabilitation outcomes for people with PD.

This article will introduce the reader to the science and practice motivating intensive amplitude-specific therapeutic approaches. Specifically, we will discuss (1) why exercise is a legitimate therapeutic option for PD, (2) how to integrate the principles of neuroplasticity into mode of delivery of treatment, and (3) why training-increased amplitude as a single, overriding treatment focus can encourage cross-motor system improvements and optimize function. We will also provide data to support the successful application of the fundamentals of an amplitude-based speech therapy (LSVT/LOUD) to the limb motor system (LSVT/BIG)*; and to the limb combined simultaneously with the speech motor system (LSVT/BIG and LOUD).

THE SIGNIFICANT NEED

PD is the second most common neurodegenerative disease, after Alzheimer's disease.[16] With a mean age of diagnosis at 62 years, approximately 1.6% of the people 65 years and older suffer from PD,[17] and incidence and prevalence increase with age. At the time of diagnosis, neuronal death in the substantia nigra has already exceeded a critical threshold (ie, ~70%–80% loss).[18,19] At this time, drug therapies are able to mask many of the motor symptoms. Over time, however, the effect of drugs deteriorates and motor and psychiatric side effects develop. Neurosurgical techniques such as deep brain stimulation may be employed at this point, especially for those people who develop medication side effects of involuntary movements (dyskinesias). Deep brain stimulation effectively reduces many motor symptoms allowing patients to reduce their level of medication temporarily and thereby reducing side effects and improving motor function.[20,21] Despite medical and surgical management, most of the 1.5 million Americans with PD have significant speech and movement deficits that negatively impact their quality of life.[22,23] Affected individuals become disabled or retire early, are forced to give up activities they enjoy, incur substantial medical costs, and have increased mortality.[23–25] On the basis of 2004 estimates, PD costs the United States 34 billion annually in direct health-related expenses, disability-related costs, and lost productivity.[25,26] As the number of elderly older than 65 years increases, the prevalence of PD is predicted to grow 4-fold by 2040,[27] and these costs are expected to exceed 50 billion dollars.[28] Even a 10% slowing of progression of PD could increase the chances that individuals could maintain an improved, productive quality of life, despite living out the rest of their life with a chronic disease, and result in a significant annual savings to healthcare costs.

For the 60,000 individuals diagnosed annually with PD, therapeutic options that modify (slow, halt, or reverse) disease progression are needed regardless of the mechanism. Multiple-disease mechanisms have been shown to be involved in the cascade of events leading up to the death of dopamine (DA) cells associated with PD, including mitochondrial dysfunction, oxidative stress, excitotoxicity, and inflammation.[29] Several classes of exogenous agents have been shown in vitro and in vivo to be capable of disease modification by interfering with many of these potential disease mechanisms.[30] The most promising agents include pharmaceuticals and supplements[20,31] and use of gene or cell therapy to increase the availability of DA or neurotrophic factors locally.[32–34] To date, none of these treatments have yet been shown

*Patent pending for LSVT/BIG; LSVT/BIG and LOUD–GleeCo, LLC.

to slow, halt, or reverse disease progression in human PD and attention has recently turned to exercise as a potential therapeutic agent.

EXERCISE IS A LEGITIMATE DISEASE-MODIFYING THERAPEUTIC OPTION IN PD

The use of exercise as a physiologic tool to promote the body's own endogenous brain repair mechanisms is a virtually untapped resource for people with PD. Research in the area of exercise neurobiology has shown that exercise may interfere with multiple mechanisms involved in cell death, stimulate the proliferation of new neurons,[35,36] alter metabolic and immune system responses,[37–39] increase blood supply,[40] and protect against the "erosive neural events of aging, neurodegeneration, and brain injury."[1,41–43] Many of these neurobiological processes are triggered by the direct effect of exercise on increasing the endogenous expression of neurotrophic factors.[44–48] Because PD is a disease of aging, it is promising that exercise research with aged animal models has linked many of these same brain repair mechanisms to improved cognitive function in aged humans,[47,49,50] suggesting that they may also contribute to behavioral recovery in the case of disease or injury.

In animal models of PD, daily exercise (environmental enrichment, forced limb use, treadmill training) has been shown to reverse motor deficits, attenuate the loss of DA, and modulate genes and proteins important to BG function.[41,43,51] This behavioral recovery and neuroplasticity has been directly related to elevated levels of striatal glial-derived neurotrophic factor (GDNF) that promotes survival of DA neurons.[44,46] Even more recently, exercise has been shown to induce the generation of GDNF-producing cells (glia) in the substantial nigra where DA cells live.[52] Accordingly, it is reasonable to hypothesize that exercise in human PD promotes plasticity in the DA system through mechanisms of trophic support, with a likely candidate being the endogenous release of GDNF.[2] Supportive data in human studies suggest that people with PD have low levels of GDNF,[53] and that a history of exercise in early life may reduce risk for PD.[54,55]

The timing of exercise intervention is critical to determining which brain repair mechanisms will be induced and where in the central nervous system they will be located. For example, in animal models of PD, exercise may be prophylactic (preventative) and capable of protecting DA neurons from toxic events, but the degree of protection is dependent on baseline fitness levels and how early exercise is started.[41,42] After diagnosis of PD (injury), a continuous maintenance threshold of exercise may be required to provide the trophic support necessary to maintain the growth and survival in the remaining viable DA neurons.[1,41,43] In contrast, inactivity and failure to engage damaged systems (impairment-related or self-imposed) may be prodegenerative contributing to further degradation of function[41] and a downregulation of endogenous neurotrophic factors.[1,56,57] In more advanced disease (longer duration), exercise has been shown to produce molecular changes within the damaged BG pathways, but progressively higher intensity, velocity, longer duration practice, and task-specific paradigms may be required.[51]

Altogether, these data suggest that multiple time-dependent mechanisms are capable of contributing to behavioral recovery in PD. They suggest a need for exercise interventions in human PD that are available at diagnosis, promote continuous exercise, and avoid inactivity. It is unknown how these data will translate to human PD because of the difference in acute animal models of PD versus the chronic DA neuronal death in human PD.[58–60] Despite these caveats, these data are so compelling that they have led basic science researchers to suggest that early physical training interventions may actually halt the bilateral progression of the disease.[1,2,42–44] It is time to partner with these basic scientists, translate these data to human clinical trials, and integrate them into a new era of clinical

practice for people with PD. We will first explore more traditional rehabilitative models for PD and then propose an alternative neuroplasticity-principled approach.

CURRENT REHABILITATION PARADIGMS

People with PD are rarely seen by a physical or occupational therapist until they begin to experience disability and impaired function, usually because of loss of balance. By this time, what started out as a primary motor impairment of bradykinesia or hypokinesia has advanced to secondary complications and general deconditioning, perhaps exaggerated by progressive inactivity. The goal of rehabilitation has been to enable motor function as long as possible for using (1) general exercise programs customized to address the list of problems in people with PD including exercises for cardiovascular fitness, strength, range of motion, posture, gait, coordination, and balance as a group,[61–66] home-based,[67–70] or individualized,[71–75] or (2) specialized behavioral strategies to teach patients compensations. For example, external cues (auditory, visual, tactile) are used to elicit larger steps, faster walking speeds, decrease freezing of gait, improve posture and rotation, and overcome freezing.[9,12,13,76–87] Another strategy is to use instructional techniques that teach patients to avoid difficult tasks by (1) modifying the task (avoid dual tasks, divide complex sequential movement into chunks of simpler movements) and (2) restructuring the environment (avoid clutter, narrow walkways). Patients are also instructed to use attentional mechanisms to replace automaticity with focused attention on key aspects of movement. This may involve techniques that emphasize attention to size, video feedback, mental imagery, rehearsal, or breathing and relaxation.[82,88–92]

These specialized behavioral strategies may enhance the duration of treatment effects when combined with traditional problem-based exercise approaches.[9,78] When combined with task-specific over ground gait training (1 day/~328 feet) they have been shown to improve gait performance (2 hours[82]), but more intensive training (10 days/~1800 feet/day) may be necessary for retention (4 weeks[80]). No studies, however, have demonstrated generalization of these techniques (ie, carryover to "untrained" tasks or contexts).

To integrate the use of these behavioral strategies into clinical practice, guidelines are needed for clinical decision making about task and patient selection, modality (auditory, visual, attentional), parameters to use for correction (frequency, step size), and dosage. Consequently, the RESCUE project has recently developed 15 evidence-based guidelines with video examples, methods, and patient handouts to provide clinicians with the needed practical tools to implement standardized cueing training (www.rescueproject.org). The use of 3 of these external cueing techniques for gait training in a home setting has recently been tested in a multicentered randomized crossover trial[12] (see also reference 93).

A NEUROPLASTICITY-PRINCIPLED MODEL

Traditional approaches that are problem-based or that focus on teaching compensations imply that neurophysiologic changes are no longer possible (ie, that it is too late for people with PD to retrain "lost" motor control). Thus, the approaches are typically not based on physiologic hypotheses to directly counteract disease-specific pathophysiology (ie, impaired internally cued amplitude regulation) or principles of motor learning. Exceptions include a few studies that have incorporated high-intensity and/or progressive exercise protocols for task-specific strengthening,[71,94] postural stability,[95] over ground walking,[80] and treadmill training.[96–98] However, these approaches are seldom used in clinical settings. Instead, therapists target the management of multiple symptoms incorporating multiple therapeutic compensatory strategies for improving gait, balance,

posture, transfers, self-care, and leisure. As a result, the therapeutic intensity is low to moderate, and both the therapists' and the patient's efforts may become diffused.

This diffusion of focus and minimal therapeutic intensity may partially explain the lack of robust and lasting benefits in previous published systematic evidenced-based reviews for physical therapy.[99–102] To date, no one approach has been identified as superior in a comparative trial.[102] This is not due to the lack of approaches, as almost every type of general exercise approach (group or individual) has been investigated at least once, as well as task-specific training (treadmill, balance, aerobic, strength, flexibility), or "cued" exercise programs.[99–102] Despite methodological challenges and differences among these randomized controlled studies, dosage intensity (frequency or duration) was relatively similar (ie, 2–4 times per week for 4–10 weeks) and would satisfy sports physiology requirements for athletes of at least 2 to 3 times per week for approximately 6 weeks to achieve training effects.[103] On the other hand, other exercise parameters that affect therapeutic intensity (ie, complexity, difficulty, repetition) were not typically documented or controlled and may be critical to achieving the most robust and sustained treatment effects.

The systematic manipulation of these essential exercise parameters in animal studies suggests that "what you do matters" and may determine the nature of plasticity that occurs. For example, these studies have shown that repetition alone (for reaching, locomotion, strengthening tasks) does not produce brain reorganization of the cortical maps representing the practicing limb.[104–106] Instead, tasks that are difficult (small-well pellet retrieval) require new skill acquisition or that are complex (acrobatic training) are essential to driving the changes in morphology that reorganize cortical maps (ie, increased dendrites, synapse number).[107–109] Other studies suggest that repetition may be necessary to induce sustained changes in activation (neuronal or network) that transfer and carry over outside the therapeutic environment.[105,110] This is supported by transcranial stimulation studies in humans showing that stimulation trains of 1800 pulses, but not 150 pulses, were sufficient to induce lasting changes in corticospinal excitability.[111] Altogether, these data suggest that there may be no one superior approach, as long as a critical threshold of high effort (complexity, difficulty) exists over an adequate period of time (repetition). This is supported in animal models of PD, showing that 3 very different approaches were capable of inducing neurochemical sparing and behavioral recovery. These approaches included exploration of a novel new environment, forced use of a limb during everyday activities, or general whole-body progressive locomotion training.[41–43,46,51,52] One could infer from the aforementioned studies, that an adequate combination of complexity, difficulty, and repetition was present across each of the interventions to have produced these changes.

Specificity of exercise provides another way to increase therapeutic intensity. Studies in humans with stroke-related hemiparesis and spinal cord injury have shown that it is through the activation and use of the impaired limbs in patterns of movement that emphasize "relearning" normal patterns of use that drive changes in or around those parts of the central nervous system that are damaged.[4,112] The translation of these data to people with PD would suggest that task-specific approaches should focus directly on trying to reverse the impairments (ie, bradykinesia or hypokinesia) by engaging the patient to retrain bigger and faster movements for everyday movement. However, task-specific studies to date have been problem-based or they trained compensatory strategies by using external or attentional cues.[79,80,95] Preliminary clinical trials in human PD suggest that repetitive task-specific approaches may be tolerated by patients,[71,79,80,94,95] result in longer retention,[80,97,98] and produce task-specific changes in the brain.[79,96] However, it is unknown how well training with one cue on one task will transfer to other tasks or motor systems. If generalization is

limited, the requirement of therapist and patient time may prove to be monumental to address improvement in multiple functional tasks for different motor systems. We propose here a novel approach to maximize therapeutic intensity in people with PD through the manipulation of complexity, difficulty, repetition, and to increase generalization through a single amplitude-specific focus.

ONE SOLUTION: INTENSIVE AMPLITUDE-SPECIFIC TRAINING

We hypothesize that amplitude-specific training is "task-specific" for people with PD,[113] thereby targeting the proposed pathophysiologic mechanisms underlying bradykinesia or hypokinesia—inadequate muscle activation.[114–116] Because of DA loss, this impairment emerges as a result of faulty processing of kinesthetic feedback, motor output, and context feedback within the BG. This faulty sensorimotor processing leads to a reduced gain in the motor command for selecting and reinforcing movement amplitude.[114,117–119] This hypothesis is supported by single cell recording studies[120] and brain activation imaging studies.[113,117,121] Therefore, rather than trying to bypass BG pathology in therapy, we hypothesize that retraining "normal amplitude use" may enhance activation of damaged BG pathways and slow or halt their degradation.[1,113] This amplitude-specific approach is further supported by animal and human models of stroke-related hemiparesis that have used "forced-use" paradigms to improve function of the impaired limb and promote greater movement-associated activation in the remaining cortex of the injured hemisphere and in remote interconnected regions.[122–124] We predict that by incorporating intensity into an amplitude-specific training approach for people with PD, we will be able to similarly target the repetitive activation of the damaged system across multiple interconnected motor regions involved in "relearning" normal amplitude use. Therefore, intensive amplitude-specific training may give rise to distributed effects across "untrained" tasks or systems.[125]

In addition to targeting BG pathology, the amplitude-specific therapeutic approaches to be discussed here are delivered in a standardized manner and adhere to the fundamental treatment principles of a speech therapy intervention for people with PD (LSVT/LOUD). Over 15 years of efficacy, data have established that intensive, high effort, amplitude training taught with self-monitoring of vocal loudness results in significant long-term improvements (out to 2 years) in loudness and speech intelligibility,[126] and a transfer of improvements across motor symptoms (articulation, swallow, facial expression).[22,126–128] Preliminary imaging results with positron emission tomography have documented the first neural changes (ie, neural plasticity) following an intensive rehabilitation treatment of any kind for people with PD.[129,130] Specifically, changes represented a shift from abnormal cortical motor activation pre-LSVT to more normal subcortical organization of speech-motor output post-LSVT.

We have recently developed 2 derivative treatments from the fundamental principles of LSVT/LOUD. These include a physical or occupational therapy approach (LSVT/BIG) and a hybrid physical or occupation therapy combined with speech therapy approach (LSVT/BIG and LOUD). The use of a standardized approach ensures that all subjects get the adequate dosage, delivered in the same manner, as has been shown to be effective in clinical trials. The single focus on amplitude reduces the cognitive load for patients and allows for the simple and redundant practice of amplitude. The intensity is acquired through dosage, repetition, high effort or difficulty, and complexity. The approach is described below for LSVT/BIG.

For example, patients complete multiple repetitions (minimum 12) of 12 daily maximal whole-body bigness tasks. This repetitive practice of amplitude is performed with high intensity and effort. Thus, it is delivered face-to-face at a treatment dosage of 4 days a week for 4 weeks (1-hour sessions). Therapists push

patients to perform at a patient-perceived effort level of 8 or more (scale 1–10, with 10 being the most) on every repetition. To increase carryover to real-world context, the intensive or high effort and repetitive practice becomes progressively more difficult (ie, longer sequences), and complex (ie, dual tasks) over the course of 4 weeks. Starting day 1, patients are required to transfer their "bigness effort" established in the daily maximal tasks to emotionally salient hierarchical tasks, chosen by the subject (ie, getting out of bed, walking to the mailbox, golfing).

The goal of LSVT/BIG is to teach patients a new way of moving in everyday life so that everyday movements provide continuous exercise. To achieve this carryover and maintenance, it is necessary to address the sensorimotor mismatch that accompanies the production of larger, normal amplitude movements—as normal amplitude movements "feel" too BIG.[131–134] Multiple studies have documented impairments in kinesthesia[132,133,135–137] that may result from abnormal higher order processing of afferent information.[138] By directly addressing this sensory mismatch, patients may become "recalibrated" such that by the end of 1 month, they learn to recognize the effort required to internally regulate normal amplitude movements.

IMPACT OF LSVT/BIG ON LIMB MOTOR SYSTEM IN PD

Preliminary results on a subset of data from an RCT have been published and presented as abstracts[139,140] In that study, we compared LSVT/BIG (BIG, $n = 18$) to an age-matched untreated PD control group (PDC, $n = 11$). Eligible subjects were Hoehn and Yahr stages I–III. All testers were blinded and testing was "uncued" to speed or bigness. The standardized protocol for the LSVT/BIG intervention was delivered 4 days/week for 4 weeks, as described in the previous section and further illustrated in Table 1. Pre- and posttesting revealed significant improvements in both trained tasks (trunk rotation and stride length) and untrained tasks (gait and reaching velocity) in the short term. The improvements in preferred walking (12% velocity, 9% stride length) and functional axial rotation were still different from baseline at a 3-month follow-up ($P \leq .01$, Wilcoxon rank sum test).[139,140] Interestingly, after intervention, subjects were able to maintain their new improved preferred walking velocity and stride length when challenged with a dual task (walk and say days of week backward), even outperforming an age-matched elderly control group ($P = .01$, Mann-Whitney U test).[140] These improvements in bradykinesia or hypokinesia also generalized to significant clinical improvements on the activities-balance-confidence scale and in quality of life using the summary score from the PD Questionnaire (PDQ-39) (both $P \leq .01$).[140]

To determine whether improvements were equivalent across levels of disease severity, change scores for subjects were grouped and graphed according to their Hoehn and Yahr category. Subjects with milder impairment (Stage I) tended to make more improvement than other subjects with moderate impairment (stages II and III). This trend was strongest for the change in gait velocity ($P = .004$, see Fig 2b in Farley and Koshland).[139] A similar finding for subjects with milder impairment or shorter disease duration has been reported in the literature with a general exercise approach (3/week for 4 months).[73] Future studies will need to determine whether training capacity is truly limited in subjects with moderate impairment or whether patients are unable to access their new skills spontaneously and/or require longer duration training.

These data suggest that mildly involved subjects with PD have the potential for bigger and faster movements, yet, they do not use that capacity to make normal amplitude or velocity movements in everyday situations. This pattern of early "nonuse" is especially relevant as recent research in animal models of PD have shown that inactivity may actually contribute to degeneration[42] and that continuous practice and forced use of

Table 1. An example of how a neuroplasticity-principled rehabilitation model can be used to guide the integration of basic science research to disease-specific therapeutic rationale and interventions[*,†]

Timing matters[41,43,46,152,153]		
Principle	*Deficit specific to PD*	*LSVT/BIG and LOUD*
Early exercise has the potential to: rescue DA neurons, prevent chronic disuse, promote system-wide plasticity, and halt disease progression—particularly to the asymptomatic side.	People with early PD have subtle physical under activity (small movements/soft voice). This may be coupled with a lack of awareness or self-correction, leading to further inactivity.	Train people with early PD before function is compromised. Train strategies to raise awareness/avoid neglect and increase muscle activation for normal big/loud. Train whole body—not just impaired side.
Complexity matters[154–158]		
Principle	*Deficit specific to PD*	*LSVT/BIG and LOUD*
Complex movements or environmental enrichment have been shown to promote greater structural plasticity and synaptic efficacy in adjacent and remote interconnected regions than simple movements	As basal ganglia pathology progresses complex, adaptive, everyday movements are reduced. This loss in automaticity requires conscious attention to task—interfering with dual task performance.	Train complexity of movement with single patient focus (amplitude) to multiple, motor tasks. Retrain automaticity of amplitude in everyday movements progressing complexity by varying contexts, adding dual cognitive/motor loads, and sequential tasks.
Intensity matters[51,96,159,160]		
Principle	*Deficit specific to PD*	*LSVT/BIG and LOUD*
Intensive practice is important for maximal, sustained plasticity. Intensity can be increased via frequency/duration, reps, difficulty (effort/accuracy), and complexity Intensity for amplitude increases activation of basal ganglia circuitry and induces synaptic plasticity in striatum	Intensive, high effort training can be difficult in PD due to sensory deficits, force control, fatigue, depression, and progressive loss of cardiac sympathetic innervation	Train intensively 1-hour/day, 4 days/week, for 4 weeks; manipulate reps (12 or more); resistance (weight), amplitude effort, duration, accuracy (within healthy range), establish daily homework/carryover exercises. Recalibrate effort required for normal amplitude
Use it or lose it/ use it and improve it[1,42,153]		
Principle	*Deficit specific to PD*	*LSVT/BIG and LOUD*
Spared, but compromised DA neurons highly vulnerable to bouts of inactivity/activity. Inactivity may accelerate deficits. Postexercise intervention, there may be a minimum use required to maintain positive effects	Deficits are subtle—not "red flag" to seek physical/speech therapy. Getting early PD to recognize need for exercise and then convincing them to continually exercise is challenging. Decreased physical activity may be a catalyst in degenerative process	Recruit and target people with early PD, educate them on subtle deficits, and improve motor function that directly impacts real life Retrain a new way of speaking and moving in everyday life—normal activity offers continuous exercise

(*continues*)

Table 1. An example of how a neuroplasticity-principled rehabilitation model can be used to guide the integration of basic science research to disease-specific therapeutic rationale and interventions*,† (*Continued*)

Sailency matters[22,129,161–163]		
Principle	*Deficit specific to PD*	*LSVT/BIG and LOUD*
Practicing rewarding tasks (success/emotionally salient) activates basal ganglia circuitry Rewards are associated with phasic modulation of DA levels critical to induction of striatal plasticity and learning/relearning in PD	People with early PD may experience lack of awareness of subtle motor deficits, depression, loss of motivation and a feeling of "helplessness" Thus, they do not feel they need or would not benefit from exercise/therapy	We retrain salient whole-body familiar movements (core patterns) promoting success. We provide homework tasks that reinforce success of Big and Loud in emotional social interactions. We provide extensive positive feedback

*DA indicates dopamine; PD, Parkinson's disease.

† Six key principles of neural plasticity in column 1 and their relationship to proposed pathophysiologic deficits in PD are described in column 2. The corresponding rationale and possible therapeutic solutions as they pertain to LSVT/BIG and LOUD are described in column 3.

impaired limbs prevent and/or reverse motor impairments.[41–43,51] These types of data provide further justification for exercise as a legitimate therapeutic option immediately upon *diagnosis*—when there is the most potential for blocking the bilateral progression of the disease and improving motor function on the already-impaired side through multiple mechanisms of plasticity.

Results from the complete RCT using an intention-to-treat analysis to compare (LSVT/BIG to traditional physical therapy [TRAD]) are in preparation and confirm these preliminary data (described for LSVT/BIG vs PDC above). To match dosage (frequency or duration), both treatment groups (LSVT/BIG and TRAD) met according to the standardized protocol for LSVT/BIG (4/week for 4 weeks). In this case, both groups improved, but the changes in LSVT/BIG are consistently more robust and sustained. Because dosage (frequency or duration) was controlled across interventions, these data suggest that an amplitude-specific approach may produce more significant changes than a TRAD general exercise approach (even when delivered at the same dosage). However, subjects in LSVT/BIG were required to work at high effort (8 or more of self-perceived effort) continuously during the daily interventions. To determine whether amplitude has a specific effect, future comparative studies should match for both dosage *and* effort.

IMPACT OF LSVT/BIG AND LOUD ON LIMB AND SPEECH MOTOR SYSTEMS IN PD

This work has been extended to the development of a novel combined treatment program that *simultaneously* targets speech and limb motor disorders in people with early PD (LSVT/BIG and LOUD).[141–143] The program, and how it is integrated with the principles of neuroplasticity and PD-specific pathophysiology, is detailed in Table 1. Our hypothesis is that amplitude-specific exercises delivered simultaneously to these apparently diverse motor systems will be complementary and result in enhanced function in targeted behaviors (system-specific effects). The idea that a combined therapeutic approach may be complementary is supported by recent experiments with patients with stroke-related hemiparesis. Specifically, transcranial direct current stimulation of the motor cortex combined with motor training results in enhanced recovery and greater morphological plasticity as compared with motor training alone in these

patients.[144,145] Similar studies have not been completed in patients with PD.[146] We propose that LSVT/BIG and LOUD may be analogous to a paired motor training paradigm such that increased activation required for greater amplitude for one task (louder speech) may induce an increase in excitability of common circuitry that is further enhanced by the addition of another amplitude task (bigger whole-body movements).[123,124]

This approach was recently applied to 11 people with early PD (9 stage I, 3 de novo; 2 stage II). Results revealed that all subjects significantly increased vocal sound pressure levels (SPL) (loudness) during sustained vowels and reading (an average of 8–10 db SPL at 30-cm distance from the microphone) and increased stride length (12 cm on the average) and velocity (14 cm/s on the average) during preferred walking.[141–143] The gains in vocal loudness and gait were comparable to previously published data from earlier studies that targeted speech or limb movements independently.[139,147,148] These system-specific changes in speech and gait function were accompanied by (1) a 28% decrease in disease severity as revealed by the motor score for the Unified Parkinson's Disease Rating Scale and (2) a 27% improvement in quality of life as revealed by the PDQ-39 summary score.[141–143] A 30% improvement in the Unified Parkinson's Disease Rating Scale is considered clinically significant and would be evidence for disease modification in studies investigating putative neuroprotective agents.[149] These preliminary data are extremely encouraging and merit additional experimental attention.

In addition to system-specific training effects, we hypothesize that LSVT/BIG and LOUD will result in enhanced function that spreads to behaviors that are *not* specifically targeted by the therapeutic regime.[125] If improvements are seen, this may indicate that there are distributed effects on motor function that may emerge from the common treatment focus of increased amplitude of movement. For this, we assessed performance on an untrained fine motor task (handwriting) in a subset of the subjects who received the combined LSVT/BIG and LOUD treatment as compared with an untreated PDC group. Using a pen on a digitizer pad, subjects were instructed to write consecutive cursive *"lll"*s in their everyday way inside rectangular boxes of various heights (1.0, 1.5, 2.0, 3.0, and 5.0 cm). A between-group comparison of velocity change scores revealed that after intervention, the LSVT/BIG and LOUD group significantly increased velocity for target sizes 1.5, 2.0, and 3 cm by decreasing movement duration while maintaining segment size constant ($P = .02$; unpaired t test).[150]

Certainly, these data are preliminary and future studies are needed to determine whether the combined treatment maximizes these cross-system effects or whether they may also be observed when individually treating speech and/or limb movement amplitude. It could be predicted, for example, that the added complexity, attention, and engagement of the simultaneous treatment task "drive" greater improvements in function when contrasted with these behaviors targeted individually. Altogether, these data indicate that an intensive combined therapeutic exercise approach that *simultaneously* targets increased amplitude for speech and whole-body movements is complementary and may result in treatment effects both within and beyond targeted systems. In this manner, the training of a global motor control parameter may potentiate plasticity across brain networks involved in amplitude regulation.[113,117,121,151] Focusing the enhanced activation on the impaired BG pathways may provide one solution to triggering the body's own endogenous brain repair mechanisms and thereby may interfere with disease progression.

SUMMARY

We have documented that standardized intensive speech and limb treatments focusing on amplitude are effective rehabilitative tools, the results of which can give us insight about the neural mechanisms of disordered motor

control in individuals with PD. The impact of training a single global motor control parameter is powerful in its ability to have maximum functional impact while increasing clinical efficiency. Continued research will further evaluate the distributed effects of LSVT/LOUD, LSVT/BIG, and LSVT/BIG and LOUD across multiple motor systems (speech, reaching, dexterity, balance, articulation, facial expression, swallowing, respiration) to more clearly discern cross-system interactions. We will also continue to systematically investigate the impact of intensive amplitude-based therapies across disease severity and in young and older onset PD in longitudinal studies. To translate the research from animal models of PD to human PD, we propose to use brain imaging techniques to examine the effect of exercise in early PD on restoring function to compromised BG circuits. These data would provide the justification for a delayed-start randomized clinical trial to test the use of exercise as a legitimate disease-modifying therapeutic option immediately upon *diagnosis.*

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