A Comparison Between Effects of Specific and Nonspecific Exercises on Parkinson's Disease Progression

Hamzah S. Shariff, Kyle Manetz, Matthew Barrett, M.D., MSc David A. Edwards, Ph.D., Steven K. Malin, Ph.D, FACSM

Introduction

Parkinson's disease is a progressive, terminal neurodegenerative disorder, usually diagnosed at ages older than 50, that progressively debilitates motor function.[1] The disease is prevalent, affecting over 6 million people worldwide.[1] Disease pathology is characterized by the death of dopaminergic neurons in the substantia nigra of the midbrain.[2] The substantia nigra acts on the caudate and putamen of the basal ganglia, which in turn impacts output to the VA/VL of the thalamus and subsequently the motor cortex as part of the nigrostriatal pathway.[3]

The nigrostriatal pathway is crucial for initiating and coordinating motor activity.[4] Deficits lead to disorganized, slowed, and reduced movement.[4] The death of dopaminergic neurons appears histologically as blanching of the substantia nigra as less dark-colored dopamine is present.[5] Blanching of the substantia nigra leads to a cascade of non-motor and motor symptoms as disease pathology originates in more caudal sections of the brain and migrates rostrally.[5] The exact mechanism of neuron death is currently unknown. A variety of environmental and genetic factors play a role.[5] While most cases are sporadic, 5-10% of cases can be classified as familial and linked to a specific mutation.[6] One such gene is Park1.[5] Mutations at that locus can lead to a non-functional form of alpha-synuclein, a protein whose abnormal buildup is strongly associated with Parkinson's pathology.[5] On a cellular level, oxidative stress, chronic inflammation, and mitochondrial dysfunction damage dopaminergic neurons.[6]

Motor symptoms include tremors, rigidity, gait and balance deficits, bradykinesia, hunched posture, and flat affect.[7] Motor deficits frequently present asymmetrically, with greater dyskinesia in both upper and lower extremities on one side.[7] Non-motor symptoms include cognitive deficits, olfactory deficits, delusions, hallucinations, sleep disturbances, and mood changes[7]. Depression and dementia are both strongly associated with Parkinson's Disease.[8] Parkinson's Disease is not currently definitively associated with any radiological or biochemical markers, necessitating a differential diagnosis involving neurological and motor tests conducted by a movement disorder specialist.[9] Due to the substantial differences in presentation between patients and subjectivity of diagnosis, there can be a significant time interval between onset of symptoms and diagnosis. This delays treatment and acts as an impetus for effective disease management.

Treatment for Parkinson's involves a combination of strategies for symptom management and slowing disease progression, but no current therapies address the root cause of the condition. Common medications include Levidopa, a synthetic form of a precursor to dopamine called L-DOPA.[10] As dopamine is typically converted by DOPA decarboxylase in the bloodstream before it has a chance to bypass the blood brain barrier, Levidopa is typically paired with Carbidopa, a DOPA decarboxylase inhibitor, in order to increase absorption.[10] This increases drug efficacy and reduces side effects such as nausea.[10] Other medications that stimulate dopamine receptors and modulate the synthetic pathway of dopamine and L-DOPA exist.[10] In addition to pharmaceutical interventions, surgical interventions have had some success. Deep brain stimulation through surgical implantation of electrodes reduces motor symptoms of Parkinson's through unknown mechanisms.[3] Electrical stimulation is thought to overcome dysregulation of the nigrostriatal pathway to some degree.[3] Unfortunately, these interventions are both transient and insufficient.

Consistent physical, occupational, and speech therapy can have a significant impact on disease progression and quality of life. Lifestyle interventions, including various forms of aerobic activity such as high intensity interval training (HIT) are a subject of current study. Exercise has been associated with improved health-related quality of life, strength, balance, gait speed, and overall physical functioning in individuals living with Parkinson's Disease.[11] Physical activity, in particular aerobic exercise, is additionally associated with reduced depression associated with Parkinson's Disease.[11] Even a single bout of aerobic activity can improve performance on a motor learning task.[12] A variety of organizations, including Rock Steady Boxing, an international nonprofit founded in Indiana in 2006, seek to provide exercise regimens tailored toward combating motor and non-motor symptoms of Parkinson's. Rock Steady Boxing participants take 2-3 classes a week where they engage in high intensity interval training, core work, strength training, and boxing. Boxing in particular is a focus of the group because the kinesthetic awareness required to participate in the sport, and the use of large amplitude movements required for boxing has been previously demonstrated as effective in other settings.

The mechanisms behind findings related to exercise and Parkinson's Disease progression are still the subject of current research, but may relate to improved neuroplasticity or reduced build-up of alpha-synuclein. In addition to understanding the mechanisms underlying the benefits of exercise of people living with Parkinson's, current research seeks to better illuminate the quantity, consistency, and type of exercise that has the greatest impact on quality of life in patients. As such, the study below had two primary aims. The first was to determine a positive relationship between the amount of exercise and self-reported quality of life in Parkinson's disease patients. The second was to determine the relationship between self-reported quality of life in Parkinson's Disease patients and participation in Rock Steady Boxing.

Methods

Mobile, mentally competent subjects aged 40-90 diagnosed with classical Parkinson's Disease for at least 6 months were recruited with the help of nonprofit groups such as Rock Steady Boxing and support groups from within 200 miles of Charlottesville, VA. Although the study aimed to recruit 90 participants, only 30 entered the study. Only participants who have the mental capacity to participate were included. Mental capacity, in this study, will be defined as the ability to understand the purpose, process, potential risks, and potential benefits of this research study. This was assessed based on verbal interaction between the experimenter and the subject during the consenting process; recommendations by rock steady coaches, family members, and caregivers; in addition to the personal experience of the experimenters with Parkinson's related dementia. Afflicted individuals unable to walk or write were excluded from the study.

Quality of life was assessed using four NIH Neuro-QoL Toolbox surveys and the International Physical Activity Questionnaire (IPAQ). The four surveys pertained to a specific modality that contributes to the quality of life. These items were lower extremity function (mobility), upper extremity function (fine motor tasks), cognitive function, and satisfaction with social roles and activities. Subjects rated statements on the surveys within a range from 1-5, with 5 as the best score and 1 as the worst score. For each Neuro-QoL survey, the ratings were totaled and divided over the total score. Super-scoring was conducted by summing the subject's scores from each survey and dividing the sum over the total expected score. The IPAQ required the subjects to estimate the amount of high intensity and low intensity exercise (work-related and recreational) that they performed in one week. Based on the amount of exercise per week and participation in Rock Steady Boxing, the subjects were organized into three cohorts: the Rock Steady Boxing group, the non-specific exercise active group, and the relatively sedentary group.

For clarification, non-specific exercises are defined as physical activity that is not tailored to hindering disease progression. All subjects who participated in the Rock Steady Boxing program were placed in the Rock Steady Boxing cohort. The non-specific exercise cohort and the relatively sedentary cohort were differentiated based on the weekly amount of exercise recorded in the IPAQ. Thresholds were set based on the American Heart Association requirements for weekly exercise: 150 minutes of low intensity or 75 minutes of high intensity exercise. If subjects met either of these criteria, they were placed in the non-specific exercise cohort. Additionally, subjects provided their age, sex, BMI, race, medications, and approximate date of diagnosis on a demographics form.

Results

Linear regression and t-tests were incorporated to assess the current data. First, linear regression analysis was performed to determine any positive relationship between exercise and quality of life in Parkinson's disease patients. The relationship between weekly total exercise, both high and low intensity combined, and Neuro-QoL survey super-score was evaluated (Figure 1). The coefficient of determination, R^2, was 0.169, and the p-value was 0.024, which suggests a modest but significant correlation between the two variables. The second linear regression evaluated the relationship between weekly high intensity exercise and the Neuro-QoL super-score (Figure 2). The R^2 value and p-value were calculated to be 0.226 and 0.008, respectively. Given the higher coefficient of determination and the lower p-value relative to the relationship between total weekly exercise and NeuroQoL super-score, the linear regression suggests that high intensity exercise is more positively associated with the NeuroQoL super-score. There were no significant results found for the relationship between the amount of weekly low intensity exercise and NeuroQoL super-score.

The t-tests were applied to determine if quality of life in Parkinson's disease patients depended on the type of exercise cohort. The two-sample t-test compared two cohorts at a time to determine if there was a significant difference in Neuro-QoL super-scores. The first t-test compared the Neuro-QoL super-scores in the Rock Steady Boxing group and the sedentary group (Figure 3). The Rock Steady Boxing group showed a mean super-score of 0.79854689, while the mean super-score for the sedentary group was 0.70124904. The p-value was determined to be 0.05, suggesting a potentially significant difference between the two groups. The second t-test compared the Neuro-QoL super-scores in the non-specific exercise group and the sedentary group (Figure 4). The means for the non-specific exercise and sedentary super-scores were 0.80000567 and 0.70124904, respectively. The p-value was determined to be 0.063, suggesting that the difference in super-score between the groups is not significant within a 95% confidence interval. However, more data needs to be included to validate this result. The t-test comparing the Rock Steady Boxing and non-specific exercise cohorts was not reported because the p-value was 10-fold higher than that of the first two t-tests. The paucity of data for the Rock Steady boxing cohort and the resultant small number of degrees of freedom draws the validity of any apparent cohort differences into question. Data collection is on-going for the Rock Steady cohort.

Discussion

The aims of this study were to determine if there was a positive association between the level of exercise and the quality of life in Parkinson's patients, and if the participation in a specific exercise regimen like Rock Steady Boxing was associated with a higher quality of life than found in subjects a similar quantity of non-specific weekly aerobic activity. The large number of questions in each Neuro-QoL survey, the built in redundancy of each questionnairre, and the creation of a Neuro-QoL superscore based on a broad range of questions about quality of life provides a robust, yet subjective, finding. Furthermore, the results of this study suggest that there may be a significant relationship between the amount of weekly exercise per week and quality of life in Parkinson's disease patients. The linear regression analysis for weekly high intensity exercise and Neuro-QoL super-scores showed that 22.6% of the variation in Neuro-QoL data can be explained by the amount of weekly vigorous activity. For total weekly exercise and Neuro-QoL super-score, 16.9% of the variation in Neuro-QoL data can be explained by total weekly exercise. This data suggests that the quality of life in Parkinson's disease could be partially explained by the amount of physical activity in a Parkinson's disease patient's weekly routine. Although the positive correlations found in Figure 1 and Figure 2 were modest, the lack of a stronger correlation could be due to the slight negative correlation that was found between symptom progression and Neuro-QoL superscores (R^2= 28.9%, p-value = 0.010) (Figure 5). Parkinson's disease is a progressive disorder, and symptom onset can occur years before diagnosis. Therefore, disease progression must be taken into account because it may serve as a strong factor for limiting quality of life, despite the amount of weekly exercise.

The two-sample t-test showed a statistically significant difference in Neuro-QoL super-scores between the Rock Steady Boxing cohort and the sedentary cohort, suggesting that Rock Steady Boxing should be further investigated to understand how it is positively tailored for Parkinson's disease patients. The data does not completely support the second hypothesis, given the low sample size of the Rock steady cohort. In future studies, more Rock Steady Boxing participants need to be recruited in the study to support the hypothesis that engaging in the boxing program is associated with a positive quality of life. Additional research is required to assess the additional benefit of Parkinson's specific regimens such as Rock Steady Boxing. Significantly improved outcomes for the Rock Steady cohort would indicate a need for inclusion of such programs into standard care regimens. Further research in this field is crucial in order to adequately meet the needs of a vulnerable patient population.

References

1. Covy, J. P. & Giasson, B. I. α-Synuclein, leucine-rich repeat kinase-2, and manganese in the pathogenesis of Parkinson disease. *Neurotoxicology* **32**, 622–629 (2011).

2. Antony, P. M. A., Diederich, N. J., Krüger, R. & Balling, R. The hallmarks of Parkinson's disease. *FEBS J.* **280**, 5981–5993 (2013).

3. Galvan, A. & Wichmann, T. Pathophysiology of parkinsonism. *Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol.* **119**, 1459–1474 (2008).

4. *Neuroscience*. "Basal Ganglia." (Sinauer Associates, 2001)

5. Houlden, H. & Singleton, A. B. The genetics and neuropathology of Parkinson's disease. *Acta Neuropathol. (Berl.)* **124**, 325–338 (2012).

6. Lill, C. M. Genetics of Parkinson's disease. *Mol. Cell. Probes* **30**, 386–396 (2016).

7. Taylor, J. M., Main, B. S. & Crack, P. J. Neuroinflammation and oxidative stress: Co-conspirators in the pathology of Parkinson's disease. *Neurochem. Int.* **62**, 803–819 (2013).

8. Chahine, L. M. & Stern, M. B. Parkinson's Disease Biomarkers: Where Are We and Where Do We Go Next? *Mov. Disord. Clin. Pract.* **4**, 796–805 (2017).

9. Wu, P.-L., Lee, M. & Huang, T.-T. Effectiveness of physical activity on patients with depression and Parkinson's disease: A systematic review. *PloS One* **12**, e0181515 (2017).

10. Connolly, B. S. & Lang, A. E. Pharmacological Treatment of Parkinson Disease: A Review. *JAMA* **311**, 1670 (2014).

11. Maldyk, E. [Role of the anatomo-pathologist in the postmortem diagnosis of diseases of the connective tissues]. *Patol. Pol.* **21**, 261–272 (1970).

Appendix

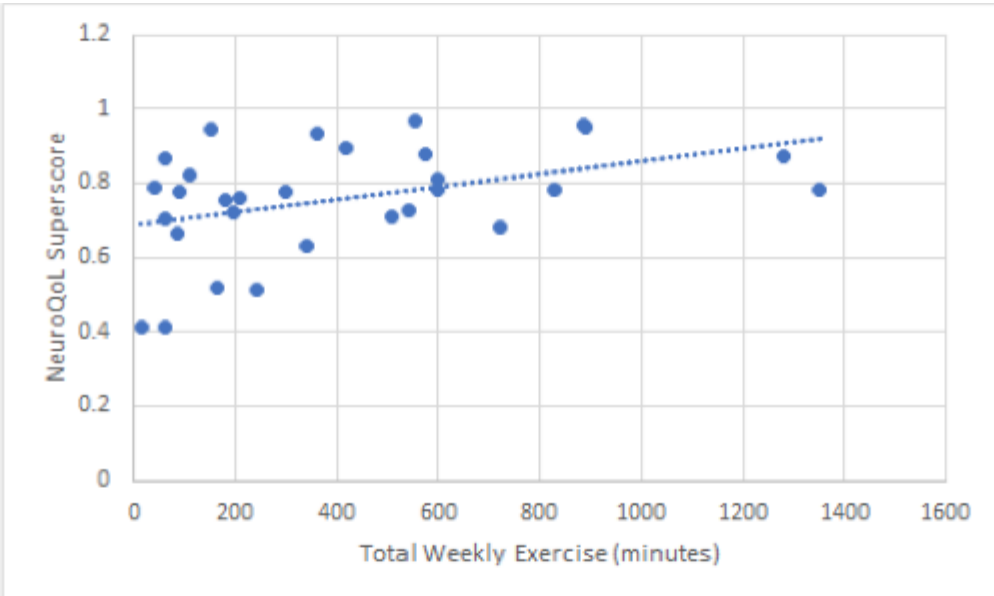

Figure 1. Linear regression of the relationship between total weekly exercise and NeuroQol Superscore

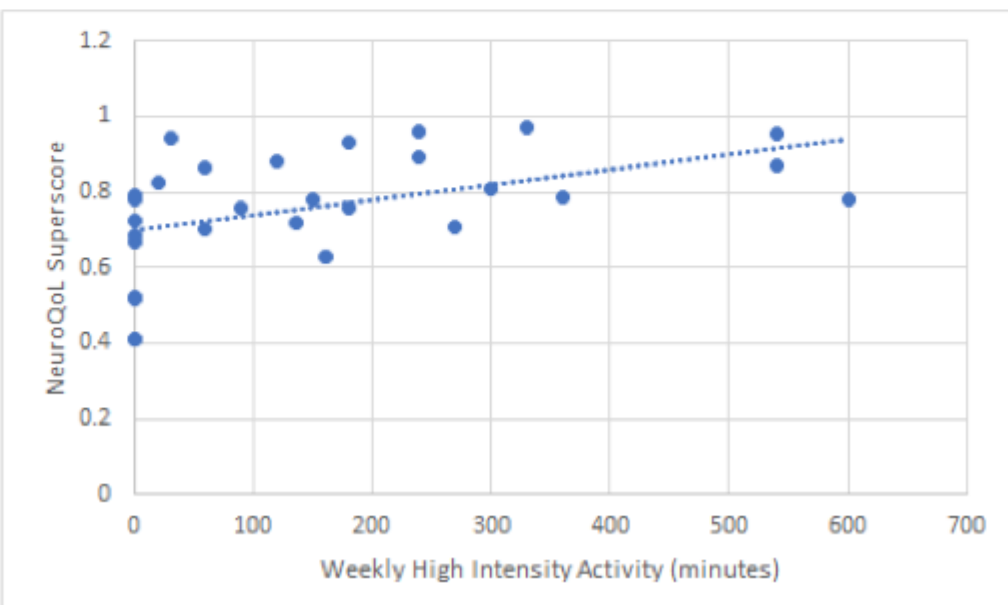

Figure 2. Linear regression of the relationship between the amount of weekly high intensity exercise and NeuroQol Superscore

t-Test: Two-Sample Assuming Unequal Variances		
	RSB	*less-active*
Mean	0.79854689	0.70124904
Variance	0.00249122	0.02945401
Observations	4	12
Hypothesized Mean Difference	0	
df	14	
t Stat	1.7539527	
P(T<=t) one-tail	0.05064628	

Figure 3. Two-sample t-Test that compares the mean Neuro-QoL superscores between the Rock Steady Boxing cohort and sedentary (less active) cohort

t-Test: Two-Sample Assuming Unequal Variances		
	active	*less-active*
Mean	0.80000567	0.70124904
Variance	0.01918542	0.02945401
Observations	14	12
Hypothesized Mean Difference	0	
df	21	
t Stat	1.59682337	
P(T<=t) one-tail	0.06262228	

Figure 4. Two-sample t-Test that compares the mean Neuro-QoL superscores between the non-specifc exercise cohort and sedentary (less active) cohort

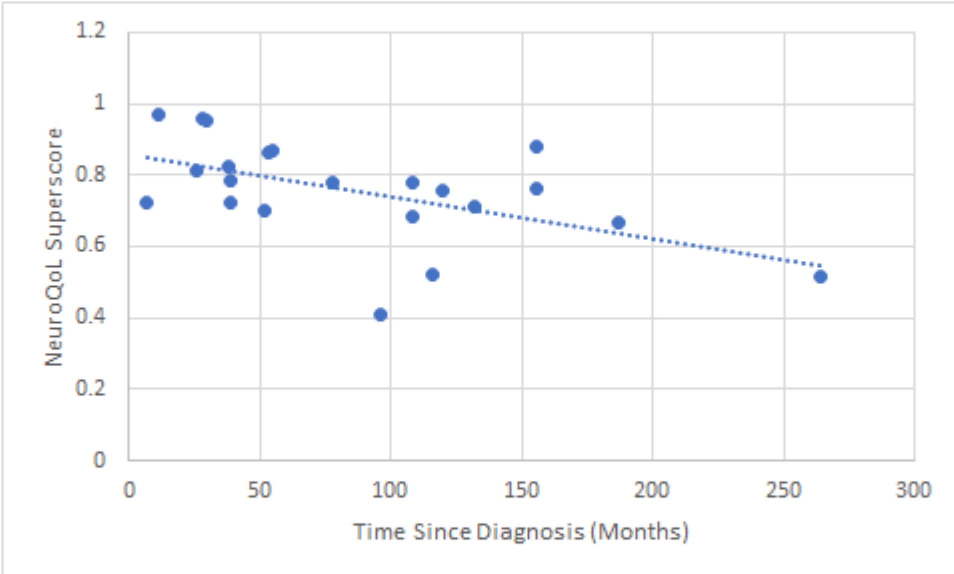

Figure 5. Linear regression of the relationship between the time since diagnosis with Parkinson's disease and Neuro-QoL superscore Parkinson's disease progression