Exercise Mode Moderates the Relationship Between Mobility and Basal Ganglia Volume in Healthy Older Adults

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OBJECTIVES: To examine whether 12 months of aerobic training (AT) moderated the relationship between change in mobility and change in basal ganglia volume than balance and toning (BAT) exercises in older adults.

DESIGN: Secondary analysis of a randomized controlled trial.

SETTING: Champaign-Urbana, Illinois.

PARTICIPANTS: Community-dwelling older adults (N = 101; mean age 66.4).

INTERVENTION: Twelve-month exercise trial with two groups: AT and BAT.

MEASUREMENTS: Mobility was assessed using the Timed Up and Go test. Basal ganglia (putamen, caudate nucleus, pallidum) was segmented from T1-weighted magnetic resonance images using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library Integrated Registration and Segmentation Tool. Measurements were obtained at baseline and trial completion. Hierarchical multiple regression was conducted to examine whether exercise mode moderates the relationship between change in mobility and change in basal ganglia volume over 12 months. Age, sex, and education were included as covariates.

RESULTS: Exercise significantly moderated the relationship between change in mobility and change in left putamen volume. Specifically, for the AT group, volume of the left putamen did not change, regardless of change in mobility. Similarly, in the BAT group, those who improved their mobility most over 12 months had no change in left putamen volume, although left putamen volume of those who declined in mobility levels decreased significantly.

CONCLUSION: The primary finding that older adults who engaged in 12 months of BAT training and improved mobility exhibited maintenance of brain volume in an important region responsible for motor control provides compelling evidence that such exercises can contribute to the promotion of functional independence and healthy aging. **J Am Geriatr Soc 64:102–108, 2016.**

Key words: basal ganglia; mobility; aging; exercise mode

With the number of adults aged 65 and older expected to triple worldwide by 2050,[1] understanding the factors that contribute to healthy and successful aging is an important public health priority. Mobility and brain health (e.g., structure and function of the brain) deteriorate with age and can negatively affect quality of life and functional independence of older adults. For example, changes in gait speed predicted mortality in an 8-year prospective study,[2] with 0.1-m/s greater usual gait speed predicting a 58% lower relative risk of death. Similarly, greater reductions in brain volume over time are associated with greater risk of impairment in instrumental activities of daily living (IADLs).[3] Thus, extending knowledge about developmental changes in brain volume and mobility may provide insight into how functional decline can be effectively combated in an aging population.

Recent literature has highlighted the connection between mobility and structural integrity of the brain. In a population-based longitudinal study of adults aged 60 to 86, smaller total white matter volume and greater white matter lesion progression were significantly associated with slower gait speed over 2.5 years.[4] In another population-based study of community-dwelling adults aged 65 and older that examined gray matter volumes in regions specif-

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ically relevant for motor control—such as the putamen and cerebellum—smaller volumes were significantly associated with poorer mobility, including slower gait speed and poorer balance.[5] Although such studies point toward a clear correlation between mobility and brain health, it is important to consider that it is likely that these constructs have a bidirectional relationship; that is, deterioration in one can negatively affect the other and vice versa. Therefore, identifying strategic interventions that improve mobility and brain health is an important public health goal.

Exercise training is a promising intervention strategy that has multiple systemic benefits. In cross-sectional and intervention strategies alike, exercise has been found to improve mobility [6] and brain health,[7–11] but different modes of exercise have differential physiological effects on the body. For example, aerobic training (AT), which includes activities such as walking and running, is aimed at improving cardiovascular health. A second type of exercise is balance and toning (BAT), which includes exercises aimed at improving muscle tone, flexibility, and balance. Given that BAT exercises can target lower extremity strength and balance, it is likely that they are better than AT for improving important components of mobility, such as postural stability. Individuals who completed a 12-month BAT program exhibited greater improvements on the Timed Up and Go (TUG)—a measure of mobility in older adults—than those in an AT program.[6] Given that different types of exercise have different physiological objectives, it was hypothesized that they might they have different effects on the relationship between changes in mobility and brain volume.

The primary aim of this secondary analysis of a 12-month randomized controlled trial (RCT)[6,12–14] was to examine the association between change in mobility and change in brain volume in subcortical regions of the basal ganglia that are part of the motor circuit: the putamen, caudate nucleus, and pallidum. The basal ganglia was focused on because of its role in locomotion and motor coordination.[15] An additional goal was to examine whether exercise type moderates this relationship between mobility and basal ganglia volume. Specifically, the effects of an AT exercise program on the relationship between mobility and basal ganglia volume was compared with those of a BAT program. Given that BAT training includes mobility-relevant exercises, it was hypothesized that a stronger relationship between changes in mobility and regional volume would be observed in this group than in the AT group. Such findings would have the potential to inform future intervention strategies for older adults to improve multiple outcomes critical for maintaining an independent, active lifestyle.

METHODS

Participants

Older community-dwelling adults were recruited to participate in a 12-month RCT examining the effects of exercise on cognition and brain health. Details of the study have been reported elsewhere.[6,13,16] Briefly, participants were eligible if they were aged 60 to 80 years; were right handed; had a score of 51 or greater on the modified Mini-Mental State Examination,[17] a screening questionnaire for cognitive status; had a score of <3 on the Geriatric Depression Scale;[18] had normal color vision and corrected visual acuity of at least 20/40; had been physically inactive over the past 6 months (having been physically active for ≥30 minutes no more than two times per week in the last 6 months). Ethics approval was obtained from the institutional review board at the University of Illinois at Urbana-Champaign, and all participants provided written informed consent.

Exercise Intervention

This was a 12-month RCT with assessments at baseline, midpoint, and trial completion. Participants were randomized into an AT group or a BAT control group. Both programs consisted of three 40-minute group sessions per week and were led by trained exercise leaders.

In the AT program, participants started by walking for 10 minutes on an indoor track, increased their walking duration weekly by 5-minute increments until a duration of 40 minutes was achieved at Week 7, and then walked for 40 minutes per session for the remainder of the program. All walking sessions started and ended with 5 minutes of stretching to warm up and cool down. Exertion was monitored using heart rate monitors, and participants were encouraged to walk at 50% to 60% of their maximum heart rate reserve (HRR) for Weeks 1 to 7 and to increase to 60% to 75% of their maximum HRR for the remainder of the program.

The BAT program consisted of warm-up and cool-down stretches, four muscle toning exercises using dumbbells or resistance bands, two balance exercises, a yoga sequence, and an exercise of their choice. New exercises were introduced every 3 weeks to maintain interest. Participants were encouraged to exercise at an intensity of 13 to 15 on the Borg rate of perceived exertion scale.[19] This group served as a control for nonexercise-based effects of participation in a program, such as socialization and study commitment.

Measures

Mobility

To assess mobility, participants completed a modified version of the TUG test,[20] which requires participants to stand up from a seated position, walk a distance of eight feet at their usual pace, return to the chair, and sit back down. The shortest time of two trials was recorded in seconds. Change over time for TUG performance was calculated as baseline score minus trial completion score, with higher scores indicating improved mobility over the 12-month trial. The TUG is a useful measure of mobility given that it can differentiate between healthy older adults and those at risk of falling [21] and correlates with other measures of mobility.[20]

Magnetic resonance imaging

Participants underwent magnetic resonance imaging (MRI) on a 3T head-only scanner (Allegra, Siemens, Erlangen, Germany). High resolution T1-weighted brain images using a three-dimensional magnetization prepared rapid

gradient echo imaging protocol with 144 contiguous axial slices collected in ascending fashion parallel to the anterior and posterior commissures, and echo time of 3.87 ms, a repetition time of 1,800 ms, a field of view of 256 mm, an acquisition matrix of 192 by 192 mm, a slice thickness of 1.3 mm, and a flip angle of 8°.

Brain volume of the left and right putamen, caudate (head and tail), and pallidum were calculated using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library Integrated Registration and Segmentation Tool Software Library (FSL) Integrated Registration and Segmentation Tool (FIRST)[22] a semiautomated, model-based segmentation and registration tool within the Oxford Centre's FSL software package version 5.0. FIRST uses a point distribution model to extract the volume of segmented subcortical structures based on priori manually segmented images of subcortical structures provided by the Center for Morphometric Analysis (Massachusetts General Hospital, Boston, MA). First, the algorithm uses an affine transformation to register the T1-weighted image to the Montreal Neurological Institute template. Next, the algorithm searches through linear combinations of shape modes of variation for the most-probable shape instance given the observed intensities on the T1-weighted image. The algorithm then transfers the images back to native space. Finally, boundary correction is applied to classify whether the boundary voxels belong to the structure or not, using a threshold of $P < .001$ ($z > 3.00$), before the final volume estimation is extracted. Raters blind to participant exercise group allocation manually checked the quality of the segmentations. See [22] for further details on the FIRST algorithm.

Statistical Analysis

Volumetric data were imported into SPSS version 21 (SPSS, Inc., Chicago, IL) for analysis. To control for baseline basal ganglia volume, percentage change over time for subcortical brain volume was calculated as ((trial completion volume–baseline volume)/baseline volume) × 100; higher scores indicate greater increases in volume over the 12-month trial. To examine the relationship between mobility, basal ganglia volume, and exercise mode, hierarchical multiple regression analyses was conducted separately for each brain region (left and right putamen, caudate, pallidum). In the first step, age, sex, and education were included because of their relationship to brain processes and mobility. Next, change in TUG performance and exercise mode (AT vs BAT) were included to predict percentage change in basal ganglia brain volume. Last, the interaction term between change in TUG performance and exercise mode was added to the regression model. Alpha was set at $P \leq .05$.

RESULTS

Baseline demographic characteristics are presented in Table 1. Of 179 participants recruited and randomized for the RCT, 101 had usable MRI scans and mobility assessments at baseline and trial completion and were therefore included in the secondary analysis. The mean age of participants included in the secondary analysis was 66.4 ± 5.8, which was nearly identical to the mean age of all participants in the intervention (66.4).

Change scores over the 12-month intervention for relevant variables are presented in Table 2. The effects of the exercise intervention on physical functioning,[6] cognition,[12] and brain structure [16] and function [12] have been reported elsewhere. Pertinent to the current study, there was a significant interaction between time and exercise group for TUG performance, whereby participants in the BAT group improved their mobility significantly more than those in the AT group.[6] In terms of basal ganglia volume, the BAT group had significantly greater decreases in the left

Table 1. Participant Baseline Demographic Characteristics

Characteristic	Aerobic Training, n = 54	Balance and Tone, n = 47	Total, N = 101
Age, mean ± SD	67.4 ± 5.7	65.3 ± 5.9	66.4 ± 5.8
Female, %	74.1	61.7	68.3
Education, n (%)			
≤Grade 9	1 (1.9)	0 (0.0)	1 (1.0)
High school graduate	7 (13.0)	7 (14.9)	14 (13.9)
Some college or vocational school	17 (31.5)	11 (23.4)	28 (27.7)
College graduate	11 (20.4)	10 (21.3)	21 (20.8)
Master's degree	13 (24.1)	12 (25.5)	25 (24.8)
PhD or equivalent	5 (9.3)	7 (14.9)	12 (11.9)
Modified Mini-Mental State Examination score, mean ± SD (range 0–100)	54.9 ± 1.9	55.3 ± 1.7	55.1 ± 1.8
Timed Up and Go, seconds, mean ± SD	5.6 ± 1.0	5.7 ± 1.0	5.6 ± 1.0
Brain volume, mm^3, mean ± SD			
Left putamen	4,378.36 ± 575.62[a]	4,624.53 ± 597.81	4,492.91 ± 596.01
Right putamen	4,444.74 ± 505.05	4,616.81 ± 608.85	4,524.81 ± 559.60
Left caudate	3,110.28 ± 449.90	3,103.53 ± 485.24	3,107.14 ± 464.33
Right caudate	3,280.88 ± 470.40	3,287.53 ± 443.81	3,283.97 ± 455.95
Left pallidum	1,842.43 ± 334.25	1,815.55 ± 333.94	1,829.92 ± 332.71
Right pallidum	1,810.97 ± 349.39	1,772.57 ± 264.54	1,793.10 ± 311.86

[a] $P \leq .05$.

SD = standard deviation.

putamen over the 12-month intervention period than the AT group, as indicated by a significant interaction between time and exercise group, covarying for age, sex, and education evidenced ($F_{1,96} = 5.27$, $P = .02$, partial $\eta^2 = 0.05$). There were no between-group differences for the other basal ganglia regions (right putamen, left and right caudate, pallidum; all $P > .07$).

For the hierarchical regression (Table 3), change in mobility and exercise mode accounted for a significant amount of variance in percentage change in left putamen volume (coefficient of determination (R^2) = 0.165, $F_{5,95}$) = 3.75, $P = .004$. (Examining the data for heteroskedasticity, there was one outlier for change in left putamen volume (z = –6.09). Inclusion and exclusion of this participant did not significantly change any results or interpretations, so the participant was included in the analyses.) In addition, the interaction term between change in mobility and exercise mode accounted for significant variance in predicting percentage change in volume of the left putamen ($\Delta R^2 = 0.07$, $\Delta F_{1,94} = 7.93$, $P = .006$, b = 5.571, t (94) = 2.82, $P = .006$). The data (Figures 1 and 2) show that volume of the left putamen did not change for the AT group, regardless of change in mobility. Similarly, those in the BAT group who improved their mobility most over 12 months had little to no change in left putamen volume, but those who declined in mobility levels had a significant decrease in left putamen volume. Exercise type did not significantly moderate the relationship between mobility and brain volume for any other basal ganglia regions (right putamen or bilateral caudate and pallidum; all $P > .06$).

Table 2. Change Scores over 12 Months

Variable	Aerobic Training, n = 54	Balance and Tone, n = 47	Total, N = 101
	Mean ± Standard Deviation		
Timed Up and Go, seconds[a]	0.5 ± 0.8	0.7 ± 0.9	0.6 ± 0.8
Brain volume[b], mm^3			
Left putamen	26.3 ± 241.9[c]	−189.8 ± 507.3	−74.2 ± 401.4
Right putamen	−120.0 ± 260.1[d]	−276.2 ± 459.7	−192.7 ± 373.1
Left caudate	−25.4 ± 177.8	−49.6 ± 300.1	−36.7 ± 241.5
Right caudate	−26.6 ± 189.5	−70.9 ± 197.8	−47.2 ± 193.7
Left pallidum	−33.4 ± 102.9	−41.2 ± 314.7	−37.0 ± 226.2
Right pallidum	−63.8 ± 206.1	−84.7 ± 206.3	−73.5 ± 205.5

[a]Baseline minus trial completion.
[b]Trial completion minus baseline.
$P \leq$ [c].01, [d].05.

DISCUSSION

This secondary analysis of a RCT of exercise training showed that exercise mode moderated the relationship between change in mobility and change in left putamen volume. Specifically, in the BAT exercise group, decline in

Table 3. Hierarchical Regression Model

Independent Variable	Percentage Change in Left Putamen Volume[a]					
	Correlation Coefficient	R^2	R^2 Change	Unstandardized β (Standard Error)	Standardized β	P-Value
Model 1	0.281	0.079	0.079			
Age	0.232[d]			0.314 (0.148)	0.209	.04
Sex	0.059			0.381 (1.864)	0.020	.84
Education	−0.189			−1.037 (0.671)	−0.155	.12
Model 2	0.406	0.165	0.086			
Age	0.232[d]			0.261 (0.145)	0.173	.07
Sex	0.059			0.495 (1.826)	0.026	.79
Education	−0.189			−0.818 (0.650)	−0.122	.21
Δ TUG[b]	0.184			2.155 (1.007)	0.205	.03
Exercise mode[c]	−0.263[e]			−4.158 (1.691)	−0.237	.02
Model 3	0.479	0.230	0.065			
Age	0.232[d]			0.199 (0.141)	0.132	.16
Sex	0.059			1.122 (1.777)	0.060	.53
Education	−0.189			−1.081 (0.635)	−0.161	.09
Δ TUG	0.184			−0.579 (1.374)	−0.055	.67
Exercise mode	−0.263[e]			−7.502 (2.018)	−0.428	<.001
Δ TUG by exercise mode	0.146			5.571 (1.978)	0.429	.006

[a]Calculated as ((trial completion—baseline)/baseline) × 100.
[b]Calculated as baseline minus trial completion.
[c]Aerobic training coded as reference group in model.
$P \leq$ [d].05, [e].01.
R^2 = coefficient of determination.

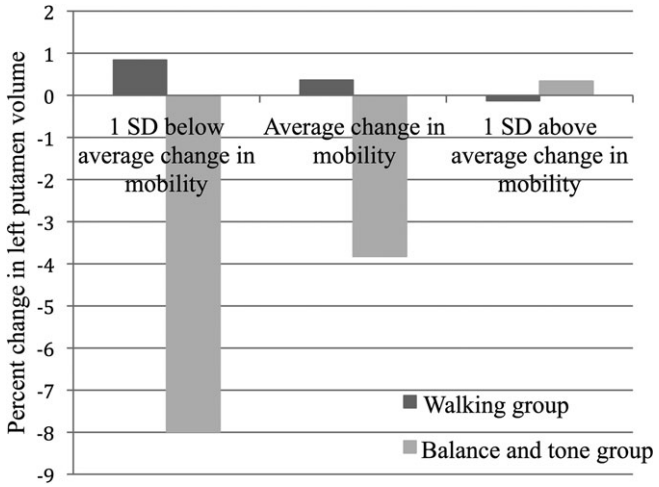

Figure 1. Percentage change in left putamen volume as a function of change in mobility and group (walking vs balance and tone). Negative values of percentage change in left putamen volume represent decreases in volume over time. Change in mobility represents average change in Timed Up and Go (TUG) scores ± 1 SD. Type of exercise moderates the association between change in volume of the left putamen and change in mobility, whereby change in left putamen volume remains stable across change in mobility in the walking group, whereas left putamen volume depends on change in mobility in the balance and tone group.

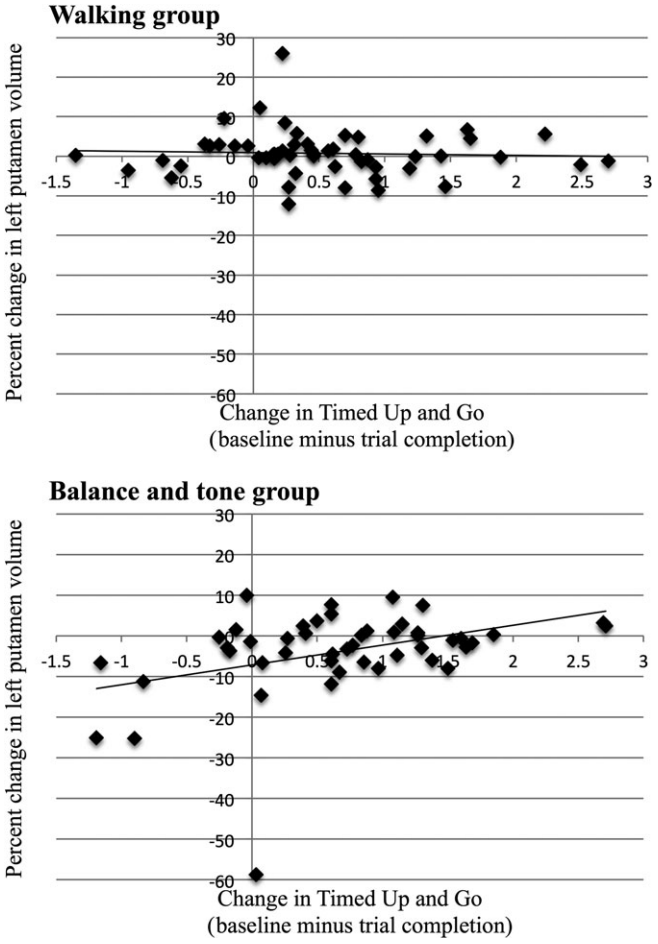

Figure 2. Scatterplots displaying the relationship between percentage change in left putamen volume and change in mobility over 12 months in the walking group (top) and balance and tone group (bottom).

mobility function over 12 months was significantly associated with reduction in subcortical brain volume in the left putamen—a brain region involved in motor control, including selection of movement.[23] Although previous work has established a link between mobility and brain health, this study is the first to examine this relationship in the context of longitudinal changes as a function of two distinct modes of exercise training. Hence, these results provide evidence of effective strategies to maintain mobility and putamen volume in older adults—two essential components of successful aging.

Twelve months of regular aerobic exercise resulted in maintenance of basal ganglia volume in older adults. This finding aligns with previous studies that independently found that aerobic exercise significantly increased hippocampal volume in healthy older adults [14] and those with mild cognitive impairment.[24] Another study found that greater aerobic fitness was associated with greater volume of the basal ganglia in children. [25] Aging brains lose volume globally,[26,27] including atrophy in the putamen,[28] but larger-than-normal declines in volume are associated with neurodegenerative disease;[29] it is estimated that annual global brain atrophy is 5 to 10 times as great in individuals with Alzheimer's disease as in healthy controls.[30] More specifically, changes in putamen volume are associated with motor-related disorders, such as Parkinson's disease.[31] Thus, the maintenance of brain volume over time may help to avoid cognitive and motor-related impairment, including risk of Parkinson's disease, in older age. The AT group exhibited preservation of putamen volume without any concomitant changes in mobility. Although it is beyond the scope of the current study, one possible mechanism through which AT may affect brain health is physical fitness, such as improvement of maximum oxygen uptake. Future research is required to extend understanding of the biological and physiological mechanisms that affect brain volume.

Furthermore, individuals in the BAT group who improved their mobility the most after 12 months of training also had the greatest preservation of left putamen volume. Therefore, the results suggest that, even though BAT training may not directly provide the same neuroprotective benefits as AT, it appears to buffer against brain volume loss through improvement in mobility. That is, participants in this group improved their mobility significantly more than the AT group, which in turn indicates the preservation of subcortical brain volume. Although this longitudinal study does not provide insight into the mechanisms that may account for this result, it may be that improving mobility in the BAT group strengthened relevant brain regions, which is certainly viable given the role of the putamen in motor control. Nevertheless, future studies to further examine the relationship between mobility, brain volume, and exercise type are warranted, including those that may elucidate how type of exercise may affect other brain regions, such as the cerebellum or motor cortex.

The strengths of this study include a large sample size with a long intervention period, although it had limitations

as well. First, the sample comprised highly educated older adults, which is not representative of the entire population; thus, the results may not generalize to more-heterogeneous samples. Second, mobility was defined according to TUG performance. Given that the TUG may not be sensitive to subtle changes in mobility, future studies encompassing diverse measures of mobility are essential before broad generalizations can be made. Related to this, the scope of the current study was limited to analysis of basal ganglia volume; future studies should investigate whether other subcortical volumes, such as the cerebellum, may also play a role in the relationship between exercise and mobility. The study did not include a no-contact control group. Although this means that it was not possible to examine changes in brain volume and mobility over 1 year in the absence of exercise, it allowed extraneous variables that may affect functional outcomes, such as participation in a study and socialization, to be controlled for. Last, the moderation model only permitted correlational inferences to be made. It is likely that the relationship between changes in mobility and brain health are bidirectional, such that each may affect the other. Furthermore, this is a dynamic, complex relationship with multiple other relevant variables. As such, elucidating factors that may contribute to individual-level differences in mobility improvement in the BAT group in addition to age, sex, and education would be an important next line of inquiry; the model accounted for a modest 23% of variance for predicting change in left putamen volume. Hence, future intervention studies to examine the intricacies of this model are warranted.

In conclusion, this is the first study to examine whether exercise mode moderates the relationship between change in mobility and change in basal ganglia brain volume. The primary novel finding that improving mobility through BAT training may buffer against brain volume loss in a region critical for motor control provides compelling evidence that BAT training can contribute to the promotion of functional independence and healthy aging in older men and women. To the extent that AT may not be accessible to a significant portion of older adults, such as those with poor mobility, BAT training may provide a feasible alternative for this population. Such findings should also be considered in light of the federal guidelines for physical activity participation, which recommend the accumulation of at least 30 minutes of aerobic activity on 5 or more days per week and participation in flexibility and strengthening activities on at least 2 days per week. Incorporating the combination of these activities in older adults' lifestyles is likely to result in an array of psychological and physical health benefits, not the least being the potential preservation of brain volume.

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