Dopamine-Related Genotypes and Physical Activity Change During an Intervention: The Lifestyle Interventions and Independence for Elders Study

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OBJECTIVES: To determine whether intervention-induced physical activity (PA) changes in sedentary older adults differed according to dopamine-related genotype.
DESIGN: Randomized clinical trial (Lifestyle Interventions and Independence for Elders Trial (2010–13)).
SETTING: Multicenter study, 8 U.S. locations.
PARTICIPANTS: Volunteer sample of sedentary adults aged 70 to 89 at risk of disability (N=1635).
INTERVENTIONS: Structured PA versus health education (HE) for an average of 2.6 years.
MEASUREMENTS: Single-nucleotide polymorphisms of dopamine-related genes (dopamine receptor (DR) D1, DRD2, DRD3, and catechol-O-methyltransferase (COMT)) were assessed. Average moderate to vigorous PA (MVPA) was calculated using accelerometry (min/d) at baseline and 6, 12, and 24 months. Between-arm MVPA differences according to genotype and genotype with square root–transformed MVPA separately according to arm were tested, stratified according to race, and adjusted for multiple comparisons.

RESULTS: White participants in the PA arm (n=513) had higher average square root transformed MVPA (4.91±1.91)than those in the HE arm (n=538) (4.51±1.82) (p=.001). Between-arm differences were greater for DRD2 Met/Met (high dopamine; HE: 4.76±1.80, PA: 5.53±1.60, p=.03) than Val/Val (low dopamine; HE: 4.58±1.92, PA: 4.81±1.83, p=.16); results were similar for COMT. In the PA arm, DRD2 Met/Met was associated with higher average MVPA (5.39±2.00) than Met/Val (4.46±2.51) (p=.01) and Val/Val (4.65±2.71) (p=.01). There were no associations for other genes. Associations were not significant in blacks but followed similar trends.
CONCLUSION: Higher dopamine signaling may support changes in PA during an intervention. The role of dopamine-related pathways in promoting PA participation and enhancing response to interventions in sedentary older adults should be studied.
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Key words: randomized controlled trial; physical activity; aging; dopamine

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Physical activity (PA) has well-documented benefits for older adults, including lower risk of disability[1] and dementia,[2] but physical inactivity and sedentary behavior are common, with only 8.5% of adults aged 60 to 69 and 6.3% of those aged 70 and older meeting the recommended 150 min/wk of PA.[3] Even with intervention-induced increases, PA levels typically wane over time.[1] Identification of phenotypes and mechanisms that explain

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low response to PA interventions may improve promotion efforts.

It has been theorized that dopamine plays a role in PA participation.[4,5] Cerebral dopaminergic function regulates factors related to PA in older adults,[6] including cognitive control,[7] physical function,[8] motivation and reward response,[9] and depressive mood.[10] Several genes regulate dopaminergic neurotransmission, and polymorphisms in these genes have functional and behavioral consequences.[7,11,12] These genes include those related to dopamine receptor density (dopamine receptor (DR) D1, DRD2, DRD3) and metabolism (catechol-O-methyltransferase (COMT)). Prior observational studies have largely found no associations between these genes and self-reported PA across the lifespan,[13–16] but associations with changes in PA during structured interventions have not been studied.

We tested associations between DR and COMT polymorphisms and changes in objectively measured PA in the Lifestyle Interventions and Independence for Elders (LIFE) randomized controlled study. LIFE tested a 2-year structured PA intervention for prevention of mobility disability in at-risk older adults. We hypothesized that genotypes related to higher dopamine function would be associated with greater increases in PA than genotypes related to lower dopamine function. We further explored individual characteristics that might explain associations between dopamine-related genotypes and PA, including changes in physical and cognitive function and mood.

METHODS

Study population

Details of the LIFE study are provided elsewhere.[1,17] Participants were recruited[18] at 8 centers across the United States (University of Florida, Gainesville and Jacksonville, Florida; Northwestern University, Chicago, Illinois; Pennington Biomedical Research Center, Baton Rouge, Louisiana; University of Pittsburgh, Pittsburgh, Pennsylvania; Stanford University, Stanford, California; Tufts University, Boston, Massachusetts; Wake Forest School of Medicine, Winston-Salem, North Carolina; Yale University, New Haven, Connecticut). Participants were eligible if they were aged 70 to 89, were sedentary (reporting <20 min/wk regular PA in past month), had a Short Physical Performance Battery (SPPB)[19] score of 9 or less, were able to walk 400 m in less than 15 minutes without assistance, had no major cognitive impairment, and could safely participate in a walking-based PA intervention; 1,635 participants were randomized (818 to PA, 817 to health education (HE)) between February 2010 and December 2011. Institutional review boards at all institutions approved the study, and all participants provided written informed consent.

Participants were excluded from analyses if they did not have accelerometer data at baseline and at least 2 additional time points (n=231), if they did not self-identify as black or white (n=108), or if they were missing genotype data (n=262); categories not mutually exclusive. Genotypes were randomly distributed according to intervention arm (Supplemental Table S1). Our analytical sample was less likely to be female (p=.02) or black (p<.001) and had higher baseline Modified Mini-Mental State Examination (3MS) scores (p<.001), faster 400-m walk time (p=.001), and higher percentage session attendance for the duration of the intervention (68.4% vs 40.7%; p<.001) than those excluded. They did not differ on other characteristics, including change in functional measures (all p>.11).

Participant flow is shown in Supplemental Figure S1.

Interventions

The active intervention period was 24 to 42 months (average 31 months), with the end point for these analyses at 24 months.

The PA intervention consisted of walking (goal of 150 min/wk) and strength, flexibility, and balance training.[17] Participants attended 2 center-based visits per week and were instructed to complete home-based activities 3 to 4 times per week. The intervention was personalized, with a target of 30 min/d of moderate intensity walking.

The HE program consisted of weekly workshops on successful aging for the first 26 weeks, followed by monthly sessions. The workshops did not include PA recommendations but included light upper extremity stretching and flexibility exercises.

Independent Variable—Dopamine Genotypes

Deoxyribonucleic acid samples were genotyped using TaqMan allelic discrimination (Life Technologies/Fisher Scientific, Foster City, CA). Polymerase chain reaction primers and probes for COMT single-nucleotide polymorphism (SNP) rs4680, DRD1 rs265981, DRD2 rs6275, and DRD3 rs6280 (C__25746809_50, C__11592758_10, C___1011775_20, C___2601173_20, and C____949770_10) TaqMan assays were from Applied Biosystems/Fisher Scientific (Foster City, CA). Genotyping assays were performed and analyzed according to the manufacturer's recommendations. Five-μL reactions in 384-well plates were prepared using Eppendorf epMotion 5070 (Eppendorf North America, Inc., Westbury, NY) liquid-handling and sample-processing robotics. Genotype accuracy was verified by genotyping 5% to 10% randomly selected duplicate samples for each SNP and Hardy-Weinberg analysis. Genotyping was performed at the University of Florida Center for Pharmacogenomics Genotyping Core Laboratory.

SNPs and their anticipated effects on the dopaminergic system are outlined in Table 1. COMT is an enzyme that metabolizes dopamine and other monoamines. The methionine (Met) allele of rs4680 is less efficient at producing COMT and, consequently, is associated with slower clearance and higher levels of dopamine than the valine (Val) allele.[20] The DRD1s are involved in the dopaminergic direct pathways, with more receptors leading to greater signaling along these pathways.[11] The DRD1 rs265981 Met allele leads to lower receptor density, lower dopaminergic signaling, and consequently, lower dopamine activity than the Val allele.[14,21] The DRD2s are pre- and postsynaptic and act in a self-regulating manner.[11]

Table 1. Dopamine-Related Single Nucleotide Polymorphisms and Their Hypothesized Effects on the Dopaminergic System

Gene	Variant	Allele	Effect on Dopaminergic System	Effect on Dopamine Synaptic Levels or Signaling Relative to Alternate Allele
Catechol-O-methyltransferase	rs4680	Met	Slower metabolism of dopamine	Higher
DRD1	rs265981	Met	Lower DRD1 expression	Lower
DRD2	rs6275	Met	Lower DRD2 expression, lower inhibitory feedback	Higher
DRD3	rs6280	Glycine	Higher binding affinity, lower transmission	Lower

DR = dopamine receptor; Met = methionine.

The Met allele of DRD2 rs6275 is associated with lower receptor density, less self-modulating presynaptic activity, and therefore, higher dopamine activity.[14] Finally, DRD3s are part of the D2 family and are located primarily in the limbic system. The glycine (Gly) allele in the DRD3 variant rs6280 demonstrates has an affinity for dopamine binding that is 5 times as strong as that of the serine (Ser) allele,[22] resulting in lower dopaminergic activity.

PA Monitoring

Participants were to wear an accelerometer (GT3X, Actigraph, Pensacola, FL) on their right hip for 7 consecutive days before randomization and 6-, 12-, and 24-month follow-up visits. Participants were to remove the device only for sleeping and water activities. Activity during structured PA intervention visits was not recorded. Movement was captured along the vertical axis in 1-minute epochs, and nonwear time was defined as 90 minutes of consecutive 0 counts.[23] Analyses were limited to participants with wear time of at least 600 min/d for 3 or more days (mean daily minutes of wear time at each visit ranged from 812.8±93.3 to 833.8±109.5, and mean valid days at each visit ranged from 6.5±2.4 to 7.8±3.5).

Dependent Variable—PA

The dependent variable was total minutes per day of moderate to vigorous PA (MVPA), defined as time at or above 760 counts per minute[24] according to accelerometry. Because meaningful cut-points are established for older adults with physical function limitations, sensitivity analyses considered alternate cut-points of 500 counts per minute, 1,041 counts per minute, and 1,500 counts per minute. Differences in associations using different cut-points did not change the interpretation of results (data not shown).

Covariates

Race was self-reported at baseline. Dopamine-related SNP alleles distributions differ according to race, and PA levels may differ according to race, so all analyses were a priori stratified according to black and white race to avoid confounding. Other races had samples too small to conduct stratified analyses and were therefore excluded.

Age, sex, and highest education level were self-reported at baseline. Body mass index (BMI) was calculated in kg/m^2 using standard measurements for height and weight. History of cardiovascular disease and diabetes were self-reported. Blood pressure was measured at the upper arm using a standard seated protocol. Intervention adherence was calculated as percentage of sessions attended.

Mobility limitations were measured according to time to walk 400 m at usual pace.[25] The SPPB consists of 3 components measuring lower extremity performance: balance in side-by-side, semitandem, and tandem positions; 4-m usual-pace gait speed; and 5 repeated chair stands.[26] Each component is assigned a score from 0 (unable to complete) to 4 (best performance) and summed to a total score of 0 to 12. We also considered gait speed (m/s) alone. Global cognitive function was assessed using the 3MS.[27] Composite executive function included average normalized scores from the n-back, task-switching, and Flanker tests.[28] Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale.[29]

The dopaminergic system modulates executive function, gait speed, and mood,[7,8,10] which PA can modify,[30–32] so changes in these measures were examined as explanatory factors for the association between genotype and PA.

Statistical analyses

Raw minutes of MVPA with standard errors were plotted according to study visit and genotype. Raw values were skewed, so root-transformed values of minutes per day of MVPA were used for statistical comparisons. Linear and quadratic models did not fit the shape of the MVPA changes over time, so we used an average value of the transformed MVPA calculated for each participant from baseline to 24 months. Effects of interactions between genotype and arm on average MVPA were tested using linear regression. For genotypes with suggested interactions ($p<.2$), linear regressions of arm and MVPA were conducted stratified according to genotype.

Pairwise comparisons of MVPA according to genotype within the PA arm were conducted using t-tests. False discovery rate adjustment was used to account for multiple comparisons of multiple genes. For genotypes that were significantly associated with MVPA, we assessed bivariate associations between genotype and potential explanatory factors in the covariate section above. Comparisons were

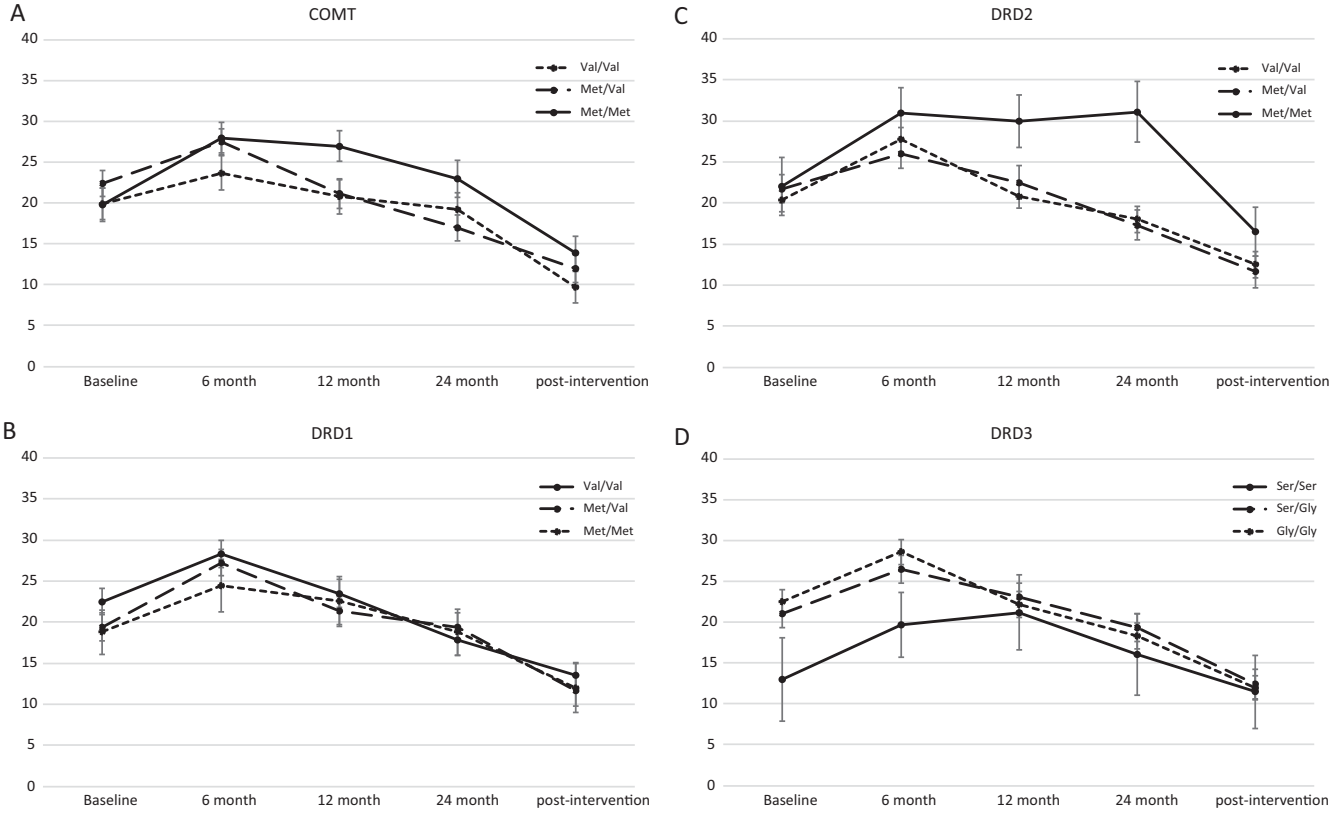

Figure 1. Median (standard error) minutes of moderate to vigorous physical activity (MVPA) per day according to time period for whites in the physical activity arm of the Lifestyle Interventions and Independence for Elders Study (N=513) according to genotype: (A) catechol-O-methyltransferase, (B) dopamine receptor (DR)D1, (C) DRD2, and (D) DRD3. A solid line indicates the genotype associated with the highest dopamine signaling, and a short dashed line indicates the lowest dopamine signaling. The long dashed line indicates heterozygotes.

conducted using analysis of variance for continuous variables and the chi-square test for categorical variables. Linear regression models were then used to assess the association between genotype and average log-transformed MVPA, with adjustment for basic demographic characteristics (age, sex, clinic site) and for covariates associated with genotype in bivariate analyses at $p<.1$. We decided a priori to adjust for changes in gait speed, executive function, and depressive symptoms over 24 months. All analyses were conducted in 2017 using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

The analytical sample had a mean age of 78.8±5.2; 20.0% were black, and 64.9% were female.

Interactions between study arm and DRD2 (p=.18) or COMT (p=.12) genotype were suggestive of a differential intervention effect according to genotype in white participants. Mean between-arm differences in MVPA were larger for those with the DRD2 Met/Met genotype (HE: 4.76±1.80, PA: 5.53±1.60, p=.03) than for those with the Met/Val (HE: 4.38±1.70, PA: 4.87±2.04, p=.01) or Val/Val genotype (HE: 4.58±1.92, PA: 4.81±1.83, p=.16). Similarly, between-arm differences in MVPA were larger for those with the COMT Met/Met genotype (HE: 4.31±1.79, PA: 5.07±1.83, p=.001) than for those with the Met/Val (HE: 4.56±1.83, PA: 4.88±1.96, p=.06) or Val/Val genotype (HE: 4.74±1.89, PA: 4.09±1.21, p=.68).

Raw minutes of PA are shown according to genotype for white participants in the PA arm (n=513) in Figure 1 (data in Supplemental Table S2). There were no baseline differences in PA according to genotype (all p>.1; Table 2). There were significant associations between DRD2 genotype and average MVPA (Table S2). Participants with the Met/Met DRD2 genotype had higher levels of MVPA than those with the Met/Val (p=.01) and Val/Val genotypes (p=.01). No other genotypes were significantly associated with average MVPA (Table 2).

Of the covariates assessed, there was a trend for an association only with history of cardiovascular disease with DRD2 genotype (p=.09; Supplemental Table S3). There were also trends toward maintenance of gait speed in Met/Met genotype, whereas there were declines in the other genotypes (p=.14). Similarly, there was a trend toward improvement in depressive symptoms for the Met/Met genotype but no change in other genotypes (p=.18; Supplemental Table S3). Regression models of the DRD2 genotype with the average square root minutes of MVPA per day were largely robust to adjustment for basic demographic characteristics or cardiovascular disease, although adjustment for demographic characteristics slightly attenuated the difference between Met/Met and heterozygotes

Table 2. Pairwise Comparisons of Average Square Root Minutes of Moderate to Vigorous Physical Activity (MVPA) per Day (Baseline To 24 Months) for White Participants in the Physical Activity Arm of the Lifestyle Interventions and Independence for Elders Study (N = 513)

	Val/Val	Met/Val	Met/Met	Val/Val vs Met/Val	Val/Val vs Met/Met	Met/Val vs Met/Met
Gene	**Mean ± Standard Deviation**			**P-Value**		
Catechol-O-methyltransferase	n = 118	n = 254	n = 141			
Baseline MVPA	4.43 ± 1.90	4.77 ± 2.09	4.73 ± 1.97	.27	.75	.77
Average MVPA	4.52 ± 2.70	4.58 ± 2.51	4.77 ± 2.34	.17	.80	.77
DRD1[1]	n = 211	n = 228	n = 71			
Baseline MVPA	4.73 ± 1.91	4.67 ± 2.09	4.66 ± 2.13	.67	.73	.94
Average MVPA	4.77 ± 2.48	4.55 ± 2.59	4.75 ± 2.89	.63	.99	.99
DRD2	n = 248	n = 215	n = 50			
Baseline MVPA	4.61 ± 1.95	4.71 ± 2.11	5.06 ± 1.94	.71	.16	.30
Average MVPA	4.65 ± 2.71	4.46 ± 2.51	5.39 ± 2.00	.91	.01	.01
	Ser/Ser[a]	**Ser/Gly[b]**	**Gly/Gly[c]**	**Ser/Ser vs Ser/Gly**	**Ser/Ser vs Gly/Gly**	**Ser/Gly vs Gly/Gly**
DRD3[1]	n = 41	n = 239	n = 228			
Baseline MVPA	4.51 ± 2.48	4.69 ± 1.99	4.73 ± 1.96	.11	.97	.64
Average MVPA	4.42 ± 3.15	4.65 ± 2.43	4.73 ± 2.51	.24	.83	.83

p-values are false discovery rate adjusted to account for multiple comparisons.
[1]Data were missing for 3 in the dopamine receptor (DR)D1 genotype group and 5 in the DRD3 genotype group.
Val = valine; Met = methionine; Ser = serine; Gly = glycine.

(Table 3). Adjustment for either in executive function or in depressive symptoms did not alter the results, although adjustment for change in gait speed partially attenuated the difference for the Met/Val and Val/Val genotypes relative to the Met/Met genotype (Table 3).

There were no significant associations observed for black participants (Supplemental Tables S4 and S5).

DISCUSSION

In an intervention study of older adults at risk of mobility disability, polymorphisms in the DRD2 and COMT genes related to higher dopamine signaling, compared to polymorphisms related to lower dopamine signaling, were associated with greater increases in MVPA in the PA than the HE arm. Furthermore, the DRD2 Met/Met genotype was associated with greater change in MVPA in the PA arm than the Met/Val and Val/Val genotypes. Demographic and health characteristics, which largely did not differ according to genotype, did not explain these differences. Changes in executive function or mood during the intervention did not explain these differences, but changes in gait speed attenuated them somewhat. Differences in PA according to DRD2 genotype were not evident at baseline, and polymorphisms in COMT, DRD1, and DRD3 genes were not related to MVPA changes in the PA arm. Moreover, the effect was observed for white but not black participants.

The Met allele of the rs6275 SNP is associated with less DRD2 receptor density, resulting in less autoregulating presynaptic activity and higher dopamine signalling.[14] The Met/Met homozygotes had greater average MVPA during the intervention than the Val/Val and Met/Val genotypes, but there were no differences at baseline.

Table 3. Linear Regression of Average Square Root Minutes of Moderate to Vigorous Physical Activity (MVPA) per Day from Baseline to 24 Months According to Genotype for White Participants in the Physical Activity Arm of the Lifestyle Interventions and Independence for Elders Study

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Genotype (reference Met/Met)	**β, P-Value**					
Val/Val	–0.72, 0.02	–0.66, 0.02	–0.77, 0.01	–0.56, 0.05	–0.79, 0.01	–0.79, 0.01
Met/Val	–0.66, 0.03	–0.50, 0.08	–0.67, 0.02	–0.54, 0.06	–0.70, 0.03	–0.76, 0.02

Model 1: unadjusted.
Model 2: adjusted for clinical site, age, sex.
Model 3: adjusted for history of cardiovascular disease.
Model 4: adjusted for change in gait speed over 24 months.
Model 5: adjusted for change in executive function over 24 months.
Model 6: adjusted for change in Center for Epidemiologic Studies Depression Scale score.
Val = valine; Met = methionine.

DRD2 receptors are primarily located within the basal ganglia and are involved in reward[11] and motor control.[33] Positron emission studies have shown that DRD2 binding increases after acute bouts of exercise in individuals with Parkinson's disease[34] and in methamphetamine users.[35] These results were not observed in young, healthy individuals,[36] suggesting that exercise-induced increases in DRD2 binding occurs only in those with disease-related or pharmacologically induced changes in dopaminergic neurotransmission. Dopaminergic function declines with age,[8] but whether these declines alter DRD2 binding in response to acute bouts of exercise is untested. It is also unknown whether D2 receptor density as determined according to genotype may alter D2 binding response to exercise or whether these acute changes in binding potential have long-term consequences for maintenance of PA.

We further found that that changes in gait speed partially attenuated the association between DRD2 and MVPA. We were unable to determine the direction of this association; higher PA could lead to better maintenance of gait speed, or greater maintenance of gait speed could allow for greater PA participation.[37] Finally, we found associations in white but not black participants. It is unclear why, although this is consistent with a prior study that found associations between DRD2 and PA only in white individuals.[16] We had a small sample of black participants, and although the results were not significant, they were in a consistent direction with those for white participants, indicating that the lack of significant results is because of limited power. In addition, black individuals may experience more barriers to PA participation,[38] which could eclipse the effects of a single gene.

To our knowledge, this is the first study to examine dopamine-related genotypes in relation to changes in PA during an intervention. Studies[13–16] of dopaminergic genotypes and PA have been observational and relied on self-reported PA. Only one prior study identified an association between DRD2 and amount of PA.[16] Others were unable to replicate this finding or identify associations between other dopamine-related genotypes and PA.[13–15] The lack of association between DRD2 genotype and PA levels in our baseline data confirm these prior negative findings. The effects of a single genotype on a complex behavior such as PA are expected to be small, and other behavioral and environmental influences may overshadow them, but with a PA intervention that involves scheduled, center-based activity with a social group of peers and access to trainers, many of the behavioral and environmental barriers are removed, and the effect of genotype may be more evident. Evidence from intervention trials for neurobiological drivers of PA participation is limited. Two recent studies[39,40] in older adults have identified grey matter regions related to greater intervention-related exercise class attendance. Both studies identified greater volumes of portions of the prefrontal, parietal, and temporal cortices as important correlates of higher attendance. One study identified greater volume of the basal ganglia, site of DRD2s, as being predictive of greater attendance,[40] but the other did not.[39] Neither of these studies assessed objectively measured PA levels, and no prior studies have assessed neurotransmitter involvement in PA during an intervention.

Our study had several limitations, including small sample sizes in nonwhite participants. In addition, we lacked power to examine interactions with sex; sex hormones have known effects on dopaminergic function.[41] We hypothesized that one potential pathway would be through motivation and reward pathways, but we had no measures to test this hypothesis. Finally, we were limited in our measurement of dopaminergic integrity to four genotypes; we did not have direct measures of dopaminergic function, did not test all possible genes related to dopamine, and did not examine interactions between genes.

Our study also had several strengths. Participants came from a rigorous intervention study in which center-based exercise classes were offered that were customized to the individual and were conducted in group settings with peer support. This may have reduced the barriers to PA participation, allowing the small effects of genotypes to become evident. In addition, we had objectively measured PA assessments using accelerometry, which reduced the likelihood of misclassification from self-report.

CONCLUSIONS

There is growing interest in understanding neurobiological drivers of PA participation, particularly in older adults. There is strong biological plausibility for involvement of the dopaminergic system in driving PA, but there has been little evidence from population studies to confirm this role. Although genotypes are not modifiable, and these results are preliminary, they indicate a potential role for the dopaminergic system in PA for older adults in the setting of a structured intervention. Future studies should include direct measurement of dopamine levels using positron emission tomography to explore further the role of dopamine in intervention response. By further understanding this mechanism, we may be able to develop methods to harness the dopaminergic system, including individualized pharmacotherapy, to increase and maintain PA participation in older adults.

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Conflict of Interest: The authors have no conflicts

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Distribution of dopamine-related genotypes by intervention arm of the LIFE study (n=1,281).

Table S2. Median (IQR) total minutes at moderate activity/day by dopamine-related genotype for whites in the physical activity arm of the LIFE study (n=513).

Table S3. Demographic, health, and functional characteristics for 513 white participants in the physical activity arm of the LIFE study by DRD2 genotype.

Table S4. Median (IQR) total minutes at moderate activity/day by dopamine-related genotype for blacks in the physical activity arm of the LIFE study (n=128).

Table S5. Pairwise comparisons of the average of the square root minutes of moderate physical activity (PA)/day during the active intervention period (baseline-24 months) for black participants in the physical activity arm of the LIFE study (n=128).

Appendix S1. Research Investigators for the LIFE Study

Figure S1. Flow of participants through the LIFE study

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