Dopamine-related genotypes and physical activity change during an intervention: the LIFE Study

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Impact Statement:

We certify that this work is novel clinical research.

This work demonstrates that dopaminergic genes are related to changes in physical activity of older adults in a physical activity intervention. A further understanding of how dopaminergic function plays a role in promoting moderate to vigorous physical activity could lead to enhanced physical activity interventions in sedentary older adults.

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Abstract

Background/Objective: Physical activity (PA) interventions increase PA in older adults but effects vary. Dopaminergic signaling which is genetically regulated may explain response variability to interventions. We assessed whether intervention-induced PA changes in sedentary older adults differed by dopamine-related genotypes.

Design: The Lifestyle Interventions and Independence for Elders randomized clinical trial (2010-2013).

Setting: Multicenter study, 8 US locations.

Participants: Volunteer sample of sedentary adults aged 70-89 at risk for disability (n=1635).

Interventions: Structured PA versus health education (HE) for average 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 from accelerometry (minutes/day) at baseline, 6-, 12- and 24-months. Between-arm MVPA differences by genotype and of genotype with square root transformed MVPA separately by arm were tested, stratified by race and adjusted for multiple comparisons.

Results: White participants in the PA arm (n=513) had higher average log transformed MVPA compared to HE arm (n=538; HE mean=4.51 (SD=1.82), PA mean=4.91 (SD=1.91); p=0.001). Between arm differences were greater for DRD2 Met/Met (high dopamine; mean HE=4.76 (SD=1.80), mean PA=5.53 (SD=1.60); p=0.03) compared to Val/Val (low dopamine; mean HE=4.58 (SD=1.92), mean PA=4.81 (SD=1.83); p=0.2); results similar for COMT. Within the PA arm, DRD2 Met/Met was associated with higher average MVPA (mean=5.39 (SD=2.00)) compared with Met/Val (mean=4.46 (SD=2.51); p=0.01) and Val/Val (mean=4.65 (SD=2.71); p=0.01). There were no associations for other genes. Associations were non-significant in blacks, but with similar trends.

Conclusion: Higher dopamine signaling may support changes in PA during an intervention. The role of dopamine-related pathways to promote PA participation and enhance response to interventions in sedentary older adults should be studied.

Trial Registration: clinicaltrials.gov Identifier: NCT01072500

Key words: randomized controlled trial, physical activity, aging, dopamine

Introduction

Physical activity (PA) has well documented benefits for older adults, including reduced risk of disability[1] and dementia[2]. However, physical inactivity and sedentary behavior are still common with only 8.5% of adults aged 60-69 years and 6.3% of adults 70 years and older meeting the recommended 150 minutes/week of PA[3]. Even with intervention-induced increases, PA levels typically wane over time[1]. Identification of phenotypes and mechanisms that explain low response to PA interventions may improve promotion efforts.

Dopamine has been theorized to play a role in PA participation[4, 5]. Factors related to PA in older adults[6], including cognitive control[7], physical function[8], motivation/reward response[9], and depressive mood[10], are regulated by cerebral dopaminergic function. 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]. However, associations with changes in PA during structured interventions have not been studied.

We tested associations of DR and COMT polymorphisms with changes in objectively measured PA in the Lifestyle Interventions and Independence for Elders (LIFE) randomized controlled study. LIFE tested a two-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 compared to those with 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 70-89 years, sedentary (reporting <20 minutes/week regular PA in past month), had a Short Physical Performance Battery (SPPB)[19] score of ≤9, were able to walk 400 meters in less than 15 minutes without assistance, had no major cognitive impairment, and could safely participate in a walking-based PA intervention. A total of 1635 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 our analyses if they did not have accelerometer data at baseline and at least two additional time points (n=231), if they did not self-identify as black or white race (n=108), or if they were missing genotype data (n=262); categories not mutually exclusive. Genotypes were randomly distributed by intervention arm (Supplemental Table 1). Compared to those excluded, our analytic sample was less likely to be female (p=0.02) or black (p<0.001), had higher baseline Modified Mini-Mental State Examination (3MS) scores (p<0.001), had a faster 400 m walk time (p=0.001), and had higher percentage session attendance for the duration of the intervention (68.4% vs. 40.7%; p<0.001). They did not differ on other characteristics, including change in functional measures (all p>0.11).

Participant flow is in Supplemental Figure.

Interventions

The active intervention period was 24-42 months, averaging 2.6 years, with the end point for these analyses at 24 months.

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

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

DNA samples were genotyped by TaqMan allelic discrimination (Life Technologies/Fisher Scientific, Foster City, CA). PCR primers and probes for COMT single nucleotide polymorphism (SNP) rs4680, DRD1 rs265981, DRD2 rs6275, and DRD3 rs6280 SNPs (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, California, USA). Genotyping assays were performed and analyzed according to manufacturer's recommendations. Five µL reactions in 384-well plates were prepared using Eppendorf epMotion 5070 (Eppendorf North America, Inc., Westbury, NY, USA), liquid handling/sample processing robotics. Genotype accuracy was verified by genotyping 5–10% 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 compared to the valine (Val) allele[20]. The dopamine D1 receptors 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 compared to the Val allele[14, 21]. The dopamine D2 receptors are both pre- and post-synaptic and act in a self-regulating manner[11]. The Met allele of DRD2 rs6275 is associated with lower receptor density, less self-modulating pre-synaptic activity, and therefore, higher dopamine activity[14]. Finally, dopamine D3 receptors are part of the D2 family and are located primarily in the limbic system. The

glycine (Gly) allele in the DRD3 variant rs6280 demonstrates a 5-fold higher affinity to dopamine binding compared to the serine (Ser) allele[22], resulting in lower dopaminergic activity.

PA Monitoring

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

Dependent Variable – PA

The dependent variable was total minutes/day of moderate or vigorous PA (MVPA), defined as time at or above 760 counts per minute[24] from accelerometry. Because meaningful cut-points are established for older adults with physical function limitations, sensitivity analyses considered alternate cut-points of 500 counts/minute (lighter activity), 1041 counts/minute, and 1500 counts/minute (more vigorous activity). 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 by race and PA levels may differ by race; therefore, all analyses were *a priori* stratified by 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) in kg/m^2 used 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 by time to walk 400 meters at usual pace[25]. The SPPB consists of three components measuring lower extremity performance: balance in side-by-side, semi-tandem and tandem positions; 4 meter 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 0-12. We also considered gait speed (m/s) alone. Global cognitive function was assessed by the 3MS[27]. Composite executive function included average normalized scores from n-back, task-switching, and Flanker tests[28]. Depressive symptoms were assessed using the Center for Epidemiology Studies-Depression scale (CES-D)[29].

Executive function, gait speed, and mood are all modulated by the dopaminergic system[7, 8, 10] and can be modified by PA[30-32]. Therefore, changes in these measures were examined as explanatory factors for the association between genotypes and PA.

Statistical analyses

Raw minutes of MVPA with standard errors were plotted by study visit and genotype. Raw values were skewed; therefore, statistical comparisons utilized square root transformed values of minutes of MVPA/day. 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-24 months. Interactions of genotype and arm on average MVPA were tested by linear regression. For genotypes with suggested interactions ($p<0.2$), linear regressions of arm and MVPA were conducted stratified by genotype.

Pairwise comparisons of MVPA by genotype within the PA arm were conducted by t-tests. False discovery rate (FDR) adjustment was utilized to account for multiple comparisons across 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 conducted using analysis of variance (ANOVA) for continuous variables and chi-square test for categorical ones. Linear regression models were then used to assess the association between genotype and average log transformed MVPA with adjustment for basic demographics (age, gender, clinic site) and for covariates associated with genotype in bivariate analyses at p<0.1. 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 analytic sample was 78.8 (SD=5.2) years old on average; 20.0% were black and 64.9% were female.

Interactions between study arm and DRD2 (p=0.18) or COMT (p=0.12) genotype were suggestive of a differential intervention effect by genotype in white participants. Mean between-arm differences in MVPA were larger for those with the DRD2 Met/Met genotype (mean HE=4.76 (SD=1.80), mean PA=5.53 (SD=1.60), p=0.03) compared to those with the Met/Val (mean HE=4.38 (SD=1.70), mean PA=4.87 (SD=2.04), p=0.01) or Val/Val genotype (mean HE=4.58 (SD=1.92), mean PA=4.81 (SD=1.83), p=0.2). Similarly, between-arm differences in MVPA were larger for those with the COMT Met/Met genotype (mean HE=4.31 (SD=1.79), mean PA=5.07 (SD=1.83), p=0.001) compared to those with the Met/Val (mean HE=4.56 (SD=1.83), mean PA=4.88 (SD=1.96), p=0.06) or Val/Val genotype (mean HE=4.74 (SD=1.89), mean PA=4.09 (SD=1.21), p=0.2).

Raw minutes of PA by genotype for white participants in the PA arm (n=513) are shown in Figure 1 (data in Supplemental Table 2). There were no baseline differences in PA by any genotype (all p>0.1; Table 2). There were significant associations of DRD2 genotype with average MVPA (Table 2). Participants with the Met/Met DRD2 genotype had higher levels of MVPA compared to Met/Val (p=0.01) and Val/Val genotype (p=0.01). 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=0.09; Supplemental Table 3). There were also trends towards maintenance of gait speed in Met/Met genotype compared to declines in the other genotypes (p=0.14). Similarly, there was a trend towards improvement in depressive symptoms for the Met/Met genotype with no change in other genotypes (p=0.18; Supplemental Table 3). Regression models of DRD2 genotype with the average square root minutes of MVPA/day were largely robust to adjustment for basic demographics or cardiovascular disease, though adjustment for demographics did slightly attenuate the difference between Met/Met and heterozygotes (Table 4). Adjustment for either change in executive function or change in depressive symptoms did not alter the results. However, adjustment for change in gait speed did partially attenuate the difference for both Met/Val and Val/Val relative to Met/Met genotype (Table 3).

There were no significant associations observed for black participants (Supplemental Tables 4-5).

Discussion

In an intervention study of older adults at risk for mobility disability, we found that polymorphisms in 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 compared to the HE arm. Further, DRD2 Met/Met genotype was associated with greater change in MVPA within the PA arm compared to Met/Val and Val/Val genotypes. These differences were not explained by demographic or health characteristics which largely did not differ by genotype. They also were not explained by changes in executive function or mood induced by the intervention, but were somewhat attenuated by changes in gait speed. Differences in PA by 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 lower DRD2 receptor density, resulting in less auto-regulating, pre-synaptic activity and higher dopamine signalling[14]. We found that, compared to the Val/Val and Met/Val genotypes, the Met/Met homozygotes had greater average MVPA during the intervention, but there were no differences at baseline.

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 receptor 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 by 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 the association of DRD2 with MVPA was partially attenuated by changes in gait speed. With our analyses, 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 only in white but not black participants. It is unclear why, though this is consistent with a prior study that found associations of DRD2 with PA only in whites[16]. We had a small sample of black participants and while the results were not significant, they were in a consistent direction with those for whites, indicating the lack of significant results is likely due to limited power. In addition, blacks 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 examining dopamine-related genotypes in relation to changes in PA during an intervention. To date, 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[13-15] were unable to replicate this finding or identify associations between other dopamine-related genotypes and PA. 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 may be overshadowed by other behavioral and environmental influences. However, in the presence of 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 to date. 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 DRD2 receptors, as being predictive of greater attendance[40], but the other study 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 limited sample sizes in non-white participants. In addition, we lacked power to look at interactions with gender; sex hormones have known effects on dopaminergic function[41]. We hypothesized that one potential pathway would be through motivation and reward pathways; however, 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. However, our study also had several strengths. Participants came from a rigorous intervention study in which center-based exercise classes were offered that were tailored 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 by accelerometry that 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. While genotypes are not modifiable and these results are preliminary, they do 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 via positron emission tomography to further explore 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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Author Contributions:

Study concept and design – ALR, ALM, NWG, RMB, WJR, CR

Data analysis – ALR, ALM, RMB, HC

Interpretation of data - ALR, ALM, NWG, RMB, WJR, NB, CR

Preparation of manuscript – all authors

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Table 1. Dopamine-related single nucleotide polymorphisms (SNPs) 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**
COMT	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	Gly	Higher binding affinity, lower transmission	Lower

Table 2. Pairwise comparisons of average square root minutes of moderate to vigorous physical activity (MVPA)/day (baseline-24 months) for white participants in the physical activity arm of the LIFE study (n=513).

	Val/Val[a]	Met/Val[b]	Met/Met[c]	P-values [a] vs [b]	P-values [a] vs [c]	P-values [b] vs [c]
	Mean (SD)	**Mean (SD)**	**Mean (SD)**			
COMT	n=118	n=254	n=141			
Baseline MVPA	4.43 (1.90)	4.77 (2.09)	4.73 (1.97)	0.27	0.75	0.77
Average MVPA	4.52 (2.70)	4.58 (2.51)	4.77 (2.34)	0.17	0.80	0.77
DRD1*	n=211	n=228	n=71			
Baseline MVPA	4.73 (1.91)	4.67 (2.09)	4.66 (2.13)	0.67	0.73	0.94
Average MVPA	4.77 (2.48)	4.55 (2.59)	4.75 (2.89)	0.63	0.99	0.99
DRD2	n=248	n=215	n=50			
Baseline MVPA	4.61 (1.95)	4.71 (2.11)	5.06 (1.94)	0.71	0.16	0.30
Average MVPA	4.65 (2.71)	4.46 (2.51)	5.39 (2.00)	0.91	0.01	0.01
	Ser/Ser[a]	**Ser/Gly[b]**	**Gly/Gly[c]**			
DRD3*	n=41	n=239	n=228			
Baseline MVPA	4.51 (2.48)	4.69 (1.99)	4.73 (1.96)	0.11	0.97	0.64
Average MVPA	4.42 (3.15)	4.65 (2.43)	4.73 (2.51)	0.24	0.83	0.83

p-values are false discovery rate adjusted to account for multiple comparisons.

* n=3 were missing data for DRD1 genotype and n=5 were missing data for DRD3 genotype

Table 3. Linear regression of average square root minutes of moderate physical activity (MVPA)/day from baseline-24 months by genotype for white participants in the physical activity arm of the LIFE study.

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value	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
Met/Met	Ref		Ref		Ref		Ref		Ref		Ref	

Model 1: unadjusted;

Model 2: adjusted for clinical site, age, gender;

Model 3: history of CVD;

Model 4: change in gait speed over 24 months;

Model 5: change in executive function over 24 months;

Model 6: change in CES-D score

Figure 1. Median (standard error) of minutes of moderate physical activity (MVPA)/day by time period for whites in the physical activity arm of the LIFE study (n=513) by A) COMT, B) DRD1, C) DRD2, and D) DRD3 genotypes. For all, the genotype associated with the highest dopamine signaling is shown in a solid line and the lowest dopamine signaling in the short dashed line. Heterozygotes are shown in the long dashed line.

Supplemental Material

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

Supplemental Table 2. 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).

Supplemental Table 3. Demographic, health, and functional characteristics for 513 white participants in the physical activity arm of the LIFE study by DRD2 genotype.

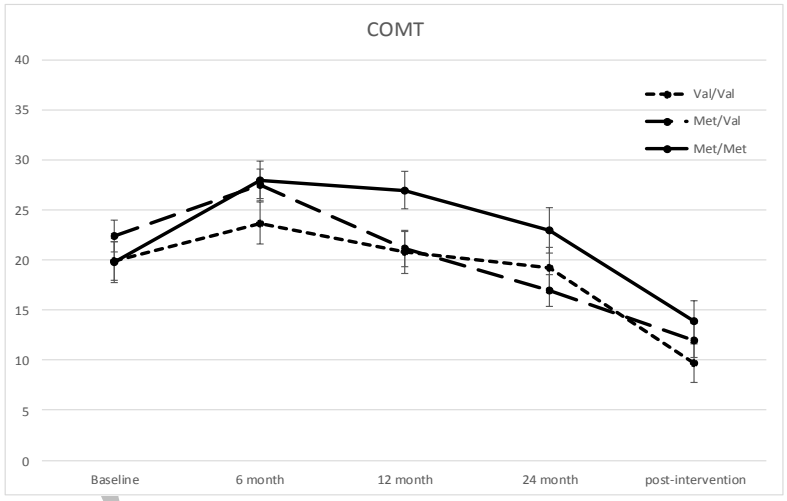
Supplemental Table 4. Median (IQR) total minutes at moderate activity/day by dopamine-related genotype for blacks in the physical activity arm of the LIFE study (n=128).

Supplemental Table 5. 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: Research Investigators for the LIFE Study

Supplemental Figure. Flow of participants through the LIFE study

A



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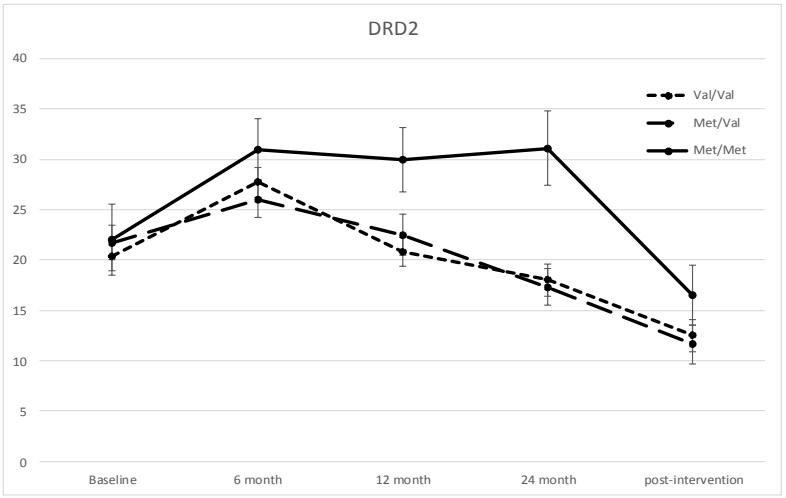

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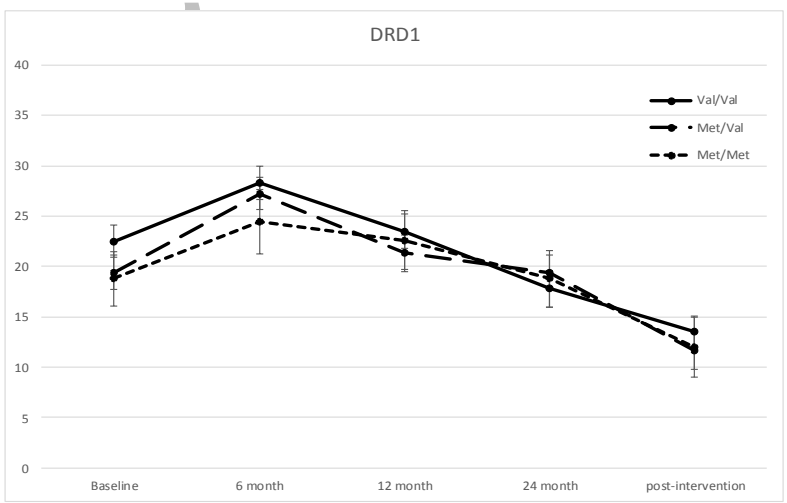

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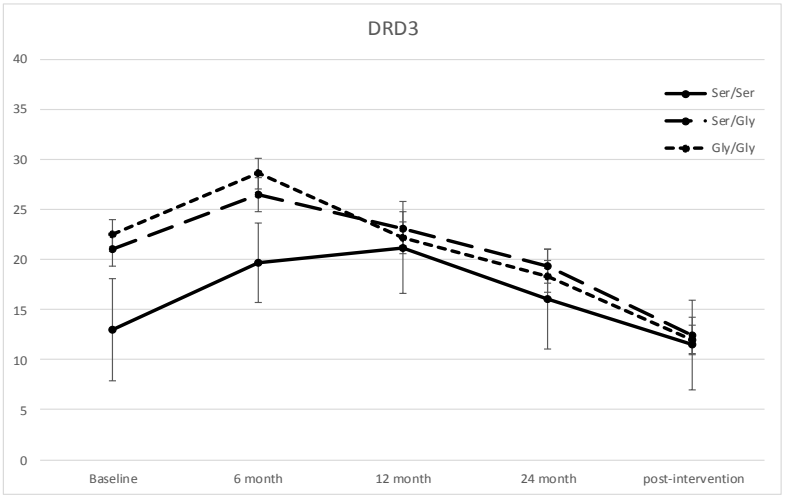

Supplemental Tables

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

	Successful Aging Arm **n=640**	**Physical Activity Arm** **n=641**	**p-value***
COMT			0.36
Val/Val	196 (30.6%)	176 (27.5%)	
Met/Val	283 (44.2%)	307 (47.9%)	
Met/Met	158 (24.7%)	157 (24.5%)	
DRD1			0.21
Val/Val	284 (44.4%)	315 (49.1%)	
Met/Val	267 (41.7%)	252 (39.3%)	
Met/Met	86 (13.4%)	73 (11.4%)	
DRD2			0.93
Val/Val	274 (42.8%)	273 (42.6%)	
Met/Val	272 (42.5%)	278 (43.4%)	
Met/Met	94 (14.7%)	90 (14.0%)	
DRD3			0.43
Ser/Ser	107 (16.7%)	97 (15.1%)	
Ser/Gly	266 (41.6%)	289 (45.1%)	
Gly/Gly	259 (40.5%)	248 (38.7%)	

* from chi-square test

Supplemental Table 2. 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).

	Val/Val	Met/Val	Met/Met
COMT			
Enrollment Visit	19.9 (21.1)	22.4 (24.7)	19.8 (24.8)
6-month Visit	23.7 (24.1)	27.5 (28.7)	28.0 (25.6)
12-month Visit	20.8 (31.0)	21.2 (31.9)	27.0 (29.4)
24-month Visit	19.2 (24.9)	17.0 (26.6)	23.0 (30.5)
DRD1			
Enrollment Visit	22.5 (21.3)	19.4 (22.9)	18.8 (31.1)
6-month Visit	28.3 (27.2)	27.2 (27.8)	24.4 (28.3)
12-month Visit	23.5 (30.7)	21.3 (31.8)	22.6 (28.6)
24-month Visit	17.8 (24.7)	19.4 (28.3)	18.8 (26.5)
DRD2			
Enrollment Visit	20.4 (23.1)	21.7 (22.4)	22.0 (24.8)
6-month Visit	27.7 (28.7)	26.0 (28.3)	31.0 (29.2)
12-month Visit	20.8 (29.0)	22.5 (29.6)	30.0 (31.9)
24-month Visit	18.0 (27.5)	17.3 (24.4)	31.1 (28.9)
	Ser/Ser	**Ser/Gly**	**Gly/Gly**
DRD3			
Enrollment Visit	13.0 (26.0)	21.0 (22.3)	22.5 (24.6)
6-month Visit	19.7 (31.9)	26.5 (28.2)	28.6 (26.6)
12-month Visit	21.2 (36.7)	23.1 (27.8)	22.2 (32.4)
24-month Visit	16.1 (23.4)	19.4 (29.6)	18.3 (25.5)

Supplemental Table 3. Demographic, health, and functional characteristics for 513 white participants in the physical activity arm of the LIFE study by DRD2 genotype.

	Val/Val **n=248** Mean (SD) or N (%)	**Met/Val** **n=215** Mean (SD) or N (%)	**Met/Met** **N=50** Mean (SD) or N (%)	**p-value**
Baseline Characteristics				
Age	79.1 (5.2)	79.7 (5.1)	78.4 (4.5)	0.19
Female sex	158 (63.7)	124 (57.7)	28 (56.0)	0.33
Education (≤high school)	82 (33.1)	73 (34.1)	18 (36.0)	0.92
BMI	29.7 (5.8)	29.6 (5.3)	30.7 (6.4)	0.49
History of cardiovascular disease	59 (23.8)	69 (32.1)	17 (34.0)	0.09
History of diabetes	53 (21.4)	54 (25.1)	15 (30.0)	0.35
Average SBP	125.4 (17.7)	127.7 (18.1)	128.8 (19.1)	0.26
Average DBP	68.2 (9.9)	68.8 (10.2)	70.5 (11.2)	0.34
SPPB total score	7.6 (1.5)	7.4 (1.6)	7.5 (1.6)	0.20
400 m walk time (sec)	492.5 (106.9)	498.1 (113.0)	500.0 (118.2)	0.83
Gait speed (m/s)	0.85 (0.17)	0.84 (0.16)	0.84 (0.17)	0.85
3MS score	92.8 (4.9)	92.5 (5.2)	92.0 (4.9)	0.58
Executive function	0.06 (1.07)	0.06 (1.11)	0.07 (1.08)	0.99

CES-D score	7.9 (7.6)	8.2 (7.0)	8.4 (8.8)	0.89
Change in Function				
Change in gait speed (m/s)	-0.05 (0.15)	-0.05 (0.15)	-0.01 (0.11)	0.14
Change in executive function score	-0.03 (0.69)	-0.10 (0.74)	-0.18 (0.58)	0.37
Change in CES-D score	0.9 (7.7)	0.1 (7.213)	-1.3 (7.0)	0.18
Percentage session attendance	61 (26)	58 (27)	64 (24)	0.56

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; SPPB = short physical performance battery; 3MS = Modified Mini-Mental State Examination; CES-D = Center for Epidemiology Studies-Depression scale

Supplemental Table 4. 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).

	Val/Val	Met/Val	Met/Met
COMT			
Enrollment Visit	24.4 (29.5)	26.3 (25.3)	26.2 (24.3)
6-month Visit	21.0 (17.5)	30.3 (25.4)	30.5 (23.0)
12-month Visit	30.7 (27.1)	28.0 (27.8)	21.5 (39.5)
24-month Visit	21.5 (28.4)	24.7 (33.0)	17.2 (15.8)
DRD1			
Enrollment Visit	24.7 (29.2)	29.2 (19.8)	42.6 (38.4)
6-month Visit	27.4 (29.5)	31.0 (19.9)	36.3 (36.4)
12-month Visit	26.0 (30.1)	37.9 (28.3)	39.0 (22.0)
24-month Visit	17.9 (26.5)	24.7 (25.6)	36.8 (21.0)
DRD2			
Enrollment Visit	25.5 (18.0)	24.3 (25.5)	28.8 (39.1)
6-month Visit	29.4 (30.8)	25.3 (17.7)	36.0 (29.4)
12-month Visit	27.2 (33.2)	22.0 (27.3)	38.3 (27.8)
24-month Visit	28.3 (35.5)	16.5 (20.3)	27.5 (29.0)
	Ser/Ser	**Ser/Gly**	**Gly/Gly**
DRD3			
Enrollment Visit	24.9 (28.7)	26.6 (23.7)	19.2 (21.3)
6-month Visit	27.1 (23.4)	28.5 (25.4)	29.4 (25.9)
12-month Visit	30.6 (29.1)	28.0 (32.2)	26.0 (29.2)
24-month Visit	16.5 (26.3)	25.9 (29.0)	17.5 (35.6)

Supplemental Table 5. Pairwise comparisons of the cumulative 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).

	Val/Val[a]	Met/Val[b]	Met/Met[c]	P-values [a] vs [b]	P-values [a] vs [c]	P-values [b] vs [c]
	Mean (SD)	**Mean (SD)**	**Mean (SD)**			
COMT	n=59	n=53	n=16			
Baseline PA	5.13 (2.04)	5.34 (2.00)	5.25 (1.85)	0.89	0.89	0.89
Cumulative average PA	5.32 (2.31)	5.32 (2.31)	4.88 (1.67)	0.89	0.89	0.89
DRD1	n=96	n=27	n=5			
Baseline PA	5.08 (1.91)	5.88 (2.27)	5.76 (1.56)	0.84	0.84	0.84
Cumulative average PA	4.97 (2.31)	5.65 (2.05)	5.32 (2.81)	0.84	0.84	0.84
DRD2	n=25	n=63	n=40			
Baseline PA	5.10 (1.85)	5.18 (2.00)	5.43 (2.10)	0.87	0.47	0.65
Cumulative average PA	5.32 (2.12)	4.93 (2.18)	5.66 (2.46)	0.28	0.21	0.61
	Ser/Ser[a]	**Ser/Gly[b]**	**Gly/Gly[c]**			
DRD3	n=45	n=60	n=23			
Baseline PA	4.94 (1.93)	5.28 (1.93)	5.54 (1.89)	0.57	0.39	0.57
Cumulative average PA	4.74 (2.21)	5.27 (2.18)	5.48 (2.15)	0.39	0.39	0.39

p-values are false discovery rate adjusted to account for multiple comparisons.

Appendix: Research Investigators for the LIFE Study

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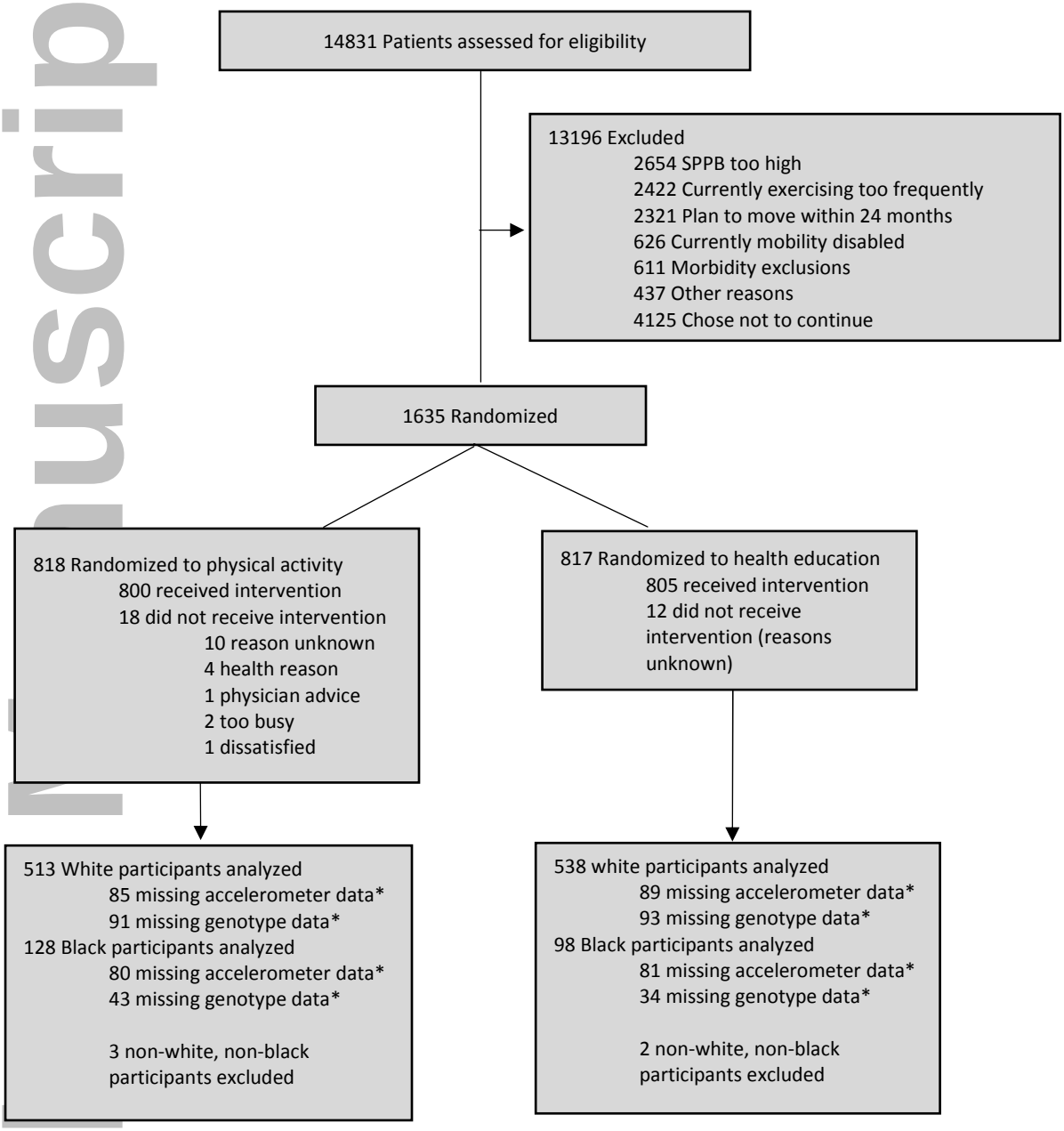

*Numbers for missing data on accelerometry and genotype are not mutually exclusive.
SPPB=short physical performance battery