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Catechol-O-methyltransferase (COMT) polymorphism predicts rapid gait speed changes in healthy older adults

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Abstract

IMPORTANCE: Adapting one's gait speed to external circumstances is critical for safe ambulation. Dopamine (DA), critical for adapting to increased task demands, predicts usual gait speed and may exert a greater role in complex tasks like rapid gait speed.

OBJECTIVE: We hypothesized that a genotypic proxy indicator of greater prefrontal DA signaling would predict significantly faster rapid gait.

DESIGN: Longitudinal cohort study over 8 years

SETTING: Community-dwelling adults with no baseline mobility disability

PARTICIPANTS: N = 2,353 participants from the Health ABC Study

MEASUREMENTS: Repeated measures of walking speed (meters/sec) were obtained in response to: "walk as fast as possible… (rapid gait) or "walk at your usual pace (usual gait)." Catechol-O-methyltransferase (COMT) val158met polymorphism indicated DA signaling (val/val=higher metabolism, lower DA signaling; met/met=lower metabolism, higher DA signaling).

RESULTS: Participants declined in rapid gait from 1.55 (SD=.33) to 1.35 m/s (SD=0.34). Across the full follow-up period, the met/met genotype was associated with significantly greater rapid gait slowing. In mixed effect models, between-group differences were independent of covariates, and remained similar after adjustment for sensorimotor function, cognition, depressive symptoms, and energy. Follow-up analyses indicated the met/met genotype had a significantly faster rapid gait speed compared to the val/val genotype for the first 3 years ($p < .01$) but not years 4–8 ($p > .05$).

CONCLUSION: Greater prefrontal DA measured with COMT polymorphism may facilitate short-term adaptation to rapid walking demands that are lost over time. Studies should examine whether these effects are long-term and the underlying mechanistic pathways.

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Keywords

COMT; rapid gait speed; trajectory; motor task adaptation

Introduction

Gait slowing predicts adverse health, including greater disability [1] and mortality [2]. Usual gait is commonly assessed [3], but rapid gait, or walking "as fast as possible", appears more sensitive to age-related decline [4–6]. Rapid gait outperforms usual gait in predicting older adult health metrics, including cognitive decline [7, 8] and may be more relevant for safe ambulation [9]. The ideal usual gait speed is ≥ 1.0 m/s [10], but certain everyday activities may require faster speeds (e.g., speed of 1.34 m/s to safely maneuver a crosswalk [11]).

The ability to increase gait to varying circumstances [12] may reflect a successful adaptive response. The central nervous system (CNS) may play an important role in regulating rapid gait. Surprisingly, little is known about CNS contributions to rapid gait, but evidence suggests that complex gait tasks-including rapid gait- may have greater prefrontal cognitive involvement compared to simpler, usual gait speed task conditions [13]. For example, lower cognitive function [14] and greater fatigue/fatigability [15] are associated with slower rapid gait, but the neurobiological basis of these associations have only recently been examined [16]. Because of the increased reliance of the prefrontal cortex in complex walking conditions, it is feasible that polymorphisms implicated in both motor and cognitive actions would contribute to one's ability to maintain rapid gait across time.

Genetic variation in the catechol-O-methyltransferase (COMT) val158met polymorphism can approximate prefrontal DA availability [17]. COMT encodes monoamine-metabolizing enzymes in the brain with an important effect in the prefrontal cortex (PFC). The COMT val158met polymorphism determines the COMT enzyme level, which mediates synaptic DA levels. The val allele is associated with higher COMT (i.e., more DA-metabolizing enzymes) and results in faster DA clearance and lower tonic DA levels; the met allele is associated with lower COMT enzyme activity causing slower DA clearance and resulting in higher prefrontal tonic DA levels [17]. Homozygosity for either genotype is associated with a slower usual gait speed both cross-sectionally [18] and longitudinally [19]. Whether this is evident in complex tasks like rapid gait speed is unknown.

The current study examines whether COMT gene polymorphism is associated with rapid gait speed, cross-sectionally and longitudinally. Further, we explore whether such association would be modified after adjustment for potential explanatory pathways, specifically: lower sensorimotor and cognitive function and depressive symptoms. We hypothesized the COMT-rapid gait speed association was robust to health-related confounders but would be attenuated (i.e., weakened) by these possible explanatory DA sub-pathways.

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Methods

Participants

The current study used data from the Health, Aging, and Body Composition (Health ABC) study which included 3,075 community-dwelling White and Black older adults 70 – 79 years living in Memphis, TN, or Pittsburgh, PA. Exclusion criteria for the parent study were reported difficulty walking ¼ mile, climb 10 stairs, or inability to perform activities of daily living. Those requiring assistive devices or had life-threatening cancers were also excluded. For the current analyses, our sample included participants with available data for the COMT gene polymorphism, rapid pace gait speed at Year 2 (first year of assessment) and at least one additional follow-up, resulting in 2,353 participants (n = 722 missing ≥1 of the inclusion criteria). Unless stated, the baseline value for a given variable was an individual's Year 2 (1998–1999) value. Participants were followed across eight years (mean follow-up time = 7.10, SD = 2.35 years).

Measures

Outcome. *Rapid gait speed*.—Participants were asked to walk down a 20-meter hallway as fast as they could and timed with a stopwatch once per visit. Higher scores reflected faster gait in meters per second.

Predictor. *COMT*.—The Val158Met polymorphism (rs4680) of COMT was measured from genomic DNA extracted from ethylenediaminetetraacetic acid (EDTA) anticoagulated whole blood by standard methods (Gentra Systems, Minneapolis, MN) and polymerase chain reaction (PCR)-based COMT genotyping [20].

Covariates.—All covariates were identified as possible risk or protective factors for maintaining rapid gait speed based on their association with either usual or rapid gait speed. Variables indicating potential explanatory pathways linking COMT polymorphism with rapid gait speed includes measures of function in sensorimotor, cognitive, depressive symptoms, and energy domains.

Usual gait speed.: Participants walked down a 20-meter hallway at their usual pace and timed with a stopwatch. To account for overall change in usual gait speed, we calculated person-specific gait speed slopes by a linear mixed model with random intercepts and random slopes similarly to previously published data [7, 21]. All available usual gait speed values from a given individual informed the person-specific slope. Negative values indicated declining and positive values indicated increasing usual gait speed over time, respectively.

Demographics.: Demographics included self-reported age, race (Black or White), and gender.

Health factors.: Body mass index (BMI) was calculated from Year 1 (1997–1998) height and weight. Ankle-brachial index was obtained in Year 1 (1997–1998) from systolic blood pressure in both the arm and ankle measured twice then averaged. Lower index values indicated peripheral arterial disease. The Bailey-Lovie distance visual acuity test indicated

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whether a participant had corrected vision better (0) or worse (1) than 20/50. Self-reported presence or absence of diabetes, coronary heart disease, congestive heart failure, and cerebrovascular disease were obtained via self-report/medical records at the Year 1 (1997–1998) assessment.

Sensorimotor function.: For the standing balance test, we summed the time each position (semi-tandem, full-tandem, and single leg stand, for a maximum time of 30 seconds each) was held without any support [22]. Times were converted to standardized scores by dividing the results by the maximal performance achievable in cohorts of older adults comparable to our study population (i.e., 90 seconds for standing balance). This procedure converted the balance score to a ratio ranging from 0 (worst performance) to 1 (best performance achievable by a population of this age and condition). Speed in meters/second on the 400m walk test from Year 1 was used to indicate functional fitness [23]; participants were asked to walk 10 laps that were ¼ mile each as quickly and comfortably as possible without running.

Knee pain.: The self-reported absence (0) or presence (1) of knee pain with activities was obtained in Year 3.

Exercise and Walking.: Self-reported time in the prior week engaging in exercise and walking was converted in kcal/kg/week.

Cognitive function.: Cognitive status was assessed using the Teng Modified Mini-Mental State Examination (3MS) [24]. Higher scores indicated better cognitive function. Cognitive processing speed was measured by the Digit Symbol Substitution Task (DSST) [25]. Participants were instructed to write symbols that correspond to numbers as quickly as possible in 90 seconds. Higher scores indicated more correctly copied symbols. For both cognitive domains, person-specific slopes were calculated using cognitive data from all available waves. Positive values reflected better performance and negative values reflected worse performance across time.

Depressive symptoms.: Depressive symptoms were measured using the Center for Epidemiological Studies- Depression (CES-D) scale [26]. A person-specific slope was calculated using all available CES-D assessments.

Energy.: Self-reported energy was a single-item question asking about a participant's usual energy level in the previous month. Scores ranged from 0 (no energy) to 10 (most energy they have ever had).

Analytic Approach

Bivariate associations of covariates with baseline rapid gait speed were analyzed with Spearman correlations or independent samples t-tests to assess group differences. We also examined whether there were significant between-genotype differences in average rapid gait speed with a separate ANOVA for each year; ANOVAs were not adjusted for any covariates. This was done to identify whether there were potential critical periods where there between-group differences, as mixed effects models examine overall change over time but do not identify between-group differences within a particular timepoint.

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To calculate the unadjusted usual gait speed, cognition, and depressive symptoms slopes, we applied longitudinal mixed effect models and used random intercept and random slope of years for each participant to control for repeated measures and varying slopes across individuals. Linear mixed effects models were used to examine whether there was a significant COMT*time interaction after controlling for time, time^2, and usual gait speed slope. Models were adjusted for demographics and other health factors. To address collinearity, separate models were adjusted for those variables indicating potential explanatory pathways: sensorimotor, cognition, depressive symptoms, and energy. A final parsimonious model retaining COMT and all significant covariates and explanatory pathways ($p < .05$, uncorrected for multiple comparisons) was determined using backward selection procedures.

Analyses were completed in SAS, Version 9.4 (SAS Institute, Cary, NC), and two-tailed significance was set at $p < .05$.

Results

The analytic sample ($N = 2,353$) had an average age of 74.60 years ($SD = 2.84$) at baseline; a majority of the sample was White ($n = 1,467$, 62.3%), there were slightly more women ($n = 1,223$, 52.0%), and the sample was generally healthy (Table 1). The average baseline rapid gait speed was 1.55 m/s ($SD = 0.33$), comparable to other healthy older adult samples [4, 27, 28]. Over an average follow-up time of 7.10 ($SD = 2.35$) years, rapid gait declined by 13% to 1.35 m/s ($SD = 0.34$) at the study's end.

At baseline, there was a marked advantage in rapid gait for met carriers compared to val/val. The met/met genotype was significantly faster than the val/val genotype and marginally faster than the met/val genotype (Table 1). These between-group differences were maintained at each year of follow-up (Figure 1), although they were statistically significant at baseline through year three and not in years four through eight. (Figure 1).

In LME models with a COMT*time interaction, adjusted for usual gait speed slope, met/val (est. = 0.004, $SE = 0.001$, $p = .005$) and val/val genotypes (est. = 0.003, $SE = 0.002$, $p = 0.498$) were both associated with significantly less decline in rapid gait compared to the met/met genotype across the full study period (Table 2, Model 1). Results remained similar after the inclusion of demographics and health factors (Table 2, Models 2–3). Associations remained similar also after adjustment for variables indicating potential explanatory pathways (Table 2, Models 4–7). In the final parsimonious model retaining only the significant covariates from each block, both met/val (est. = 0.004, $SE = 0.001$, $p = .015$) and val/val (est. = 0.003, $SE = 0.002$, $p = .048$) genotypes were associated with significantly less decline compared to the met/met genotype. In this model, less decline in rapid gait was associated with: less decline in usual gait speed, younger age, male gender White race, better balance, no knee pain with activities, no cerebrovascular disease, lower BMI, less decline in Teng 3MS and DSST, and improvement in depressive symptoms.

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Discussion

In this sample of community-dwelling older adults, COMT polymorphism was associated with rapid gait cross-sectionally and over time, independent of usual gait speed, health factors and other potential explanatory factors. Specifically, those with the met/met genotype, a proxy marker of greater tonic prefrontal DA, experienced significantly greater decline in rapid gait speed across the follow-up period compared to those with at least one val allele. Follow-up analyses indicated that for the first three years, met/met carriers were significantly faster than val/val carriers. In comparison, there were no significant differences in rapid gait speed by COMT polymorphism for the later years of follow-up. Taken together, these results suggest that while greater prefrontal DA may be associated with greater slowing over time, this was only partly attributable to their higher baseline rapid gait.

Participants increased their gait speed in response to the instructions "Walk as fast as you can, until I tell you to stop," as shown by the difference of 0.41 m/s between gait conditions. This increase may indicate motor adaptation, which requires an integrated contribution of multiple domains in addition to sensorimotor, including attention, motivation, and adequate energy. The dopaminergic network is critical in regulating these domains; thus, it is possible the relationship between COMT polymorphism and changes in rapid gait may have occurred through several pathways. Accumulating evidence implicates the COMT val158met polymorphism as important for motor adaptation [18, 29–32]. Our data appear to support this evidence; we found that in the first three years rapid gait was significantly slower for val/val than for the met/met genotype. COMT also influences motivation responsivity, which in turn can influence the performance changes in response to external stimuli. The COMT met/met allele is associated with more activation during reward anticipation, greater motivation, and greater reward sensitivity compared to the val/val allele [33]. Thus, those with the met/met genotype were possibly more motivated to perform well on the task. Our study did not have specific measures of motor adaptation or motivation to test these pathways; the study's measures of depressive symptoms, energy, and fitness may only capture some facets of these domains. Future studies with more tailored motivation and motor adaptation tasks should further explore this pathway.

Since COMT is one indicator of prefrontal DA [34] , our results suggest that decline in rapid gait may be modulated, at least in part, by DA signaling effects in the prefrontal cortex [30]. Increasing one's walking speed and maintaining that rapid gait in response to external stimuli requires attention, a cognitive ability that is regulated by DA in the prefrontal cortex. It is also possible that COMT polymorphism is associated with rapid gait through its association with memory efficacy (i.e., ability to learn, recall, adapt to memory tasks) [35], which allows individuals to learn and adapt to motor tasks more quickly [29, 36]. Although memory efficacy was not assessed, we adjusted for two cognitive tests reflecting some aspects of these domains, the Teng 3MS and DSST. While changes in both cognitive domains were positively associated with better rapid gait, they did not fully attenuate the COMT*time interaction. Cognitive-related processes - at least as determined by our measures - do not fully attenuate the association between prefrontal DA and changes in rapid

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gait. Domains not measured by these assessments may, however, attenuate this relationship and should be considered in future work.

Our multivariable results replicated findings that older age, being a woman, and higher weight status were associated with slower rapid gait [4, 37] but do not significantly influence the role of COMT on changes in rapid gait. While we controlled for sensorimotor function, it is possible that rapid gait is influenced by peripheral mechanisms we were unable to account for, e.g., peripheral COMT or other diseases that impair gait.

Rapid gait is multifactorial, and we found no evidence that one variable alone could fully predict rapid gait changes. In conjunction with prior research, our study suggests that demographic, peripheral, and CNS function uniquely contribute to one's ability to maintain the capacity to increase their gait speed. We also partially replicated prior work that rapid gait was associated with demographic [4] and peripheral locomotor measures [4]. Up to 1/3 of the variability in rapid gait performance may be driven by genetics [38, 39], and our findings indicate the COMT polymorphism at least partially explains these group differences.

Our findings have important implications for future research. Those with the val/val genotype could be targeted in an effort to prevent or delay the onset of mobility limitations, as those with poorer baseline function or greatest risk of mobility decline tend to receive the greatest benefits from behavioral intervention efforts [40]. Targeting those with the val/val genotype prior to major declines in rapid gait can ensure their ability to maintain safe community ambulation. Providing targeted prevention/intervention programs for those at risk of poorest rapid gait may effectively allocate treatment efforts to those likely to receive the greatest benefits.

Our findings suggest that a frontal cortical relatively higher dopaminergic state – illustrated by the met/met COMT genotype - in older adults enhances the ability of the brain to adapt to rapid speed gait in the short-term but may lose its influence on rapid gait over time. Furthermore, these results suggest the COMT-rapid gait relationship may not follow the U-shaped function seen in usual gait [18] but rather follow a dose-dependent pattern whereby greater tonic DA availability is associated with faster rapid gait. That is, there is less evidence that COMT heterozygosity is optimal for rapid compared to usual gait. The current results also failed to replicate gender-specific differences of COMT genotype on gait as previously demonstrated [18, 41]. Prior work from our group found evidence of a significant U-shaped association between COMT genotype and usual gait where those with val/val and met/met genotypes had more gait slowing over 10 years compared to those with the met/val genotype among Black older adults [19]. In the current analyses, there were too few Black older adults to confidently draw conclusions based on subgroup analysis. Future replication is warranted, but there is weak evidence that demographic characteristics moderate the COMT-rapid gait association.

The average loss of gait speed over the 8-year period in our study participants demonstrated a biphasic curve where an initial, less prominent decline in rapid gait speed may be modulated by frontal DA functions but then converged to a steeper decline without specific advantages of the COMT genotype. Such a biphasic curve suggest that effects

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of prefrontal DA compensation assessed by the val158met polymorphism only provide temporary protection. These results fail to support the resource modulation hypothesis which states that genetic variability may exert a greater influence when brain resources become limited like that seen in normative aging [42]. It is important to note, however, that DA changes in non-prefrontal regions, other non-DA aging factors, or a complex combination of genes may become the driving forces of age-associated decline in rapid gait. For example, brain-derived neurotrophic factor (BDNF) and dopamine D3 receptor (DRD3) had a stronger association with timed walking among the oldest-old men but not women [41]. Therefore, findings could be related to multi-gene profiling effects where interactions between COMT and DRD3 may play important but less predictable roles. Future research is warranted to examine the changing influence of multiple SNPs on complex gait as individuals age.

Declining rapid gait speed has consequences for safe mobility and should be a public health priority. DA-related genetic polymorphisms may exert short-term influence in one's capacity to adapt to increasing motor demands, even among high-functioning older adults. Future examinations should consider whether more circulating DA or DA concentrated in other pathways [29] are associated with greater maintenance of rapid gait. Such studies would further inform if dopaminergic drugs in targeted older persons with hypodopaminergic states may be a promising approach to maintain older adult mobility.

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KEY POINTS

Across eight years, those with the genotype indicative of greater dopamine signaling experienced significantly greater decline in rapid gait speed, even after adjusting for demographic and health confounders. Follow-up analyses indicated that those with greater dopamine signaling, however, were significantly faster for the first three years but then performed similarly to the other genotypes for the remaining five years.

A proxy indicator of greater prefrontal dopaminergic signaling offers short-term protection against gait slowing among healthy older adults, but eventually this advantage is lost.

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WHY DOES THIS PAPER MATTER?

The ability to adapt one's gait is important for safe everyday mobility, and this article is the first to identify the role of genetic variability on one's ability to maintain this skill.

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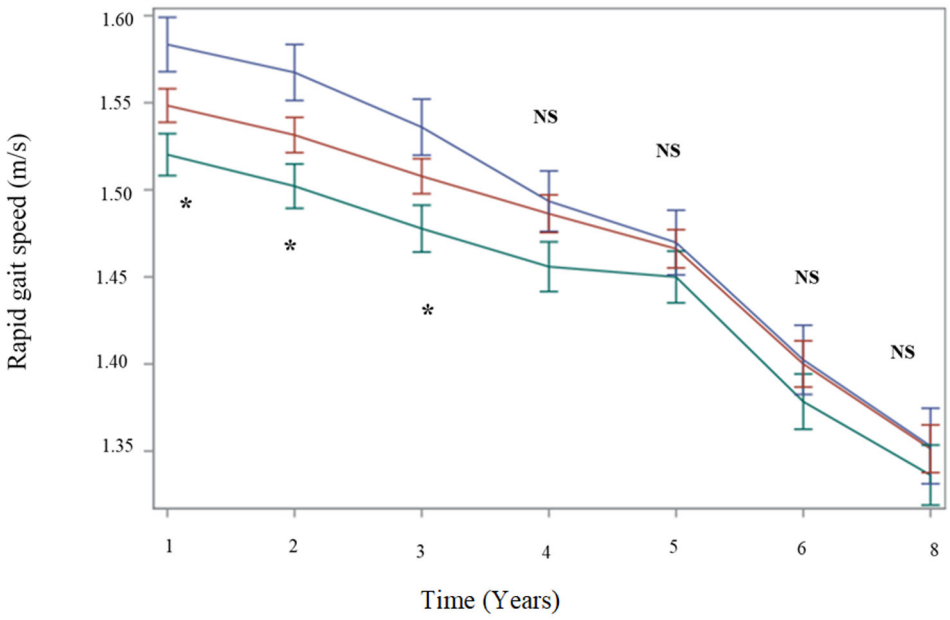

Figure 1. Estimated unadjusted rapid gait speed (m/s) across time by COMT genotype.

Note. Year = 1 indicates the analytic baseline. Blue = met/met; Red = met/val; Green = val/val. * denotes significant between-group differences among homozygous val compared to homozygous met genotype, $p < .05$. NS = nonsignificant differences among three COMT genotypes.

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Table 1.

Analytic sample (N = 2,353) characteristics and bivariate association with baseline rapid gait speed.

		N (%) or *Mean (SD)*	Spearman's rho with baseline rapid gait speed or group mean differences *(SE)*	*p*-value
Rapid Gait Speed (m/s)		1.55 (0.33)	--	--
COMT Genotype, *n* (%)	Val/Val:	769 (32.7%)	−.06 (.02)	.001
	Met/Val:	1,137 (48.3%)	−.03 (.18)	.055
	Met/Met (REF):	447 (19.0%)	--	--
Demographics.				
Age, years		74.60 (2.84)	−.15	<.001
White, *n* (%)		1,467 (62.3%)	.21 (.01; White > Black)	<.001
Women, *n* (%)		1,223 (52.0%)	−.21 (.01; men > women)	<.001
Usual Gait Speed (m/s)		1.14 (0.21)	.76	<.001
Other health factors.				
Body mass index (kg/m^2)		27.31 (4.80)	−.21	<.001
Ankle-Brachial Index (mm Hg)		1.07 (.18)	.20	<.001
Visual Acuity ≤20/50, *n* Yes(%) (Y3)		101 (4.5%)	−.20 (.03; better > worse acuity)	<.001
Diabetes, *n* Yes (%) (Y1)		121 (5.1%)	−.09 (.03; no > yes)	.004
Coronary Heart Disease, *n* Yes(%) (Y1)		404 (17.2%)	.02 (.02; yes > no)	.205
Congestive Heart Failure, *n* Yes(%) (Y1)		55 (2.3%)	−.18 (.05; no > yes)	.002
Cerebrovascular Disease, *n* Yes(%) (Y1)		152 (6.5%)	−.16 (.03; no > yes)	<.001
Sensorimotor.				
EPESE score, Balance (Y1)		3.75 (.75)	.22	<.001
400m Walk Speed (m/s) (Y1)		1.26 (.21)	.71	<.001
Subjective Knee Pain.				
Knee Pain with Activity, *n* Yes(%) (Y3)		538 (23.1%)	−.15 (.02; no pain > pain)	<.001
Exercise and Walking.				
Weekly exercise/walking (kcal/kg/week)		3.46 (6.87)	.344	<.001
Cognition.				
3MS, points		90.79 (7.77)	.26	<.001
DSST (*n* correct, Y1)		36.92 (14.26)	.31	<.001
Depressive Symptoms.				
CES-D score (Y1)		4.59 (5.24)	−.13	<.001
Energy.				
Self-Reported Energy, points		6.69 (1.75)	.18	<.001

Note. SD = standard deviation. EPESE = Establishing Population for the Epidemiological Study of the Elderly. DSST = Digit Symbol Substitution Test. 3MS = Teng Modified Mini-Mental State Examination. CES-D = Center for Epidemiologic Studies-Depression scale. Y = year from Health ABC dataset (e.g., Y3 = Year 3). If not indicated, data are from Year 2.

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Table 2.

Results of linear mixed effects models predicting rapid gait speed.

	Unstandardized estimate (SE), p-value	
	Time*Met/Val	**Time*Val/Val**
Model 1: Usual gait speed	.004 (.001), p=.015	.003 (.002), p=.050
Model 1 + Demographic (Model 2)	.004 (.001), p=.005	.003 (.002), p=.056
Model 1 + Health Factors (Model 3)	.004 (.001), p=.004	.004 (.002), p=.067
Model 1 + Sensorimotor Function (Model 4)	.005 (.002), p=.005	.004 (.002), p=.042
Model 1 + Knee Pain (Model 5)	.004 (.001), p=.005	.003 (.002), p=.049
Model 1 + Exercise & Walking (Model 6)	.005 (.001), p= .002	.003 (.001), p=.042
Model 1 + Cognition (Model 7)	.004 (.001), p=.015	.003 (.002), p=.035
Model 1 + Depressive Symptoms (Model 8)	.004 (.0001), p=.006	.003 (.002), p=.035
Model 1 + Energy (Model 9)	.004 (.001), p=.015	.003 (.002), p=.050

Note. Time*Met/Met was the reference group. Model 1 was additionally adjusted for the main effects of COMT genotype and time. SE = Standardized error.