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Differential effects of COMT on gait and executive control in aging

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Abstract

Walking speed is associated with attention and executive control processes subserved by the prefrontal cortex. Because polymorphisms in COMT influence these cognitive processes we hypothesized that the same polymorphisms may influence gait velocity. We examined the associations between the Val¹⁵⁸ Met polymorphism in COMT and gait velocity as well as attention and executive function. Participants were 278 non-demented older adults. The results revealed that Met/Val was associated with faster gait velocity. This association can be explained by the putative role of the Val allele in regulating tonic dopamine release in the striatum. In contrast, Met/Met was associated with better attention and executive function. Stratification by gender revealed that the association between COMT genotype and gait was significant only in men. Conversely, the association between COMT genotype and attention and executive function was significant only in women. These findings suggest a differential effect in relating the Val¹⁵⁸ Met polymorphism to gait and to cognitive function while supporting the previously described sexual dimorphism in the phenotypic expressions of COMT.

Keywords

Gait velocity; COMT; Cognition; Aging; Attention; Executive Function

1. Introduction

The prevalence of gait disorders in community samples increases with age reaching 35 percent in individuals age 70 and older. Because gait disorders are associated with a range of adverse outcomes (Verghese et al., 2006) understanding the mechanisms of gait decline and developing strategies for ameliorating them is paramount, especially as the population ages. The

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mechanisms of normal and abnormal gait in the elderly are complex and incompletely understood. We (Holtzer, Verghese, Xue, & Lipton, 2006) and others (for a recent review see (Scherder et al., 2007) have shown that attention and executive control processes subserved by the prefrontal cortex (Tekin & Cummings, 2002) have potent associations with gait performance in non-demented older adults. Dopamine neurotransmission is critical in regulating these attention and executive functions (Seamans, Gorelova, Durstewitz, & Yang, 2001; Sawaguchi & Goldman-Rakic, 1994; Williams & Goldman-Rakic, 1995). These associations suggest that the genes that regulate dopamine transmission may influence gait in non-demented older adults.

Catechol-O-methyltransferase (COMT) facilitates dopamine degradation and is expressed in the cortex and striatum (Matsumoto et al., 2003). The COMT gene, located on chromosome 22q11.1–q11.2, contains a functional polymorphism that codes for a substitution of Valine (Val) for Methionine (Met) at codon 158. The Met allele has one-fourth the enzymatic activity of the Val allele. Individuals homozygous for the Met allele are thought to have decreased COMT activity and increased pre-frontal dopamine levels (Blasi et al., 2005; Lotta et al., 1995). The Val¹⁵⁸Met polymorphism in COMT has been linked to attention and executive functions in a variety of samples (Egan et al., 2001; Goldberg & Weinberger, 2004; Joobert et al., 2002; Mattay & Goldberg, 2004; Malhotra et al., 2002) including the elderly (de Frias et al., 2005). A recent meta-analysis suggested that the COMT Met/Met genotype was associated with better executive function than the Val/Val genotype in healthy individuals but not in patient samples (Barnett, Jones, Robbins, & Muller, 2007). To our knowledge associations between the Val¹⁵⁸Met polymorphism in COMT and gait in non-demented older adults have not been reported. Consistent with the aforementioned findings, one can reasonably hypothesize that the COMT Met allele would be associated with better gait performance compared to the Val allele.

However, phenotypes characterized with impaired functions have been associated with the Met allele including aggression in schizophrenic patients (Strous et al., 2003), suicide attempts (Rujescu, Giegling, Gietl, Hartmann, & Moller, 2003), susceptibility to alcoholism (Kauhanen et al., 2000; Tiihonen et al., 1999), and poor treatment outcome in schizophrenia (Illi, Kampman et al., 2003; Illi, Mattila et al., 2003). The relationship between COMT genotype and function is complex. Predicting the influence of genotype on walking speed is difficult as phenotypes representing both impaired and better functions were related to the same allele; this phenotypic heterogeneity suggests that interactions with other genes (Handoko et al., 2005) and possibly other effect modifiers such as gender (Pooley, Fineberg, & Harrison, 2007) might influence phenotypic expressions of COMT. To address these seemingly conflicting findings Bilder, Volavka, Lachman, and Grace (2004) suggested using the tonic phasic dopamine hypothesis (Grace, 1991) as a conceptual framework to study phenotypic expressions of COMT. Briefly, this theory contends that dopamine regulation within the striatum occurs via two processes. The first process, generated in response to a cognitive or motor challenge, consists of a phasic burst of firing by dopamine neurons resulting in the release of dopamine. The second is a constant low-level 'background' tonic dopamine that is regulated by baseline dopamine neuron firing and corticostriatal glutamatergic afferents. It has been suggested that tonic dopamine levels regulate phasic release of dopamine arising as a response to environmental challenges. Of specific relevance to this paper is the putative role of COMT in regulating subcortical tonic dopamine release (Bilder et al., 2004). The higher enzymatic activity of the Val allele is expected to reduce tonic dopamine levels setting a low response threshold for phasic dopamine release in response to a challenge. In contrast, the lower enzymatic activity of the Met allele is expected to raise tonic dopamine levels increasing the response threshold of phasic dopamine release. Adaptation to environmental stimuli while walking appears to be better served by low tonic dopamine levels suggesting that the Val allele may be associated with better gait at least when measured in uninterrupted conditions.

1.2. Current Study

The current paper examined whether the Val¹⁵⁸Met polymorphism in COMT was related to gait velocity in non-demented older adults. Specifically, two opposing hypotheses were evaluated. First, previous associations between Met/Met and improved attention and between attention and gait suggest that Met/Met might be associated with faster gait velocity. Conversely, the putative role of COMT in regulating sub-cortical tonic dopamine levels suggests that either Val/Val or Met/Val might be associated with faster gait velocity. Additionally, it was of interest to evaluate whether the association between COMT and attention/executive function seen in previous studies could be demonstrated in this normative aging sample. This approach can be especially informative as it facilitates the interpretation of novel genotype phenotype associations (i.e., gait) in the context of previously studied and relevant associations (i.e., attention executive function) within the same sample. Finally, because gender is related to gait performance (Kozakai et al., 2000; Kwon et al., 2001) and also appears to influence phenotypic expressions of the COMT genotype (Pooley et al., 2007) it was of interest to examine whether the associations between COMT and gait were mediated by gender.

2. Methods

2.1. Participants

Participants in this study were a sub-sample of the Einstein Aging Study (EAS) for whom COMT genotyping was available. The EAS, a longitudinal study of aging dementia, has used telephone-based screening procedures to recruit and follow a community-based cohort since 1999 (Lipton et al., 2003; Verghese et al., 2004). The primary aim of the EAS is to identify risk factors for dementia. Eligibility criteria are age 70 over, residing in Bronx, and English speaking. Exclusion criteria include severe audiovisual disturbances that would interfere with completion of neuropsychological tests, inability to ambulate even with a walking aid or in a wheelchair, and institutionalization. Potential participants over age 70 from the Center for Medicaid Medicare Services population lists of Medicare eligible individuals were first contacted by letter, then by telephone, explaining the purpose nature of the study. The telephone interview included verbal consent, a brief medical history questionnaire, and telephone-based cognitive screening tests (Lipton et al., 2003). Following the interview, participants who met eligibility criteria over the phone were invited for further screening and evaluations at our clinical research center. Informed consents were obtained at clinic visits according to study protocols and approved by the local institutional review board. Participants were followed at yearly intervals. A total of 310 EAS subjects were genotyped for the Val¹⁵⁸Met polymorphism in COMT. Of those subjects 28 who met diagnostic criteria for dementia (Association, 1994) as determined by a consensus clinical diagnostic case conference and 4 who had Parkinsonian gait (Verghese, Lipton et al., 2002) diagnosed by the study neurologists were excluded. Hence, a total of 278 non-demented participants were eligible for the present study.

2.2. Measures

2.2.a. Quantitative gait assessment—Research assistants conducted quantitative gait evaluations independent of the clinical evaluation. Quantitative gait variables were collected by using a 12-ft instrumented walkway (180 × 35.5 × 0.25 in.) with embedded pressure sensors (GAITRite, CIR systems, Havertown, PA). Excellent reliability and validity for GAITRite assessments were reported in previous research in our center (Verghese, Buschke et al., 2002) and in other studies (Bilney, Morris, & Webster, 2003). The quantitative gait assessment provides several parameters. However, for this analysis, for the sake of simplicity and comparability with prior work (Holtzer et al., 2006) we focused on gait velocity, the most commonly used metric in gait research. Velocity (cm/s) is obtained by dividing the distance covered on two trials by the ambulation time.

2.2.b. Walking protocol—Participants were asked to walk on the instrumented walkway in a well-lit hallway at their “normal walking speed” for two trials. Start and stop points were marked by white lines on the floor and included three feet each for initial acceleration and terminal deceleration. Monitoring devices were not attached to the participants during the test. To reduce learning effects, participants were given practice trials to familiarize themselves with the procedure.

2.2.c. Genotype Determination—Blood specimens were collected from subjects by the EAS phlebotomist, centrifuged, and stored in freezers at -80°C following standard procedures. DNA was extracted from white blood cells using standard procedures. The Val¹⁵⁸Met polymorphism in COMT (rs4680, G>A SNP) was amplified using standard conditions 95°C for 10 min followed by 38 cycles of 95°C for 30 sec, 59°C for 30 sec, 72°C for 35 sec with a final step of 72°C for 10 min and resulted in a PCR product of 55bps. The primers used for amplification and sequencing were designed using PSQ version 1.0.6 software (Biotage) are as follows: forward, 5'AGCGGATGGTGGATTTCG 3'; reverse, 5'AACGGGTCAGGCATGCAC 3' sequencing, 5'GCACACCTTGTCCTTC 3'. The forward primer contained a biotin labeled primer. Genotyping was performed using a Pyrosequencing PSQ HS 96A system 1.2 (Biotage, for a recent review see (Ronaghi, 2003). The Hardy-Weinberg (HW) analysis was not significant χ^2 (1, N=278) = .049, $p=0.82$ indicating that the SNP genotypes were in equilibrium.

2.2.d. Total disease score—Dichotomous rating (present or absent) of diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson's disease, chronic obstructive lung disease, angina, and myocardial infarction, was used to calculate a summary score (range 0–10) of disease comorbidity (Holtzer et al., 2007; Verghese, Wang, Lipton, Holtzer, & Xue, 2007).

2.2.e. Cognitive assessment—General cognitive function was assessed with the Blessed Information-Memory-Concentration test (Blessed, Tomlinson, & Roth, 1968). In addition, a comprehensive battery of neuropsychological tests which have been validated for use in aging populations (Katzman et al., 1989; Masur, Sliwinski, Lipton, Blau, & Crystal, 1994; Sliwinski, Buschke, Stewart, Masur, & Lipton, 1997) provided detailed information regarding the participants' neuropsychological function. Our recent studies showed that factor analysis of the neuropsychological battery¹ consistently yielded three statistically orthogonal cognitive domains capturing the domains of Executive Attention, Verbal IQ and Memory (Holtzer et al., 2006; 2007). For the purpose of this paper only the Executive Attention factor was considered and subjected to analyses assessing its associations with COMT. This empirically derived factor encapsulates facets of higher order cognitive abilities that are typically considered representative of attention and executive processes. It is noteworthy that individual tests that contribute to this factor are timed and visually mediated.

2.3. Statistical analyses

Demographic characteristics, gait velocity, and the Executive Attention factor summary score were tabulated for the entire sample and per COMT genotype. Consistent with our previous studies (Holtzer et al., 2006; 2007) neuropsychological raw test scores were submitted to principal components factor analysis (PCA) in order to reduce the number of measures. Because the PCA was run on the correlation matrix, the raw scores were normalized based on the distribution of the entire sample. Varimax rotation was used to derive orthogonal factor scores and the minimum eigenvalue for extraction was set at 1.

¹The individual neuropsychological tests and the factor analytic procedures are described in details in our previous studies (see Holtzer et al., 2006; 2007).

2.3.a. Associations between COMT genotypes and outcomes—Continuous associations between the Val¹⁵⁸Met polymorphism in COMT, gait velocity and Executive Attention were examined with linear or robust regression (Fomenko, Durst, & Balaban, 2006; Motulsky & Brown, 2006) as appropriate. To elucidate the associations between the COMT genotype and the outcome variables, gait velocity and Executive Attention were dichotomized to the best performance quartile vs. the remaining lower three quartiles. Logistic regressions evaluated the odds of group membership in the best quartile of gait velocity and Executive Attention as a function of the COMT genotype treated as a three-level categorical variable (Met/Met, Met/Val, and Val/Val) with Met/Met serving as the reference group. In secondary analyses, the logistic regressions were stratified by gender. Internal validity of the logistic regressions was examined using the Hosmer and Lemeshow Goodness-of-Fit Test (Hosmer & Hjort, 2002). All analyses were conducted with SPSS (Version 12; SPSS Incorporated, 2003).

3. Results

3.1. Sample characteristics

Demographic characteristics and performance on the main outcome measures are tabulated for the entire sample and per COMT genotype (see Table 1).

Table 1 shows that, as expected, more women than men were included in the study. The participants were relatively healthy, as indicated by their low Total Disease Scores, and reported an average education level that exceeded high school diplomat level. Demographic characteristics were comparable across the three COMT genotype groups. The majority of the participants were Caucasians (n=194; 70%), followed by African Americans (n=71; 25%) and other ethnicities including Asians and Hispanics (n=13; 5%). The demographic characteristics of the sub-sample described in this study were comparable to those of the entire EAS sample, which is representative of individuals age 70 years and older residing in the Bronx².

3.2. Factor analysis – neuropsychological tests

Consistent with our previous studies PCA of the neuropsychological test scores yielded exactly three significant orthogonal factors that accounted for 60 percent of the variance in neuropsychological test scores (Holtzer et al., 2007; 2006). The three factors captured the domains of Executive Attention, Verbal IQ, and Memory with each of the factors accounting for 23, 24, and 13 percent of the variance in the neuropsychological tests, respectively. As indicated earlier, of the cognitive factors only Executive Attention was reported and subjected to analyses evaluating its associations with COMT. The Executive Attention factor encapsulated facets of higher order cognitive abilities that are typically considered representative of attention and executive processes. Individual tests that contributed to this factor were all timed and visually mediated including the Trail Making Tests and the Digit Symbol and Block Design subtests of the Wechsler Adult Intelligence Scale-Revised.

3.3. Associations between COMT and gait velocity

Linear regression assessed associations between COMT and gait velocity when treated as a continuous variable. Histogram and scatter plot analyses of the distribution of gait velocity scores for the entire sample and per COMT genotype suggested that internal validity for the regression was adequate. The results revealed that the Met/Val genotype was associated with

²Demographic characteristics of the EAS sample at baseline (n=1251 non-demented participants): Mean age in years = 78.8(5.2); Percent female = 60; Percent Caucasians = 70; Percent African Americans = 25; Mean years of education = 12.9(3.9); Mean Blessed scores = 2.9(2.5).

faster velocity compared to Met/Met. Associations with velocity were not statistically different between Val/Val and Met/Met genotypes (see Table 2).

To further elucidate the relationship between COMT and gait velocity, logistic regressions assessed the odds of group membership in the best (fastest) gait velocity quartile compared to the remaining lower three quartiles as a function of COMT genotype with Met/Met serving as the reference group. Descriptively, 30 percent of the participants with the Met/Val genotype were placed in the best velocity quartile compared to 23 and 10 percent in the Val/Val and Met/Met genotypes, respectively. The Hosmer–Lemeshow goodness-of-fit test was not significant indicating that internal validity for the logistic model was adequate $X^2(1, N=278) = .000, p=1.00$. Participants with Met/Val were almost four times more likely to be placed in the best velocity quartile compared to participants with Met/Met, $OR=3.85, 95\%CI=1.42-10.39, p=0.008$. Differences in the odds of being placed in the best velocity quartile were not statistically significant between the Met/Met and Val/Val genotypes (see Table 2). Logistic regressions stratified by gender revealed that, in men, individuals with Met/Val were four times more likely to be placed in the best overall velocity quartile group compared to individuals with Met/Met $OR=4.29, 95\%CI=1.12-16.38, p=0.033$. However, although in the same direction, these differences were not significant in women (Table 2).

3.4. Associations between COMT and Executive Attention

Due to heteroskedasticity (i.e. unequal variance in the linear regression errors between the three genotype groups) robust regression was applied to assess associations between COMT and the median scores of Executive Attention. The results revealed that consistent with the literature Met/Met was associated with higher (i.e., better) Executive Attention scores compared to Val/Val. Met/Val was associated with intermediate Executive Attention scores that were not significantly lower than the scores obtained by the Met/Met genotype (Table 3).

To further elucidate the relationship between COMT and Executive Attention, logistic regressions assessed the odds of group membership in the best Executive Attention quartile compared to the lower three quartiles as a function of COMT genotype with Met/Met serving as the reference group. Descriptively, 39 percent of the participants with the Met/Met genotype were placed in the best Executive Attention quartile compared to 25 and 17 percent in the Met/Val and Val/Val genotypes, respectively. The Hosmer–Lemeshow goodness-of-fit test was not significant indicating that internal validity for the logistic model was adequate $X^2(1, N=278) = .000, p=1.00$. Compared to Met/Met, the Val/Val genotype was associated with significantly reduced odds of placement in the best Executive Attention quartile, $OR=.337, 95\%CI=.153-.741, p=0.007$. Differences in the odds of being placed in the best Executive Attention quartile between the Met/Met and Met/Val genotypes were intermediate but not statistically significant (see Table 3). Logistic regressions stratified by gender revealed that, in women, Val/Val, $OR=.227, 95\%CI=.083-.618, p=0.004$, and Met/Val $OR=0.339, 95\%CI=.139-.828, p=0.0018$, were associated with significantly reduced odds of placement in the best overall Executive Attention quartile compared to individuals with the Met/Met genotype. However, differences in Executive Attention as a function of the COMT genotype were not significant in men.

4. Discussion

The prevalence of gait disorders is high in the elderly (Verghese et al., 2006) and in individuals with dementias (Allan, Ballard, Burn, & Kenny, 2005). Gait is an indicator of the individual's ability to function independently, especially in old age, and gait impairment is associated with a multitude of adverse outcomes including but not limited to dementia, (Abbott et al., 2004; Weuve et al., 2004; Verghese, Lipton et al., 2002) falls, (Verghese, Buschke et al., 2002) institutionalization and death (Verghese et al., 2006). Hence, understanding mechanisms of

normal and abnormal gait is paramount for scientific and public health reasons. To our knowledge this is the first study to report on associations between COMT genotypes and gait in older adults. The findings revealed that the Met/Met genotype was associated with reduced gait velocity in non-demented older adults and that this association was more pronounced in men. Cortical control of gait is complex with frontal basal ganglia circuitry having a prominent role (for review see Snijders, van de Warrenburg, Giladi, & Bloem, 2007). Although COMT functionality appears to be predominantly at the level of the cortex (Tunbridge, Harrison, & Weinberger, 2006) it also affects dopamine neurotransmission in the striatum (Akil et al., 2003; Meyer-Lindenberg et al., 2005) where significant age-related pre and post-synaptic losses have been reported (Backman, Nyberg, Lindenberg, Li, & Farde, 2006). As discussed below, it appears that associations of the Val¹⁵⁸Met polymorphism with gait may be best understood vis-à-vis the effect of COMT on dopamine signaling sub-cortically.

The findings reported herein are contrary to predictions made on the basis of previous associations between the Met/Met genotype and improved Executive Attention functions in aging (de Frias et al., 2005) which are related to better gait (Holtzer et al., 2006; Inzitari et al., 2007). These findings, however, are consistent with the putative role of COMT in regulating tonic dopamine levels in the striatum (Bilder et al., 2004). Specifically, lower tonic dopamine levels which are attributed to the higher enzymatic activity of the Val allele presumably set a lower response threshold for phasic dopamine release in response to a challenge. Inasmuch as the individual's ability to respond to environmental challenges while walking is enhanced by lower tonic dopamine levels the association between the Met/Val genotype and improved gait performance, at least when uninterrupted by environmental challenges, appears theoretically sound. Moreover, it appears that intermediate levels of dopamine tonic release were associated with better gait performance. That is, faster velocity was associated with Met/Val suggesting that the previously reported inverted U-shaped dopamine – cognition curve (Cai & Arnsten, 1997; Li & Sikstrom, 2002) maybe applicable to the current findings as well. Assuming that walking in uninterrupted conditions is a task that is sensitive to tonic dopamine signaling in the striatum it appears that the Val/Met genotype is associated with optimal functional efficiency whereas having two copies of the Val allele or none would place the individual on the “up-slope” or “down-slope” of the inverted U shape, respectively. This prediction can be further evaluated in future studies by correlating gait performance with dopamine synthesis as measured via positron emission tomography imaging or by using pharmacologic manipulation of dopamine levels in the striatum. The latter approach has already been used in a previous functional magnetic resonance imaging study of working memory revealing that amphetamine enhanced efficiency in prefrontal task-related activation in individuals with the Val homozygous genotype but caused deterioration in individuals with the Met homozygous genotype (Mattay et al., 2003).

Consistent with previous meta-analytic findings (Domschke, Deckert, O'Donovan M, & Glatt, 2007) the Met/Met genotype was associated with better attention and executive function in this sample. Thus, we were able to demonstrate a differential effect of the Val¹⁵⁸Met polymorphism in COMT on gait and cognitive function within the same sample. These opposing findings may be explained in terms of the differential effect of COMT on dopamine regulation in the brain regions involved in mediating gait and executive control. Whereas the association of Met/Met with better Executive Attention may be best understood in terms of the effect of COMT on dopamine signaling in the prefrontal cortex, the association of Met/Val with better gait performance appears to be attributed to the effect of COMT on tonic dopamine regulation in the striatum. It is noteworthy that the Met allele has been previously associated with phenotypes representing both positive and impaired functions in schizophrenic patients in the same study (Bilder et al., 2002).

The associations between COMT, gait and executive function were influenced by gender. The COMT genotype was related to gait velocity in men but not in women. Although in the same direction, the lack of significant association between COMT and gait in women is noteworthy, especially since more women participated in this study. The association between the COMT genotype and Executive Attention was significant overall and in women but not in men. This latter effect can potentially be attributed to the lower number of males present after the stratification by gender. However, there was no detectable trend between the COMT genotype and Executive Attention in men, making lack of power unlikely. Recent evidence suggests that gender has a role in diverse phenotypic expressions of COMT including but not limited to Obsessive Compulsive Disorder (Pooley et al., 2007) and the risk of non-vertebral fracture (Stolk et al., 2007). Levels of COMT enzyme activity in the human brain are higher in women compared to men (Chen et al., 2004). Whereas the basis for these gender differences is not clear, some evidence suggests that estrogen may have a role in regulating the expression of COMT (Jiang, Xie, Ramsden, & Ho, 2003; Xie, Ho, & Ramsden, 1999). Consistent with this putative function a recent study demonstrated that deficiency in estrogen was associated with a decrease in protein levels of COMT and that estrogen replacement increases COMT expression in male mice (Hill et al., 2007). Finally, a recent PET study reported greater dopamine release in the striatum in men compared to women in response to amphetamine challenge (Munro et al., 2006). This finding appears consistent with the findings reported herein, especially if the effect of COMT on gait velocity in men is indeed localized to the striatum. The above findings further emphasize that gender should be considered in studies that examine phenotypic expressions of COMT and likely other genes that affect dopamine as well.

Gait and Executive Attention are complex functions influenced by a number of genetic and environmental factors as well their interactions. Relevant to this investigation are studies that have begun to shed light on the epistasis between COMT and other genes in the context of phenotypes such as novelty seeking (Benjamin et al., 2000), extraversion (Golimbet, Alfimova, Gritsenko, & Ebstein, 2007) and the stress response (Jabbi et al., 2007). Moreover, a recent functional magnetic resonance imaging study of working memory revealed that the COMT Met homozygous genotype mediated against inefficient task related brain activations observed in the combined presence of glutamate receptor mgluR3 (GRM3) and the homozygous COMT Val genotype (Tan et al., 2007). Future studies should examine whether interactions between COMT and other genes that affect dopamine catabolism and other neurotransmitter systems influence gait in young and old individuals as well as in disease states where gait and executive functions become impaired. For instance, one might hypothesize that due to the significant dopamine loss in the striatum in Parkinson's disease (PD) associations between COMT and gait could be different than those observed in this study. Indeed, there is some evidence that administration of the COMT inhibitor Entacapone improved motor function and fluctuations in PD patients (Larsen et al., 2003). Whether the association between COMT and gait could be replicated in diseases that do not primarily affect dopamine but where motor functions including gait become impaired (e.g., Alzheimer's disease) remains to be evaluated.

Conclusion

This study reports for the first time on associations between COMT and gait velocity in non-demented older adults. These associations were significant only in men. The effect of COMT on gait can be understood in terms of regulation of tonic dopamine levels in the striatum.

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Table 1

Summary of sample characteristics and main outcome measures for the entire sample (n=278) and per COMT genotype.

	COMT genotype			
	Entire sample	Met/Met	Met/Val	Val/Val
N	278	49	138	91
Age years: M(SD)	78.5(5.1)	78.5(5.0)	78.8(5.0)	77.9(5.3)
Education years: M(SD)	14.2(3.3)	14.6(3.5)	13.9(3.2)	14.3(3.3)
Blessed total: M(SD)	2.0(2.0)	1.75(1.6)	2.1(2.1)	2.0(2.0)
Total disease score	1.5(1.2)	1.5(1.1)	1.5(1.2)	1.4(1.2)
% Female	60.8	55	61.5	62.3
Gait Velocity: M(SD)	98.1(22.4)	92.9(21.9)	100.5(23.4)	97.3(20.9)
* E/A: Med(SE)	0.01(0.05)	0.31(.05)	0.03(0.08)	-.06(0.09)

* E/A = Executive Attention factor scores are standardized regression scores. Higher scores indicate better performance. Median (SE) scores were used to assess associations with COMT genotype.

Table 2

Associations between the COMT genotype and gait velocity

Gait Velocity			
Linear Regression	β	t	P
Met/Met vs. Met/Val	0.129	2.03	0.043
Met/Met vs. Val/Val	0.098	1.15	0.251
Logistic Regression	OR	95% CI	P
Met/Met vs. Met/Val	3.85	1.42 – 10.39	0.008
Met/Met vs. Val/Val	2.64	.928 – 7.51	0.069
Stratified by Sex			
Females (n=169)			
Met/Met vs. Met/Val	4.03	.882 – 18.50	0.072
Met/Met vs. Val/Val	2.71	.552 – 1.38	0.219
Males (n=109)			
Met/Met vs. Met/Val	4.29	1.12 – 16.38	0.033
Met/Met vs. Val/Val	2.90	.708 – .11.90	0.139

Table 3

Associations between the COMT genotype and Executive Attention

Executive Attention			
Robust Regression	β	t	P
Met/Met vs. Met/Val	−0.27	−1.79	0.073
Met/Met vs. Val/Val	−0.37	−2.27	0.023
Logistic Regression	OR	95% CI	P
Met/Met vs. Met/Val	.537	.269 – 1.071	0.077
Met/Met vs. Val/Val	.337	.153 – .741	0.007
Stratified by Sex			
Females (n=169)			
Met/Met vs. Met/Val	.339	.139 – .828	0.018
Met/Met vs. Val/Val	.227	.083 – .618	0.004
Males (n=109)			
Met/Met vs. Met/Val	.567	.143 – 2.24	0.418
Met/Met vs. Val/Val	1.02	.311 – 3.34	0.974