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Dopaminergic Polymorphisms Associated with Medication Responsiveness of Gait in Parkinson's Disease

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Abstract

Background—Gait dysfunction is a common symptom of Parkinson's disease that can cause significant disability and put patients at risk for falls. These symptoms show variable responsiveness to dopaminergic therapy.

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Conflict of Interest

The following authors have no conflicts of interest with this work, financial or otherwise, to declare: NSM, KLC, NIB, MLTMM or RDS.

Author Contributions

RDS, NIB, and MLTMM designed the study; NSM collected and analyzed data and wrote the first manuscript draft. All authors contributed to data interpretation and manuscript preparation.

Objective—To determine whether dopaminergic (rs1076560 *DRD2* G>T and rs4680 catechol-o-methyltransferase (*COMT*) Val158Met) or brain derived neurotrophic factor (rs6265 *BDNF* Val66Met) genetic polymorphisms are associated with gait function and medication responsiveness in Parkinson's disease.

Method—Gait function was evaluated on two days for patients (ON and OFF medication in a counterbalanced fashion) and a single session for controls. Investigators were blinded to genotype during data collection. Associations between genotype and medication responsiveness were analyzed using mixed model ANOVAs. A priori hypotheses were tested using GAITRite® electronic mat spatiotemporal gait parameters including step length, step width, velocity, portion of double and single support per gait cycle, and variability of these measures ON and OFF medication.

Results—We found that the *DRD2* polymorphism, but neither *COMT* nor *BDNF*, was consistently associated with gait function and medication responsiveness in the patients. Specifically, Parkinson's disease patients with reduced striatal D2 expression (*DRD2* T allele carriers) had worse gait dysfunction and showed greater dopamine responsiveness of gait function compared to patients who were homozygous for the G allele. There was no effect of any of the genetic polymorphisms on gait for controls.

Conclusions and Relevance—The findings suggest that genetic subgrouping, in particular for *DRD2*, may be used to identify Parkinson's disease patient subgroups that are more dopamine responsive for gait function.

Keywords

Parkinson's disease; gait; individual/subgroup differences; *DRD2*; dopaminergic medication responsiveness

Introduction

Gait dysfunction in Parkinson's disease is characterized by slow, shuffling steps, postural changes and reduced arm swing. These symptoms present early in the disease, increase risk for falls, and potentially cause significant disability [1]. The gait in Parkinson's disease is less responsive to dopaminergic medications and surgical interventions than other symptoms [2], suggesting that dopaminergic denervation may not entirely modulate gait dysfunction [2, 3]. Some recent studies have linked Parkinson's disease gait dysfunction to cholinergic denervation (cf. [3]), while others have shown that some gait parameters improve with dopaminergic treatment [2, 4]. Individual differences may explain, at least in part, this rather mixed literature on the medication responsiveness of Parkinson's disease gait.

We previously reported that the single nucleotide polymorphism (SNP) rs1076560 in the dopamine D2 receptor (*DRD2*) gene is associated with the magnitude of L-DOPA improvements in motor sequence learning in Parkinson's disease patients; L-DOPA improved learning only in patients carrying the minor T allele [5]. These findings have potential implications for clinical treatment decisions, but genetic associations with L-DOPA responsiveness for more clinically relevant behaviors such as locomotion have been evaluated in only one study. This study found that genotype for the dopamine transporter

gene *SLC6A3* was associated with Unified Parkinson's Disease Rating Scale (UPDRS) motor score and gait responsiveness to both an acute L-DOPA challenge and 90 days of methylphenidate treatment [6]. These patients were all implanted with deep brain stimulators, however, raising the question of whether less severely affected patients would also show similar gene-medication associations.

In the current study, we evaluated whether the genetic polymorphisms *COMT* Val158Met (rs4680), *DRD2* G>T (rs1076560) and *BDNF* Val66Met (rs6265) would predict medication responsiveness of gait function in Parkinson's disease. The *COMT* SNP (rs4680) regulates dopamine availability in the prefrontal cortex and corticostriatal circuits [7]. A substitution of the valine (Val) with methionine (Met) allele at this codon reduces COMT enzymatic activity, resulting in higher prefrontal dopamine availability [8]. *COMT* genotype has been associated with gait speed in healthy older adults [9]. The *DRD2* G>T polymorphism (rs1076560) influences dopamine availability by regulating striatal dopamine receptor expression. Healthy T allele carriers—who have reduced D2 receptor expression—often perform worse on cognitive and motor tasks [10, 11]. We also evaluated the *BDNF* Val66Met polymorphism (rs6265) that regulates BDNF secretion. Met allele carriers frequently show reduced short-term brain plasticity and worse performance on motor learning tasks [12]. Moreover, BDNF protein is associated with dopamine release and uptake *in vitro* [13, 14].

Here, we analyzed gait parameters in Parkinson's disease patients, both ON and OFF antiparkinsonian medication, and controls. We evaluated the association between the genetic variants *COMT* Val158Met (rs4680), *DRD2* G>T (rs1076560) and *BDNF* Val66Met (rs6265) and Parkinson's disease gait dysfunction and medication responsiveness.

Materials and Methods

Experimental Design

We tested the effects of antiparkinsonian medications on gait parameters while patients walked at their fastest, preferred, and slowest speeds. For clinical relevance, we present only the preferred walking speed data but results for the other conditions were qualitatively similar. We evaluated whether medication responsiveness of gait parameters was associated with genotype for the *COMT* Val158Met, *DRD2* G>T, and *BDNF* genetic polymorphisms.

Participants

Thirty-nine Parkinson's disease patients and 30 healthy volunteers participated. We excluded participants with known neurological or psychiatric diseases other than Parkinson's disease, who were not taking dopaminergic antiparkinsonian medication(s) or who had undergone surgery for deep brain stimulation.

A movement disorder specialist diagnosed patients with idiopathic Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [15]. All patients had mild-to-moderate stage Parkinson's disease. Patients' antiparkinsonian medications were heterogeneous; several patients took DA agonists alone or in combination with other antiparkinsonian medications (levodopa+ = 50%, levodopa+ & dopamine agonist

= 27.78%, dopamine agonist only = 16.67%, monoamine oxidase B inhibitor only = 5.56%). We evaluated Parkinson's disease motor severity with the Movement Disorder Society's Unified Parkinson's Disease Rating Scale [MDS-UPDRS; 16]. Additionally, all participants completed the Montreal Cognitive Assessment (MOCA; [17]). Table 1 provides participant characteristics. The experiment was conducted in accord with the Declaration of Helsinki and was approved by the Institutional Review Board. All participants provided written, informed consent.

Gait data from four patients were removed from analyses due to: MOCA scores suggestive of dementia ($n = \text{one}$; 17], a recent medication change ($< \text{six months}$; $n = \text{one}$), a recent knee surgery ($n = \text{one}$), and abnormal neurological findings on examination ($n = \text{one}$). Analyses were performed on the remaining data from 36 patients (10 females) and 29 controls (16 females). Two control participants declined to consent to genotyping and were not included in the genotype analyses.

Genotyping

We obtained saliva samples using an Oragene DNA self-collection kit. Genotyping was performed using a polymerase chain reaction following previously published protocols [11]. The SNPs for rs4680, rs1076560 and rs6265 were determined. The distributions of individuals within each genotype group are presented in esupp Table 1; these were in accord with an exact test of the Hardy-Weinberg equilibrium [$ps > .09$; 18].

Apparatus

We used a GAITRite® electronic mat to collect gait parameters (CIR Systems, Inc., Sparta, NJ) using GAITRite® Software (Version 3.8A) and a sampling rate of 80 Hz. This system has high reliability and strong concurrent validity for both older adults and Parkinson's disease patients [19, 20].

Procedure

Parkinson's disease patients underwent two test sessions: one ON and one OFF their regular antiparkinsonian medications in a counterbalanced fashion (17 patients tested ON first). Patients arrived to the ON medication session having taken their antiparkinsonian medication(s) as usual ($M = 2.02$ hours; $SD = 1.57$). The OFF state was achieved by overnight medication withdrawal ($M = 15.48$ hours; $SD = 4.57$) [21]. Controls participated in a single session.

We measured participants' leg length (greater trochanter to the floor, bisecting the lateral malleolus) prior to testing. Participants wore their preferred walking shoes. We instructed them to walk at a speed that was "comfortable and natural for them" for the preferred walking speed. Participants performed four repetitions of steady-state walking; walks began and ended at least three meters beyond the walkway to account for acceleration and deceleration.

Statistical Analysis

Primary gait measures are presented in esupp Table 2. We chose them to capture gait dysfunction previously reported in studies of Parkinson's disease, while balancing the high intercorrelations between gait parameters and different gait measures reported across studies.

A minimum of 16 steps was collected for patients ($M = 26.24$; $SD = 7.42$) and controls ($M = 22.48$; $SD = 3.43$). We normalized velocity and step length to participant's leg length. We averaged individual footfall data to derive gait variability measures, reported as coefficients of variation ($\%CV = 100 \times \text{standard deviation/mean}$).

Separate two-tailed ANOVAs for mixed measures compared gait parameters between genotype groups when patients were ON and OFF medication. These ANOVAs tested whether the medication response of gait was associated with genotype for the *COMT* Val158Met polymorphism, *DRD2* G>T and *BDNF* polymorphisms. Similar ANOVAs were also performed on gait parameters between Parkinson's disease patients and controls. Two-tailed, between- and within-subject *t* tests compared potential differences between genetic variant groups and patients/controls on demographic and other characteristics.

The Huynh-Feldt epsilon [22] determined whether data met the assumption of sphericity ($\Sigma > 0.75$). The *F* statistic was evaluated using the Huynh-Feldt adjusted degrees of freedom when the sphericity assumption was violated. We performed all analyses using IBM® SPSS® Version 22 (IBM, Chicago). Significance was taken as $p < .05$.

Results

Participant Characteristics

Patients' motor symptoms (MDS-UPDRS) improved when they were ON compared to OFF medication, $t_{35} = 3.93$, $p < .001$. The magnitude of this change was small but within the range expected given that about half of the patients were on dopamine agonists. There were no differences in demographic variables nor disease characteristics between patients in the *COMT* nor *DRD2* variants ($ps > .12$). The Met/Met group for *BDNF* had a significantly higher LED ($M = 913.33$; $SD = 499.03$) than the Val/Met group ($M = 383.50$; $SD = 170.92$; $p = .04$), but no other differences were found ($ps > .32$).

Controls were significantly younger than patients by 4.56 years on average, $t_{62} = 2.92$, $p < .01$; both groups had equivalent years of education ($p > .81$). MOCA scores were equivalent between patients, both ON and OFF medication, and controls ($ps > .16$).

Disease and medication effects on gait function

Parkinson's disease patients had slower gait and took shorter steps, along with greater variability in step length between footfalls, when OFF versus ON their medication (Supplemental materials, Table 2). Patients also spent a marginally greater percentage of the gait cycle in double support, and less in single support, when OFF medication.

The gait speed of Parkinson's disease patients ON medication was slower than controls. Patients also spent a greater percentage of the gait cycle in double support, and less in single support, compared to controls. Patients ON medication were also more variable in the length, width and timing between steps, along with the amount of time spent in single support, relative to controls.

A similar pattern was found when patients were OFF medication compared to controls. Patients OFF medication had slower gait speed, spent a greater percentage of the gait cycle in double support and were more variable in the timing between steps and the amount of time they spent in single support than controls. However, patients OFF medication also had shorter steps and were more variable in the time they spent in double support and their stride velocity, compared to controls. Cadence was also marginally slower in patients OFF medication. Interestingly, patients OFF medication did not show the differences in step length and step width variability when compared to controls that we found when they were ON medication, which is likely due to high inter-step variability. ANCOVA with age as a covariate revealed a similar pattern of results.

In sum, gait speed, the percentage of gait cycle spent in double support, along with stride time variability and the variability of time spent in double support were significantly worse in patients compared to controls. However, medications were effective for mitigating a limited number of gait impairments, such as step length and to some extent walking speed, in Parkinson's disease.

Genotype associations with gait function and medication responsiveness

Gait parameters in Parkinson's disease patients ON and OFF their medication were significantly associated with the *DRD2* polymorphism (Fig. 1). Significantly worse gait impairments were found in T allele carriers compared to G homozygote patients. T allele carriers walked slower (allele main effect: $F_{1,34} = 5.43$, $p = .03$), had shorter steps (allele main effect: $F_{1,34} = 5.88$, $p < .02$) and spent more of the gait cycle in double support (allele main effect: $F_{1,34} = 5.06$, $p = .02$) compared to patients who were G homozygotes. No differences were found between T allele carriers and G allele homozygotes for any gait parameters in the healthy controls ($ps > .19$).

The *DRD2* polymorphism was also associated with medication responsiveness of gait parameters (Figures 1–2). For example, the amount of time spent in the double support phase of gait was only improved by medication in T allele carriers, but not in the G allele homozygotes (Fig. 1, allele by medication interaction: $F_{1,34} = 4.09$, $p = .05$).

Fig. 2 shows the associations between *DRD2* variants and gait variability measures. Parkinson's disease patients who were T allele carriers were more variable in their gait speed, step length, time spent in double support between footfalls, and stride time compared to G homozygotes (allele main effects: $ps = .001 - .05$). The interaction between *DRD2* variants and medication state for single support time CV ($F_{1,34} = 9.77$, $p < .01$) and a trend for stride velocity CV ($F_{1,34} = 3.32$, $p = .08$) provide further support that certain gait parameters are responsive to medication in T allele carriers, but not G homozygotes.

Pearson correlation coefficients were computed to examine associations between medication responsiveness of gait and L-DOPA Equivalency Dose [LED; 23] for the *DRD2* allele subsets. A negative relationship was found between stride velocity variability and medication responsiveness in patient G homozygotes; this relationship was only marginal for T allele carriers ($r_{25} = -.52$, $p < .01$ and $r_{11} = -.55$, $p = .08$, respectively). Stride velocity variability showed a positive medication responsiveness for patient G homozygotes, and to a marginal degree T allele carriers, with lower LEDs. No other relationships were found ($ps > .21$). These findings suggest that L-DOPA equivalency doses were not related to medication responsiveness of T allele carriers for most gait parameters where we observed an allele by medication interaction.

When patients were subgrouped by *COMT* or *BDNF* variants, there were no main effects of allele nor allele by medication interactions for the measured gait parameters ($ps > .09$).

Discussion

We found that the *DRD2* polymorphism, but neither the *COMT* nor *BDNF* polymorphisms, was associated with gait dysfunction and medication responsiveness in Parkinson's disease. T allele carriers walked more slowly, had smaller and more variable step sizes and spent a greater portion of time in the double support phase of gait than patients homozygous for the G allele. Moreover, we found that T allele carriers had improved gait performance when ON versus OFF their antiparkinsonian medications while G allele homozygotes did not. This effect parallels our previous finding that a single-blind, placebo control L-DOPA administration improves motor sequence learning in patients who are *DRD2* T allele carriers [5]. The current study extends our findings to gait function, which can cause significant disability in Parkinson's disease patients [1, 24]. Gait tends to be less responsive to both dopaminergic treatment and deep brain stimulation in Parkinson's disease [2, 4]. Therefore, identifying a subset of patients who show greater medication benefits is clinically important. Interestingly, several studies have found associations between the *DRD2* polymorphism and antipsychotic medication responsiveness in patients with schizophrenia, supporting the notion that this particular polymorphism is a sensitive index of endogenous dopaminergic transmission [25].

The dopamine responsiveness that we observed in *DRD2* T allele carriers, but not G homozygotes, is consistent with the dopamine overdose hypothesis. This hypothesis proposes that responses to exogenous dopamine administration are dependent on endogenous dopamine transmission levels [cf. 5, 26], which can be affected by disease, age, genotype for specific polymorphisms and other factors. T allele carriers would presumably fall lower along the left-hand arm of the inverted-U shaped function describing the relationship between dopamine and performance than G homozygotes. Thus, dopaminergic treatment would move them up the curve, whereas G homozygotes would presumably only move along the flat top portion of the curve.

Alternatively, our findings are also consistent with a complex interaction between multisystem denervation and gait. Gait function in *DRD2* T allele carriers may respond to dopamine medication due, in part, to their worse gait dysfunction. However, dopaminergic

medications only improve gait in T allele carriers to an equivalent level as patient G homozygotes, but not controls. This might reflect a ceiling effect in the response of Parkinsonian gait function to dopaminergic medications. Cholinergic changes may also explain the difference observed in gait between patients and controls. Several recent studies support a role for the cholinergic system in Parkinson's disease gait and balance [3, 27], in addition to the known role of the cholinergic system in cognitive factors that play a role in gait function [27]. Our mild-to-moderate patient sample without dementia may have been relatively less affected by cholinergic denervation than more severe Parkinson's patients, potentially explaining why we did not see large differences in gait or cognitive function compared to previous studies [cf. 28]. However, this patient sample is the optimal group to assess the dopaminergic response of gait.

The current study design does not allow us to distinguish these two explanations. Worsening of gait function with higher L-DOPA equivalency is consistent with both explanations, due to either an 'overdose' of dopamine impairing gait function or medication only improving gait variability for this parameter to a certain degree. Future research should consider designs that better adjudicate these competing accounts.

Our results were specific to the *DRD2* polymorphism; *COMT* and *BDNF* alleles did not associate with gait performance nor with medication responsiveness in our sample. Moreau et al. [6] reported that the *SLC6A3* polymorphism but not *COMT* was associated with improvements in UPDRS motor scores with dopaminergic treatment; they did not evaluate *DRD2*. Thus, it seems that some polymorphisms are more effective at predicting medication responsiveness in Parkinson's disease. There are several other genetic polymorphisms that play a role in dopaminergic metabolism that could be investigated; we selected the specific ones here due to their previously reported associations with locomotor function or anti-Parkinsonian medication responsiveness. Future, larger-scale studies should examine whether the effects of *SLC6A3* and *DRD2* polymorphisms are additive in their predictability of dopamine responsiveness as has been reported for healthy individuals with other SNPs [29].

One limitation of our study is the unbalanced distribution of participants across genotypes, resulting in relatively small group sizes. The distribution was consistent with those observed in the general population however, and our sample size is well on par with previous studies of Parkinson's disease gait. Nevertheless, future research would benefit from larger samples of both patients and controls to better delineate genotype associations with gait and dopamine responsiveness in Parkinson's disease patients.

In summary, our results support a role for the *DRD2* G>T polymorphism in predicting Parkinson's disease gait impairment and medication responsiveness of specific gait functions. Patients with reduced striatal D2 receptor expression (T allele carriers) had worse gait dysfunction compared to patients who were homozygous for the G allele. We also found greater dopamine responsiveness of gait for patient carriers of the T allele, but not for homozygous G allele carriers. Neither *COMT* nor *BDNF* polymorphisms were associated with gait dysfunction, nor dopamine responsiveness, in Parkinson's disease patients. These

findings have important clinical implications for predicting dopamine responsiveness of gait dysfunction in Parkinson's disease patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- *DRD2* genetic polymorphism associates with gait in patients with Parkinson's disease
- Patients carrying the *DRD2*T allele show more gait improvements ON medication
- *COMT* and *BDNF* genetic polymorphisms did not associate with treatment response

Fig. 1.

General gait characteristics for PD patients ON and OFF medication as a function of *DRD2* (rs1076560) genotype for preferred walking speed. Control data is included for illustrative purposes. Several gait parameters were worse for T carriers compared to G homozygotes in patients; however, this was not the case for controls. *DRD2* genotype was associated with medication responsiveness of Parkinson's disease gait. Antiparkinsonian medications only improved the percentage of the gait cycle spent in single- and double-support for T allele carriers but not G homozygotes. SL = stride length; LL = leg length.

Fig. 2.

Gait variability measures for PD patients ON and OFF medication as a function of *DRD2* (rs1076560) genotype for preferred walking speed. Control data is included for illustrative purposes. Gait parameters were more variable in T carriers relative to G homozygotes in patients, but no differences were found for controls. Antiparkinsonian medications significantly improved single support time CV and marginally improved stride velocity CV for T allele carriers but not G homozygotes.

Table 1

Participant Characteristics

	Age (years)	Education (years)	MOCA		Years Diagnosed	MDS-UPDRS		LED (mg)
			ON	OFF		ON	OFF	
Parkinson's disease	67.46 ^a (8.40)	16.44 ^c (3.00)	27.11 ^d (2.71)	26.92 ^d (2.23)	5.07 (3.38)	30.64 (9.08)	35.00 (10.88)	517.24 (323.91)
Controls	62.90 ^b (5.28)	16.86 ^c (2.92)	—	27.17 ^d (2.51)	—	—	—	—

Note. Values in parentheses are standard deviations. Abbreviations: — = No Data; Parkinson's disease-Specific Measure; MDS-UPDRS = Movement Disorder Society's Unified Parkinson's Disease Rating Scale (Motor Section); MOCA = Montreal Cognitive Assessment; LED = L-DOPA Equivalency Dose [23]. Group comparisons with the same superscript are not significantly different.