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Research report

Task-dependent interactions between Dopamine D2 receptor polymorphisms and L-DOPA in patients with Parkinson's disease

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HIGHLIGHTS

- Interaction between DRD2 polymorphism and L-DOPA during motor task performance.
- L-DOPA selectively improved sequence learning performance in the T allele carriers.
- L-DOPA improved manual motor behavior regardless of DRD2 genotype.
- Genes explain the variance in how dopamine contributes to task performances.

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ABSTRACT

Variants in genes regulating dopamine transmission affect performance on tasks including working memory and executive function as well as temporal processing and sequence learning. In the current study, we determined whether a dopamine D2 receptor DNA sequence polymorphism interacts with L-DOPA during motor tasks in patients with Parkinson's disease (PD). Forty-five PD patients were genotyped for the DRD2 polymorphism (rs 1076560, G > T). Patients performed an explicit motor sequence learning task and the grooved pegboard test in both ON and OFF L-DOPA states. For motor sequence learning, DRD2 genotype mediated L-DOPA effects such that L-DOPA associated improvements were only observed in the minor T allele carriers (associated with lower D2 receptor availability, $t_{10} = -2.71$, $p = 0.022$), whereas G homozygotes showed no performance change with L-DOPA. For the grooved pegboard test, performance improved with L-DOPA independent of patients' DRD2 genotype. Collectively these results demonstrate that common DRD2 allelic differences found in the human population may explain how dopamine differentially contributes to performance across tasks and individuals.

1. Introduction

Polymorphisms for genes regulating dopamine transmission are associated with individual differences in brain and cognitive function. For example, the catechol-O-methyltransferase (COMT) gene, which regulates the rate of dopamine breakdown, mediates working memory, attention, and executive control in healthy participants [1–4]. Likewise genetic variation in the dopamine D2 receptor (DRD2) gene is associated with both cognitive and motor abilities including working memory, automatic temporal processing and movement time in healthy participants [5–8].

The effects of genetic polymorphisms on performance have also been investigated in Parkinson's disease (PD) [9–16]. Most of these studies have focused on genetic effects on prefrontal cortex (PFC) mediated cognitive behaviors such as attentional control, planning and verbal reasoning [11,12,15]. Despite the fact that PD patients primarily exhibit motor symptoms associated with striatal dopamine depletion, studies investigating genetic effects on motor functions in these patients are scant.

In the current study, we evaluated the association of one DRD2 (rs 1076560, G > T) genotype on L-DOPA responsiveness in PD with two motor tasks that rely on different striatal circuitries: early motor sequence learning and the grooved pegboard

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test. Motor sequence learning is a form of skill acquisition that underlies everyday motor activities including for example typewriting or route finding. The early phase of sequence learning in particular involves a combination of multiple cognitive abilities such as working memory and error processing in addition to motor functions [17]. Neuroimaging studies have shown that in the early phase of learning, when subjects acquire sequences of action in a controlled manner by engaging in cognitive processes, the ventral/anterior striatal pathway (i.e. associative striatum, encompassing the nucleus accumbens, ventral caudate and ventral putamen) including the anterior cingulate and dorsolateral prefrontal cortex, is involved [18–24]. The grooved pegboard task has been repeatedly used as a measure of simple manual motor function [25–27]. Such tasks are known to involve the dorsal/posterior striatal pathway (i.e. sensorimotor striatum, encompassing the dorsal/posterior subregion of both the caudate and putamen) including the primary and secondary motor cortices [28–30]. While there is no direct evidence that the pegboard task taps the dorsal subregion of the striatum, several studies have shown association between dopamine transmission levels of the striatum as a whole and grooved pegboard performance [31,32]. Based on the well-identified distinction of ventral and dorsal striatum function, with ventral striatum primarily involved in motivation, reward processing, goal directed behavior and executive function and the dorsal striatum involved in motor execution [33–36], it is plausible that the pegboard performance relies more on the dorsal than the ventral subregion of the striatum.

DNA sequence variants in the DRD2 gene are effective markers to capture genetic contributions to striatal dopamine transmission, due to the abundant expression of D2 receptors in the striatum [37,38]. Amongst various DRD2 polymorphisms, an intronic DRD2 polymorphism (rs 1076560, G > T) is associated with mRNA splicing of the short isoform of the D2 receptor (D2S) [39]. Many studies have consistently found significant effects of this DRD2 polymorphism on behavior and brain activation, showing declines in working memory performance and altered brain activation patterns in the minor T allele carriers that results in reduced D2S expression [5,39–41].

As proposed by other studies in PD [11,12,15], depending on an individual's genotype for dopamine regulating genes, an individual's performance will be differentially affected by L-DOPA administration. We predicted that for the early phase of sequence learning, there would be a relatively greater L-DOPA associated performance *decrease* in G allele carriers that allows for higher D2 receptor availability compared to T allele carriers of the DRD2 gene. This is based on our previous observation of deleterious medication effects on early motor sequence learning [42], a manifestation of the dopamine overdose effect [43]. In this previous study, we found a range of variability in the degree of overdose effect across patients, which may be explained by one's genotype in dopamine regulating genes such as the DRD2 gene. The overdose effect will be greater in G allele carriers who are predisposed with relatively higher endogenous dopaminergic activity compared to T allele carriers. Our prediction can be justified by the inverted-U relationship illustrating that both insufficient and excess dopamine transmission impair performance [44–46]. Because early sequence learning relies on the associative striatum, which is relatively intact in early stage PD patients [47–51], the two DRD2 genotype groups will be located near the peak of the curve indicating relatively intact striatal dopamine transmission (see Fig. 1). G allele carriers with higher D2 receptor availability compared to T allele carriers will be located more toward the right hand side of the curve. With L-DOPA, both genotype groups will be shifted downward toward the right, showing worsening of performance as predicted by the dopamine overdose effect [43]. L-DOPA effects will be larger for G allele carriers due to their positioning on the right hand side of the curve. In case of the grooved pegboard test, performance will *increase* with L-DOPA in both genotype groups. This can also be predicted from the inverted-U framework. For this task which relies on the sensorimotor striatum which is more denervated in PD [47–51], both genotype groups will be situated on the left hand side of the curve reflecting a dopamine depleted state. The T allele carriers will be lower toward the left than the G allele carriers (see Fig. 1). With L-DOPA, both groups will be shifted upward to the right improving their performance. The degree of improvement in the two groups will be different showing more L-DOPA benefits in the T allele carriers than G allele carriers.

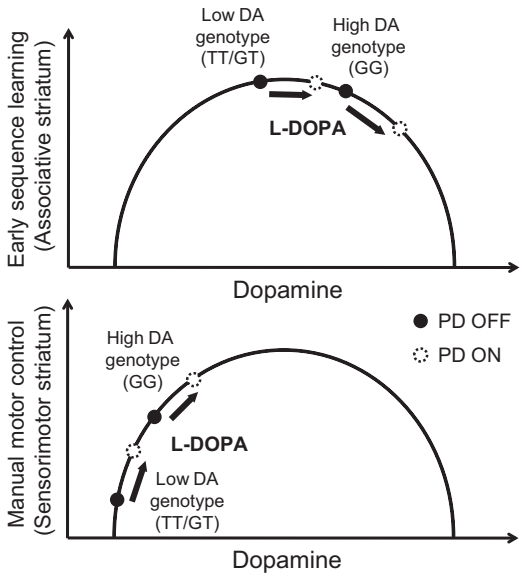

Fig. 1. Hypothesized 'inverted-U' shaped relationship between performance and dopamine level in sequence learning (top) and manual motor control (grooved pegboard, bottom). For early sequence learning which relies on the relatively intact associative striatum, exogenous L-DOPA administration (arrow pointing toward right) will result in worsening of performance for the high DA genotype group (G allele carriers) compared to the low DA genotype group (T allele carriers). For manual motor control which relies on the more denervated sensorimotor striatum, L-DOPA administration will result in improvement for both the high (G allele carriers) and low (T allele carriers) DA genotype groups.

2. Material and methods

2.1. Participants

45 mild to moderate stage PD patients (65 ± 8 years, 9 females, disease duration: 4.3 ± 3 years) falling within Hoehn and Yahr (H & Y) stages 1–3 [52] participated in this study. All study participants were of Caucasian/European descents. Subsets of these patients participated in two different studies of motor sequence learning [53]. Their behavioral data were combined and re-analyzed in association with genotype in the current study. Patients were excluded for any neurological or psychiatric disease other than PD. Patients were included as long as they were on a stable dosage of dopaminergic medications for the previous 6 months, and were evaluated using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS, [54]) by a neurologist. UPDRS is a rating scale widely used in both clinical practice and research to quantitatively assess disease severity and progression of PD. Participants were compensated for their participation, which comprised two testing days. All participants signed a consent form approved by the Institutional Review Board of the University of Michigan. See Table 1 for additional demographics.