Genetic factors influence dopamine effects on learning and plasticity

Kristin M. Pearson-Fuhrhop¹, Brian Minton², Daniel Acevedo², Babak Shahbaba³, Steven C. Cramer¹,²

Departments of Anatomy & Neurobiology, Neurology and Statistics, University of California, Irvine

Introduction
● Dopamine is central to many processes, including movement, learning and plasticity.
● Polymorphisms in the genes that code for dopamine receptors and degradation contribute to inter-individual differences in some forms of learning and brain plasticity.
● Studies in humans and animals have established a role for dopamine in learning and cortical plasticity in the motor system. Drugs that increase brain dopamine improve learning, plasticity and stroke rehabilitation in some studies but not others.
● Dopamine drugs are currently prescribed for several common motor disorders such as Parkinson’s disease, restless legs syndrome and stroke. Inter-individual variation in response to therapy is high.
● Genetic variation might influence the effects of dopaminergic therapy, contributing to the variation seen in learning and plasticity studies and in response to dopaminergic drugs.
● A gene score can provide a more powerful form of examining genetic associations than a candidate gene approach, without the size and signal constraints of a GWAS.
● This study used a randomized, double-blind, placebo-controlled design to examine the influence of a poly-gene score on motor learning and L-dopa administration.

Hypotheses
(1) Genetic polymorphisms affecting dopaminergic neurotransmission influence skilled motor learning and motor cortex plasticity in the basal state (placebo condition).
(2) Increasing brain dopamine levels via L-Dopa administration promotes learning and plasticity.
(3) The influence of L-Dopa will vary with dopamine genetics, and a gene score will be a better predictor than any individual gene.

Method
50 healthy, right-handed participants (age 20.5 ± 2.4, 26M/24F) completed the following protocol:

Day 1 2 3 4 5 6 7 8 9 10
2 week washout

Participants were genotyped for 5 dopamine-related genes (Table 2) and the BDNF val66met polymorphism. Individuals lacking the BDNF polymorphism were invited to participate.

TMS map area of the right FDI was determined on Day 1.

A marble navigation task was practiced (Figure 2). Time to completion (TTC) of each 100-target sequence was recorded. Four 100-target trials were performed each day.

A gene score was created representing the additive effects of five polymorphisms related to dopaminergic neurotransmission (see Table 2).

Gene scores ranged from zero (lowest basal dopamine neurotransmission) to 5 (highest basal dopamine neurotransmission).

Results

Figure 3. Effect of L-Dopa on skilled motor learning varied with gene score. For gene scores below 2, L-Dopa provides better learning, and for gene scores above 2, Placebo provides better learning. Values are derived from the mixed-effects model and reflect the percent improvement from the reference condition of gene score = 0 during the placebo week, using the average value for all covariates.

Figure 4. Effect of L-Dopa on TMS Map area change by gene score. Values reflect the mean TMS map area change for each gene score group. Error bars are the SEM.

Figure 5. Example TMS maps from a low gene score participant and a high gene score participant.

Figure 6. Effect of L-Dopa on TMS Map area change by gene score. Values reflect the mean TMS map area change for each gene score group. Error bars are the SEM.

Table 1. Beta coefficients

<table>
<thead>
<tr>
<th>Gene Score</th>
<th>Beta</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>-11.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Gene Score*Drug</td>
<td>5.7</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Table 2. Classification and frequency of alleles.

<table>
<thead>
<tr>
<th>Allele</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/A</td>
<td>9/9</td>
</tr>
<tr>
<td>A/G</td>
<td>9/10</td>
</tr>
<tr>
<td>G/G</td>
<td>10/10</td>
</tr>
</tbody>
</table>

Conclusions
● Higher dopamine gene scores are associated with greater motor skill acquisition.
● Overall, L-Dopa enhanced learning.
● The effects of L-Dopa on learning varied in relation to the dopamine gene score.
● The gene score improved the ability to predict which subjects would benefit from L-Dopa.

Acknowledgments
This study was supported by the American Heart Association, and grants NS058755 and 5M01RR00827-29 from NIH. We thank the following institutions for their support: the University of California, Irvine, the University of California, Los Angeles, the University of California, San Francisco, the University of California, San Diego, and the University of California, Davis. We also thank the following organizations for their support: the American Heart Association, the National Institute of Neurological Disorders and Stroke, the National Institute of Aging, the National Institute of Mental Health, the National Institute of Biomedical Imaging and Bioengineering, the National Institute of General Medical Sciences, the National Institute of Allergy and Infectious Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Nursing Research, the National Cancer Institute, the Office of the Director, and the National Institute of Standards and Technology. This project was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1TR000154.