PRIORITY COMMUNICATION

Dopamine Receptor D4 Polymorphism Predicts the Effect of L-DOPA on Gambling Behavior

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Background: There is ample evidence that a subgroup of Parkinson's disease patients who are treated with dopaminergic drugs develop certain behavioral addictions such as pathological gambling. The fact that only a subgroup of these patients develops pathological gambling suggests an interaction between dopaminergic drug treatment and individual susceptibility factors. These are potentially of genetic origin, since research in healthy subjects suggests that vulnerability for pathological gambling may be linked to variation in the dopamine receptor D4 (DRD4) gene. Using a pharmacogenetic approach, we investigated how variation in this gene modulates the impact of dopaminergic stimulation on gambling behavior in healthy subjects.

Methods: We administered 300 mg of L-dihydroxyphenylalanine (L-DOPA) or placebo to 200 healthy male subjects who were all genotyped for their DRD4 polymorphism. Subjects played a gambling task 60 minutes after L-DOPA administration.

Results: Without considering genetic information, L-DOPA administration did not lead to an increase in gambling propensity compared with placebo. As expected, however, an individual's DRD4 polymorphism accounted for variation in gambling behavior after the administration of L-DOPA. Subjects who carry at least one copy of the 7-repeat allele showed an increased gambling propensity after dopaminergic stimulation.

Conclusions: These findings demonstrate that genetic variation in the DRD4 gene determines an individual's gambling behavior in response to a dopaminergic drug challenge. They may have implications for the treatment of Parkinson's disease patients by offering a genotype approach for determining individual susceptibilities for pathological gambling and may also afford insights into the vulnerability mechanisms underlying addictive behavior.

Key Words: Decision making, dopamine, impulse control disorder, Parkinson's disease, pathological gambling, pharmacogenetics

A challenging question in the fields of neuroscience and addiction research is why some individuals are more vulnerable to addictive disorders than others. A possible solution for this question lies in pharmacogenetic studies that investigate how genetic variation leads to a differential drug response. Several lines of evidence link the dopaminergic system to impulse control (1) and substance addiction (2,3), as well as to nonsubstance addictions such as pathological gambling (4). Existing evidence for the latter comes from clinical research describing the development of pathological gambling in Parkinson's disease after initiation of dopaminergic drug treatment (5–7). However, not all individuals with Parkinson's disease are at risk of developing pathological gambling during dopaminergic treatment. The fact that only a subgroup of these patients develops pathological gambling suggests an underlying vulnerability (8), possibly mediated by genetic factors. Support for this notion derives from research in healthy subjects suggesting that genetic vulnerability for pathological gambling may be linked to variation in the dopamine receptor D4 (DRD4) gene (9,10). The DRD4 gene contains a highly polymorphic region within its third exon, also referred to as the DRD4 exon III variable tandem number repeat polymorphism (DRD4 polymorphism) (11). The polymorphism is an imperfect repeat translated into 16 amino acids found to be present 2 to 11 times in different alleles of the DRD4 gene (12). Presence of the 7-repeat (7R) allele has been associated with pathological gambling and other impulse control disorders such as attention-deficit/hyperactivity disorder (ADHD) (13–15). Furthermore, the 7R allele has been associated with poor performance on laboratory measures of impulse control among individuals with ADHD as well (16,17). Finally, poor impulse control and ADHD are both associated with pathological gambling (18,19).

These lines of evidence suggest that genetic variation in the DRD4 gene might determine an individual's behavioral response to a dopaminergic drug challenge. Up to now, no study has yet investigated how the interaction of genetic factors with the administration of a dopaminergic drug affects gambling behavior. This can be achieved by using a pharmacogenetic approach.

Building on the above-mentioned evidence, we hypothesized that the administration of a dopaminergic drug has a differential effect on gambling behavior depending on variation in the DRD4 gene. To explore a gene-drug interaction on gambling behavior systematically, we used healthy subjects to avoid the confounding effects of Parkinson's disease. We used L-dihydroxyphenylalanine (L-DOPA) versus placebo administration to investigate how the presence or absence of the 7R allele determines the impact of dopaminergic stimulation on gambling behavior measured in the laboratory. We hypothesized that subjects who carry a 7R allele would show increased gambling propensity in response to the administration of a dopaminergic drug.

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Methods and Materials

Subjects

A total of 205 healthy young male subjects of Caucasian origin with mean (±SD) age of 23.5 years (±3.6) took part in a double-blind, placebo-controlled experiment that the local ethics committee had previously approved. Standardized interviews, under supervision of a neurologist (P.S.S.), revealed that the subjects had no significant general psychiatric, medical, or neurological disorders. They were included in the study after having provided written informed consent. Three subjects reported nausea and their data were discarded. Two subjects were excluded from further analysis because they did not understand the instructions.

Experimental Procedure

All experiments took place at the experimental laboratory of the Institute for Empirical Research in Economics in Zurich, Switzerland, where a total of 10 sessions were conducted. All sessions started at 8:30 AM; an average of 20 subjects per session participated simultaneously. Subjects were randomly assigned to receive either a single dose of 300 mg of madopar (consisting of 300 mg L-DOPA and 75 mg benserazide, a peripheral L-dihydroxyphenylalanine-decarboxylase inhibitor; in the text further referred to as L-DOPA) or a placebo. They then received a standardized meal and 100 mL of water. Twelve hours (i.e., on the evening before the behavioral experiment) and 30 minutes before L-DOPA administration, subjects were required to ingest 10 mg of domperidone to avoid possible peripheral dopaminergic side effects such as nausea and orthostatic hypotension. After subjects read the instructions, we checked whether they understood the rules of the gambling task by having them answer control questions. All but two of the subjects answered these control questions correctly. Subjects were also asked to rate their subjective feelings using visual analogue scales to assess potential side effects of L-DOPA treatment.

Subjects performed 40 trials of the gambling task 60 minute after L-DOPA intake, when the plasma level of L-DOPA reached its peak, as a separate pharmacokinetic study involving 10 healthy male subjects previously determined (Figure 1). The task was implemented in z-Tree software (University of Zurich, Zurich, Switzerland) and presented on computer screens (20). After the gambling task, subjects also filled out personality questionnaires that assessed measures of impulsivity, i.e., a subscale of the Barratt Impulsivity Scale-II (BIS-II), which measures motor impulsivity ("acting without thinking") (21), and the Tangney *et al.* (22) Self-Control Scale. Subjects were also asked to perform a mouthwash to collect buccal epithelial cells for the preparation of DNA. Subjects received a flat fee of Swiss Frank (CHF) 100 (CHF 1.00 ~ $.90) for participation in the experiment. In addition, they received a variable payoff for the gambling task, in which each point was worth CHF .25. Each subject received payment in private at the end of the experiment, based on the points earned.

Genotyping

Subjects were instructed to rinse their mouths with 25 mL of mouthwash and to spit the fluid into sterile 50 mL polypropylene tubes. The samples were stored at 4°C if they could not be processed within 2 hours of collection. DNA from these samples was extracted and amplified (Genetica, Zurich, Switzerland).

The following procedure was performed: the tubes were centrifuged at 1600 relative centrifugal force/g using a Hettich

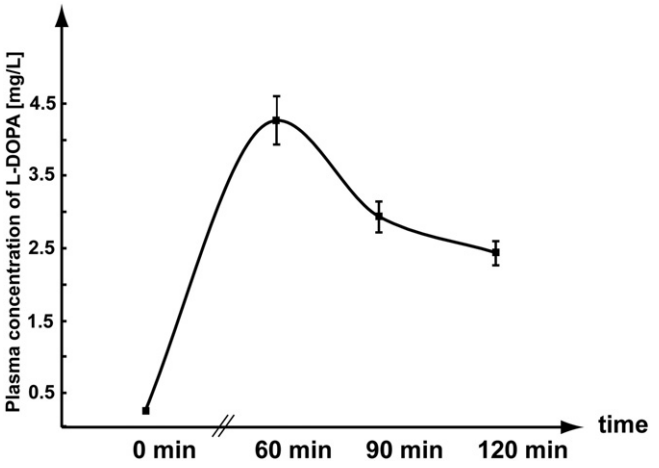

Figure 1. Pharmacokinetics of L-DOPA concentration (mg/L) in serum (y axis) after oral administration of 300 mg of Madopar to 10 healthy young men. X axis indicates time in minutes after drug administration. Error bars indicate ± one standard error of the mean. L-DOPA, L-dihydroxyphenylalanine.

Rotina 46 S centrifuge (Hettich AG Laborapparate, Baech, Switzerland). The remaining pellet was resuspended in 180 μL Tissue Lysis Buffer (Qiagen AG, Hombrechtikon, Switzerland) and proteinase K was added (30 μL of a 20 mg/mL stock solution). This solution was hybridized for 3 hours at 58°C. The solution was then stirred and transferred into a 2-mL test tube. The tube was centrifuged for 1 minute at 10,000 rpm. A standard EZ1 DNA extraction was performed from this mixture using the BioRobot EZ1 following the QIAamp Blood Kit Protocol (obtained from Qiagen AG). The obtained DNA concentration was then measured using a photometer (Nanodrop, Fisher Scientific, GmbH, Schwerte, Germany). The exon III repeat region of the DRD4 receptor was characterized by polymerase chain reaction (PCR) amplification employing the following primers:

F5′-TTCCTACCCTGCCCGCTCATGCTGCTGCTCATCTGG-3′
R5′-ACCACCACCGGCAGGACCCTCATGGCCTTGCGCTC-3′

The PCRs were performed using 5 μL Master Mix (Thermo Scientific, Waltham, Massachusetts), 2 μL primers (.5 μmol/L), .6 μL magnesium chloride (Mg/Cl2) (2.5 mmol/L), .4 μL dimethyl sulfoxide 5%, and 1 μL of water to total of 9 μL total volume and an additional 1 μL of genomic DNA was added to the mixture. All PCRs were performed on a Biometra T1 thermocycler (Biometra, Göttingen, Germany). The PCR conditions were as follows: preheating step at 94.0°C for 5 minutes, 34 cycles of denaturation at 94.0°C for 30 seconds, reannealing at 55°C for 30 seconds, and extension at 72°C for 90 seconds. The reaction proceeded to a hold at 72°C for 5 minutes. The reaction mixture was then electrophoresed on a 3% agarose gel (AMRESCO, Solon, Ohio) with ethidium bromide to screen for genotypes.

Subject Grouping According to the DRD4 Polymorphism Genotype

One approach reported in the literature is to group subjects according to the two most frequent genotypes revealed in the sample (Table 1). The 4/4 and the 4/7 genotypes account for most of the observed genotypes (64% and 20%, respectively) at a global level (12) and in our sample (47.5% and 21%, respectively). We thus compared a group of subjects who are homozygous for the 4-repeat (4R) allele (4/4 homozygotes, $n = 95$) with

Table 1. Genotype Frequencies for the Dopamine Receptor D4 Exon III Variable Number Tandem Repeat Polymorphism, Sorted According to Frequency

Genotype	Number of Subjects	Frequency
4/4	95	47.5%
4/7	42	21.0%
2/4	32	16.0%
3/4	13	6.5%
2/7	5	2.5%
7/7	5	2.5%
2/2	2	1.0%
3/7	2	1.0%
4/5	2	1.0%
2/5	1	.5%
3/3	1	.5%
Total	200	100%

a group of subjects who carry a 4R and a 7R allele (4/7 heterozygotes, $n = 42$).

An alternative approach reported in the literature is to group subjects according to the presence or absence of the 7R allele. Accordingly, we compared a group of subjects who carry at least one 7R allele ($n = 54$) with those who do not carry the 7R allele ($n = 146$).

Gambling Task

Gambling behavior was measured by a task where the risk associated with acting increases dynamically with each additional action taken (23). In each of a total of 40 trials, subjects were presented with an array of 10 closed boxes on a computer screen. In a sequence from left to right, subjects had the possibility of opening box after box. They were told that nine boxes contained monetary rewards ("win boxes"), while one box ("loss box") contained a "devil" that would make them lose all the money they had collected in the current trial, simultaneously ending that trial. Opening a win box was associated with a payoff of one point (= CHF .25). After opening a win box, subjects had to decide whether they wanted to open another box or to terminate the trial and keep all the points they had won in the trial. Once the loss box was opened, subjects earned nothing for that trial. The devil was randomly assigned to one of the 10 boxes in each trial; thus, no learning was involved in this task. The average number of boxes opened in those trials that subjects voluntarily terminated served as an indicator of a subject's level of gambling behavior.

Measures of Drug-Related Side Effects

Visual analogue scales were recorded before substance administration and then immediately before the gambling task was performed. Items in the scale were alert/drowsy, calm/excited, strong/feeble, muzzy/clear-headed, well coordinated/clumsy, lethargic/energetic, contented/discontented, troubled/tranquil, mentally slow/quick-witted, tense/relaxed, attentive/dreamy, incompetent/proficient, happy/sad, antagonistic/amicable, interested/bored, and withdrawn/gregarious. These dimensions were presented as 10 cm lines on a computer screen and subjects marked their current states on each line with a mouse click. In line with previous studies (24,25), the factors alertness, contentedness, and calmness were calculated from these items.

Data Analysis

We examined the interaction of L-DOPA (with a binary indicator for L-DOPA indicating whether the subject received L-DOPA [= 1] or placebo [= 0]) and DRD4 genotype (with a binary indicator for 4/7 genotypes [= 1] or 4/4 genotypes [= 0]) in a univariate analysis of variance on the average number of boxes opened in the gambling task as the dependent variable. Post hoc comparisons between genotypes and drug treatment groups were made using Student *t* tests. We also compared genotype and drug treatment group differences in self-reported impulsivity and self-control and drug-related side effects using Student *t* tests. The relationship between self-report measures and genotype and between self-reports and gambling behavior were examined using linear correlation analyses.

Effect sizes are reported as Cohen's d ($d = .2$: small effect size, $d = .5$: medium effect size, $d = .8$: large effect size [26]). Analyses were performed using Stata 10.0 (Stata Corporation, College Station, Texas).

Results

Pharmacogenetic Effect on Gambling Behavior

In the gambling task, participants opened 6.05 out of 10 boxes on average (SD = .82). Analysis of variance revealed no increase in gambling behavior associated with L-DOPA compared with placebo administration [$F(1,198) = .17$, p = ns] (Figure 2A). As expected, however, L-DOPA administration differed with respect to its impact on gambling behavior as a function of the subjects' DRD4 polymorphism. We found a significant main effect of genotype [$F(1,133) = 4.76$, $p < .05$] and a significant interaction between drug treatment and genotype on gambling behavior [$F(1,133) = 5.43$, $p < .05$] (Figure 2B). Specifically, we observed increased gambling in subjects who carry the 4/7 genotype and who received L-DOPA but not in those who received L-DOPA and who carry the 4/4 genotype [$t(64) = 3.27$, $p < .01$; Cohen's $d = .90$]. In contrast, no genotype effect on gambling behavior was observed in the placebo group [$t(65) = .11$, p = ns]. Furthermore, we found a significant positive effect of drug on gambling behavior in the 4/7 genotype group [$t(40) = 2.14$, $p < .05$; Cohen's $d = .32$], which was not present in the 4/4 genotype group [$t(93) = 1.25$, p = ns].

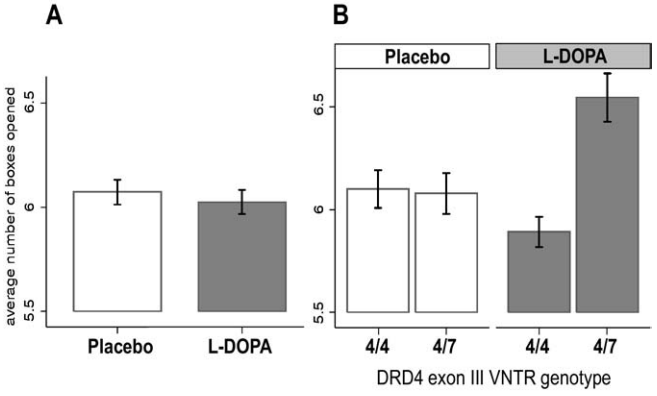

Figure 2. Gambling behavior as indexed on the y axis by the average number of opened boxes over all trials that were ended by the subject voluntarily. Error bars indicate ± one standard error of the mean. **(A)** No increase in gambling behavior was observed following L-DOPA compared with placebo administration. **(B)** Increased gambling behavior was observed in subjects who carry the 4/7 genotype of the DRD4 exon III variable number tandem repeat polymorphism and who received L-DOPA but not in those who carry the 4/4 genotype. This genotype effect on gambling behavior was absent in the placebo group. DRD4, dopamine receptor D4; L-DOPA, L-dihydroxyphenylalanine; VNTR, variable number tandem repeat.

The alternative grouping according to the presence or absence of the 7R allele yielded similar results. Analysis of variance revealed again a significant interaction between drug treatment and genotype on gambling behavior [$F(1,196) = 4.73$, $p < .05$] but no significant main effect of allele groups [$F(1,196) = 2.52$, p = ns]. In the L-DOPA group, 7R allele carriers opened significantly more boxes than those who do not carry the 7R allele [$t(97) = 2.67$, $p < .01$; Cohen's $d = .63$]. Again, there was no genotype effect present in the placebo group [$t(99) = .42$, p = ns]. Finally, there was a trend for a significant differential effect of drug in the 7R allele carriers [$t(52) = 2.14$, $p < .10$] but not in those who do not carry a 7R allele [$t(144) = 1.3605$, p = ns].

Side Effects of L-DOPA

The observed effect on gambling behavior was not attributable to side effects of drug administration. There were no significant drug treatment group differences on measures of side effects at baseline and before the gambling task was performed (all $p > .10$), except for the factor alertness, for which a trend for a significant positive effect of L-DOPA administration was revealed [$t(198) = 1.68$, $p < .10$]. However, the interaction term between drug treatment and genotype (4/7 vs. 4/4) on gambling behavior remains significant if we control for this factor [$F(1,132) = 5.43$, $p < .05$]. Moreover, when subjects were grouped according to the presence or absence of the 7R allele, the interaction term also remains significant if we control for alertness [$F(1,196) = 4.66$, $p < .05$].

Impulsivity and Self-Control

To assess whether the observed differential drug effect on gambling behavior could be attributed to preexisting trait differences in subjects' propensity to act impulsively, we measured subjects' self-reported impulsivity and self-control capacity using self-report questionnaires. However, we found no differences across drug treatment groups for either impulsivity [$t(198) = .34$, p = ns] or self-control [$t(198) = .32$, p = ns]. In addition, the interaction term between drug treatment and genotype on gambling behavior remains significant if we control for impulsivity and self-control [$F(1,131) = 5.58$, $p < .05$]. Finally, measures of impulsivity and self-control neither correlated with gambling behavior [$r(198) = -.02$, p = ns; $r(198) = -.03$, p = ns, respectively] nor with genotype [$r(135) = -.07$, p = ns; $r(135) = -.04$, p = ns, respectively].

Discussion

This study is the first to show that individual genetic predispositions predict the effect of the administration of a dopaminergic drug on gambling propensity in a nonclinical sample. Specifically, we found that L-DOPA administration was associated with increased gambling behavior in carriers of the 4/7 genotype of the DRD4 polymorphism but not in carriers of the 4/4 genotype. These findings highlight the importance of including genetic information in pharmacological intervention studies investigating behavior and might explain the failure of previous attempts to find an effect of dopaminergic stimulation on gambling behavior (27).

Previous association studies have linked the 7R allele of the DRD4 polymorphism with higher self-reported novelty seeking (28) and laboratory measures of impulsivity (29) in the healthy population. These findings suggest an important role of the D4 receptor in the modulation of inhibitory control processes. Poor inhibitory control has been discussed as a critical vulnerability marker for drug abuse in humans (30), drug addiction severity (31), and predicted high doses of cocaine self-administration in rats (3). Our findings suggest that the relative ability for impulse control as determined by the DRD4 polymorphism genotype might be predictive of whether an individual is able to avoid excessive drug intake after exposure to a dopaminergic drug.

A limitation in the present study is that we cannot stringently exclude the possibility that genotype-dependent differences in peripheral D4 receptors also influence the behavioral effect in part. For example, it is known that peripheral dopamine receptors play a role in the regulation of blood pressure (32), which has been shown to be associated with impulsivity (33). Other research shows that the long alleles of the DRD4 exon III polymorphism are associated with increased systolic blood pressure in individuals aged over 60 (34). To counteract the potential influence of L-DOPA on blood pressure regulation, e.g., orthostatic hypotension, subjects were premedicated with the peripheral D2 antagonist domperidone (35). Moreover, subjects were all young (age: 23.5 years [±3.6 SD]) and the DRD4 polymorphism has not been shown to be related to blood pressure in their age group (34). Finally, and most importantly, the fact that L-DOPA was administered in combination with the peripheral DOPA-decarboxylase inhibitor benserazide, which inhibits the conversion of L-DOPA to dopamine in the periphery, further diminishes the likelihood that peripheral DRD4 receptors mediate the observed behavioral effects.

The finding that gambling behavior was not related to self-reported measures of impulsivity and self-control is consistent with other studies that also failed to observe relations between self-reports and behavioral measures (36,37). The lack of such a correlation might be due to the fact that self-report measures rely on subjects' self-perceptions that may not accurately reflect their behavior, whereas performance on a behavioral task is both less sensitive to biased self-perceptions and less influenced by social desirability (38). In line with previous data (29), we found a nonsignificant association between self-reported impulsivity and the DRD4 polymorphism; this is possibly due to the fact that the personality construct assessed here might be a less relevant endophenotype of the polymorphism examined (39). Moreover, our results are in line with findings of a recent meta-analysis suggesting that the reported associations between the DRD4 polymorphism and approach-related personality traits in general is highly heterogeneous (40).

Although recent studies found an association between the DRD4 polymorphism and behavior in financial investment tasks (41,42), we failed to observe a similar relationship in our placebo group. However, future large-scale studies are necessary to confirm the association reported between the DRD4 polymorphism and risk-taking behavior.

In summary, our results are of clinical relevance for Parkinson's disease patients, as the individual DRD4 polymorphism genotype might assist in predicting the probability of developing an impulse control disorder, such as a pathological gambling. On a more general basis, our findings show that a pharmacogenetic approach is promising for the understanding of the role of the dopaminergic system in human decision making.

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