Research Paper

Decision-Making and Impulse-Control Disorders in Parkinson's Disease: Influence of Dopaminergic Treatment

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Abstract

Objective: Dopaminergic treatment is proved to ameliorate motor deficits in Parkinson's disease (PD); however, it could have negative effects on behavior and cognition, including impulse controlling and decision-making. We aimed (1) to investigate the decision-making and impulse-control disorders (ICDs) of PD patients and their correlations with sociodemographical and clinical variables, dopaminergic treatment in particular, and (2) to determine the relation of decision-making with ICDs. **Methods:** The sample of 39 patients with PD and 37 healthy controls underwent cognitive tests and the task which analyzed decision-making (Iowa Gambling Task [IGT]). Besides assessing motor and nonmotor symptoms of patients with PD, ICDs were also scanned using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease. **Results:** Although patients with PD performed similarly to healthy controls on IGT, decision-making profile in PD related to clinical variables: dopaminergic treatment and duration of illness. In addition to this younger age of onset, higher dose of dopamine agonists, longer duration of illness, and impaired decision-making were together accounted for a substantial amount of variance in impulsive behaviors. **Conclusions:** Dopaminergic medication likely contributes to the impairment in decision-making, which may be the underlying mechanism of ICDs. Further studies will be necessary to understand the potential implications of this finding.

Keywords: *Decision-making, dopamine, impulse-control disorders, Parkinson's disease*

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Introduction

Dopaminergic treatment improves motor symptoms in Parkinson's disease (PD), but it may also cause nonmotor symptoms that include a set of complex disinhibitory psychomotor pathologies. These pathological behaviors include impulse-control disorders (ICDs) such as pathological gambling, hypersexuality, compulsive buying, compulsive eating, and other repetitive or compulsive behaviors such as punding, walkabout, and dopamine dysregulation syndrome.[1]

Although the prevalence of ICDs in PD is an issue of debate, evidence suggests that these compulsive behaviors are seen more frequently in patients with young-age onset and high novelty-seeking personality traits. Other risk factors of ICDs include male sex, a pre-PD history of ICD symptoms, personal or family history of substance abuse or bipolar disorder, severity of PD, on–off fluctuating condition, depressive mood, and lower cognitive performance.[2,3] Dopaminergic treatment, especially dopamine agonist (DA), is the most strongly associated factor to ICDs.[4] Moreover, recent studies showed decision-making[5] which includes evaluation of the potential risks or benefits of a new stimulus, integration with information about internal states and current goals, and reward-based control of behavior related to ICDs. These studies suggest that PD patients with ICDs fail to learn from negative

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consequences of their decisions and tent to intensely pay attention to immediate gains. Besides these findings, there are several real-life examples which show impaired decision-making of patients with ICDs. They can consume their financial resources by gambling or shopping, put in danger their relationships or marriages to satisfy sexual drives, or spend hours on their hobbies instead of daily responsibilities.[6] These behaviors could be a representation of misevaluation of risks and benefits.

Although impaired decision-making in PD is controversial, most of the studies revealed that PD patients show risky decision-making which is characterized by a bias toward immediate gain despite the long-term loss (see for a meta-analysis).[7] Impaired decision-making of PD patients is thought to be affected by the disease pathology and dopaminergic treatment,[8,9] rather than by cognitive functions and demographic variables.[10] Cools *et al*.[8] stated that dopaminergic medication normalizes dopamine-depleted circuits such as the dorsal striatum with a positive effect on executive functions, but at the same time, it "overdoses" relatively intact circuits such as the ventral striatum with negative effects on reversal learning. Frank *et al*.[11] found that PD patients who did not receive any dopaminergic medication experienced difficulties on reversal learning from positive consequences of a decision and they tended to learn from negative feedbacks of a decision. More importantly, the authors showed that dopaminergic medication reverses this situation, as patients who were on a dopaminergic treatment were better at learning from positive feedbacks, whereas they usually fail to avoid decisions causing negative outcomes. At this point, these reversal learning deficits and risk-taking behaviors could be thought of as a possible contributing mechanism for the emergence of ICD in PD patients.[6,12]

Although both decision-making and ICDs have been studied often in previous researches on PD, the nature of the relation between these two fields remains unclear. There are also a few studies investigating the role of dopaminergic treatment on decision-making and ICDs. In this respect, our study will provide a basis for the relationship between ICDs and decision-making abilities and the effect of dopaminergic treatment on these two fields. Taking this into account, we aimed (1) to compare the performance of decision-making between PD patients and healthy controls, (2) to scan impulsive behaviors in PD, and (3) to determine the relation of the ability of decision-making with impulsive behaviors in PD.

Methods

Participants

The research protocol was approved by the Ethics Committee of the Dokuz Eylul University. All the participants were presented with oral and written information about the research procedures, and informed consent was received from each participant.

Thirty-nine PD patients were prospectively recruited from a sample of outpatients who are monitored with PD diagnostic criteria in the Movement Disorders Clinic at Dokuz Eylul University. Two neurologists specializing in movement disorders confirmed the diagnosis of idiopathic PD. Patients' medical histories were controlled, and they were screened for global dementia and major depression using the Mini-Mental State Examination (MMSE)[13] and Hamilton Depression Rating Scale (HDRS),[14] respectively. Patients who scored under 24/30 points on the MMSE and over 14/53 on the HDRS were excluded. Patients were also excluded if they had a history of neurological or psychiatric conditions known to compromise cognitive functioning such as stroke, traumatic brain injury, and psychotic disorders. Although 27 patients received combination therapy (levodopa + DA), 7 patients were taking just levodopa and 5 patients were on a DA. Patients were tested only "on" medication. Our sample also consisted of 37 healthy controls whose age and educational status matched those of the patients with PD in order to compare the ability of decision-making with the patient group. Healthy controls were recruited through poster advertisement in the local community. They met the same exclusion criteria as the patients, and they were interviewed and excluded if they endorsed a neurological or psychiatric disease, or had lower scores on MMSE and HDRS.

Parkinson's disease evaluation

Motor status and disease severity were evaluated with the Unified PD Rating Scale and the Hoehn and Yahr Scale. Nonmotor symptoms, on the other hand, were assessed using the Nonmotor Symptoms Scale for PD,[15] which contains 30 items examining 9 dimensions that are cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, and miscellany dimensions.

Patients were just scanned for symptoms of ICDs at any stage of their disease, by the utilization of an adapted version of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP).[1] This questionnaire screens four ICDs (gambling, sexual, buying, and eating behaviors), compulsive medication use, and related behaviors (punding, hobbyism, and walkabout). The total score of QUIP was analyzed.

Medication type and daily dosage were recorded, and levodopa equivalent daily doses were calculated based on the formula which used in the study of Weintraub

et al.,[2] as follows: 100 mg of levodopa = 130 mg of levodopa in controlled-release form = 77 mg levodopa with entacapone = 1 mg pergolide = 1 mg pramipexole = 5 mg ropinirole = 10 mg bromocriptine. Other PD medications (e.g., anticholinergics and monoamine oxidase inhibitors) which are not associated with ICDs were not analyzed.

Decision-making task and neuropsychological assessment

All PD patients and healthy controls were subjected to standardized neuropsychological tests and decision-making task. Neuropsychological assessment followed a fixed sequence and was completed over a period of 60 min. The global cognitive function was assessed by the MMSE test and semantic (category) verbal fluency.[16] Verbal memory was examined by the Öktem Verbal Memory Processes Test which was developed based on the Rey Auditory Verbal Learning Test.[17] Scores of immediate memory, learning, and delayed free recall were analyzed in this study. The Trail Making Test (TMT)-A Part was applied to evaluate basic attention and motor speed, while the TMT-B Part was used to assess executive functions including complex attention, planning, set-shifting, and inhibition abilities.[18]

Decision-making abilities of patients were evaluated with the computerized version of the Iowa Gambling Task (IGT).[19] The mentioned task includes four decks of cards: two of them disadvantageous (high gains and unpredictable higher penalties) and the other two advantageous (small gains and lower penalties). In the task, the participants are asked to win much as money as possible and similarly to avoid losing money as much as possible. After turning each card, the participant receives a reward in play money; however, after turning some cards, participants were required to pay a penalty in addition to a reward. The task ends automatically after the participant chooses 100 cards. A net IGT score is calculated by subtracting the number of cards chosen from the disadvantageous decks (A and B) from the number of cards chosen from the advantageous ones (C and D). In this study, IGT performance was analyzed conventionally by dividing the task into five blocks of 20 consecutive card selections (e.g., block 1 = cards 1–20, block 2 = cards 21–30, etc.), and net scores of these five blocks were computed.

Statistical analysis

Data were analyzed with SPSS version 21.0 (SPSS, Chicago, IL, USA). For continuous variables, the normality of distribution was explored with the Shapiro–Wilk test. Because our data were normally distributed, we analyzed our data using parametric tests. To compare variables between patients and healthy controls, we applied the Chi-square test for categorical variables and independent samples *t*-test for independent continuous variables. IGT was analyzed with a 5 × 2 mixed model analysis of variance (ANOVA) with the between-subject groups (patients with PD-healthy controls) and the within-subject factor condition (5 blocks of IGT). To determine the relationship between continuous variables, we used Pearson's correlation analyses. In addition to the correlational analysis, we conducted a linear multiple regression model to test whether clinical variables and performance of IGT contributed variance to impulsive and related behaviors. $P < 0.05$ (two-tailed) was set as the significance threshold for all the tests.

Results

Our results showed that patients with PD and healthy controls did not differ in age, education years, and gender ($P > 0.05$). Descriptive statistics for sociodemographical and clinical variables and scores of cognitive measures are shown in Table 1.

Decision-making

According to the mixed model ANOVA which was conducted to statistically compare the performance of PD patients with healthy controls across IGT blocks [Graph 1], there was no significant difference between groups or within groups and no significant interaction ($P > .05$).

As we expected, no relationship was found between decision-making and demographic data, including age and years of educations. On the other hand, some clinical data were found as related to IGT performance among patients with PD. Although no correlations were observed between the severity of motor/nonmotor symptoms, age of onset, and IGT performance, duration of disease was found to be significantly correlated with the second block ($r = -0.34$ $P = 0.04$) and the third block in a negative way ($r = -0.35$, $P = 0.04$). Furthermore, the total daily dose of DA was found related to the third block ($r = -0.52$, $P < 0.001$) and the forth block in a negative way ($r = -0.39$ $P = 0.02$), which means that as the dose of DA increases, the performance of decision-making decreases. Correlation analyses indicated no relationship between IGT performance and cognitive test scores which were evaluated by TMT, RALT, and verbal fluency tests.

Impulsive-compulsive behaviors

In this study, we scanned for patients' symptoms of ICDs at any stage of their disease; however, 4 of 37 patients have acute symptoms of ICD. Because of this small size of this group, we did not analyze it as a separate group.

Table 1: Summary of participants

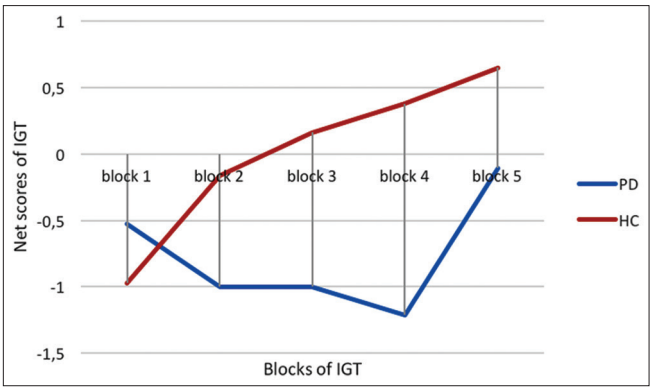
	PD (*n*=39)	HC (*n*=37)	*P*
Men, % (*n*)	79% (31)	76% (28)	0.79*
Women, % (*n*)	21% (8)	24% (9)	
Age, years	65.9±7.3	64.4±8.0	0.43
Education, years	10.7±4.4	10.7±4.4	0.98
Age of onset, years	57.7±8.9	-	
Disease duration, years	7.8±4.3	-	
UPDRS - motor	11.6±6.1	-	
Hoehn and Yahr stage (range, 0-5)	1.9±0.6	-	
Total NMS	8.9±3.5	-	
L-dopa daily dose, mg/d	424.3±300.3	-	
Agonist LEDD[a], mg/d	273.2±201.7	-	
Total LEDD[b], mg/d	697.6±289.9	-	
TMT-A duration	75.5±44.6	57.1±32.4	0.049
TMT-B duration	180.5±87.5	135.7±76.7	0.025
Verbal fluency	17.6±4.3	21.1±4.7	0.002
VMPT immediate recall	3.7±1.4	5.4±2.1	0.000
VMPT learning	85.4±21.1	104.9±16.4	0.000
VMPT delayed recall	10.0±2.5	10.9±2.4	0.139

P values according to independent samples *t*-test were reported, *Chi-square test was applied, [a]Agonist LEDD was calculated only from doses of dopamine agonists, [b]Total LEDD was calculated as the dose of L-dopa plus the doses of dopamine agonists multiplied by theoretical equivalence (see text). Except where indicated otherwise, data are mean SD (range) values. PD: Patients with Parkinson's disease, HC: Healthy controls, UPDRS: Unified Parkinson's Disease Rating Scale, NMS: Nonmotor scale, LEDD: Levodopa equivalent daily dose, TMT: Trail Making Test, VMPT: Verbal Memory Processes Test, SD: Standard deviation

The mean values of impulse-control and related behavior symptoms were as follows: compulsive gambling –0.18 (standard deviation [SD] = 0.51), compulsive sexual behavior –0.34 (SD = 0.58), compulsive buying –16 (SD = 0.49), compulsive eating –08 (SD = 0.27), and related behavior –39 (SD = 0.64). Finally, the mean of total score of QUIP was found to be 1.32 (SD = 1.57).

The correlational analysis pointed out that age of onset (r = −0.41, P < 0.01) and duration of illness (r = 0.35, P =0.03) significantly correlated with QUIP total score. Moreover, a positive correlation was observed between the daily dose of DA and QUIP total score (r = 0.35, P = 0.03). There were no significant correlations between cognitive test scores and QUIP scores.

According to the analyses focusing on the relation of ICD behavior with decision-making, QUIP total score was found to be correlated with only the third block of IGT (r = −0.32, P = 0.04). In addition to this correlational analysis, we conducted a linear multiple regression model to test whether clinical variables and decision-making performance contributed variance to impulsive and related behaviors. The predictor variables for ICD behaviors were as follows: age of onset, duration of illness, daily dose of DA, and the performance of IGT-third block. A regression model with these predictors corresponded to 27% of the variance in compulsive behaviors to the prediction of compulsive behaviors (F (4) = 2.71, P = 0.04).



Graph 1: Performance of the Iowa Gambling Task. PD: Patients with Parkinson's disease, HC: Healthy controls, IGT: Iowa Gambling Task

Discussion

Consistent to our result, some previous studies[9,20] reported that patients with PD perform similarly to healthy controls, while others[10,21-23] indicated an impaired decision-making performance in PD. Besides this, we found that decision-making performance among patients differed according to the daily dose of DA and duration of illness.

Although some recent studies[24] suggested that dopaminergic medication improves decision-making performance and task-based learning rate, others showed the negative effect of dopaminergic treatment on decision-making.[25] There were also reports suggesting that patients in "on" medication state showed a risky decision-making pattern compared to patients who were in "off" state.[7] It seems that dopaminergic treatment adversely affects the performance in tasks associated with the orbitofrontal loop such as IGT, while the performance associated with the dorsolateral loop improves.[26] DA increases positive reward prediction errors (better than expected) which is related to striatal regions; at the same time, it decreases reward processing in the lateral orbitofrontal cortex.[27,28] Accordingly, our result indicating the association of longer duration of illness with impaired IGT performance may be a result of the dopaminergic overstimulation of orbitofrontal loop which is less affected by dopaminergic cell loss. On the other hand, Evens *et al*.[7] failed to find an evidence, indicating that impaired decision-making in PD was related to dopaminergic medication dose. A recent study[29] also showed a reduced volume of lateral orbitofrontal cortex to be correlated with the lower performance of IGT in PD, but there was no

link between orbitofrontal volume and dopaminergic medication dose. These controversial findings should be carefully reviewed in future studies.

We found that IGT performance of patients with PD was not related to cognitive functions. Even though cognitive dysfunction in PD is considered as a cause of impaired decision-making, this hypothesis has not been fully supported by the experimental studies. Consistent with our results, studies revealed that decision-making under ambiguity is independent from cognitive functions related to the dorsolateral prefrontal cortex.[22,23]

In our study, we also scanned ICDs of PD patients and investigated their correlations with sociodemographical and clinical variables. Our results, which were obtained in a small group of participants and may need confirmation in larger cohort studies, indicated that the younger age of onset, longer duration of illness, and higher dose of DA are related to ICDs.[2,3,27] On the other hand, previous studies showed that being male, depressive mood, longer duration of PD, severity of motor symptoms, lower cognitive performance, and prior history of ICDs are risk factors.[2]

Consistent with our findings, some studies pointed out a possible link between impaired decision-making and compulsive behaviors.[26,30] Rossi *et al*.[5] have found PD patients with pathological gambling performed on IGT significantly worse than PD patients without pathological gambling, indicating a poorer ability to learn from negative outcome while making decisions. In addition to this, PD patients without clinically apparent ICDs could also tend to make impulsive decisions.[31] It has been stated that the emergence of impulsive behaviors in PD could be a result of modulation of reward sensitivity by changing the function of "hot"-limbic/"cool"-executive system.[32] Neuroimaging studies[33,34] also pointed out that ICDs and decision-making in PD share a common neural mechanism.

In contrast to levodopa, DA tonically stimulates specific dopaminergic receptor subtypes and disrupts reversal learning due to inhibition of the phasic release of dopamine, which is the major component of learning signaling.[11] Although DA treatment increases the tendency to overweight good outcomes through D1 signaling, it may prevent pauses in D2 signaling and, consequently, deteriorate the negative reinforcing effect of bad outcome which could promote reward-seeking behaviors and impulsivity.[28] Moreover, dopaminergic stimulation causing postsynaptic changes and an enhancement of synaptic efficacy is associated with the on–off fluctuating in PD. These synaptic alterations appear similar to the sensitization of the limbic circuits proposed for addiction and ICDs.[35] Therefore, it can be considered that DA treatment and also longer duration of treatment may be potential developing and facilitating factors for continuity of ICDs due to their negative effects on reward-based learning and decision-making.[11,36]

This study has some limitations. First, in this current study, we scanned only ICDs anytime during PD. However, there could be a distinction between impulsive actions and impulsive choices;[34] thus, patients with active ICDs may have more severe decision-making impairments. Furthermore, the evaluation of ICDs in PD patients including different methods such as the Minnesota Impulsive Disorders Interview could provide additional information. We also did not assess the decision-making performance of patients with PD while "on" and "off" periods; however, there are inconsistent findings regarding the effects of dopaminergic medication on decision-making.[8,24,21] Therefore, future studies are needed to evaluate decision-making performance both under on and off states and focus on the modulation of dopamine dose levels by applying a repeated testing model. In general, decision-making abilities are examined under two paradigms: decision-making under ambiguity and decision-making under risk.[37] We used only Iowa Gambling Task which evaluates decision-making under ambiguity; however, adding one of the tasks of decision-making under risk such as the Cambridge Gambling Task or Balloon Analog Risk-Taking Task could provide a holistic evaluation of decision-making in PD. Finally, our sample consisted of a small group of PD patients; therefore, our study could have biases in subject selection and the results need confirmation in larger studies.

Conclusions

Although dopaminergic treatment in PD provides improvement for motor symptoms, it may cause reversal learning deficits and risky decision-making which probably trigger ICDs. Because impulsive behaviors could cause difficulties in daily life and lower psychosocial functioning, interventions to improve ICD symptoms are essential to preserve patients' functioning. Modulation of DA dosage in drug treatment and evaluation of the ability of decision-making in clinical assessment of PD patients who have ICD risk may be a resolution of ICD symptoms. Nondopaminergic treatment such as opioid antagonists that target the ventral striatum could be useful to improve ICD symptoms without worsening the motor symptoms.[33] Moreover, recent studies began to argue whether deep brain stimulation of the subthalamic nucleus which also improves

motor symptoms of PD causes behavioral disturbances including impulse controlling or not.[38] Nevertheless, the unresolved question of how dopamine affects the association between impaired decision-making and ICDs should be looked through in future studies.

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Conflicts of interest

There are no conflicts of interest.

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