Personality traits and brain dopaminergic function in Parkinson's disease

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Edited by Marcus E. Raichle, Washington University School of Medicine, St. Louis, MO, and approved September 10, 2001 (received for review June 20, 2001)

A distinctive personality type, characterized by introversion, inflexibility, and low novelty seeking, has been suggested to be associated with Parkinson's disease. To test the hypothesis that Parkinson's disease is associated with a specific dopamine-related personality type, the personality structures of 61 unmedicated Parkinson's disease patients and 45 healthy controls were examined. Additionally, in 47 Parkinson's disease patients, the dopaminergic function in the brain was directly measured with 6-[^{18}F]fluoro-L-dopa (^{18}F-dopa) positron emission tomography (PET) with MRI coregistration. The novelty-seeking personality score, supposedly associated with the parkinsonian personality, was slightly lower in the Parkinson's disease group compared with controls, but it did not have a significant relationship with ^{18}F-dopa uptake in any of the brain regions studied ($r = -0.12$ to 0.11, $P > 0.15$). The harm-avoidance personality score, associated with anxiety and depression, was clearly increased in patients with Parkinson's disease and it had a paradoxical, highly significant positive correlation with the ^{18}F-dopa uptake in the right caudate nucleus ($r = 0.53$, $P = 0.04$, Bonferroni corrected for 220 comparisons). Although the results of this study are not in disagreement with the concept of low-novelty-seeking personality type in Parkinson's disease, the personality type does not seem to be dopamine dependent. The correlation between the personality trait of harm avoidance and ^{18}F-dopa may reflect a specific feedback circuitry of neurotransmitters that is associated with negative emotionality in Parkinson's disease.

For nearly a century, it has been suggested that Parkinson's disease could be associated with a specific personality type (1). The ''parkinsonian personality'' has been described as compulsive, industrious, introverted, morally rigid, punctual, serious, stoic, and quiet (2, 3). There are studies that have indicated that Parkinson's disease patients score lower than controls on a personality trait called novelty seeking (2, 4), which, according to Cloninger's (5) theory, is the temperament trait primarily modulated by dopamine. The description of low-novelty-seeking personality type is similar to the descriptions of parkinsonian personality type in the literature (2). It has thus been hypothesized that when people approach novel stimuli, the normal pleasurable rewarding increase in dopamine is not possible in patients with Parkinson's disease and the result is less novelty seeking—the parkinsonian personality (2).

Because the risk factors for Parkinson's disease are unclear, the possibility of a distinctive parkinsonian personality is intriguing and of clinical importance. If there is indeed a premorbid, dopamine-related, low-novelty-seeking personality type in Parkinson's disease, relatively simple personality screenings could be used to evaluate individual risk for the disease. However, in a such a long-term, complex, and controversial issue as the parkinsonian personality, together with the small number of controlled studies, a publication bias is a possibility. In recent years, negative results that do not support the concept of parkinsonian personality either premorbidly or after the onset of motor symptoms have also been reported (6, 7). Moreover, earlier studies on parkinsonian personality have been based on data describing the personality in medicated patients. It is possible that the personality in medicated Parkinson's disease, because of disease progression, severe motor disability and/or long-term dopaminergic medication, does not reflect well the premorbid personality or the personality at the early stages of the disease.

Modern *in vivo* neuroimaging methods provide exceptional means to investigate human psychobiology. Recently, positron emission tomography (PET) studies have been carried out to directly investigate central dopaminergic function in relation to personality. In healthy subjects, the PET results either support (8) or do not support (9) a link between novelty seeking and dopaminergic function, or else the results provide support for an association of dopamine with other personality traits, such as harm avoidance (10), presumably associated with the serotonergic system and depression, or a personality trait that involves personal detachment (9, 11, 12). In patients with Parkinson's disease, Menza and colleagues (13) have reported an association between novelty seeking and dopaminergic function, a finding that is in line with the concept of a dopamine-dependent parkinsonian personality.

To date, all published PET studies focusing on dopamine and personality have been relatively small (9–24 subjects per study), and in the only study with Parkinson's disease patients, the sample was 9 medicated patients (13). If the PET results in Parkinson's disease could be replicated in an independent study with a large number of unmedicated patients, it would provide strong support for the concept of a dopamine-dependent, low-novelty-seeking parkinsonian personality. On the other hand, if there is no link between novelty seeking and dopamine in Parkinson's disease, the entire hypothesis of the parkinsonian personality needs to be re-evaluated. In addition, although the frontal lobe may be important in the regulation of introversion/extraversion-related personality (14), so far no attempts have been made to study the frontal monoaminergic projections with personality measurements in patients with Parkinson's disease. In fact, there are no studies that have examined the personality of unmedicated patients with Parkinson's disease, with or without functional brain imaging.

The present study consisted of two parts. The first part of the study aimed simply to compare the personality structure of unmedicated patients with Parkinson's disease to the personality of healthy controls. The second part of the study focused on the brain dopaminergic function in Parkinson's disease patients in relation to their personality. Accordingly, the present study had two primary objectives: (*i*) to determine whether unmedicated early Parkinson's disease patients score lower on novelty seeking than healthy subjects, as would be expected on the basis of the hypothesized parkinsonian personality, and (*ii*) to determine whether there is a positive correlation between novelty seeking

This paper was submitted directly (Track II) to the PNAS office.

Abbreviations: ^{18}F-dopa, 6-[^{18}F]fluoro-L-dopa; PET, positron emission tomography; UPDRS, Unified Parkinson's Disease Rating Scale; TCI, Temperament and Character Inventory; KSP, Karolinska Scales of Personality; BMI, body mass index.

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www.pnas.org/cgi/doi/10.1073/pnas.231313198

and brain dopaminergic function in unmedicated Parkinson's disease patients in the striatum, or in the frontal lobe, measured with 6-[^{18}F]fluoro-L-dopa (^{18}F-dopa) PET, as would be expected on the basis of the hypothesized parkinsonian personality and the earlier study by Menza and colleagues (13).

Subjects and Methods

Subjects. In part I of the present study, unmedicated Parkinson's disease patients were compared with healthy controls by using personality questionnaires. Sixty-one Caucasian patients with Parkinson's disease (41 men, 20 women), with a motor symptom duration of less than 5 years, and 45 Caucasian healthy age-matched controls (19 men, 26 women) participated in the study. All Parkinson's disease patients had been diagnosed by an experienced neurologist and at least two of the three cardinal symptoms of Parkinson's disease (rest tremor, rigidity, bradykinesia) were present in all patients without atypical features. The severity of Parkinson's disease was assessed according to the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS) (15) (mean score = 31.9, SD = 7.4, range 14–53). The mean age of the Parkinson's disease patients was 62.1 years (SD = 7.9, range 47–79), and the mean age of controls was 59.8 years (SD = 8.7, range 40–74). None of the subjects had received any antiparkinsonian medication or any other medication known to affect dopaminergic neurotransmission. None of the control subjects had a history of neurologic or psychiatric diseases.

In part II, unmedicated Parkinson's disease patients were scanned with three-dimensional-mode ^{18}F-dopa PET. Forty-seven Parkinson's disease patients [mean age = 62.7 years, SD = 7.7, range 47–79; mean body mass index (BMI): 26.7 kg/m^2, SD = 3.5, range 20.9–37.9; 33 men and 14 women] of the 61 early Parkinson's disease patients were examined with PET. Thirty-three patients had predominantly right-sided symptoms and 14 patients had predominantly left-sided symptoms. One patient was left-handed. None of the subjects in part I or II was aware of the study hypotheses. The joint ethical committee of the University of Turku and Turku University Central Hospital approved the study. All participants gave their informed consent after the procedures had been fully explained according to the Declaration of Helsinki.

Personality Questionnaires and PET Imaging. Each subject filled out the Temperament and Character Inventory (TCI) (16) and the Karolinska Scales of Personality (KSP) (17) questionnaires. In part II, the patients filled out the personality questionnaires either at the PET Centre when the imaging took place or within 1 week after the PET examination.

Electrophilic [^{18}F]F_2 was produced according to Bergman and Solin (18). The radiochemical synthesis of ^{18}F-dopa was carried out according to the methods of Namavari and colleagues (19) and Bergman and colleagues (20). The radiochemical purity exceeded 98% in every case. Dynamic 90-min three-dimensional scans with General Electric Advance PET scanner were performed as described (21). The mean (±SD) injected dose of ^{18}F-dopa was 169 (±24) MBq. Each subject also underwent a 1.5-T MRI scan (Siemens Magnetom, Erlangen, Germany). The region of interest (ROI) analysis was carried out by delineating the head of the caudate nucleus, the putamen, the ventral striatum, the medial frontal cortex (Brodmann's areas 24 and 32), the dorsolateral prefrontal cortex (Brodmann's area 46), and the occipital region containing both gray and white matter; we did one ROI on each hemisphere. PET and MRI planes were realigned as described (21). The investigator who drew the ROIs (E.N.) was not aware of the personality scores. A graphical analysis method was used to calculate the metabolic rate of ^{18}F-dopa, by using radioactivity concentration in the occipital region as the input function (22).

Statistical Analyses. The statistical computations were performed with the SAS system for Windows, release 8.00 (SAS, Cary, NC). No *T*-score transformations for the personality scores were performed. Instead, because sex and age may affect the personality trait scores (parts I and II) (16, 17), and sex and UPDRS score may affect the ^{18}F-dopa uptake (part II) (21), unadjusted raw personality scores and ^{18}F-dopa uptake values were used, and the effects of sex, age, and UPDRS score were controlled for in the statistical analysis.

For part I, differences between Parkinson's disease patients and controls on each personality scale were tested with one-way ANOVA with sex and age as covariates. The associations of personality scores and UPDRS were analyzed by applying linear regression analyses and Pearson partial correlation coefficients with sex and age partialled out. Bonferroni corrections were used to correct for 22 comparisons (7 TCI scales and 15 KSP scales) between Parkinson's disease patients and controls. Corrected *P* values below 0.05 were considered statistically significant. For novelty seeking, the personality scale with *a priori* hypothesis, the level of significance for a lower score in the Parkinson's disease group was set at $P < 0.05$ uncorrected.

For part II, the associations of ^{18}F-dopa uptake and personality scores were analyzed by applying linear regression analyses. Pearson's partial correlation coefficients were calculated with age, sex, and UPDRS score partialled out. Additionally, because there are indications that the BMI may be associated with brain dopaminergic function (10, 23), also the effect of BMI was partialled out in the analysis. The individual effects of age, UPDRS, and BMI on ^{18}F-dopa uptake were also examined. In the striatal regions, ^{18}F-dopa uptake was studied separately for the hemisphere contra- and ipsilateral to the predominant symptoms of Parkinson's disease and for the left and right hemisphere. Also, because a sex difference in the right prefrontal ^{18}F-dopa uptake has been demonstrated in Parkinson's disease (21), the results of men and women were studied separately for the ^{18}F-dopa uptake in the right dorsolateral prefrontal cortex. In other brain regions, men and women were studied as one group with the effect of sex partialled out in the analysis. Bonferroni corrections were used to correct for 220 comparisons [22 personality scales × 10 brain regions]. Corrected *P* values below 0.05 were considered statistically significant. For TCI novelty seeking, the personality scale with *a priori* hypothesis, the level of significance for a positive association with ^{18}F-dopa uptake was set at $P < 0.05$ uncorrected.

Results

Part I, Personality Questionnaires. The Parkinson's disease patients scored lower than controls on the TCI novelty-seeking scale ($P = 0.04$, uncorrected) (Table 1). The patient group scored higher than controls on the TCI harm avoidance scale ($P = 0.03$, corrected) and on the KSP muscular-tension scale ($P = 0.009$, corrected) (Table 1). The other differences between patients and controls did not reach statistical significance after correction for multiple comparisons ($P > 0.44$, corrected). The TCI harm-avoidance scale correlated positively with the KSP muscular-tension scale both in the Parkinson's disease group ($r = 0.31$, $P = 0.02$, uncorrected) and in the control group ($r = 0.46$, $P = 0.002$, uncorrected). The motor UPDRS score did not significantly correlate with any of the personality scales ($r = -0.23$ to 0.17, $P > 0.10$, uncorrected).

Part II, ^{18}F-dopa PET. The mean influx constant values of ^{18}F-dopa, using occipital cortex as reference region, K_i^{occ}, are presented in Table 2. The TCI novelty-seeking scale did not significantly correlate with ^{18}F-dopa uptake in any of the studied brain regions in the striatum ($r = -0.07$ to 0.11, $P > 0.15$, uncorrected) (Table 3), or in the frontal cortex ($r = -0.12$ to 0.11, $P > 0.41$, uncorrected). Also in the left caudate, where a relationship

Table 1. Mean scores of 61 unmedicated Parkinson's disease patients and 45 healthy controls on the TCI and the KSP

Scale	Score: Parkinson (n = 61)	Score: Control (n = 45)	P value*
TCI			
Novelty seeking	13.1 (0.76)	15.6 (0.89)	0.040
Harm avoidance	18.8 (0.83)	14.4 (0.97)	0.0013†
Reward dependence	14.1 (0.47)	14.2 (0.55)	0.84
Persistence	3.51 (0.26)	4.20 (0.30)	0.10
Self-directedness	31.4 (0.78)	33.5 (0.91)	0.083
Cooperativeness	32.2 (0.63)	33.1 (0.74)	0.38
Self-transcendence	12.7 (0.88)	14.5 (1.03)	0.20
KSP			
Somatic anxiety	21.7 (0.63)	20.6 (0.74)	0.25
Psychic anxiety	25.2 (0.61)	22.8 (0.71)	0.015
Psychasthenia	25.1 (0.50)	23.6 (0.59)	0.065
Inhibition of aggression	25.9 (0.48)	25.1 (0.56)	0.31
Muscular tension	22.9 (0.56)	19.7 (0.65)	0.0004†
Impulsiveness	22.4 (0.53)	23.6 (0.62)	0.16
Monotony avoidance	21.8 (0.55)	23.4 (0.65)	0.063
Detachment	23.8 (0.46)	22.5 (0.54)	0.073
Socialization	61.9 (0.80)	62.6 (0.94)	0.57
Social desirability	27.5 (0.46)	28.7 (0.54)	0.11
Suspicion	10.9 (0.29)	10.1 (0.33)	0.090
Guilt	12.7 (0.26)	12.6 (0.30)	0.78
Indirect aggression	11.0 (0.33)	10.1 (0.39)	0.10
Verbal aggression	12.1 (0.29)	11.7 (0.34)	0.37
Irritability	10.9 (0.27)	10.7 (0.31)	0.73

Sex- and age-adjusted least-square means and SE for means are presented.
*One-way ANOVA with age and sex as covariates.
†Statistically significant P values after Bonferroni correction for 22 comparisons.

between novelty seeking and ^{18}F-dopa uptake has been reported in Parkinson's disease, no significant correlation was seen (r = 0.11, P = 0.49, uncorrected).

A significant correlation between the TCI harm avoidance and ^{18}F-dopa uptake was seen in the right (r = 0.53, P = 0.04, corrected), but not in the left (r = 0.43, P = 0.88, corrected) caudate nucleus (Table 3, Fig. 1). The statistical significance of the correlation in the right caudate was only slightly weaker in the analysis when the effects of age, sex, UPDRS, and BMI were not partialled out (r = 0.48, P = 0.13, corrected), indicating that these variables had a small effect on the result. When the values from the hemispheres contra- and ipsilateral to the predominant symptoms of Parkinson's disease were used, no significant correlations were seen (^{18}F-dopa uptake in the contralateral caudate vs. harm avoidance: r = 0.49, P = 0.15, corrected; ^{18}F-dopa uptake in the ipsilateral caudate vs. harm avoidance: r = 0.50, P = 0.15, corrected). In the analysis of the KSP, the somatic anxiety, the psychic anxiety, the indirect aggression, the irritability scale and the psychasthenia scales had positive correlations with the ^{18}F-dopa uptake in the caudate (r = 0.39 to 0.49, $P < 0.01$, uncorrected) (Table 3). These correlations did not remain significant after corrections for multiple comparisons. KSP muscular tension did not correlate with the ^{18}F-dopa uptake in the right caudate (r = 0.02, P = 0.87, uncorrected).

The KSP detachment score did not correlate with ^{18}F-dopa uptake in any of the studied brain regions (r = −0.11 to 0.22, $P > 0.15$, uncorrected). Nor did the TCI attachment (RD3) significantly correlate with the ^{18}F-dopa uptake (r = −0.12 to 0.32, $P > 0.02$, uncorrected).

The UPDRS score did not significantly correlate with the ^{18}F-dopa uptake in any of the brain regions studied, though the correlations were all negative (r = −0.05 to −0.34, $P > 0.03$, uncorrected) (effects of age, sex, and BMI partialled out). Age did not significantly correlate with ^{18}F-dopa uptake (r = −0.20 to 0.25, $P > 0.10$, uncorrected) (effects of sex, BMI, and UPDRS partialled out). The BMI did not significantly correlate with any of the personality scales or regional ^{18}F-dopa uptake (r = −0.28 to 0.32, $P > 0.02$, uncorrected; TCI harm avoidance vs. BMI: r = 0.03, P = 0.87, uncorrected) (effects of sex, age, and UPDRS partialled out). The correlations between BMI and UPDRS (r = −0.29, P = 0.05, uncorrected), between age and BMI (r = −0.17, P = 0.25, uncorrected) and between age and UPDRS (r = 0.14, P = 0.34, uncorrected) were nonsignificant.

When the results were studied separately for men and women for the ^{18}F-dopa uptake in the right dorsolateral prefrontal cortex, none of the personality traits had significant correlations with the dorsolateral ^{18}F-dopa uptake in men or women.

Table 2. Mean (SD) ^{18}F-dopa uptake values in the 47 unmedicated Parkinson's disease patients studied with PET

Brain region	$K_i^{occ}\times10^{-3}$: Mean	$K_i^{occ}\times10^{-3}$: Right	$K_i^{occ}\times10^{-3}$: Left
Putamen	6.67 (2.09)	7.11 (2.18)	6.23 (2.45)
Caudate	9.52 (1.44)	9.73 (1.59)	9.31 (1.64)
Ventral striatum	9.27 (1.82)	9.28 (1.88)	9.26 (1.92)
Medial frontal cortex	2.08 (0.47)	2.01 (0.53)	2.14 (0.56)
Dorsolateral prefrontal cortex	1.08 (0.57)	1.08 (0.67)	1.08 (0.59)

Discussion

This study shows that high harm avoidance in unmedicated Parkinson's disease patients (part I) is associated with high ^{18}F-dopa uptake in the right caudate nucleus (part II). The results do not support a link between dopaminergic function and low novelty seeking in Parkinson's disease.

Personality of Parkinson's Disease Patients vs. Controls. In part I of the present study, early unmedicated Parkinson's disease patients were compared with healthy controls by using personality questionnaires that have been previously used in PET studies and in studies with medicated patients. In particular, part I of the present study aimed to determine whether unmedicated Parkinson's disease patients score lower than controls on novelty seeking, as has been reported in medicated patients (2, 4). The present results indicate that low novelty seeking is mildly associated with unmedicated Parkinson's disease. It should be noted, however, that the statistical significance of the comparison between novelty seeking in Parkinson's disease patients and controls was just below 0.05 and the comparison, being the *a priori* hypothesis, was not corrected for multiple comparison as were the other 21 personality traits studied.

It is possible that the difference in novelty seeking would have become statistically more significant had there been a larger subject sample in the present study. However, the smaller groups of subjects in previous positive studies (2, 24) indicate that the present sample should have been sufficient to clearly demonstrate the differences in novelty seeking. Furthermore, although in the earlier studies (2, 24), control groups consisted of patients recruited from the rheumatology and orthopedic services, controls in the present study were healthy individuals. Unless there is increased novelty seeking in patients with rheumatologic and orthopedic illnesses, one would expect to see an equal or greater difference in novelty seeking when patients with Parkinson's disease are compared with healthy subjects, than when Parkinson's disease patients are compared with equally disabled patients. Although the effect size (difference between Parkinson's disease and controls, divided by SE) found for novelty seeking

Table 3. Pearson's partial correlations between caudate and putamen ^{18}F-dopa uptake and personality traits in 47 unmedicated patients with Parkinson's disease (effects of age, sex, level of motor disability, and body mass index partialled out)

	Partial correlation			
	Putamen		Caudate	
Scale	Right	Left	Right	Left
TCI				
Novelty seeking	0.02	0.22	0.07	0.11
Harm avoidance	0.31*	0.29	0.53†	0.43‡
Reward dependence	0.18	0.12	0.04	0.07
Self-directedness	−0.29	−0.29	−0.47‡	−0.44‡
Cooperativeness	−0.23	−0.35*	−0.35*	−0.38*
Self-transcendence	0.12	−0.09	0.08	0.02
Persistence	0.24	−0.03	0.10	−0.18
KSP				
Somatic anxiety	0.24	0.29	0.41‡	0.44‡
Psychic anxiety	0.27	0.23	0.36*	0.28
Psychasthenia	0.15	0.31*	0.29	0.28
Inhibition of aggression	0.06	−0.02	0.32*	0.09
Muscular tension	−0.01	0.20	0.06	0.31*
Impulsiveness	0.20	0.24	0.09	0.05
Monotony avoidance	−0.04	−0.09	−0.04	0.05
Detachment	0.02	0.03	0.10	0.15
Socialization	−0.19	−0.13	−0.24	−0.27
Social desirability	0.09	0.23	0.12	0.14
Suspicion	−0.08	0.02	0.09	0.03
Guilt	0.07	0.10	0.21	0.03
Indirect aggression	0.21	0.28	0.34*	0.42‡
Verbal aggression	0.23	0.13	0.35*	0.25
Irritability	0.22	0.22	0.32*	0.49†

*, $P < 0.05$, uncorrected.
†, $P < 0.001$, uncorrected.
‡, $P < 0.01$, uncorrected.

is similar in the present study compared with the preliminary study by Menza and colleagues (24) with 20 Parkinson's disease patients (≈3), in their later study with 50 Parkinson's disease patients (2), the effect size was much greater than in the present study (≈10). Therefore, although the results of the present study indicate that the low-novelty-seeking personality type may also be present in unmedicated patients with Parkinson's disease, both the statistical significance and the effect size in the present study are smaller than in the study by Menza and colleagues (2). The present results thus suggest that the previously demonstrated low-novelty-seeking behavior in Parkinson's disease could be partly related to the effects of long-term dopaminergic medication. There are indications that the mood response to levodopa is different in early and advanced Parkinson's disease, probably because of long-term sensitization to levodopa in advanced disease (25). Although a group of medicated Parkinson's disease patients could have been added to the present study to study the effects of levodopa, a paired study would be ideal, where the confounding factors of cross-sectional studies are avoided. If the personalities of the unmedicated patients in the present study are studied again once antiparkinsonian medications have been started and used, the role of dopaminergic drugs and disease progression in lowered novelty seeking can be clarified.

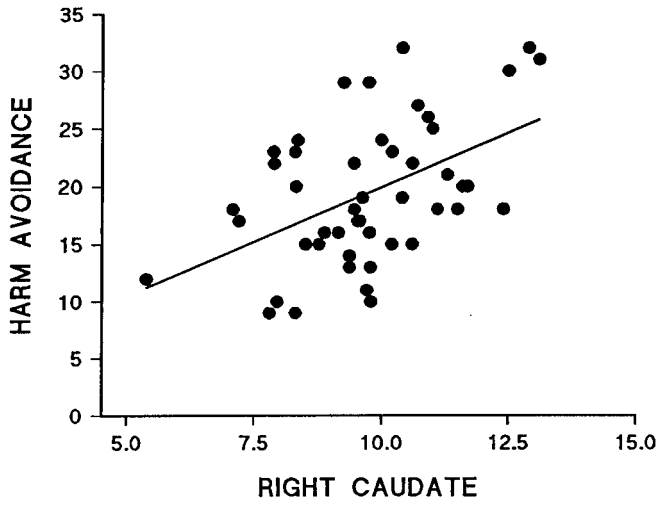

Fig. 1. Right caudate ^{18}F-dopa uptake ($K_i^{occ} \times 10^{-3}$) plotted against the harm avoidance score of the Temperament and Character Inventory in 47 unmedicated Parkinson's disease patients. Unadjusted raw values are presented ($r = 0.48$, $P = 0.13$, Bonferroni corrected). The correlation was stronger when the effects of age, sex, BMI, and motor disability were controlled for ($r = 0.53$, $P = 0.04$, Bonferroni corrected).

Even with the present subject sample, and the highly conservative Bonferroni correction, statistically significant differences in temperament traits other than novelty seeking, TCI harm avoidance, and KSP muscular tension were demonstrated. People who score high on harm avoidance describe themselves as fearful, pessimistic, shy, and easily fatigued, whereas those scoring low on harm avoidance are optimistic, outgoing risk-takers (26). High harm avoidance has been reported in several chronic diseases, for instance, in major depression (27, 28), obsessive–compulsive disorder (27), chronic fatigue syndrome

(29), multiple sclerosis (29), anorexia nervosa (30), and bulimia nervosa (31). In medicated Parkinson's disease, high harm avoidance has also been demonstrated when Parkinson's disease patients are compared with healthy controls (4, 7). Although it is possible that high harm avoidance is related to the pathophysiology and neurotransmitter function in Parkinson's disease, the above-mentioned results with other chronically ill patients indicate that the personality profile of high harm avoidance is not disease-specific. High harm avoidance possibly reflects a psychological response to a chronic disease.

The only significant difference on the KSP questionnaire was seen in muscular tension, which correlated with the TCI harm avoidance in both the patients and the controls and, therefore, cannot be considered an independent finding. The high KSP muscular-tension score in Parkinson's disease is likely to reflect the muscular rigidity of the disease or the anxiety related to the rigidity, or both.

Dopaminergic Function and Personality in Parkinson's Disease. The primary purpose of part II of the present study was to replicate the investigation by Menza and colleagues (13) of personality and ^{18}F-dopa uptake in Parkinson's disease, with a larger number of patients. Predictions concerning the association between novelty seeking and the striatal or frontal dopamine system in Parkinson's disease were not confirmed. The novelty-seeking personality trait did not significantly correlate with ^{18}F-dopa uptake in any of the brain regions studied. The major finding of part II was the unexpected, highly significant positive correlation between right caudate ^{18}F-dopa uptake and TCI harm avoidance in Parkinson's disease.

Novelty Seeking. In Cloninger's model (5), people who score lower than average on the dopamine-dependent novelty-seeking scale are typically described as reflective, rigid, loyal, stoic, slow-tempered, frugal, orderly, and persistent. In the study by Menza and colleagues, low ^{18}F-dopa uptake in the left caudate in nine Parkinson's disease patients was associated with low scores on novelty seeking (13). In the present sample of 47 unmedicated Parkinson's disease patients, novelty seeking was not significantly associated with ^{18}F-dopa uptake in any of the striatal or frontal brain regions studied, including the left caudate ($r = 0.11, P = 0.49$). In addition to the major difference between the studies [unmedicated patients with early Parkinson's disease (the present study) or more advanced medicated patients (13)], there are several other differences between the two studies that may contribute to the differences seen in the results: the number of patients, the use of MRI reference in the analysis (used in the present study), the statistical analysis (effects of age, sex, UPDRS, and BMI were partialled out in the present study) and the instrumentation (three-dimensional sensitivity used in the present study). The methodological differences between the two studies suggest that there were probably fewer confounding factors and more statistical power in the present study compared with the earlier one.

It is still possible that novelty seeking is related to dopaminergic function in Parkinson's disease as measured with tracers other than ^{18}F-dopa. Recently, Suhara and colleagues (8) have reported a negative correlation between novelty seeking and dopamine D_2-like receptors in the insular cortex in healthy subjects. However, no relationship has been seen between striatal D_2-like receptors (9, 11) or striatal dopamine transporter density (12) and novelty seeking/impulsiveness.

Twin studies indicate that personality traits measured by self-report questionnaires show moderate heritability with typical heritabilities in the 30–50% range (32). Although several replicated reports have found associations between attention deficit hyperactivity disorder and the D_4 receptor gene (33), for the novelty-seeking personality trait, there are both positive and negative results about the relationship (32). Although dopamine receptor genes, particularly the D_2 receptor gene, may be associated with Parkinson's disease (34), there are no reported attempts to study the personality structure together with dopamine D_2 receptor polymorphisms in patients with Parkinson's disease. Although the genetic aspect in the development of parkinsonian personality is of interest, the majority of Parkinson's disease is probably influenced by both environmental factors and combinations of genes (rather than single gene mutations).

Harm Avoidance. The present study demonstrates that in unmedicated Parkinson's disease patients, high harm avoidance is related to high ^{18}F-dopa uptake in the right caudate nucleus. Healthy subjects generally have higher caudate ^{18}F-dopa uptake values (21, 35), and lower harm-avoidance scores compared with unmedicated Parkinson's disease patients (part I). Paradoxically, in part II, the correlation between harm avoidance and ^{18}F-dopa uptake was positive. In other words, the higher the pessimism, fear of uncertainty, and shyness in Parkinson's disease, the higher the caudate ^{18}F-dopa uptake. The demonstrated positive correlation is difficult to explain with our current knowledge. One possibility is a negative feedback circuitry of neurotransmitters in Parkinson's disease, but any conclusions at this time are premature and probably too simplistic. As personality–PET studies expand to serotonergic, noradrenergic, and cholinergic neurotransmitter systems, it is possible that the nature of this relationship will be better understood. Also, there are no studies to date on the relationship between ^{18}F-dopa uptake and personality traits in healthy subjects. Data on healthy subjects would be useful in the full interpretation of the present study, which was designed to examine parkinsonian personality. Regardless of the underlying mechanism, in the present Parkinson's disease patients with the highest harm-avoidance scores, the caudate ^{18}F-dopa uptake was, in fact, higher than the caudate ^{18}F-dopa uptake reported in healthy subjects (21) (Fig. 1), which indicates that the increasing effect of harm avoidance on caudate ^{18}F-dopa uptake in unmedicated Parkinson's disease may be stronger than the lowering effect of the disease.

The present study measured personality traits, not directly depressive symptomatology. There is evidence that indicates that dopamine could have an important role in depression (36). Depression occurs in ≈40% of patients with Parkinson's disease (37), and the level of depression and anxiety in Parkinson's disease is higher than would be expected on a purely reactive psychological basis (38). Patients with both depression (39) and Parkinson's disease (part I) score high on harm avoidance. Importantly, depressive symptoms also seem to correlate with harm avoidance in medicated Parkinson's disease patients (2), in depressed patients (40), and in healthy subjects (41). It is likely that also in the present patients, harm avoidance and the correlating variables, KSP anxiety, aggression, and muscular tension, partly reflect depressive symptoms. If this is the case, the present results, in fact, imply that depressive symptomatology in Parkinson's disease is positively related to caudate dopaminergic function. In healthy subjects, D_2-receptor binding in the striatum was recently found to correlate positively with a personality facet of depression in the NEO Personality Inventory–Revised (42). In patients with major depression, the dopamine transporter density has been found to be higher than in healthy controls (43), a finding that was unexpected because it is generally believed that monoaminergic neurotransmission is lower in depression. In advanced Parkinson's disease, however, there does not seem to be any relationship between ^{18}F-dopa uptake and depressive symptomatology (35, 44). The depression in Parkinson's disease can be a specific issue because it seems to be distinguished from other depressive disorders by greater anxiety and less self-punitive ideation (37). Another interpretation is indeed that high

harm avoidance reflects anxiety more than depression. Although the possibility of a link between depression/anxiety and caudate ^{18}F-dopa uptake is particularly interesting, the interpretation needs to be corroborated in future studies with more direct depression and anxiety scales.

Conclusion

Rather than attempting to propose a new hypothesis on the role of dopamine in personality, the present study instead attempted to elucidate the relationships between dopaminergic function and personality traits in Parkinson's disease within the framework of the existing knowledge. The results of the present study provide some support for the hypothesis of a low-novelty-seeking personality type in Parkinson's disease. However, as both the statistical significance and the size of the effect were rather small in the present unmedicated patients, it is possible that the earlier, more positive results may partly be related to the effects of dopaminergic medications or disease progression. Further, the present study demonstrates that novelty seeking is not associated with striatal presynaptic dopaminergic function in Parkinson's disease. On the other hand, harm avoidance was found to be related to unmedicated Parkinson's disease and to right caudate dopaminergic function. It is possible that there is a unique disturbance of circuitry in Parkinson's disease that could explain the paradoxical, highly significant relationship between harm avoidance and dopaminergic function in the caudate. It is also possible that harm avoidance and high caudate dopaminergic activity reflect depression/anxiety in other chronic diseases as well.

We thank Dr. Jarmo Hietala for help with personality questionnaires and the staff of the Turku PET Centre. This work was supported by the Päivikki and Sakari Sohlberg Foundation and Turku University Central Hospital (EVO clinical research grant).

1. Menza, M. (2000) *Curr. Psychiatry Rep.* **2,** 421–426.
2. Menza, M. A., Golbe, L. I., Cody, R. A. & Forman, N. E. (1993) *Neurology* **43,** 505–508.
3. Hubble, J. P. & Koller, W. C. (1995) *Adv. Neurol.* **65,** 43–48.
4. Fujii, C., Harada, S., Ohkoshi, N., Hayashi, A. & Yoshizawa, K. (2000) *Am. J. Med. Genet.* **96,** 1–3.
5. Cloninger, C. R. (1987) *Arch. Gen. Psychiatry* **44,** 573–588.
6. Glosser, G., Clark, C., Freudlich, B., Kliner-Krenzel, L., Flaherty, P. & Stern, M. (1995) *Mov. Disord.* **10,** 201–206.
7. Jacobs, H., Heberlein, I., Vieregge, A. & Vieregge, P. (2001) *Acta Neurol. Scand.* **103,** 82–87.
8. Suhara, T., Yasuno, F., Sudo, Y., Yamamoto, M., Inoue, M., Okubo, Y. & Suzuki, K. (2001) *Neuroimage* **13,** 891–895.
9. Breier, A., Kestler, L., Adler, C., Elman, I., Wiesenfeld, N., Malhotra, A. & Pickar, D. (1998) *Am. J. Psychiatry* **155,** 1440–1442.
10. Yasuno, F., Suhara, T., Sudo, Y., Yamamoto, M., Inoue, M., Okubo, Y. & Suzuki, K. (2001) *Neurosci. Lett.* **300,** 59–61.
11. Farde, L., Gustavsson, P. & Jönsson, E. (1997) *Nature (London)* **385,** 590 (lett.).
12. Laakso, A., Vilkman, H., Kajander, J., Bergman, J., Haaparanta, M., Solin, O. & Hietala, J. (2000) *Am. J. Psychiatry* **157,** 290–292.
13. Menza, M. A., Mark, M. H., Burn, D. J. & Brooks, D. J. (1995) *J. Neuropsych. Clin. Neurosci.* **7,** 176–179.
14. Johnson, D. L., Wiebe, J. S., Gold, S. M., Andreasen, N. C., Hichwa, R. D., Watkins, G. L. & Boles Ponto, L. L. (1999) *Am. J. Psychiatry* **156,** 252–257.
15. Fahn, S., Elton, R. L. and Members of the UPDRS Development Committee (1987) in *Recent Developments in Parkinson's Disease,* eds. Fahn, S., Marsden, C. D., Calne, D. B. & Goldstein, M. (Macmillan Healthcare Information, Florham Park, NJ), pp. 153–163.
16. Cloninger, C. R., Svrakic, D. M. & Przybeck, T. R. (1993) *Arch. Gen. Psychiatry* **50,** 975–990.
17. Schalling, D., Åsberg, M., Edman, G. & Oreland, L. (1987) *Acta Psychiatr. Scand.* **76,** 172–182.
18. Bergman, J. & Solin, O. (1997) *Nucl. Med. Biol.* **24,** 677–683.
19. Namavari, M., Bishop, A., Satyamurthy, N., Bida, G. & Barrio, J. R. (1992) *Int. J. Rad. Appl. Instrum.* **43,** 989–996.
20. Bergman, J., Haaparanta, M., Lehikoinen, P. & Solin, O. (1994) *J. Label. Compounds Radiopharm.* **35,** 476–477.
21. Kaasinen, V., Nurmi, E., Brück, A., Eskola, O., Bergman, J., Solin, O. & Rinne, J. O. (2001) *Brain* **124,** 1125–1130.
22. Ruottinen, H. M., Rinne, J. O., Ruotsalainen, U. H., Bergman, J. R., Oikonen, V. J., Haaparanta, M. T., Solin, O. H., Laihinen, A. O. & Rinne, U. K. (1995) *J. Neural Transm. Park. Dis. Dement. Sect.* **10,** 91–106.
23. Wang, G. J., Volkow, N. D., Logan, J., Pappas, N. R., Wong, C. T., Zhu, W., Netusil, N. & Fowler, J. S. (2001) *Lancet* **357,** 354–357.
24. Menza, M. A., Forman, N. E., Goldstein, H. S. & Golbe, L. I. (1990) *J. Neuropsychiatry Clin. Neurosci.* **2,** 282–287.
25. Maricle, R. A., Valentine, R. J., Carter, J. & Nutt, J. G. (1998) *Neurology* **50,** 1890–1892.
26. Cloninger, C. R. (1994) *Curr. Opin. Neurobiol.* **4,** 266–273.
27. Kusunoki, K., Sato, T., Taga, C., Yoshida, T., Komori, K., Narita, T., Hirano, S., Iwata, N. & Ozaki, N. (2000) *Acta Psychiatr. Scand.* **101,** 403–405.
28. Kimura, S., Sato, T., Takahashi, T., Narita, T., Hirano, S. & Goto, M. (2000) *Psychiatry Clin. Neurosci.* **54,** 181–189.
29. Christodoulou, C., Deluca, J., Johnson, S. K., Lange, G., Gaudino, E. A. & Natelson, B. H. (1999) *J. Psychosom. Res.* **47,** 597–607.
30. Klump, K. L., Bulik, C. M., Pollice, C., Halmi, K. A., Fichter, M. M., Berrettini, W. H., Devlin, B., Strober, M., Kaplan, A., Woodside, D. B., *et al.* (2000) *J. Nerv. Ment. Dis.* **188,** 559–567.
31. Berg, M. L., Crosby, R. D., Wonderlich, S. A. & Hawley, D. (2000) *Int. J. Eat. Disord.* **28,** 148–154.
32. Ebstein, R. P., Benjamin, J. & Belmaker, R. H. (2000) *Eur. J. Pharmacol.* **410,** 205–214.
33. Swanson, J. M., Flodman, P., Kennedy, J., Spence, M. A., Moyzis, R., Schuck, S., Murias, M., Moriarity, J., Barr, C., Smith, M., *et al.* (2000) *Neurosci. Biobehav. Rev.* **24,** 21–25.
34. Plante-Bordeneuve, V., Taussig, D., Thomas, F., Said, G., Wood, N. W., Marsden, C. D. & Harding, A. E. (1997) *Neurology* **48,** 1589–1593.
35. Broussolle, E., Dentresangle, C., Landais, P., Garcia-Larrea, L., Pollak, P., Croisile, B., Hibert, O., Bonnefoi, F., Galy, G., *et al.* (1999) *J. Neurol. Sci.* **166,** 141–151.
36. Brown, A. S. & Gershon, S. (1993) *J. Neural. Transm.* **91,** 75–109.
37. Cummings, J. L. (1992) *Am. J. Psychiatry* **149,** 443–454.
38. Menza, M. A. & Mark, M. H. (1994) *J. Neuropsych. Clin. Neurosci.* **6,** 165–169.
39. Richter, J., Eisemann, M. & Richter, G. (2000) *Eur. Arch. Psychiatry Clin. Neurosci.* **250,** 40–47.
40. Hansenne, M., Reggers, J., Pinto, E., Kjiri, K., Ajamier, A., Ansseau, M. (1999) *J. Psychiatr. Res.* **33,** 31–36.
41. Tanaka, E., Kijima, N. & Kitamura, T. (1997) *Psychol. Rep.* **80,** 251–254.
42. Kestler, L. P., Malhotra, A. K., Finch, C., Adler, C. & Breier, A. (2000) *Neuropsychiatry Neuropsychol. Behav. Neurol.* **13,** 48–52.
43. Laasonen-Balk, T., Kuikka, J., Viinamäki, H., Husso-Saastamoinen, M., Lehtonen, J. & Tiihonen, J. (1999) *Psychopharmacology* **144,** 282–285.
44. Rinne, J. O., Portin, R., Ruottinen, H., Nurmi, E., Bergman, J., Haaparanta, M. & Solin, O. (2000) *Arch. Neurol.* **57,** 470–475.