

PAPER

Novelty seeking and harm avoidance in Parkinson's disease: effects of asymmetric dopamine deficiency

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Objectives: Although changes in novelty seeking and harm avoidance have been reported among patients with Parkinson's disease (PD), the findings regarding the neurochemical correlates of such changes are inconsistent. This study was designed to examine the hypothesis that different patterns of motor and neurochemical asymmetry in PD may have contributed to the conflicting results.

Methods: Forty PD patients (divided into two groups according to initial asymmetry in dopamine deficit: left hemisphere, n=22; right hemisphere, n=18) and 17 age matched healthy controls completed the Tridimensional Personality Questionnaire (Cloninger, 1987).

Results: Only patients with greater dopamine loss in the left hemisphere showed reduced novelty seeking, whereas only patients with reduced dopamine in the right hemisphere reported higher harm avoidance than matched healthy controls. Novelty seeking was not associated with disease duration, current motor symptoms, or medication, whereas harm avoidance was significantly correlated only with the severity of bradykinesia and depression.

Conclusions: Approach and avoidance reflect different patterns of dopaminergic asymmetry. Whereas reduced novelty seeking reflects deficit in the mesolimbic branch of ascending dopamine transmission in the left hemisphere, increased harm avoidance is associated with greater dopamine loss in the right striatum.

In recent years, several attempts have been made to relate dimensions of personality to specific brain systems. Most notably, Cloninger¹ has described three dimensions (novelty seeking, harm avoidance, and reward dependence) that are related to brain systems modulated by dopamine, serotonin, and noradrenaline, respectively. Following this formulation, a number of studies have examined the relation between dopaminergic brain systems and novelty seeking (NS), in healthy and pathological populations. Cloninger's model was supported by some studies of healthy subjects,² but not by others.³ Similarly, some studies of patients with known dopaminergic deficiency (Parkinson's disease (PD)) have shown that the degree of reduced NS in these patients was correlated with specific patterns of impaired DA functioning.⁴ However, other studies⁵⁻⁶ did not find a significant correlation between reduced NS and dopaminergic activity in PD.

A similar pattern of conflicting results emerges with respect to another trait discussed by Cloninger—that of harm avoidance (HA). This was reported to be associated with serotonergic activity in healthy subjects⁷ and patients with major depression.⁸ However, other studies reported that this trait, as measured by the Tridimensional Personality Questionnaire (TPQ), was correlated with dopaminergic, rather than serotonergic, activity.⁹

One factor that may explain at least some of the contradictory results is asymmetry in the neurotransmitter systems examined. Both NS and HA were found to correlate with brain activity in an asymmetric manner. Thus, Sahara *et al*² found a significant negative correlation between NS and D2 receptor binding only in the right insular cortex, in healthy young males. In healthy elderly adults, Kaasinen *et al*¹⁰ reported significant negative correlation between reward dependence and [18F]dopa uptake in the right, but not left caudate. Among PD patients, Menza *et al*⁶ reported significant correlation between NS and [18F]dopa uptake in the left caudate only, whereas Kaasinen *et al*⁶ did not find significant

correlations between NS and [18F]dopa, but did find a correlation between HA and right caudate uptake. Although both studies report lack of correlation between disease characteristics and TPQ scores, neither included data regarding motor asymmetry in the patients, and whether it was related to their findings. The onset of PD motor symptoms is typically asymmetric, and this has been shown to reflect asymmetric degeneration of dopaminergic neurons in the substantia nigra¹¹ even at later stages, when the motor signs have become bilateral. Onset asymmetry has been shown to have a differential effect on cognitive performance in PD, such that patients with left side onset were more impaired on most tasks, compared with patients with similar overall severity of illness, whose symptoms appeared first on the right side.¹² In a different study, the severity of obsessive-compulsive symptoms in PD patients was correlated with the severity of left but not right side motor symptoms.¹³ Other behavioural changes in PD may also be related to neurochemical asymmetry in these patients.

The present study was therefore designed to test the hypothesis that changes in NS and HA in PD may be related to asymmetric loss of dopamine, as reflected by asymmetric onset of motor symptoms.

METHODS

Subjects

Forty patients with unilateral onset of PD were referred to the Cognitive Neurology Unit, Rambam Medical Center, for a cognitive and behavioural evaluation. Only non-demented patients according to DSM-IV criteria¹⁴ were recruited for participation in the present study, and none had suffered from any neurological disease (other than PD), head injury,

Abbreviations: BDI, Beck Depression Inventory; HA, harm avoidance; MMSE, Mini-Mental State Examination; NS, novelty seeking; PD, Parkinson's disease; TPQ, Tridimensional Personality Questionnaire; UPDRS, United Parkinson's Disease Rating Scale.

or psychiatric illness. Patients who underwent surgical relief of PD symptoms were excluded. Each patient gave informed consent for participation in this study. Seventeen age and education matched healthy volunteers served as control subjects. All were screened for previous medical (including psychiatric) history, as well as current mental status. Table 1 presents the demographic and clinical data of the sample.

Procedure

Stage of illness was determined using the Hoehn and Yahr scale.¹⁵ Degree of disability was assessed by a neurologist blind to the cognitive data within one week of the cognitive testing, using the motor section (part III) of the United Parkinson's Disease Rating Scale (UPDRS).¹⁶ A total score was calculated for each patient, in addition to separate scores for tremor, rigidity, and bradykinesia. Tremor, rigidity, finger taps, hand grip, hand pronate/supinate, and leg agility were rated for the left and right sides of the body separately and two lateralised symptoms scores ("left" and "right") were derived by adding the scores for all the left and right symptoms, respectively.

Side of onset

Patients were divided into two groups (left or right side onset) based on the initial neurological examination and the patients' reports regarding the side and presentation of motor symptoms. Patients whose reports were equivocal or who demonstrated bilateral motor involvement at the time that the diagnosis of PD was made were excluded.

Behavioural assessment

The Mini-Mental State Exam (MMSE)¹⁷ served as an overall estimate of current level of cognitive functioning. The Beck Depression Inventory (BDI)¹⁸ was used to assess the presence and severity of depression.

The Hebrew version of the Tridimensional Personality Questionnaire (TPQ)¹⁹ was used to assess three dimensions of temperament (novelty seeking, harm avoidance, and reward

dependence). Each subject completed this self report questionnaire, consisting of 98 true/false statements. Subjects were encouraged to answer all questions spontaneously, without thinking too long. Separate scores were calculated for each of the three personality dimensions.

The above behavioural measures were collected as part of a larger longitudinal study of cognitive and behavioural correlates of disease progression in PD (Aharon-Peretz *et al*, unpublished data). Patients completed the TPQ and BDI as part of the cognitive battery administered by a neuropsychologist blind to the patient's history and current UPDRS data (results of the cognitive data are not included in the present report).

RESULTS

Table 1 summarises the demographic and clinical characteristics of the sample. As it shows, PD patients did not differ from the control subjects in age or overall cognitive status, and the two patient groups (left and right side onset) did not differ from each other on these measures. However, one way ANOVA revealed a significant difference in education ($F[2;54] = 3.966, p = 0.025$). Post hoc analysis (Scheffe) showed that the two PD subgroups did not differ from each other and each subgroup was marginally different from the controls (left onset *v* control, $p = 0.056$; right onset *v* control, $p = 0.055$). Because of this difference, level of education was used as a covariate in the following analyses. The three groups also differed significantly in the degree of depressive symptomatology reported (BDI scores: $F[2;54] = 7.166, p = 0.002$). Post hoc analysis (Scheffe) showed that this difference was due to greater severity of depression among patients with left onset. This group was significantly more depressed than control subjects ($p = 0.002$), but there was only a trend towards greater severity when patients with left onset were compared with the right onset group ($p = 0.084$).

The two PD subgroups did not differ in the clinical characteristics of the disease, including duration of illness, severity of current symptoms (Hoehn & Yahr stage, UPDRS scores other than asymmetry of symptoms), and medication status (see table 1).

TPQ measures and onset asymmetry

Table 2 presents the TPQ scores for the PD patients and the control subjects. One way ANOVA was used to assess the differences between the controls and the two PD subgroups, with post hoc comparisons where appropriate. As the control group had significantly more years of education, this variable was used as a covariate in all analyses. Education was not significant for any of the TPQ measures (NS, $p = 0.579$; HA, $p = 0.166$; RD, $p = 0.546$). To rule out the possibility that differences in TPQ scores reflect the differences in the severity of depression, BDI scores were also used as a covariate. Depression was marginally significant for NS ($p = 0.088$) and HA ($p = 0.074$), but not for RD. Parkinson's disease patients scored significantly lower on NS and significantly higher on HA, as compared with the control subjects. There were no differences in RD. However, post hoc analysis (Scheffe) showed that the two PD subgroups (left and right side onset) showed an opposite pattern of differences from controls: novelty seeking was reduced significantly only among right onset PD ($p = 0.02$, compared with control subjects) whereas left onset PD patients did not differ from controls. The reverse was found with respect to harm avoidance: patients with left onset had significantly higher scores of HA than control subjects ($p = 0.042$), whereas those whose disease began on the right side of the body did not differ significantly from the control subjects.

Table 1 Demographic and clinical description of the subjects (mean (SD))

	Parkinson's disease (PD) patients (n = 40)		
	Left onset (n = 18)	Right onset (n = 22)	Control subjects (n = 17)
Age	66.7 (9.1)	62.7 (9.0)	63.8 (10.1)
Education (years)*	12.2 (3.1)	12.3 (2.5)	14.5 (2.3)
Sex	13 M; 5 F	15 M; 7 F	8 M; 9 F
Mini-Mental State Exam	27.7 (2.1)	28.4 (1.2)	28.9 (0.9)
Beck Depression Inventory	14.2 (7.3)†	9.4 (7.1)	5.8 (5.1)
Stage (Hoehn & Yahr)	1.5 (0.7)	1.5 (0.8)	
Severity of motor symptoms			
Tremor	2.28 (1.9)	1.23 (2.2)	
Rigidity	4.55 (4.1)	3.23 (3.6)	
Bradykinesia	1.44 (0.8)	1.02 (1.0)	
Total severity score	19.1 (11.7)	16.0 (15.4)	
Duration of illness (years)	3.7 (2.9)	4.1 (4.1)	
Medication (number of patients)			
Unmedicated	3	3	
L-dopa	10	13	
Dopamine agonists	2	5	
MAO inhibitors	7	7	
Anticholinergic	3	2	

*One way ANOVA: $F[2;54] = 3.966, p = 0.025$.

†Left onset PD significantly different from controls ($p = 0.002$).

Table 2 TPQ scores for PD patients and control subjects (mean (SD))

	Left onset PD (n = 18)	Right onset PD (n = 22)	Controls (n = 17)	p Value
Novelty seeking	12.5 (3.6)	11.5 (2.9)*	14.9 (4.7)	0.021
Harm avoidance	18.6 (4.8)†	13.6 (5.9)	12.1 (6.1)	0.032
Reward dependence	16.0 (3.9)	16.9 (3.6)	16.6 (3.5)	0.919

Univariate ANOVA (education and BDI scores used as covariates).

*Significantly different from controls (Scheffe; $p=0.02$).

†Significantly different from controls (Scheffe; $p=0.042$).

TPQ scores and disease characteristics

The overall severity of the motor symptoms was not correlated with any of the TPQ scores: NS, $r=0.04$; HA, $r=0.198$; RD, $r=0.094$. The severity of tremor and rigidity was similarly not correlated with any of the TPQ scores. However, harm avoidance scores were significantly correlated with the severity of bradykinesia ($r=0.436$, $p=0.005$). Bradykinesia was not correlated with the degree of NS or RD. TPQ scores were not correlated with any of the demographic variables (age, education, or MMSE scores). Medicated PD patients did not differ from the unmedicated patients, and the duration of illness was not related to any of the TPQ scores. However, HA scores were correlated with the BDI score, such that higher HA scores were associated with higher depression scores ($r=0.405$, $p<0.001$). Neither NS nor RD was correlated with BDI scores. To clarify further the contribution of depression and bradykinesia to the differences in TPQ scores, we conducted a partial correlation analysis between TPQ scores and clinical/demographic variables, using BDI and bradykinesia as covariates. The severity of depression (as measured by BDI) and the severity of bradykinesia were not correlated ($r=0.2517$, $p=0.122$). Harm avoidance was still correlated with depression, even when Bradykinesia was partialled out ($r=0.366$, $p=0.024$). When covarying for the severity of depression, HA was still significantly correlated with bradykinesia ($r=0.377$, $p=0.02$). This suggests that the association of HA with depression and bradykinesia are independent.

To assess the contribution of current asymmetry in motor symptoms, an asymmetry index (AI) was calculated, using the total score of left (L) and right (R) symptoms [$AI = (R-L)/(R+L)$]. The current asymmetry of motor symptoms was not correlated with any of the TPQ measures, suggesting a dissociation between asymmetry of motor signs at disease onset and current asymmetry of motor signs, with respect to their relation with traits such as NS and HA.

DISCUSSION

The present results replicate earlier findings of reduced novelty seeking and increased harm avoidance among PD patients.^{5, 20–22} More interesting, however, is the finding that changes in NS and HA are related to the asymmetric pattern of disease onset. Thus, we found that only patients whose illness was manifested initially on the right side of the body showed reduced level of NS, as compared with matched healthy control subjects. The reverse pattern was seen with respect to HA: only those patients whose illness began on the left side of the body reported increased levels of HA. These findings were independent of the overall severity of the disease, overall level of cognitive functioning, or treatment variables. There is evidence (from clinical, imaging, and postmortem studies), suggesting that the initial asymmetry in dopamine loss still exists even at later stages, when the motor manifestations of the disease are less lateralised.^{11, 23, 24} Therefore, we suggest that reduced NS is associated with

reduced dopamine in the left hemisphere, whereas increased HA is related to loss of dopamine in the right hemisphere.

Davidson²⁵ suggested that asymmetry in anterior brain systems is related to approach and avoidance behaviour. According to his formulation, deficient activation in left anterior regions is associated with approach related deficits, whereas selective activation of right anterior regions is associated with withdrawal related emotional states. The present results support this model, suggesting that approach and avoidance reflect different patterns of dopaminergic asymmetry.

Novelty seeking has been described as behavioural activation associated with exploration of novel environmental stimuli and pursuit of and approach to potential rewards.¹ Spontaneous exploratory behaviour in a novel environment has been shown to depend on the integrity of the mesolimbic dopaminergic projections.²⁶ Degeneration of the mesocorticolimbic dopaminergic system, as well as the nigrostriatal system, has been shown to occur in PD.²⁷ Our findings suggest that it is the reduced level of mesolimbic dopamine activity in the left hemisphere that is responsible for the lower NS in our PD patients. The lack of correlation between NS and the severity of motor symptoms (which is known to reflect the degree of dopamine loss in the striatum),²⁸ supports the suggestion that it is the reduction of dopamine in the mesolimbic branch of ascending dopamine projections, rather than in the nigrostriatal pathway, that is responsible for reduced NS.

As mentioned above, Davidson²⁵ related avoidance behaviour to increased activation in right anterior brain systems. In the present study, however, increased harm avoidance was associated with left side onset of PD, suggesting reduced dopamine levels in the right hemisphere. Furthermore, unlike NS, HA was significantly correlated with the severity of bradykinesia, suggesting that increased levels of HA are associated with greater DA loss in the right striatum. Recently, Mattay *et al*²⁹ reported greater prefrontal cortical activation (associated with poor performance) during a hypodopaminergic state in PD (as measured by end of dose higher UPDRS scores). Electrical stimulation of mesocortical dopaminergic neurons located in the ventral tegmental area of the midbrain inhibited spontaneous activity of layer III–VI neurons of the prefrontal cortex,³⁰ suggesting that loss of VTA dopaminergic neurons in PD is associated with loss of such inhibition, and increased frontal activation. In our sample, the greater loss of DA in the right striatum (among patients with left side onset) would be associated with greater right frontal activation, and increased HA, as suggested by Davidson's model.

Other studies support the suggestion that asymmetric pattern of DA activity is associated with NS and HA. Thus, Sugiura *et al*³¹ reported significant positive correlations between NS scores and rCBF in paralimbic regions such as the left insula and left anterior cingulate, in a group of healthy subjects. They interpreted these results as supporting Cloninger's model regarding the relation between NS and dopamine, as cortical D2 receptor density has been reported to be particularly high in limbic and paralimbic regions.³² Their results also support our suggestion that NS is associated with dopaminergic activity in the left hemisphere. Menza *et al*⁶ reported that NS scores were correlated with [¹⁸F]dopa uptake in the left, but not right, caudate in nine PD patients. The authors had no explanation for this asymmetry and considered it an artifact of the small sample size. However, their finding is in agreement with the present results, lending yet further support to the suggestion that NS is dependent upon the integrity of left hemisphere dopamine systems. On the other hand, Kaasinen *et al*⁶ did not replicate this finding in a larger sample of unmedicated patients. They interpreted

this lack of correlation between NS and [18F]dopa uptake in the caudate as suggesting that the earlier findings reflected the effects of long term medication. In Kaasinen *et al.*'s study, however, there was no reference to the asymmetry of motor symptoms (either initial or current). Considering the relation found in the present study between onset asymmetry and NS, it is possible that this asymmetry may have been a confounding factor in Kaasinen *et al.*'s study.

The above discussion emphasises the relation between HA and dopamine, whereas Cloninger's¹ formulation proposed that HA was modulated by serotonin. Earlier studies reported close association between HA and depression.³³⁻³⁵ In our study, patients with right hemisphere onset indeed scored higher on a self rating questionnaire of depression (see table 1). However, the same pattern of asymmetry with respect to HA was found when depression scores were partialled out in the statistical analysis. Also, unlike NS, HA was significantly correlated with the severity of bradykinesia, which is known to reflect the degree of dopamine loss in the striatum.²⁸ Thus, we believe that both depression and HA are related to initial involvement of the right hemisphere in PD, but these two behavioural symptoms reflect different pathophysiological processes. Whereas depression is most likely related to loss of serotonergic activity, possibly in the right hemisphere, HA is related to dopaminergic loss in the right hemisphere. Asymmetry of 5HT₂ receptors in the inferofrontal cortex of depressed patients (right > left) was reported by D'Haenen *et al.*,³⁶ supporting the role of right hemisphere serotonergic systems in depression. As mentioned earlier, Kaasinen *et al.*⁶ reported a significant correlation between [18F]dopa uptake in the right caudate and HA score among PD patients, again suggesting that in PD, HA is associated with greater loss of DA in the right hemisphere.

The present study did not employ direct measures of dopaminergic activity, and the above interpretation is based on indirect indices, such as motor signs. Further studies, in which the relations between these personality dimensions and asymmetries in the dopaminergic brain systems will be examined directly, are therefore needed.

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