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Parkinson's Disease Motor Subtypes and Mood

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Abstract (240 words)

Background: Parkinson's disease is heterogeneous, both in terms of motor symptoms and mood. Identifying associations between phenotypic variants of motor and mood subtypes may provide clues to understand mechanisms underlying mood disorder and symptoms in Parkinson's disease.

Methods: 513 patients were assessed using the Hospital Anxiety and Depression Scale, and separately classified into anxious, depressed and anxious-depressed mood classes based on latent class analysis of a semi-structured interview. Motor subtypes assessed related to age of onset, rate of progression, presence of motor fluctuations, lateralization of motor symptoms, tremor dominance and the presence of postural instability and gait symptoms and falls.

Results: The directions of observed associations tended to support previous findings with the exception of lateralization of symptoms, where there were no consistent or significant results. Regression models examining a range of motor subtypes together indicated increased risk of anxiety in patients with younger age of onset and motor fluctuations. In contrast, depression was most strongly related to axial motor symptoms. Different risk factors were observed for depressed patients with and without anxiety, suggesting heterogeneity within Parkinson's disease depression.

Conclusion: Such association data may suggest possible underlying common risk factors for motor subtype and mood. Combined with convergent evidence from other sources, possible mechanisms may include cholinergic system damage and white matter changes contributing to non-anxious depression in Parkinson's disease, while situational factors related to threat and unpredictability may contribute to the exacerbation and maintenance of anxiety in susceptible individuals.

Introduction

Depression and anxiety are common and clinically important features of Parkinson's Disease (PD). They can precede the onset of the motor symptoms[1;2] suggesting that Lewy-related and other pathology in selectively vulnerable structures may contribute to both motor and non-motor features.[3] Pathological data has suggested greater neuronal loss and gliosis in catecholaminergic areas of the brain (specifically, the locus coeruleus, dorsal vagus nerve and substantia nigra, pars compacta) in depressed patients,[4] while *in vivo* imaging studies suggest possible associations with both serotinergic and noradrenergic systems [5] and white matter abnormalities.[6] The presence and severity of depression and anxiety has no linear relation with disease duration and is either unrelated (or only modestly associated) with the severity of the motor symptoms,[7] observed in patients with early, mild disease as well as those with more advance symptoms.[8] This implies that any association between depression, anxiety and motor symptoms does not directly reflect common nigrostriatal pathology and fronto-striatal pathophysiology.

PD is a complex and variable disease with distinct clinical phenotypic subtypes involving both motor and non-motor features.[9] Depression has been linked to the akinetic-rigid form of PD compared to patients with a tremor dominant profile [10-13], and in patients with postural instability and gait disturbance (PIGD) particularly falls, versus those with a non-PIGD profile [13-16]. Depression has also been associated with more rapid progression [10;17;18], and with motor complications of therapy [15;19] although not in all studies.[11;14;20] There is also some evidence that patients with a younger age at disease onset show increased risk of depression [17;19;21] although other studies have found either no such association or even shown increased risk with later onset [10;11;14;15;22]. Finally, an association between depression and right sided motor asymmetry has been suggested [21;23;24] but not confirmed in all studies.[25;26]

For anxiety, associations with the akinetic-rigid or PIGD motor phenotype are few and inconsistent [12;15;27] while there is no evidence regarding rate of disease progression and only a single negative report relating to lateralization of motor symptoms.[28] The strongest evidence emerging is an association between anxiety and young age of onset [15;20;28-30] and the presence of motor complications of treatment.[15;28-31]

The present study assessed, in a large sample of patients, a range of clinical and motor features suggested by previous research to be associated with depression and/or anxiety. Using a regression approach we aimed to determine the relative (rather than individual) significance of these often interdependent factors, providing better clues to guide research and improved management

Subjects and Methods

Patients with a diagnosis of PD were recruited from specialist movement disorder and care of the elderly clinics as described elsewhere.[32] Self-reported depressive and anxiety symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS).[33] A subscale score of ≥11 on the HADS was taken to indicate significant depressive or anxiety symptoms. Phenomenological data relating to depression and anxiety were collected by trained staff using a semi-structured interview, the Geriatric Mental State, designed and validated for use in older adults including patients with dementia [34]. Based on a Latent Class Analysis (LCA) of these data patients were categorised into four classes: 'Anxious-Depressed' (8.6%), 'Depressed' (9.0%) and 'Anxious' (22%), while a fourth group (60.4%) comprised patients with low levels of psychiatric symptomatology [32]. Activities of daily living and motor function were assessed using the UPDRS parts II and III [35] and disease stage with the Hoehn and Yahr Scale.[36] Cognitive function was assessed using the Addenbrooke's Cognitive Examination-Revised (ACE-R)[37] which incorporates the Mini-Mental State Examination (MMSE).[38] Levodopa equivalent daily dose (LEDD) was calculated as described elsewhere.[39]

Classification of Parkinson subtypes was based on previously reported studies. Younger age of onset was defined as onset of motor symptoms before the age of 55 years. Motor subtype was identified as PIGD or tremor dominant/indeterminate [40] and as tremor dominant or non-tremor dominant (akinetic-rigid).[10] Patients were also classified according to whether they reported postural instability and falls (PIF) (UPDRS Part II item 13>1) and freezing of gait (FOG) (UPDRS Part II item 14>1).[16] Rate of disease progression was estimated from cross-sectional data by dividing the UPDRS-III total by duration of disease since diagnosis in years [10] and dichotomized on the sample median. Motor complications of treatment (present or absent) were defined as motor fluctuations and/or sudden onset fluctuations (UPDRS Part IV). Lateralization was determined from the left and right side motor

symptom scores on the UPDRS part III. The study was approved by the South East Research Ethics Committee (ref 07/MREC01/9). All participants gave written informed consent.

Statistical analysis

The clinical characteristics of the dichotomized subtypes were compared using parametric or non-parametric ANOVA. These comparisons were not hypothesis or model testing and no correction was made for multiple comparisons. The p-values provide an indication of the strength of evidence supporting differences between subtypes comparable to previous reports. Continuous measures of anxiety and depression were compared between the dichotomized Parkinson subtypes using parametric parametric ANOVA, again for descriptive purposes, with age as a covariate where this was found to differ between subtypes. Three types of categorical data were compared (Fisher's exact or tests or linear-by-linear association) with adjustment made for multiple comparisons (critical p=0.017). Logistic regression (forced entry method) was used to indentify predictors of categorical depression, anxiety (binary regression) and mood class (multinomial regression). Analyses were performed using PASW Statistics (Chicago, IL) Version 18.

Results

Sample details (N=513) are provided in Table 1. Table 2 shows the demographic and clinical characteristics according to Parkinson subtype while Table 3 shows the relationship between motor subtypes and mood. There was no significant relationship between lateralization of motor symptoms, depression and anxiety (in all instances $p>0.10$) and these results are not considered further. Patients with onset less than 55 years had higher mean HADS anxiety score and a higher proportion showed significant anxiety. The proportion of patients in the three mood classes also differed significantly with higher proportions of early onset patients in the two anxiety-related classes (Classes 1 and 3) while the older onset group was more frequent in the 'depressed' class (Class 2). Patients with either PIGD or non-tremor dominant subtypes were somewhat more depressed on the HADS. The PIGD or non-tremor dominant subtypes were more strongly represented in all three of the empirical mood classes compared to the non-PIGD or tremor dominant patients. Patients with either FOG or PIF were more depressed and anxious as assessed by the HADS. Those with FOG also showed increased levels of significant

depression and anxiety, with the rate of depression almost four times that of patients without FOG. Patients with motor fluctuations were more depressed and anxious on the HADS, with increased rates of significant depression and anxiety and were more strongly represented in all three affective classes but particularly in the anxiety-related ones. Finally, patients with faster rate of progression were slightly more depressed and anxious than those with slower rates of progression, but did not differ in mood class distribution.

Logistic regression was used to assess which Parkinson subtype(s) best predicted the presence of depression (HADS depression ≥11), anxiety (HADS anxiety≥11) (N=490) or mood class (N=512) (Table 4). The PIGD/Non-PIGD and Non-Tremor/Tremor classifications produced similar results and only the former is reported in the final model (Table 4). The full set of dichotomized predictors was: age of onset ('early' <55, 'late' ≥55), motor subtype (PIGD, non-PIGD), PIF subtype (present, absent), FOG subtype (present, absent), motor fluctuations (present, absent) and rate of progression ('fast', 'slow') with the second category as the reference in each case. All potential predictors were entered into the models. Most associations were positive (predictor associated with worst mood) in agreement with previous findings. Significant predictors of HADS depression were FOG subtype and the presence of motor fluctuations. HADS anxiety was predicted by younger age of onset and rapid disease progression. The three mood classes were analysed in a multinomial model with class 4 (no prominent symptoms) as the reference category. Young onset, PIGD and FOG subtypes and motor fluctuations were significant in the overall model. Membership of the anxious-depressed class (class 1) was specifically predicted by young onset, PIF subtype and motor fluctuations. Anxiety (without depression) (class 3) was predicted by young onset, PIGD and motor fluctuations. Finally, depression (without anxiety) (class 2) was predicted only by PIDG subtype.

Because of the associations between some of the predictors and cognitive status (Table 2), secondary analyses were carried out to assess whether cognitive impairment (ACE-R <83) added to the three models described above. Impairment was a significant independent predictor of HADS depression (OR = 1.99, 1.08 – 3.69, p = 0.027) but not HADS anxiety (OR = 0.73, 0.42 – 1.28, p = 0.282). Similarly, cognitive impairment predicted membership of the Depression class (OR = 3.06, 1.05 – 8.92, p=0.041) but not the Anxious-Depressed (OR = 1.63, 0.59 – 4.45, p = 0.35) or Anxious classes (OR = 0.63, 0.26 – 1.51, p = 0.295).

Discussion

The present study confirms the significance of some but not all of the features of PD shown previously to be associated with depression and expands our knowledge in relation to anxiety. The univariate results lend some support for an association between younger age of onset and depression, but much more strongly for anxiety. In the regression analyses, even with other predictors in the model, age of onset below 55 years (mean 46.7) was strongly associated with the presence of clinically significant anxiety and membership of both anxiety-related classes. The profile of anxiety in these classes [32] is similar to that seen in generalized anxiety disorder (GAD). Such results are consistent with emerging evidence [15;20;28-30] and point to a specific risk an anxiety and anxiety disorder in such patients. The present and previous findings relating to depression are more equivocal. Heterogeneity within PD depression may account for some of the inconsistency if younger anxious-depressed patients, representing a distinct phenotypic subtype of depression, are combined in the same sample with older depressed patients without anxiety.[32]

Reasons for an association between anxiety and younger age of onset are currently unclear. Early onset of PD is associated with higher rates of some known genetic mutations. Psychiatric disturbance including anxiety has been reported in two parkin gene mutations (PARK2 and PARK7) [41] although the rates may be no higher than in patients without parkin mutations.[42;43] At present, the genetics of anxiety disorder is uncertain although there appear to be links to the genetics of lifetime trait neuroticism.[44] The onset of GAD can also be associated with traumatic and stressful life events in such susceptible individuals, particularly events involving loss or danger.[45] While PD can be a chronic stressor for all patients, the loss or threat of loss of social, family and occupational function is typically far greater in those developing the disease earlier in life. This offers one plausible mechanism for the observed association between anxiety and young age of onset.[46] The findings of the present study linking HADS anxiety to faster rate of motor progression may also be mediated by greater psychosocial stress and loss, rather than a direct association with pathophysiological progression. This latter finding, however, was not replicated in the two anxiety-related mood classes and so should be interpreted with caution. Previous studies have also suggested greater degree of depression in patients with more rapidly progressive disease,[10;17;18] although this was not strongly supported by the

present results. Examination of longitudinal data from the present cohort will help disentangle the potential contribution of rate of progression to risk of depression and anxiety.

Motor complications of treatment increase in prevalence with disease duration and with the duration and dose of antiparkinsonian treatment. In a prevalent cohort, younger age of onset is typically associated with longer duration of disease and treatment and hence a high rate of treatment related motor complications.[41] However, the present study suggests that motor fluctuations make a substantial independent contribution to the prediction of anxiety beyond age of onset alone. Some patients report marked anxiety restricted to the off-periods, perhaps representing a specific dopaminergic or dopa-mediated 'mood-off' phenomenon.[47] However, the present study focused on anxiety symptoms present more generally over preceding weeks and not simply acute anxiety states synchronised with motor status. The pathophysiological basis of motor fluctuations remains unclear and therefore hard to link to possible shared biological mechanisms with anxiety. However, a non-biological explanation may be found in the fact that motor-fluctuations are often unpredictable and add significantly to the lack of control that some patients perceive in their day-to-day lives. Intolerance of uncertainty is a trait cognitive bias common in anxiety disorders and particularly GAD. It is associated with high levels of worry and catastrophic predictions plus counter-productive coping behaviour.[48] Patients susceptible to motor fluctuations and who find the experience distressing report 'testing' their motor function or 'scanning' for signs of an impending off-period that would require a dose of medication. Such attentional focus on, and attempt to control, an often unpredictable event typically serves to maintain state anxiety rather than reduce it. Motor fluctuations may therefore provide a particularly salient stressor that exacerbates anxiety in already anxious individuals rather than reflecting a specific pathophysiological association.

Consistent with previous studies, the univariate data suggests that patients with a tremor-dominant motor subtype tended to be less depressed and to be under-represented in each of the three mood-classes. Such patients tended also to have shorter disease duration, less severe motor symptoms and less cognitive impairment (Table 2). The regression analysis focussed on the overlapping distinction between PIGD and non-PIGD subtypes, and the two subclasses of fallers, those with postural instability (PIF) and those with freezing of gait (FOG). Previous research [13-16] has indicated an association between such factors and depression, findings that were partially replicated in the present results. Axial

symptoms are typically unresponsive to dopaminergic medication and therefore presumed to reflect extra-nigral pathophysiology. By association, the same or parallel mechanisms may also contribute to non-motor symptoms including cognitive impairment and depression, shown to be associated, including in the present sample. For example, axial motor symptoms have been linked to loss of pedunculopontine nucleus (PPN) cholinergic neurones.[49] The role of cortical cholinergic loss in PD dementia is well established [50] and there is *in vivo* evidence for similar loss related to the severity of depressive symptoms in both demented and non-demented patients, as well as thalamic loss in fallers.[51] Arguing against a role for the cholinergic system in depression is the lack of robust evidence for a significant impact of cholinesterase inhibitors on mood in PD (e.g. [52]), although, to date, there have been no randomized trials with depression as a primary outcome. A second possible mechanism underpinning an association between axial symptoms and depression is white matter change. White matter damage is a significant predictor of gait problems and falls in the elderly [53] and is also strongly associated with depression and cognitive impairment.[54] In PD, microstructural white matters changes are similarly associated with both axial motor and cognitive symptoms [55] while recent *in vivo* studies report increased white matter changes in cortico-limbic and medial thalamic areas in depressed patients.[6;56]

In contrast to the evidence relating motor subtype to depression in PD, there is limited and inconsistent evidence for an association with anxiety. [12;15;27] Pontone and colleagues examined the motor characteristics of anxious versus non-anxious people with PD and, although they did not specifically use a motor subtype classification, they did not find any difference in motor features between groups.[30] The present results do not provide any robust evidence for an association between postural instability and anxiety, although in individual patients fear of falling may be a significant source of concern and contribute to activity limitation and social avoidance.[57;58] Already anxious patients who develop postural instability or who then experience falls may well become more anxious in response to this unpredictable and potentially harmful problem. Such specific anxiety is known to adversely affect anticipatory postural control further strengthening the relationship.[59] In patients with motor fluctuations, anxiety may also contribute to the escalation in medication use observed in some patients as they seek to ward off impending or anticipated off-periods, or even prompt requests for surgical interventions as a way of seeking to control unpredictable and distressing motor symptoms.

Although the largest study of its type, some limitations of the present study should be acknowledged. The HADS, although a valid measure of depression and anxiety in PD does not capture all of the symptoms related to syndromal disorder. Second, the absence of a comparison group makes it impossible to assess the impact of age independent of disease factors.

In conclusion, the present results reinforce and extend our understanding of the clinical associations between parkinsonian motor subtypes, depression and anxiety, and support the importance of considering heterogeneity in exploring possible aetiological models. The reported associations do not imply any single causal mechanism. Depression and anxiety are multifactorial with complex and variable factors probably contributing to both onset and symptom maintenance. There is growing evidence for the role of monoamine systems in PD depression.[5] However, when combined with evidence from other sources, the present association findings suggest a possible contribution of the cholinergic system and white matter change, at least in older non-anxious depressed patients. While specific neurochemical changes may also contribute to trait anxiety in PD, perhaps predating the onset of the motor symptoms, the evidence reported here is also consistent with an additional role for situational (state) factors such as the threat posed by the disease (e.g. to younger patients) and its symptoms (e.g. motor fluctuations) and their often inherent unpredictability. Such results can have direct clinical relevance. First, they show the potential importance on non-biological factors in driving, maintaining or exacerbating anxiety in biologically susceptible individuals. Second, anxiety may interact negatively with a patient's motor state and way they seek to manage their symptoms. Third a broader bio-psychosocial model may usefully guide the evaluation of psychological treatments using methods already used to treat similar anxiety symptoms in non-neurological populations.

Table 1 Demographic and clinical characteristics (N = 513)

Variable	Mean (SD) /Median*/%	Range
Demographic and social		
• Age (Years)	67.9 (10.3)	32 - 94
• Gender (% Male)	65.1%	-
Parkinson's disease history, symptoms and treatment		
• Age at PD onset (Years)	61.0 (12.1)	13 – 92
• Duration on PD (Years)	5.0*	0 - 39
• UPDRS-III (Total score)	26.4 (12.0)	4 - 78
• LEDD (mg/day)	600*	0 - 7565
• Hoehn and Yahr stages I/II-III/IV-V (%)	12.6/80.2/7.2%	-
• Rate of progression (median)	5.25	1 - 31
Cognitive function		
• ACE-R (Total score)	86.4 (10.7)	30 - 100
• ACE-R ≤83 (%)	29.7%	-
• MMSE (Total score)	27.9 (2.5)	16 - 30
Depression and Anxiety		
• HADS-Depression	6.3 (3.7)	0 – 17
• HADS-Depression ≥11 (%)	13.0%	-
• HADS-Anxiety	7.2 (4.5)	0 – 20
• HADS-Anxiety ≥11 (%)	22.0%	-
• HADS-Total score	13.5 (7.2)	0 - 37

Table 2 Parkinson subtypes: demographic and clinical characteristics

Subtype	N	Age (years)	Gender	Age of onset of PD (years)	PD Duration (years)	UPDRS(III) Total	LEDD (mg/day)	ACE-R Total
		Mean (SD)	(% Male)	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	Mean (SD)
Age of onset								
• <55	157	57.7 (8.3)***	63.7	46.7 (6.6)***	10.0 (0 – 39)***	26.4 (13.2)	800 (0 – 3641)***	89.0 (10.2)***
• ≥55	356	72.4 (7.6)	65.7	67.3 (7.9)	4.0 (0 – 23)	26.6 (11.4)	500 (0 – 7565)	85.3 (10.7)
Motor phenotype (a)								
• PIGD	369	68.6 (9.9)*	63.4	61.0 (12.1)	6.0 (0 – 39)***	27.9 (11.5)***	640 (0 – 7565) ***	85.5 (11.1)**
• Non-PIGD	144	66.1 (11.3)	69.4	61.0 (12.1)	3.5 (0 – 28)	23.2 (12.6)	430 (0 – 3169)	88.7 (8.9)
Motor phenotype (b)								
• Non-Tremor	420	68.2 (9.9)	63.6	60.1 (12.2)	5.0 (0 – 39)***	27.7 (11.5)***	620 (0 – 7565)***	85.9 (10.9)*
• Tremor	93	66.5 (12.0)	72.0	61.3 (11.9)	3.0 (0 – 27)	21.4 (12.7)	420 (0 – 2960)	88.7 (9.3)
Freezing of gait								
• Yes	75	67.3 (10.1)	72.0	56.1 (13.1)***	10.0 (0 – 39)***	35.5 (13.0)***	800 (0 – 7565)***	83.2 (11.6)**
• No	438	68.0 (10.4)	63.9	61.8 (11.7)	4.0 (0 – 28)	25.0 (11.1)	575 (0 – 3641)	86.9 (10.4)
Postural Instability/Falls								
• Yes	77	68.5 (9.7)	64.9	55.7 (13.9)***	13.0 (0 – 39)***	34.1 (11.8)***	920 (210 – 2800)***	81.4 (12.0)***
• No	436	67.7 (10.5)	65.1	61.9 (11.5)	4.0 (0 – 28)	25.2 (11.5)	531 (0 - 7565)	87.3 (10.2)
Motor fluctuation								
• Yes	138	64.4 (9.8)***	59.4	54.3 (10.5)***	10.0 (0 – 26)***	29.2 (12.9)**	922 (100 - 7565)***	87.2 (10.7)
• No	375	69.1 (10.2)	67.2	63.4) (11.7)	4.0 (0 – 39)	25.6 (11.5)	495 (0 - 3641)	86.1 (10.6)
Rate of progression								
• ‘fast’	259	68.7 (11.1)	68.0	65.3 (11.5)***	3.0 (0 – 13)***	29.1 (11.0)***	481 (377)***	85.8 (10.5)
• ‘slow’	254	67.0 (9.4)	62.1	56.6 (11.1)	10.0 (1 – 39)	24.0 (12.4)	924 (694)	87.1 (10.7)

* $p<0.05$, ** $p<0.01$, ***$p<0.001$

Table 3 Parkinson subtypes: relationship to depression, anxiety and mood class

	HADS Depression total	HADS Depression ≥11 (%)	HADS Anxiety total	HADS Anxiety ≥11 (%)	Class 1 (%) 'Anxious-Depressed'	Class 2 (%) 'Depressed'	Class 3 (%) 'Anxious'	Mood class signif. †
Age of onset								
• <55	6.6 (3.9)	17.3	8.7 (4.7)***	31.4*	17.8	6.4	32.5	**
• ≥55	6.1 (3.5)	11.0	6.5 (4.2)	17.6	4.5	10.1	17.4	
Motor phenotype-a								
• PIGD	6.6 (3.6)*	14.6	7.5 (4.3)	23.1	9.2	11.4	24.4	*
• Non-PIGD	5.3 (3.6)	9.2	6.5 (4.7)	19.1	6.9	2.8	16.0	
Motor phenotype-b								
• Non-Tremor	6.6 (3.6)*	14.2	7.4 (4.3)	22.9	9.3	10.0	24.3	*
• Tremor	5.0 (3.6)	7.8	6.2 (4.9)	17.8	5.4	4.3	11.8	
Freezing of gait								
• Yes	8.9 (4.5)**	34.7**	8.8 (4.6)**	33.3*	21.3	17.3	16.0	**
• No	5.8 (3.3)	9.3	6.9 (4.4)	20.0	6.4	7.5	23.1	
Postural Instability/Falls								
• Yes	7.8 (3.8)**	19.2	9.1 (4.7)**	31.5	22.1	14.3	24.7	**
• No	6.0 (3.6)	12.0	6.9 (4.3)	20.3	6.2	8.0	21.6	
Motor fluctuations								
• Yes	7.3 (3.7)**	20.0*	8.5 (4.3)*	30.4*	15.9	10.9	33.3	**
• No	5.9 (3.6)	10.4	6.7 (4.4)	18.8	5.9	8.3	17.9	
Rate of progression								
• 'fast'	6.6 (3.6)**	14.5	7.4 (4.6)**	25.2	8.1	9.7	18.5	
• 'slow'	6.0 (3.7)	11.3	7.0 (4.3)	18.5	9.1	8.3	25.7	

† Test of proportion of classes 1-3 across the two subtypes, Linear-by-Linear association
For HADS depression and anxiety totals * $p<0.05$, ** $p<0.01$, *** $p<0.001$
For HADS depression and anxiety ≥11 and mood class * $p<0.017$, ** $p<0.003$

Table 4 Predictors of significant depression and anxiety (HADS) and mood class (class 4 reference): results of logistic regression

	HADS Depression ≥11	**HADS Anxiety ≥11**	**Mood class**	**Class 1 'Anxious-Depressed'**	**Class 2 'Depressed'**	**Class 3 'Anxious'**
Model fit	χ^2 (6)=37.20**	χ^2 (6)=29.30**	χ^2 (6)=109.2**			
Predictor	OR (95% CI)	OR (95% CI)	Likelihood ratio test	OR (95% CI)	OR (95% CI)	OR (95% CI)
• Young onset	1.58 (0.84 – 2.96)	2.33 (1.46 – 3.85)**	**	5.37 (2.50 – 11.52)**	0.88 (0.38 – 2.03)	2.52 (1.52 – 4.12)**
• PIGD subtype	1.49 (0.73 – 3.02)	1.18 (0.69 – 1.99)	**	1.19 (0.52 – 2.74)	4.51 (1.55 – 13.16)*	1.94 (1.13 – 3.36)*
• PIF subtype	0.72 (0.33 – 1.61)	1.27 (0.68 – 2.40)		2.95 (1.24 – 6.99)*	1.63 (0.69 – 3.83)	1.30 (0.65 – 2.62)
• FOG subtype	5.00 (2.56 – 9.71)**	1.54 (0.83 – 2.85)	*	2.07 (0.89 – 4.83)	2.09 (0.94 – 4.67)	0.57 (0.26 – 1.24)
• Motor fluctuations	2.10 (1.17 – 3.79)*	1.58 (0.95 – 2.61)	**	2.49 (1.18 – 5.24)*	1.79 (0.85 – 3.76)	2.54 (1.52 – 4.24)**
• Fast progression	1.77 (0.99 – 3.17)	2.25 (1.38 – 3.67) **		1.90 (0.90 – 4.00)	1.24 (0.63 – 2.44)	1.00 (0.62 – 1.62)

OR = Odds ratio, 95% CI = 95% Confidence interval

* p<0.017, ** p<0.003

(NB: significance indicator for 'Mood class' indicates the contribution of the predictor in overall multinomial model; significance for individual classes 1-3 indicates the contribution of the predictor to the contrast between that class and the reference 'Healthy' class)

Reference List

(1) Ishihara L, Brayne C. A systematic review of depression and mental illness preceding Parkinson's disease. Acta Neurol Scand 2006; 113: 211-220.

(2) Weisskopf MG, Chen H, Schwarzschild MA, Kawachi I, Ascherio A. Prospective study of phobic anxiety and risk of Parkinson's disease. Mov Disord 2003; 18: 646-651.

(3) Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 2006; 5: 235-245.

(4) Frisina PG, Haroutunian V, Libow LS. The neuropathological basis for depression in Parkinson's disease. Parkinsonism Relat Disord 2009; 15: 144-148.

(5) Brooks DJ. Imaging non-dopaminergic function in Parkinson's disease. Molecular Imaging and Biology 2007; 9: 217-222.

(6) Kostic VS, Agosta F, Petrovic I et al. Regional patterns of brain tissue loss associated with depression in Parkinson disease. Neurology 2010; 75: 857-863.

(7) Cummings JL. Depression and Parkinson's disease: A review. American Journal of Psychiatry 1992; 149.

(8) Starkstein SE, Bolduc PL, Preziosi TJ, Robinson RG. Cognitive impairments in different stages of Parkinson's disease. J Neuropsychiatry Clin Neurosci 1989; 1: 243-248.

(9) van Rooden SM, Heiser WJ, Kok JN et al. The identification of Parkinson's disease subtypes using cluster analysis: a systematic review. Mov Disord 2010; 25: 969-978.

(10) Lewis SJG, Foltynie T, Blackwell AD et al. Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. Journal of Neurology Neurosurgery and Psychiatry 2005; 76: 343-348.

(11) Rojo A, Aguilar M, Garolera MT et al. Depression in Parkinson's disease: clinical correlates and outcome. Parkinsonism Relat Disord 2003; 10: 23-28.

(12) Starkstein SE, Petracca G, Chemerinski E et al. Depression in classic versus akinetic-rigid Parkinson's disease. Mov Disord 1998; 13: 29-33.

(13) Starkstein SE, Merello M, Jorge R et al. A validation study of depressive syndromes in Parkinson's disease. Mov Disord 2008; 23: 538-546.

(14) Riedel O, Klotsche J, Spottke A et al. Frequency of dementia, depression, and other neuropsychiatric symptoms in 1,449 outpatients with Parkinson's disease. J Neurol 2010.

(15) Negre-Pages L, Grandjean H, Lapeyre-Mestre M et al. Anxious and depressive symptoms in Parkinson's disease: the French cross-sectionnal DoPaMiP study. Mov Disord 2010; 25: 157-166.

(16) Factor SA, Steenland NK, Higgins DS et al. Postural instability/gait disturbance in Parkinson's disease has distinct subtypes: an exploratory analysis. J Neurol Neurosurg Psychiatry 2010.

(17) Reijnders JS, Ehrt U, Lousberg R, Aarsland D, Leentjens AF. The association between motor subtypes and psychopathology in Parkinson's disease. Parkinsonism Relat Disord 2009; 15: 379-382.

(18) Brown RG, MacCarthy B, Gotham AM, Der GJ, Marsden CD. Depression and disability in Parkinson's disease: A follow-up of 132 cases. Psychol Med 1988; 18: 49-55.

(19) Starkstein SE, Berthier ML, Bolduc PL, Preziosi TJ, Robinson RG. Depression in patients with early versus late onset of Parkinson's disease. Neurology 1989; 39: 1441-1445.

(20) Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M. Young- versus older-onset Parkinson's disease: impact of disease and psychosocial consequences. Mov Disord 2003; 18: 1250-1256.

(21) Cole SA, Woodard JL, Juncos JL et al. Depression and disability in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1996; 8: 20-25.

(22) Tandberg E, Larsen JP, Aarsland D, Cummings JL. The occurrence of depression in Parkinson's disease. A community-based study. Arch Neurol 1996; 53: 175-179.

(23) Leentjens AF, Lousberg R, Verhey FR. Markers for depression in Parkinson's disease. Acta Psychiatr Scand 2002; 106: 196-201.

(24) Starkstein SE, Preziosi TJ, Bolduc PL, Robinson RG. Depression in Parkinson's disease. J Nerv Ment Dis 1990; 178: 27-31.

(25) Barber J, Tomer R, Sroka H, Myslobodsky MS. Does unilateral dopamine deficit contribute to depression? Psychiatry Res 1985; 15: 17-24.

(26) Nation DA, Katzen HL, Papapetropoulos S, Scanlon B, Levin B. Subthreshold depression in Parkinson's disease. International Journal of Geriatric Psychiatry 2009; 24: 937-943.

(27) Starkstein SE, Robinson RG, Leiguarda R, Preziosi T. Anxiety and depression in Parkinson's disease. Behav Neurol 1993; 6: 151-154.

(28) Dissanayaka NN, Sellbach A, Matheson S et al. Anxiety disorders in Parkinson's disease: prevalence and risk factors. Mov Disord 2010; 25: 838-845.

(29) Vazquez A, Jimenez-Jimenez FJ, Garcia-Ruiz P, Garcia-Urra D. "Panic attacks" in Parkinson's disease. A long-term complication of levodopa therapy. Acta Neurol Scand 1993; 87: 14-18.

(30) Pontone GM, Willaims JR, Anderson KE et al. Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. Mov Disord 2009.

(31) Menza MA, Robertson HD, Bonapace AS. Parkinson's disease and anxiety: Comorbidity with depression. BIOL PSYCHIATRY 1993; 34: 465-470.

(32) Brown RG, Landau S, Hindle JV et al. Depression and anxiety related subtypes in Parkinson's disease. J Neurol Neurosurg Psychiatry 2011; 82: 803-809.

(33) A S Zigmond, R P Snaith. The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica 1983; 67.

(34) Copeland JR, Kelleher MJ, Kellett JM et al. A semi-structured clinical interview for the assessment of diagnosis and mental state in the elderly: the Geriatric Mental State Schedule. I. Development and reliability. Psychol Med 1976; 6: 439-449.

(35) Fahn S, Elton RL, members of the UPDRS development committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, editors. Recent Developments in Parkinson's Disease. Florham Park, N.J.: Macmillan Health Care Information; 1987. 153-164.

(36) Hoehn MM, Yahr MD. Parkinsonism: onset progression and mortality. Neurol 1967; 17: 427-442.

(37) Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriatr Psychiatry 2006; 21: 1078-1085.

(38) Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-198.

(39) Tomlinson CL, Stowe R, Patel S et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010; 25: 2649-2653.

(40) Jankovic J, McDermott M, Carter J et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 1990; 40: 1529-1534.

(41) Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. Lancet Neurol 2006; 5: 355-363.

(42) Lohmann E, Thobois S, Lesage S et al. A multidisciplinary study of patients with early-onset PD with and without parkin mutations. Neurology 2009; 72: 110-116.

(43) Kasten M, Kertelge L, Bruggemann N et al. Nonmotor symptoms in genetic Parkinson disease. Arch Neurol 2010; 67: 670-676.

(44) Stein MB. Neurobiology of generalized anxiety disorder. J Clin Psychiatry 2009; 70 Suppl 2: 15-19.

(45) Kendler KS, Hettema JM, Butera F, Gardner CO, Prescott CA. Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. Arch Gen Psychiatry 2003; 60: 789-796.

(46) Calne SM, Lidstone SC, Kumar A. Psychosocial issues in young-onset Parkinson's disease: current research and challenges. Parkinsonism Relat Disord 2008; 14: 143-150.

(47) Jankovic J. Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. Mov Disord 2005; 20 Suppl 11: S11-S16.

(48) Lee JK, Orsillo SM, Roemer L, Allen LB. Distress and avoidance in generalized anxiety disorder: exploring the relationships with intolerance of uncertainty and worry. Cogn Behav Ther 2010; 39: 126-136.

(49) Karachi C, Grabli D, Bernard FA et al. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. J Clin Invest 2010; 120: 2745-2754.

(50) Bohnen NI, Albin RL. The cholinergic system and Parkinson disease. Behav Brain Res 2010.

(51) Bohnen NI, Kaufer DI, Hendrickson R et al. Cortical cholinergic denervation is associated with depressive symptoms in Parkinson's disease and parkinsonian dementia. J Neurol Neurosurg Psychiatry 2007; 78: 641-643.

(52) Thomas AJ, Burn DJ, Rowan EN et al. A comparison of the efficacy of donepezil in Parkinson's disease with dementia and dementia with Lewy bodies. INT J GERIATR PSYCHIATRY 2005; 20: 938-944.

(53) Srikanth V, Beare R, Blizzard L et al. Cerebral white matter lesions, gait, and the risk of incident falls: a prospective population-based study. Stroke 2009; 40: 175-180.

(54) Alexopoulos GS, Murphy CF, Gunning-Dixon FM et al. Microstructural white matter abnormalities and remission of geriatric depression. Am J Psychiatry 2008; 165: 238-244.

(55) Bohnen NI, Albin RL. White matter lesions in Parkinson disease. Nat Rev Neurol 2011.

(56) Li W, Liu J, Skidmore F et al. White matter microstructure changes in the thalamus in Parkinson disease with depression: A diffusion tensor MR imaging study. AJNR Am J Neuroradiol 2010; 31: 1861-1866.

(57) Ashburn A, Stack E, Pickering RM, Ward CD. A community-dwelling sample of people with Parkinson's disease: characteristics of fallers and non-fallers. Age Ageing 2001; 30: 47-52.

(58) Brozova H, Stochl J, Roth J, Ruzicka E. Fear of falling has greater influence than other aspects of gait disorders on quality of life in patients with Parkinson's disease. Neuro Endocrinol Lett 2009; 30: 453-457.

(59) Adkin AL, Frank JS, Carpenter MG, Peysar GW. Fear of falling modifies anticipatory postural control. Exp Brain Res 2002; 143: 160-170.

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