Depression and anxiety subtypes in Parkinson's disease

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Depression and anxiety-related subtypes in Parkinson's disease

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Key words: Parkinson's disease, depression, anxiety, heterogeneity, latent class analysis

Number of words in abstract: 235

Number of words in main text: 3,848 (including tables) 3,258 (excluding tables)

Number of figures: 3

Number of tables: 3

Competing Interest: None declared.

ABSTRACT

Background: Depression and anxiety are common in Parkinson's disease and although clinically important remain poorly understood and managed. To date, research has tended to treat depression and anxiety as distinct phenomena. There is growing evidence for heterogeneity in Parkinson's disease in the motor and cognitive domains, with implications for pathophysiology and outcome. Similar heterogeneity may exist in the domain of depression and anxiety.

Objective: To identify the main anxiety and depression-related subtype(s) in Parkinson's disease and their associated demographic and clinical features.

Methods: A sample of 513 patients with PD received a detailed assessment of depression and anxiety related symptomatology. Latent Class Analysis (LCA) was used to identify putative depression and anxiety-related subtypes.

Results: LCA identified four classes, two interpretable as 'anxiety-related': one anxiety alone (22.0%) and the other anxiety co-existing with prominent depressive symptoms (8.6%). A third subtype (8.9%) showed a prominent depressive profile only without significant anxiety. The final class (60.4%) showed a low probability of prominent affective symptoms. The validity of the four classes was supported by distinct patterns of association with important demographic and clinical variables.

Conclusion: Depression in PD may manifest in two clinical phenotypes, one 'anxious-depressed' and the other 'depressed'. However, a further large proportion of patients can have relatively isolated anxiety. Further study of these putative phenotypes may identify important differences in pathophysiology and other aetiologically important factors and focus research on developing more targeted and effective treatment.

INTRODUCTION

As well as causing of distress, depression in Parkinson's disease has been associated with greater functional disability,[1] rate of physical and cognitive decline,[2] dementia risk,[3] and mortality,[4] and reduced quality of life.[5] Anxiety is also a prominent feature of PD [6;7] although implications for outcome are less well understood. Evidence for the efficacy of pharmacotherapy remains weak and often inconsistent,[8;9] although there is a growing number of trials of pharmacological and psychological interventions for depression (e.g. see *http://ClinicalTrials.Gov*). Trials are needed in PD anxiety although there is some evidence that anxiety symptoms improve in depressed PD patients treated with the SSRI citalopram.[10]. Although depression and anxiety symptoms can occur in isolation in PD, they frequently co-exist.[11;12] While some have suggested that this reflects the co-morbidity of distinct pathophysiological substrates,[11] others argue that anxious-depression represents a specific and common depressive subtype in PD.[7]

The relationship between depression and anxiety has important implications for treatment and clinical trials. Non-PD patients with Major Depression (MD) with marked anxiety (anxious-depression) show poorer outcomes than those with MD alone when treated with SSRI's and when switched/augmented with other agents.[13] If anxious-depression is common in PD, similar reduced treatment efficacy may be anticipated, while combining subtypes could produce aggregate results that do not adequately inform the response to treatment of either subgroup.

Broader clinical heterogeneity of PD has been examined using empirical approaches such as cluster analysis (CA) or latent class analysis (LCA).[14] In contrast to pre-specified clinical or theoretically defined subgroups, data-driven methods seek to identify clusters of patients defined by low intra-group but high inter-group differences across a set of selected variables. Applying similar methods to depression and anxiety related symptoms may identify empirical subgroups that then become available for validation and further study. Differences in pathophysiology and other factors involved in symptom onset and maintenance could guide the development of more targeted treatment. The present study describes the first use of a data-driven approach to explore possible heterogeneity in depressive and anxiety-related symptoms in patients with PD.

METHODS

Eligibility and recruitment

Patients were recruited over a 12-month period from specialist PD or movement disorder outpatient clinics (Ethics ref 07/MRE01/9) as part of a longitudinal study (PROMS-PD) (UKCRN ID 2519). Inclusion criteria were a clinical diagnosis of idiopathic PD,[15] the ability to provide informed consent at entry into the study, and living within two hours travel time of a study research centre. Exclusion criteria were the presence of sensory loss or communication difficulty (including inadequate command of English) sufficient to interfere with assessment. Patients with cognitive impairment or severe psychiatric disorder were excluded only if these interfered with the capacity to consent. The eligibility criteria were deliberately chosen to include as broad a range of patients as possible in terms of age and clinical severity.

Assessments

Participants were assessed over two sessions, typically in their own home. Where possible patients were assessed in their motor 'on' state. Depressive, anxiety and related symptoms were assessed using a semi-structured interview based on the Geriatric Mental State (GMS),[16] an instrument designed to assess psychopathology in older adults including those with significant cognitive impairment. Items were rated 0=absent or 'normal'; 1=present but not prominent (mild to moderate intensity, infrequent or fleeting), 2=prominent (severe, frequent or persistent). Symptoms were rated as reported or observed.[17] Self-reported depression and anxiety was assessed using the Hospital Anxiety and Depression Scale (HADS),[18] with subscale scores of ≥11 indicating significant symptoms. Motor function and disability was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS)[19] Parts II and III, Hoehn and Yahr Scale[20] and Schwab and England Scale.[21] The ratio of tremor to non-tremor motor symptoms was calculated as previously described.[22] Cognition was assessed using the Addenbrooke's Cognitive Examination - Revised (ACE-R),[23] with a score of ≤83 indicating significant impairment.[24] Annual assessments are planned for up to 4 years.

Statistical analysis

Latent Class Analysis (LCA) can identify unobserved (latent) subgroups of cases that share similar symptoms from a set of multivariate categorical data. Model-based CA methods such as LCA avoid a criticism of conventional heuristic CA approaches such as linkage that do not provide a formal basis for

determining the optimal number of clusters or indeed the existence of more than a single cluster. LCA provides inferences for statistically comparing the fit of solutions across different numbers of clusters, and is also better able to handle missing data. We employed LCA of binary symptom variables using M-Plus software.[25] Subjects were allocated to classes based on the maximum estimate of *a posteriori* probability of cluster membership (Maximized Allocation Probability method). Individual GMS symptoms were dichotomized as 'prominent' (score=2), or 'absent or present but not prominent' (score<2), to provide a classification based on the presentation of symptoms with clear clinical significance. Symptoms with a frequency of less than 2% (N<10) were excluded. In total 28 items were identified as relevant to phenotyping (see fig 1).

Preliminary assessment of validity was conducted by examining the association between the defined classes and other variables not included in the LCA. One-way analysis of variance (ANOVA) with paired comparisons (Tukey's HSD, $P<0.05$) was used to determine whether LCA classes could be discriminated on continuous demographic and clinical variables, and χ^2 for categorical data. Finally, multinomial logistic regression was used to examine clinical and demographic predictors of class membership. This latter analysis included a range of dichotomized measures associated with broad clinical heterogeneity in previous studies.[14]

RESULTS

Sample

941 patients were invited to participate of whom 525 consented but 12 subsequently withdrew before completing the initial assessment. Complete assessment was obtained from 513. The sample had a wide range of disease durations and severities although the majority were in Hoehn and Yahr stages II-III (table 1) with a non-tremor dominant motor profile.[26] Motor symptom onset preceded the age of 50 in 18.7%. Approximately 30% of participants showed evidence of significant cognitive impairment on the ACE-R. On the HADS 13% reported marked depressive symptomatology and 22% anxiety. Mild to moderate symptoms (HADS subscale score 8-10) were reported in a further 22% and 23% respectively. Almost all (94.9%) were taking antiparkinsonian drugs, and 24% reported taking antidepressant and/or anxiolytic medication.

Figure 1 shows the ranked profile of 28 GMS items. The most frequent prominent symptoms were worry (33.5%), subjective tension and restlessness (33.2%) and fatigue (27.6%). Symptoms such as excessive energy, belief about punishment and suicidal thinking were rare (<2%, data not shown) and not included in the LCA.

Empirically defined patient subgroups

Seven LCA solutions were evaluated, with a 4-class solution providing the best overall fit across a range of information indices (table 2). The median allocation probability was 99% with 90% of the sample allocated to their final class with a probability of 80% or more. The largest class (class 4) included 59.4% of the sample, class 3 22%, and classes 1 and 2 8.9% and 9.0% respectively.

Interpreting classes from cluster-based methods is a largely non-empirical process and involves visually identifying those features which most clearly (a) define an individual class and (b) distinguish it from other classes. Figure 2a and 2b shows the symptom probability profiles for the 28 variables for each of the individual class. Features of classes 1 and 2 were sad and/or empty mood, loss of interest, slow thinking, loss of confidence, lack of energy and poor concentration. In contrast, loss of enjoyment was rare and symptoms of hopelessness, worthlessness and guilt relatively uncommon, particularly in class 2. In addition, and in contrast to class 2, patients in class 1 also showed high probabilities of prominent worry and tension/restlessness, irritability, general anxiety/panic, specific fear and autonomic symptoms of anxiety. Class 3 was marked by a profile of prominent worry and tension/restlessness, and moderate probabilities of other severe anxiety-related symptoms but with a low probability of depressive symptomatology. Finally, class 4 was characterized by overall low probability of prominent symptoms.

Table 1. Demographic, social and clinical characteristics at the time of assessment (N=513)

Variable	Mean (SD) /%	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 (since diagnosis) (Years)	6.9 (6.0)	0-39
• UPDRS-III (Total score)	26.4 (12.0)	4-78
• Tremor/non-tremor ratio	0.63 (0.76)	0-10.8
• Hoehn and Yahr stages I/II-III/IV-V (%)	12.6/80.2/7.2%	-
• Motor disability (Schwab and England)	76.2 (17.3)	100-10
• Levodopa Equivalent Daily Dose (mg/day)	700 (598)	0-7565*
Cognitive function		
• ACE-R (Total score)	86.4 (10.7)	30-100
• % below ACE-R cutoff (≤83)	29.7%	-
• MMSE (Total score)	27.9 (2.5)	16-30
• % below MMSE cutoff (≤24)	10.2%	-
Depression and Anxiety		
• HADS-Depression	6.3 (3.7)	0 – 17
• % above HADS-depression cutoff (≥11)	13.0%	-
• HADS- Anxiety	7.2 (4.5)	0 – 20
• % above HADS-Anxiety cutoff (≥11)	22.0%	-
• Total score	13.5 (7.2)	0-37

*extreme case was a patient receiving continuous high dose subcutaneous apomorphine infusion

Table 2. Latent Class Analysis: Model fit indices comparing different cluster solutions (well fitting indices are underlined)

Index	Number of clusters (k)						
	1	2	3	4	5	6	7
AIC	16718	8059	7883	7810	7805	7790	7832
BIC	16863	8300	8247	8297	8416	8523	8689
VLMR LR-test (p-value)	n.a.	<0.0001	0.051	0.115	0.845	0.262	0.380
Entropy	1.00	0.895	0.874	0.885	0.797	0.834	0.856
Estimated class probabilities	100%	33.3%	13.7%	8.9%	8.2%	4.5%	15.4%
		66.7%	24.9%	9.0%	7.0%	4.5%	8.0%
			61.4%	22.7%	19.4%	4.8%	5.6%
				59.4%	27.2%	19.3%	13.3%
					38.2%	23.5%	8.2%
						43.2%	45.9%
							3.5%

AIC: Akaide's information criterion: lower values indicate better model fit, known to favor complex solutions

BIC: Bayesian information criterion: lower values indicate better model fit, known to select less complex solutions

VLRM: Vuong-Lo-Mendell-Rubin Likelihood Ratio Test: significance test to compare the null hypothesis of k-1 clusters with the alternative of k clusters

Entropy: a measure of classification quality, the larger the better, should be approximately 0.9

Table 3 shows the main demographic and clinical characteristics of the 4 classes. All variables showed highly significant differences ($P < 0.001$) including when age was used as a covariate. Patients in class 4 tended to be older, with a high proportion of males, later age at onset and shorter disease duration, with lower levels of motor symptoms, disability and medication. Non-tremor symptoms were least common in this class. Class 2 was a similar to class 4 in terms of age, age of onset, duration of PD and level of medication, but showed more cognitive and motor impairment and disability, and somewhat higher levels HADS depression and anxiety. This class also displayed the most pronounced non-tremor dominant symptom profile. Classes 1 and 3 were the youngest with more advanced disease and higher mean levels of antiparkinsonian medication than classes 2 and 4. Class 1 in particular showed early mean age of onset and long disease duration. Class 1 patients also showed greater disability and twice the level of significant cognitive impairment than class 3, and markedly increased levels and rates of anxiety and depression.

Predictors of class membership

Class membership was assessed using multinomial logistic regression with a set of dichotomised demographic and clinical variables: age (<70/≥70 years), gender (female/male), age at diagnosis (<55/≥55 years), PD duration (<5/≥5 years), levodopa equivalent daily dose (LEDD) (<600/≥600mg/day), Schwab and England (<80/≥80), UPDRS III (<23/≥23), ACE-R (<83/≥83). Class 4 was the reference category. Duration of PD did not independently predict class membership in any model and was therefore not included in the final analysis.

Relative to class 4, membership of class 1 was significantly (P<0.05) predicted by younger age (Odds Ratio (OR)=2.6, 95% confidence interval=1.0-6.6), PD onset less than 55 years (OR=3.9, 1.6-9.3), greater level of disability (Schwab and England) (OR=2.6, 1.2-6.0) and higher UPDRS III score (OR=2.4, 1.0-5.5). Female gender approached but did not reach significance (P<0.10). Membership of class 3 was predicted by a similar set of variables: younger age (OR=2.2, 1.2-4.0), female gender (OR=3.0, 1.8-4.8), younger age of PD onset (OR=1.7, 1.0-3.1), higher LEDD (OR=1.8, 1.1-2.9) and greater disability (OR=2.3, 1.3-4.1). Only cognitive impairment significantly predicted membership of class 2 (OR=3.7, 1.8-7.7).

Table 3. Demographic, social and clinical characteristics of the four latent classes (Mean(SD)/%).

Variable	Class 1 (N=44)	Class 2 (N=46)	Class 3 (N=113)	Class 4 (N=310)	Paired differences
Demographic and social					
• Age (Years)	61.4 (9.0)	70.3 (10.2)	65.2 (9.2)	69.4 (10.4)	13<24
• Gender (% Female)	40.9%	37.0%	52.2%	27.4%	-
Parkinson's disease, symptoms and treatment					
• Age at PD onset (Years)	51.6 (10.8)	62.9 (13.0)	57.6 (10.9)	63.2 (11.7)	1<234, 3<24
• Duration (Years)	9.6 (8.2)	7.6 (6.2)	7.7 (6.1)	6.1 (5.4)	1>4
• UPDRS-III (Total score)	33.0 (14.6)	30.5 (10.6)	27.0 (10.9)	24.9 (11.7)	1>34, 2>4
• Tremor/non-tremor ratio	0.52 (0.59)	0.40 (0.36)	0.48 (0.47)	0.73 (0.88)	4>3,2
• % Hoehn and Yahr stage ≥III	68.3%	54.3%	60.2%	28.5%	-
• Schwab and England	64.1 (24.0)	71.7 (18.1)	73.7 (15.4)	79.5 (15.7)	4>123, 3>1
• LED (mg/day)	1129 (1171)	728 (439)	1017 (763)	694 (608)	1>24,3>4
Cognitive function					
• ACE-R (Total score)	83.1 (13.3)	81.0 (11.9)	89.1 (8.7)	86.7 (10.3)	12<3, 2<4
• % below cutoff (≤83)	34.1%	52.2%	16.8%	26.0%	-
• MMSE (Total score)	26.8 (3.5)	26.6 (2.6)	28.6 (2.0)	28.0 (2.3)	1<3, 2<34
Depression and Anxiety					
• HADS-Depression	10.7 (4.1)	8.8 (6.7)	6.7 (3.0)	5.2 (3.2)	12>34, 3>4
• % above cutoff (≥11)	50.0%	33.3%	9.9%	6.4%	-
• HADS- Anxiety	12.5 (3.8)	8.4 (3.8)	9.6 (3.8)	5.4 (3.8)	1>234, 23>4
• % above cutoff (≥11)	66.7%	25.6%	34.2%	10.7%	-
• Total score	23.2 (6.5)	17.2 (5.1)	16.3 (5.8)	10.6 (6.1)	1>234, 23>4

DISCUSSION

This study provides the first detailed investigation of affective heterogeneity in PD using a broad range of indicator variables associated with (although not specific to) the psychiatric constructs of depression and anxiety. The results supported a four class solution with empirically defined subgroups that appear distinctive in terms of clinical and demographic features. We should not equate such subgroups with syndromal disorders, nor probabilistically defined class membership with diagnosis. Nevertheless, it is useful to suggest provisional clinically meaningful labels to the classes. Patients in the largest group (class 4) showed low levels of prominent symptomatology and can be labeled 'Psychologically healthy', although the high symptom threshold does not rule out some problems. Class 3 showed prominent anxiety-related features with a profile similar to Generalized Anxiety Disorder (GAD)[27] and can be labeled 'Anxious'. The profiles of classes 1 and 2 were more complex. Both showed elevated probabilities of core depressive symptoms of sad or empty mood and loss of interest, along with other supporting features such as poor concentration, slow thinking and fatigue, although loss of enjoyment were largely absent, and feelings of worthless, hopelessness and self-blame evident only in class 1. Patients in class 1 had a higher probability of prominent depression-related symptomatology but also showed marked prevalence of subjective tension, worry and general anxiety or panic and irritability in class 1, suggesting the label 'Anxious-depressed'. Class 2, together with depressive features also showed high levels of cognitive impairment and may reflect a 'Depressed' or possibly 'Apathetic-depressed' subtype.

A recent systematic review and meta-analysis.[14] summarized studies using similar approaches to define broad clinical heterogeneity in PD. Two studies [22;28] independently identified four subgroups of patients labeled 'Young onset', 'Tremor dominant', 'Non-tremor dominant' and 'Rapid disease progression'. Only the 'Non-tremor dominant' group (including akinesia and postural instability and gait symptoms) was associated with increased levels of depression. A young onset cluster, with typically slow rate of progression was associated with low levels of depression, although another study [29] found the opposite result. Other studies, not included in the systematic review, have examined non-motor heterogeneity. One study [30] analysed 10 broad psychiatric and behavioural symptoms of the Neuropsychiatric inventory (NPI)[31] identifying a large 'low-total NPI' subgroup and four others exhibiting predominant apathy, psychosis, depression or anxiety. However, substantial levels of

depression and particularly anxiety were evident in all of the groups except for the first. Another study considered depression, anxiety, apathy, daytime somnolence and cognition,[32] and defined four subgroups with the largest showing good cognitive and psychiatric function. The remainder showed cognitive impairment, psychiatric impairment or both. No evidence of heterogeneity was found within the psychiatric symptoms themselves, although the use of a single global index for each precluded detailed assessment.

Cluster-based methods are subject to a variety of methodological factors that can influence the robustness and therefore potential validity of the solutions. As noted, LCA has advantages over traditional CA methods in providing a range of indices to inform decisions about the optimal number of clusters. The present results strongly supported a 4-class solution over one with more or fewer subgroups. The high allocation probabilities further suggest that patients were assigned unequivocally to one of the 4 classes. Ideally, we would have liked to replicate the classification in an independent sample to further confirm its reliability, as done in one similar study using cluster analysis.[30] Unfortunately, our sample size, although large, was insufficient given the number of parameter estimates being modelled (N=115).

Face validity was high and the subgroups clinically interpretable. Validity was further supported by the associations of the classes with a range of variable not included in the LCA. These converged on evidence from previous studies describing associations between depression and broad clinical and motor phenotypes. Our results support a link between psychopathology and non-tremor dominant motor phenotype, with the ‘Healthy’ subgroup showed the highest proportion of tremor symptoms and the ‘Apathetic-depressed’ group the least. Younger age of onset emerged as a distinguishing feature in class 3 but particularly in class 1, along with female gender and higher LEDD. However, unlike the apparently benign psychiatric profile of the ‘Young onset’ groups of some previous studies[22;28] younger age of onset in the present study was associated with marked anxiety (classes 1 and 3). The present study also suggests that at least some patients with younger onset (class 1) experience significant depressive symptomatology, particularly those with longer duration, advanced disease and greater disability, similar to a previous report.[29]

An important question is whether subtypes remain stable or patients move between subtypes. Pending longitudinal study, a partial answer can be found in evidence on the duration of the individual symptoms

that define class membership (see supplementary information). Almost all prominent symptoms reported had been present for most days in the past 6 months in over 80% of patients, and for many, most days in the past 2 years. Although not proving that the subtypes are stable, it suggests that that the symptoms on which they are based are persistent in this sample.

A criticism of cross-sectional studies is that empirically distinct clusters may simply reflect observations of patients at different stages of a homogenous but progressive disease.[14] A number of facts suggest that this is not the case with the present findings. The between-group differences were modest compared to the range observed within the classes, with the 'Anxious' and 'Depressed' subgroups showing almost identical mean disease durations and levels of disability. Also, the logistic regression analysis failed to indicate a role of disease duration in predicting subtype. In contrast, age of onset emerged as a more significant influence, with younger onset (independent of duration) associated with the two anxiety-related subtypes.

The high level of anxiety-related symptomatology in this sample, and specifically in two of the subgroups, is consistent with emerging evidence.[6;7;33] Even when sub-syndromal, GAD-like symptoms of subjective tension, worry and irritability can be a significant source of distress, particularly if chronic, but may be missed without adequate screening. Anxiety-related symptoms are a common feature of depressive disorder although the depressive symptoms are generally held to be primary and the target of treatment. However, anxiety symptoms may turn out to have a high prominence in some PD patients with depression,[34] while symptoms such as anhedonia and guilt may be less characteristic with implications for assessment and diagnosis. If anxious-depression is common in PD it would also have important implications for management and outcome. In the elderly, remission rates of co-morbid depression and GAD is only 27% over 3 years compared to 41% for depression and 48% for GAD.[35] In a major trial of citalopram (STAR*D), time to remission was longer for anxious-depression, remission rates were significantly lower and reported side-effects higher.[13] The broad phenotypic similarity of patients in classes 1 and 3, suggests that these two subtypes may be closely associated. Longitudinal study will test the hypothesis that persistent GAD-like anxiety symptoms are a risk factor for anxious-depression. If so, then early identification and treatment of the chronic anxiety symptoms such as worry and tension may be indicated.

Heterogeneity of affective disturbance in PD may have implications for pathophysiology. Apathetic-depressive subtype, associated with non-tremor dominant PD and cognitive dysfunction, may have a mainly dopaminergic substrate with involvement of the ventral striatum and associated prefrontal regions, plus higher burden of cortical pathology in addition to the more typical nigro-striatal changes.[36] This subtype may have contributed to the previously reported associations between depression and rate of cognitive decline and dementia risk.[2;3] In contrast, non-dopaminergic mechanisms may be the major factor in the anxious-depressed and anxious subtypes. Evidence of serotinergic involvement in depression in PD is inconsistent,[37] (perhaps due to heterogeneity) although there is some support for the involvement of the noradrenergic system in PD depression,[38] with monoamine uptake ([^{11}C]RTI 32) in noradrenergic areas related to the severity of the anxiety but not depressive symptoms.

Demonstrating heterogeneity of depression in PD has implications for clinical trials. If studies combine patients with potentially different pathophysiology the outcome may be different response rates to treatment. This dilution of effect may account, at least in part, for the apparently poor overall response rates observed with conventional SSRI-based antidepressants in PD.[8] Selecting homogeneous samples with specifically targeted treatment may provide more reliable and useful evidence to focus clinical management.

The present study used convenience sample of outpatient clinic attenders. The rates of significant self-rated depressive (13%) and anxiety-related (22%) symptomatology from the HADS were comparable to that reported in two recent validation studies with figures of 17% and 20%,[39] and 14% and 22%[40] respectively, and with very similar mean scores. However, the purpose of the present study was not to define the prevalence of the subtypes (the absolute values for which should be treated with caution) but to identify their characteristics and associated features. Studies in different populations may produce different prevalence rates of the 4 subtypes, just as the rate of the ‘rapid disease-progression and old age-at-onset’ clinical subtype described in other studies has varied from 6 to 64%.[14] Such variability in prevalence, however, does not challenge the validity of the subtype.

In conclusion, this study suggests that models of depression and anxiety as distinct unitary conditions in PD may be inaccurate. GAD-like anxiety symptoms were amongst the most common in the sample and occurred both independently and in association with significant depressive symptoms. The distinctive

clinical and demographic profiles suggest that anxious-depression may represent a subtype distinct from depression. Such heterogeneity may need to be considered when carrying out research into the pathophysiological substrate of affective disorder in PD and in planning current management and future clinical trials.

FIGURE LEGENDS

Figure 1.

Frequencies of selected symptoms from the GMS, rated present but not prominent (white bar) or prominent (grey bar)

Figure 2a.

Symptom profiles (predicted probabilities) for class 1 (N=44) (-○ -) and class 2 (N=46) (- ● -) (NB Symptoms are organized for ease of interpretation rather than by frequency).

Figure 2b.

Symptom profiles (predicted probabilities) for class 3 (-□-) (N=113) and class 4 (-■-) (N=310)

ACKNOWLEDGEMENTS

The authors acknowledge support from:

Parkinson's UK; NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust (SLaM) and Institute of Psychiatry, King's College London; NIHR Dementias and Neurodegenerative Diseases Research Network (DeNDRoN); Wales Dementias and Neurodegenerative Diseases Research Network (NEURODEM Cymru); NIHR Mental Health Research Network (MHRN); British Geriatric Society.

In addition to the listed authors, we thank the following members of the PROMS-PD Study Group who all made a significant contribution to the work reported in this paper

London

KR Chaudhuri, King's College Hospital NHS Foundation Trust, London (participant recruitment)

C Clough, King's College Hospital NHS Foundation Trust, London (participant recruitment)

B Gorelick, Parkinson's Disease Society, London (member of the study management group)

A Simpson, Institute of Psychiatry, King's College London, London (data collection)

R Weeks, King's College Hospital NHS Foundation Trust, London (participant recruitment)

Liverpool and North Wales

M Bracewell, Ysbyty Gwynedd, Bangor (participant recruitment, data collection)

M Jones, University of Wales Bangor, Bangor (participant recruitment, data collection)

L Moss, Wythenshawe Hospital, Manchester (participant recruitment, data collection)

P Ohri, Eryri Hospital, Caernarfon (participant recruitment)

L Owen, Wythenshawe Hospital, Manchester (participant recruitment, data collection)

G Scott, Royal Liverpool University Hospital, Liverpool (participant recruitment)

C Turnbull, Wirral Hospitals NHS Trust, Wirral (participant recruitment)

Newcastle

S Dodd, Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne (participant recruitment, data collection)

R Lawson, Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne (participant recruitment, data collection)

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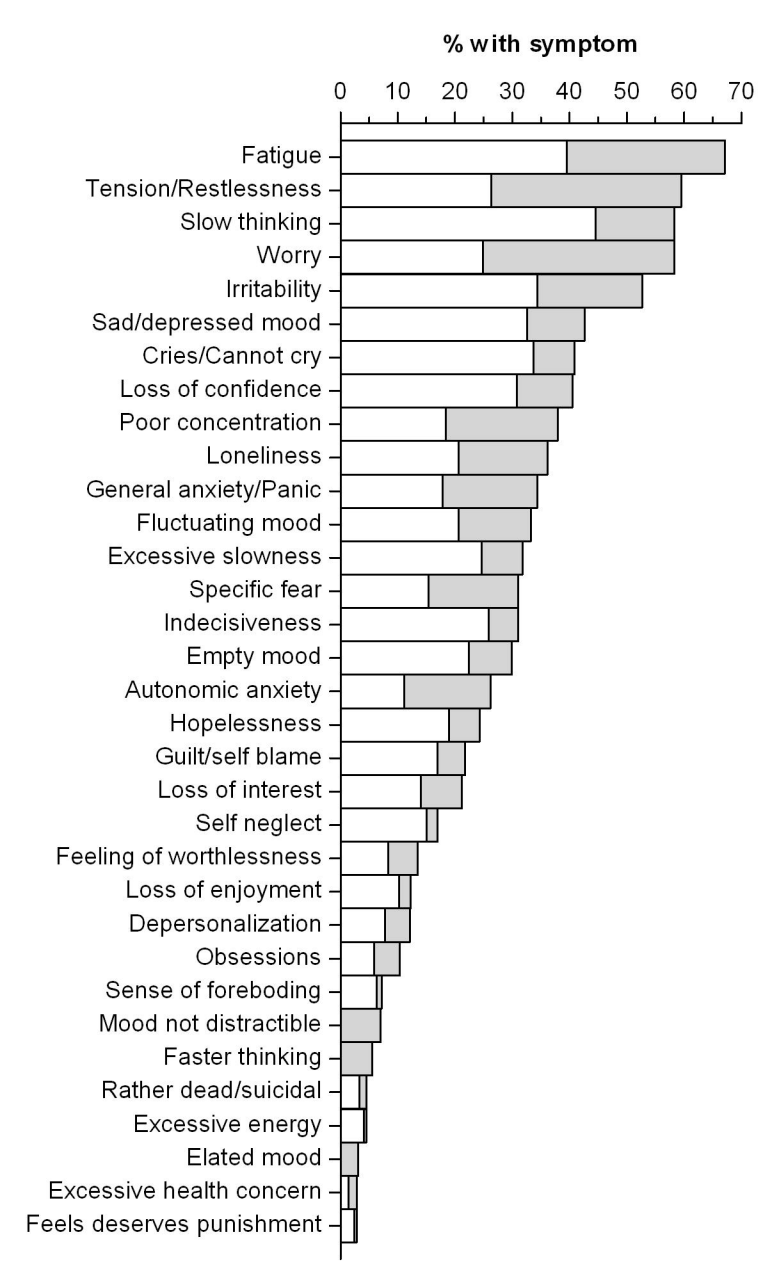
% with symptom
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10
20
30
40
50
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70
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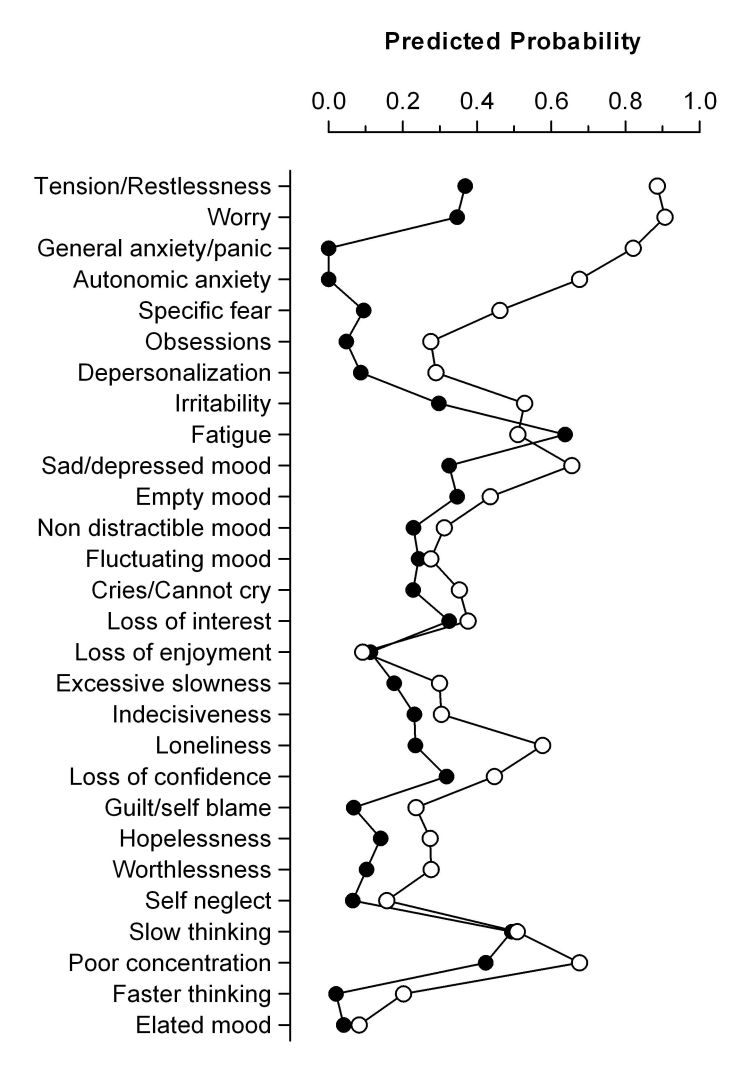
Tension/Restlessness
Slow thinking
Worry
Irritability
Sad/depressed mood
Cries/Cannot cry
Loss of confidence
Poor concentration
Loneliness
General anxiety/Panic
Fluctuating mood
Excessive slowness
Specific fear
Indecisiveness
Empty mood
Autonomic anxiety
Hopelessness
Guilt/self blame
Loss of interest
Self neglect
Feeling of worthlessness
Loss of enjoyment
Depersonalization
Obsessions
Sense of foreboding
Mood not distractible
Faster thinking
Rather dead/suicidal
Excessive energy
Elated mood
Excessive health concern
Feels deserves punishment


Predicted Probability
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Tension/Restlessness
Worry
General anxiety/panic
Autonomic anxiety
Specific fear
Obsessions
Depersonalization
Irritability
Fatigue
Sad/depressed mood
Empty mood
Non distractible mood
Fluctuating mood
Cries/Cannot cry
Loss of interest
Loss of enjoyment
Excessive slowness
Indecisiveness
Loneliness
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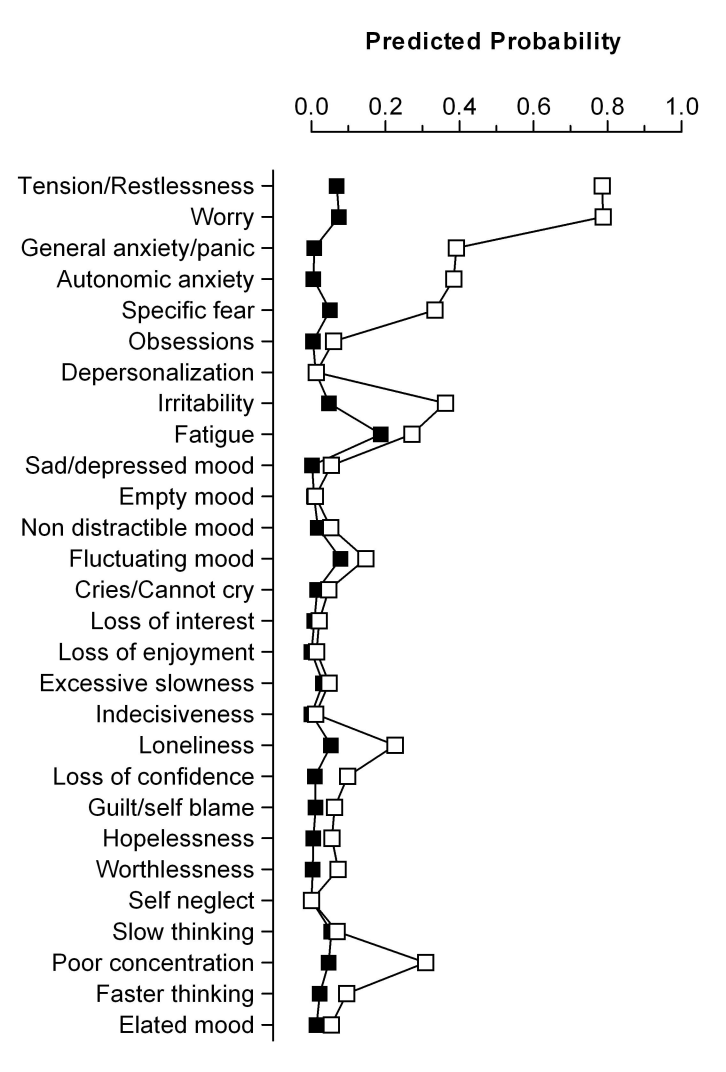
Guilt/self blame
Hopelessness
Worthlessness
Self neglect
Slow thinking
Poor concentration
Faster thinking
Elated mood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