REVIEW

Parkinson's disease subtypes: lost in translation?

Connie Marras,[1,2] Anthony Lang[1,2]

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[1]Morton and Gloria Shulman Movement Disorders Centre, Toronto Western Hospital, University of Toronto, Ontario, Canada
[2]The Edmond J Safra Program in Parkinson's Research, Toronto Western Hospital, University of Toronto, Ontario, Canada

Correspondence to
Dr C Marras, Toronto Western Hospital, Movement Disorders Centre, 399 Bathurst St 7 MCL, Toronto, ON M5T 2S8, Canada; cmarras@uhnres.utoronto.ca

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ABSTRACT

Like many neurodegenerative disorders, Parkinson's disease (PD) is clinically highly heterogeneous. A number of studies have proposed and defined subtypes of PD based on clinical features that tend to cluster together. These subtypes present an opportunity to refine studies of aetiology, course and treatment responsiveness in PD, as clinical variability must represent underlying biological or pathophysiological differences between individuals. In this paper, we review what subtypes have been identified in PD and the validation they have undergone. We then discuss what the subtypes could tell us about the disease and how they have been incorporated into studies of aetiology, progression and treatment. Finally, with the knowledge that they have been incorporated very little into PD clinical research, we make recommendations for how subtypes should be used and make some practical recommendations to address this lack of knowledge translation.

INTRODUCTION

Parkinson's disease (PD) is a remarkably variable condition, to the extent that 'Parkinson's diseases' has been proposed as a more appropriate term to describe the clinical entities.[1] This variability has prompted a number of studies investigating the existence of PD subtypes, which divide PD patients into groups based on clinical or demographic features. Many different groupings or subtype classification systems have been proposed, which raises questions about which are most useful and their implications for future research. Despite extensive research efforts to subtype PD, and evidence that subtypes are associated with disease progression, subtypes have been integrated into very few clinical research studies. We argue that subtypes are only useful if they have an underlying relationship to aetiology, prognosis or treatment responsiveness. If they do, they can be useful tools to improve research methods and thus find a cure or better treatments, or help us to counsel patients or direct existing therapies. These opportunities can only be seized if subtypes are incorporated into clinical research studies. In this paper, we will discuss the purpose of subtyping, the current state of knowledge of PD subtypes and how subtypes can optimally be used in studies of aetiology, progression and treatment of PD.

DEFINING SUBTYPES

Because of the chronic multifaceted and progressive nature of PD, there are many possible ways to define subtypes. For example, PD subtypes may be based on motor features (eg, 'tremor dominant'), cognitive features, age at onset, rate of progression or a combination of these. Subtyping may be based on presenting symptoms (eg, presence or absence of tremor), evolution of disease (fast or slow progression) or on the occurrence of a symptom at a point in the course of the disease (eg, dementia). In our framework, we have not considered subtypes based on aetiology (eg, genetically determined forms vs apparently non-genetic). Although these may have a distinctive phenotype (eg, Parkinson's disease due to mutations in the gene encoding Parkin), others may have a very variable phenotype and may also require other contributing and unrecognised aetiological factors (eg, Parkinson's disease associated with *LRRK2* mutations). Mixing the concepts of aetiology and phenotype subtype classifications could be quite misleading and therefore we only consider phenotypically defined subtypes in this review.

PD SUBTYPES: THE CURRENT STATE OF KNOWLEDGE

Two main approaches to deriving subtype classifications have been used: empirical classifications based on clinical observation of the heterogeneity of PD and data driven classifications where the relationships between variables are used to find those that group together within individuals, with no a priori hypothesis regarding how the chosen variables should contribute to the subtypes other than the number of groups. In each of the following sections we will first discuss the subtypes that have been proposed using data driven techniques (eg, cluster analysis) and then discuss empirically assigned subtypes.

What subtypes have been identified?

In 2010, Van Rooden *et al* published a review of studies that described clusters (subtypes) using data driven techniques.[2] Using their search strategy, we repeated their search and updated it to include studies published until May 2012. We restricted our review to those studies that separated PD into subtypes and excluded studies that examined subtypes of specific symptoms of PD (eg, subtypes of cognitive impairment).

The studies using data driven techniques and the subtypes they identified are shown in table 1. Details of the variables entered into these analyses are shown in the supplementary table (available online only). All of the studies used cluster analysis techniques. The variables entered into the cluster analyses vary both in the domains (motor, cognitive, other non-motor) they represent and when in the disease course they were measured. The number of variables entered into the cluster analyses varied from 3 to 18. One study incorporated

Table 1 Parkinson's disease subtypes identified by data driven studies

Author, year	Subtypes identified
Graham 1999[3]	Short duration (mean 5 years): 1. Good motor control without cognitive impairment 2. Good motor control, executive cognitive deficits 3. Older age at onset, poor motor control + complications, mild cognitive impairment Longer duration (mean 14 years): 1. Poor motor control, no cognitive impairment 2. Poor motor control, moderately severe cognitive impairment
Gasparoli 2002[4]	1. Rapid progression 2. Slow progression
Dujardin 2004[5]	1. Mild motor impairment, relatively preserved cognition 2. 'Reduced overall cognitive efficiency', subcorticofrontal syndrome and more severe motor dysfunction
Lewis 2005[6]	1. Young onset 2. Non-tremor dominant, cognitive impairment and depression 3. Rapid progression without cognitive impairment 4. Tremor dominant
Schrag 2006[7]	1. Young onset 2. Older onset, more rapid progression, less dyskinesias and fluctuations
Post 2008[8]	1. Young onset with slow progression 2. Intermediate age onset with anxiety and depression 3. Oldest onset
Reijnders 2009[9]	1. Rapid progression 2. Young onset with motor complications 3. Non-tremor dominant and psychopathology 4. Tremor dominant
Van Rooden 2011[10]	1. Mild all domains, young 2. Severe motor complications, sleep and depressive symptoms, youngest 3. Medium severity, older 4. Most severe, except mild tremor, prominent motor complications, older
Liu 2011[11]	1. Non-tremor dominant 2. Rapid disease progression 3. Young onset 4. Tremor dominant

single photon emission computed tomography (SPECT) regional cerebral blood flow measurements[5] and the rest of the studies limited the variables to information that can be gathered by history, physical examination or cognitive testing. The studies also vary by the number of clusters sought, from two to five, where specified. These variations are at least in part responsible for the variability in the nature and number of subtypes identified.

The number of subtypes identified varied from two to five (table 1). Age at onset and speed of progression, as defined by Unified Parkinson's Disease Rating Scale (UPDRS) score, divided by disease duration were the most common variables used to describe the clusters. Other defining features of the clusters included 'tremor dominance,' psychopathology, cognitive impairment and motor complications.

The progressive nature of PD makes it important to consider the possibility that subtypes may differ with disease duration, and that the relationship of specific symptoms to subtypes of PD may be different across the course of the disease. Most of the studies of PD subtypes have recruited subjects with variable disease duration, making it difficult to be sure that a 'subtype' identified is not entirely or in part simply a stage in the evolution of the disease. Three studies took their measurements at a specific disease duration, thus improving the ability to make inferences regarding subtypes[4 5 8] (see supplementary table, available online only). Only one assessed patients at a uniform early time point[8]. Graham *et al*[3] dealt with this complexity without constraining the disease duration of the observations, but noting that three of them had a relatively short average disease duration while two had a relatively long duration. They proposed that their three 'early' clusters evolve into two later clusters: a motor only subtype that progresses in the absence of cognitive impairment; a 'motor and cognitive' subtype characterised by the progression of motor and cognitive problems in parallel; and a 'rapid progression' subtype with rapid progression of both motor and cognitive impairment. This is a cross sectional study that could not verify the evolution of the condition. Nonetheless this represents a hypothetical classification system that takes into account both early characteristics, disease evolution and the relationship between the two that would be useful to verify in a longitudinal sample.

Any classification system that is to be used to separate patients from independent cohorts into subtypes will need to define an algorithm for doing so. Only two studies undertook discriminant analyses to derive a method of classifying subjects into the identified subtypes.[2 4] Dujardin *et al* provided an equation which can be solved with 10 variables, including regional cerebral blood flow (corticocerebellar activity ratios for regions of interest), as measured by SPECT.[5] This equation was able to predict the cluster assignment of 95% of the cohort of 42 subjects. Van Rooden *et al* were able to correctly classify over 70% of the derivation and validation samples using categorical forms of a subset of the variables.[4] The classification algorithm was not provided in their paper, however.

Empirically assigned subtypes of PD have used more convenient easily measured disease features. The most common empirical groupings are tremor dominant versus non-tremor dominant (either postural instability gait disorder (PIGD) or akinetic–rigid) and early versus late onset. Tremor dominant, PIGD and indeterminate subtypes are most commonly defined according to the method used by Jankovic *et al*[12] as the sum of UPDRS 'tremor items' (arm tremor by history, rest tremor of face, arms, legs, postural and action tremor of arms by examination) divided by the sum of UPDRS 'PIGD' items (postural instability and gait by examination and walking, freezing and falls by history). This ratio indicates PD subtypes as follows: ≤ 1.0 is classified as PIGD, >1.5 is classified as tremor dominant and 1.0–1.5 is indeterminate. A similar division of patients into tremor dominant, akinetic–rigid and mixed phenotypes has been commonly used. Patients may be assigned to the groups based on expert judgement, or based on UPDRS item score distributions between the tremor related items and items relating to axial features (speech, facial expression, posture, gait, postural instability). These systems and their variations have been referred to as 'traditional motor subtyping'. Because of the similarity between PIGD and akinetic–rigid definitions, we consider studies using them together, however we use the terminology 'PIGD' or 'akinetic–rigid' as they were used in the original papers. Age cut-offs for early versus late onset subtypes vary but commonly use 40 or 50 years of age as a defining threshold.

Validation of PD subtypes

For data driven subtype classifications, the reproducibility must be demonstrated in independent cohorts. Using the same input variables, the subtypes are re-derived and, if reliable, the clusters will have similar characteristics to the original solution. This is not as clearly necessary for the empirically derived subtypes proposed thus far; as described above: by virtue of the relatively simple group definitions, any cohort is completely classifiable into one of the mutually exclusive groups defined by these

systems. For either empirically derived or data driven subtypes, the validity or clinical significance can be demonstrated by testing whether or not the subtypes differ on the basis of clinically relevant variables not included in the subtype definitions or derivation process. Finally, differences in blood, CSF, imaging or pathological biomarkers between subtypes can also be tested and are a strong indicator of meaningful biological differences.

Validation of data driven subtype classifications

The validation work that has been applied to the data driven subtype classifications is summarised in table 2.

Confirmation of original clusters

Two of the studies confirmed their cluster solution using independent samples.[4 7] Both studies repeated their analysis in a completely independent cohort, using the same variables and statistical methods used in the first cohort. A very similar result was obtained, with satisfactory separation of the second cohort into four groups with the same general characteristics. This suggests that their subtype classifications are robust and generalisable. The other studies' classifications remain unconfirmed.

Looking for differences between the clusters

Most of the cluster analysis subtyping studies looked for differences between the clusters on the basis of variables not included in the derivation process.[4–9] For example, Gasparoli *et al*[4] defined their subtypes on the basis of progression, and patients with rapid progression had an older age, symmetry of parkinsonian signs and a predominance of bradykinesia–rigidity and gait disturbance at baseline. In this way the clinical relevance of their progression subtypes was established. In each of the studies that undertook this type of validation, differences between the clusters were found, suggesting meaningful distinctions between the subtypes. These findings are summarised in supplementary table 2 (available online only).

Subtype–pathological correlations

Subtypes can also be validated by correlating a subtype with specific pathological findings. Selikhova[13] applied the subtype classification of Lewis *et al*[6] to a cohort of 242 autopsy verified cases of PD. Because an algorithm had not been established by Lewis *et al* for classification, they specified their own algorithm and cut-offs. Among three subtypes defined according to early clinical features (early onset, non-tremor dominant and tremor dominant), progression was most distinct between the early onset and other groups, where the early onset group had longer survival and longer time to falls, dementia and hallucinations but shorter time to dyskinesias. Pathologically, the non-tremor dominant group had higher Lewy body loads, particularly in the frontal and transentorhinal regions, as well as a higher frequency of neurofibrillary tangles and amyloid pathology. This suggests that the subtypes are reflective of potentially important underlying biological differences. Interestingly, the tremor dominant group did not differ significantly from the non-tremor dominant group in terms of variables reflective of disease progression.

Using a reverse approach, Halliday *et al* set out to identify clinical correlates of pathologically defined groups rather than to define pathological correlates of clinically defined subtypes.[14] Using brains examined as part of the Sydney Multicentre Study of PD, they identified cases where the distribution of Lewy bodies fit the Braak staging scheme.[15] These individuals had a younger onset and longer duration of disease. Severe neocortical Lewy body pathology even with short disease duration characterised patients with dementia. Finally, high Lewy body loads and coexisting amyloid plaques characterised a group with older onset, cognitive decline and a relatively short disease course. These findings also support the biological relevance of clinical subtypes.

Validation of empirically assigned subtypes

The prognostic significance of the empirically assigned subtypes (early vs late onset and akinetic–rigid vs tremor dominant) has been shown in a number of studies, which have been reviewed by Foltynie *et al*.[16] Early age at onset has been associated with a slower rate of progression, as has tremor dominant phenotype.[16 17] There is evidence that the akinetic–rigid form has more severe cell loss in the ventrolateral part of the substantia nigra pars compacts whereas the tremor dominant type shows more severe cell loss in the medial substantia nigra pars compacts.[18] Rajput *et al*[19] examined post mortem dopamine levels in groups of patients with tremor dominant, mixed and akinetic–rigid phenotypes that persisted throughout the course of the disease. They found significantly higher dopamine levels in the globus pallidus and striatum in the tremor dominant cases. Thus there is strong support for biological differences between the traditional motor subtypes of PD.

Traditional motor subtypes of PD have also been assessed for differences in functional neuroimaging. Higher caudate and putaminal FP-CIT binding has been found in tremor dominant PD compared with the akinetic–rigid or mixed phenotypes.[20–23] Regional cerebral blood flow patterns, as assessed by IMP-SPECT, have also been shown to be different between PIGD and tremor dominant subtypes.[24] Distinct metabolic networks underlying tremor, akinesia and cognitive dysfunction have been identified using fluorodeoxyglucose positron emission tomography scanning in PD.[25] Functional MRI has also demonstrated different activation of ipsilateral cerebello-thalamo-cortical and

Table 2 Feasibility of application and validation efforts of subtype classifications from data driven studies

Criterion	Graham 1999[3]	Gasparoli 2002[4]	Dujardin 2004[5]	Lewis 2005[6]	Schrag 2006[7]	Post 2008[8]	Reijnders 2009[9]	Van Rooden 2011[10]	Liu 2011[11]
Subtypes reproduced in independent cohort?	n/a	n/a	n/a	Yes‡	n/a	n/a	Yes	Yes	n/a
Algorithm for classification derived?	No	No	Yes	No‡	No	No	No	Yes	No
Percentage of cohort correctly classified by algorithm in independent cohort?	n/a	n/a	n/a	n/a	n/a	n/a	n/a	77	n/a
Distinguishing clinical/demographic features*	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Distinguishing pathological features†	n/a	n/a	n/a	Yes‡	n/a	n/a	n/a	n/a	n/a

*Were subtypes distinguishable on the basis of clinical or demographic features not included in the derivation of the clusters? (See text for details).
†Were subtypes distinguishable on the basis of pathological findings?
‡By Selikhova *et al*[13]
n/a, not assessed.

striatal-thalamo-cortical loops in akinetic–rigid PD compared with tremor dominant PD.[26] To our knowledge, no other subtyping classifications, whether data driven or empirically assigned, have been examined for distinguishing features using imaging.

WHAT MIGHT SUBTYPES TELL US ABOUT PD?

A number of authors have alluded to the theoretical implications of the existence of subtypes—namely, that they may have different pathophysiological underpinnings,[3 4 9 27] and that symptoms that co-occur or progress together (such as PIGD subtype and cognitive decline) have a common or parallel neuropathological basis.[28] At the aetiological level, differences in disease manifestations between individuals may result from differences in factors that trigger (initiate) the pathophysiological processes or in patient specific factors that modify an established process. In any one individual there is a factor or set of factors that are necessary for initiating the disease process (the 'cause') and subsequently there may be patient specific factors (such as age) that modify the phenotype (including rates of progression of disease). From the treatment perspective, different pathophysiological processes or different pathologies may also result in different responses to therapy.

If PD subtypes result from independent causes and pathophysiological processes, then they can be thought of as separate diseases. On the other hand, if there is a common cause then subtypes must result from patient specific modifiers that change the manifestations of the disease. Figure 1A and 1B show these two theoretical representations of how the simplest of subtyping classifications may be related to the cause and/or pathophysiology of PD. These two models have different implications for the design of research studies. If subtypes have common causal factors and their differences result from patient specific modifying factors, observational studies of aetiology will be able to detect the causal factors with patients of different subtypes grouped together. However, such studies will not be able to detect modifying factors that determine subtypes. These modifying factors may include those that determine the progression of disease. On the other hand, if subtypes have distinct causal factors that are responsible for the differences, when patients with different subtypes are grouped together in a study cohort observational studies of aetiology will obtain a biased estimate of the magnitude of the effect of causal factors and in the worst case may be completely unable to detect the causal factors.

Completely distinct aetiologies and pathophysiologies seem unlikely given the pathological overlap between the subtypes (eg, overlapping anatomical structures and Lewy bodies). However, the models in figure 1 are not mutually exclusive, and as there may be many causal factors contributing to PD, some may be shared across subtypes and others may be subtype specific. Pesticide exposure is a causal factor that has been successfully demonstrated using combined cohorts, indicating either a causal factor so strong for one subtype that its effect is detectable when diluted by including other unrelated subtypes or a common aetiological factor across subtypes. Discovering the correct model will only be answered by separating cohorts into subtypes for studies of aetiology and progression of PD.

For clinical trials of new treatments, subtypes could be useful if they separate patients with PD into groups that differ in their response to treatments (ie, make groups more homogeneous). Recruiting patients likely to have the best treatment response reduces sample size requirements. Alternatively, recruiting a broad spectrum of patients that can later be analysed by subtype may allow us to discover ways to predict responsiveness and individually tailor treatments, or adjust for baseline imbalances in subtypes between groups that could have confounded results related to treatment response.

Variability between patients in response to levodopa and other dopaminergic medications is well recognised clinically. No data driven subtyping study has directly incorporated responsiveness to dopaminergic medication into their cluster analysis but several have included variables that are associated with dopaminergic responsiveness, such as motor fluctuations and dyskinesias[7] or UPDRS 'levodopa unresponsive' and 'levodopa responsive' items.[8] In addition, differences between clusters in terms of responsiveness to dopaminergic medication have not been explored for any of the data driven subtyping systems. Postural instability and gait dysfunction are characteristically less levodopa responsive than other cardinal signs of parkinsonism, and therefore it is logical to assume that the traditional motor PIGD subtype of PD would be less responsive to

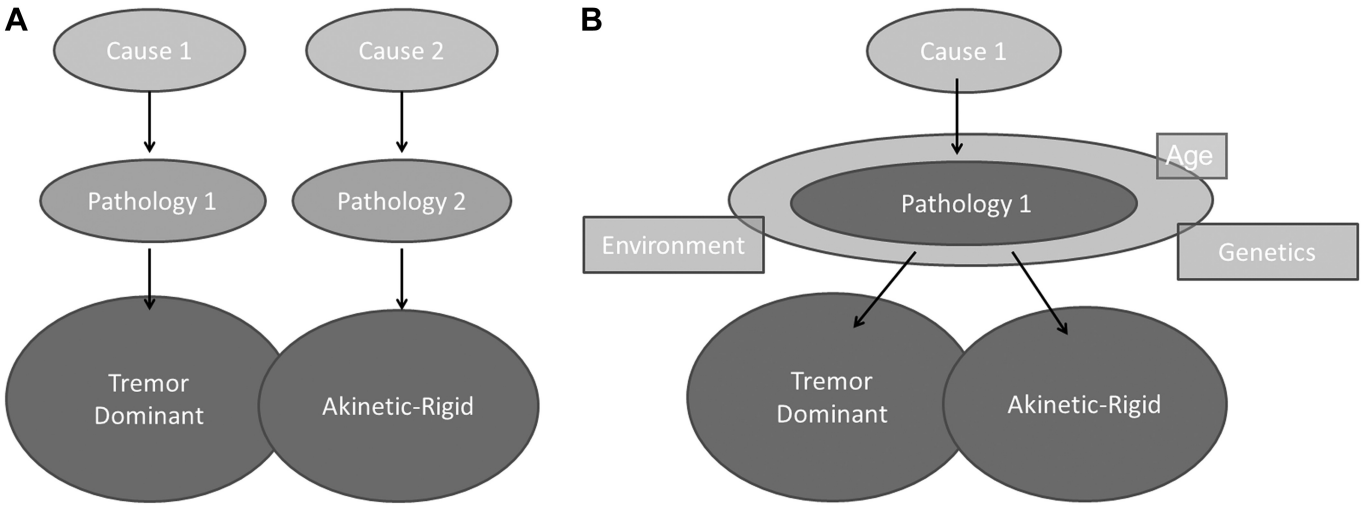

Figure 1 Possible reasons for distinct subtypes of Parkinson's disease. (A) Subtypes of Parkinson's disease may have separate causes and pathophysiology. (B) Subtypes of Parkinson's disease may share aetiological factors and pathophysiological processes, in which cases patient specific modifying factors (eg, age, environment, genetics) must account for the different manifestations.

dopaminergic therapy than the tremor dominant or mixed types. Parkinsonian tremor, however, is variably responsive to levodopa. A search of the Medline database did not reveal any studies formally comparing treatment response in PIGD versus tremor dominant subtypes of PD.

HOW HAVE SUBTYPES BEEN USED IN STUDIES OF DISEASE AETIOLOGY, PROGRESSION AND TREATMENT?

Although the theoretical implications of the existence of subtypes have been raised by a number of authors, the practical implications have been little discussed. Sutherland *et al* raised the issue of lack of success identifying risk factors for both PD and Alzheimer's disease, and proposed that this may be because of the heterogeneity of these diseases.[27] They highlighted mixed tau and α-synuclein pathology in PD and also incidental pathology in unaffected individuals coming to autopsy as evidence that Alzheimer's disease and PD are neither exclusive nor homogeneous entities but rather a complex continuum. They suggest that this heterogeneity may have contributed to the lack of reproducibility in case control studies of risk factors for both 'diseases' to date. The implication is that the methods of risk factor studies need to take into account subtypes of diseases.

Among the many studies that have assessed risk factors for PD or parkinsonism, very few have actually assessed risk factors within subtypes. Tanner *et al* studied the association between parkinsonism and a number of occupational and non-occupational factors.[29] Their analysis included subgroups of PIGD subtype and those less than 50 years of age at diagnosis. Although no significant associations were identified after adjusting for disease duration, it is interesting to note that unadjusted analyses identified a number of associations between PD and prior occupation that were entirely different depending on whether considering PIGD subtype alone or grouping all cases of PD together. Rohl *et al*[30] used the traditional motor and early/late onset classification systems and found more frequent premorbid travel among tremor dominant patients and higher frequencies of premorbid head trauma and rural living in early onset (compared with late onset) patients. Two studies have examined the relationship between smoking, coffee drinking and alcohol and either tremor dominant versus akinetic–rigid[31] or tremor dominant versus PIGD subtypes[32] of PD. Both studies found stronger inverse associations between disease and smoking and alcohol use in the akinetic–rigid or PIGD subtype. Neither found differences between the subtypes in the association with coffee drinking.

We found two clinical trials that assessed the effects of a treatment on PD symptoms within subtypes of PD. Navan *et al*[33] studied the effects of pergolide and pramipexole on tremor in tremor dominant PD and found benefits over placebo in only 10 patients recruited. Vesper *et al*[34] studied the effects of deep brain stimulation on parkinsonian symptoms within groups of tremor dominant and akinetic–rigid PD. This was not a direct comparison, rather two separate analyses; they had used the subtypes to choose the electrode location (Vim thalamus in tremor dominant PD and subthalamic nucleus in akinetic–rigid PD) with very different therapeutic goals (thalamic stimulation to control tremor and subthalamic nucleus stimulation to improve all cardinal features of PD).

Even though the literature is sparse, the few available observational studies support the argument that there may be fundamental differences in aetiology and pathophysiology between the subtypes and that important insights can be gained by separating cohorts into subtypes for analyses. This has successfully occurred using empirical motor subtypes and to a lesser extent early versus late onset PD. Clinical trials have made little use of any PD subtypes to date. To our knowledge, the subtypes derived using cluster analysis have not been applied to either observational or interventional studies of PD.

RECOMMENDATIONS

Considering all of the preceding information, which subtype classification system(s) should be used in clinical research studies of PD? Liu *et al* assessed the relationship between the data driven subtypes they derived and the empirically assigned motor subtypes.[11] They derived a four cluster solution with subtypes described as non-tremor dominant, rapid disease progression, young onset and tremor dominant. They concluded that a four cluster solution was largely corroborated by the work of Lewis *et al*[6] and Reijnders *et al*[9] with similar subtypes. They then assessed the distribution of traditional motor phenotypes (tremor dominant, PIGD and indeterminate, as defined by Jankovic *et al*[12]) and found that motor phenotype did not tend to group together within their four clusters but were spread across them. This suggests that the traditional 'motor phenotype' method of subtyping PD is not equivalent to the most common subtypes identified by cluster analysis methods and the question of which subtype classification is most relevant to the underlying cause and progression of PD is indeed critical.

We propose the following criteria for choosing a subtyping system to use in studies of aetiology, progression or treatment. The subtyping system should:

1. be relatively easy to implement (ie, include a small number of routinely used scales or physical measurements that can be applied at the beginning of a clinical trial or observational study),
2. include the smallest number of subtypes without losing fidelity, as each additional subgroup in analyses has implications for statistical power and
3. best reflect the underlying aetiological or pathophysiological processes that determine the observed heterogeneity of PD.

According to these recommendations, empirically assigned classifications appear to have the advantage of ease of implementation and small number of subtypes. Additionally, all patients can easily be assigned to one or other subtype. Cluster analysis derived subtypes are inherently more complicated, incorporating more variables and often variables that are not regularly measured in clinical practice. Some individuals may not be classifiable according to the clusters' multidimensional descriptions. Furthermore, some specify the measurement of variables at a certain disease duration, which significantly reduces the chance that it will be possible to apply them in cohorts not prospectively designed for the specific purpose of using that classification system. These disadvantages may have discouraged the use of data driven subtype classification systems in observational or interventional studies of PD to date. Selikhova successfully made their own algorithm based on general descriptions of the clusters identified by Lewis *et al* and tailored it to what was available in their database.[13] This demonstrated the feasibility of applying data driven subtype classifications in at least some retrospective cohort studies.

As described above, only two studies have sought to derive a classification algorithm and only one has assessed the reproducibility of their algorithm. This gap between derivation and implementation needs to be filled, as data driven approaches have the advantage of being objective and may provide more robust subtypes than classification systems derived from clinical

intuition (eg, dividing PD patients into groups based on an arbitrarily chosen age at onset). A related but distinct aspect of validation of subtypes to consider is the recruitment source. Almost invariably, the findings discussed above are based on convenience samples recruited from specialty clinics. It is possible that this may provide a biased and non-representative view of the subtypes of Parkinson's disease. Where possible, future studies should strive to study subtypes in population based cohorts.

A final consideration pertaining to the practicality of adopting a data driven subtyping system is the number of subtypes, which has been four in most studies. Dividing cohorts into four groups may be a major disincentive to using subtypes as primary analytic groups in clinical studies of PD due to the sample size demands of this approach. From this perspective, the three group solution of traditional motor subtyping is less demanding. However, if the subgroups are more homogeneous in terms of their association with the exposure of interest then the net effect of analysing the results within subgroups may be an increase in the power to detect an effect. Furthermore, not all subtypes from a classification system have to be included in any one study. A related issue is how large the subtype groups are; an individual subtype will be difficult to study if only a small proportion of PD patients are classified into that subtype.

The relationship to the underlying pathophysiology of PD is both the most important and the most difficult criterion to ascertain. We can start by choosing those subtyping systems that have shown the most robust correlations with biomarkers: biochemical analysis of blood, CSF or brain tissue, imaging and, if available, pathology. The empirical traditional motor classification has been much more extensively examined for biological differences than any data driven system and, as described above, has revealed differences in nigral cell loss, pallidal and striatal dopamine levels, striatal dopamine transporter binding and cerebral blood flow patterns between the motor subtypes. Among the data driven classification systems, only the subtyping system of Lewis *et al* has been tested for distinguishing pathological features and, as mentioned, pathological differences were found between the non-tremor dominant group from the other groups. To our knowledge, there are no studies evaluating the ability of other biomarkers to distinguish data driven subtypes.

Despite the appealing objectivity and rigour of the data driven approach to subtyping, at this time the available evidence does not provide support for choosing any of these classification systems over the traditional motor subtyping system. Furthermore, the simplicity of the traditional motor subtyping offers major advantages if applying it to retrospective cohorts. We would suggest that studies of aetiology and prognosis of PD routinely stratify their analyses by these three motor subtypes, at least in secondary analyses. It would make sense for future treatment studies to incorporate subgroup analyses by motor subtypes as well, but a logical next step for the field would be to assess the responsiveness of the different subtypes to already approved treatments. This knowledge may permit a more educated guess of whether or not such an approach is likely to be a relevant issue for new agents. As described above, definitions of the motor subtypes have varied and the field would benefit from a consensus on how the motor subtypes should be defined.

We are not suggesting that data driven subtyping should be abandoned as potentially useful classification systems. Rather, we propose that they be further developed in terms of practical classification algorithms to guide exploration of their correlation with biochemical, imaging and pathological changes, and ultimately to enable their implementation in clinical research. Despite a substantial body of literature on PD subtypes there has been very little translation of this knowledge into changes in clinical research practice. Suggested next steps for these studies are summarised in box 1. If these advances can be achieved, we believe that the knowledge of PD subtypes could be used as a tool to accelerate discovery of causal and risk factors for this complex disease as well as improve our ability to individualise treatment in order to optimise clinical benefit.

Box 1 Next steps for research into data driven Parkinson's disease subtypes

1. Derive algorithms to sort cohorts into groups based on the subtypes
2. Evaluate the performance of the algorithms in independent cohorts based on:
   a. Proportion of the cohort classifiable according to the algorithm
   b. Number of subtypes and proportion of cohort assigned to each subtype
   c. Ability to distinguish subtypes on the basis of clinical, demographic, biological or pathological measures.
   d. Likelihood that cohorts will contain the data necessary for subtyping.

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Supplementary Table – Web only file

Author, year	Disease features included	When measured	Number of clusters sought	Subtypes identified
Graham, 1999[4]	Age at onset Disease duration Alternate finger tapping UPDRS motor UPDRS Activities of daily living Depression Cognitive battery Time to dyskinesias Time to falls Time to fluctuations	Variable	Not stated	Short duration (mean 5 years) 1: good motor control without cognitive impairment 2: good motor control, executive cognitive deficits 3: older age at onset, poor motor control + complications, mild cognitive impairment Longer duration (mean 14 years) 1: poor motor control, no cognitive impairment 2: poor motor control, moderately severe cognitive impairment
Gasparoli 2002[5]	UPDRS motor score at 5 years Dyskinesias at 5 years Motor fluctuations at 5 years	At 5 years duration	2	1. Rapid progression 2. Slow progression
Dujardin 2004[3]	-UPDRS-III score -"Interference cost" index of the Stroop word colour test -Number of different words named in the alternating word fluency test -Number of words correctly free recalled - Free and cued word list recall -Mattis Dementia Rating Scale score -Number of different words named in the semantic word fluency test	Three years post diagnosis	2, maximum not stated	1. Mild motor impairment, relatively preserved cognition 2. "Reduced overall cognitive efficiency, an exacerbated subcorticofrontal syndrome and more severe motor dysfunction"

	-Delayed free recall -Ten SPECT scan regions of interest			
Lewis 2005[6]	Age at onset Levodopa dose >1gm or <1gm per day Motor phenotype score (Tremor score/non-tremor UPDRS score) Mini Mental State Examination National Adult Reading Test Pattern recognition memory Tower of London Beck Depression Inventory Total UPDRS/disease duration	Variable	2-5	1. Young onset 2. Non-tremor dominant, with cognitive impairment and depression 3. Rapid progression without cognitive impairment 4. Tremor dominant
Schrag 2006[7]	Age at onset Age Dementia Fluctuations Dyskinesias Hoehn and Yahr score per year	Variable	2-5	1. Young onset 2. Older onset, more rapid progression, less dyskinesias and fluctuations
Post 2008[8]	Age Age of onset Levodopa responsive UPDRS item sum Levodopa poorly responsive UPDRS item sum Anxiety and depressive symptoms (HADS) Mini Mental State Examination UPDRS motor score/disease duration	Newly diagnosed	2 and 3	1. Young onset with slow progression 2. Intermediate age onset with anxiety and depression 3. Oldest onset
Reijnders 2009[9]	UPDRS tremor score UPDRS bradykinesia/rigidity score	Variable	2-5	1. Rapid progression 2. Young onset with motor complications

	UPDRS PIGD score Motor complications: UPDRS part IV Age at onset Mini Mental State Examination Depressive symptoms (MADRS) Apathy (UPDRS item 4) Hallucinations (UPDRS item 2) UPDRS total/disease duration			3. Non-tremor dominant and psychopathology 4. Tremor dominant
Van Rooden 2011[10]	Tremor Bradykinesia/rigidity On freezing, speech, swallowing Postural Instability Gait Disorder Cognitive impairment (SCOPA-Cog) Psychotic symptoms Autonomic dysfunction (SCOPA-AUT) Depressive symptoms (HADS) Daytime sleepiness (SCOPA-SLEEP) Sleep dysfunction (SCOPA-SLEEP) Motor fluctuations Dyskinesias	Variable (adjusted for disease duration)	Not stated	1: Mild all domains, young 2. Severe motor complications, sleep and depressive symptoms, youngest 3. Medium severity, older 4. Most severe, except mild tremor, prominent motor complications, older.
Liu 2011[11]	Age Age at onset Disease duration Hoehn and Yahr stage Tremor (UPDRS) Rigidity (UPDRS) Bradykinesia (UPDRS) PIGD score	Variable	3-5	1. Non-tremor dominant 2. Rapid disease progression 3. Young onset 4. Tremor dominant

	Ratio of tremor to non-tremor score (UPDRS) Mini Mental State Examination Depressive symptoms (HAM-D) Sleep quality (PSQI) Constipation Fatigue severity scale score Motor complications (UPDRS IV) UPDRS total/disease duration UPDRS motor/disease duration UPDRS ADL/disease duration			

Supplementary Table 2– Web only file

Author, year	Subtypes identified	Differences found between subtypes (variables not included in derivation process)
Graham, 1999[4]	Short duration (mean 5 years) 1: good motor control without cognitive impairment 2: good motor control, executive cognitive deficits 3: older age at onset, poor motor control + complications, mild cognitive impairment Longer duration (mean 14 years) 1: poor motor control, no cognitive impairment 2: poor motor control, moderately severe cognitive impairment	Not reported
Gasparoli 2002[5]	1. Rapid progression	Older Greater symmetry of parkinsonism Greater bradykinesia/rigidity and gait disturbance at baseline
	2. Slow progression	
Dujardin 2004[3]	1. Mild motor impairment, relatively preserved cognition	
	2. "Reduced overall cognitive efficiency, an exacerbated subcorticofrontal syndrome and more severe motor dysfunction"	Best predicted by lower educational level and poorer performance at **baseline** on: -Stroop colour-word interference index, -Semantic fluency -MMS SPECT scan differences also found
Lewis 2005[6]	1. Young onset	More dyskinesias More motor fluctuations More frequently treated with dopamine agonists
	2. Non-tremor dominant, with cognitive impairment and depression	

	3. Rapid progression without cognitive impairment	
	4. Tremor dominant	More frequently treated with anticholinergic medications
Schrag 2006[7]	1. Young onset	Higher levodopa mean dose Higher depression scores
	2. Older onset, more rapid progression, less dyskinesias and fluctuations	
Post 2008[8]	1. Young onset with slow progression	
	2. Intermediate age onset with anxiety and depression	Poorer Short Form (SF)-36 mental component score
	3. Oldest onset	More physical disability
Reijnders 2009[9]	1. Rapid progression	
	2. Young onset with motor complications	Lower mean age Longer disease duration
	3. Non-tremor dominant and psychopathology	Longer disease duration Higher Hoehn and Yahr stage Higher UPDRS ADL scores
	4. Tremor dominant	
Van Rooden 2011[10]	1: Mild all domains, young	
	2. Severe motor complications, sleep and depressive symptoms, youngest	Youngest age at onset More women Longer disease duration
	3. Medium severity, older	
	4. Most severe, except mild tremor, prominent motor complications, older.	More women

Liu 2011[11]	1. Non-tremor dominant 2. Rapid disease progression 3. Young onset 4. Tremor dominant	Not reported