On the ‘classification’ of neurodegenerative disorders: discrete entities, overlap or continuum?

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Abstract
The traditional method of classifying neurodegenerative diseases is based on the original clinico-pathological concept supported by 'consensus' criteria and data from molecular pathological studies. This review discusses first, current problems in classification resulting from the coexistence of different classificatory schemes, the presence of disease heterogeneity and multiple pathologies, the use of 'signature' brain lesions in diagnosis, and the existence of pathological processes common to different diseases. Second, three models of neurodegenerative disease are proposed: (1) that distinct diseases exist ('discrete' model), (2) that relatively distinct diseases exist but exhibit overlapping features ('overlap' model), and (3) that distinct diseases do not exist and neurodegenerative disease is a 'continuum' in which there is continuous variation in clinical/pathological features from one case to another ('continuum' model). Third, to distinguish between models, the distribution of the most important molecular 'signature' lesions across the different diseases is reviewed. Such lesions often have poor 'fidelity', i.e., they are not unique to individual disorders but are distributed across many diseases consistent with the overlap or continuum models. Fourth, the question of whether the current classificatory system should be rejected is considered and three alternatives are proposed, viz., objective classification, classification for convenience (a 'dissection'), or analysis as a continuum.

Key words: neurodegenerative disease, discrete entities, disease overlap, continuum, fidelity, ‘signature’ brain lesions.

Introduction
The traditional method of classifying neurodegenerative diseases is based on the original clinico-pathological concept, viz., a disease entity is a specific combination of clinical features and a distinctive neuropathology [40,45,59]. It was this principle, originally applied to small numbers of cases, that resulted in the first descriptions of Alzheimer’s disease (AD) [1,60], Pick’s disease (PiD) [116], dementia with Lewy bodies (DLB) [45,87], Creutzfeldt-Jakob disease (CJD) [32,75], and progressive supranuclear palsy (PSP) [128]. Subsequently, the definition of these diseases has been refined and modified by two further developments. First, the establishment of ‘consensus criteria’ the aim of which was to achieve agreement among leading experts regarding the clinical and pathological features most useful in diagnosis [90,95,133]. Second, the discovery of disease-specific antibodies enabled aggregates of insoluble and/or misfolded proteins to be detected and therefore the molecular ‘signature’ of brain lesions to be established [46]. As
a result, neurodegenerative diseases are often regarded as relatively distinct ‘entities’. In this traditional model, cases that exhibit the features of more than one disorder (‘multiple pathologies’), e.g., DLB in combination with AD [52], are often considered to represent the co-occurrence of common neuropathologies [16].

Two aspects of recent studies have questioned the validity of the traditional model, viz., the degree of heterogeneity commonly observed within disorders and the extent of the overlap or ‘interface’ between them [6,16,42,45,61]. Overlap between neurodegenerative disorders is defined as the coexistence of clinical and/or neuropathological features of more than one disorder in the same individual case [16]. Hence, multiple pathological processes are common in dementia cases and significantly affect the clinical presentation of the disease [144]. If there is extensive overlap, it raises a question of the ‘distinctiveness’ of the individual diseases and therefore, how they may be classified. Some closely related neurodegenerative diseases may even be ‘unclassifiable’ and essentially form a ‘continuum’ in which there is a gradual clinical and pathological change from one case to another [6]. The frequent use by authors of such terms as ‘complex syndrome’ [30, 49,132], ‘spectrum of disorders’ [50], or even ‘continuum’ [30,49,132] testifies to the extent to which the boundaries between different disorders may in reality be more indistinct than previously thought.

This review considers various aspects of the question of how neurodegenerative disease should be ‘classified’. First, the traditional clinico-pathological concept is described and problems resulting from the coexistence of different classificatory schemes, the presence of disease heterogeneity, the use of ‘signature’ brain lesions in diagnosis, and pathological processes common to different diseases are discussed. Second, three models of neurodegenerative disease are proposed, viz., (1) that distinct diseases exist (‘discrete’ model), (2) that distinct diseases exist but exhibit overlapping features (‘overlap’ model), and (3) that distinct diseases do not exist and neurodegenerative disease forms a ‘continuum’ in which there is continuous variation in clinical/pathological features from one case to another (‘continuum’ model). Third, the distribution of the major molecular ‘signature’ lesions among the different disease entities is reviewed. Fourth, the question of whether the current classification of neurodegenerative disease should be rejected is discussed and three alternative conceptual systems are proposed, viz., objective classification, classification for convenience (a dissection), or analysis as a continuum.

Traditional method of classification

Clinico-pathological concept

The original description of some disorders was based on studies of small numbers of cases and on the correlation of clinical symptoms with neuropathology. Hence, the original clinico-pathological description of AD originated in Alzheimer’s detailed report of 1907 [1] of a case of presenile dementia associated with the presence of numerous senile plaques (SP) and neurofibrillary tangles (NFT) [59,60]. Similarly, the description of PiD was based on a series of patients characterised by cognitive disturbance, personality change and focal symptoms [116] and DLB on the description of patients by Lewy with ‘paralysis agitans’ accompanied by the formation of SP and NFT [45,87]. Similarly, PSP was defined as an entity in 1964 based on nine cases of progressive brain disease [84,128]. Notably, many of these disorders were not described originally as ‘discrete’ diseases by the original investigators who often interpreted such cases as examples of more complex ‘syndromes’.

Consensus criteria

Consensus criteria, the purpose of which was to provide a set of agreed objective criteria for diagnosis, have now been established or proposed for the majority of neurodegenerative diseases. Hence, AD is diagnosed according to the ‘National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association’ (NINCDS/ADRDA [133]), the histological diagnosis being established by the presence of widespread neocortical senile plaques (SP) consistent with the ‘Consortium to Establish a Registry of Alzheimer’s Disease’ (CERAD) criteria [98] and now extended by the NIA-Reagan Institute criteria [76]. DLB is diagnosed according to the ‘Consortium on Dementia with Lewy bodies’ (CDLB) guidelines for DLB [96], and PSP by the National Institute of Neurological Disorders and Stroke (NINDS) and the Society of PSP (SPSP) [68,90,91]. Recently, consensus criteria have also been proposed for many of the disorders included within frontotemporal dementia (FTD) and its pathological substrate frontotemporal lobar degeneration (FTLD) [29].

Molecular pathology

The major molecular constituents of brain lesions, e.g., β-amyloid (Aβ, tau, and α-synuclein have played a defining role in diagnosis and classification. In
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Uncovering the complexities of neurodegenerative disorders: discrete entities, overlap or continuum?

In the world of neurodegenerative disorders, a direct link has been postulated between the presence of a specific gene mutation and the formation of a ‘signature’ brain lesion. Hence, mutations of the amyloid precursor protein (APP) [31,54] and presenilin (PSEN) genes PSEN1 [126] and PSEN2 [86], have been linked to familial forms of AD (FAD), the tau gene (MAPT) to FTD with parkinsonism linked to chromosome 17 (FTDP-17) [119], and α-synuclein [143], leucine-rich repeat kinase 2 (LRRK2) [143], and PARK7 (DJ-1) [112] genes to familial forms of Parkinson’s disease (PD). In addition, the majority of familial cases of FTLD with ubiquitin-immunoreactive and tau-negative inclusions (FTLD-U), are associated with mutations of the progranulin (GRN) gene [21,24,33,102,118], with smaller numbers of cases associated with valosin-containing protein (VCP) gene mutation [47] or variants in the ubiquitin associated binding protein 1 (UBAP1) gene [93,121].

Originally, the majority of neurodegenerative disorders were classified into two major molecular groups, viz., the tauopathies: AD, PiD, argyrophilic grain disease (AGD) [123], PSP, corticobasal degeneration (CBD), and FTLD-U; and the synucleinopathies, viz., PD, DLB, and multiple system atrophy (MSA) [55]. Subsequently, cases that did not possess either tau or α-synuclein-immunoreactive inclusions were reported. First, a proportion of FTLD-U cases were shown to have inclusions immunoreactive to the product of the transcriptor repressor gene (TARDBP), viz. transactive response (TAR) DNA-binding protein of 43kDa (TDP-43) [107] and these cases are now referred to as TDP-43 proteinopathy (FTLD-TDP). Second, neuronal intermediate filament inclusion disease (NIFID) was originally associated with inclusions containing epitopes of ubiquitin and neuronal intermediate filament (IF) proteins such as α-internexin (INT) [17,18,25,27,77]. Subsequently, these cases have also been shown to be associated with the product of the ‘fused in sarcoma’ (FUS) gene [108] which is also implicated in familial amyotrophic lateral sclerosis (ALS) with FUS mutation [83,139,140], basophilic inclusion body disease (BIBD) [103], and atypical FTLD with ubiquitin-immunoreactive inclusions (aFTLD-U) [109].

Problems arising from the traditional model

Problems of classification

Problems arising from the clinico-pathological concept are well illustrated by FTD, the second most common cause of dementia in industrialised countries [29]. Recent genetic and molecular data have led to considerable changes in the classification and nomenclature within this group [29]. Hence, discrimination between the different entities is often only possible using neuropathological criteria, the majority of which are based on the morphology and molecular composition of ‘signature’ inclusions such as neuronal cytoplasmic inclusions (NCI), neuronal intranuclear inclusions (NII), and glial inclusions (GI) including glial cytoplasmic inclusions (GCI) and astrocytic ‘plaques’ [106].

FTD is a clinical diagnosis and FTLD is an ‘umbrella term’ used for the currently identified neuropathological variants [29,137]. The clinical variants of FTD include the behavioural variant, the language variants, e.g., semantic dementia (SD) and primary progressive aphasia (PPA), and motor variants such as CBD and motor neuron disease (MND). The pathological variants of FTLD include those with tau, ubiquitin, TDP-43, and FUS-immunoreactive inclusions [29]. The clinical features of FTD, however, may not predict their pathology and neuropathological features alone cannot establish a diagnosis of FTD. Hence, some authors consider FTD to define a group of cases loosely united by clinical presentation but with heterogeneous pathologies [62] and therefore, cannot be described by strict clinico-pathological criteria alone. Recent studies have also questioned whether some of the present members of the group should be classified within FTD. For example, CBD is a predominantly extrapyramidal motor disorder in which there is a poor correlation between neuropathology and clinical syndrome [95]. A further problem is posed by cases exhibiting frontal lobe dementia but accompanied by a typical motor neuron disease (MND)-type pathology not typical of any single entity currently classified within FTD [25]. Hence, FTD represents a range of clinical syndromes that do not map reliably onto the spectrum of recognised pathologies [70,80] and therefore challenge the conventional clinico-pathological concept.

The coexistence of different classificatory schemes

Genetic and molecular biological data have played a crucial role in diagnosis [81]. In AD, for example, identification of Aβ was made by purification from congophilic angiopathy or SP [57]. Subsequently, the study of a small number of early-onset familial cases revealed them to be linked to mutations of the APP gene [31,54] resulting in β-amyloid (Aβ) being identified as
the ‘signature’ lesion of the disease [53]. In addition, the presence of tau-immunoreactive NFT in AD separates the disorder from DLB, which possesses α-synuclein-immunoreactive inclusions, the two disorders therefore, being distinct at the molecular level [129]. Nevertheless, advances in genetics and molecular biology also suggest that the traditional concept accommodates clinically and pathologically heterogeneous conditions within the same group [44].

The initial division of disorders into tauopathies and synucleinopathies established a molecular classification of disease that may be at variance with that of the traditional concept. As a consequence, the classification of the tauopathies has altered considerably. For example, Sergeant et al. [124] recognised three groups of tau diseases, viz., AD, PiD and PSP/CBD and suggested that the clinical phenotype was correlated with specific tau isoforms expressed in vulnerable neuronal populations. Tolnay and Probst [134], however, identified the major tauopathies to be AD, AGD, PiD, PSP, and CBD and included them as one of their four ‘main’ categories of neurodegenerative disease, viz., tauopathies, synucleinopathies, polyglutamine diseases, and diseases with ubiquitin-immunoreactive inclusions, the latter being the most frequent, and now identified as FTLD-TDP [29]. Subsequently, a more detailed classification of the tauopathies was proposed by Trojanowski and Dickson [137]. Hence, cases with tau-immunoreactive inclusions composed of three-repeat (3R) tau were likely to be PiD or FTDP-17; tau-immunoreactive inclusions composed of four-repeat (4R) tau CBD, PSP, or FTDP-17; while lesions composed of both 3R and 4R-immunoreactive tau NFT-dementia or FTDP-17. If ‘broad criteria’ are used to define the typical phenotypes of AD and DLB, then it is inevitable that there will be a significant number of intermediate cases which do not fall naturally into either of the defined categories. It may then be necessary to define and name the intermediates, e.g., ‘mixed’ DLB/AD [52]. If ‘broad criteria’ are used, in contrast, then the degree of heterogeneity now contained within each of the groups will result in overlapping clinical and pathological features and the presence of a significant interface in which there are varying contributions of the two pathologies. In either of these models, the problem is how to describe and classify the intermediate cases.

### Disease heterogeneity

The presence of disease heterogeneity, viz., variation in clinicopathological features between individual cases classified within the same group, is a major cause of overlap [16]. This problem is particularly acute in AD. Early DSM-III criteria for AD greatly broadened the definition of the disease and the effect of this can be seen by examining, for example, the relationship between AD and DLB. Hence, if there is continuous variation from one disorder to another and if ‘restrictive criteria’ are used to define the typical phenotypes of AD and DLB, then it is inevitable that there will be a significant number of intermediate cases which do not fall naturally into either of the defined categories. It may then be necessary to define and name the intermediates, e.g., ‘mixed’ DLB/AD [52]. If ‘broad criteria’ are used, in contrast, then the degree of heterogeneity now contained within each of the groups will result in overlapping clinical and pathological features and the presence of a significant interface in which there are varying contributions of the two pathologies. In either of these models, the problem is how to describe and classify the intermediate cases.

### The use of ‘signature’ inclusions in diagnosis

Studies of familial cases of disease, and subsequently of the molecular composition of the resulting inclusions, resulted in the identification of ‘signature’ pathological lesions, the presence and/or absence of which have become an important criterion in neuro-pathological classification. Hence, Aβ, the protease resistant form of prion protein (PrPe), three-repeat (3R)
and four-repeat (4R) tau, α-synuclein, TDP-43, and FUS are currently recognised as the most important molecular markers of disease. There are several problems resulting from this approach [7,19]. First, inclusions often comprise several molecular constituents and therefore the scientific basis for using any individual marker in classification has to be established. Second, when many chemical constituents are present, there is the problem of distinguishing the primary ‘pathological’ protein from the breakdown products of the cell, and compounds acquired later by binding to existing proteins [19]. Familial cases have usually provided the strongest evidence of the ‘primary’ pathogenic protein, the results then being extrapolated to sporadic disease of similar phenotype. Many primary ‘pathogenic’ proteins, however, may themselves be deposited as a consequence rather than being the cause of cellular degeneration, although in more common sporadic disease it is more likely that abnormal protein deposition is causative [15,19]. Third, the chemical composition of an inclusion may change as the disease develops and activity of the primary protein may decrease or become substantially altered with time, which may affect the classification of longer duration cases [19]. Fourth, data are limited regarding the densities of ‘signature’ inclusions across disease entities and therefore, on their degree of ‘fidelity’ to a specific disease. Fifth, quantitative information on the densities of signature inclusions in control cases is often lacking and therefore, the potential occurrence of the lesions as a consequence of normal aging.

**Similar pathogenic cascades in different diseases**

A genetic cause has been identified in familial forms of many diseases including AD, PD, Huntington’s disease (HD), ALS, FTLD, prion disease, and in many ataxic syndromes [65]. In these diseases, a pathogenic model is often proposed in which genetic change initiates a cascade of events leading to the accumulation of an abnormally folded and/or aggregated protein resulting in cell death [46]. There may be relatively few cellular pathways, however, leading to cell death in different diseases, and as a consequence, diseases classified within different groups may have pathological mechanisms in common. In the tauopathies, for example, phosphorylated tau occurs in several of the diseases leading to the accumulation of 3R and 4R-tau-immunoreactive inclusions. In addition, recent studies of ALS have led to the concept of the ‘clinico-pathological spectrum’ and to include groups that are likely to share the same aetiology such as progressive lateral sclerosis (PLS), progressive muscular atrophy (PMA), ALS-dementia, and ALS-frontal lobe dementia [73]. These diseases are all likely to be syndromes exhibiting a similar pathogenic cascade in which the resulting clinical phenotype depends largely on anatomical selectivity [73]. Hence, common pathological processes blur the ‘distinctiveness’ of disorders causing overlap and may even result in a continuum between some traditional disorders.

**Three models of neurodegenerative disease**

In the light of these concerns, three possible models of neurodegenerative disease are proposed: (1) that distinct diseases exist (‘discrete’ model), (2) that distinct diseases exist but exhibit overlapping features (‘overlap’ model), and (3) that distinct diseases do not exist and neurodegenerative disease is a ‘continuum’ in which there is continuous variation in clinical/pathological features from one case to another (‘continuum’ model). The three models are illustrated in Fig. 1.

![Fig. 1. Three models of neurodegenerative disease based on the theoretical distribution of three cases each representing a different disorder: (A) the three cases are classified into three categories of disease with little overlap between them (‘discrete’ model), (B) each case falls more or less into three categories of disease but exhibit overlapping features (‘overlap’ model), and (C) the three cases do not fall into separate categories but show a continuous change from one case to another (‘continuum’ model).](image-url)
Discrete model

If disorders are distinct from each other, then there should be clinical and pathological features unique to each disorder with little overlap between them (Fig. 1A). If this model is correct, many of the clinical and pathological features associated with each disorder would be ‘constant’ or exhibit a ‘high fidelity’, i.e., they should occur in a high percentage of cases with the disorder and not in any other disorder. Each disorder should then be characterised by a unique combination of clinical and pathological features consistent with the clinico-pathological concept. In addition, there should be positive correlations between groups of clinical and pathological features leading to distinguishable disease entities. Two different neuropathological features may occur together if they are ‘dependent features’ i.e., the formation of one pathological feature directly leads to another. For example, the ‘amyloid cascade hypothesis’ of AD [64] proposes that the formation of NFT is a direct consequence of the deposition of Aβ in the form of SP and therefore both lesions should be characteristic of AD [5]. Alternatively, two or more features that occur together may be ‘commensal’, i.e., they are dependent features not because one causes the development of the other but because they require a common pathological event for their formation. For example, NFT in AD may not be caused by the deposition of Aβ [9] but both may be the consequence of neuronal degeneration, NFT being formed within neuronal perikarya and its processes and SP at the degenerating axon terminals [4,34,114].

Overlap model

Neurodegenerative disorders may be relatively distinct but exhibit a degree of overlap in their clinical and neuropathological features resulting in cases which exhibit characteristics of both disorders (Fig. 1B). There are many studies which support this type of model and they have been discussed in previous reviews [6,16]. Hence, AD shares features with normal aging, vascular dementia (VD), members of the tauopathies and synucleinopathies, and with prion disease [6]. Hence, there is an age-related reduction in brain volume and weight, enlargement of the ventricles, and loss of synapses and dendrites in selected areas in normal brain [72]. Accompanying these changes are many of the pathological features characteristic of AD, viz., senile plaques (SP) and neurofibrillary tangles (NFT) [5]. The major molecular constituent of the SP is Aβ [53] and hence, Aβ deposition in the form of diffuse (‘pre-amyloid’), primitive, and classic (‘dense-cored’) deposits is often regarded as a ‘signature’ pathological feature of AD [36,53]. Nevertheless, studies of Aβ deposition have also demonstrated overlaps between AD and normal brain [37,94]. In addition, there are overlaps reported between the various entities which comprise FTD [16], and within and between the disorders comprising the tauopathies and synucleinopathies [16]. Multiple pathologies are common in dementia cases. For example, in a study of 45 cases, 21 (46.7%) had multiple significant pathologies with some cases exhibiting three or more different pathologies [144].

Continuum model

The degree of overlap between two disorders may become so extensive that there is essentially continuous variation in clinical and neuropathological features from one disorder to another, each case being essentially unique. If neurodegenerative disease as a whole was distributed as a strict continuum, then no two individual cases would be identical, cases would exhibit continuous variation and as a consequence, diseases would
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Table I. Major neurodegenerative diseases, their molecular determinants, and ‘signature’ lesions

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<tr>
<th>Disease</th>
<th>Abbreviation</th>
<th>‘Signature’ lesions</th>
<th>Major molecular determinant</th>
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<tr>
<td>Familial amyotrophic lateral sclerosis</td>
<td>FALS</td>
<td>NCI</td>
<td>FUS</td>
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<td>Argyrophilic grain disease</td>
<td>AGD</td>
<td>NCI</td>
<td>4R tau</td>
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<td>Alzheimer’s disease</td>
<td>AD</td>
<td>SP</td>
<td>3R/4R tau β-amyloid (Aβ)</td>
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<td>Basophilic inclusion body disease</td>
<td>BIBD</td>
<td>GCI</td>
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<td>Corticobasal degeneration</td>
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<td>Creutzfeldt-Jakob disease</td>
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<td>PrP deposits</td>
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<td>Dementia with Lewy bodies</td>
<td>DLB</td>
<td>NCI</td>
<td>α-synuclein</td>
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<td>Down’s syndrome</td>
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<td>FTD with parkinsonism linked to chromosome 17</td>
<td>FTDP-17</td>
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<td>Frontotemporal lobar degeneration with motor neuron disease</td>
<td>FTLD-MND</td>
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<td>Frontotemporal lobar degeneration with TDP proteinopathy</td>
<td>FTLD-TDP</td>
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<td>Frontotemporal lobar degeneration with Ub inclinations (atypical)</td>
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<td>Motor neuron disease with dementia</td>
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<td>Multiple system atrophy</td>
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<td>Neuronal intermediate filament inclusion disease</td>
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<td>Parkinson’s disease</td>
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<td>NFT</td>
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<td>Parkinsonian-dementia complex of Guam</td>
<td>Guam PDC</td>
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<td>3R/4R tau</td>
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<td>Pick’s disease</td>
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<tr>
<td>Progressive supranuclear palsy</td>
<td>PSP</td>
<td>NCI, GCI</td>
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not be readily delimited as definable units (Fig. 1C). A number of studies have used the term ‘continuum’ to describe groups of heterogeneous diseases or the relationships between one disease entity and another. For example, Garraux et al. [49] reported that certain patients with FTD developed the clinical features of MND and that there existed a functional continuum between classical MND, and FTD. Talbot et al. [132] carried out a single-photon emission computed tomography (SPECT) study of classical MND, FTD/MND and FTD and also came to the conclusion that there was a common pattern of cortical involvement in these diseases which was most pronounced in FTD/MND and FTD. It was subsequently concluded that these diseases could represent the clinical range of a functional continuum. Moreover, Caselli et al. [30] studied asymmetric cortical degenerative syndromes (aphasic, perceptive, motor, frontal lobe, bitemporal) which constitute a range of atypical cortical dementias. These disorders appeared to be genetically heterogeneous and the question was raised as to whether they represented individual syndromes or a functional continuum.

Few studies have been designed specifically to demonstrate whether a continuum exists between disorders. As an example, β-amyloid (Aβ) deposition was quantified in the temporal lobe of elderly control cases, cases of DLB, and AD [14]. A principal components analysis (PCA) of these data suggested that the first three principal components (PC) accounted for 26% of the total variance. A plot of the cases in relation to PC1 and PC2 (Fig. 2) showed considerable overlap between patient groups with no distinct boundary between the control, DLB, and AD cases. In addition, there was no clear boundary between FAD and sporadic AD (SAD).

<table>
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<tr>
<th>Disorder</th>
<th>Aβ</th>
<th>pPrP</th>
<th>3R tau (NCI)</th>
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**Fig. 3.** The distribution of the major pathological variables across different neurodegenerative diseases to exhibit their ‘fidelity’.
although the FAD cases as a group had lower loadings on PC2. Hence, with reference to the variable ‘Aβ deposition’, control, ‘pure’ DLB, DLB/AD, and ‘pure’ AD cases appear to form a continuum with no abrupt boundaries between the groups of cases. Whether a continuum would still be a viable description of these cases if other neuropathological features were included in the analysis, such as LB or NFT, remains to be established.

**Fidelity of pathological changes**

To investigate which of the three models is the most plausible, a comparative study of the distribution of the ‘signature’ inclusions across disorders would be necessary. If the discrete model was valid, then ‘defining’ pathological features would exhibit high ‘fidelity’ and there would be combinations of such features linked to the same disease. By contrast, if a continuum model is a better description, then the pathological changes would be distributed over several diseases and each feature would be distributed more or less independently. The problem of this approach is the paucity of studies which examine the distribution of the various molecular signatures across disorders, and hence there are many gaps in the literature. The ‘signature’ neuropathological lesions associated with the major disorders, based on current data, are listed in Table I and the distribution of the major lesions across disease entities are summarised in Fig. 3.

**Aβ deposits**

Aβ deposition is regarded as the ‘signature’ lesion of AD [53]. Nevertheless, Aβ deposits also occur in Down’s syndrome (DS) with dementia caused by triplication of the APP gene on chromosome 21 [11] and in a proportion of cases of DLB [14]. In fact, DLB can be divided into neocortical, limbic, cerebral, and brainstem types [74] and each into a ‘common’ (DLB/AD) and ‘pure’ form based on the degree of Aβ pathology. Similar densities of Aβ deposits may be found in AD and in DLB/AD [11] suggesting that these disorders may represent a ‘spectrum’ of pathologies involving APP processing [50,58], however, concluded that the pathology of DLB was distinct enough for it to be regarded as a separate disease and not a variant of AD. This conclusion was supported by data which demonstrated that although protease resistant, tau-immunoreactive NFT were a feature of AD, only very low densities were found in DLB [66]. In addition, Aβ pathology, neuritic plaques (NP), NFT, and neuropil threads (NT) were studied in control subjects, DLB and AD and it was concluded that apart from the common feature of diffuse plaques, pure DLB and AD were distinct disorders [89]. Similarly, Kawanishi et al. [78] concluded that DLB and AD were distinct disorders but with a common mechanism with reference to amyloid formation.

In addition to DLB, Aβ pathology has been reported in PD [125], FTD [125], CBD [8,125], ALS [63], and in PSP [125]. ALS is characterised by the degeneration of upper and lower tract motor neurons and some patients also exhibit dementia or aphasia [63]. Approximately 30% of ALS cases have AD-like symptoms and some ALS cases without overt dementia have significant AD pathology. In ALS cases with AD pathology, Aβ deposits are a common feature [63]. In addition, a patient with a progressive asymmetrical parietal syndrome and the clinical symptoms of CBD also developed the pathological features of AD including Aβ deposits and phosphorylated tau-immunoreactive NFT [92]. A similar result was reported by Schneider et al. [125] who reported the presence of Aβ deposits in CBD and especially in those cases expressing apolipoprotein E allele E4. Hence, the pathological feature ‘Aβ deposition’ does not exhibit ‘high fidelity’ to AD but occurs across a range of disorders. Studies of the overlap of pathological and clinical features of patients with brain amyloidosis came to a similar conclusion [51].

**Neurofibrillary tangles**

The second of the two original cases of ‘AD’ described by Alzheimer was characterised by numerous SP but lacked NFT [59]. Hence, even in the earliest described cases of AD there was pathological heterogeneity raising the question as to whether ‘plaque-only’ cases should be regarded as AD [99]. A large number of dementia cases were studied by Bancher and Jellinger [22], many being characterised by abundant NFT in the entorhinal cortex, subiculum, and sector CA1 of the hippocampus. Few SP or Aβ deposits were present in these cases which therefore, have been referred to as NFT-dementia. Hence, SP and NFT are neither ‘dependent’ nor ‘commensal’ lesions but appear to be distributed relatively independently. The lack of specificity of SP and the relative independence of SP and NFT raises a further question regarding the status of AD. First, what pathological criteria should be used to define AD? Jellinger and Bancher [76] recognised that defining morphological criteria for AD is difficult due to phenotyp-
ic heterogeneity, absence of specific markers, and overlap with related disorders [6] and suggested that both SP and NFT should be considered as the ‘signature’ lesions of AD. Second, is there any advantage in continuing to attempt to define AD as an entity? Trojanowski et al. [135] concluded that although AD is a ‘polygenic dementing disorder’, there is continued merit in defining an AD phenotype as defined by progressive cognitive impairment and the presence of SP/NFT. Nevertheless, studies of the distribution of lesions across disorders suggest that AD may be a part of a larger ‘continuum’ or ‘spectrum’ of neurodegenerative disease rather than a distinct entity.

**Prion deposits**

Deposition of the disease form of prion protein (PrPSc) is characteristic of the various forms of prion disease including Creutzfeldt-Jakob disease (CJD), Gerstmann-Strassler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI). There are considerable similarities, however, between the pathology of CJD and AD [35]. In both disorders, an abnormal amyloidogenic membrane glycoprotein is deposited as discrete extracellular deposits or plaques. In addition, definite or probable AD occurs in 11% of CJD patients [61]. The occurrence of AD pathology in CJD may be age-related but could also represent a functional interaction between the two pathogenic proteins [61]. In addition, Dermant et al. [38] described a case of AD with a PSEN1 mutation and an insertion of a 7-octapeptide coding repeat within the PrP gene. Elongate cerebellar PrPSc deposits were present but no AD pathology was observed. In the cases reported by El Hachini et al. [41], however, a family with a mutation at codon 163 of the PSEN1 gene, the clinicopathological features of CJD and AD were both present with substantial deposition of Aβ and PrPSc. The coexistence of Aβ and PrPSc pathology was also reported by Muramoto et al. [104] who described a case of a 75-year-old female with conspicuous AD associated with a mild form of CJD. Aβ plaques were present but with diffuse PrPSc immunoreactivity in the grey matter of the cerebral cortex and cerebellum. Similar cases were described by Barcikowska et al. [23] in which CJD occurred together with diffuse Aβ plaques.

**Tau-immunoreactive lesions**

There are differences of opinion regarding which entities should be included within the tauopathies. Cases with abundant tau-immunoreactive NFT and Aβ deposits are usually regarded as AD while those with tau-immunoreactive lesions but lacking Aβ deposits comprise the ‘classical’ tauopathies viz., CBD, PSP, PiD and FTDP-17 [85]. Tau is antigenically similar in several of the tauopathies [127] and a number of classifications have been proposed most notably by Trojanowski and Dickson [137] and Cairns et al. [29]. Nevertheless, the different molecular isoforms of tau do not exhibit high fidelity, 4-repeat (4R) tau occurs in AD, CBD, PSP, FTDP-17 as well as FTLD-MND, AGC, and the parkinsonism dementia complex of Guam (PDC-G) [97] while 3-repeat (3R) tau is present in AD, PiD, and PDC-G. Tau-immunoreactive GI have also been found in ALS with dementia [146], FTDP-17 [119], PiD [120], CBD, PSP, parkinsonism-dementia complex and ALS of Guam (ALS/PDC) [112], and in a few cases of MSA [131].

**α-synuclein-immunoreactive lesions**

α-synuclein is the major protein of the inclusions of DLB [82] and the glial and neuronal inclusions of MSA [113]. By contrast, relatively little α-synuclein immunoreactivity was recorded in AD, PiD, PSP, CBD, MND or in triplet-repeat disease [141]. More recently, α-synuclein-immunoreactive PB have been observed in the dentate gyrus in PiD [100] and α-synuclein-immunoreactive NCI in the amygdala in a proportion of PDC-Guam [145]. The use of antibodies immunoreactive to α-synuclein, however, has revealed the coexistence of cortical LB and AD pathology in many cases of dementia [130]. This conclusion was also reached by Trojanowski and Lee [136] who argued that the biological significance of the LB was therefore unclear. In addition, Lippa et al. [89] found that α-synuclein-immunoreactive LB were present in 22% of cases of familial AD and were most numerous in the amygdala where they coexisted with tau-immunoreactive NFT. Similarly, in a study by Rosenberg et al. [122] of an AD family linked to an APP717 mutation, one individual had the limbic form of DLB, two had neocortical DLB, and other members of the family had no LB. The presence of LB has now been detected in 53% of post-mortems with the APP717 mutation [122].

Overlap between the synucleinopathies and tauopathies has also been reported. Hulette et al. [71], for example, found neuropathological features characteristic of clinical PD in 78 AD cases while 20% of these cases also had features of PD pathology, i.e., degeneration of the substantia nigra and the presence
of LB, neocortical LB being present in 50% of cases. In addition, Arai et al. [3] emphasised that AD and PD share many common clinical and pathological features, α-synuclein-immunoreactive lesions being observed in 27 cases of AD. Some DS cases may also possess α-synuclein-immunoreactive inclusions and a number of cases have been reported with both LB and α-synuclein-immunoreactive dystrophic neurites [89]. Moreover, 50% of cases in which LB were present in the amygdala also possessed AD-type changes elsewhere in the cerebral cortex. Argyrophilic grains immunoreactive to phosphorylated and non-phosphorylated tau but negative to α-synuclein have been recorded in MSA [142]. In addition, α-synuclein-immunoreactive GI were present but negative to phosphorylated tau.

GCI immunoreactive for α-synuclein are regarded as the ‘signature’ lesion of MSA and helped to establish this disease as a distinct entity [113]. Similar neuronal lesions and less frequent GCI, however, are also present in DLB [39] suggesting that DLB and MSA may be part of a disease ‘spectrum’ or ‘continuum’ that includes both sporadic and genetic disorders. Furthermore, Takanashi et al. [131] described a patient exhibiting the pathological features of both MSA and PSP. The original diagnosis of this patient was MSA because of the presence of numerous GCI. Nevertheless, NFT and tufted astrocytes (TA) were also present in the basal ganglia and brainstem thus demonstrating the coexistence of α-synuclein-immunoreactive inclusions in oligodendrocytes with phosphorylated tau-immunoreactive inclusions in neurons and glia.

**TDP-43 proteinopathies**

The spectrum of TDP proteinopathies includes most cases of sporadic and familial FTLD-TDP with or without associated MND and also includes FTD linked to chromosome 9p, but not FTD with charged multivesicular body protein 2B mutations [29]. Accumulation of TDP-43, however, also occurs in other neurodegenerative diseases including AD [138], AGD [48], DLB [69], ALS [26], ALS/PDC complex of Guam [67,97], and hippocampal sclerosis (HS) [2].

**FUS**

Cases of NIFID were originally studied neuropathologically using antibodies that recognized either the phosphorylated neurofilament, heavy polypeptide (NFEH) or INA [17,18,25,28,77] one of the four proteins that comprise the type IV neuronal intermediate filament (IF) proteins. Not all inclusions in NIFID, however, are immunolabelled by anti-NFEH or INA antibodies and therefore, the primary molecular defect remains uncertain [108]. However, FUS protein has also been shown to be a component of the inclusions of FALS with FUS mutation [84,139,140], and two further FTLD entities, viz., BIBD [103], and atypical FTLD with ubiquitin-immunoreactive inclusions (aFTLD-U) [109]. Hence, FUS immunoreactivity also appears to be distributed across different disorders.

In conclusion, the distribution of molecular signature lesions across disorders suggests that many exhibit poor ‘fidelity’. It is probable that with more extensive data an even greater lack of fidelity would be apparent than suggested in Figure 3. Hence, it is unlikely that the discrete model is a credible description of neurodegenerative disease. There is considerable evidence, however, to support the overlap model [16] and this overlap may be extensive enough to consider whether neurodegenerative disease as a whole should be considered as a continuum.

**Fig. 4. An example of an objective ‘classification’ of Alzheimer’s disease (AD) cases into subtypes resulting in a dendrogram.** There is an initial division of cases into two groups based on the overall density and distribution of lesions. Both these groups can then be subdivided further into those with and without significant capillary amyloid angiopathy (CAA). One of the resulting groups is then divided further based on the disease onset.
Should a new type of ‘classification’ be considered?

If neurodegenerative disorders actually comprise a series of overlapping phenotypes or even a continuum, should a new conceptual system of describing them be considered [101,115]? More specifically, should attempts to assign an individual case to any type of classification be dispensed with altogether and all cases of neurodegenerative disease considered as points or ‘loci’ in a multi-dimensional continuum? Three alternative methods of approach are discussed, viz., objective classification, classification for convenience (a dissection), or analysis as a continuum.

Objective classification

If neurodegenerative diseases are distinct entities, it would be logical to use quantitative and statistical methods to attempt to classify individual cases more objectively. Hence, a ‘natural classification’ is assumed and the objective would be to define objectively the groupings which ‘actually’ exist. This approach has been little used in neurodegenerative disease research to date but an example of a classification of AD cases, in an attempt to identify subtypes of the disease, was described by Armstrong and Wood [10]. Cluster analysis was used to classify 78 cases of AD each of which was defined by quantitative assessment of 47 neuropathological features including those of the gross brain and the density and distribution of SP and NFT in a range of cortical and subcortical regions. The result was a hierarchical classification of the 78 cases displayed as a ‘dendrogram’ (Fig. 4). The majority of AD cases included in the study (83%) were classified into five subgroups which could represent phenotypic subtypes of the disease. The advantage of such an approach is that it can determine whether the units (cases) are naturally classifiable into distinct groups based on their clinical and pathological features. The act of ‘classification’ does not in itself, however, answer the question of whether the cases consist of a number of distinct entities or whether the cases merge imperceptibly one into another. Any group of cases can be classified regardless of their degree of overlap and hence, the validity (i.e., distinctiveness) of the resulting groups has to be independently verified. Objective classification applied to existing diseases and based on quantitative data might support the retention of the traditional model, indicate modifications to the system, or even suggest that classification should be abandoned in favour of a new approach.

Classification of convenience (‘dissection’)

Even if a considerable degree of overlap between diseases was present, it may still be desirable to classify for ‘convenience’, i.e., it may be useful to have a classificatory system of neurodegenerative disease however imperfect. Such an ‘unnatural’ classification has also been called a ‘dissection’ [79]. As an analogy, it is often convenient to show the relief of a geographical area in the form of a map with contour layer colouring. No person examining such a map, however, would suppose that the boundaries between colours represented stepwise discontinuities in elevation of the ground [117]. Hence, in such a system it would be necessary to establish the boundaries between diseases, i.e., the contours, and then to apply them to the classification of individual cases regardless of the degree of overlap or continuous variation.

Continuum

Classification may be considered to be an inappropriate or even an undesirable method of approach in the presence of extensive overlap or a continuum. Nevertheless, there still remains the problem of providing a suitable conceptual system of describing neurodegenerative disease that is useful to clinicians and researchers. One possible method is to use a non-hierarchical system based on ‘ordination’, i.e., by arranging cases of disease with reference to a coordinate frame so that the interrelationships between cases are spatially represented [117]. Such methods have been used to examine the degree of neuropathological heterogeneity in cases of AD [13] and FTLD-TDP [20] and often reveal a continuum but have not to date been used to provide a conceptual framework for the ‘classification’ of neurodegenerative disease.

In such a system there would be no attempt to ‘name’ a disorder or to arbitrarly classify cases into groups but only to assign an individual case to a particular region of the continuum. In a strict continuum, all cases would be regarded as unique and the traditional disease entities would not assume any primary importance. Location within the continuum would predict the biochemical pathways involved and ultimately, may suggest appropriate treatment options. To define such a system, appropriate quantitative criteria to enable an individual case to be located with precision within the coordinate system would need to be established. It is likely that within such a scheme,
dementia-type disorders would segregate in a different area of the continuum than movement disorders. Such an approach could also help to establish which disorders are likely to form a continuum and which might show greater degrees of discontinuity.

Conclusion

Three models are proposed to describe the distribution of neurodegenerative disease, viz., discrete, overlap, and continuum models. Studies suggest varying degrees of overlap between neurodegenerative diseases and even the possibility of a continuum involving some diseases [16]. Examination of the ‘signature’ lesions commonly used to define disease entities reveals them to have both poor ‘fidelity’ and not consistent with the existence of discrete diseases. An important question, therefore, is: should attempts to assign an individual case to a pathological classification be dispensed with altogether and all cases of neurodegenerative disease considered as points or ‘loci’ in a multi-dimensional continuum? Three possible methods of approach are suggested, viz., objective classification, classification for convenience (a dissection), or analysis as a continuum. Analysis of neurodegenerative disease as a continuum may have some advantages over a traditional classificatory scheme.

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