What causes neurodegenerative disease?

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Abstract

A hypothesis is proposed to explain the pathogenesis of neurodegenerative disease and the diversity of its phenotypes. The hypothesis is based on seven main propositions: 1) neurodegenerative disease is associated with multiple risk factors, 2) age is the most important of the risk factors, 3) aging differentially affects neuroanatomical pathways, 4) degeneration of these pathways results in the formation of pathogenic proteins, 5) pathogenic proteins spread along anatomical pathways, 6) the phenotypes of familial and sporadic forms of disease are similar and 7) neurodegenerative disease is characterised by heterogeneity, overlapping phenotypes, and multiple pathology. It is hypothesised that most cases of neurodegenerative disease are multifactorial in which interactions between external environmental and internal genetic risk factors act cumulatively over a lifetime to determine the 'allostatic load' of an individual. The allostatic load determines the rate of neural aging and results in the differential breakdown of neuro-anatomical pathways influenced by their relative use or disuse during life. The consequence is the formation of one or more pathogenic proteins, some of which may exhibit 'prion-like' behaviour and propagate through the brain from initial sites of formation along neuro-anatomical pathways to affect connected brain regions. Variations in the pathological proteins formed and their anatomical spread are ultimately responsible for the clinical and pathological diversity of disease phenotypes. Minimising the factors which contribute to the allostatic load over a lifetime and maximising cognitive and physical exercise may be necessary to reduce the incidence of neurodegenerative disease.

Key words: *neurodegenerative disease, hypothesis, aging, allostatic load, cell to cell transfer.*

Introduction

In 2019, approximately 50 million individuals worldwide had a neurodegenerative disease often resulting in dementia, a number expected to rise to 152 million by 2060 [2]. The overall prevalence of neurodegenerative disease leading to dementia, calculated by the European dementia meta-analysis (EURDEM) of all European studies, is 1.6% and 1% for males and females respectively in the 65-69 age class, rising to 11% and 12.6% in the 85-89 age class [137]. Of the different types of dementia, 62% of cases are attributable to Alzheimer's disease (AD), 17% to vascular dementia (VaD), 10% to a combination of VaD and AD, while dementia with Lewy bodies (DLB) accounts for 4%, frontotemporal dementia (FTD) for 2%, Parkinson's disease dementia (PDD) for 2%, and all other causes collectively for 3% of dementias [77,79,84,125,137].

Given the present and future potential burden on health systems worldwide and the absence of effective therapies, credible hypotheses are needed which can explain the pathogenesis of neurodegenerative disease and which can provide a basis for new treatment strategies. In a previous review [14], it was suggested

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that in AD, the most common neurodegenerative disease, genetic and environmental risk factors interact to increase the rate of normal aging ('the allostatic load') [57]. The allostatic load determines the degree of lifetime stress experienced by the body, the brain being the ultimate mediator of stress-related mortality through hormonal changes resulting in hypertension, glucose intolerance, cardiovascular disease, and immunological problems [57]. The consequent degeneration of neurons and blood vessels results in the formation of abnormally aggregated 'reactive' proteins. Hence, in AD, deposition of β-amyloid (Aβ) [95] and phosphorylated forms of the microtubule associated protein (MAP) tau [97] lead to the formation of the 'signature' lesions of AD, viz. senile plaques (SP) and neurofibrillary tangles (NFT) respectively. Gene mutation may directly influence the outcome of this age-related neuronal degeneration in AD by causing excessive amounts of Aβ to be formed, which quickly overwhelms protection systems causing early-onset familial AD (EO-FAD). Where specific gene mutations are absent and a more complex combination of risk factors present, Aβ and tau accumulate in the brain more slowly not overwhelming the cellular protection systems until much later in life causing late-onset sporadic AD (LO-SAD). Once formed, Aβ and tau may exhibit 'prion-like' behaviour and spread through the brain *via* cell to cell transfer along neuroanatomical pathways to affect connected brain regions [98]. Subsequently, variations in the pathways of this spread may result in the clinical and pathological heterogeneity particularly characteristic of AD [25].

The objective of this review is to extend this hypothesis to explain all forms of neurodegenerative disease [19]. The hypothesis is based on seven main propositions: 1) neurodegenerative disease is associated with multiple risk factors, 2) age is the most important of the risk factors, 3) aging differentially affects neuroanatomical pathways, 4) degeneration of these pathways results in the formation of pathogenic proteins, 5) pathogenic proteins spread along anatomical pathways, 6) the phenotypes of familial and sporadic forms of disease are similar and 7) neurodegenerative disease is characterised by heterogeneity, overlapping phenotypes, and multiple pathology.

Proposition 1: Neurodegenerative disease is associated with multiple risk factors

Early reviews identified many of the risk factors associated with dementia in general and AD in particular [107,109-111,133]. Over 20 different risk fac-

tors associated with AD were discussed by Henderson [109] and a common pathogenesis proposed as to how they might cause the pathological changes characteristic of the disease [95,97]. In a more recent review [20], a large number of risk factors were identified in AD, rare forms of EO-FAD being strongly linked to causal gene mutations, viz. mutations in *amyloid precursor protein* (*APP*) [59,96] and *presenilin* (*PSEN1/2*) genes [134,179]. By contrast, LO-SAD is a multifactorial disorder in which age-related changes, genetic risk factors, such as allelic variation in *apolipoprotein E* (*Apo E*) and many other genes [1], vascular disease, traumatic brain injury (TBI), and risk factors associated with diet, the immune system, mitochondrial function, metal exposure, and infection are all implicated (Table I). Moreover, over 60 environmental risk factors alone have been identified in AD and classified into six categories, viz. air quality, heavy metals, other metals, trace elements, occupational exposure, and miscellaneous [124]. Although there are fewer data on risk factors in other disorders, in Parkinson's disease (PD), for example, higher body mass index [173], alcohol consumption [173], milk consumption [131], and low-income status [136], have all been linked to an increasing risk. It remains a major challenge to explain how so many apparently disparate risk factors could contribute to these disorders [20,109].

Proposition 2: Age is the most important risk factor

Of the multiple risk factors associated with neurodegenerative disease, age has been consistently identified as the most important [20,109]. In addition, direct evidence that neurodegenerative disease may be an accelerated form of aging is provided most notably by AD [60] and PD [63,73]. Most if not all AD neuropathological change (ADNC) [115,153] also occurs in normal aged brains [43]. Hence, in cognitively normal brain, there is an age-related reduction in volume and weight, enlargement of ventricles, and loss of synapses and dendrites in selected regions [116]. Accompanying these changes are the histological features of AD, viz., SP and NFT albeit at lower densities than controls [3,36,45,145,183]. A study of the changes in density of SP and NFT with age in 199 individuals suggests an abrupt increase in the numbers of both lesions in the early part of the seventh decade [150]. As a consequence, it is often difficult to distinguish early-stage AD from normal

Table I. List of risk factors associated with Alzheimer's disease (AD). Based on Henderson [109] and Armstrong [20]

Grouping	Risk factor
Demographic	Age
	Education
	Gender
	Race
	Social class
Genetics	*Amyloid precursor protein* (*APP*)
	Presenilin 1 and 2 (*PSEN1/2*)
	Apolipoprotein E (*APOE*)
	ATP-binding cassette transporter A1 (*ABCA1*) *Adaptor protein evolutionarily conserved signalling intermediate in Toll pathway* (*ECSIT*)
	Clusterin gene (*CLU*)
	Estrogen receptor gene (*ESR*)
	Fermitin family homolog 2 gene (*FERMT2*)
	Glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*)
	Histocompatibility locus antigen (*HLA class III*)
	mtDNA haplotype
	Transferrin gene (*Tf*)
	Triggering receptor expressed on myeloid cells 2 (*TREM 2*)
	Vascular protein sorting-10 domain (*VpS10*) genes [108]
	Vitamin D receptor gene (*VDR*)
	Epigenetic factors
Lifestyle	Alcohol
	Lack of exercise, lack of cognitive activity
	Malnutrition
	Poor diet
	Smoking

Grouping	Risk factor
Medical	Cancer
	Cardiovascular disease
	Congestive heart failure
	Immune system dysfunction
	Micro-infarcts
	Obesity
	Poor cholesterol homeostasis
	Poorly controlled type-2 diabetes
	Stroke
	Traumatic brain injury (TBI)
Psychiatric	Depression
	Early stress
Environmental	Air pollution
	Calcium deficiency
	Geographic location
	Metals (especially aluminium, copper, zinc)
	Military service
	Organic solvents
	Occupation
	Vitamin deficiency
Infection	Bacteria, e.g., *Chlamydophila pneumoniae*, *Treponema*
	Dental infections
	Fungi
	Viruses

aging at post-mortem [145] and there may be a 'continuum' of pathological change from elderly non-demented brains, early-stage ('prodromal') AD, to more advanced AD [11].

Many studies have commented upon the frequency of ADNC in normal aging. First, certain morphological types of SP, i.e., those with a distinct central core ('classic plaques'), are encountered with greater frequency than expected in mentally able elderly [43], the density of classic SP in AD being similar to controls [42]. In addition, nearly all older individuals with no cognitive impairment exhibit ADNC, 75% with amyloid deposition, while 13% also have Lewy bodies (LB) [43]. In a study by Sonnen *et al.* [183], 47% of cognitively normal individuals had moderate to frequent SP, 6% had NFT in layers V/VI of the cerebral cortex, and 15% had medullary LB. In addition, in 87 individuals clinically normal at death, 33 had ADNC, 17 had LB, and four had a pathology characteristic of progressive supranuclear palsy (PSP) [73]. A number of studies have also implicated vascular factors in the development of SP in the normal elderly. Hence, SP occur in frontal and temporal cortex in 15/20 patients with critical stenosis, most often in the depths of the sulci [184] suggesting first, that alterations in cerebral perfusion may play a role in SP formation and second, that SP may not always be causally related to dementia. A further study of non-demented patients with critical coronary artery disease suggested that some patients had similar densities of SP to AD, numbers of SP being directly proportional to the duration of arterial disease [185].

β-amyloid is the major component of the SP in AD [95] and there is quantitative overlap in deposition between AD and normal aging [7,19]. Aβ deposits
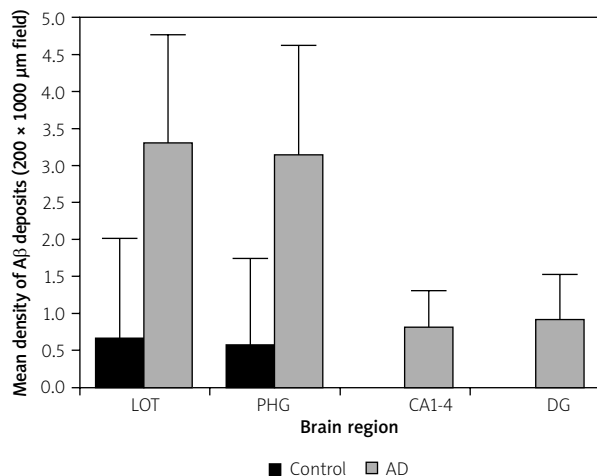
Fig. 1. Mean densities (200 × 1000 μm sample field, with standard errors) of β-amyloid (Aβ deposits in regions of the medial temporal lobe (LOT – lateral-occipitotemporal gyrus, PHG – parahippocampal gyrus, CA1-4 – cornus ammonis sectors of hippocampus, DG – dentate gyrus) in elderly non-demented control cases (*n* = 14) and Alzheimer's disease (AD) (*n* = 15). Data from Armstrong [7].

are frequently present in non-demented individuals older than 60 years but are rare before this age [146]. In addition, after 60 years, Aβ deposits are present in a variety of disorders due to aging, especially in temporal cortex, thus blurring the distinction between AD and related disorders [146]. In quantitative studies, the densities of Aβ deposits in the medial temporal lobe (MTL) in elderly non-demented control cases, DLB, FAD and SAD show considerable overlap, some cases of AD having low numbers of Aβ deposits while some cognitively normal individuals have significantly greater numbers [7]. Figure 1 shows the density of Aβ deposits in the MTL in normal elderly patients and in AD and shows first, that in some regions, e.g., the lateral-occipitotemporal gyrus (LOT) and parahippocampal gyrus (PHG), there is considerable overlap in density and second, that there may be significant differences in the degree to which Aβ pathology may affect the CA sectors of the hippocampus and the dentate gyrus, with little evidence of such deposition in control cases [7,19]. The spatial patterns of Aβ deposits are also similar in control and AD cases, i.e., deposits are aggregated into clusters that are regularly distributed parallel to the pia mater suggesting a common pathogenesis [7].

In a study of centenarians, Aβ deposits were recorded in the PHG, whether the patient was demented or not, but the hippocampus was not affected and there was little relationship between lesion density and severity of mental deficit [69]. In addition, using Pittsburgh compound-B (PIR) positron emission tomography (PET), a specific marker for Aβ, Aβ was observed in 10-30% of healthy elderly [165].

The frequency and abundance of tau pathology in normal aging has been more controversial. Many individuals cognitively normal at death have minimal tau-immunoreactive NFT [126] and with less astrocytosis or microglial reaction [62]. By contrast, Bouras *et al.* [48] found that all non-demented cases had NFT at least in layer II of the entorhinal cortex and sector CA1 of the hippocampus. Moreover, in non-demented individuals, NFT were more numerous in the MTL and in cortical association areas if memory deficits were present suggesting NFT could be the pathological substrate for memory loss in non-demented as well as demented cases [100]. Tau-immunoreactive NFT also appear early in the locus coeruleus in normal aging, mild cognitive impairment (MCI), and AD, apparently forming a continuum [99]. Within the MTL, however, the perforant path appears particularly sensitive to tau pathology in AD and these changes may be distinct from those seen in controls even in the oldest individuals [86].

The distinction between aging and neurodegenerative disease is further blurred by the discovery of 'primary age-related tauopathy' (PART), a tau-immunoreactive pathology present associated with aging and independent of amyloid pathology [64,72]. PART is characterised by: 1) a diffuse cerebral atrophy most severe in the temporal lobe, 2) NFT in the MTL, hippocampus, and amygdala, 3) extracellular 'ghost' tangles, and 4) sparse diffuse Aβ deposits but with very few SP [64,72]. Hence, PART may describe a pathological condition intermediate between that of normal aging and the tauopathies.

Phosphorylation and truncation of α-synuclein are characteristic of the 'synucleinopathies' PD, DLB, and multiple system atrophy (MSA) and are also normal events in adult human brain [156]. Phosphorylation and nitration of α-synuclein have been observed in dopamine neurons in the substantia nigra as a result of normal aging in monkey brain [149]. Age-related elevation of modified protein also paralleled an increase in the number of neurons immunoreactive for unmodified α-synuclein suggesting a mechanis-

tic link between aging, α-synuclein abundance, and enhanced vulnerability to neurodegeneration. In addition, in 110 cognitively normal individuals, 36% exhibited transactive response (TAR) DNA-binding protein (TDP-43) pathology, a hallmark of a common subtype of fronto-temporal lobar degeneration (FTLD) [56]. Finally, many cognitively normal individuals exhibit the signs of two or more different pathologies [29,73,119]. Hence, in the normal elderly, the presence of ADNC alone may double the chance of developing a cognitive impairment while multiple pathologies further increase the risk [207].

Proposition 3: Aging differentially affects anatomical pathways

The efficiency of brain function depends on both its long and short-range anatomical connections, there being fewer long-range connections as greater resources are required to maintain them [101]. Normal adolescence is characterised by selective strengthening of the long-range connections while in disorders such as schizophrenia, there is a widespread synaptic disconnection, in which there is a disproportionate reduction in long-range connections affecting subcortical, inter-hemispherical, and pathways associated with the 'will to persevere' ('salience network') [101]. There are also marked structural changes in the brain with age including cortical thinning, degradation of myelin, and reduced connectivity [106,200]. This reduced connectivity often results in a functional reorganisation later in life to compensate for the structural losses attributable to aging [106]. Several pathways appear to be particularly vulnerable. First, aging affects the 'structural covariance networks' which are involved in the language-related semantic, the executive control, and the default-mode networks [152]. Second, changes in hippocampus volume occur accompanied by thinning of the entorhinal cortex, which can affect memory function before reductions are evident in the default-mode network [199]. Third, both increases and reductions in functional connectivity affect the resting state motor network [182]. Fourth, there are selective age-related alterations in synaptic connectivity associated with rapid sensory learning [154]. Fifth, visual changes in aging, such as a decline in visual acuity, spatial contrast sensitivity, temporal frequency sensitivity, spatial-temporal interactions, binocular processing, and response to motion are likely to be attributable, not to specific changes in the eye, but to aging affecting the retino-cortical pathway and central visual pathways [186].

In neurodegenerative disease, there is enhanced disruption of connectivity principally affecting the long-range connections to hub nodes with consequent loss of network efficiency [135]. Hence, there is a functional continuum between healthy aging, MCI, and early AD [191] with in MCI, a decrease in antero-posterior functional connectivity [38] and in AD, a further decline in the efficiency of connections associated with more localised modular organisation of the cortex and related regions resulting in less effective local communication [191]. There are significant variations, however, in the anatomical pathways affected in different disorders (Table II) [17]. Hence, the disruption of afferent and efferent connections between the hippocampal formation and the rest of the brain is especially characteris-

Table II. The main neuro-anatomical pathways affected in various neurodegenerative disorders

Disorder	Cortical/Subcortical	Anatomical pathways affected
AD	Primarily cortical	Afferent and efferent connections between HC and rest of brain
CBD	Cortical/subcortical	Pathways involving GP and SN significantly affected. Pathology spreading to affect cerebral cortex
DLB	Cortical/subcortical	Neocortical, limbic, and brainstem in different subtypes
FTLD	Primarily cortical	Largely frontal/temporal HC less affected than in AD
FTLD-17	Cortical/subcortical	Pathways involving GP and SN significantly affected
FTLD-MND	Cortical/subcortical	Motor pathways including motor cortex and spinal cord
MSA	Primarily subcortical	SN, striatum, ION, cerebellum
PD	Cortical/subcortical	Subcortical in PD. Spread to cortex in PDD

AD – Alzheimer's disease, DLB – dementia with Lewy bodies, FTLD – fronto-temporal lobar degeneration, FTLD-17 – fronto-temporal lobar degeneration with parkinsonism linked to chromosome 17, CBD – corticobasal degeneration, FTLD-MND – fronto-temporal lobar degeneration with motor neuron disease, MSA – multiple system atrophy, PD – Parkinson's disease, HC – hippocampus, GP – globus pallidus, SN – substantia nigra, MC – motor cortex, ION – inferior olivary nucleus, PDD – Parkinson's disease with dementia

tic of AD, essentially isolating the hippocampus [67]. There also may be anatomical differences in the pathways affected in AD and DLB, the primary visual cortex (area V1) being more affected [138,151] and the hippocampus less affected in DLB [39]. In FTLD, the pathological changes predominantly affect frontal and temporal lobes [188] but with selective anatomical degeneration within various members of this group [22,32,46,91,167]. By contrast, disorders such as MSA, PD, and PSP exhibit a predominantly subcortical pathology at least in the initial stages [16,28,71,118,132,141,180,202].

The selective disruption of anatomical pathways observed in different disorders could be the result of the aging process differentially affecting anatomical pathways. One factor which could determine such selectivity is the relative degree of use or lack of use during a lifetime. Hence, in individuals that suffer early blindness, there is a significant reduction in white matter volume in the optic tracts and radiation and significant loss of grey matter in visual cortex [162]. The reduction in grey matter volume progresses with age and duration of blindness, suggesting a response to lack of functional activity in the relevant pathways. In aged rats, voluntary running can restore presynaptic density in the dentate gyrus and sector CA3 of the hippocampus to levels greater than in younger animals suggesting that activity may reverse degradation of the hippocampal network due to aging [181]. Moreover, moderate intensities of physical activity may protect against volumetric brain loss most commonly affecting pre-frontal cortex and the hippocampus [75]. In a further study, regular physical activity resulted in pathways being less affected by typical age-related decline in cognitive function [106]. In addition, individuals who exercised regularly reduced the risk of AD, the beneficial effect mediated by the effect of brain-derived neurotrophic factor (BDNF) on neuroplasticity and stress resistance [158]. In PD, there is evidence that heavy leisure-time physical activity lowers the risk suggesting continued activity in motor pathways reduces specifically their rate of aging [173]. In addition, treadmill exercise in a murine model of PD improved motor performance and reduced α-synuclein expression while promoting the expression of tyrosine hydroxylase, dopamine transfer, and plasma dopamine levels [128]. Hence, differential aging resulting from variations in the level of activity could be a fac-

tor influencing the anatomical selectivity observed in neurodegenerative disease [17].

Proposition 4: Neurodegeneration results in the formation of pathogenic proteins

Abnormally aggregated or misfolded proteins have played an important role in diagnosis, classification, and studies of pathogenesis [80]. A key question is: are these proteins the causal factor or a later consequence of age-related neurodegeneration [27]? Several observations suggest the latter. First, each of the different subtypes of Aβ deposit in AD viz., the diffuse, primitive, and classic deposits [8,68] are associated with specific anatomical features. Hence, diffuse Aβ deposits have a close spatial association with clusters of larger neuronal cell bodies [9], primitive deposits with synapto-axonal degeneration not involving the cell body [90], and classic deposits with cerebral blood vessels [10]. These results suggest that degeneration of a particular anatomical structure results in the release of Aβ and subsequently the formation of a deposit with a specific morphology [8]. Extracellular protein deposits also occur in prion disease in the form of prion protein (PrP^{sc}) deposits which vary in morphology. Hence, 'synaptic-type' PrP^{sc} deposits occur in the 'classical' form of sporadic Creutzfeldt-Jakob disease (sCJD) [178] while 'florid-type' plaques are characteristic mainly of the variant form of CJD (vCJD) [117]. In addition, in the cerebellum of vCJD cases, synaptic-type deposits occur almost exclusively within the molecular layer while florid plaques are confined to the granular layer suggesting, as in AD, that morphological differences are related to degeneration of specific cell types and anatomical structures [31].

Second, the morphology and molecular constituents of cellular inclusions are dependent on cell type and location. Hence, in AD, cortical and subcortical NFT comprise morphologically similar but antigenically different paired helical filaments (PHF) [192]. By contrast, cortical and brain stem LB are morphologically different but antigenically similar [51], brainstem LB having an electron-dense core with radially oriented filaments differing significantly from cortical LB. In the tauopathies, inclusions are consistently present in both neurons and glia especially in PSP, corticobasal degeneration (CBD), and Pick's disease (PiD) [127] and different pools of tau isoforms within degenerating cells appear to be characteristic of the

various disorders [54]. These data suggest differences in molecular composition of inclusions depend on the degeneration of the cell types expressing these constituents [53] and therefore, that their formation could be determined by the anatomical pathways which age most rapidly.

Third, α-synuclein immunoreactive glial cytoplasmic inclusions (GCI) are composed of 10-15 nm coated filaments and are characteristic of MSA [132]. α-synuclein is enriched at presynaptic terminals and reversibly binds to lipid vesicles, and hence, may be an integrator of presynaptic signalling associated with membrane function [40,61]. Hence, in DLB, PDD and MSA synaptic disconnection may result in the release of α-synuclein which is taken up by glial cells accumulating as GCI.

Fourth, in some cases of traumatic brain injury (TBI), amyloid precursor protein (APP) is observed in neuronal perikarya and in the dystrophic neurites (DN) surrounding Aβ deposits. Processing of APP within the synaptic terminal fold of axons into Aβ suggests the production of APP may be a component of the brain's response to neuronal injury [89]. In addition, specific neurons in the MTL secrete large quantities of APP and more APP-immunoreactive neurons occur in these areas in TBI cases [148]. Hence, increased expression of APP after head trauma could be an acute-phase response to neuronal injury [171], the overexpression of APP leading to increased deposition of Aβ. Several acute-phase proteins are localised within Aβ deposits in AD including amyloid-P, complement factors, and α-antichymotrypsin [121]. Furthermore, it was proposed that in AD, APP helps to maintain cell function, an observation supported by the fact that APP shares structural features with the precursor for epidermal growth factor [168].

Fifth, in lesion experiments, damage to the nucleus basalis in the rat decreased cortical choline acetyltransferase (CAT), elevated somatostatin and neuropeptide Y [5], and caused neuronal loss and the formation of SP in the cortex. Lesions of the nucleus basalis also elevated APP synthesis in the cerebral cortex suggesting a specific response to loss of functional innervation [198]. Furthermore, 4-7 days after damage to the nucleus basalis, APP was present in axonal varicosities, cell bodies, and DN as a consequence of the inhibition of axonal transport [189]. In addition, chemically induced lesions of the nucleus basalis using N-methyl D-aspartate (NMDA) elevat-

ed APP synthesis in cortical polysomes [198] and, in areas of brain damaged by kainite [123], APP_{695} occurred in DN close to the lesion. In addition, intrathecal or intra-parenchymal injections of excitotoxin induced APP in hippocampal neurons subsequent to neuronal damage [122].

Sixth, tau formation may also be part of the neurons response to injury [203]. Hence, denervation of dopamine pathways and septal lesions affect both the cholinergic system and GABA neurons projecting to the dentate gyrus, and result in a loss of dendritic MAP2 and the appearance of tau-immunoreactive dentate gyrus granule cells [194]. Denervation may also cause trans-synaptic changes in the dentate gyrus and these changes could be a precursor to NFT. Axonal injury may also result in the cytoplasmic accumulation of α-synuclein, an important constituent of LB [157]. Moreover, primates given 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) developed inclusion-type bodies which may result from the redistribution of α-synuclein from its normal synaptic location to the cell body [130].

Proposition 5: Pathological proteins spread along anatomical pathways

Several observations suggest an association between neurodegenerative disease and the breakdown of specific neuro-anatomical pathways. First, loss of synaptophysin reactivity has been reported in the cortex in AD suggesting synapse loss, especially in temporal lobe [177], while a decrease in the synaptic marker SP6 has been found in all regions of AD brain [197]. Second, NFT in AD are located in cell bodies that give rise to the cortico-cortical pathways, SP forming at their ends and on collateral branches [67,163]. Disease could therefore spread along these pathways in either an orthograde and/or retrograde direction [67]. In addition, ADNC appears to have an anatomical basis as regions severely affected are interconnected by the cortico-cortical pathways [112]. The most complete description of this 'disconnection hypothesis' of AD is the seminal review by De Lacoste and White [67] in which the disease is characterised by disruption of all afferent/efferent connections between the hippocampus, cerebral cortex, and the rest of the brain. The cortico-cortical pathways appear selectively vulnerable in AD, the pathology spreading in stages *via* these connections [67,163], SP developing on the distal

axonal projections of NFT-bearing neurons [67]. In addition, Hoesen and Solodkin [113] demonstrated that NFT were associated with cortical pathways in AD, as they selectively damaged strips of cortex and hippocampus, with columns of resulting NFT exhibiting a regular periodicity (80-120 μm) representing 4-5 cell diameters and with a spacing of 300 μm. With greater duration of disease, NFT gradually 'filled up' the columns giving rise to clusters of NFT of increasing size, a result also reported by Armstrong [6].

Populations of neurons that are lost in a particular disease are often functionally related and share a common metabolic abnormality and therefore, neuronal connections between different regions could specify the pattern of cell losses in each disease [175]. Subsequently, it was shown that pathogenic proteins such as tau and α-synuclein can be secreted from cells, enter other cells, and seed small intracellular aggregates within these cells [98,187]. This raises the possibility, originally with reference to PD, that pathogenic agents may transfer along unmyelinated axons to basal areas of brain, the brain stem and then to the cerebral cortex [105]. If pathogenic proteins spread from cell to cell, then the resulting inclusions may exhibit a spatial distribution which reflects this process. A number of studies have suggested non-random distributions of inclusions in the cerebral cortex of various disorders including not only the tauopathies and synucleinopathies but also TDP-43 and 'fused in sarcoma' (FUS) proteinopathies, the inclusions often exhibiting a distinct clustering pattern, i.e., a regular distribution of clusters parallel to the pia mater, consistent with their spread *via* cortico-cortical pathways [21,26] (Table III). Hence, once formed as a consequence of age-related breakdown of anatomical pathways several resulting proteins may have the ability to propagate among regions thus causing phases of secondary degeneration which could involve more local circuits and glial cells.

Proposition 6: The phenotypes of familial and sporadic cases are similar

Studies have demonstrated similarities in the pathology of familial and sporadic forms of various diseases. Hence, variations in the distribution and abundance of SP and NFT in 23 brain regions were compared in sporadic and familial AD using principal components analysis (PCA) [25]. Cases of AD formed a large cluster, pathological change varying continuously across the cluster and with no clear distinction between SAD and FAD (Fig. 2). In addition, there are

Table III. Frequency of the different types of spatial pattern (R – random, U/RG – uniform or regular, RGC – regularly distributed clusters, 50-1600 μm in diameter, LC – large clusters, ≥ 1600 μm in diameter without regular spacing) exhibited by pathological inclusions in the cortex of various neurodegenerative disorders

Disorder	Molecular pathology	Type of spatial pattern						
		NCI	*N*	R	U/RG	RGC	LC	%RGC
AD	3R/4R tau	NFT	30	1	0	22	7	73
AGD	4R tau	NFT	61	15	2	30	9	49
CBD	4R tau	NCI	76	2	2	48	24	63
CTE	3R/4R tau	NFT	42	11	11	15	5	36
DLB	α-synuclein	LB	70	2	1	43	24	61
FTDP-17	3R/4R tau	NFT	13	3	2	5	3	38
FTLD-TDP	TDP-43	NCI	49	18	1	27	3	55
GPDC	3R/4R tau	NFT	16	2	2	9	3	56
MSA	α-synuclein	NCI	9	5	0	3	1	33
NIFID	FUS	NCI	53	7	3	39	4	74
PiD	3R tau	PB	48	1	0	27	20	53
PDD	α-synuclein	LB	41	9	2	28	2	68
PSP	4R tau	NFT	23	11	0	10	2	43

AD – Alzheimer's disease, AGD – argyrophilic grain disease, CTE – chromic traumatic encephalopathy, DLB – dementia with Lewy bodies, FTLD – fronto-temporal lobar degeneration, FTLD-17 – fronto-temporal lobar degeneration with parkinsonism linked to chromosome 17, GPDC – Guam parkinsonism dementia complex, PiD – Pick's disease, CBD – corticobasal degeneration, FTLD-TDP – fronto-temporal lobar degeneration with TDP-43 proteinopathy, MSA – multiple system atrophy, NIFID – neuronal intermediate filament inclusion disease, PD – Parkinson's disease, PSP – progressive supranuclear palsy, FUS – 'fused in sarcoma', NFT – neurofibrillary tangles, NCI – neuronal cytoplasmic inclusions, PB – Pick bodies, N – total number of cortical regions analysed for each disorder

no essential differences in the spatial patterns of Aβ deposits in FAD and SAD, both being distributed similarly in regularly spaced clusters [12]. There are no differences either in the spatial pattern in AD cases expressing or not expressing the *Apo E* e4 allele, a major risk factor for AD [176,190]. Furthermore, the laminar distribution of Aβ deposits, an indicator of the pattern of degeneration across the cortical layers, is similar in both FAD and SAD, maximum density of the diffuse and primitive Aβ deposits occurring in upper cortical layers while the distribution of the classic Aβ deposits is more variable occurring either in the lower layers, or in both upper and lower layers [16]. The cortical layer where Aβ deposits reached maximum density and the maximum density is also similar in FAD and SAD. In addition, there are no significant differences in distribution in cases expressing one or more *Apo E* e4 alleles compared with cases not expressing this allele. These results suggest that gene expression had relatively little effect on the pattern of cortical degeneration in FAD and SAD.

Similar results have also been reported in FTLD with TDP-43-immunoreactive pathology (FTLD-TDP). A significant number of familial cases of FTLD-TDP are caused by defects in the *chromosome 9 open reading frame 72* (*C9ORF72*) gene [66,140,169] and the *progranulin* (*GRN*) gene [41,65,155,166]. Rarer cases are caused by mutations of the *TAR DNA-binding protein* (*TARDBP*) [94,204] *TANK-binding kinase 1* (*TBK1*) [93], and *valosin-containing protein* (*VCP*) genes [81,201]. A quantitative study of 94 cases of FTLD-TDP using PCA, suggested that as in AD, the familial cases as a whole did not have a pathological phenotype that was distinct from the sporadic cases [32]. In addition, the frequencies of the different types of laminar distribution in FTLD-TDP associated with *GRN* mutations [15] was similar to those previously reported in sporadic FTLD-TDP [33] suggesting that the *GRN* mutations were not associated with a specific pattern of laminar degeneration in FTLD-TDP.

Proposition 7: Neurodegenerative disease is characterised by heterogeneity, overlap, and multiple pathology

Any hypothesis to explain neurodegenerative disease has to account for the diversity and complexity of its clinical and pathological phenotypes [13]. Three aspects of neurodegenerative disease contribute to this diversity: 1) the degree of heterogeneity within individual disorders [25,32], 2) the degree of over-

lap or 'interface' between closely-related disorders [11,29], and 3) 'multiple pathology', i.e., the co-existence of two or more different pathologies in the same case [119,205].

Considerable variations in the severity and distribution of the pathology have been observed within many neurodegenerative diseases, most notably in AD [25,83,195] and FTLD [32,56]. Three hypotheses may account for this heterogeneity [170]. First, that within each disease there are distinct subtypes ('subtype hypothesis'). For example, AD consists of both sporadic and familial forms, the latter associated with mutations of at least three genes, viz., *APP* [59,96], and *presenilin* genes *PSEN1* [179] and *PSEN2* [134]. More complex forms of AD have also been described, e.g., AD in combination with PD [47], or AD with DLB [70], AD with significant degeneration of white matter [52], VaD [109], or with capillary amyloid angiopathy (CAA) [196]. Studies suggest that FTLD-TDP is also diverse [32] with division into four possible subtypes (currently designated A, B, C, and D) based on the distribution and density of 'signature' pathological inclusions in the cortex [56,120,142-144,174]. Second, heterogeneity may reflect the stage of the disease present at death ('phase hypothesis') and therefore, may be related
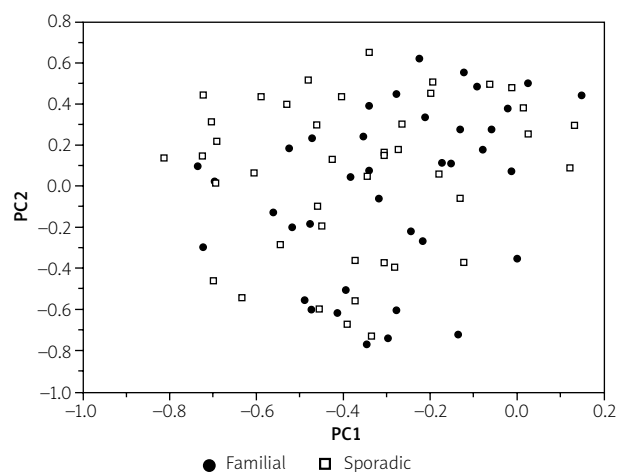

Fig. 2. Principal components analysis (PCA) of Alzheimer's disease (AD) cases (*N* = 80) based on the distribution and severity of senile plaques (SP) and neurofibrillary tangles (NFT) in 23 cortical and subcortical brain regions. A plot in relation to the first two principal components (PCA1/2) illustrating the relative similarity among cases. Data from Armstrong *et al.* [25].

to disease duration [50]. Third, there may be topographical variations in the site or sites of initial neurodegeneration followed by differences in the subsequent propagation of the pathology through the brain ('compensation hypothesis') [67,163].

Many studies have reported overlaps between closely related disorders [78,82,102]. Many such overlaps involve AD, reflecting both its prevalence and the fact that ADNC has been recorded in the majority of non-AD disorders. Hence, AD and VaD commonly coexist, 18% of a dementia autopsy series showing evidence of both [109]. In addition, overlaps have also been reported among the various tauopathies, synucleinopathies, within FTLD, and between AD and CJD [29].

Third, more complex examples of 'multiple pathology' have been reported which cannot be explained as simply a region of 'overlap' between two relatively distinct disorders. For example, the number of pathologies encountered in cases comprising a selection of neuropathological studies is shown in Table IV. Of a total of 417 cases, 204 (49%) had evidence of at least one additional co-pathology. In addition, in studies of the parkinsonian syndromes, 38% of cases of PD have ADNC, 9% PSP, 25% argyrophilic grains (ARG), and 24% CAA while in DLB, 89% have ADNC pathology, 1% PSP, 21% ARG, and 25% CAA [73]. Overlap among parkinsonian syndromes is very evident between PSP and CBD and between PDD and DLB, questioning whether these disorders are actually distinct [44]. In addition, in a recent comparative study of 1032 cases representing ten different disorders, 361 cases, approximately 35% of the sample, were excluded largely as a result of multiple pathology [35]. Some neurodegenerative diseases may even be indistinguishable, cases essentially forming a 'continuum' in which there is gradual clinical and pathological change from one case to another [13]. The frequent use by authors of such terms as 'complex syndrome' [58,87,193], 'spectrum of disorders' [88], or 'continuum' [13,58,87,193] testifies to the extent to which there may be no distinct boundaries between neurodegenerative disorders.

Multiple pathology may be the result of either the random co-occurrence of different disorders or that one pathology may induce or encourage the presence of another. Hence, the coexistence of features of AD and PD or AD and VaD in the same case may be frequent because both disorders are common and show a rapid increase in incidence with age [47]. In Table IV, the frequency of cases revealing 0, 1, 2, or 3 additional pathologies totalled over the various studies does not deviate significantly from a Poisson distribution ($\chi^2 = 0.16$, $p = 0.92$) suggesting that the frequency of multiple pathology diminishes rapidly with the increasing number of co-pathologies consistent with chance associations. Nevertheless, if two disorders are truly independent and their co-existence is random, their joint occurrence should approximate to the product of their respective prevalence rates. On this basis, the combination AD/VaD is more frequent than predicted suggesting either that the effects of mild AD and VaD are additive thus increasing the likelihood of detecting the combination or that the ischaemia resulting from VaD accelerates the formation of ADNC [109]. In addition, AD and PD may be found together more commonly

Table IV. Frequency of 'multiple pathology' in a selection of neuropathological studies of neurodegenerative disease

Primary diagnosis	Number of cases	Number of associated pathologies				
		0	1	2	3+	Reference
AD	101	43	52	2	0	[25]
AGD	25	4	4	15	2	UP
CTE	11	1	1	5	4	[34]
FTD	56	38	17	0	1	UP
FTLD	128	78	44	6	0	[32]
PDD	32	12	19	1	0	[129]
'Various dementias'	45	24	19	2	0	[205]
'Various tauopathies'	19	9	8	1	1	[18]
Total	417	209	164	32	8	

AD – Alzheimer's disease, AGD – argyrophilic grain disease, CTE – chronic traumatic encephalopathy, DLB – dementia with Lewy bodies, FTLD – fronto-temporal lobar degeneration, PDD – Parkinson's disease dementia, UP – R.A. Armstrong unpublished data

than expected based on prevalence [47]. In a pathological study of PD patients, a high proportion had the characteristic symptoms of AD with SP, NFT, and granulovacuolar change in the hippocampus [103]. The apparent frequency of patients combining the features of AD and PD suggests a common aetiology [47]. As a consequence, there has been a search for unifying concepts to explain this co-occurrence, e.g., failure of neurotrophic hormone causing retrograde degeneration [4] or that AD and PD are both disorders of the 'isodendritic core' [172].

The presence of one type of pathology could encourage or induce the formation of another. An important aspect of the 'amyloid cascade hypothesis' (ACH) of AD is that the formation of Aβ directly causes NFT [104]. Several attempts have been made, however, to explain how Aβ may lead to NFT, but none have become universally accepted [55,92,160,161]. Hence, SP and NFT occur alone separately in different disorders, e.g., NFT in tangle-only dementia [206] and Aβ in hereditary cerebral haemorrhage with amyloidosis of the Dutch type (HCHA-D) [114]. Studies also suggest that SP and NFT exhibit distinct but independently distributed topographic patterns in the cerebral cortex in AD [23,114]. Braak and Braak [49] showed that tau pathology occurred first in entorhinal cortex, often in the absence of SP, whereas the subsequent spread and distribution of Aβ was more variable. Studies of the spatial patterns of SP and NFT also show them to be clustered, the clusters being regularly distributed relative to the pia mater [23]. Clusters of SP and NFT, however, are not in a phase, which would not support a direct pathogenic link between them. Perez *et al.* [164], however, showed that $Aβ_{25-35}$ could result in tau aggregation and that a decrease in Aβ aggregation was induced by tau peptides. Consequently, aggregation of tau may be correlated with disassembly of Aβ which could explain the lack of spatial correlation [24]. In addition, SP and NFT may be temporally separated in the brain [147]; in entorhinal cortex [74] and in sector CA1 of the hippocampus [85], for example, NFT may precede the appearance of SP against the prediction of the ACH. In sector CA1, it is possible that Aβ is present in neurons before NFT are formed but not easily detectable by conventional methods [85].

A likely explanation of multiple pathology is that it is the consequence of the diversity of pathological proteins that are formed as a result of age-related neurodegeneration and their pattern of spread in the nervous system, a version of the 'compensation hypothesis' first proposed to explain heterogeneity in AD [25,170]. Allelic variations among individuals determine which pathologic proteins are formed and variation in spread determines which pathways are affected thus creating a possible 'continuum' of clinical and pathological forms of disease [13]. Ultimately, the clinical features of an individual patient may depend on the anatomical pathways affected, the rate of spread of one or more proteins, and the summation of their pathological effects over the nervous system as a whole.

Discussion

The hypothesis

First, the primary cause of neurodegenerative disease is accelerated aging and is determined by the allostatic load (Fig. 3). This process results in differential aging of anatomical pathways, especially the more vulnerable long-range connections, related, in part, to their degree of use or disuse during life.

Second, the consequence of this neural aging is gradual synaptic disconnection, neuronal degeneration, and the upregulation, release, and deposition of various reactive and breakdown products such as Aβ, tau, α-synuclein, TDP-43, and FUS [121,168,198]. The most overt manifestation of this process is in those individuals in which specific mutations or allelic polymorphisms influence directly the outcome of age-related degeneration by determining the solubility and/or toxicity of the molecular products [30]. Cells have mechanisms to protect against the accumulation of misfolded and aggregated proteins including the ubiquitin system [76] and the phagosome-lysosome system [159]. In individuals with specific gene mutations, accelerated formation of an insoluble, misfolded protein may rapidly overwhelm these protection systems. Early-onset familial disease is the consequence of this process. By contrast, in individuals without a specific genetic mutation, but where more complex allelic variation and/or environmental risk factors are present, the outcome of age-related loss of synapses is mainly soluble and smaller quantities of several insoluble proteins which are degraded by the cellular protection systems and do not significantly accumulate to form pathogenic lesions. With advancing age, how-
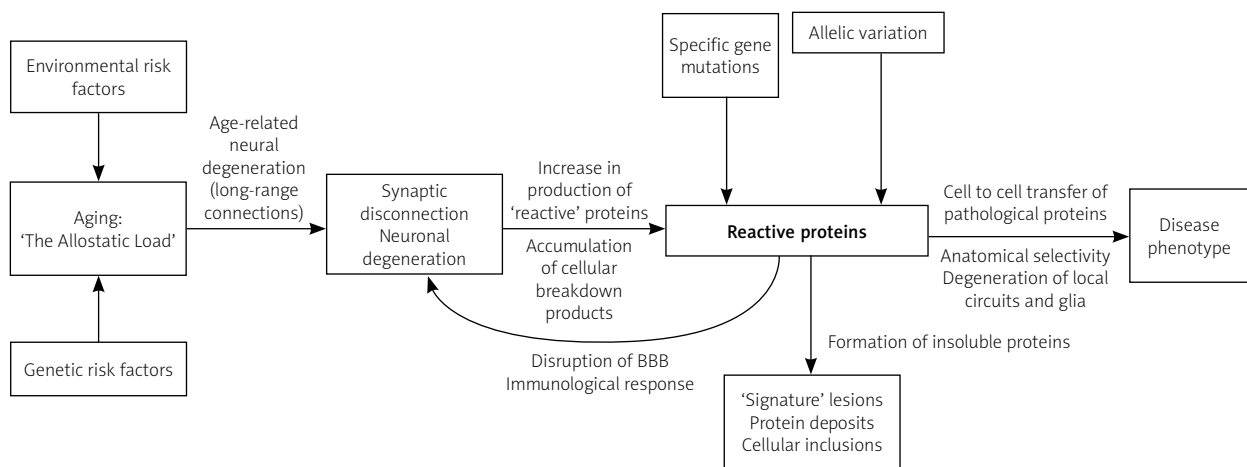
Fig. 3. A hypothesis to explain neurodegenerative disease. BBB – blood brain barrier.

ever, the protective systems become less effective resulting in slowly accumulating quantities of insoluble proteins. As a result, the cellular protection systems do not become overwhelmed until much later in life, the result being late-onset sporadic forms of disease often phenotypically similar to their familial counterparts [12,15,16]. In other individuals, the accumulating allostatic load may not be severe enough to result in significant synaptic disconnection during their lifetime, and death may intervene from other causes before such individuals succumb to an age-related neurodegenerative disease.

Third, once abnormal proteins are formed they spread 'prion-like' through the brain by cell to cell transfer along interconnected neuroanatomical pathways [98,187] and increasingly affect more local circuits and associated glial cells. As a consequence, there may be disruption of the blood brain barrier, release of plasma proteins, and further neural degeneration adjacent to blood vessels, as can be observed in AD [10]. There is considerable evidence to support the hypothesis that PrP^{sc}, tau and α-synuclein propagate through the brain *via* anatomical pathways [98,187], and also indirect evidence that Aβ, TDP-43, and 'fused in sarcoma' (FUS) proteins may behave similarly (Table IV) [22]. As they spread, these proteins may contribute to further degeneration by acting as foci for the accumulation and growth of protein deposits and encouraging more local degeneration. Variation in the molecular phenotype results from: 1) differential vulnerability of specific neural pathways, 2) individual genotypic variation which affects

the outcome of cellular degeneration and therefore, the number, type, and frequency of pathological proteins [30], and 3) variations in the pathways of spread of various proteins along neuroanatomical pathways. These processes result in the complex overlap of different pathologies with cases of neurodegenerative disease likely to form a continuum rather than comprising a series of distinct disorders [13].

Implications

The hypothesis suggests that neurodegenerative disease constitutes a single complex syndrome dependant on the rate of aging and determined by the allostatic load and its differential effects on the nervous system. These processes result in a continuum of pathological change not only from normal aging, through MCI, to AD but also among the different forms of neurodegenerative disease. A major future challenge will be to explain how all possible variants of neurodegenerative disease are formed and therefore, to account completely for the diversity of resulting disease phenotypes. Subsequently, it will be necessary to establish a system for describing this diversity, i.e., should a classificatory system be used or does neurodegenerative disease represent such a continuum of clinical and pathological change, that it is not amenable to any type of classification [13,17]? New systems may need to be devised to provide a framework for the description of all variants of disease. A recent review [17] proposed four key neuropathological features (the 'primary determinants') that could be used to pro-

vide such a framework, viz., the anatomical pathways affected by the disease ('anatomy'), the cell populations affected ('cells'), the molecular pathology of 'signature' pathological lesions ('molecules'), and the morphological types of neurodegeneration ('morphology'). These primary determinants could be used in combination with quantitative methods based on multivariate geometry to describe all cases of neurodegenerative disease [17].

If the cumulating allostatic load is the most important factor causing neurodegenerative disease, should the presence, distribution, and molecular composition of pathogenic lesions continue to play such a dominant role in description and diagnosis? If abnormal proteins are the products of brain degeneration and not their primary cause, then they may occur at various stages and possibly even late in the disease. Hence, there may be cases of disease that are difficult to identify because they may have insufficient numbers of deposits or inclusions or exhibit early developmental stages of these pathologies.

A major implication of the hypothesis is that it is unlikely that neurodegenerative disease will be amenable to treatment by simple pharmacological intervention [108]. Therefore, should significant effort continue to be devoted to immunotherapy and other treatments designed to remove specific pathogenic proteins from the brain? Removing Aβ in AD, for example, could be beneficial in limiting its spread and therefore, the degree of secondary degeneration, potentially slowing the progress of the disease. However, Aβ and other proteins might also be beneficial to the nervous system by promoting neurogenesis [139] and having a range of other protective functions. Hence, excessive removal of Aβ could reduce chelation within the brain and result in enhanced oxidative stress [37]. By contrast, the present hypothesis suggests that attention should also be directed to reducing those factors which contribute to the life-time allostatic load [57] and to encourage activity through life, which contributes to exercising both cognitive and motor pathways. Therefore, there is an urgent need to develop strategies to slow down cognitive and motor decline resulting from aging. This process will require the identification of modifiable lifestyle and health-related variables to identify optimal combinations of such factors which could slow down the accumulating allostatic load [108].

Finally, there are individuals that reach considerable age without developing a neurodegenerative disease and which represent a 'survival elite' [109]. The hypothesis predicts that such individuals should be associated with fewer known risk factors and carry a low allostatic load. Such individuals may even possess 'protective factors' which may actively reduce the risk of neurodegenerative disease and more studies of such individuals are urgently needed.

Conclusions

This review proposes a hypothesis to explain the different forms of neurodegenerative disease based on seven main propositions: 1) neurodegenerative disease is associated with multiple risk factors, 2) age is the most important of the risk factors, 3) aging differentially affects neuroanatomical pathways, 4) degeneration of these pathways results in the formation of pathogenic proteins, 5) pathogenic proteins spread along anatomical pathways, 6) the phenotypes of familial and sporadic forms of disease are similar and 7) neurodegenerative disease is characterised by heterogeneity, overlapping phenotypes, and multiple pathology. The hypothesis suggests that there is unlikely to be a simple solution to the treatment of neurodegenerative disease. Instead, reducing the extent of the allostatic load over a lifetime and encouraging activity to exercise both motor and cognitive brain pathways especially in later life may be necessary to reduce the incidence of neurodegenerative disease.

Disclosure

The author reports no conflict of interest.

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