Review

Knowing Me, Knowing You: Can a Knowledge of Risk Factors for Alzheimer's Disease Prove Useful in Understanding the Pathogenesis of Parkinson's Disease?

Greg T. Sutherland[a,*], Gerhard A. Siebert[c], Jillian J. Kril[a,b] and George D. Mellick[c,d,e]

[a]*Discipline of Pathology, Sydney Medical School, University of Sydney, Sydney, NSW, Australia*
[b]*Discipline of Medicine, Sydney Medical School, University of Sydney, Sydney, NSW, Australia*
[c]*Eskitis Institute for Cell and Molecular Therapies, School of Biomolecular and Physical Sciences, Griffith University, Brisbane, QLD, Australia*
[d]*Department of Neurology, Princess Alexandra Hospital, Brisbane, QLD, Australia*
[e]*Department of Neurology, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia*

Abstract. Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative disorders. Why some individuals develop one disease rather than the other is not clear. Association studies with a case-control design are the time-honored approach to identifying risk factors. Extensive association studies have been carried out in both diseases creating a large knowledge database, however, reproducible risk factors remain rare. This general lack of knowledge of pathogenesis prevents us from reducing the worldwide burden of these diseases. Case-control studies are reductionist paradigms that assume, for maximum power, that the two populations being compared are exclusive and homogenous. The common occurrence of incidental AD and PD-type pathology combined with 'intermediate phenotypes' such as dementia with Lewy bodies suggest that aging itself, AD, and PD are part of a complex continuum characterized by variable amounts of amyloid-β, tau, and α-synuclein pathology. This heterogeneity may be a contributor to the lack of reproducibility in association studies to date. Here, we speculate on alternative experimental approaches to the case-control paradigm and consider how the association-study literature for AD and PD might be re-interpreted in terms of a disease spectrum.

Keywords: Alzheimer's disease, association studies, dementia, neuropathology, Parkinson's disease

INTRODUCTION

An ever-increasing world population, with a growing proportion of elderly, poses an immense challenge from the rising socio-economical burden of neurodegenerative disease. An epidemic seems unavoidable unless therapies can be found to prevent, delay, or reverse these conditions. The two most common neurodegenerative disorders are Alzheimer's disease (AD) and Parkinson's disease (PD), both of which are the subject of major research efforts, consistent with their social and economic importance. Monogenic forms of these diseases are known and their identification

*Correspondence to: Dr Greg T. Sutherland, Discipline of Pathology, Sydney Medical School, University of Sydney, Sydney, NSW 2006, Australia. Tel.: +61 2 9036 7233; Fax: +61 2 9351 3429; E-mail: g.sutherland@sydney.edu.au.

has been invaluable for elucidating aspects of the pathogenic mechanisms. However, such forms are rare, and the majority of PD and AD cases occur sporadically, without familial or geographical clustering. These common forms are referred to as "idiopathic" or literally, of unknown pathogenesis. In the absence of known causative factors, it is widely assumed that the majority of sporadic cases are caused by a complex interaction between common genetic variants and environmental factors on a background of aging [1, 2].

Risk factors are often assessed by association studies, in a case-control setting. In more recent years, technological advances have greatly enhanced the breadth of the questions that can be asked with global analyses such as genome wide association and transcriptomic studies applied to both diseases. However, in general, these genome-scale platforms have only confirmed known risk factors and not identified the novel targets needed to reduce the burden of these diseases [3].

The underlying premise for this review is a consideration of the potential reasons behind this lack of success. Moreover, it is to discuss whether the combined research knowledge within AD and PD could be harnessed to gain greater research traction for either disease. Importantly it builds on the previous work of colleagues who have considered AD and PD pathologies within a wider neurodegenerative spectrum [4–6].

PART I: EXCLUSIVITY AND HOMOGENEITY

The case-control study is a reductionist paradigm that assumes the two populations under consideration are exclusive and homogenous. However, a lack of homogeneity is recognized in both AD and PD. In PD, for example, there is a common division between tremor-dominant and bradykinetic (PIGD) sub-phenotypes [7], and these subtypes have different patterns of pathology [8, 9]. This suggests that different pathophysiological mechanisms are operating [8], an important consideration for the design of association studies. However such variation is often (pragmatically) dismissed to maximize statistical power. Less appreciated is the possible lack of exclusivity between cases and the "unaffected controls" used in the comparison groups.

AD phenotype

AD manifests clinically as a loss of cognitive functions including memory, language, visuoconstructive,

and executive function. AD is the most common neurodegenerative disease, with a mean age at disease onset during the eighth decade. AD accounts for approximately 60% of dementia cases [10, 11] and affects approximately 1% of the population in Western countries [10, 12, 13].

The neuropathology of AD is characterized by two pathognomonic entities: the intraneuronal neurofibrillary tangle (NFT) and the extracellular neuritic plaque. NFTs are chiefly composed of fibrillar forms of a hyperphosphorylated protein called microtubule associated protein tau (MAPT or tau), while plaques are predominantly composed of fibrillated short peptides collectively termed amyloid-β (Aβ). A staging scheme for the neuropathological progression of AD based on the density and distribution of NFTs has been proposed by Braak and Braak (the 'Braak staging scheme') [14] and this has been incorporated into current diagnostic criteria [15]. For most individuals, there is a good correlation between Braak stage (i.e., the spread of NFT pathology from the medial temporal lobe, through the temporal and frontal neocortices, and into the primary cortices) and the probability of dementia [14, 16]. However in the hippocampus neuronal loss may actually exceed NFT formation [17].

Neuritic plaques ('plaques') are an important part of the diagnostic criteria for AD, but the extracellular amyloid load does not correlate as well with duration and severity of AD as the NFT count [18, 19]. Nevertheless, the major working hypothesis for AD pathogenesis, the Aβ hypothesis, suggests that extracellular Aβ precipitates a cascade of events resulting in the formation of NFTs and neuronal loss [20].

PD phenotype

PD is clinically characterized by the presence of two or more cardinal signs: tremor, postural instability, and bradykinesia. The mean age at disease onset is during the seventh decade of life [21]. The prevalence of PD in European, North American, and Australian populations is around one third of AD, with estimates of 0.3–0.4% of the population [22, 23]. The characteristic motor signs of PD result from the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) located in the midbrain [24, 25]. It has long been considered that at diagnosis PD patients have lost more than 50% of their SNc dopaminergic neurons [26]. However, a recent review suggests this figure is more likely to be 30% with the additional loss of 50–60% of the terminal axons of these cells [27].

Pathology in PD also affects the olfactory pathway, including the amygdala, the spinal cord, and dorsal cranial nuclei of the medulla [28–32]. However, relative to the gross atrophy seen in AD, atrophy of the terminal PD brain is minimal (see [33]). PD is characterized by a pathognomonic entity, the Lewy body (LB), an intraneuronal inclusion composed of multiple proteins including fibrillar forms of α-synuclein [34]. LB pathology also incorporates the accumulation of insoluble α-synuclein immunopositive protein in cell processes, called Lewy neurites. Current staging of PD is based on α-synuclein immunoreactivity, although there is not a strong correlation between LB density and neuronal loss [35].

Normal aging

Association studies set out to identify differences between groups of individuals with a clinical phenotype (e.g., AD or PD) and those who do not express this phenotype (the control group). In so doing it is hoped to inform the related question as to why "cases" develop the AD-type or LB-associated pathologies that lead to the clinical phenotype, while the majority of the aged population do not. However, the existence of incidental pathology and disease prodromes in clinically unaffected individuals has major implications for the interpretation of most case-control findings.

Aging is associated with cerebral atrophy due to decreases in both grey and white matter, white matter hyperintensities (WMH) [36], and cognitive decline [37]. Our work shows that white matter loss is more extensive than grey matter loss [38, 39]. Consistent with our findings and contrary to popular belief, the total number of neurons in the human adult brain does not change greatly with aging [40–43]. However, there are areas of the brain that show greater decline in neuron numbers with age, such as the SNc [44]. In the case of the SNc, the pattern of neuronal loss is distinct from and less extensive than that seen in PD [44].

In contrast to neuronal loss, diagnostic entities such as LBs, NFTs, and plaques are common in the postmortem brain tissue of neurologically normal individuals. An accurate quantification of the frequency of these pathological entities is difficult to make as today brain postmortem examinations of control individuals is often under the auspices of specific research programs and may not be representative of the entire population. Estimates suggest that senile plaques are seen in as many as 30% of all brains examined; here the plaques are almost exclusively of the diffuse type, a likely predecessor to the neuritic plaques common

in AD [45, 46]. A similar percentage of cognitively normal individuals have tau-positive neuritic pathology [47–50], although tau pathology confined to just the entorhinal-perirhinal cortex appears to be seen in most, if not all, aged brains [51–53]. Studies vary considerably as to the proportion of neurologically normal persons harboring LBs at the time of their death (8–31%), but they are less common than plaques [54–57]. The common occurrence of incidental AD and PD-type pathology may be an important factor in the small effect sizes and lack of reproducibility in association studies to date.

A clinical threshold and the oldest old

The most obvious explanation for the relatively high prevalence of asymptomatic neuropathological phenotypes is threshold effects. That is pathology, in the absence of lethal co-morbidities, would continue to accumulate until it reached the threshold for onset of clinical disease [58, 59]. However, there is increasing evidence that the association between increasing AD pathology and severity of dementia does not hold in the oldest old (usually defined as >90 years) [60]. There is considerable overlap in the density of AD pathology in the oldest old patients with and without dementia [61–63], whereas brain atrophy and neuronal loss are strongly associated with dementia at all ages [64]. In addition, there is an increased frequency of mixed pathology, and in particular AD with cerebrovascular disease, in the oldest old with dementia [65–67], suggesting that AD pathology *per se* is not a good marker for neurodegeneration in these individuals.

Similarly, α-synuclein positive structures were found in 35% of centenarians and were not related to cognitive status [68]. The LB pathology was, however, mainly Lewy neurites with few or no LBs. The frequency of LB pathology was related to senile plaque density but interestingly, given the potential interactions between α-synuclein and tau discussed below, not to NFT staging. The distribution pattern of LB pathology was actually similar to that seen in PD but the pigmented neurons in the SN were relatively well preserved.

Therefore, in the oldest old, additional factors appear to modify the impact of neuropathology [64]. One idea is that the oldest old rely more on compensatory mechanisms to offset the effects of neurodegenerative pathologies, thus avoiding the tipping point of any particular disease threshold [69]. Here Liao et al. regard compensation to result from a more facile use of alternative brain circuits instead of local synaptic plasticity

or direct interactions at a molecular level. How well the findings from these 'special' individuals can be extrapolated to moderately aged individuals remains to be seen, but it raises the possibility that factors that 'drive' pathology are less important than those that confer susceptibility or resistance [70].

The case-case paradigm

Given the common occurrence of incidental pathology among aged but neurologically normal individuals, we pose the following question: *Would greater progress be made by directly comparing AD and PD cases in association studies?* For example, would the knowledge of AD specific risk factors improve our knowledge of why other individuals develop PD? Could case-case comparisons of AD and PD be more informative than parallel case-control studies? At the outset such an approach might seem illogical given the distinctive clinical and pathological features of these diseases. However, these two proteinopathies share age as their leading risk factor and are the first and second most common late-onset neurological conditions. In contrast to case-control studies, individuals can be almost definitively classified on a clinical basis as having either AD or PD. By applying the same premises of exclusivity and homogeneity, the case-case paradigm would be most effective if incidental or mixed pathology was generally absent from the brains of sufferers of either disease.

Lewy body pathology in AD cases

Unfortunately for our proposed case-case paradigm, it appears that up to 50% of autopsy-proven AD cases show some LB pathology [71, 72]. Notably, this high proportion might actually reflect the sampling bias of research cohorts, as Schneider and colleagues were able to show in a community-based cohort of older persons that only 12% of non-demented, 13% of mild cognitively impaired and 24% of AD cases had Lewy bodies [73]. In a further study, Uchikado and colleagues reported that 43% of their AD cases had α-synuclein-positive neuronal lesions that resembled LBs but they could divide these cases into those with typical Lewy body disease (diffuse distribution including neocortex) and those (24% of all cases) where LBs were confined to the amygdala [74]. The authors suggested that these groups represent two different subtypes of AD. This finding also highlights the fact there are various forms of α-synucleinopathies, LBs

themselves are only one specific form. In the remainder of this review we will use the term "α-synuclein pathology" to represent all forms of synucleinopathy including, but not restricted to, LBs. Other AD studies have also reported α-synuclein pathology confined to the amygdala and have come to the conclusion that α-synuclein pathology is common in AD without signs of parkinsonism [72]. The susceptibility of the amygdala to α-synuclein pathology is predictably unknown, but nigra-amygdala connections are known to be important for the enhancement of attention in associative learning that is modulated by the cholinergic system [75].

AD pathology in PD cases

The proportion of non-demented PD cases showing typical AD pathology is difficult to assess from the literature. Estimates of the number of cases that also meet diagnostic criteria for AD are as low as 3% [76]. However it appears that approximately 50% of non-demented PD patients may have some Alzheimer's type pathology [77, 78]. Furthermore in studies that have included demented PD patients, the degree of cognitive decline significantly correlated with AD pathology [76]. The occurrence of AD pathology in the context of PD is further complicated by the presence of a spectrum of clinical entities characterized by both dementia and parkinsonism. These are largely categorized in the clinic on the basis of primary symptom presentation and the temporal nature of these symptoms. Two common clinical designations on this spectrum are Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD).

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) can have a clinical presentation very similar to AD [79, 80], including a similar age at disease onset. DLB probably accounts for 15% of total dementia cases making it almost as common as PD itself [10, 81]. DLB cases also incorporate different mixes of the characteristic AD and α-synuclein pathology [82, 83] with neocortical Aβ deposition being particularly prominent [84].

PD with dementia

It is commonly quoted that approximately 30% of PD cases develop dementia [85, 86] although recent data from the longitudinal Sydney Multicentre Study

of PD suggests that dementia in PD may actually be inevitable given sufficient longevity [87]. A diagnosis of PDD is made if dementia does not occur within a year of a clinical diagnosis of PD, if it does then the alternative diagnosis of DLB is made [80].

Mixed pathology and cognitive decline?

In both DLB and PDD there remains debate over both the regional and pathological basis for cognitive decline. In DLB, both subcortical [88] and cortical α-synuclein pathology [89] have been suggested to be the main determinant. It should be noted that LBs do not correlate well with the degree of neuronal loss in the cortex of DLB patients and small α-synuclein aggregates in presynaptic terminals may be the major α-synuclein pathology [90]. These aggregates result in axonal degeneration [91] and therefore emulate the findings in PD [27]. However, others suggest that AD pathology is more important, particularly when the Aβ load can be similar to that seen in AD [92].

The situation is even less clear in PDD, although classically α-synuclein pathology has been regarded as the primary pathologic substrate for dementia [93]. In reality, the neuropathology of PDD patients is heterogeneous with variable amounts of Aβ, tau, α-synuclein and other pathological proteins [94]; thus a specific clinopathological classification may be purely academic.

An alternative and increasingly popular view is that these pathologies combine synergistically to cause neurodegeneration [94, 95]. *In vivo* interactions between tau and α-synuclein are seen in double transgenic mice [96] and are supported by genetic studies [97]. In non-demented PD cases, Uchikado et al. found that the amygdala LB density correlated with the density of NFTs, but not plaques. However other studies have suggested the Aβ was more likely to promote the deposition of α-synuclein than tau [98, 99]. Certainly the latter two studies would appear to reflect the situation in most DLB cases. Recently a triple transgenic animal model demonstrated the synergistic effects of tau, α-synuclein and Aβ pathologies in accelerating neurodegeneration and cognitive decline [100]. Interestingly a decrease in α-synuclein solubility preceded the changes in tau solubility.

In summary AD, PD, DLB, PDD, and aging itself appear to be part of a complex continuum characterized by variable amounts of Aβ, tau, and α-synuclein pathology. Under these circumstances, our proposed AD-PD case-case design is unlikely to confer any significant advantage over the classic case-control paradigm. The way forward for determining risk factors in late-onset neurodegenerative diseases is not entirely clear but it is obviously important to try and work the idea of a disease continuum into our approaches. In the next part we re-examine aspects of the AD-PD association study literature with this in mind.

PART II: RISK FACTORS FOR A DEMENTIA-PD SPECTRUM

Disease pathogenesis is a dynamic interplay between a causative factor(s) and the host (tissue). The development of disease will be a combination of the exposure dosage and the resistance of the individual to that exposure. Late-onset neurodegenerative diseases, with their long disease trajectories, make it difficult to retrospectively determine factors that initiate or result from the drivers of the disease process. Thus it is unclear whether the associated neuropathological entities are representative of mechanisms that require attenuation or bolstering.

The occurrence of these Aβ, tau, and α-synuclein pathologies in aged brains is far more common than the clinical neurodegenerative diseases themselves. This implies that most aged individuals have been exposed to factors that promote or 'drive' the development of AD or PD, but very few actually succumb to this disease process by the time of their death. These findings confer limitations on case-control studies to find the factors that 'drive' the disease, because many of these factors may also be operating in the "control" group. Nevertheless, the correlation between pathological load and clinical decline in most (young-old) individuals suggests that these entities are themselves deleterious or closely associated with what is driving the disease process. This lends itself to studies that substitute disease status with pathological load as a continuous variable. This experimental design is obviously limited to postmortem cases. In contrast, the putative factors that protect brain tissue against, or compensate for, these pathologies may show greater disparity between cases and controls than the pathology-promoting factors. However, the caveat here is that real protective factors may remain hitherto unexplored because candidate factors to date have been largely chosen based on our knowledge of neuropathology and genetics.

In the previous section we described how mixtures of AD and PD pathology are common in both the aged brain and even more so in the brains of those clinically diagnosed with either disease. This could represent

individuals unfortunate enough to have risk factors for both diseases but it also appears that the presence of either pathology increases the risk of the other developing. We suggested that the clinical syndromes were part of a complex (non-linear) continuum of overlapping pathologies.

Here we attempt to re-interpret aspects of the extensive AD and PD association study literature. The effect sizes of the risk factors discussed here are summarized in Table 1. By considering these diseases as part of an AD-PD spectrum. The intermediate phenotypes such as DLB and PDD can be used to test hypotheses for putative pathology-specific factors. For example, DLB brains contain similar Aβ loads to AD and therefore we might expect risk factors driving Aβ pathology to be similar in effect size when compared with controls. Furthermore, the tau load for PDD patients is generally

less than in AD brains, and therefore one might expect that their exposure to a tau pathology-driving factor to be intermediate between an AD cohort and neurologically normal controls. Expanding on this idea further, the effect size for a factor precipitating tau pathology in a pure tauopathy such as (tau-positive) frontal temporal dementia (FTD) should equal or exceed that for an AD cohort but be similar to controls for Aβ pathology-inducing factors (given that the appropriate experiments have been carried out).

This represents a very cursory and selective exploration of the association study literature with considerable reliance on the online sites Alzforum (http://www.alzforum.org/) [101] and PDgene (http://www.pdgene.org/) [102] and their meta-analyses. Where meta-analyses are unavailable we have subjectively included the most representative study.

Table 1
Quantification of risk factors for the Dementia-PD spectrum

Factor	Effect size (RR, OR, or HR)[a]				
	FTD	AD	DLB	PDD	PD
Gender	M = F[109]	1.20 (0.93–1.56) F/M [103]	>M (pure LB disease) [93] or equal [107]	M = F [108]	**1.49 (1.24–1.95) M/F [106]**
Low education	FTD > AD [109]	**1.80 (1.43–2.27) [115]**	**DLB = AD [123]**	**High Ed. 0.93 (0.90–0.96) [122]**	**2.0 (1.1–3.6) [118]**
Head injury	**3.3 (1.3–8.1) [127]**	1.58 (1.21–2.06) [252]	ILBD 1.44 (0.16–13.2) [59][b]	0.9 (0.4–2.2) [121]	**4.3 (1.2–15.2) [126]**
Pesticide	n/a	1.62 (0.64–4.11) [253]	n/a	PDD > PD [254][c]	**1.85 (1.31–2.60) [177]**
Smoking	n/a	**1.45 (1.16–1.80) [162]**	DLB vs. AD – no effect [255]	PDD vs. PD – no effect [256]	**0.70 (0.63–0.78) [149]**
Coffee	n/a	**0.73 (0.58–0.92) [257][d]**	n/a	n/a	**0.75 (0.64–0.86) [147]**
Diabetes yes/no	n/a	**1.51 (1.31–1.73)[e]**	n/a	0.8 (0.3–2.3) [121]	1.04 (0.74–1.46) [141][f]
Family history of disease (FHx)	20–40% [258, 259]	2.3 (1.5–3.4) [183] 49% Hx of dementia [260]	67% FHx of dementia [260]	FHx of PD but not dementia [185]	2.2 (1.2–4.0) [183]; 15–25% [261]
NACP Rep 1 (SNCA) 263 : 261	n/a	No effect [262, 263]	n/a	n/a	**1.25 (1.11–1.41)[g]**
CYP2D6 *4 vs. WT	No effect [264]	1.08 (0.88–1.32)[h]	0.61 (0.20–1.85) [265]	No effect [266]	**1.13 (1.02–1.27)[g] *4 (B) vs. other**
ApoE ε4 vs. ε3	1.14 (0.87–1.49) [209]	**3.68 (3.31–4.11)[h]**	DLB = AD [212]; DLB > PDD [267]	1.6 (1.0–2.5) [214]	1.01 (0.91–1.13)[g]
MAPT H2 vs. H1	0.69 (0.43–1.10) [225]	1.0 (0.94–1.07)[h]	n/a	**PDD v. PD H1/H1 −12.1 (1.26 −117.4) [97]**	**0.77 (0.71–0.84)[g]**

Reported significant differences in bold type for relative (RR), odds (OR) or hazard ratios (HR).
[a] Utilizing either meta-analysis, collaborative study or largest case-control series. Values are relative to unaffected controls unless stated otherwise; [b] Incidental Lewy body disease (ILBD); not DLB due to insufficient numbers; [c] Interaction between CYP2D6 × pesticide for risk of PD+dementia (PDD) compared to PD; [d] Pooled estimate but heterogeneity across methodologies of the 4 contributing studies; [e] Weuve J, McQueen MB, Blacker D. The AlzRisk Database, available at: http://www.alzrisk.org/*; [f] Vascular risk factors such as diabetes decreased in medicated patients [144, 145]; [g] Cumulative meta-analysis. The PDGene Database, available at: http://www.pdgene.org/; [h] The Alzgene database [101].

Gender

The majority of research points to a higher prevalence of AD in females, but at least one large study found no difference [103]. It was originally thought that longevity *per se* could account for the higher female prevalence but the effect remains after adjustment for age and education [104]. One hypothesis is that AD pathology is more likely to manifest clinically as dementia in women than in men [105]. However this may contradict findings in the oldest old and those of Ruitenberg et al. who found that the incidence of AD increased in women over 90 years of age.

The opposite gender effect is seen in PD with a moderate relative risk effect in men (1.5 fold) [106]. The lack of gender differences in the intermediate phenotypes of DLB [107] and PDD [108] seem consistent with the contrasting effects in AD and PD if gender differences are associated with the pathology as opposed to resisting its effects. Similarly the lack of effect in FTD patients [109] could suggest that the female gender augments Aβ rather tau pathology in AD [110, 111]. In terms of biological plausibility, higher levels of oligomeric Aβ_{1-42} and insoluble Aβ have been found in the brain tissue of women [112] as well as in female mutant AβPP transgenic mice [113, 114].

Education

The prevalence of AD is inversely associated with years of education [115], but increased education is also directed related to the amount of AD pathology and cerebral hypoperfusion on imaging studies [69, 116]. This apparent paradox, where a factor appears to augment and resist pathology simultaneously, has been explained by education imparting a cognitive reserve that delays the onset of clinical symptoms [117]. It is worthwhile emphasizing that this postulated protective mechanism is acting mechanistically and spatially remote from the pathology itself. Therefore such an effect would not be detectable by sampling of the affected region and the increasingly commonplace assay by the genome-scale platforms.

In contrast, higher levels of education appear to be a risk factor for PD [118]. The hypothesis that increased education protects against cognitive decline is supported by comparisons between PDD and non-demented PD patients [119–122]. It is also consistent with the equivalent education levels between AD and DLB patients [123], as the global severity of dementia is very similar between DLB and AD patients [123].

Head injury

Dementia pugilistica is a progressive memory disorder common in ex-boxers associated with AD-like brain pathology. Traumatic brain injury is also implicated in the development of AD [124, 125] and PD [126], but in seems likely to only account for only a few cases of both diseases. The relatively high risk of head trauma in FTD [127] suggests that head trauma may modify the risk of AD via a tau-driven mechanism, although less than half FTD are tau-positive, and data are not stratified for tau-positive versus tau-negative FTD.

High levels of cleaved tau are observed in the cerebrospinal fluid (CSF) and serum of patients with acute brain injury [128]. The cleavage of tau is being increasingly seen as a pivotal step in NFT formation and neurodegeneration in AD [129–131]. In fact tau cleavage events may even be the link between Aβ and tau in the pathogenesis of AD according to recent work in a tau transgenic mouse model [132]. Interestingly acute brain trauma has also been associated with increases in AβPP and Aβ [133, 134] and α-synuclein [57, 135]. This suggests that the aberrant expression of all the proteins of interest could be general responses to brain trauma rather than disease specific [136]. This fits well with the development of mixed pathologies but does not explain the initial susceptibility of certain cell populations or the primary pathology that develops within them.

Cardiovascular disease risk factors

Cardiovascular risk factors have been of particular interest in AD given the dual role of ApoE ε4 variant in AD and systemic dyslipidemia [137, 138]. Perhaps surprisingly then, given the impact of ApoE ε4 on AD risk, it is only concurrent diabetes that is replicable across multiple independent studies (http://www.alzforum.org). This may reflect defective insulin signaling [139], a factor that appears to result in the abnormal phosphorylation of tau [140].

In contrast, no cardiovascular risk factors, including diabetes or ApoE ε4 status, appear to be associated with PD [141–143]. The lack of association with PD may be confounded by the sympathetic modulation of the cardiovascular system by PD medications [144, 145] and systemic manifestations of PD. In terms of intermediate phenotypes diabetes does not appear to influence the development of dementia among PD patients [121]. The artificial induction of diabetes mellitus in a tau transgenic model of FTD was shown to

cause a massive deposition of hyperphosphorylated, insoluble tau [146]. If diabetes is acting via tau pathology one might expect an association between diabetes and FTD, although we are not aware of any studies to date that support this idea.

Smoking

Cigarette smoking is one of the few environmental exposures that has been consistently shown to be associated with a reduced risk of PD [147–151]. It also seems that this effect depends more on smoking duration than on intensity [152]. Nicotine, through direct effects on receptors, or indirect effects such as inhibition of monoamine oxidase activity or induction of P450 enzymes, is the main suspect [153]. Work by ourselves, and others, has shown that both passive smoking and other forms of tobacco provide the same protective effect [154, 155], adding weight to a direct role of tobacco-related constituents in the association. Furthermore the protective effect of smoking may rely on interactions with xenobiotic metabolism genes [156, 157] similar to pesticide exposure discussed below. Other researchers have extended these gene × environmental interactions to include variants of genes involved in dopamine signaling [157] and the *SNCA* gene [158, 159]. *SNCA* encodes α-synuclein and is one of the few genes whose common variants are reproducibly shown to be risk factors in sporadic forms of PD [160]. The positive interactions with smoking [158, 159] and pesticides [159], hints at the mechanistic drivers of α-synuclein dysfunction.

In what appears to be a clear contrast with PD, smoking is a risk factor for AD [161–165], although other studies suggest that the effect is limited to ApoE ε4 carriers [166, 167]. The independent effects of smoking and ApoE genotype on cardiovascular disease (CVD) risk provide an obvious interactive mechanism for AD development, but as discussed above, diabetes seems to be the only CVD factor with a robust association with AD. Smoking is positively associated with type 2 diabetes but whether this is causal remains to be determined [168]. However, irrespective of the role of smoking, ApoE ε4 (discussed below) and diabetes combine to enhance the risk of AD [169].

Heavy smoking has been shown to reduce the risk of α-synuclein pathology in a community-based study with the greatest reductions being seen in the SN [165]. So in comparison to education in AD, smoking appears to act directly to reduce the pathological load. A deduction from this work is that α-synuclein pathology is either deleterious itself or a reliable barometer of the disease process in PD. As an aside, there was no concurrent increase in AD pathology in other regions suggesting that the smoking effect in AD is not mediated by exacerbating Aβ or tau pathology [170].

Pesticides

The interest in pesticides and PD pathogenesis stems from the chemical similarities of common pesticides like paraquat, to the Demerol derivative, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [171]. Accidental MPTP intoxication causes an acute form of parkinsonism [172, 173]. Like its toxic metabolite, MPP$^+$ [174], the herbicide paraquat can also induce parkinsonism in animal models [175]. Surprisingly paraquat does not appear to act as a substrate for the dopamine transporter, nor does it effectively inhibit mitochondrial complex I [176]. Studies investigating pesticide exposure in PD have produced variable results, but a meta-analysis suggests that it is a moderate risk factor [177]. Evidence from our laboratory suggests that the true risk associated with pesticides may well be higher but is effectively masked by heterogeneity of xenobiotic metabolism gene variants within the case and control groups [178].

In contrast, there appears to be no pesticide effect with AD or the intermediate phenotypes consistent with the proposed selective effect on SNc dopaminergic neurons [176, 179]. Nevertheless one needs to be cautious in emphasizing mitochondrial dysfunction as being PD-specific because one recent paper describes the synergistically deleterious effects of tau and Aβ on murine respiratory complex 1 and IV respectively [180].

Family history

In looking at family history as a risk factor we might appear to be asking the nonsensical question of how much of the etiology of a sporadic disease (no familial clustering) can be attributed to genetics? PD was always regarded as the archetypal non-genetic disease but the discovery of monogenic forms of the disease combined with the re-evaluation of twin studies has some researchers now suggesting that the sporadic PD is entirely genetic [181]. This suggestion is further supported by recent evaluations of common genetic variability in genome-wide association studies (GWAS), which have apportioned up to 25% of the population attributable risk in PD to small-effect sized common genetic variants [182]. Family history as a risk factor appears to be similar between PD (OR = 2.2 (95% CI = 1.2–4.0)) and AD (OR = 2.3 (95% CI = 1.5–3.4)) [183]. In terms of common genetic

risk factors, there are conflicting studies supporting an increased risk of dementia in PD relatives [184–186]. A family history of dementia is however a risk factor for DLB [187] and four-fold greater in magnitude than for PDD or PD [185, 187]. In contrast a family history of PD is similar for PD, PDD, and DLB patients [185].

Monogenic forms of AD and PD are proof that these diseases, or at least phenocopies of them, can be totally genetic in nature. Autosomal dominant forms of AD are caused by mutations in the presenilin 1 (*PS1*) gene and more rarely in the *PS2* and *AβPP* genes [188]. Autosomal dominant forms of PD are caused by mutations in *SNCA* and the genes that encode the proteins, leucine-rich region Kinase 2 (*LRRK2*) and Ubiquitin C-terminal hydrolase-1 (*UCHL-1*) while autosomal-recessive forms are caused by mutations in genes for parkin (*PARK2*), *DJ-1* (*PARK7*) and PTEN-induced putative kinase 1 (*PINK1*). More recently mutations have also been found in the genes encoding HtrA serine peptidase 2 (*HTRA2*), lysosomal ATPase type 13A2 (*ATP13A2*) and Glucocerebrosidase (*GBA*) [189]. *GBA* mutations have also been linked to DLB and may be a specific driver for α-synuclein pathology [190]. Most of these mutations result in early disease onsets although *LRRK2* mutations are a notable exception in PD.

An obvious question seems to be how common variants of these genes might modify the risk for sporadic disease [191]. Monogenic disease gene variants have not been detected in GWASs of AD, but PD GWASs suggest that *SNCA* [182, 192, 193] and *LRRK2* [182, 192] variants are risk factors. However, both have very modest effect sizes, particularly when compared to the ApoE ε4 variant in AD [194, 195]. It has been suggested that ApoE ε4, by itself, could account for as much as 50% of attributable risk in sporadic AD [196].

ApoE

GWASs in AD have universally detected the ApoE ε4 risk effect [197–204]. However despite the effect size it is still far from clear how ApoE ε4 increases the risk of AD. An important observation may be that plaques are more frequent in ApoE ε4 allele carriers [205], but there is no difference in NFT load between the different ApoE genotypes [206]. A mechanistic link with Aβ pathology is certainly supported by animal studies [207, 208] and seems consistent with the lack of ApoE ε4 effect in PD and FTD [209], while female gender could also to play an important interrelated role [112].

The frequency of ApoE ε4 in DLB patients is similar to AD [210–212] with a lessened, but nevertheless sig-

nificant, risk effect on the development of dementia in PD [213–215]. Neuropathological [84] and neuroimaging studies [216] studies both support increased Aβ loads in DLB compared with PDD. A caveat here is that Drzezga et al. and a second imaging study failed to show a link between ApoE genotype and brain atrophy in AD patients despite the association with Aβ loads [205, 217]. This suggested to Vemuri and colleagues that neurodegeneration in AD may be mediated by tau pathology and sequential to amyloidosis [217], a course of events first suggested by the 'amyloid cascade' hypothesis [218].

MAPT

Until recently microtubule-associated protein tau (MAPT or tau) had largely played second fiddle to Aβ in efforts to unravel the pathogenesis of AD. The presence of tau-based inclusions across so many neurodegenerative diseases hints at a general mechanism of neurodegeneration but the protein itself remains an enigma. No mutations in the *MAPT* gene, have been described in AD or PD patients, but they are responsible for an inherited variant of frontotemporal dementia with parkinsonism (FTDP-17) [219]. A 900-kb inversion polymorphism around the tau gene has led to two distinct lineages in the human population, H1 and H2 [220]. Surprisingly the variant H2 allele does not affect risk for the most common tauopathy, AD, but is protective in PD (Table 1). The common H1 extended tau haplotype is also associated with progressive supranuclear palsy, one of the parkinsonian syndromes characterized by tau deposition [221].

Associations between single nucleotide polymorphisms (SNPs) marking this haplotype and PD have been confirmed in two large GWASs of Caucasian populations [182, 193] but not, as expected, in a Japanese GWAS where the H2 haplotype is largely absent [192]. The modifying effect of tau in PD may be mediated via the putative interactions with α-synuclein as described above. Interestingly patients harboring either *SNCA* (A53 T) [222] or *LRRK2* (G2019S) mutations [223] can feature tau rather than α-synuclein-predominant pathology.

No studies have looked at whether the H1 allele has an effect on DLB risk, but the H1/H1 genotype is a predictor of PDD [97, 224]. This effect combined with the protective trend of the H2 allele in FTD [225] suggests that increased tau expression [226] drives dementia either independently, or through an interaction with α-synuclein pathology. The Aβ load in AD and DLB may be sufficient through direct [97] or indirect means [217] to precipitate tau aberrant expression or post-

translational modification in the absence of genetic predispositions.

However, if common variants of tau can drive dementia, then what is happening in the >50% of tau-negative cases of FTD? Some familial, and the majority of sporadic FTLD patients without tau, have deposits of the TAR DNA binding protein 43 (TDP-43) [227]. Interestingly, TDP-43 pathology is also commonly found in DLB and AD cases suggesting a general role in neurodegeneration [228–231]. In contrast, studies in PD suggest that TDP-43 pathology is either absence [232], or very uncommon [231] (Fig. 1). TDP-43 is transposed to the cytoplasm under pathological conditions, but the link between tau and TDP-43 pathology is still unclear despite their indistinguishable end stage degeneration in FTD.

In principle, the AD-PD risk factor literature does seem to support the idea of a neurodegenerative disease spectrum. We suggest that the risk factors for Aβ, tau, and α-synuclein pathologies occur commonly and often together. How they might combine to form the myriad of individual disease phenotypes is speculative but we have summarized our ideas in diagrammatic form to facilitate further discussion of this area (Fig. 1). Looking at the Fig. 1, the aging influence in neurodegeneration has been stylistically represented by an hourglass. Aging results in cellular deterioration but it is not entirely a haphazard process. Stochastic damage is a driving force but the rates of damage accumulation and decline relies on regulation by pathways that have been conserved during evolution [233, 234]. Furthermore postulated aging mechanisms such as decreased
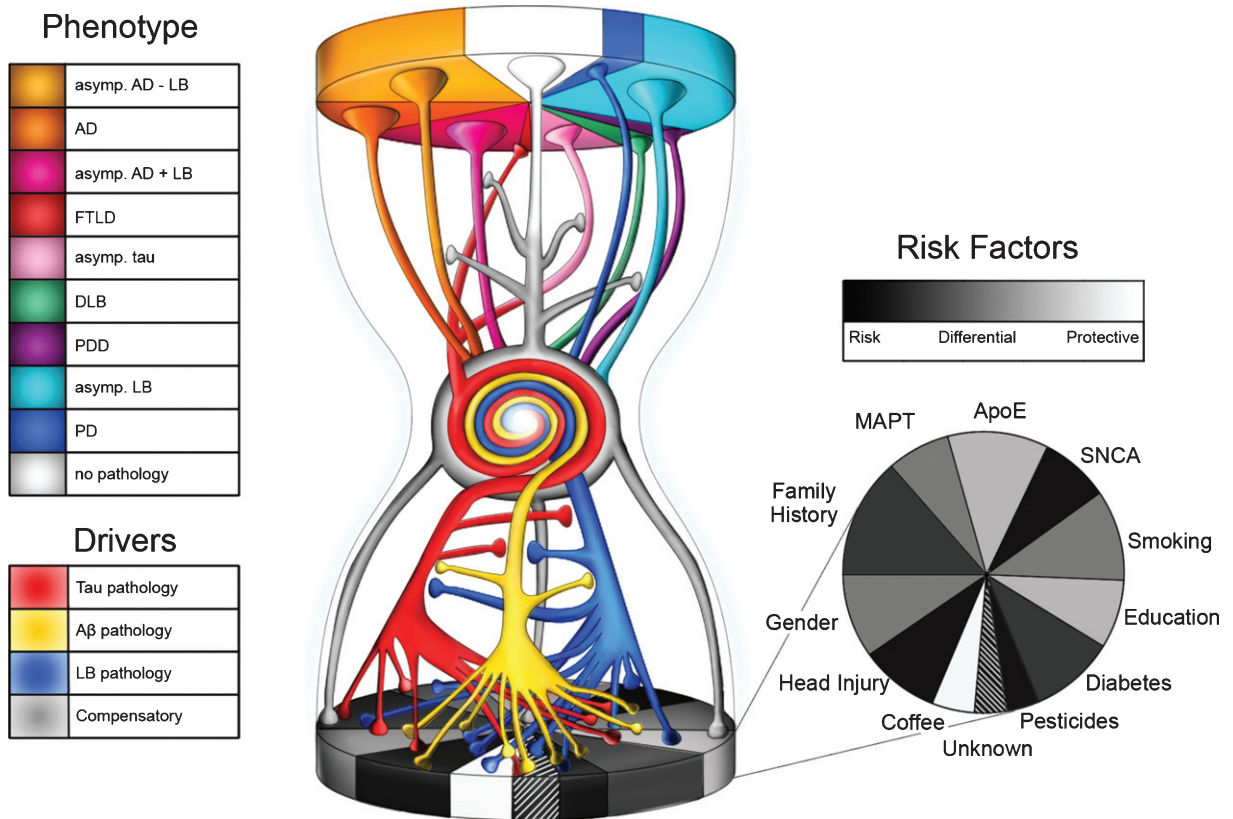

Fig. 1. A schematic of how risk factors might produce the dementia-PD spectrum. Using an hourglass analogy for ageing, this schematic summarizes how risk factors might contribute to neurodegeneration across the dementia-PD spectrum. Risk factors, both deleterious and protective, combine to produce the three pathological 'drivers': Amyloid-β, tau, and α-synuclein pathology represented by the yellow, red, and blue dendritic clusters respectively. The risk factor scale ranges from largely protective 'white' (e.g., coffee), through differential 'grey' effects (e.g., smoking) to largely deleterious 'black' (e.g., head injury). Dendro-dendritic synapses represent putative competing or excluding risk factors. Other factors will have their effects by acting directly on cellular resistance or via compensatory mechanisms (grey dendrites). The perikaryon represents the temporal and spatial 'mix' of factors in a typical aged human brain (80 years). Axons lead to the final phenotypes with protective or compensatory mechanisms (grey axons) continuing to minimize the impact of pathology and the clinical manifestations of disease (via axo-axonal synapses).

ability to manage oxidative stress [235] and proteotoxicity [235–237] are remarkably similar to the working hypotheses for AD and PD. Interestingly ApoE ε4 confers a four-fold decrease in longevity compared to ε2 in persons over 85 years [238] although this may reflect reduced morbidity from cardiovascular disease rather than increased neurodegenerative disease burden [239]. Nevertheless it is not a simple process to delineate 'cause' and 'effect' issues between aging and neurodegeneration.

The other aspect of these late-onset diseases is the time component itself. This allows the possibility that chronic exposure to very subtle risk factors could be sufficient for disease; a challenging scenario for association studies. The time component also increases the likelihood that multiple rounds of compensatory or protective host responses will mask primary pathogenic clues from postmortem detection. Such secondary or incidental findings can misdirect the subsequent research focus or result in therapeutics that will prove palliative at best. Lastly, the time component is difficult to accelerate accurately in cell culture or laboratory animal models aimed at recapitulating the disease history.

The base of the hourglass encloses a reservoir of these known, putative, or as yet, unknown risk factors. We envisage that subsets of these factors, both deleterious and protective interact to create 'drivers' for the three pathologies. We have used yellow, red and blue 'dendrites' to designate the Aβ, tau, and α-synuclein pathologies, respectively (color available in online version only; otherwise left to right respectively). In contrast to drivers of 'pathology' other factors will modify risk by enhancing or attenuating cellular protection or compensatory mechanisms (grey 'dendrites'). In particular we are referring to the effects of female gender and education on creating a 'cognitive reserve' that acts to postpone clinical manifestations of dementia.

The neuronal cell body is a mixer for the impact of individual 'drivers' against the general resolve of the human brain to maintain homeostasis or employ compensatory mechanisms in response to injury. This maintenance of homeostasis is what we have termed cellular resistance while compensation is likely to be 'multiscalar', potentially operating on all levels from a molecular basis, through enhanced local plasticity to the use of alternative circuitry [240].

Finally, 'axons' from the cell body carry the blend of Aβ, tau, and α-synuclein pathologies towards the final neuropathological and clinical phenotypes. The axo-axonal synapses (grey) reinforce the idea that some individuals enjoy a heightened resistance to, or an inherent ability or compensate for, these pathologies. The top of the hourglass shows the dementia-PD phenotypes displayed according to their estimated prevalence. We suggest that approximately 75% of aged individuals die with some neuropathology but less than 10% are clinically affected. Notwithstanding dosage effects this suggests that nearly all individuals are exposed factors that drive these 'pathologies'.

PART III: THE FUTURE DIRECTION OF ASSOCIATION STUDIES

The original hypothesis of this essay was to examine whether knowledge of disease-specific risk factors for AD could assist in focusing efforts into understanding the pathogenesis of sporadic forms of PD, or and *vice versa*. 'Intermediate' diseases and incidental pathology suggested that there is actually a dementia-PD spectrum involving various combinations of Aβ, tau, α-synuclein, and probably TDP-43 pathology, in a non-linear pattern. Although not altogether explained by a threshold effect, the amount and extent of pathology generally reflects the degree of neurological dysfunction. Given this continuum, we thought that our hypothesis might be better pursued in terms of factors that appeared to promote or attenuate Aβ, tau, or α-synuclein pathology across the various phenotypes. In the case of smoking in PD, this certainly seemed to be the case [165], but other known risk factors appeared to be acting in a compensatory capacity that was physically remote from pathology itself.

In the introduction we also suggested that using AD controls for PD, or *vice versa*, may be a more effective strategy to finding risk factors than the classic case-control paradigm. This approach seems particularly apt given the prevalence of incidental pathology in unaffected controls. However the commonality of mixed pathology amongst AD and PD cases suggests that the utility of AD-PD case comparisons may be just as limited, or effective, as the classic-case control paradigm.

Single disease entities are far easier to explore in experimental paradigms but here they are not entirely accurate. The risk factors for Aβ, tau, and α-synuclein pathologies often occur together across the AD-PD spectrum and show strong interrelations [94, 95]. Perhaps thinking in terms of a neurodegenerative disease continuum may be one way to advance our scientific investigation of these diseases. For example, one could study pathologically confirmed cases and consider the "load" of specific pathologies as continuous dependent variables in relation to particular indepen-

dent risk factors. Excitingly, the continuing progress of neuroimaging initiatives allowing a more accurate quantification of pathological (Aβ) load and regional atrophy creates the possibility that the research findings could actually benefit the patients involved [241].

Similarly, potential treatments in various stages of preclinical or clinical trials are largely aimed at the attenuation of pathology. The best known example is Aβ immunotherapy that, despite setbacks in human clinical trials, still holds considerable promise [242]. Similarly, strategies aimed at reducing NFTs [243] and α-synuclein pathology [244] or their formation [245, 246] are also being developed.

The reduction of pathology is not the only treatment option. It appears equally prudent, to identify and subsequently augment neuronal survival mechanisms. In the absence of pathology-attenuating therapeutics these will still reduce the burden of disease by extending the quality of life and reducing the need for high-dependence care. In addition, it is important to consider the role of inflammation in the overall disease processes as inflammatory correlates such as activated microglia are seen to a variable extent in all diseases across the AD-PD spectrum [247]. However, a greater exploration of this area, and particularly the research effort into finding effective modulators of neuroinflammation, falls outside the scope of this review (see [248]).

Whatever the treatment rationale, success is likely to hinge on the concurrent discovery of pre-clinical markers to identify at-risk individuals. This will facilitate the utilization of a therapeutic window where neuronal numbers remain consistent with adequate functionality. Luckily the discovery of a rational therapeutic target and preclinical marker may be mutually inclusive tasks. They both require investigation of early disease paradigms to find the primary pathogenic mechanisms. In this respect, the advent of patient derived stem cell models looks very promising for the *in vitro* modeling of disease history on differentiable susceptible genetic backgrounds [249]. Similarly, presymptomatic stages of animal models and the prospective studies of prodromal conditions and asymptomatic mutation carriers [250] could be employed.

It is an exciting time to be involved in disease research with genome-scale technologies enabling thousands of parameters to be tested simultaneously. These multidimensional platforms, in combination with improving annotational algorithms, are moving us steadily towards a systems biology approach to health, or as recently described, 'network medicine' [251]. However these powerful approaches still rely on the relevance of the question being asked and the context it is being asked in. Case-control studies are reductionist paradigms that assume, for maximum power, that the two populations being compared are exclusive and homogenous. We, and others [94, 95], suggest that AD and PD are neither exclusive nor homogenous entities but rather part of a complex continuum characterized by variable amounts of Aβ, tau, and α-synuclein pathology. This heterogeneity may be an important factor in the lack of reproducibility in case-control studies to date. The consideration of incidental and mixed pathologies will make experimental design and interpretation more challenging but it should also lead to greater clarity from our studies of late-onset neurodegenerative diseases such as AD and PD.

ACKNOWLEDGMENTS

REFERENCES

[1] Le Couteur DG, Muller M, Yang MC, Mellick GD, McLean AJ (2002) Age-environment and gene-environment interactions in the pathogenesis of Parkinson's disease. *Rev Environ Health* **17**, 51-64.

[2] Tol J, Roks G, Slooter AJ, van Duijn CM (1999) Genetic and environmental factors in Alzheimer's disease. *Rev Neurol (Paris)* **155** (Suppl 4), S10-S16.

[3] Mellick GD, Silburn PA, Sutherland GT, Siebert GA (2010) Exploiting the potential of molecular profiling in Parkinson's disease: current practice and future probabilities. *Expert Rev Mol Diagn* **10**, 1035-1050.

[4] Lippa CF, Smith TW, Swearer JM (1994) Alzheimer's disease and Lewy body disease: a comparative clinicopathological study. *Ann Neurol* **35**, 81-88.

[5] McKeith IG, Ince P, Jaros EB, Fairbairn A, Ballard C, Grace J, Morris CM, Perry RH (1998) What are the relations between Lewy body disease and AD? *J Neural Transm Suppl* **54**, 107-116.

[6] Strobel G (2009) The spectrum series: grappling with the overlap between Alzheimer's and Parkinson's diseases. 9 th International Conference on Alzheimer's and Parkinson's Diseases, 11–15 March 2009, Prague, Czech Republic. *J Alzheimers Dis* **18**, 625-640.

[7] Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, Huber S, Koller W, Olanow C, Shoulson I, et al. (1990) Variable expression of Parkinson's disease: a baseline analysis of the DATATOP cohort. The Parkinson Study Group. *Neurology* **40**, 1529-1534.

[8] Jellinger KA (1999) Post mortem studies in Parkinson's disease – is it possible to detect brain areas for specific symptoms? *J Neural Transm Suppl* **56**, 1-29.

[9] Selikhova M, Williams DR, Kempster PA, Holton JL, Revesz T, Lees AJ (2009) A clinico-pathological study of subtypes in Parkinson's disease. *Brain* **132**, 2947-2957.

[10] Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, Copeland JR, Dartigues JF, Jagger C, Martinez-Lage J, Soininen H, Hofman A (2000) Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* **54**, S4-S9.

[11] Fratiglioni L, De Ronchi D, Aguero-Torres H (1999) Worldwide prevalence and incidence of dementia. *Drugs Aging* **15**, 365-375.

[12] Jorm AF, Dear KB, Burgess NM (2005) Projections of future numbers of dementia cases in Australia with and without prevention. *Aust N Z J Psychiatry* **39**, 959-963.

[13] Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DC, Willis RJ, Wallace RB (2007) Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology* **29**, 125-132.

[14] Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol (Berl)* **82**, 239-259.

[15] NIA-Reagan Institute Working Group (1997) Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. *Neurobiol Aging* **18**, S1-S2.

[16] Newell KL, Hyman BT, Growdon JH, Hedley-Whyte ET (1999) Application of the National Institute on Aging (NIA)-Reagan Institute criteria for the neuropathological diagnosis of Alzheimer disease. *J Neuropathol Exp Neurol* **58**, 1147-1155.

[17] Kril JJ, Patel S, Harding AJ, Halliday GM (2002) Neuron loss from the hippocampus of Alzheimer's disease exceeds extracellular neurofibrillary tangle formation. *Acta Neuropathol* **103**, 370-376.

[18] Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT (1992) Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* **42**, 631-639.

[19] Bierer LM, Hof PR, Purohit DP, Carlin L, Schmeidler J, Davis KL, Perl DP (1995) Neocortical neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. *Arch Neurol* **52**, 81-88.

[20] Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* **297**, 353-356.

[21] Mellick GD, Maraganore DM, Silburn PA (2005) Australian data and meta-analysis lend support for alpha-synuclein (NACP-Rep1) as a risk factor for Parkinson's disease. *Neurosci Lett* **375**, 112-116.

[22] de Rijk MC, Launer LJ, Berger K, Breteler MM, Dartigues JF, Baldereschi M, Fratiglioni L, Lobo A, Martinez-Lage J, Trenkwalder C, Hofman A (2000) Prevalence of Parkinson's disease in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* **54**, S21-S23.

[23] Weintraub D, Comella CL, Horn S (2008) Parkinson's disease – Part 1: Pathophysiology, symptoms, burden, diagnosis, and assessment. *Am J Manag Care* **14**, S40-S48.

[24] Hughes AJ (1997) Clinicopathological aspects of Parkinson's disease. *Eur Neurol* **38** (Suppl 2), 13-20.

[25] Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* **55**, 181-184.

[26] Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F (1973) Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. *J Neurol Sci* **20**, 415-455.

[27] Cheng HC, Ulane CM, Burke RE (2010) Clinical progression in Parkinson disease and the neurobiology of axons. *Ann Neurol* **67**, 715-725.

[28] Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* **24**, 197-211.

[29] Braak H, Muller CM, Rub U, Ackermann H, Bratzke H, de Vos RA, Del Tredici K (2006) Pathology associated with sporadic Parkinson's disease – where does it end? *J Neural Transm Suppl* **70**, 89-97.

[30] Harding AJ, Stimson E, Henderson JM, Halliday GM (2002) Clinical correlates of selective pathology in the amygdala of patients with Parkinson's disease. *Brain* **125**, 2431-2445.

[31] Hubbard PS, Esiri MM, Reading M, McShane R, Nagy Z (2007) Alpha-synuclein pathology in the olfactory pathways of dementia patients. *J Anat* **211**, 117-124.

[32] Kalaitzakis ME, Graeber MB, Gentleman SM, Pearce RK (2008) Controversies over the staging of alpha-synuclein pathology in Parkinson's disease. *Acta Neuropathol* **116**, 125-128.

[33] Jellinger K, Mizuno H (2003) Parkinson's disease. In *Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders*, Dickson D, ed. ISN Neuropath Press, Basel, pp. 159-187.

[34] Leverenz JB, Umar I, Wang Q, Montine TJ, McMillan PJ, Tsuang DW, Jin J, Pan C, Shin J, Zhu D, Zhang J (2007) Proteomic identification of novel proteins in cortical lewy bodies. *Brain Pathol* **17**, 139-145.

[35] Jellinger KA (2009) A critical evaluation of current staging of alpha-synuclein pathology in Lewy body disorders. *Biochim Biophys Acta* **1792**, 730-740.

[36] Young VG, Halliday GM, Kril JJ (2008) Neuropathologic correlates of white matter hyperintensities. *Neurology* **71**, 804-811.

[37] Ziegler DA, Piguet O, Salat DH, Prince K, Connally E, Corkin S (2010) Cognition in healthy aging is related to regional white matter integrity, but not cortical thickness. *Neurobiol Aging* **31**, 1912-1926.

[38] Double KL, Halliday GM, Kril JJ, Harasty JA, Cullen K, Brooks WS, Creasey H, Broe GA (1996) Topography of brain atrophy during normal aging and Alzheimer's disease. *Neurobiol Aging* **17**, 513-521.

[39] Piguet O, Double KL, Kril JJ, Harasty J, Macdonald V, McRitchie DA, Halliday GM (2009) White matter loss in healthy ageing: a postmortem analysis. *Neurobiol Aging* **30**, 1288-1295.

[40] Harding AJ, Halliday GM, Kril JJ (1998) Variation in hippocampal neuron number with age and brain volume. *Cereb Cortex* **8**, 710-718.

[41] Terry RD, DeTeresa R, Hansen LA (1987) Neocortical cell counts in normal human adult aging. *Ann Neurol* **21**, 530-539.

[42] Pakkenberg B, Gundersen HJ (1997) Neocortical neuron number in humans: effect of sex and age. *J Comp Neurol* **384**, 312-320.

[43] Kubis N, Faucheux BA, Ransmayr G, Damier P, Duyckaerts C, Henin D, Forette B, Le Charpentier Y, Hauw JJ, Agid Y, Hirsch EC (2000) Preservation of midbrain catecholaminergic neurons in very old human subjects. *Brain* **123**(Pt 2), 366-373.

[44] Fearnley JM, Lees AJ (1991) Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain* **114**(Pt 5), 2283-2301.

[45] Braak H, Braak E (1997) Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging* **18**, 351-357.

[46] Davis DG, Schmitt FA, Wekstein DR, Markesbery WR (1999) Alzheimer neuropathologic alterations in aged cognitively normal subjects. *J Neuropathol Exp Neurol* **58**, 376-388.

[47] Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (2001) Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. *Lancet* **357**, 169-175.

[48] Knopman DS, Parisi JE, Salviati A, Floriach-Robert M, Boeve BF, Ivnik RJ, Smith GE, Dickson DW, Johnson KA, Petersen LE, McDonald WC, Braak H, Petersen RC (2003) Neuropathology of cognitively normal elderly. *J Neuropathol Exp Neurol* **62**, 1087-1095.

[49] Pikkarainen M, Kauppinen T, Alafuzoff I (2009) Hyper-phosphorylated tau in the occipital cortex in aged nondemented subjects. *J Neuropathol Exp Neurol* **68**, 653-660.

[50] McKee AC, Au R, Cabral HJ, Kowall NW, Seshadri S, Kubilus CA, Drake J, Wolf PA (2006) Visual association pathology in preclinical Alzheimer disease. *J Neuropathol Exp Neurol* **65**, 621-630.

[51] Price JL, McKeel DW Jr, Buckles VD, Roe CM, Xiong C, Grundman M, Hansen LA, Petersen RC, Parisi JE, Dickson DW, Smith CD, Davis DG, Schmitt FA, Markesbery WR, Kaye J, Kurlan R, Hulette C, Kurland BF, Higdon R, Kukull W, Morris JC (2009) Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease. *Neurobiol Aging* **30**, 1026-1036.

[52] Schmitt FA, Davis DG, Wekstein DR, Smith CD, Ashford JW, Markesbery WR (2000) "Preclinical" AD revisited: neuropathology of cognitively normal older adults. *Neurology* **55**, 370-376.

[53] Troncoso JC, Martin LJ, Dal Forno G, Kawas CH (1996) Neuropathology in controls and demented subjects from the Baltimore Longitudinal Study of Aging. *Neurobiol Aging* **17**, 365-371.

[54] Jellinger KA (2004) Lewy body-related alpha-synucleinopathy in the aged human brain. *J Neural Transm* **111**, 1219-1235.

[55] Markesbery WR, Jicha GA, Liu H, Schmitt FA (2009) Lewy body pathology in normal elderly subjects. *J Neuropathol Exp Neurol* **68**, 816-822.

[56] Adler CH, Connor DJ, Hentz JG, Sabbagh MN, Caviness JN, Shill HA, Noble B, Beach TG (2010) Incidental Lewy body disease: clinical comparison to a control cohort. *Mov Disord* **25**, 642-646.

[57] Uryu K, Giasson BI, Longhi L, Martinez D, Murray I, Conte V, Nakamura M, Saatman K, Talbot K, Horiguchi T, McIntosh T, Lee VM, Trojanowski JQ (2003) Age-dependent synuclein pathology following traumatic brain injury in mice. *Exp Neurol* **184**, 214-224.

[58] Dickson DW, Fujishiro H, DelleDonne A, Menke J, Ahmed Z, Klos KJ, Josephs KA, Frigerio R, Burnett M, Parisi JE,

Ahlskog JE (2008) Evidence that incidental Lewy body disease is pre-symptomatic Parkinson's disease. *Acta Neuropathol* **115**, 437-444.

[59] Frigerio R, Fujishiro H, Ahn TB, Josephs KA, Maraganore DM, Delledonne A, Parisi JE, Klos KJ, Boeve BF, Dickson DW, Ahlskog JE (2009) Incidental Lewy body disease: Do some cases represent a preclinical stage of dementia with Lewy bodies? *Neurobiol Aging* doi:10.1016/j.neurobiolaging.2009.05.019

[60] Kril JJ (2009) Alzheimer disease: Alzheimer disease neuropathology in the oldest old. *Nat Rev Neurol* **5**, 411-412.

[61] Haroutunian V, Schnaider-Beeri M, Schmeidler J, Wysocki M, Purohit DP, Perl DP, Libow LS, Lesser GT, Maroukian M, Grossman HT (2008) Role of the neuropathology of Alzheimer disease in dementia in the oldest-old. *Arch Neurol* **65**, 1211-1217.

[62] Polvikoski T, Sulkava R, Rastas S, Sutela A, Niinisto L, Notkola IL, Verkkoniemi A, Viramo P, Juva K, Haltia M (2006) Incidence of dementia in very elderly individuals: a clinical, neuropathological and molecular genetic study. *Neuroepidemiology* **26**, 76-82.

[63] Prohovnik I, Perl DP, Davis KL, Libow L, Lesser G, Haroutunian V (2006) Dissociation of neuropathology from severity of dementia in late-onset Alzheimer disease. *Neurology* **66**, 49-55.

[64] Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C (2009) Age, neuropathology, and dementia. *N Engl J Med* **360**, 2302-2309.

[65] Jellinger KA, Attems J (2010) Prevalence of dementia disorders in the oldest-old: an autopsy study. *Acta Neuropathol* **119**, 421-433.

[66] Laukka EJ, Fratiglioni L, Backman L (2010) The influence of vascular disease on cognitive performance in the preclinical and early phases of Alzheimer's disease. *Dement Geriatr Cogn Disord* **29**, 498-503.

[67] Strozyk D, Dickson DW, Lipton RB, Katz M, Derby CA, Lee S, Wang C, Verghese J (2010) Contribution of vascular pathology to the clinical expression of dementia. *Neurobiol Aging* **31**, 1710-1720.

[68] Ding ZT, Wang Y, Jiang YP, Hashizume Y, Yoshida M, Mimuro M, Inagaki T, Iwase T (2006) Characteristics of alpha-synucleinopathy in centenarians. *Acta Neuropathol (Berl)* **111**, 450-458.

[69] Liao YC, Liu RS, Teng EL, Lee YC, Wang PN, Lin KN, Chung CP, Liu HC (2005) Cognitive reserve: a SPECT study of 132 Alzheimer's disease patients with an education range of 0–19 years. *Dement Geriatr Cogn Disord* **20**, 8-14.

[70] Frigerio R, Fujishiro H, Maraganore DM, Klos KJ, Delle-Donne A, Heckman MG, Crook JE, Josephs KA, Parisi JE, Boeve BF, Dickson DW, Ahlskog JE (2009) Comparison of risk factor profiles in incidental Lewy body disease and Parkinson disease. *Arch Neurol* **66**, 1114-1119.

[71] Hamilton RL (2000) Lewy bodies in Alzheimer's disease: a neuropathological review of 145 cases using alpha-synuclein immunohistochemistry. *Brain Pathol* **10**, 378-384.

[72] Jellinger KA (2003) Alpha-synuclein pathology in Parkinson's and Alzheimer's disease brain: incidence and topographic distribution – a pilot study. *Acta Neuropathol* **106**, 191-201.

[73] Schneider JA, Aggarwal NT, Barnes L, Boyle P, Bennett DA (2009) The neuropathology of older persons with and without dementia from community versus clinic cohorts. *J Alzheimers Dis* **18**, 691-701.

[74] Uchikado H, Lin WL, DeLucia MW, Dickson DW (2006) Alzheimer disease with amygdala Lewy bodies: a distinct form of alpha-synucleinopathy. *J Neuropathol Exp Neurol* **65**, 685-697.

[75] Braak H, Braak E, Yilmazer D, Bohl J (1996) Functional anatomy of human hippocampal formation and related structures. *J Child Neurol* **11**, 265-275.

[76] Jellinger KA, Seppi K, Wenning GK, Poewe W (2002) Impact of coexistent Alzheimer pathology on the natural history of Parkinson's disease. *J Neural Transm* **109**, 329-339.

[77] Mann DM, Jones D (1990) Deposition of amyloid (A4) protein within the brains of persons with dementing disorders other than Alzheimer's disease and Down's syndrome. *Neurosci Lett* **109**, 68-75.

[78] Papapetropoulos S, Lieberman A, Gonzalez J, Mash DC (2005) Can Alzheimer's type pathology influence the clinical phenotype of Parkinson's disease? *Acta Neurol Scand* **111**, 353-359.

[79] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* **65**, 1863-1872.

[80] McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH (1996) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* **47**, 1113-1124.

[81] Zaccai J, McCracken C, Brayne C (2005) A systematic review of prevalence and incidence studies of dementia with Lewy bodies. *Age Ageing* **34**, 561-566.

[82] McKeith I (2007) Dementia with Lewy bodies and Parkinson's disease with dementia: where two worlds collide. *Pract Neurol* **7**, 374-382.

[83] Halliday G, Hely M, Reid W, Morris J (2008) The progression of pathology in longitudinally followed patients with Parkinson's disease. *Acta Neuropathol* **115**, 409-415.

[84] Halliday GM, McCann H (2010) The progression of pathology in Parkinson's disease. *Ann N Y Acad Sci* **1184**, 188-195.

[85] Dodel R, Csoti I, Ebersbach G, Fuchs G, Hahne M, Kuhn W, Oechsner M, Jost W, Reichmann H, Schulz JB (2008) Lewy body dementia and Parkinson's disease with dementia. *J Neurol* **255** (Suppl 5), 39-47.

[86] Aarsland D, Zaccai J, Brayne C (2005) A systematic review of prevalence studies of dementia in Parkinson's disease. *Mov Disord* **20**, 1255-1263.

[87] Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG (2008) The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord* **23**, 837-844.

[88] Kraybill ML, Larson EB, Tsuang DW, Teri L, McCormick WC, Bowen JD, Kukull WA, Leverenz JB, Cherrier MM (2005) Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. *Neurology* **64**, 2069-2073.

[89] Aarsland D, Ballard C, Larsen JP, McKeith I (2001) A comparative study of psychiatric symptoms in dementia with Lewy bodies and Parkinson's disease with and without dementia. *Int J Geriatr Psychiatry* **16**, 528-536.

[90] Kramer ML, Schulz-Schaeffer WJ (2007) Presynaptic alpha-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with Lewy bodies. *J Neurosci* **27**, 1405-1410.

[91] Siebert H, Kahle PJ, Kramer ML, Isik T, Schluter OM, Schulz-Schaeffer WJ, Bruck W (2010) Over-expression of alpha-synuclein in the nervous system enhances axonal degeneration after peripheral nerve lesion in a transgenic mouse strain. *J Neurochem* **114**, 1007-1018.

[92] Deramecourt V, Bombois S, Maurage CA, Ghestem A, Drobecq H, Vanmechelen E, Lebert F, Pasquier F, Delacourte A (2006) Biochemical staging of synucleinopathy and amyloid deposition in dementia with Lewy bodies. *J Neuropathol Exp Neurol* **65**, 278-288.

[93] Barker WW, Luis CA, Kashuba A, Luis M, Harwood DG, Loewenstein D, Waters C, Jimison P, Shepherd E, Sevush S, Graff-Radford N, Newland D, Todd M, Miller B, Gold M, Heilman K, Doty L, Goodman I, Robinson B, Pearl G, Dickson D, Duara R (2002) Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. *Alzheimer Dis Assoc Disord* **16**, 203-212.

[94] Jellinger KA (2011) Interaction between alpha-synuclein and tau in Parkinson's disease comment on Wills et al.: elevated tauopathy and alpha-synuclein pathology in postmortem Parkinson's disease brains with and without dementia. *Exp Neurol* **227**, 13-18.

[95] Jellinger KA (2010) Basic mechanisms of neurodegeneration: a critical update. *J Cell Mol Med* **14**, 457-487.

[96] Giasson BI, Forman MS, Higuchi M, Golbe LI, Graves CL, Kotzbauer PT, Trojanowski JQ, Lee VM (2003) Initiation and synergistic fibrillization of tau and alpha-synuclein. *Science* **300**, 636-640.

[97] Williams-Gray CH, Evans JR, Goris A, Foltynie T, Ban M, Robbins TW, Brayne C, Kolachana BS, Weinberger DR, Sawcer SJ, Barker RA (2009) The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain* **132**(Pt 11), 2958-2969.

[98] Mikolaenko I, Pletnikova O, Kawas CH, O'Brien R, Resnick SM, Crain B, Troncoso JC (2005) Alpha-synuclein lesions in normal aging, Parkinson disease, and Alzheimer disease: evidence from the Baltimore Longitudinal Study of Aging (BLSA). *J Neuropathol Exp Neurol* **64**, 156-162.

[99] Pletnikova O, West N, Lee MK, Rudow GL, Skolasky RL, Dawson TM, Marsh L, Troncoso JC (2005) Abeta deposition is associated with enhanced cortical alpha-synuclein lesions in Lewy body diseases. *Neurobiol Aging* **26**, 1183-1192.

[100] Clinton LK, Blurton-Jones M, Myczek K, Trojanowski JQ, LaFerla FM (2010) Synergistic interactions between Abeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline. *J Neurosci* **30**, 7281-7289.

[101] Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE (2007) Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet* **39**, 17-23.

[102] Lill CM, Bagade S, McQueen, Bagade S, Kavvoura F, Schjeide BMM, Allen NC, Tanzi R, Khoury MJ, Ioannidis JPA, Bertram L (2009) The PDGene Database. Alzheimer

Research Forum, http://www.pdgene.org/, Accessed 08/10/09.

[103] Ruitenberg A, Ott A, van Swieten JC, Hofman A, Breteler MM (2001) Incidence of dementia: does gender make a difference? *Neurobiol Aging* **22**, 575-580.

[104] Yue X, Lu M, Lancaster T, Cao P, Honda S, Staufenbiel M, Harada N, Zhong Z, Shen Y, Li R (2005) Brain estrogen deficiency accelerates Abeta plaque formation in an Alzheimer's disease animal model. *Proc Natl Acad Sci U S A* **102**, 19198-19203.

[105] Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA (2005) Sex differences in the clinical manifestations of Alzheimer disease pathology. *Arch Gen Psychiatry* **62**, 685-691.

[106] Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J (2004) Are men at greater risk for Parkinson's disease than women? *J Neurol Neurosurg Psychiatry* **75**, 637-639.

[107] Fujimi K, Sasaki K, Noda K, Wakisaka Y, Tanizaki Y, Matsui Y, Sekita A, Iida M, Kiyohara Y, Kanba S, Iwaki T (2008) Clinicopathological outline of dementia with Lewy bodies applying the revised criteria: the Hisayama Study. *Brain Pathol* **18**, 317-325.

[108] Riedel O, Klotsche J, Spottke A, Deuschl G, Forstl H, Henn F, Heuser I, Oertel W, Reichmann H, Riederer P, Trenkwalder C, Dodel R, Wittchen HU (2008) Cognitive impairment in 873 patients with idiopathic Parkinson's disease. Results from the German Study on Epidemiology of Parkinson's Disease with Dementia (GEPAD). *J Neurol* **255**, 255-264.

[109] Borroni B, Alberici A, Agosti C, Premi E, Padovani A (2008) Education plays a different role in Frontotemporal Dementia and Alzheimer's disease. *Int J Geriatr Psychiatry* **23**, 796-800.

[110] Kraszpulski M, Soininen H, Helisalmi S, Alafuzoff I (2001) The load and distribution of beta-amyloid in brain tissue of patients with Alzheimer's disease. *Acta Neurol Scand* **103**, 88-92.

[111] Johnson JK, McCleary R, Oshita MH, Cotman CW (1998) Initiation and propagation stages of beta-amyloid are associated with distinctive apolipoprotein E, age, and gender profiles. *Brain Res* **798**, 18-24.

[112] van Helmond Z, Miners JS, Kehoe PG, Love S (2010) Oligomeric Abeta in Alzheimer's disease: relationship to plaque and tangle pathology, APOE genotype and cerebral amyloid angiopathy. *Brain Pathol* **20**, 468-480.

[113] Callahan MJ, Lipinski WJ, Bian F, Durham RA, Pack A, Walker LC (2001) Augmented senile plaque load in aged female beta-amyloid precursor protein-transgenic mice. *Am J Pathol* **158**, 1173-1177.

[114] Hirata-Fukae C, Li HF, Hoe HS, Gray AJ, Minami SS, Hamada K, Niikura T, Hua F, Tsukagoshi-Nagai H, Horikoshi-Sakuraba Y, Mughal M, Rebeck GW, LaFerla FM, Mattson MP, Iwata N, Saido TC, Klein WL, Duff KE, Aisen PS, Matsuoka Y (2008) Females exhibit more extensive amyloid, but not tau, pathology in an Alzheimer transgenic model. *Brain Res* **1216**, 92-103.

[115] Caamano-Isorna F, Corral M, Montes-Martinez A, Takkouche B (2006) Education and dementia: a meta-analytic study. *Neuroepidemiology* **26**, 226-232.

[116] Perneczky R, Drzezga A, Diehl-Schmid J, Schmid G, Wohlschlager A, Kars S, Grimmer T, Wagenpfiel S, Monsch A, Kurz A (2006) Schooling mediates brain reserve in Alzheimer's disease: findings of fluoro-deoxy-glucose-positron emission tomography. *J Neurol Neurosurg Psychiatry* **77**, 1060-1063.

[117] Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R (1994) Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* **271**, 1004-1010.

[118] Frigerio R, Elbaz A, Sanft KR, Peterson BJ, Bower JH, Ahlskog JE, Grossardt BR, de Andrade M, Maraganore DM, Rocca WA (2005) Education and occupations preceding Parkinson disease: a population-based case-control study. *Neurology* **65**, 1575-1583.

[119] Cohen OS, Vakil E, Tanne D, Nitsan Z, Schwartz R, Hassin-Baer S (2007) Educational level as a modulator of cognitive performance and neuropsychyatric features in Parkinson disease. *Cogn Behav Neurol* **20**, 68-72.

[120] Glatt SL, Hubble JP, Lyons K, Paolo A, Troster AI, Hassanein RE, Koller WC (1996) Risk factors for dementia in Parkinson's disease: effect of education. *Neuroepidemiology* **15**, 20-25.

[121] Levy G, Tang MX, Cote LJ, Louis ED, Alfaro B, Mejia H, Stern Y, Marder K (2002) Do risk factors for Alzheimer's disease predict dementia in Parkinson's disease? An exploratory study. *Mov Disord* **17**, 250-257.

[122] Louis ED, Tang MX, Mayeux R (2004) Parkinsonian signs in older people in a community-based study: risk of incident dementia. *Arch Neurol* **61**, 1273-1276.

[123] Tiraboschi P, Salmon DP, Hansen LA, Hofstetter RC, Thal LJ, Corey-Bloom J (2006) What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? *Brain* **129**, 729-735.

[124] Guo Z, Cupples LA, Kurz A, Auerbach SH, Volicer L, Chui H, Green RC, Sadovnick AD, Duara R, DeCarli C, Johnson K, Go RC, Growdon JH, Haines JL, Kukull WA, Farrer LA (2000) Head injury and the risk of AD in the MIRAGE study. *Neurology* **54**, 1316-1323.

[125] Starkstein SE, Jorge R (2005) Dementia after traumatic brain injury. *Int Psychogeriatr* **17** (Suppl 1), S93-S107.

[126] Bower JH, Maraganore DM, Peterson BJ, McDonnell SK, Ahlskog JE, Rocca WA (2003) Head trauma preceding PD: a case-control study. *Neurology* **60**, 1610-1615.

[127] Rosso SM, Landweer EJ, Houterman S, Donker Kaat L, van Duijn CM, van Swieten JC (2003) Medical and environmental risk factors for sporadic frontotemporal dementia: a retrospective case-control study. *J Neurol Neurosurg Psychiatry* **74**, 1574-1576.

[128] Zemlan FP, Jauch EC, Mulchahey JJ, Gabbita SP, Rosenberg WS, Speciale SG, Zuccarello M (2002) C-tau biomarker of neuronal damage in severe brain injured patients: association with elevated intracranial pressure and clinical outcome. *Brain Res* **947**, 131-139.

[129] de Calignon A, Fox LM, Pitstick R, Carlson GA, Bacskai BJ, Spires-Jones TL, Hyman BT (2010) Caspase activation precedes and leads to tangles. *Nature* **464**, 1201-1204.

[130] Gamblin TC, Chen F, Zambrano A, Abraha A, Lagalwar S, Guillozet AL, Lu M, Fu Y, Garcia-Sierra F, LaPointe N, Miller R, Berry RW, Binder LI, Cryns VL (2003) Caspase cleavage of tau: linking amyloid and neurofibrillary tangles in Alzheimer's disease. *Proc Natl Acad Sci U S A* **100**, 10032-10037.

[131] Kim W, Lee S, Hall GF (2010) Secretion of human tau fragments resembling CSF-tau in Alzheimer's disease is modulated by the presence of the exon 2 insert. *FEBS Lett* **584**, 3085-3088.

[132] Ittner LM, Ke YD, Delerue F, Bi M, Gladbach A, van Eersel J, Wolfing H, Chieng BC, Christie MJ, Napier IA, Eckert A, Staufenbiel M, Hardeman E, Gotz J (2010)

Dendritic function of Tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. *Cell* **142**, 387-397.

[133] Gentleman SM, Nash MJ, Sweeting CJ, Graham DI, Roberts GW (1993) Beta-amyloid precursor protein (beta APP) as a marker for axonal injury after head injury. *Neurosci Lett* **160**, 139-144.

[134] Roberts GW, Gentleman SM, Lynch A, Murray L, Landon M, Graham DI (1994) Beta amyloid protein deposition in the brain after severe head injury: implications for the pathogenesis of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **57**, 419-425.

[135] Newell KL, Boyer P, Gomez-Tortosa E, Hobbs W, Hedley-Whyte ET, Vonsattel JP, Hyman BT (1999) Alpha-synuclein immunoreactivity is present in axonal swellings in neuroaxonal dystrophy and acute traumatic brain injury. *J Neuropathol Exp Neurol* **58**, 1263-1268.

[136] Uryu K, Chen XH, Martinez D, Browne KD, Johnson VE, Graham DI, Lee VM, Trojanowski JQ, Smith DH (2007) Multiple proteins implicated in neurodegenerative diseases accumulate in axons after brain trauma in humans. *Exp Neurol* **208**, 185-192.

[137] Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L (1999) The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. *JAMA* **282**, 40-46.

[138] Helzner EP, Luchsinger JA, Scarmeas N, Cosentino S, Brickman AM, Glymour MM, Stern Y (2009) Contribution of vascular risk factors to the progression in Alzheimer disease. *Arch Neurol* **66**, 343-348.

[139] Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, de la Monte SM (2005) Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. *J Alzheimers Dis* **8**, 247-268.

[140] Hong M, Lee VM (1997) Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons. *J Biol Chem* **272**, 19547-19553.

[141] Driver JA, Smith A, Buring JE, Gaziano JM, Kurth T, Logroscino G (2008) Prospective cohort study of type 2 diabetes and the risk of Parkinson's disease. *Diabetes Care* **31**, 2003-2005.

[142] Haugarvoll K, Aarsland D, Wentzel-Larsen T, Larsen JP (2005) The influence of cerebrovascular risk factors on incident dementia in patients with Parkinson's disease. *Acta Neurol Scand* **112**, 386-390.

[143] Scigliano G, Musicco M, Soliveri P, Piccolo I, Ronchetti G, Girotti F (2006) Reduced risk factors for vascular disorders in Parkinson disease patients: a case-control study. *Stroke* **37**, 1184-1188.

[144] Becker C, Brobert GP, Johansson S, Jick SS, Meier CR (2008) Diabetes in patients with idiopathic Parkinson's disease. *Diabetes Care* **31**, 1808-1812.

[145] Scigliano G, Ronchetti G, Girotti F, Musicco M (2009) Sympathetic modulation by levodopa reduces vascular risk factors in Parkinson disease. *Parkinsonism Relat Disord* **15**, 138-143.

[146] Ke YD, Delerue F, Gladbach A, Gotz J, Ittner LM (2009) Experimental diabetes mellitus exacerbates tau pathology in a transgenic mouse model of Alzheimer's disease. *PLoS One* **4**, e7917.

[147] Hernan MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ (2002) A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol* **52**, 276-284.

[148] Quik M (2004) Smoking, nicotine and Parkinson's disease. *Trends Neurosci* **27**, 561-568.

[149] Ritz B, Ascherio A, Checkoway H, Marder KS, Nelson LM, Rocca WA, Ross GW, Strickland D, Van Den Eeden SK, Gorell J (2007) Pooled analysis of tobacco use and risk of Parkinson disease. *Arch Neurol* **64**, 990-997.

[150] Sugita M, Izuno T, Tatemichi M, Otahara Y (2001) Meta-analysis for epidemiologic studies on the relationship between smoking and Parkinson's disease. *J Epidemiol* **11**, 87-94.

[151] Thacker EL, O'Reilly EJ, Weisskopf MG, Chen H, Schwarzschild MA, McCullough ML, Calle EE, Thun MJ, Ascherio A (2007) Temporal relationship between cigarette smoking and risk of Parkinson disease. *Neurology* **68**, 764-768.

[152] Chen H, Huang X, Guo X, Mailman RB, Park Y, Kamel F, Umbach DM, Xu Q, Hollenbeck A, Schatzkin A, Blair A (2010) Smoking duration, intensity, and risk of Parkinson disease. *Neurology* **74**, 878-884.

[153] Benedetti MD, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, Schaid DJ, Rocca WA (2000) Smoking, alcohol, and coffee consumption preceding Parkinson's disease: a case-control study. *Neurology* **55**, 1350-1358.

[154] Mellick GD, Gartner CE, Silburn PA, Battistutta D (2006) Passive smoking and Parkinson disease. *Neurology* **67**, 179-180.

[155] O'Reilly EJ, McCullough ML, Chao A, Henley SJ, Calle EE, Thun MJ, Ascherio A (2005) Smokeless tobacco use and the risk of Parkinson's disease mortality. *Mov Disord* **20**, 1383-1384.

[156] Deng Y, Newman B, Dunne MP, Silburn PA, Mellick GD (2004) Case-only study of interactions between genetic polymorphisms of GSTM1, P1, T1 and Z1 and smoking in Parkinson's disease. *Neurosci Lett* **366**, 326-331.

[157] De Palma G, Dick FD, Calzetti S, Scott NW, Prescott GJ, Osborne A, Haites N, Mozzoni P, Negrotti A, Scaglioni A, Mutti A (2010) A case-control study of Parkinson's disease and tobacco use: gene-tobacco interactions. *Mov Disord* **25**, 912-919.

[158] McCulloch CC, Kay DM, Factor SA, Samii A, Nutt JG, Higgins DS, Griffith A, Roberts JW, Leis BC, Montimurro JS, Zabetian CP, Payami H (2008) Exploring gene-environment interactions in Parkinson's disease. *Hum Genet* **123**, 257-265.

[159] Gatto NM, Rhodes SL, Manthripragada AD, Bronstein J, Cockburn M, Farrer M, Ritz B (2010) alpha-Synuclein gene may interact with environmental factors in increasing risk of Parkinson's disease. *Neuroepidemiology* **35**, 191-195.

[160] Saad M, Lesage S, Saint-Pierre A, Corvol JC, Zelenika D, Lambert JC, Vidailhet M, Mellick GD, Lohmann E, Durif F, Pollak P, Damier P, Tison F, Silburn PA, Tzourio C, Forlani S, Loriot MA, Giroud M, Helmer C, Portet F, Amouyel P, Lathrop M, Elbaz A, Durr A, Martinez M, Brice A (2011) Genome-wide association study confirms BST1 and suggests a locus on 12 q24 as risk loci for Parkinson's disease in the European population. *Hum Mol Genet* **20**, 615-627.

[161] Anstey KJ, von Sanden C, Salim A, O'Kearney R (2007) Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *Am J Epidemiol* **166**, 367-378.

[162] Cataldo JK, Prochaska JJ, Glantz SA (2009) Cigarette smoking is a risk factor for alzheimer's disease: an analysis controlling for tobacco industry affiliation. *J Alzheimers Dis* **19**, 465-480.

[163] Ott A, Slooter AJ, Hofman A, van Harskamp F, Witteman JC, Van Broeckhoven C, van Duijn CM, Breteler MM (1998) Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. *Lancet* **351**, 1840-1843.

[164] Reitz C, den Heijer T, van Duijn C, Hofman A, Breteler MM (2007) Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study. *Neurology* **69**, 998-1005.

[165] Tsuang D, Larson EB, Li G, Shofer JB, Montine KS, Thompson ML, Sonnen JA, Crane PK, Leverenz JB, Montine TJ (2010) Association between lifetime cigarette smoking and lewy body accumulation. *Brain Pathol* **20**, 412-418.

[166] Kivipelto M, Rovio S, Ngandu T, Kareholt I, Eskelinen M, Winblad B, Hachinski V, Cedazo-Minguez A, Soininen H, Tuomilehto J, Nissinen A (2008) Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. *J Cell Mol Med* **12**, 2762-2771.

[167] Rusanen M, Rovio S, Ngandu T, Nissinen A, Tuomilehto J, Soininen H, Kivipelto M (2010) Midlife smoking, apolipoprotein E and risk of dementia and Alzheimer's disease: a population-based cardiovascular risk factors, aging and dementia study. *Dement Geriatr Cogn Disord* **30**, 277-284.

[168] Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J (2007) Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* **298**, 2654-2664.

[169] Irie F, Fitzpatrick AL, Lopez OL, Kuller LH, Peila R, Newman AB, Launer LJ (2008) Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: the Cardiovascular Health Study Cognition Study. *Arch Neurol* **65**, 89-93.

[170] Sabbagh MN, Tyas SL, Emery SC, Hansen LA, Alford MF, Reid RT, Tiraboschi P, Thal LJ (2005) Smoking affects the phenotype of Alzheimer disease. *Neurology* **64**, 1301-1303.

[171] Barbeau A, Roy M, Cloutier T, Plasse L, Paris S (1987) Environmental and genetic factors in the etiology of Parkinson's disease. In *Parkinson's Disease. Advances in Neurology.* Yahr MD, Bergmann KJ, eds. Raven Press, New York, pp. 299-306.

[172] Davis GC, Williams AC, Markey SP, Ebert MH, Caine ED, Reichert CM, Kopin IJ (1979) Chronic Parkinsonism secondary to intravenous injection of meperidine analogues. *Psychiatry Res* **1**, 249-254.

[173] Langston JW, Ballard PA Jr (1983) Parkinson's disease in a chemist working with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *N Engl J Med* **309**, 310.

[174] Langston JW, Irwin I, Langston EB, Forno LS (1984) 1-Methyl-4-phenylpyridinium ion (MPP+): identification of a metabolite of MPTP, a toxin selective to the substantia nigra. *Neurosci Lett* **48**, 87-92.

[175] Nicklas WJ, Youngster SK, Kindt MV, Heikkila RE (1987) MPTP, MPP+ and mitochondrial function. *Life Sci* **40**, 721-729.

[176] Richardson JR, Quan Y, Sherer TB, Greenamyre JT, Miller GW (2005) Paraquat neurotoxicity is distinct from that of MPTP and rotenone. *Toxicol Sci* **88**, 193-201.

[177] Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS (2001) Environmental risk factors and Parkinson's disease: a metaanalysis. *Environ Res* **86**, 122-127.

[178] Mellick GD (2006) CYP450, genetics and Parkinson's disease: gene × environment interactions hold the key. *J Neural Transm Suppl* **70**, 159-165.

[179] Choi WS, Kruse SE, Palmiter RD, Xia Z (2008) Mitochondrial complex I inhibition is not required for dopaminergic neuron death induced by rotenone, MPP+, or paraquat. *Proc Natl Acad Sci U S A* **105**, 15136-15141.

[180] Rhein V, Song X, Wiesner A, Ittner LM, Baysang G, Meier F, Ozmen L, Bluethmann H, Drose S, Brandt U, Savaskan E, Czech C, Gotz J, Eckert A (2009) Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice. *Proc Natl Acad Sci U S A* **106**, 20057-20062.

[181] Hardy J (2006) No definitive evidence for a role for the environment in the etiology of Parkinson's disease. *Mov Disord* **21**, 1790-1791.

[182] Simon-Sanchez J, Schulte C, Bras JM, Sharma M, Gibbs JR, Berg D, Paisan-Ruiz C, Lichtner P, Scholz SW, Hernandez DG, Kruger R, Federoff M, Klein C, Goate A, Perlmutter J, Bonin M, Nalls MA, Illig T, Gieger C, Houlden H, Steffens M, Okun MS, Racette BA, Cookson MR, Foote KD, Fernandez HH, Traynor BJ, Schreiber S, Arepalli S, Zonozi R, Gwinn K, van der Brug M, Lopez G, Chanock SJ, Schatzkin A, Park Y, Hollenbeck A, Gao J, Huang X, Wood NW, Lorenz D, Deuschl G, Chen H, Riess O, Hardy JA, Singleton AB, Gasser T (2009) Genome-wide association study reveals genetic risk underlying Parkinson's disease. *Nat Genet* **41**, 1308-1312.

[183] Rosen AR, Steenland NK, Hanfelt J, Factor SA, Lah JJ, Levey AI (2007) Evidence of shared risk for Alzheimer's disease and Parkinson's disease using family history. *Neurogenetics* **8**, 263-270.

[184] Rocca WA, Bower JH, Ahlskog JE, Elbaz A, Grossardt BR, McDonnell SK, Schaid DJ, Maraganore DM (2007) Risk of cognitive impairment or dementia in relatives of patients with Parkinson disease. *Arch Neurol* **64**, 1458-1464.

[185] Kurz MW, Larsen JP, Kvaloy JT, Aarsland D (2006) Associations between family history of Parkinson's disease and dementia and risk of dementia in Parkinson's disease: A community-based, longitudinal study. *Mov Disord* **21**, 2170-2174.

[186] Levy G, Louis ED, Mejia-Santana H, Cote L, Andrews H, Harris J, Waters C, Ford B, Frucht S, Fahn S, Ottman R, Marder K (2004) Lack of familial aggregation of Parkinson disease and Alzheimer disease. *Arch Neurol* **61**, 1033-1039.

[187] Papapetropoulos S, Lieberman A, Gonzalez J, Singer C, Laufer DZ, Mash DC (2006) Family history of dementia: dementia with lewy bodies and dementia in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* **18**, 113-116.

[188] Brouwers N, Sleegers K, Van Broeckhoven C (2008) Molecular genetics of Alzheimer's disease: an update. *Ann Med* **40**, 562-583.

[189] Lesage S, Brice A (2009) Parkinson's disease: from monogenic forms to genetic susceptibility factors. *Hum Mol Genet* **18**, R48-R59.

[190] Clark LN, Kartsaklis LA, Wolf Gilbert R, Dorado B, Ross BM, Kisselev S, Verbitsky M, Mejia-Santana H, Cote LJ, Andrews H, Vonsattel JP, Fahn S, Mayeux R, Honig LS, Marder K (2009) Association of glucocerebrosidase mutations with dementia with lewy bodies. *Arch Neurol* **66**, 578-583.

[191] Sutherland GT, Halliday GM, Silburn PA, Mastaglia FL, Rowe DB, Boyle RS, O'Sullivan JD, Ly T, Wilton SD, Mellick GD (2009) Do polymorphisms in the familial Parkinsonism genes contribute to risk for sporadic Parkinson's disease? *Mov Disord* **24**, 833-838.

[192] Satake W, Nakabayashi Y, Mizuta I, Hirota Y, Ito C, Kubo M, Kawaguchi T, Tsunoda T, Watanabe M, Takeda A, Tomiyama H, Nakashima K, Hasegawa K, Obata F, Yoshikawa T, Kawakami H, Sakoda S, Yamamoto M,

Hattori N, Murata M, Nakamura Y, Toda T (2009) Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. *Nat Genet* **41**, 1303-1307.

[193] Edwards TL, Scott WK, Almonte C, Burt A, Powell EH, Beecham GW, Wang L, Zuchner S, Konidari I, Wang G, Singer C, Nahab F, Scott B, Stajich JM, Pericak-Vance M, Haines J, Vance JM, Martin ER (2010) Genome-wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease. *Ann Hum Genet* **74**, 97-109.

[194] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**, 921-923.

[195] Strittmatter WJ, Weisgraber KH, Huang DY, Dong LM, Salvesen GS, Pericak-Vance M, Schmechel D, Saunders AM, Goldgaber D, Roses AD (1993) Binding of human apolipoprotein E to synthetic amyloid beta peptide: isoform-specific effects and implications for late-onset Alzheimer disease. *Proc Natl Acad Sci U S A* **90**, 8098-8102.

[196] Ashford JW (2004) APOE genotype effects on Alzheimer's disease onset and epidemiology. *J Mol Neurosci* **23**, 157-165.

[197] Abraham R, Moskvina V, Sims R, Hollingworth P, Morgan A, Georgieva L, Dowzell K, Cichon S, Hillmer AM, O'Donovan MC, Williams J, Owen MJ, Kirov G (2008) A genome-wide association study for late-onset Alzheimer's disease using DNA pooling. *BMC Med Genomics* **1**, 44.

[198] Beecham GW, Martin ER, Li YJ, Slifer MA, Gilbert JR, Haines JL, Pericak-Vance MA (2009) Genome-wide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. *Am J Hum Genet* **84**, 35-43.

[199] Bertram L, Lange C, Mullin K, Parkinson M, Hsiao M, Hogan MF, Schjeide BM, Hooli B, Divito J, Ionita I, Jiang H, Laird N, Moscarillo T, Ohlsen KL, Elliott K, Wang X, Hu-Lince D, Ryder M, Murphy A, Wagner SL, Blacker D, Becker KD, Tanzi RE (2008) Genome-wide association analysis reveals putative Alzheimer's disease susceptibility loci in addition to APOE. *Am J Hum Genet* **83**, 623-632.

[200] Carrasquillo MM, Zou F, Pankratz VS, Wilcox SL, Ma L, Walker LP, Younkin SG, Younkin CS, Younkin LH, Bisceglio GD, Ertekin-Taner N, Crook JE, Dickson DW, Petersen RC, Graff-Radford NR, Younkin SG (2009) Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease. *Nat Genet* **41**, 192-198.

[201] Coon KD, Myers AJ, Craig DW, Webster JA, Pearson JV, Lince DH, Zismann VL, Beach TG, Leung D, Bryden L, Halperin RF, Marlowe L, Kaleem M, Walker DG, Ravid R, Heward CB, Rogers J, Papassotiropoulos A, Reiman EM, Hardy J, Stephan DA (2007) A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease. *J Clin Psychiatry* **68**, 613-618.

[202] Feulner TM, Laws SM, Friedrich P, Wagenpfeil S, Wurst SH, Riehle C, Kuhn KA, Krawczak M, Schreiber S, Nikolaus S, Forstl H, Kurz A, Riemenschneider M (2010) Examination of the current top candidate genes for AD in a genome-wide association study. *Mol Psychiatry* **15**, 756-766.

[203] Li H, Wetten S, Li L, St Jean PL, Upmanyu R, Surh L, Hosford D, Barnes MR, Briley JD, Borrie M, Coletta N, Delisle R, Dhalla D, Ehm MG, Feldman HH, Fornazzari L, Gauthier S, Goodgame N, Guzman D, Hammond S, Hollingworth

P, Hsiung GY, Johnson J, Kelly DD, Keren R, Kertesz A, King KS, Lovestone S, Loy-English I, Matthews PM, Owen MJ, Plumpton M, Pryse-Phillips W, Prinjha RK, Richardson JC, Saunders A, Slater AJ, St George-Hyslop PH, Stinnett SW, Swartz JE, Taylor RL, Wherrett J, Williams J, Yarnall DP, Gibson RA, Irizarry MC, Middleton LT, Roses AD (2008) Candidate single-nucleotide polymorphisms from a genomewide association study of Alzheimer disease. *Arch Neurol* **65**, 45-53.

[204] Webster JA, Myers AJ, Pearson JV, Craig DW, Hu-Lince D, Coon KD, Zismann VL, Beach T, Leung D, Bryden L, Halperin RF, Marlowe L, Kaleem M, Huentelman MJ, Joshipura K, Walker D, Heward CB, Ravid R, Rogers J, Papassotiropoulos A, Hardy J, Reiman EM, Stephan DA (2008) Sorl1 as an Alzheimer's disease predisposition gene? *Neurodegener Dis* **5**, 60-64.

[205] Drzezga A, Grimmer T, Henriksen G, Muhlau M, Perneczky R, Miederer I, Praus C, Sorg C, Wohlschlager A, Riemenschneider M, Wester HJ, Foerstl H, Schwaiger M, Kurz A (2009) Effect of APOE genotype on amyloid plaque load and gray matter volume in Alzheimer disease. *Neurology* **72**, 1487-1494.

[206] Kok E, Haikonen S, Luoto T, Huhtala H, Goebeler S, Haapasalo H, Karhunen PJ (2009) Apolipoprotein E-dependent accumulation of Alzheimer disease-related lesions begins in middle age. *Ann Neurol* **65**, 650-657.

[207] Holtzman DM, Bales KR, Tenkova T, Fagan AM, Parsadanian M, Sartorius LJ, Mackey B, Olney J, McKeel D, Wozniak D, Paul SM (2000) Apolipoprotein E isoform-dependent amyloid deposition and neuritic degeneration in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* **97**, 2892-2897.

[208] Sadowski MJ, Pankiewicz J, Scholtzova H, Mehta PD, Prelli F, Quartermain D, Wisniewski T (2006) Blocking the apolipoprotein E/amyloid-beta interaction as a potential therapeutic approach for Alzheimer's disease. *Proc Natl Acad Sci U S A* **103**, 18787-18792.

[209] Verpillat P, Camuzat A, Hannequin D, Thomas-Anterion C, Puel M, Belliard S, Dubois B, Didic M, Lacomblez L, Moreaud O, Golfier V, Campion D, Brice A, Clerget-Darpoux F (2002) Apolipoprotein E gene in frontotemporal dementia: an association study and meta-analysis. *Eur J Hum Genet* **10**, 399-405.

[210] Feher A, Juhasz A, Rimanoczy A, Kalman J, Janka Z (2009) Association between BDNF Val66Met polymorphism and Alzheimer disease, dementia with Lewy bodies, and Pick disease. *Alzheimer Dis Assoc Disord* **23**, 224-228.

[211] Nervi A, Reitz C, Tang MX, Santana V, Piriz A, Reyes-Dumeyer D, Lantigua R, Medrano M, Jimenez-Velazquez IZ, Lee JH, Mayeux R (2008) Comparison of clinical manifestations in Alzheimer disease and dementia with Lewy bodies. *Arch Neurol* **65**, 1634-1639.

[212] Singleton AB, Wharton A, O'Brien KK, Walker MP, McKeith IG, Ballard CG, O'Brien J, Perry RH, Ince PG, Edwardson JA, Morris CM (2002) Clinical and neuropathological correlates of apolipoprotein E genotype in dementia with Lewy bodies. *Dement Geriatr Cogn Disord* **14**, 167-175.

[213] Parsian A, Racette B, Goldsmith LJ, Perlmutter JS (2002) Parkinson's disease and apolipoprotein E: possible association with dementia but not age at onset. *Genomics* **79**, 458-461.

[214] Huang X, Chen P, Kaufer DI, Troster AI, Poole C (2006) Apolipoprotein E and dementia in Parkinson disease: a meta-analysis. *Arch Neurol* **63**, 189-193.

[215] Williams-Gray CH, Goris A, Saiki M, Foltynie T, Compston DA, Sawcer SJ, Barker RA (2009) Apolipoprotein E genotype as a risk factor for susceptibility to and dementia in Parkinson's disease. *J Neurol* **256**, 493-498.

[216] Gomperts SN, Rentz DM, Moran E, Becker JA, Locascio JJ, Klunk WE, Mathis CA, Elmaleh DR, Shoup T, Fischman AJ, Hyman BT, Growdon JH, Johnson KA (2008) Imaging amyloid deposition in Lewy body diseases. *Neurology* **71**, 903-910.

[217] Vemuri P, Wiste HJ, Weigand SD, Knopman DS, Shaw LM, Trojanowski JQ, Aisen PS, Weiner M, Petersen RC, Jack CR Jr (2010) Effect of apolipoprotein E on biomarkers of amyloid load and neuronal pathology in Alzheimer disease. *Ann Neurol* **67**, 308-316.

[218] Hardy JA, Higgins GA (1992) Alzheimer's disease: the amyloid cascade hypothesis. *Science* **256**, 184-185.

[219] Hutton M (2000) Molecular genetics of chromosome 17 tauopathies. *Ann N Y Acad Sci* **920**, 63-73.

[220] Stefansson H, Helgason A, Thorleifsson G, Steinthorsdottir V, Masson G, Barnard J, Baker A, Jonasdottir A, Ingason A, Gudnadottir VG, Desnica N, Hicks A, Gylfason A, Gudbjartsson DF, Jonsdottir GM, Sainz J, Agnarsson K, Birgisdottir B, Ghosh S, Olafsdottir A, Cazier JB, Kristjansson K, Frigge ML, Thorgeirsson TE, Gulcher JR, Kong A, Stefansson K (2005) A common inversion under selection in Europeans. *Nat Genet* **37**, 129-137.

[221] Baker M, Litvan I, Houlden H, Adamson J, Dickson D, Perez-Tur J, Hardy J, Lynch T, Bigio E, Hutton M (1999) Association of an extended haplotype in the tau gene with progressive supranuclear palsy. *Hum Mol Genet* **8**, 711-715.

[222] Duda JE, Giasson BI, Mabon ME, Miller DC, Golbe LI, Lee VM, Trojanowski JQ (2002) Concurrence of alpha-synuclein and tau brain pathology in the Contursi kindred. *Acta Neuropathol (Berl)* **104**, 7-11.

[223] Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, Kachergus J, Hulihan M, Uitti RJ, Calne DB, Stoessl AJ, Pfeiffer RF, Patenge N, Carbajal IC, Vieregge P, Asmus F, Muller-Myhsok B, Dickson DW, Meitinger T, Strom TM, Wszolek ZK, Gasser T (2004) Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron* **44**, 601-607.

[224] Goris A, Williams-Gray CH, Clark GR, Foltynie T, Lewis SJ, Brown J, Ban M, Spillantini MG, Compston A, Burn DJ, Chinnery PF, Barker RA, Sawcer SJ (2007) Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease. *Ann Neurol* **62**, 145-153.

[225] Verpillat P, Camuzat A, Hannequin D, Thomas-Anterion C, Puel M, Belliard S, Dubois B, Didic M, Michel BF, Lacomblez L, Moreaud O, Sellal F, Golfier V, Campion D, Clerget-Darpoux F, Brice A (2002) Association between the extended tau haplotype and frontotemporal dementia. *Arch Neurol* **59**, 935-939.

[226] Kwok JB, Teber ET, Loy C, Hallupp M, Nicholson G, Mellick GD, Buchanan DD, Silburn PA, Schofield PR (2004) Tau haplotypes regulate transcription and are associated with Parkinson's disease. *Ann Neurol* **55**, 329-334.

[227] Burrell JR, Hodges JR (2010) From FUS to Fibs: what's new in frontotemporal dementia? *J Alzheimers Dis* **21**, 349-360.

[228] Arai T, Mackenzie IR, Hasegawa M, Nonoka T, Niizato K, Tsuchiya K, Iritani S, Onaya M, Akiyama H (2009) Phosphorylated TDP-43 in Alzheimer's disease and dementia with Lewy bodies. *Acta Neuropathol* **117**, 125-136.

[229] Jellinger KA (2008) Neuropathological aspects of Alzheimer disease, Parkinson disease and frontotemporal dementia. *Neurodegener Dis* **5**, 118-121.

[230] Kadokura A, Yamazaki T, Lemere CA, Takatama M, Okamoto K (2009) Regional distribution of TDP-43 inclusions in Alzheimer disease (AD) brains: their relation to AD common pathology. *Neuropathology* **29**, 566-573.

[231] Nakashima-Yasuda H, Uryu K, Robinson J, Xie SX, Hurtig H, Duda JE, Arnold SE, Siderowf A, Grossman M, Leverenz JB, Woltjer R, Lopez OL, Hamilton R, Tsuang DW, Galasko D, Masliah E, Kaye J, Clark CM, Montine TJ, Lee VM, Trojanowski JQ (2007) Co-morbidity of TDP-43 proteinopathy in Lewy body related diseases. *Acta Neuropathol* **114**, 221-229.

[232] Higashi S, Iseki E, Yamamoto R, Minegishi M, Hino H, Fujisawa K, Togo T, Katsuse O, Uchikado H, Furukawa Y, Kosaka K, Arai H (2007) Concurrence of TDP-43, tau and alpha-synuclein pathology in brains of Alzheimer's disease and dementia with Lewy bodies. *Brain Res* **1184**, 284-294.

[233] Kenyon C (2005) The plasticity of aging: insights from long-lived mutants. *Cell* **120**, 449-460.

[234] Niedernhofer LJ, Garinis GA, Raams A, Lalai AS, Robinson AR, Appeldoorn E, Odijk H, Oostendorp R, Ahmad A, van Leeuwen W, Theil AF, Vermeulen W, van der Horst GT, Meinecke P, Kleijer WJ, Vijg J, Jaspers NG, Hoeijmakers JH (2006) A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis. *Nature* **444**, 1038-1043.

[235] Kregel KC, Zhang HJ (2007) An integrated view of oxidative stress in aging: basic mechanisms, functional effects, and pathological considerations. *Am J Physiol Regul Integr Comp Physiol* **292**, R18-R36.

[236] Bandyopadhyay U, Cuervo AM (2007) Chaperone-mediated autophagy in aging and neurodegeneration: Lessons from alpha-synuclein. *Exp Gerontol* **42**, 120-128.

[237] Cohen E, Bieschke J, Perciavalle RM, Kelly JW, Dillin A (2006) Opposing activities protect against age-onset proteotoxicity. *Science* **313**, 1604-1610.

[238] Corder EH, Lannfelt L, Viitanen M, Corder LS, Manton KG, Winblad B, Basun H (1996) Apolipoprotein E genotype determines survival in the oldest old (85 years or older) who have good cognition. *Arch Neurol* **53**, 418-422.

[239] Christensen K, Johnson TE, Vaupel JW (2006) The quest for genetic determinants of human longevity: challenges and insights. *Nat Rev Genet* **7**, 436-448.

[240] Valenzuela MJ, Breakspear M, Sachdev P (2007) Complex mental activity and the aging brain: molecular, cellular and cortical network mechanisms. *Brain Res Rev* **56**, 198-213.

[241] Weiner MW, Aisen PS, Jack CR Jr, Jagust WJ, Trojanowski JQ, Shaw L, Saykin AJ, Morris JC, Cairns N, Beckett LA, Toga A, Green R, Walter S, Soares H, Snyder P, Siemers E, Potter W, Cole PE, Schmidt M (2010) The Alzheimer's disease neuroimaging initiative: progress report and future plans. *Alzheimers Dement* **6**, 202-211, e207.

[242] Lemere CA, Masliah E (2010) Can Alzheimer disease be prevented by amyloid-beta immunotherapy? *Nat Rev Neurol* **6**, 108-119.

[243] Sigurdsson EM (2009) Tau-focused immunotherapy for Alzheimer's disease and related tauopathies. *Curr Alzheimer Res* **6**, 446-450.

[244] Masliah E, Rockenstein E, Adame A, Alford M, Crews L, Hashimoto M, Seubert P, Lee M, Goldstein J, Chilcote T, Games D, Schenk D (2005) Effects of alpha-synuclein immunization in a mouse model of Parkinson's disease. *Neuron* **46**, 857-868.

[245] Schneider A, Mandelkow E (2008) Tau-based treatment strategies in neurodegenerative diseases. *Neurotherapeutics* **5**, 443-457.

[246] Hashimoto M, Rockenstein E, Mante M, Crews L, Bar-On P, Gage FH, Marr R, Masliah E (2004) An antiaggregation gene therapy strategy for Lewy body disease utilizing beta-synuclein lentivirus in a transgenic model. *Gene Ther* **11**, 1713-1723.

[247] Mrak RE, Griffin WS (2007) Common inflammatory mechanisms in Lewy body disease and Alzheimer disease. *J Neuropathol Exp Neurol* **66**, 683-686.

[248] Skaper SD (2007) The brain as a target for inflammatory processes and neuroprotective strategies. *Ann N Y Acad Sci* **1122**, 23-34.

[249] Sutherland GT, Sidhu KS (2011) Pluripotent stem cells for (neurodegenerative) disease modelling. In *Frontiers in Pluripotent Stem Cells Research and Therapeutic Potentials; Bench-to-Bedside*, Sidhu KS, ed. Bentham Press.

[250] Brice A (2010) Learning from genetic forms of neurodegeneration. *Nat Med* **16**, 1371.

[251] Barabasi AL, Gulbahce N, Loscalzo J (2011) Network medicine: a network-based approach to human disease. *Nat Rev Genet* **12**, 56-68.

[252] Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A (2003) Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. *J Neurol Neurosurg Psychiatry* **74**, 857-862.

[253] Gauthier E, Fortier I, Courchesne F, Pepin P, Mortimer J, Gauvreau D (2001) Environmental pesticide exposure as a risk factor for Alzheimer's disease: a case-control study. *Environ Res* **86**, 37-45.

[254] Hubble JP, Kurth JH, Glatt SL, Kurth MC, Schellenberg GD, Hassanein RE, Lieberman A, Koller WC (1998) Gene-toxin interaction as a putative risk factor for Parkinson's disease with dementia. *Neuroepidemiology* **17**, 96-104.

[255] Olichney JM, Murphy C, Hofstetter CR, Foster K, Hansen LA, Thal LJ, Katzman R (2005) Anosmia is very common in the Lewy body variant of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **76**, 1342-1347.

[256] Pankratz N, Byder L, Halter C, Rudolph A, Shults CW, Conneally PM, Foroud T, Nichols WC (2006) Presence of an APOE4 allele results in significantly earlier onset of Parkinson's disease and a higher risk with dementia. *Mov Disord* **21**, 45-49.

[257] Barranco Quintana JL, Allam MF, Serrano Del Castillo A, Fernandez-Crehuet Navajas R (2007) Alzheimer's disease and coffee: a quantitative review. *Neurol Res* **29**, 91-95.

[258] McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ (2001) Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol* **58**, 1803-1809.

[259] Snowden JS, Neary D, Mann DM (2002) Frontotemporal dementia. *Br J Psychiatry* **180**, 140-143.

[260] Woodruff BK, Graff-Radford NR, Ferman TJ, Dickson DW, DeLucia MW, Crook JE, Arvanitakis Z, Brassler S, Waters C, Barker W, Duara R (2006) Family history of dementia is a risk factor for Lewy body disease. *Neurology* **66**, 1949-1950.

[261] Sellbach AN, Boyle RS, Silburn PA, Mellick GD (2006) Parkinson's disease and family history. *Parkinsonism Relat Disord* **12**, 399-409.

[262] Hellman NE, Grant EA, Goate AM (1998) Failure to replicate a protective effect of allele 2 of NACP/alpha-synuclein polymorphism in Alzheimer's disease: an association study. *Ann Neurol* **44**, 278-281.

[263] Xia Y, Rohan de Silva HA, Rosi BL, Yamaoka LH, Rimmler JB, Pericak-Vance MA, Roses AD, Chen X, Masliah E, DeTeresa R, Iwai A, Sundsmo M, Thomas RG, Hofstetter CR, Gregory E, Hansen LA, Katzman R, Thal LJ, Saitoh T (1996) Genetic studies in Alzheimer's disease with an NACP/alpha-synuclein polymorphism. *Ann Neurol* **40**, 207-215.

[264] Siddons MA, Pickering-Brown SM, Mann DM, Owen F, Cooper PN (1996) Debrisoquine hydroxylase gene polymorphism frequencies in patients with amyotrophic lateral sclerosis. *Neurosci Lett* **208**, 65-68.

[265] Huckvale C, Richardson AM, Mann DM, Pickering-Brown SM (2003) Debrisoquine hydroxylase gene polymorphism (CYP2D6*4) in dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry* **74**, 135-136.

[266] Golab-Janowska M, Honczarenko K, Gawronska-Szklarz B, Potemkowski A (2007) CYP2D6 gene polymorphism as a probable risk factor for Alzheimer's disease and Parkinson's disease with dementia. *Neurol Neurochir Pol* **41**, 113-121.

[267] Lane R, He Y, Morris C, Leverenz JB, Emre M, Ballard C (2009) BuChE-K and APOE epsilon4 allele frequencies in Lewy body dementias, and influence of genotype and hyperhomocysteinemia on cognitive decline. *Mov Disord* **24**, 392-400.