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

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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 homogeneous. 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-beta, tau, and a-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...
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 a-synuclein [34]. LB pathology also incorporates the accumulation of insoluble a-synuclein immunoreactive protein in cell processes, called Lewy neurites. Current staging of PD is based on a-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-parahippocampal 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, a-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 a-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 that 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 synergetic 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-control 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 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**

<table>
<thead>
<tr>
<th>Factor</th>
<th>FTD Effect size (RR, OR, or HR)</th>
<th>AD Effect size (RR, OR, or HR)</th>
<th>DLB Effect size (RR, OR, or HR)</th>
<th>PDD Effect size (RR, OR, or HR)</th>
<th>PD Effect size (RR, OR, or HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low education</td>
<td>FTD &gt; AD [109]</td>
<td>[115]</td>
<td>[123]</td>
<td>[127]</td>
<td>[129]</td>
</tr>
<tr>
<td>Head injury</td>
<td>3.3 (1.3-8.4) [127]</td>
<td>1.58 (1.21-2.06) [252]</td>
<td>ILBD 1.44 (0.16-13.2) [19]</td>
<td>0.9 (0.4-2.2) [121]</td>
<td>4.3 (1.2-15.2) [128]</td>
</tr>
<tr>
<td>Postcide</td>
<td>n/a</td>
<td>1.62 (0.64-4.11) [253]</td>
<td>n/a</td>
<td>PDD vs. PD [254]</td>
<td>1.85 (1.31-2.40) [177]</td>
</tr>
<tr>
<td>Smoking</td>
<td>n/a</td>
<td>1.45 (1.16-1.80) [162]</td>
<td>n/a</td>
<td>PSD vs. PD − no effect [256]</td>
<td>0.70 (0.63-0.78) [149]</td>
</tr>
<tr>
<td>Coffee</td>
<td>n/a</td>
<td>0.73 (0.58-0.92) [257]</td>
<td>n/a</td>
<td>n/a</td>
<td>0.75 (0.64-0.86) [147]</td>
</tr>
<tr>
<td>Diabetes yes/no</td>
<td>n/a</td>
<td>1.51 (1.3-1.7) [13]</td>
<td>n/a</td>
<td>PSF of dementia [260]</td>
<td>1.0 (0.7-1.4) [141]</td>
</tr>
<tr>
<td>Family history of disease (FHS)</td>
<td>49% FHS of dementia [260]</td>
<td>49% FHS of dementia [260]</td>
<td>0.8 (0.3-3) [121]</td>
<td>1.04 (0.74-1.46) [141]</td>
<td>0.77 (0.63-0.92) [265]</td>
</tr>
<tr>
<td>NACRP Rep 1 (SNCA)</td>
<td>n/a</td>
<td>No effect [262]</td>
<td>n/a</td>
<td>No effect [266]</td>
<td>1.25 (1.1-1.41) [263]</td>
</tr>
<tr>
<td>CYP2D6 *4 vs. WT</td>
<td>n/a</td>
<td>No effect [264]</td>
<td>1.08 (0.48-1.32) [265]</td>
<td>0.61 (0.20-1.85) [266]</td>
<td>1.13 (1.05-1.27) [4 R] vs. other</td>
</tr>
<tr>
<td>APOE ε4 vs. ε3</td>
<td>1.14 (0.87-1.49) [209]</td>
<td>3.68 (3.31-4.11) [267]</td>
<td>1.84 (1.2-2.5) [214]</td>
<td>1.01 (0.91-1.13) [268]</td>
<td>0.77 (0.71-0.84) [269]</td>
</tr>
<tr>
<td>MAPT H2 vs. H1</td>
<td>0.69 (0.43-1.10) [225]</td>
<td>1.0 (0.94-1.07) [225]</td>
<td>n/a</td>
<td>PDD vs. PD HLP [129]</td>
<td>12.1 (1.26-117.4) [97]</td>
</tr>
</tbody>
</table>

Reported significant differences in bold type for relative (RR), odds (OR) or hazard ratios (HR).

- Utilizing either meta-analysis, collaborative study or largest case-control series. Values are relative to unaffected controls unless stated otherwise.
- Incidental Lewy body disease (ILBD): not DLB due to insufficient numbers.
- Interaction between CYP2D6 and pesticide for risk of PD (PDD vs. PD) compared to PD.
- Pooled estimate but heterogeneity across methodologies of the 4 contributing studies.
- Vascular risk factors such as diabetes decreased in medicated patients [144, 145].
- 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 Ruitenber 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 Aβ1-42 and insoluble Aβ have been found in the brain tissue of women [112] as well as in female mutant APP 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 hyperperfusion 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 nondemented 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 e4 variant in AD and systemic dyslipidemia [137, 138]. Perhaps surprisingly then, given the impact of ApoE e4 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 e4 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 PTD, 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 an apparent 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 e4 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 e4 (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 the genotypes 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 onset 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 e4 allele in AD [194, 195]. It has been suggested that ApoE e4, 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 e4 risk effect [197–204]. However despite the effect size it is still far from clear how ApoE e4 increases the risk of AD. An important observation may be that plaques are more frequent in ApoE e4 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 e4 effect in PD and FTD [209], while female gender could also to play an important interrelated role [112].

The frequency of ApoE e4 in DLB patients is similar to AD [210–212] with a lessened, but nevertheless significant, 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 suggests gene interaction and 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 (A53T) [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

![Diagram of risk factors and neurodegeneration](image-url)
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 spectrum and show strong interrelations [94, 95]. Per-haps 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 stages of disease history on differentiable susceptible genetic backgrounds 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.

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