Introduction

Alzheimer’s disease (AD) most commonly presents in later life as an amnestic syndrome, with impairment in other domains, including language and executive function emerging as disease progresses [1]. Symptoms occur in association with a breakdown in the brain’s acetylcholine network [2,3] and pathological degeneration, the hallmarks of which are beta-amyloid senile plaques (SPs) and neurofibrillary tangles (NFTs) containing hyperphosphorylated tau [4]. In addition to this disease prototype, there are AD subtypes. Variations in cognitive profile, age of onset, and rate of decline exemplify the heterogeneity of AD [5].

Similar patterns of variability within neuropsychiatric features may define behavioural AD sub syndromes [6] with consistent symptom-lesion correlates [7] and association with specific neurotransmitter dysfunction, such as dopamine [8]. Familial AD syndromes may also exist, resulting from highly penetrant but variably expressed mutations in key genes, such as presenilin (PSEN)-1, PSEN-2, and amyloid precursor protein [9]. As with sporadic AD syndromes, there is significant heterogeneity among the different mutations. These behavioural and familial-genetic sub syndromes represent a potentially rich area of inquiry, which is beyond the scope of the
current discussion. Instead this review will focus on sporadic cognitive subsyndromes.

The growing recognition in recent years of AD variability reflects increasing understanding of its complexity, building upon convergent streams of evidence from clinical, imaging, and pathological studies. While it is legitimate to focus on prototypic illness, as this represents the majority of cases and thus the bulk of disease burden, understanding the rarer AD subtypes and the influence of common comorbidities may open new targets for therapy and better allow the tailoring of existing ones - personalized medicine. Concurrently, knowledge of AD's syndromic inhomogeneity may disentangle its confounding effects in clinical trials, as efforts to exclude atypical subtypes are not always successful.

**Origins of the AD heterogeneity concept: a historical perspective**

The observation that AD demonstrates phenotypic heterogeneity is not new. In 1969, McDonald [10] identified two distinct subgroups among dementia patients in a chronic geriatric hospital setting. Using simple tests of memory, parietal function, and aphasia, he noted that some had difficulties predominantly with praxis, visual construction, and cortical sensation. They exhibited more severe progression on follow-up. These he termed the 'parietal group'. Other patients had predominantly memory dysfunction, later age of onset, and slower disease progression. These he termed 'benign memory dysfunction of aging'. Unfortunately, this early demonstration of AD heterogeneity failed to generate widespread recognition for subtype variability. In large part this was due to the prevailing theory of the time, which held that clinical variation arose from observing the disease at different stages of progression (phase hypothesis), rather than truly distinct disease phenotypes (subtype hypothesis) [11].

Additional support for the subtype hypothesis would later be provided by early positron emission tomography (PET) studies. These demonstrated that just as there were clinically distinct profiles of AD, there were distinct topographic patterns of brain hypometabolism. Asymmetry in PET imaging among AD subjects [12,13] was consistently associated with greater language impairment if the left hemisphere was more affected. Conversely, visuospatial impairment predominated in those with mainly right parietal hypometabolism [14,15]. This variability exhibited good anatomic correlation. Left angular hypometabolism, for example, was associated with Gerstmann's syndrome in AD [14]. Importantly, longitudinal follow-up demonstrated that these different syndromes remained distinct over time [16], and with clinical worsening of disease [17].

The one remaining observation that still supported the phase hypothesis was that these variant cases were associated with an earlier age of onset [18,19]. This was later addressed in studies taking advantage of standardized neuropsychological assessments. Using the CERAD (Consortium to Establish a Registry for Alzheimer’s Disease) database, Fisher and colleagues [20] demonstrated neuropsychologically defined subtypes of AD. Subjects with predominantly anoma, impairment of constructional praxis, and mixed impairments mirrored the left, right, and general subgroups of the earlier PET studies, respectively. Importantly, Fisher's subtypes had the same age of onset, strongly suggesting that these observed differences were not merely alternative stages, but true variants of AD. As with PET studies, these subtypes remained distinct over longitudinal follow-up, again supporting the idea of true distinct subtypes of disease [21].

**Alzheimer’s disease syndromes**

**Typical Alzheimer’s disease**

Prototypic AD is a late-onset AD syndrome with amnestic impairment predominating in association with hippocampal and temporal-parietal atrophy and/or decreased perfusion/metabolism [22]. It is the most commonly observed AD phenotype in the clinical setting and serves as a good starting point against which the rare AD subtypes can be compared. Clinically, memory decline is accompanied by similar worsening in other cognitive domains, setting typical AD apart from temporal variant AD where memory decline occurs in isolation, and the other variants wherein non-amnestic presentations predominate. Relatively symmetric and generalized atrophy and hypometabolism/hypoperfusion distinguish typical AD from the more focal topography of temporal variant (hippocampal), frontal variant (frontal), language variant (left parietal), and visuoperceptive variant (right parietal) AD. Typical AD progresses more slowly than language, visuoperceptive, and frontal variant AD. Conversely, deterioration is quicker than temporal variant AD, perhaps owing to greater cognitive reserve in these individuals (consistent with their older ages of onset), the more focal mesiotemporal distribution of pathology that tends to spare cortical areas, or some combination of both.

**Temporal (pure amnestic) variant Alzheimer’s disease**

Focal temporal lobe dysfunction, pure amnestic AD, and temporal variant AD all refer to the late-onset AD syndrome of isolated episodic memory impairment with notably slow decline (Figure 1) [23]. Single-photon emission computed tomography (SPECT) imaging in temporal variant AD demonstrates hypoperfusion limited to the mesiotemporal lobes, while the temporal-parietal changes seen in typical AD are absent [24]. Longitudinal studies of temporal variant AD individuals demonstrate slow or no change in Mini-Mental State Examination scores, and even when memory is significantly impaired,
visuospatial and executive function remain borderline to normal [23,25]. Pathologically, studies have demonstrated a subgroup of patients with plaques and neurofibrillary tangles limited to the limbic regions with little or no spread to the neocortical areas [26]. Clinically these individuals have a later age of onset and slower rates of cognitive decline. Although the genetic factors contributing to temporal variant AD remain unknown, there is some evidence to suggest that the apolipoprotein E (APOE) ε4 allele is absent [23]. Unique among atypical AD variants, temporal variant AD is a late-onset AD syndrome, and may present even later than typical AD.

**Left (language) variant and logopenic progressive aphasia**

Language variant AD is often an early-onset AD (EOAD) syndrome of gradually worsening non-fluent speech typified by significant agrammatism, phonemic paraphasias, relative preservation of memory, and often atrophy of the left perisylvian region on imaging (Figure 2) [27–29]. These individuals have pathologically confirmed AD with a topographically atypical distribution of neurofibrillary tangles predominantly within the left neocortex, sparing in some cases the hippocampus.

The early non-fluent language impairment of this subtype distinguishes it from the language syndrome of later stage typical AD, which is generally fluent in nature, with anoma, semantic paraphasias, progressing to surface dyslexia and jargon speech [30,31].

This non-fluency also distinguishes language variant AD from the second atypical AD language syndrome, logopenic progressive aphasia (LPA). In LPA, speech rate is slowed but grammar and articulation are preserved.

**Figure 1. Temporal variant Alzheimer’s disease.** A 69 year old woman presenting with short-term memory loss and very slow progression with conversion to mild dementia about 5 years later. Her last neuropsychological testing after 11 years of follow-up revealed normal language and visuospatial function, with very mild executive dysfunction and significant impairment on memory items. Ten years into her course, imaging including coronal T1 MRI at the level of the hippocampus (bottom left) demonstrated marked hippocampal atrophy (white arrows) while single-photon emission computed tomography (SPECT) done at the same time (bottom right) showed mesiotemporal hypoperfusion (red arrows). Axial T1 MRI (top left) and SPECT (top right) at the level of the basal ganglia demonstrated no atrophy in the parietal and frontal association areas and no hypoperfusion in the same areas.
rather, impaired repetition typifies LPA [33]. LPA is commonly associated with AD pathology [34], demonstrates left posterior temporal and inferior parietal hypoperfusion [32], and strong association with β-amyloid deposition on Pittsburgh compound B PET [35]. Despite their shared features, both being language predominant syndromes, the basis for these two forms of different aphasic manifestations is unclear.

Right (visuoperceptive) variant (visuoperceptive AD)
Visuospatial dysfunction does not commonly occur as the initial or predominant symptom in AD. When it does, it may portend the onset of PCA (Figure 3) [36]. In other cases, visuospatial dysfunction suggests a subtler, non-memory variant, associated with greater right versus left hemisphere pathology and atrophy (Figure 4), a distinct pattern that is maintained over time and with disease progression [14,15,17,21].

As with language variant AD and LPA, the relationship between visuoperceptive AD and PCA remains relatively unknown. Also unknown is whether individuals with visuoperceptive impairment represent a prodromal stage of diffuse Lewy body disease, rather than a true AD subtype, as sometimes happens anecdotally. While it is true that Lewy bodies can co-occur in PCA alongside AD pathology with clinically evident hallucinations and parkinsonism, AD changes can also be seen in isolation, with topography being the only apparent driver of phenotype [36]. Pathologic and biomarker imaging studies may help resolve some of these questions.

Frontal (executive) variant (frontal variant AD)
Frontal variant AD is an extremely rare EOAD subtype, associated with significant frontal cognitive and behavioural symptoms (Figure 5), first described by Johnson and colleagues [37], who found 3 cases among 63 individuals with pathologically confirmed AD. Alladi and colleagues [34] likewise identified only 2 instances among their 100 case series, of whom only one had a true dysexecutive syndrome, the other having only behavioural features. Pathologically there is a predominance of NFTs in the frontal regions (ten-fold increase over typical AD), with comparable loading in the entorhinal cortex and other regions [37]. Amyloid plaques and the lack of cell loss, microvacuolarization, and gliosis in layers II and III distinguish frontal variant AD from FTD. Biochemically, frontal variant AD shows focally reduced calcium-independent phospholipase A2 activity within the frontal regions compared to typical AD on post-mortem protein assay (8.8 pmol/mg versus 15.2 pmol/mg), a neuronal-specific isofrom of phospholipase and indirect marker of neuronal health [38]. In one case report, cerebrospinal fluid (CSF) amyloid beta (Aβ) was found to be decreased, although tau levels were only borderline [39].
In part because of its rarity, the clinical identification of frontal variant AD has proven troublesome. One study used the Frontal Behavioural Inventory to define a ‘high frontality’ AD group based on the presence of frontal symptoms such as apathy, aspontaneity, loss of empathy (negative symptoms) and disinhibition, utilization behaviour, and alien limb phenomenon (positive symptoms) [40]. However, except for three items on the Frontal Behavioural Inventory - hyperorality, perseveration, and aspontaneity - there was no distinction between Woodward’s ‘high frontality’ group and FTD and there were no between-group differences on global cognition screening tests. Furthermore, Woodward and colleagues in another study [41] found that frontal variant AD can be associated
with co-occurring FTD pathology. In light of this overlapping pathology and diagnostic uncertainty, CSF biomarker profiles and amyloid imaging will likely be needed to convincingly demonstrate frontal variant AD in a cohort large enough to perform the necessary neuropsychological, imaging, and genetic studies to define this subtype.

**Common features and potential factors contributing to AD heterogeneity**

**Age of onset**

EOAD accounts for 32% of atypical, that is, non-amnestic, cases of AD, in contrast to only 6% of typical AD [42]. In retrospect, this is consistent with earlier studies, wherein atypical subgroups of AD were
consistently associated with younger age. As alluded to previously, these early-onset individuals evince a more aggressive disease course, in distinction from the more gradual progression of typical AD, and in contrast to the very slow decline of temporal variant AD. The mechanism and significance of this association remain unclear.

Disease topography

The distribution of AD pathology and associated atrophy varies among individuals [43] and may affect phenotype. For example, histopathological asymmetry with associated left (language) and right (visuospatial) syndromes similar to those found in PET studies have been described [44]. Conversely, focal cortical, non-amnestic presentations can be associated with underlying AD in 34% of cases, including bilateral PCA, aphasia, behavioural executive syndromes, and cortical basal syndrome, all of which tended to be EOAD [34].

In one recent study, Armstrong and colleagues [26] used principal components analysis to identify three clusters of NFT and senile plaque distribution: cortical (cingulate gyrus, gyrus rectus, orbital frontal gyrus, occipital lobe), deep grey (thalamus, nucleus basalis of Meynert, striatum), and limbic (ventral tegmentum, raphe, amygdala). Similarly, Murray and colleagues [45] described three pathologically distinct patterns of AD in a large cohort of 889 cases: hippocampal-sparing, limbic-predominant, and ‘typical’. These subdivisions were based on NFT and senile plaque burden, as defined by thioflavin-S counts, comparing between mesiotemporal lobe (CA1, subiculum) and cortical (middle frontal, inferior parietal, superior temporal association areas) regions of interest. Hippocampal-sparing AD occurred in younger individuals (mean age 72 years, versus 79 for typical and 86 for limbic-predominant AD), consistent with the association between atypicality and EOAD. Hippocampal-sparing AD revealed the fastest rate of cognitive decline (-4.8 on Mini-Mental State Examination per year, versus -2.8 for typical and -1.4 for limbic-predominant AD). In keeping with their neocortically predominant pathological burden, hippocampal-sparing cases were more likely to have an atypical, non-amnestic clinical onset (30% of cases), versus individuals with typical pathological distribution, where this occurred less frequently (17%).

Genetics

ApoE genotype may be one important factor contributing to heterogeneity in sporadic AD, as non-ε4 status among EOAD patients correlates with atypicality [46]. What underlies this relationship is unknown; perhaps the absence of ε4, rather than the presence of ε2 or ε3, is...
important. ApoE ε4 is associated with greater hippocampal atrophy [47], suggesting that symptoms in non-carriers may instead reflect damage to areas normally eclipsed by hippocampal pathology (for example, parietal, temporal or frontal regions). This is in keeping with the ‘cortically predominant’ topographies of disease observed among non-ε4 EOAD carriers. This greater degree of cortical damage could be reasonably expected to result in significant, wide-spread neurologic dysfunction, potentially explaining the observation that such individuals experience a more rapid clinical decline. Alternatively, this same ‘hippocampal effect’ of ApoE ε4 may mask the influence of other genetic and epigenetic factors. If so, such factors may have a greater role in the absence of ε4; their variability in turn explaining the greater heterogeneity of non-ε4 EOAD.

Another consideration is the role of autosomal dominant mutations causing familial AD. Although a complete discussion of genotype-phenotype correlations in familial AD is beyond the scope of this review, mutations in PSEN1 and amyloid precursor protein (APP) can both produce non-aminestic, atypical EOAD [48,49]. For example, PSEN1 can result in non-fluent aphasia [50] in addition to more typical amnestic AD, while APP can be associated with severe cerebral amyloid angiopathy presenting with hemorrhage and seizures along with memory decline [51]. The same mutation may even result in different syndromes. PSEN1 has been described in spastic paraparesis, frontotemporal dementia, myoclonus with seizures, and predominantly psychiatric presentations [52]. Even within the same family, the APP mutation presented with bradykinesia and hallucinations in one individual, memory and behavioural changes in another, and memory decline followed by intracerebral hemorrhage from angiopathy in a third [53].

Ultimately, imaging-genetic endophenotype studies may provide a link between genetics and disease topography by elucidating those areas of the brain most associated with known and potential pathological genotypes. Should these patterns correlate with the topography of syndromic phenotypes of AD, it may lend support that genotype underlies at least some of these phenotypic variations. Until such links can be established, and given the variability with which genetic mutations/polymorphisms can present, decisions around genetic testing when a suspected case of atypical AD is encountered must be adjudicated on a case by case basis.

**Co-occurring pathology: Lewy body pathology**

Lewy bodies composed in part of alpha-synuclein aggregates are the hallmark of Lewy body disease, presenting in prototypic cases with visual hallucinations, extrapyramidal symptoms, and marked clinical fluctuations [54]. These same alpha synuclein inclusions can be found in pathologically confirmed AD, with neocortical Lewy bodies occurring in 10 to 30% of cases at autopsy [55,56]. These co-occurring Lewy bodies also appear associated with AD proven cases of PCA [29,57]. More generally, the presence of Lewy bodies in AD is associated with more perceptual impairment, though milder than what occurs in ‘pure’ diffuse Lewy body disease [58].

**Co-occurring pathology: white matter hyperintensities**

Best seen on T2 and FLAIR imaging by MRI, white matter hyperintensities (WMHs) reflect an array of pathophysiological processes, the precise causes of which remain under active investigation [59]. They occur in 95% of healthy adults aged over 65 years (Figure 6) [60], 92% of individuals with mild cognitive impairment aged 45 to 87 years [61], and is more common in the presence of pathologically confirmed AD (57% versus 33% in age-matched normal controls) [62]. WMHs appear associated mostly with impaired executive function, speed of processing, and mental flexibility [63-69], functions attributable to frontal lobe networks. More generally, it is associated with global decline, dementia, depression, and death [70-73]. WMHs frequently occur in the frontal regions [61,74-76], although some evidence suggests that WMH is associated with frontal-executive symptoms regardless of location [77]. The importance of WMH topography remains an area of active investigation, with periventricular WMH possibly related to venous collagensenosis [78,79].

As the degree of WMH varies widely, investigators have explored whether a dose-effect relationship for WMH exists, and if so what minimum degree of WMH is necessary for cognitive changes to be observed. To this end, Boone and colleagues [80] identified a ‘threshold’ of >10 cm³ for cognitive changes to be observed. DeCarli and colleagues [81] demonstrated similar findings using PET, showing that a threshold of >0.5% of brain parenchymal fraction was significantly associated with poorer performance on executive function and mental flexibility tasks (phonemic fluency, Trails B). They also demonstrated an association with worsened visual memory, suggesting that the influence of WMHs is potentially more widespread. Importantly, even when only accounting for those cases where WMH met or exceeded the minimum ‘threshold’ for associated clinical symptoms, co-pathology was common (6 to 20%) [60,80,81], underscoring its importance in overall AD phenotype.

A major challenge to investigating independent contributions of WMHs in AD is disentangling their contributory role to cerebral atrophy. Controlling for atrophy can eliminate the observed influence of WMHs on cognition [81,82], although Swartz and colleagues [83], using factor analysis in a dementia population, discerned an independent association between WMH burden on executive
function and memory even after atrophy was accounted for. Furthermore, vasculopathy, especially lacunar infarcts, appears to contribute to the expression of AD dementia in pathology series [84,85].

**Figure 6. White matter hyperintensities in Alzheimer’s disease.** A 68 year old man presenting with short-term memory decline. Imaging done 7 years into the course of illness, including axial T1 MRI at the level of the centrum semiovale (upper left), demonstrated severe generalized atrophy. Axial T2 (top right) and proton density (bottom left) images at the same level showed marked white matter hyperintensities, especially posteriorly (white arrows). One year prior, axial single-photon emission computed tomography (SPECT) at the corresponding level (bottom right) demonstrated mild parietal hypoperfusion bilaterally (red arrows). The patient died 9 years later and autopsy confirmed Alzheimer’s disease (Braak V/VI), with diffuse atherosclerosis throughout the white matter and basal ganglia, lacunar infarcts, remote microhaemorrhages and cortical microinfarcts. There had been no history of visual hallucinations, but parkinsonism developed very late into the disease course, and he was also found to have diffuse Lewy bodies within the brain stem and cingulum.

**Co-occurring pathology: other pathologies**
TDP-43 (TAR DNA-binding protein 43) inclusions and agyrophillic grains are two other pathologies that have been associated with AD pathology and that may nuance
the phenotype of AD [86]. A full review of their association is beyond the scope of this review, although given their association with FTD, one might expect that they would result in a blending of FTD symptomatology with prototypic AD.

**Future directions**

**Framing heterogeneity and complexity in the AD syndrome**

AD phenotype is strongly affected by age of onset, genetic profile, and comorbidities. AD subtypes reflect the interactions between these three axes. When the onset is later, ApoE ε4 is present, and comorbidities absent, the resulting pattern is generally prototypic AD. Changes along any of these three axes shift the observed phenotype towards one of the rarer AD variants (Figure 7).

Several important questions remain. Frontal variant AD appears to be the rarest variant and the potential role of WMHs in its expression needs to be further explored, in particular the role of venous collagenosis, which may contribute to executive control network dysfunction. The relationships between visuoperceptive AD and PCA, and between language variant AD and LPA remain unclear. ApoE ε4 is hypothesized to be absent in the early onset

**Figure 7. Proposed framework for Alzheimer’s disease subtypes.** Bubbles represent subpopulations of Alzheimer’s disease (AD) by subtype, located along each of the three axes of heterogeneity: age of onset, apolipoprotein E status, and co-pathology. Exact size, positioning and degree of overlap for each subtype remain uncertain areas of active research.
subtypes: frontal, visuoperceptive, and language variant AD, but its relative absence in temporal variant AD, the only late onset subtype, is also worthy of further investigation. Finally, the role of rarer co-pathologies such as TDP43, and genetic polymorphisms, other than ApoE, and epigenetic factors on clinical profile remain to be explored.

Translational implications: diagnosis and therapy
Phenotypic heterogeneity among AD subtypes and co-pathology may have particular importance for biomarker-based ante mortem diagnosis. Factors such as ApoE status, gender, age, education, and brain size appear associated with differences in CSF Aβ levels [87], with education inversely correlated with CSF Aβ in early disease [88]. Such findings suggest that, at least in the case of CSF Aβ, biomarkers must be interpreted in the context of phenotype. This interpretation in turn requires a greater understanding of AD phenotypic variation than is presently available. As atypical subtypes are relatively rare, multi-site studies specifically addressing them are urgently needed to delineate the full spectrum of AD and its interaction with biomarkers.

Beyond the clinical need for diagnostic certainty, the ability to recognize and control for phenotypic variation is important to continuing clinical trials design. The very slow rate of decline in temporal variant AD is but one example of how subtype heterogeneity can confound results. More generally, as it appears that all AD subtypes exhibit divergent trajectories of symptom progression from prototypic disease, characterizing the onset and decline across the AD syndrome spectrum [89,90], including comorbid cases, is a priority. Similarly, it is unknown how often an initially typical AD case evolves into an atypical subtype over time, or vice versa. As the occasional inclusion of an atypical individual in clinical trials may thus be unavoidable, understanding these subtypes may allow researchers to disentangle their influence from their findings.

Phenotypic variation may likewise affect response to therapeutic strategies, requiring a personalized medicine approach that will only be possible with a greater understanding of AD subtypes and their causes. For example, the presence of comorbid WMHs involving peri-insular cholinergic pathways in a case-controlled cohort study was associated with more favourable response to cholinesterase therapy [91], in contrast to more generally distributed WMHs, which show no such association. Cholinergic therapies may therefore be particularly appropriate in such co-morbid cases. Another example is the observation that synapse loss, a key correlate of cognition, is greater in early onset AD [92,93], implying a more aggressive neuronal degeneration. Clinical trials in these subgroups would therefore have to target symptoms much earlier than would normally be done for prototypic disease, in order to address the more severe cellular damage of EOAD. Along similar lines, it has been observed that early onset AD is associated with more widespread neurotransmitter dysfunction [94], affecting noradrenaline, γ-amino-butyric acid, and somatostatin levels in addition to acetylcholine. Hence, combination therapy that restores multiple neurotransmitters may be more symptomatically effective than cholinergic agents alone in EOAD. While the medications for such a clinical trial are already available, the lack of clear diagnostic criteria for EOAD subtypes hampers implementation, further underscoring the urgent need for further research in AD heterogeneity.

Conclusion
Prototypic and atypical AD subtypes exist along continuums of age, genotype, and co-pathology within the AD syndrome, presenting challenges and opportunities for both researchers and clinicians. While the pursuit of treatments and salient criteria for the more common AD prototype understandably remains a priority, these rarer subtypes pose a substantial burden of disease faced by those affected by them and their caregivers. Furthermore, unless atypical variants are understood and recognized, controlling for their potentially confounding effects in clinical trials will be more difficult, hindering treatment development even for prototypic disease.

Abbreviations
AD, amyloid beta; AD, Alzheimer’s disease; APOE, apolipoprotein E; Aβ, amyloid precursor protein; CSF, cerebrospinal fluid; EOAD, early-onset Alzheimer’s disease; FTD, frontotemporal dementia; LPA, logopenic progressive aphasia; MRI, magnetic resonance imaging; NFT, neurofibrillary tangle; PCA, posterior cortical atrophy; PET, positron emission tomography; PSEN, presenilin; SPECT, single-photon emission computed tomography; WMH, white matter hyperintensity.

Competing interests
The authors declare that they have no competing interests.

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