Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

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In 2010, we put forward a hypothetical model of the major biomarkers of Alzheimer's disease (AD). The model was received with interest because we described the temporal evolution of AD biomarkers in relation to each other and to the onset and progression of clinical symptoms. Since then, evidence has accumulated that supports the major assumptions of this model. Evidence has also appeared that challenges some of our assumptions, which has allowed us to modify our original model. Refinements to our model include indexing of individuals by time rather than clinical symptom severity; incorporation of interindividual variability in cognitive impairment associated with progression of AD pathophysiology; modifications of the specific temporal ordering of some biomarkers; and recognition that the two major proteinopathies underlying AD biomarker changes, amyloid β (Aβ) and tau, might be initiated independently in sporadic AD, in which we hypothesise that an incident Aβ pathophysiology can accelerate antecedent limbic and brainstem tauopathy.

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See **Comment** page 126

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Introduction

We proposed a model of Alzheimer's disease (AD) biomarkers that was intended to be a framework for in-vivo staging of the disease. The model focused on the five most well established biomarkers of AD, which we propose can be divided into two major categories: measures of brain amyloid β (Aβ) deposition and measures of neurodegeneration—defined as a progressive loss of neurons or their processes (axons and dendrites) with a corresponding progressive impairment in neuronal function. Brain Aβ deposition is assessed by measures of CSF $A\beta_{42}$[1–5] and by PET amyloid imaging.[6–8] Increased concentrations of CSF total tau (t-tau) and phosphorylated tau (p-tau),[2,4,5,9] hypometabolism on fluorodeoxyglucose (FDG) PET,[10] and atrophy on structural MRI[11–16] are measures of neurodegeneration. FDG PET and MRI follow a modality-specific topology that is characteristic of AD.

The model was initially presented at the International Conference on Alzheimer's Disease in July, 2009,[17] and published in January, 2010.[18] It was based on evidence available at the time with the assumption that empirical assessment was needed. The purpose of this update is to review evidence addressing our model that has accumulated since its publication and to propose modifications to the original model based on these new data.

The original model

Our AD biomarkers model is predicated on the assumption that biomarkers are related to specific pathophysiological processes. This is supported by various biomarker–autopsy correlation studies. Low CSF $A\beta_{42}$[19,20] and uptake of amyloid PET tracers[21–24] are associated with fibrillar Aβ deposits. Correlation of CSF tau and $A\beta_{42}$ with neuropathology is difficult to disambiguate because, unlike with imaging, region-to-region correlations are not possible. Increases in t-tau[20] and p-tau[20,25] are associated with neurofibrillary tangle (NFT) burden at autopsy, and in AD, p-tau and t-tau behave very similarly to each other.[2,26,27] Atrophy on MRI correlates with neuron loss,[28,29] Braak NFT stage,[30–33] and tau immunostaining burden,[33] and does not correlate well with Aβ load measured by immunohistology.[34] Thus MRI is a measure of tau-related neurodegeneration. Antemortem FDG PET hypometabolism is also correlated with NFT burden and not with plaque burden at autopsy.[35]

Our original AD biomarkers model was intended to incorporate the following principles, on the basis of data available at the time. Firstly, the major AD biomarkers become abnormal in a temporally ordered manner.[36–40] CSF $A\beta_{42}$ and amyloid PET are dynamic earliest, followed by CSF tau and FDG PET, then structural MRI, followed by clinical symptoms. Aβ biomarkers were denoted as upstream and neurodegenerative biomarkers as downstream. The 2010 model (and our updated model) does not propose that one biomarker changes and then stops, then the next one changes and then stops, and so on. Rather, the model assumes that the maximum rate of change moves sequentially from one biomarker class to the next, and as the disease progresses all biomarkers become progressively more abnormal simultaneously, albeit at rates that change over time in an ordered manner. Secondly, Aβ dysregulation, which leads to plaque formation, is necessary but not sufficient to produce the clinical AD syndrome. Cognitive decline is only loosely coupled with the rate or magnitude of amyloid PET and CSF $A\beta_{42}$,[39,40] but is closely coupled with the magnitude and rate of change in neurodegenerative biomarkers,[41–43] not only in typical AD, but also in atypical AD syndromes.[44,45] Thirdly, rates of change in each biomarker follow a non-linear temporal course,[46,47] which we postulated to be sigmoid-shaped with time. The fourth principle was that a subject-specific lag in time exists between biomarker evidence of in-situ AD pathophysiology and the emergence of cognitive impairment, which is probably mediated by differences in brain resiliency or cognitive reserve.[48] Lastly, the added contributions of other pathophysiologies (eg, vascular disease, Lewy bodies, TDP-43 inclusions) that often co-occur with ageing also contribute substantially to interindividual variations in clinical disease expression.[49]

We summarised our 2010 biomarkers model in a diagram (figure 1),[18] showing all biomarker values for one

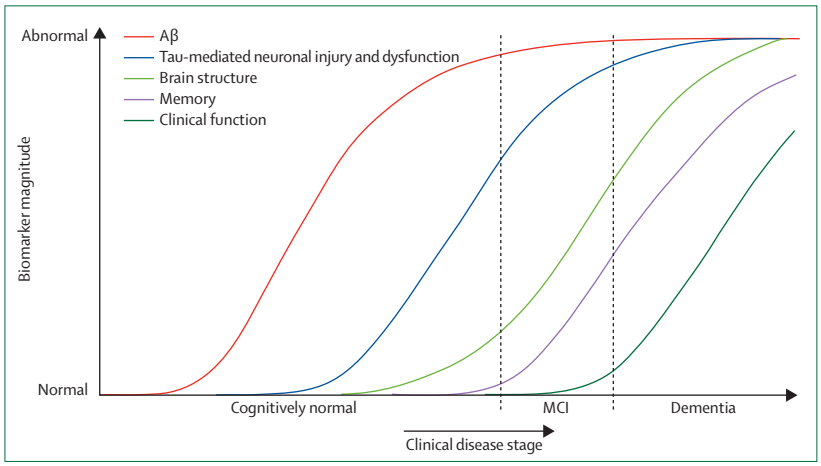

Figure 1: **2010 model of dynamic biomarkers of the Alzheimer's disease pathological cascade**
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose PET. Brain structure is measured by structural MRI. Aβ=amyloid β. MCI=mild cognitive impairment. Reproduced from Jack and colleagues,[18] by permission of Elsevier.

prototypical individual, with the vertical axis representing severity of biomarker abnormality and the horizontal axis representing progression along the AD pathophysiological pathway.

Empirical testing of basic features of the model can be approached in two ways—by addressing the order in which different biomarkers become abnormal with disease progression over time, and by addressing the shapes of the biomarker curves as a function of clinical disease severity or time. Here we review studies that empirically address these features of our model.

Temporal ordering of biomarker abnormalities

Buchhave and colleagues[26] followed up 137 individuals for an average of 9·2 years after baseline CSF analysis. All patients had been diagnosed with mild cognitive impairment at baseline and 72 (54%) progressed to AD. The investigators reported that CSF $A\beta_{42}$ was fully abnormal 5–10 years or more before dementia diagnosis. By contrast, both CSF t-tau and p-tau became progressively more abnormal as the time to diagnosis of dementia decreased. p-tau and t-tau behaved identically over time (figure 2).

Jack and colleagues[50] assessed the temporal ordering of CSF biomarkers and structural MRI in 401 elderly people from the Alzheimer's Disease Neuroimaging Initiative (ADNI) who were either cognitively normal, had mild cognitive impairment, or had AD. Temporal ordering was implied if one biomarker was abnormal more often than another earlier in the course of the disease, in a manner analogous to Braak staging from autopsies of people at different ages. Within each clinical group, CSF $A\beta_{42}$ was abnormal more often than t-tau or hippocampal volume. CSF t-tau was abnormal more often than hippocampal volume only in cognitively normal people (figure 3).[50]

Lo and colleagues[51] examined rates of change in CSF $A\beta_{42}$, FDG uptake, and hippocampal volume in 819 people from the ADNI. They concluded that the longitudinal biomarker patterns support a sequence in which amyloid deposition is an early event that precedes hypometabolism or hippocampal atrophy.

Forster and colleagues[52] followed up 20 individuals with mild AD with longitudinal FDG PET and amyloid PET. They noted little change in the anatomical extent of amyloid PET over time, whereas FDG PET hypometabolism expanded significantly. They concluded that by the time patients became demented, amyloid deposition was static whereas the expansion of FDG hypometabolism was continuing.

Landau and colleagues[53] examined associations between amyloid PET, hypometabolism on FDG PET, and retrospective longitudinal cognitive measurements in 426 individuals from the ADNI. They concluded that "amyloid deposition has an early and subclinical impact on cognition that precedes metabolic changes", and that hypometabolism becomes more pronounced later in the course of the disease when it is closely linked temporally to overt cognitive symptoms.

Reports from the Dominantly Inherited Alzheimer's Network (DIAN)[54] and studies of Colombian kindred carriers of a *PSEN1* mutation[55] support the idea of a protracted preclinical period during which biomarkers become abnormal sequentially while people remain clinically asymptomatic. Additionally, the DIAN results suggest that CSF $A\beta_{42}$ might become abnormal before amyloid PET, with CSF $A\beta_{42}$ initially starting at abnormally high concentrations followed by a progressive decline.[54] DIAN results also suggest that tau becomes abnormal before FDG PET and that FDG PET and MRI become abnormal in close temporal proximity to each other (figure 4).[54]

In summary, evidence that has accumulated since our model[18] was first published clearly supports the general temporal ordering framework of our model, in which amyloid biomarkers become abnormal first, followed by biomarkers of neurodegeneration, and then clinical symptoms. However, less evidence has been obtained to define the relative temporal ordering of CSF tau, FDG PET, and structural MRI.

Shapes of biomarker curves

In our 2010 model,[18] we proposed that biomarkers curves assume a sigmoidal shape as a function of time. A sigmoid shape implies an initial period of acceleration and later deceleration. Our reasoning was based on imaging, biofluid,[39,56] and autopsy[36] data available at the time. Since the publication of our model, several studies have assessed the shape of biomarker curve trajectories in different populations.

Caroli and Frisoni[57] analysed cross-sectional data in 576 individuals from the ADNI. They reported that baseline hippocampal volume, CSF $A\beta_{42}$, and CSF tau data were

better modelled as a function of worsening cognition with sigmoid-shaped curves rather than linear fits. Sabuncu and colleagues[58] and Schuff and colleagues[59] independently examined brain atrophy rates in participants from the ADNI. Both reported that atrophy rates in some brain regions exhibit early acceleration followed by deceleration, which is consistent with a sigmoid-shaped trajectory; however, rates of change in other areas did not seem to plateau. Both groups noted that atrophy does not affect all areas of the brain simultaneously, but perhaps in a sequential manner.

The shapes of the trajectories of CSF $A\beta_{42}$ and t-tau, amyloid and FDG PET imaging, and structural MRI have recently been assessed in 897 individuals from the Mayo Clinic Study of Aging and the ADNI.[60] In at least one of the several models assessed, baseline-adjusted hippocampal volume, amyloid PET, and FDG PET data showed evidence of reaching a plateau as mini–mental state examination score worsened, which is consistent with a sigmoid-shaped trajectory.

Jack and colleagues[61] modelled the temporal trajectory of Aβ accumulation using serial Pittsburgh compound B PET scans in 260 individuals spanning the cognitive continuum recruited at the Mayo Clinic and reported a sigmoidal relation between amyloid load and time. The same finding was reported from the Australian Imaging, Biomarkers, and Lifestyle study of ageing using flutemetamol, an ^{18}F amyloid PET ligand.[62] Thus a sigmoid-shaped trajectory with respect to time was replicated in studies of two large independent cohorts with different amyloid PET ligands.

In summary, evidence from several sources suggests that amyloid biomarkers do follow a sigmoid-shaped trajectory over time and approach a plateau. Some evidence suggests that FDG PET and some MRI atrophy measures follow a sigmoid-shaped trajectory. Some of the evidence cited above implies that in our original model (figure 1) the MRI and FDG PET curves should have been constructed with slopes that are not parallel to the amyloid biomarker curve and continue to change substantially through the dementia phase of the disease.

Challenges encountered in empirical testing of the model

Non-AD pathophysiological processes in elderly populations

Our hypothetical model[18] was intended to model pure AD, which in late-onset disease is most likely an abstraction, because AD pathophysiology usually coexists with other pathophysiological changes, particularly cerebrovascular disease and synucleinopathy (although hippocampal sclerosis, TDP-43, and potentially non-AD tauopathies

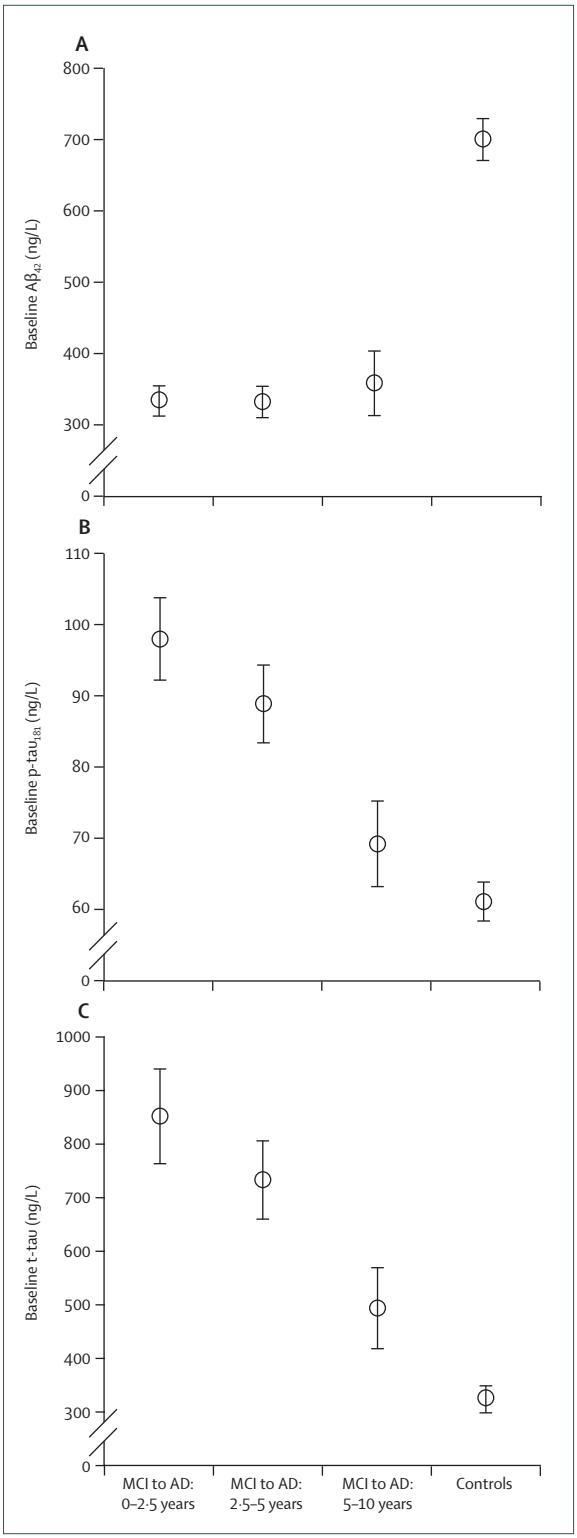

Figure 2: **Temporal ordering of CSF biomarkers**
Mean baseline concentrations of (A) CSF amyloid β_{42} ($A\beta_{42}$), (B) phosphorylated tau (p-tau), and (C) total tau (t-tau) stratified into patients with mild cognitive impairment who developed Alzheimer's disease within 0–2·5 years (n=28), 2·5–5 years (n=32), or 5–10 years (n=12). Biomarker concentrations in a cognitively healthy control group are also given. Concentrations of $A\beta_{42}$ did not differ between any of the mild cognitive impairment groups. Concentrations of t-tau and p-tau were significantly lower in late converters (5–10 years) than in very early converters (0–2·5 years). Error bars show SE. AD=Alzheimer's disease. MCI=mild cognitive impairment. Reproduced from Buchhave and colleagues,[26] by permission of the American Medical Association.

such as argyrophylic grain disease are also important contributors).[63–68] Non-AD pathophysiological processes present two closely related challenges to empirical AD biomarker modelling in elderly people: the high prevalence in elderly individuals of two or more co-occurring pathophysiological processes, one of which is AD; and the presence of individuals who have predominantly a non-AD pathophysiological process. One solution to the confounding problem of non-AD pathophysiologies in elderly cohorts[50,58,60,69] is to analyse the subset of participants who test positive for AD biomarkers to screen out people who are not following the AD pathophysiological pathway. That approach will probably require different thresholds for biomarker positivity, lenient thresholds to identify people who have just entered the AD pathway, and more stringent thresholds for clinical use as diagnostics.[70]

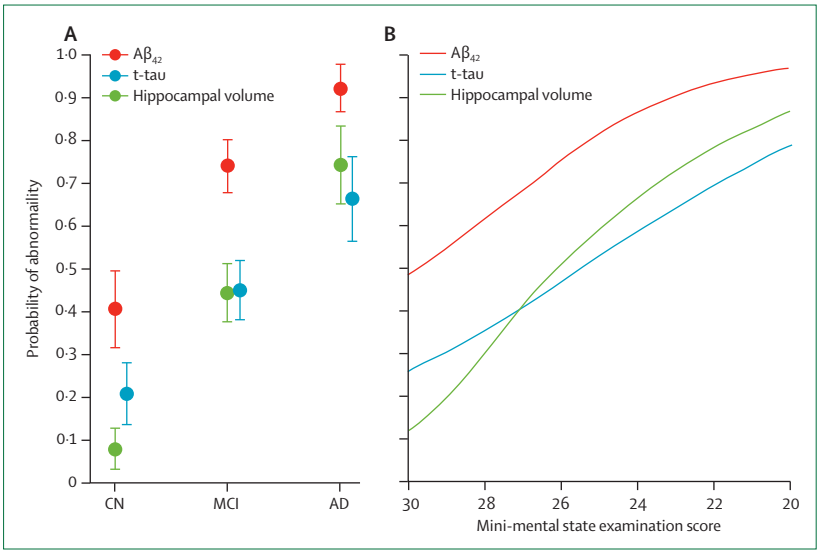

Figure 3: **Evidence for temporal ordering of CSF $A\beta_{42}$, tau, and MRI biomarkers**
The probability of an abnormal biomarker test is shown by clinical diagnosis—ie, cognitively normal (CN), mild cognitive impairment (MCI), or Alzheimer's disease (AD); all shown in A as a point estimate and 95% CI, or mini–mental state examination score (shown in B; scores of less than 27 are generally regarded as abnormal). The cutoffs are 192 pg/mL for CSF $A\beta_{42}$ concentration, 93 pg/mL for the CSF total tau (t-tau) concentration, and 0·48 cm^3 for the adjusted hippocampal volume (deviation from expected hippocampal volume for a given total intracranial volume). Aβ=amyloid β. Reproduced from Jack and colleagues,[50] by permission of the American Medical Association.

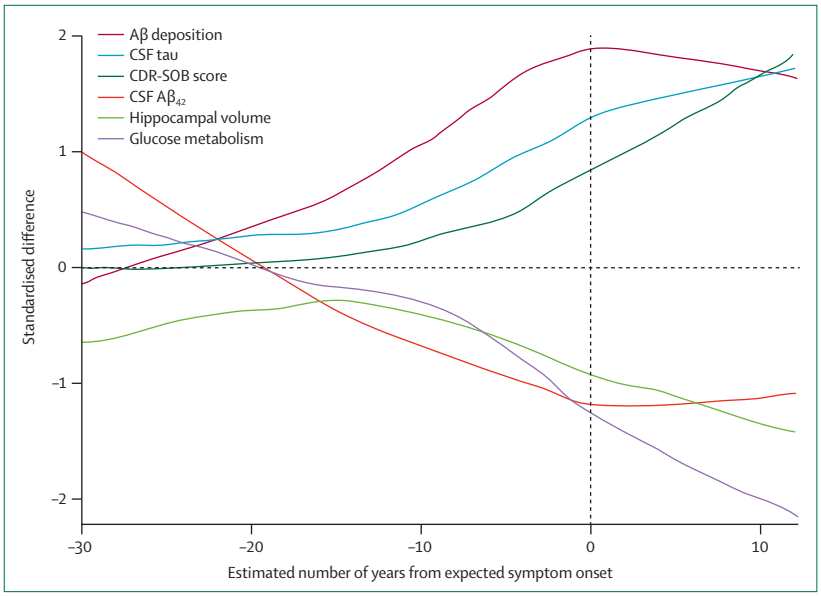

Figure 4: **Temporal ordering of biomarkers in carriers of autosomal-dominant mutations**
Cross-sectional data from the Dominantly Inherited Alzheimer's Network (DIAN) study.[54] Temporal ordering is inferred by anchoring each individual's current age to the age of dementia onset in his or her affected parent. The proposed order in which biomarkers become abnormal is: CSF $A\beta_{42}$; amyloid PET; CSF tau; fluorodeoxyglucose PET and structural MRI; followed by clinical symptoms. Aβ=amyloid β. CDR-SOB=Clinical Dementia Rating Scale Sum of Boxes. Reproduced from Bateman et al,[54] by permission of the Massachusetts Medical Society.

Definition of the vertical and horizontal axes

Our model[18] was designed to have quantifiable horizontal and vertical axes (figure 1). We constructed the vertical axis on a minimum to maximum scale, so that each biomarker is scaled in relation to its own full dynamic range from values recorded in completely unaffected individuals to maximally abnormal values (ie, patients with end-stage dementia). We placed progressive clinical disease stage on the horizontal axis (figure 1). Although it is certainly true that every person who develops AD exhibits progressive cognitive decline, indexing of individuals on the horizontal axis by clinical disease stage or continuous measures of cognitive impairment has proved to be a flawed approach for several reasons. Important pathophysiological changes occur in the preclinical phase that might constitute half or more of the total disease duration, and the preclinical stage is when measures of cognitive decline are most imprecise. Moreover, interindividual variation in cognitive reserve obscures the relation between pathophysiological severity and cognitive performance.[71–76] Furthermore, common non-AD pathophysiological changes in elderly people modulate the specific relation between AD pathophysiology and cognitive impairment in unpredictable ways on an individual basis.

Possible solutions to forming the horizontal axis

The ideal dataset with which to model AD biomarker trajectories would consist of all biomarkers obtained at several sampling points in many representative individuals followed prospectively for decades beginning in middle age. These data will take decades to acquire. In the interim, modelling will have to be done in a piecewise fashion from data from individuals at various stages of the disease. In order of increasing validity, such approaches include purely cross-sectional data, cross-sectional imaging with longitudinal clinical follow-up, and short-term (2–5 years) concurrent serial imaging and clinical assessments. All these approaches demand that individual patients' data be placed in an appropriate order along the AD pathophysiological pathway. Some recent examples are discussed below.

One approach involves forming the horizontal axis as time in years relative to an anchoring event. Buchhave and colleagues[26] and Knopman and colleagues[77] used an

incident clinical diagnosis (of either dementia or mild cognitive impairment) as the anchoring event and then compared biomarker and clinical trajectories as a function of time relative to this event. The DIAN study[78] has used the age of onset of dementia in the affected parent as the temporal anchor for mutation carriers, thus permitting estimates of the longitudinal behaviour of clinical and biomarker metrics from cross-sectional data.

Donohue and colleagues[79] modelled long-term biomarker trends from short-term within-subject data in the ADNI using shape invariant modelling that places time on the horizontal axis. These methods can model subject-specific rescaling and shifting of time in datasets with no specific common anchoring event such as incident dementia.

Jedynak and colleagues[80] and Mungas and colleagues[81] focused on novel composite horizontal axes that capture the latent trait descriptors of underlying AD pathophysiological processes by combining several biomarkers in a non-linear way; the horizontal axis represents the entire disease range with one horizontal-axis metric that can be thought of as a latent trait.[81] Each biomarker contributes to this single latent trait metric, with greater weighting where it is most dynamic in the disease range.

Model revision

Figure 5 is a revised version of our original 2010 model (figure 1) that incorporates new findings and also addresses some of the shortcomings described in the preceding paragraphs. Although our revised model has many similarities with our 2010 model, differences do exist. Firstly, the horizontal axis in our revised model is expressed as time, not clinical disease stage. The absolute time in years needed to traverse the disease pathway from left to right and the specific age at which a person enters the disease pathway will vary among individuals.

A range of possible cognitive outcomes is shown at given positions along the horizontal axis. This reflects the fact that each individual responds to AD pathophysiological changes uniquely.[73,74] People with a high risk of cognitive impairment due to AD pathophysiological processes have a cognitive impairment curve that is shifted to the left in time. Such high-risk individuals might harbour more genetic risk alleles, have low cognitive reserve, pursue lifestyles that increase the likelihood for cognitive impairment, or have other comorbid brain pathological changes. By contrast, low-risk individuals with a protective genetic profile, high cognitive reserve, no comorbid brain pathological changes, and low lifestyle risks for dementia can coexist with substantial AD pathophysiology and still maintain normal cognitive function. Thus cognitive impairment in figure 5 is shown as a zone with low-risk and high-risk borders.

The revised model includes modifications of the specific ordering of some biomarkers on the basis of reports described above. CSF $A\beta_{42}$ is now positioned slightly before amyloid PET, which is followed by CSF tau. FDG PET and MRI are drawn coincidentally as the last biomarkers to become abnormal, but those that track most closely with progressive cognitive impairment.

All biomarkers are still configured as sigmoids, but the shapes of the sigmoid curves are no longer identical. The curves have a progressively steeper slope in the right-hand tail for later-changing biomarkers. Finally, the biomarker curves are drawn closer together in the revised model, indicating less distinct temporal separation.

Autopsy evidence that tau pathophysiology can precede Aβ deposition

Ours is a model of the temporal evolution of AD biomarkers in relation to each other and to the progression of clinical symptoms. Although biomarkers do reflect

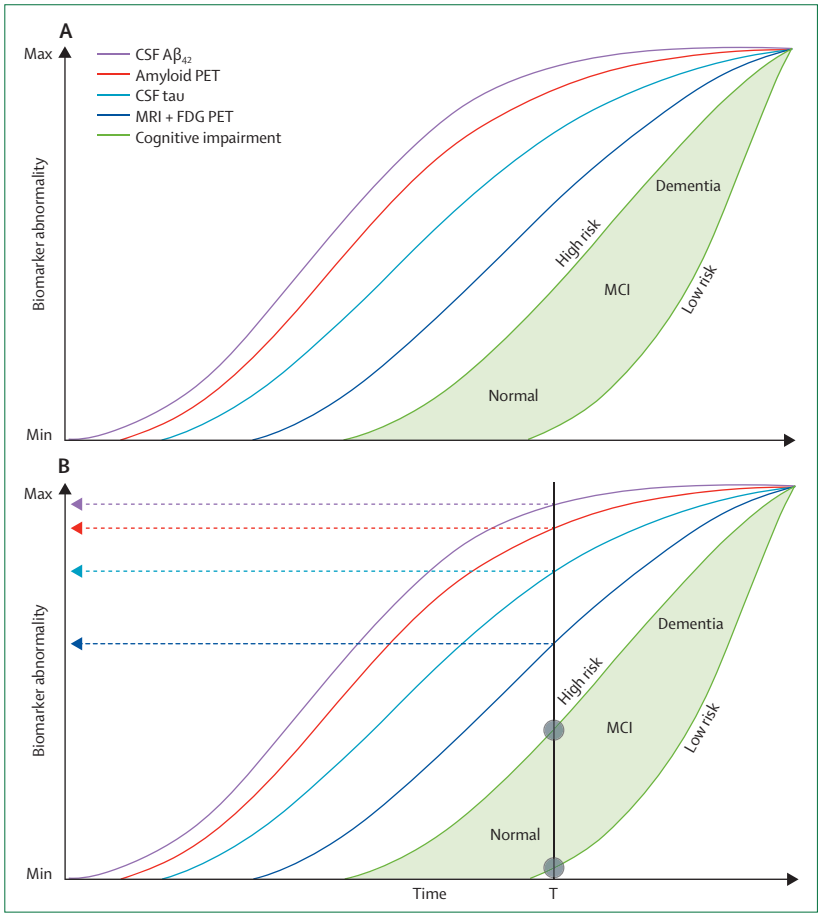

Figure 5: **Revised model of dynamic biomarkers of the Alzheimer's disease pathological cascade**
(A and B) Neurodegeneration is measured by FDG PET and structural MRI, which are drawn concordantly (dark blue). By definition, all curves converge at the top right-hand corner of the plot, the point of maximum abnormality. Cognitive impairment is illustrated as a zone (light green-filled area) with low-risk and high-risk borders. (B) Operational use of the model. The vertical black line denotes a given time (T). Projection of the intersection of time T with the biomarker curves to the left vertical axis (horizontal dashed arrows) gives values of each biomarker at time T, with the lead biomarker (CSF $A\beta_{42}$) being most abnormal at any given time in the progression of the disease. People who are at high risk of cognitive impairment due to Alzheimer's disease pathophysiology are shown with a cognitive impairment curve that is shifted to the left. By contrast, the cognitive impairment curve is shifted to the right in people with a protective genetic profile, high cognitive reserve, and the absence of comorbid pathological changes in the brain, showing that two patients with the same biomarker profile (at time T) can have different cognitive outcomes (denoted by grey circles at the intersection of time T). Aβ=amyloid β. FDG=fluorodeoxyglucose. MCI=mild cognitive impairment.

the specific pathophysiological processes that they measure, the sensitivity of histopathological assays is almost certainly greater than that of in-vivo biomarkers. This Personal View addresses three different potential concepts that should be kept distinct: biomarkers of AD pathophysiology; histopathology that can be measured at autopsy; and pathophysiological processes that are not yet accurately measurable with either biomarkers or histopathology—eg, detection of various oligomeric forms of Aβ.

One of the most important criticisms of our original AD biomarker model was that it did not account for the fact that medial temporal limbic tau pathology is a nearly universal feature of ageing and that tau pathology typically appears in individuals at a younger age than do Aβ plaques.[82] Indeed, since we presented our model, Braak and Del Tredici[83] have published the results of a study using AT8 immunostaining at autopsy of individuals aged younger than 30 years. AT8 is a phosphorylation-specific anti-tau monoclonal antibody that recognises pathologically phosphorylated tau at Ser202. AT8-positive pretangles (ie, positively stained perikarya) were reported in a high proportion of young individuals (as young as 6 years old) in select subcortical areas. On the basis of youngest age of appearance, Braak and Del Tredici[83] propose that tau pathology begins in the locus coeruleus. These changes then spread to other brainstem nuclei and to the entorhinal cortex, perhaps by direct cell-to-cell transmission.[84,85]

Braak and Del Tredici[83] therefore propose that subcortical tau deposition is the starting point of the AD pathophysiological cascade, beginning as early as the first decade of life. An alternative point of view, however, posits that since subcortical and medial temporal limbic tauopathy occurs in such a high proportion of clinically asymptomatic individuals,[82] subcortical tau deposition does not represent the beginning of the AD pathophysiological cascade, but instead is a variant of ageing that alone might lead to subtle cognitive impairment but not to AD.

The amyloid hypothesis[86] assumes serial causal events, with abnormal increases in Aβ causing tau hyperphosphorylation.[87] Small and Duff,[87] however, have suggested that tau hyperphosphorylation and Aβ accumulation might be independent pathophysiological processes that share a common upstream cause. Mesulam[88] specifically suggested that protracted exposure to upregulation of cellular activity related to neural plasticity could represent the common upstream cause of both tau hyperphosphorylation and Aβ accumulation. Duyckaerts[89] has also suggested that tau and Aβ pathological changes could be independent processes, but with pathogenic synergy.

Model incorporating tau and Aβ pathology as independent processes

Two sets of evidence exist that on the surface seem contradictory. First, several independent sources of AD biomarker evidence in elderly people and in young autosomal-dominant mutation carriers suggest that the sequence of events depicted by these biomarkers is Aβ pathophysiology first, then tau-related neurodegeneration. However, autopsy data[83] suggest that AD-like tauopathy precedes Aβ deposition. One way to integrate these apparently conflicting data into a coherent model of disease is a variation on the theme of tauopathy and Aβ pathophysiology arising independently. This integrative model recognises that the earliest evidence of AD pathophysiological changes lies beneath the detection threshold of in-vivo AD biomarkers. In this proposed integrative model (figure 6), subcortical tauopathy is the first AD pathophysiological process to arise in many individuals and is detectable only by immunostaining methods. This tauopathy, however, does not by itself lead to AD. Aβ pathophysiology arises later and independently from pre-existing tauopathy. Through unknown mechanisms, Aβ pathophysiological changes qualitatively transform and, as proposed by Price and Morris,[90] accelerate the antecedent subcortical tauopathy leading to neocortical spread of NFTs.[91] Acceleration of the initial slowly developing subcortical tauopathy occurs after Aβ biomarkers become abnormal. FDG PET and MRI biomarker changes then occur, followed last by onset of overt clinical symptoms.

In elderly people, the theme of tauopathy and amyloid pathophysiology as independent processes with a common causal factor is consistent with the notion of a general age-related failure to clear misfolded proteins, a failure of normal protective mechanisms to sequester toxic soluble forms of these proteins, or both. However, we propose in figure 6 that an independently arising Aβ pathophysiology can accelerate an antecedent tauopathy

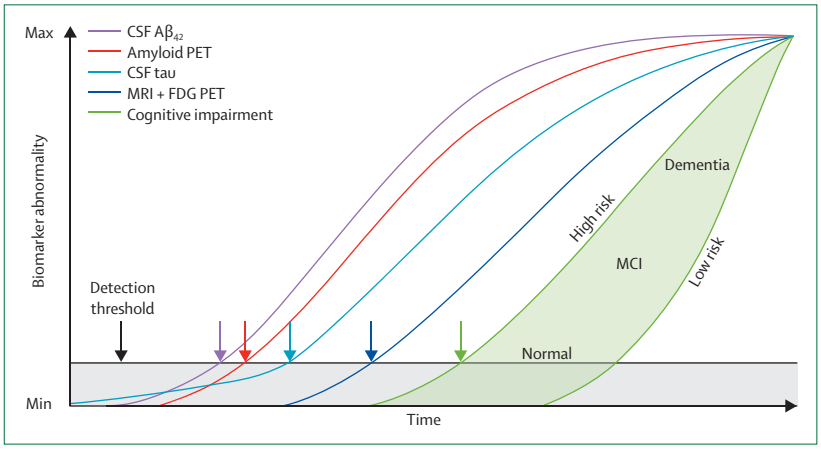

Figure 6: **Model integrating Alzheimer's disease immunohistology and biomarkers**
The threshold for biomarker detection of pathophysiological changes is denoted by the black horizontal line. The grey area denotes the zone in which abnormal pathophysiological changes lie below the biomarker detection threshold. In this figure, tau pathology precedes Aβ deposition in time, but only early on at a subthreshold biomarker detection level. Aβ deposition then occurs independently and rises above the biomarker detection threshold (purple and red arrows). This induces acceleration of tauopathy and CSF tau then rises above the detection threshold (light blue arrow). Later still, FDG PET and MRI (dark blue arrow) rise above the detection threshold. Finally, cognitive impairment becomes evident (green arrow), with a range of cognitive responses that depend on the individual's risk profile (light green-filled area). Aβ=amyloid β. FDG=fluorodeoxyglucose. MCI=mild cognitive impairment.

on the basis of the following findings. The fact that genetically determined Aβ overproduction leads to AD,[92] whereas genetically determined tauopathies do not,[93] does support a causal, instigating role for Aβ and not tau in early-onset AD. A recently discovered coding mutation in the amyloid precursor protein gene protects against late-onset AD.[94] Therefore, the case for causality points to Aβ as the disease initiator in early-onset AD, and as either the initiator or an accelerator in sporadic AD in a subject-specific manner. We do not propose that all sporadic cases follow the pattern outlined in figure 6. Rather, that at least two pathways to sporadic AD might exist—one as shown in figure 5 and the other in figure 6.

Biomarkers that precede Aβ deposition

Biomarker research is advancing in the search for biomarker abnormalities that temporally precede Aβ biomarkers. Evidence exists that FDG PET hypometabolism in an AD-like pattern occurs in some *APOE* ε4 carriers in middle-aged and young adults.[95,96] The presumption is that this hypometabolism reflects an effect of *APOE* ε4 on glucose metabolism that temporally precedes amyloid deposition. This presumption must be tempered, however, with more recent data indicating that FDG PET is a later-changing biomarker than amyloid PET or CSF $A\beta_{42}$.[51–54] Although *APOE* ε4 increases the risk and the amount of Aβ accumulation, and lowers the age at which Aβ deposition appears,[97,98] *APOE* ε4 has also been linked to mechanisms that are unrelated to amyloid deposition.[99,100]

Studies have been focusing on functional MRI as a method to probe relations between synaptic activity and features of AD. Task-free functional MRI (TF-fMRI) is particularly appealing because measures of functional connectivity and network dynamics are obtained without administering a functional activation task (which needs specialised equipment that is not available at many MRI centres). Both Mesulam[88] and Buckner and colleagues[101] have proposed pathophysiological models that relate the long-term demands of cognitive activity to AD pathophysiological processes[88] and imaging changes,[101] thus providing a mechanistic link between the physiological processes interrogated by TF-fMRI and AD pathophysiology. TF-fMRI disturbances in the task-negative (ie, default mode) and task-positive functional networks have been described in AD and mild cognitive impairment,[102–105] in elderly cognitively normal *APOE* ε4 carriers, and in cognitively normal people who are amyloid-positive.[106–108] Network disturbances have also been described in middle-aged and elderly cognitively normal people who are *APOE* ε4 carriers but who have normal amyloid PET scans,[109] in *APOE* ε4 carriers in young adulthood (in their 20s),[110] and in asymptomatic carriers of autosomal-dominant mutations years before estimated age of dementia onset.[111] Using a functional connectivity optical intrinsic signal imaging technique, Bero and colleagues[112] have shown reduced functional connectivity in young transgenic AD mice in the same topological locations where amyloid deposits appear later in life. These findings suggest that TF-fMRI might show abnormalities before amyloid biomarkers become abnormal, prompting Jagust and Mormino[113] to propose a cause-and-effect relation between lifelong synaptic activity and amyloid deposition in multimodal cortical network hubs. Greater synaptic activity generally leads to greater amyloid deposition; however, this relation is modulated by interindividual variation in cognitive reserve and the effects of *APOE*.

Conclusions and future directions

The discussion above emphasises the need for discovery of new biomarkers that would allow the testing of hypotheses that can currently be framed only in theoretical terms. This list includes CSF analytes or PET ligands that are sensitive to the AT8 tauopathy described in young people by Braak and Del Tredici[83] and PET ligands that measure NFTs and soluble Aβ.[114] Imaging and biofluid markers of TDP-43 and α-synuclein, and imaging detection of hippocampal sclerosis and microinfarctions are needed. The absence of reliable plasma biomarkers for any of the above pathophysiological processes is a major hurdle to population screening, but strategies to overcome this limitation might be on the horizon.[115]

So-called AD-signature topographical patterns of abnormality have been identified for MRI and FDG PET.[11,116–118] However, much biomarker modelling has been done by compressing multivoxel imaging data into one value representing the prototypical AD signature for each imaging modality. Additional research should be devoted to assessment of topographical spread of disease within each imaging modality as a marker of disease stage.[119,120]

In addition to the development of new biomarkers to fill in gaps in tracking relevant pathophysiological processes, appropriate cohorts for the assessment of biomarker evolution are needed. Most large longitudinal cohorts that incorporate AD biomarkers have at least three major design limitations. Firstly, middle-aged individuals are inadequately sampled. Therefore, the onset of biomarker abnormalities is not captured in those individuals in whom this process occurs in mid-life. Secondly, individuals with end-stage dementia are not included, so

Search strategy and selection criteria

References for this paper were identified through searches of PubMed for articles published between January, 1984, and October, 2012, with combinations of the search terms "Alzheimer's disease", "MCI", "PiB", "amyloid imaging", "PET AND Alzheimer's", "MRI AND Alzheimer's", and "Alzheimer's biomarkers". The search also included papers presented at the 2011 and 2012 Alzheimer's Association International Conference. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed.

the full dynamic range of biomarker abnormalities cannot be known. This bias has the particularly insidious effect of selectively truncating the apparent dynamic range of later-changing relative to earlier-changing biomarkers. Thirdly, long-term within-subject longitudinal data are missing. Most biomarker modelling studies model long-term trends with cross-sectional or short-term follow-up, which leads to conclusions that are dominated by cross-sectional trends and marred by the associated biases. Decades-long prospective multimodal observational studies, ideally in representative populations, will be necessary to provide definitive elucidation of the precise temporal sequence and time-dependent shape (or functional form) of AD biomarker changes. Finally, it will be important to follow up to autopsy as many people as possible whose biomarkers are studied during life.[68]

Contributors

All authors contributed equally to the preparation of this paper.

Conflicts of interest

CRJ serves on scientific advisory boards for Elan/Janssen AI, Bristol-Myers Squibb, Eli Lilly and Company, GE Healthcare, Siemens, and Eisai; receives research support from Baxter International, Allon Therapeutics, the National Institutes of Health (NIH)/National Institute on Aging (NIA), and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation; and holds stock in Johnson & Johnson. DSK served on a data safety monitoring board for Eli Lilly and Company and as a consultant for Elan/Janssen. WJJ served as a consultant for GE Healthcare, which manufactures flutemetamol, and collaborates with Avid Radiopharmaceuticals, which manufactures florbetapir, through the Alzheimer's Disease Neuroimaging Initiative. RCP serves on scientific advisory boards for the Alzheimer's Association, the National Advisory Council on Aging, Elan/Janssen AI, Pfizer (Wyeth), and GE Healthcare; receives royalties from publishing; serves as a consultant for Elan/Janssen AI and GE Healthcare; and receives research support from the NIH/NIA. MWW serves on the advisory boards for Elan/Wyeth, Novartis, Banner, Lilly, VACO, Biogen Idec, Araclon, and Pfizer; serves as a consultant to Elan/Wyeth, Novartis, Forest, Ispen, Daiichi Sankyo, AstraZeneca, Araclon, Pfizer, TauRx Therapeutics, Bayer, Biogen Idec, Exonhit Therapeutics, Servier, and Synarc; received honoraria from the American Academy of Neurology, Ipsen, NeuroVigil, and Institut Catala de Neurociencies Aplicades; receives research funding from Merck and Avid; and owns stock in Synarc and Elan. PSA serves on a scientific advisory board for NeuroPhage; serves as a consultant to Elan, Wyeth, Eisai, Bristol-Myers Squibb, Eli Lilly and Company, NeuroPhage, Merck & Co, Roche, Amgen, Abbott, Pfizer, Novartis, Bayer, Astellas, Dainippon, Biomarin, Solvay, Otsuka, Daiichi, AstraZeneca, Janssen, and Medivation; receives research support from Pfizer, and Baxter International; and has received stock options from Medivation and NeuroPhage. LMS serves on the technical advisory board for Saladax Biomedical. PV, HJW, SDW, TGL, and VSP declare that they have no conflicts of interest. MCD has served as consultant to Bristol-Myers Squibb. JQT might accrue revenue in the future from patents submitted by the University of Pennsylvania wherein he is co-inventor, and he received revenue from the sale of Avid to Eli Lilly as co-inventor on imaging-related patents submitted by the University of Pennsylvania; and receives research support from the NIH, Bristol-Myers Squibb, AstraZeneca, and several non-profit organisations.

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