Mol Neurobiol (2012) 45:153–172
DOI 10.1007/s12035-011-8228-7

Neuroimaging Results Impose New Views on Alzheimer's Disease—the Role of Amyloid Revised

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Received: 3 October 2011 / Accepted: 12 December 2011 / Published online: 27 December 2011

Abstract Huge progress has been made in unraveling the mysteries of Alzheimer's disease (AD), but we still do not understand the basic mechanisms that set off the cascade of pathological events. In May 2011, the National Institute on Aging–Alzheimer's Association published new diagnostic guidelines, expected to have huge impact on AD research and clinical practice. However, the new guidelines are already criticized for being biased in favor of a specific theory of the pathophysiological origins of AD—the amyloid cascade hypothesis. Shortly before publication of the guidelines, a hypothetical model of the dynamic biomarkers of the Alzheimer's pathological cascade was published, taking as starting point that biomarkers reflecting brain levels of amyloid become deviant long before brain atrophy, cognitive dysfunction, or clinical symptoms are manifest. This model has already attracted substantial interest and arguably represents a dominating view within human research on AD. Here we critically review the evidence for the view of amyloid as an initiating event in the pathological cascade and discuss how central assumptions of this hypothesis affect how results from contemporary human AD research are understood. Interpretations of new results are greatly impacted by researchers' view on the role of amyloid, and identical observations are sometimes taken to support radically opposing views on the amyloid hypothesis. We argue that the canonical view of the role of amyloid as the main causal factor in AD may not be correct and that evidence from recent neuroimaging studies indicates that amyloid is neither necessary nor sufficient, for the manifestation of AD-like brain atrophy.

Keywords Alzheimer's disease · Magnetic resonance imaging · Amyloid · Cerebrospinal fluid · Positron emission tomography · Atrophy

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Introduction

Alzheimer's disease (AD) is a devastating, slow-progressing neurodegenerative disease that affects millions of people worldwide. Enormous resources across a wide spectrum of scientific disciplines are used to understand the mechanisms of AD. Although much progress has been made, we still do not understand the mechanisms that set off the neurobiological events that eventually lead to the severe cognitive and neuropsychiatric impairments. The amyloid cascade hypothesis, stating that build-up of amyloid in the brain is the core causal mechanism setting off the disease-related changes in AD, has been dominating for years and is still highly influential. In May 2011, the National Institute on Aging–Alzheimer's Association (NIA-AA) published new diagnostic guidelines for AD. These were long awaited and expected to have huge impact on AD research and possibly clinical practice. However, the new guidelines have already been criticized for reflecting a view of the role of amyloid in AD that may not be correct [1, 2]. In one of the papers detailing the guidelines [3], description of a specific hypothetic theory on in vivo biomarkers of AD is included, the so-called dynamic biomarker model [4], which has much emphasis on neuroimaging markers. This model arguably reflects the prevailing view of

the role of amyloid in human AD research. In the present paper, we critically review the evidence in favor of the amyloid cascade hypothesis and discuss how central assumptions of this hypothesis are affecting interpretation of results from contemporary human AD neuroimaging research. We argue that the canonical view of the role of amyloid as the main causal factor in AD may not be correct and that evidence from recent neuroimaging studies indicates that amyloid is neither necessary nor sufficient for the manifestation of AD-like brain atrophy. Neuroimaging represents the most direct window into the state of the brain in vivo, and how the amyloid hypothesis applies to results from neuroimaging studies is therefore very important to consider. We start by shortly reviewing the amyloid cascade hypothesis and the status of this hypothesis in contemporary human research on AD, before we move on to discuss how this hypothesis fits with recent data, especially from neuroimaging studies. For readers not familiar with neuroanatomical nomenclature, an overview of the cortical areas most often described in this paper is given in Fig. 1.

The Amyloid Cascade Hypothesis

The amyloid cascade hypothesis comes in different forms, but the common core is that accumulation of amyloid depositions in the brain are the main initiating event that sets off a cascade of neurobiological processes that eventually end up with substantial brain atrophy and cognitive decline. The primacy of Aβ over all other factors in AD research can be traced back to Alois Alzheimer's original description of what we now refer to as neuritic plaques and neurofibrillary tangles in the brain of his patient. The presence of these on histopathological examinations is still the definite criteria for an AD diagnosis. Thus, it is not surprising that Aβ42 has a special role in AD research and that in vivo markers of Aβ

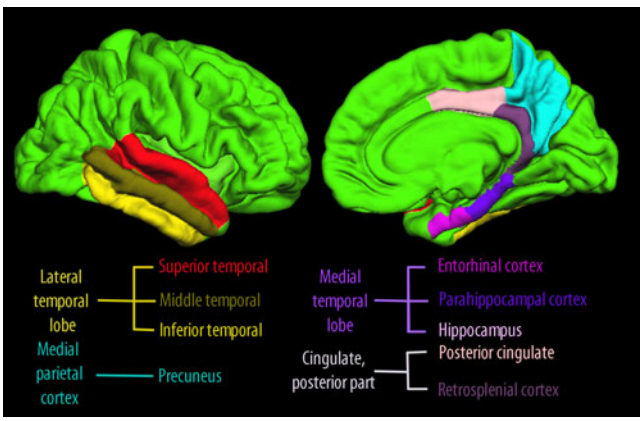


Fig. 1 Overview of important cortical areas in Alzheimer's disease. Hippocampus (not shown) is an important part of the medial temporal lobe and is located behind the entorhinal and the parahippocampal cortex

are regarded as especially important in early detection of AD.

Amyloid forms neuritic plaques in the brain. The major constituent of the amyloid plaques is Aβ42, the proteolytically derived product of amyloid precursor protein (APP) [5], resulting from sequential cleavage of APP by β-secretase and γ-secretase along the amyloidogenic pathway. Aβ42 consists of 42 amino acids and is secreted to cerebrospinal fluid (CSF) as a soluble peptide as part of the normal APP metabolism [6]. It is assumed that aggregation of Aβ in plaques reduces the amount of Aβ42 free to diffuse into the CSF, and hence low concentrations of CSF Aβ42 is taken to indicate high levels of Aβ42 in the brain [7]. This is supported by correlations between CSF Aβ42 levels and histopathological data [8] and between CSF Aβ42 and Pittsburgh compound B (PiB) retention on positron emission tomography (PET) [9, 10], which again has been related to insoluble Aβ peptide levels in vitro [11, 12]. Thus, CSF levels of Aβ42 and PiB PET are the main in vivo measures that can be used to study amyloid deposition levels in the brain. However, a reduced level of CSF Aβ42 is not a unique characteristic of AD, as this pattern is found in several neurological conditions [13, 14].

Aβ42 is part of APP, encoded by the APP gene on chromosome 21. Mutations in APP, presenilins 1 (PSEN1) and presenilins 2 (PSEN2) can account for familial AD and tend to increase levels of Aβ42. Most APP mutations cluster around the secretase sites, and both APP and PSEN mutations increase the ratio of the particularly amyloidogenic Aβ42 isoforms to the less aggregation-prone Aβ40 [6]. Transgenic mice with AD-like brain lesions are usually triggered by over-expression of APP mutations, [15]. Down's syndrome, caused by three copies of chromosome 21 and thereby also the APP gene, shows signs of early-onset AD. In addition, fibrillar Aβ induce apoptosis, neuronal cell death, and loss of synapses and dendrites when injected into tissue cultures and living mouse brains [16]. These discoveries formed the basis for the amyloid cascade hypothesis—that brain levels of Aβ instigate a chain of pathological processes that eventually ends up in AD.

While early versions of the amyloid cascade hypothesis regarded amyloid plaques as pathogenic, this view is not dominating today. Plaque load does not correlate well with disease progression, and there are patients with plaque depositions who do not experience dementia [16]. It has thus been suggested that other Aβ isoforms may be more causative for neurodegeneration, especially soluble Aβ42 oligomers [17]. So far we lack methods to test this hypothesis. To be able to conclude, one would have to show consistent increase in soluble Aβ42 oligomers in patients compared to controls, or that the oligomers for some reason are more toxic in the brains of AD patients. So far, convincing evidence has not been given to support this (see below).

The Status of the Amyloid Cascade Hypothesis in Contemporary Human Research and Clinical Practice

The new recommendations from the NIA-AA workgroups on diagnostic guidelines for Alzheimer's [18–21] constitute the first major attempt to revise the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association guidelines [22], which have been prevailing for 27 years. The influence of this major initiative on research and clinical practice is expected to be substantial. Unfortunately, it can be argued that the recommendations are biased toward the value of amyloid in both the definition of AD and its pathogenic origins [1]. In the introductory paper, it is stated that

> […] the available genetic risk data overwhelmingly point to the Aβ amyloid pathway as the initiating, or at least a very early pathophysiological event in the disease cascade

and

> Biomarkers of Aβ amyloid are indicative of initiating or upstream events which seem to be most dynamic […] before clinical symptoms. Biomarkers of neuronal injury and neuronal dysfunction are indicative of downstream pathophysiological processes which become dynamic later. [20].

An interesting feature of the new guidelines is that the etiology of the disease is brought directly into the diagnostic research criteria. The authors state that the proposed sequence of events with Aβ pathological processes becoming abnormal first and downstream neuronal injury biomarkers becoming abnormal later [4] is not sufficiently well validated for use in AD dementia [19] but is seems clear that the new guidelines reflect the canonical view on the role of amyloid in the disease. Further, several of the main authors of the revised guidelines recently published a hypothetical model of how different biomarkers develop and change during the course of the disease. This model is included in one of the guideline papers [3] and seems to reflect the status of opinion within human AD research. Therefore, we will present the model in some detail here.

The Dynamic Biomarker Model

At the time of writing, about 1.5 year has passed since the paper on the model of dynamic biomarkers of the AD pathological cascade [4, 23] was published, and it is already cited 167 times (ISI Web of Science, December 2011), hinting to the likely impact this contribution will have on the AD research field. The model sums up the conclusions from decades of AD research on humans: AD has a gradual onset with pathological processes going on for years before clinical symptoms are manifest, and different biomarkers index different pathological processes and are therefore differentially sensitive at different stages of the disease. Thus, the model is based on a hypothesized sequencing of events from normal aging to dementia and a description of the biomarkers that are active at each stage.

The model takes as starting point that the initiating event in AD is related to abnormal processing of Aβ peptide, which ultimately leads to formation of Aβ plaques in the brain. β-Amyloidosis can be detected by low CSF levels of Aβ42 or high amyloid PET tracer retention, e.g., PiB PET. This initiating event of β-amyloidosis will then after a lag that vary between individuals cause neuronal dysfunction and neurodegeneration. Neurodegeneration is now replacing β-amyloidosis as the main pathological process and can be detected by increased CSF levels of tau and brain atrophy as quantified by magnetic resonance imaging (MRI). Neurodegeneration is also associated with synaptic dysfunction, which can be detected by reduced glucose metabolism on fluorodeoxyglucose (FDG)-PET [24] (see Fig. 8). Neurodegeneraton causes cognitive dysfunction and ultimately clinical symptoms, representing the final stage of the cascade. The main chain of causation is thus β-amyloidosis→neuronal dysfunction/neuronal degeneration/synaptic dysfunction→cognitive dysfunction and clinical symptoms. Consequently, the main sequencing of when biomarkers and cognitive markers are changing the most, i.e., be most dynamic, is amyloid PET/CSF $A\beta_{1-42}$→FDG-PET ((1) posterior cingulate, (2) lateral temporal, (3) frontal)→structural MRI ((1) medial temporal, (2) lateral temporal, (3) frontal)→neuropsychological tests of memory→clinical symptoms (e.g., Clinical Dementia Rating, CDR). The fundamental question is then whether taking amyloid as the starting point is justified.

The Amyloid Cascade Hypothesis—a Suitable Starting Point for Human AD Research?

The new guidelines have already been criticized for demonstrating an unfortunate bias toward the value of amyloid in the definition of AD and its pathogenic origins [1, 2], and in the editorial comment in the same issue of Alzheimer's and dementia where the guidelines were published, the following point was made:

> The current revision of the criteria was largely based on the prevailing conceptual model of dementia/AD, which is increasingly being questioned and found to be inadequate. Future revisions of the criteria […] will require the adoption of new thinking (or models) about the full spectrum of pathogenesis. [2]

This may also be related to the problem that AD may be more of a syndrome than a well-defined single disorder. John Hardy is one of the key figures in research on the role of both amyloid and tau proteins in AD and is often regarded as one of the originators of the amyloid hypothesis [25, 26]. Recently, Hardy nicely formulated an observation on the status of the amyloid cascade hypothesis within neuroscientific research:

> Interestingly over the last three years, there has been a chorus of concern that the amyloid hypothesis was not delivering effective therapies for the disease. Whether this chorus is like the dawn chorus, heralding a bright new area of Alzheimer research, or a malcontent's chorus, merely whingeing that their grants go unfunded, is open to debate. [27]

Such critical views of the amyloid hypothesis seem to stand in stark contrast to the apparently prevailing view held by many researchers using in vivo AD biomarkers in humans, as reflected in the dynamic biomarker model and the new proposed diagnostic guidelines. In the words of one of the skeptics of the amyloid hypothesis:

> Indeed, it is now customary in some circles to begin reviews, discussions, and lectures on AD with a schematic diagram of the amyloid-β protein precursor (AβPP) molecule, implying that this molecule encapsulates AD so completely that the disease itself is almost of secondary importance. [28].

If we are correct in assuming such a discrepancy between the view of Aβ held by a majority of researchers on human AD, as reflected in the new diagnostic guidelines and the dynamic biomarker model and opinions within molecular neuroscience, this is indeed important to explore.

Predictions of the Amyloid Hypothesis

Hardy [27] argues that an important function of the amyloid hypothesis is that it has generated testable predictions, illustrated in Fig. 2. One prediction was that other causes of AD

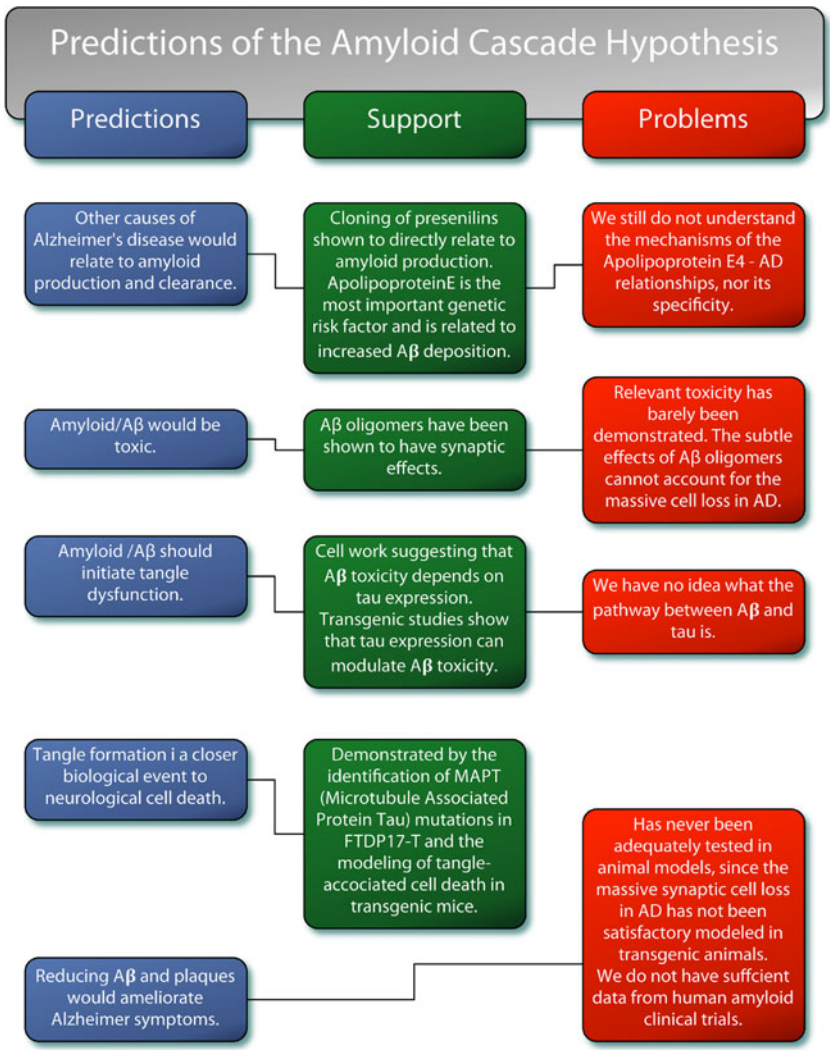


Fig. 2 Predictions of the amyloid cascade hypothesis. John Hardy [27], one of the most important researchers on the role of amyloid and tau in AD, argued that the purpose of the amyloid hypothesis was to focus research onto topics believed to be more likely to yield useful clinical results. He discusses five testable predictions generated from the amyloid hypothesis, which are presented in the flow chart. The authors thank Inge K Amlien for creating the figure

would relate to amyloid production and clearance, and this was fulfilled when it was demonstrated that presenilin mutations increased production of Aβ42. However, for most of the predictions, Hardy concludes that the evidence so far hardly favors the hypothesis. For instance, the toxicity of amyloid/Aβ has yet to be convincingly shown, and substantial Aβ induced degeneration has only been demonstrated in the context of additional microtubule associated protein tau (MAPT) mutations where the MAPT mutations themselves lead to cell death [29, 30]. Thus, the neurons were severely compromised before Aβ toxicity [27]. Also, results from clinical trials have been unconvincing. In a recent review, it was concluded that of 16 completed and phase III clinical trials of potential neuroprotective therapeutics for AD, 13 had no efficacy, two were ongoing, and one was about to commence [31]. A major part of these trials were targeted at some event related to Aβ. It is possible that the amyloid-focused trials failed because they were started too late in the progression of the disease, but it is also possible that amyloid/Aβ-independent factors caused the disease [32]. Hardy argues that amyloid trials so far have not been conclusive and that anti-amyloid trials should be carried out in individuals with APP and PSEN individuals or those with Down's syndrome. In such populations, it is known that the amyloid hypothesis is basically true.

Problems with the Amyloid Cascade Hypothesis: Animal Models

The main lines of evidence that have been used in support of the amyloid cascade hypothesis and critical issues that have been raised to each of them are presented schematically in Fig. 3. Almost 15 years have passed since the first critical review of the amyloid hypothesis was published [33]. Within molecular neuroscience, it is now commonly acknowledged that amyloid-related mechanisms cannot account for all facets of AD. Although amyloid pathology may contribute secondarily to the neuronal dysfunction of AD, it is less likely that amyloid plaques constitute the main pathological agent as a number of studies have failed to show relationships between concentration or brain distribution of neuritic plaques and degree of dementia, loss of neurons, distribution of dystrophic neuritis, or cytoskeletal abnormalities [34]. Vast overproduction of Aβ peptides in the mouse brain has failed to cause neurodegeneration [32], and decreased density of presynaptic terminals and neurons, as well as deficient synaptic transmission, has been observed well before the amyloid deposits could be detected in transgenic mice [35]. This indicates that the amyloid plaques themselves could hardly be the causal agent [35, 36].

The weakened evidence in favor of amyloid plaques as the main causal agent of AD has given rise to an alternative view of the role of amyloid in AD, where soluble Aβ oligomers are regarded as the neurotoxic species of amyloid. This theory has gained support from transgenic mouse models where the soluble Aβ oligomers are shown to interfere with hippocampal long-term potentiation [37] and cognitive function [38]. Critics argue that most of these transgenic models are based on over-expression of exogenous APP, which does not apply to AD in humans [34, 39]. For instance, Robakis [34] argues that since APP is metabolized to a large number of derivatives besides Aβ, some of which are reported to be neurotoxic (e.g., C-terminal fragments), disruptions of behavior observed in these animals cannot unambiguously be explained by the soluble Aβ oligomers [34]. Rather, the over-expressed protein in such animal models may result in neurotoxicity due to a number of Aβ-independent factors, including trafficking abnormalities driven by the overexpressed protein. Hardy stated that we have "[…] slipped into a sterile debate on what exactly is the toxic species of Aβ", obscuring "[…] the fact that relevant Aβ toxicity has barely been demonstrated" [27]. Khachaturian, in a commentary to the new guidelines, argued that "[…] a model for the pathogenesis of the disease requires a drastic shift in research […] beyond the problems of protein cleavage and aggregation." [2].

Problems with the Amyloid Cascade Hypothesis: Human Research

Thus, even though the amyloid hypothesis has been extremely important in AD research over the last two decades, the evidence in support of the hypothesis is at present not overwhelming. When it comes to results from human studies, there are at least two problems with the face validity of the amyloid hypothesis: First, presence of Aβ-plaques in the brain is not sufficient to cause AD [40–46], and typically about one third of elderly without cognitive or clinical symptoms is found to have plaques without clinical symptoms burden. Thus, if Aβ-plaques have the potential to initiate a cascade of neurodegenerative processes that eventually cause AD, some individuals are immune to this effect, or they will develop AD eventually if they live long enough, even though they at present are asymptomatic. This is often claimed as a ground for many discrepancies in research. The presence of undetected "preclinical AD" could explain a number of divergent findings, had it not been for the fact that presence of Aβ is not necessary to have an AD-like pattern of cognitive and clinical symptoms [47], as well as AD-typical atrophy of medial temporal lobes. This second point is demonstrated in several recent neuroimaging studies [48], which will be reviewed in more detail below. Thus, evidence from human studies shows that Aβ is neither necessary nor sufficient to develop the clinical manifestation of AD.

In light of the above, is amyloid the right starting point for understanding and diagnosing AD and its preceding

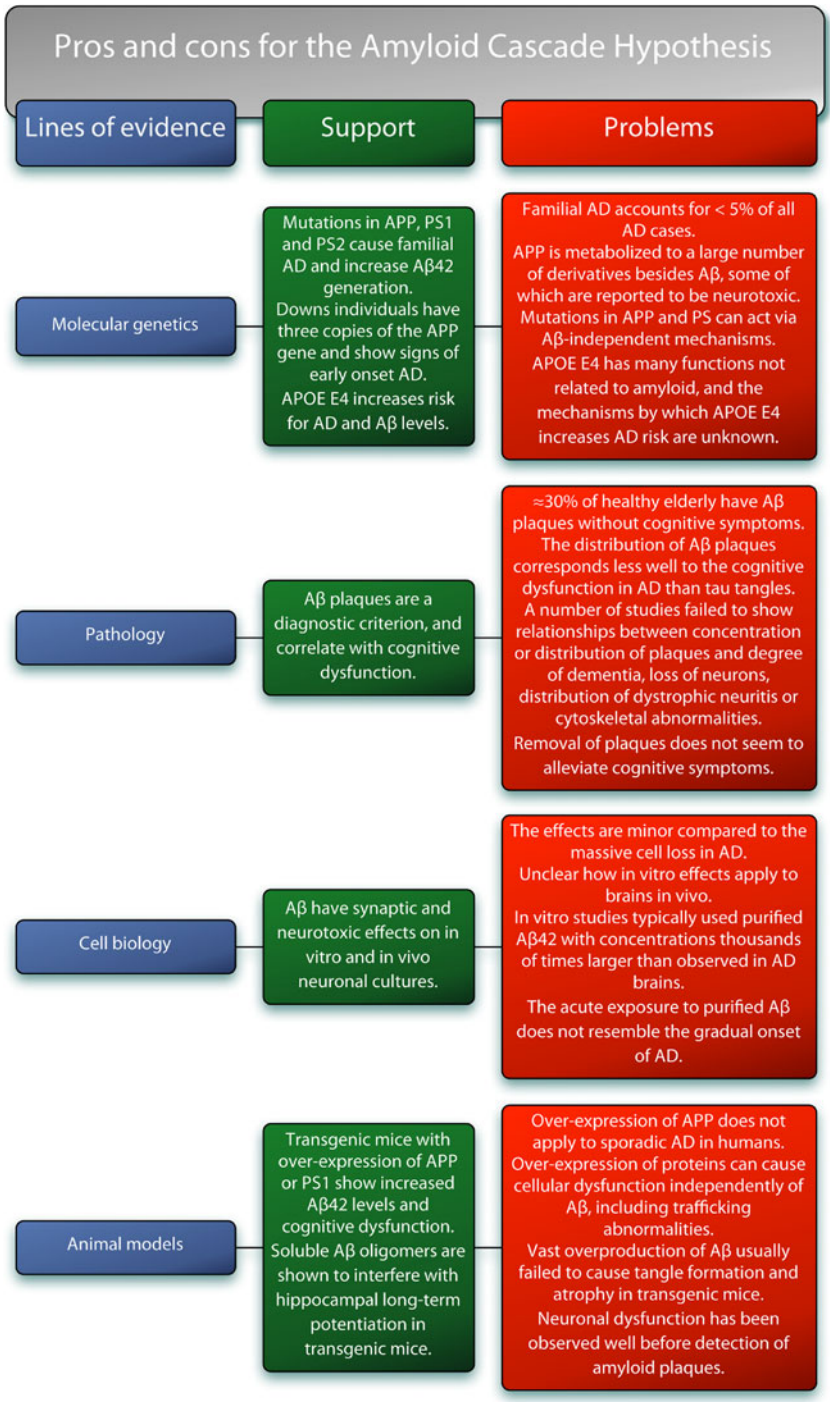


Fig. 3 Pros and cons for the amyloid cascade hypothesis. Strengths and weaknesses of the amyloid hypothesis are reviewed in detail elsewhere, and this flow chart is provided as an overview of some of the most important lines of evidence. Pimplikar [16] has suggested to evaluate the hypothesis along four themes, which we have chosen to follow. The authors thank Inge K Amlien for creating the figure

staged in humans? As argued, the revised diagnostic guidelines of the NIA-AA and the closely associated dynamic biomarker model seem to build on such a view. In the introduction to the guidelines, Jack et al. state

> The current effort at redefining the clinical diagnosis of the preclinical and symptomatic disorders associated with AD-P [AD pathophysiological processes] assumes that the fundamental characteristics of AD pathology—namely the presence of at least a moderate number of neuritic plaques containing b-amyloid […] and the extent of the regional distribution of neurofibrillary tangle pathology […]—will continue to define the neuropathological entity of AD. [20]

Contrary to this view, it can be argued that there is no inherent biological reason for why having AD without plaques should not be possible. Maybe we should not by definition exclude from AD dementia with cognitive symptoms, clinical symptoms, and even brain atrophy

characteristic of AD, even if the brains of the patients do not contain the requisite plaque burden and tangle density at autopsy [49]? Even though Aβ plaques are a defining trait of AD pathogenesis, intracellular phosphorylated tau and fibrillary tangles seem more consistent with characteristic AD-atrophy and the cognitive symptoms in early phases of the disease [50]. Medial temporal structures, i.e., hippocampus and the entorhinal cortex, show early signs of pathology on MRI (see below), and episodic memory and spatial navigation, the first cognitive functions to be affected, are known to depend heavily on these brain areas [51, 52]. While tau pathology seems initially constricted to these temporal areas, plaque accumulation appears more diffusely distributed in the cortex in initial phases, before spreading across the brain in more advanced stages.

Neuroimaging represents the most direct window into the state of the brain in vivo. Coupled with measurements of Aβ42 in CSF, this yields exciting possibilities to study progression of the disease in the earliest stages at repeated intervals. Enormous research efforts are invested in this field, evidenced for instance by the USA-based $60 million multi-center Alzheimer Disease Neuroimaging Initiative (ADNI) project, with mirror projects in Europe (AddNeuroMed) and Japan (J-ADNI). We will review some of the major findings from recent neuroimaging studies relevant for understanding the mechanisms of early AD. We will critically evaluate whether the results of these studies are in support of the view of amyloid in AD described in detail above. Thus, the main focus will be on studies using PiB PET or CSF measures of Aβ42 in combination with or in addition to structural MRI. Further, there is universal agreement that it is important to understand the earliest events in the Alzheimer cascade, which requires large multi-method studies on humans, including also participants with no symptoms of AD. Thus, studies of cognitively healthy elderly and presymptomatic individuals have the potential to provide vital information about the initial stages of the disease.

The Role of Aβ in Early AD: Results from Neuroimaging

Repeated imaging of the brain allows tracking of disease progression as the brain lesions gradually evolve. Neuroimaging can be used to aid diagnosis and inform staging of the disease, to predict progression, relevant, e.g., for selection of patients to clinical trials, and to monitor brain changes longitudinally. It is possible to use neuroimaging in combination with other biomarkers to test the accuracy of proposed models for AD.

Brain Atrophy Measured by MRI as Biomarkers for AD

MRI can be used to measure brain atrophy directly, and substantial volumetric effects are found in MCI and AD [53–59]. As seen in Figs. 4b and 5, massive differences in cortical thickness between MCI patients and healthy elderly are seen in large parts of the cerebral cortex, especially prominent in the medial temporal lobes, including the hippocampus. The differences between MCI patients and healthy controls are further amplified in AD. Consequently, dozens of studies show that quantitative MRI can be used to aid diagnosis and prediction of disease progression at relatively early disease stages [60–64], with especially strong effects in a temporoparietal neural network involved in episodic memory function [65], including the hippocampus [66–69], entorhinal, retrosplenial, posterior cingulate, and precuneus cortices [55, 58, 59, 70–76]. For instance, Bakkour et al. [77] showed that MCI patients who converted to AD 2.5 years later had between 3% and 10% thinner cortex at baseline than stable MCI patients, with the largest effects found in the medial temporal lobe. Baseline scans predicted progression to mild AD with 83% sensitivity and 65% specificity. A study from the ADNI database found annual atrophy rate of the hippocampus to increase as a function of symptom severity, with atrophy rates for normal controls of 0.86%, MCI patients with low (0.5–1.0) scores on the CDR—Sum of Boxes scale (CDR-SB) of 1.94%, MCI patients with high CDR-SB scores (1.5–2.5) of 2.39%, and patients with early AD of 3.64% (CDR-SB≥3.0) [60]. The same general pattern, although with somewhat lower rates of atrophy, was seen for several brain areas, especially lateral, inferior, and medial parts of the temporal lobes, with annual atrophy rates in AD of more than 3.0%. While the medial temporal lobes stood out as the earliest marker, frontal and parietal areas showed relatively stronger increases in atrophy rates in later stages of the disease.

Efforts have also been put down to identify patterns of brain change that may be characteristic for AD. In one study, atrophy in medial and lateral temporal, isthmus cingulate, and orbitofrontal areas aided discrimination of healthy participants from AD patients with 83% sensitivity and 93% specificity [59]. When this model was tested on MCI patients, it was found that presence of phenotypic AD atrophy at baseline was predictive of clinical decline and structural loss: 29% of MCI patients with this pattern of atrophy progressed to probable AD in 1 year, compared to 8% of the patients without the phenotypic AD pattern of atrophy at baseline. In a longitudinal study spanning 10 years, it was found that healthy participants converting to MCI showed a unique pattern of accelerated atrophy in whole brain volume, CSF volume, temporal gray matter, and orbitofrontal and temporal association cortices, including the hippocampus [64]. Thus, the use of patterns of atrophy seems to be a

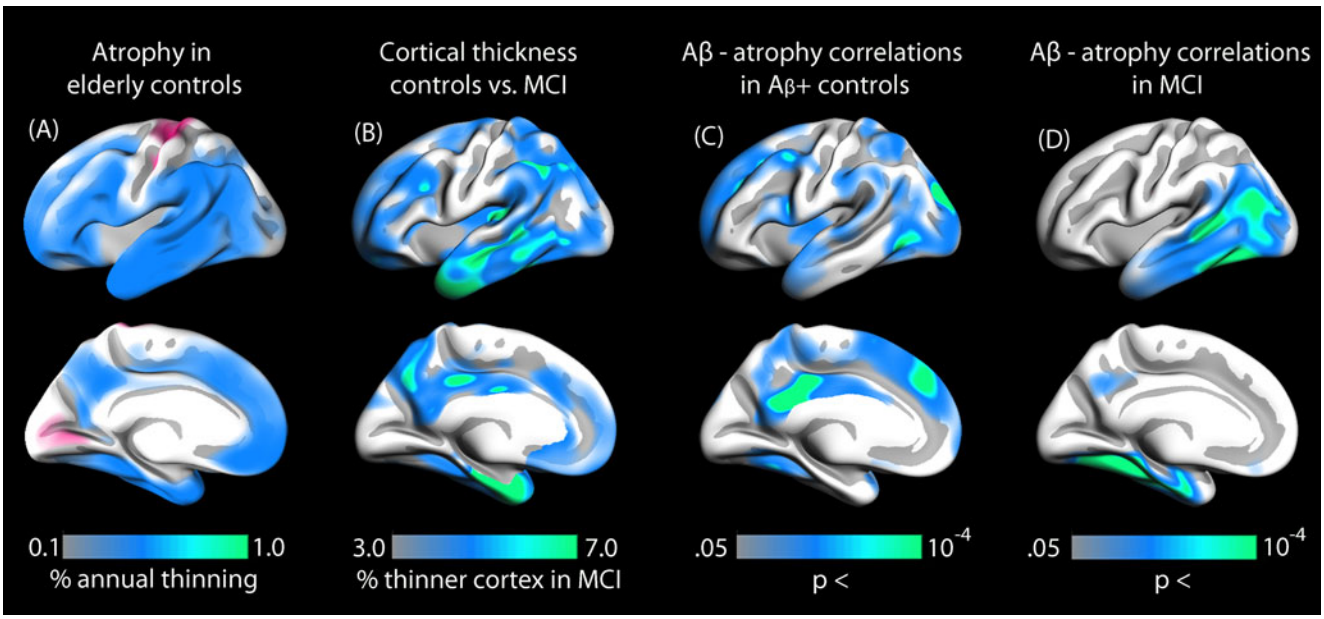


Fig. 4 Effects of age, MCI, and Aβ on cortical thickness and atrophy. **a** Rates of annual atrophy in healthy elderly (n=142). Annual thinning of about 0.5% can be seen in large areas of the cortex, especially in the temporal and the frontal lobe. Data from Fjell et al. [99]. **b** Differences in cortical thickness between healthy elderly (n=105) and MCI patients (n=175). The MCI patients had thinner cortex than the controls in several areas, but the difference is most pronounced in the medial temporal cortex (entorhinal cortex), exceeding 7% in some areas. Data from Fjell et al. [75]. **c** Correlations between CSF levels of Aβ42 and annual atrophy in healthy Aβ-positive controls (n=26). Relationships are found in several areas, but the medial temporal lobe, affected in early Alzheimer's disease, is completely spared. Data from Fjell et al. [93]. **d** Correlations between CSF levels of Aβ42 and annual atrophy in MCI patients (n=144). The relationship is almost exclusively found in the temporal lobe, both lateral and medial, with an additional effect seen in the precuneus. Data from Fjell et al. [75]. All results are displayed as *color-coded maps on the left hemisphere* of a semi-inflated template brain to allow visualization of effects within sulci

potent approach in prediction of cognitive and clinical change. Although discrepant findings exist, several studies show that MRI biomarkers are more accurate predictors of cognitive function and clinical change in MCI than CSF measures of amyloid [74, 76, 78–81].

Neuroimaging Results Put the Amyloid Hypothesis to Test

It is important to have in mind that a crucial feature of the dynamic biomarker model is that the accumulation of plaques starts years before clinical symptoms is seen, and the direct effects of Aβ will have leveled off when atrophy and cognitive symptoms appear. According to the amyloid cascade hypothesis, the dynamic biomarker model, and the guidelines from the NIA-AA workgroups, nerve cell degeneration is a downstream event from amyloid-related processes [82], which lead to the temporal and hippocampal changes measured by MRI [57, 83–86]. Thus, even when MRI biomarkers outperform CSF and PET biomarkers of Aβ in prediction of cognitive or clinical change, these do

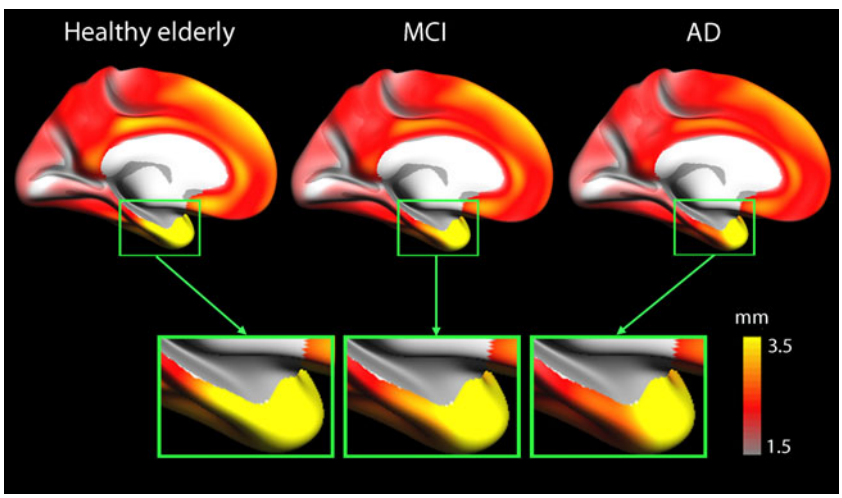


Fig. 5 Thinner cortex in medial temporal lobe cortical in MCI and AD. Thinning of the temporal lobe and reduction of hippocampal volume are the earliest signs on AD-related atrophy. As can be seen, there substantial differences in entorhinal thickness between healthy elderly, MCI patients, and Alzheimer's patients. While the healthy elderly show cortical thickness of the entorhinal cortex in the order of >3.5 mm, the AD patients have about 2.5 mm. Data from Fjell et al. [75]

not constitute evidence against the model when the patients studied are not presymptomatic. The model must therefore be tested from other angles. First, if AD-like patterns of atrophy can be identified in Aβ-negative MCI/AD patients, this will not be in accordance with the predictions from the amyloid hypothesis. Second, according to the amyloid hypothesis, MCI/AD patients will tend to be Aβ positive before they show AD-like atrophy or cognitive/clinical symptoms. Thus, if AD-like atrophy in Aβ-negative normal controls is predictive of clinical decline, this will constitute a problem for the model. Finally, if Aβ is predictive of atrophy in healthy individuals but that pattern of atrophy does not resemble that seen in AD, this will fit less well with the amyloid hypothesis, which assumes that Aβ-positive individuals will develop AD eventually. We have summarized these predictions in Fig. 6.

Evidence from neuroimaging research has yielded evidence that can illuminate each of the points above (please see Table 1 for an overview of some recent key studies). First, cortical atrophy resembling the atrophy seen in AD has been identified in Aβ-negative MCI patients. In one study from the ADNI database, it was found that MCI patients with normal CSF levels of Aβ42 still showed substantially higher rates of atrophy over 1 and 2 years than healthy controls, especially in areas that are selectively vulnerable to early AD, i.e., lateral, medial, and inferior temporal lobes, including hippocampus, and medial parts of parietal cortex (precuneus and posterior cingulate) [75].

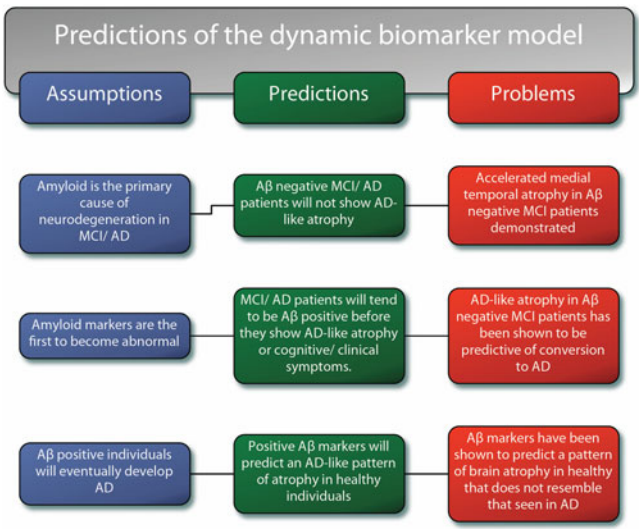


Fig. 6 Predictions of the dynamic biomarker model. The dynamic biomarker model takes as starting point that biomarkers of amyloid (CSF $A\beta_{42}$ or PiB PET) will be abnormal before biomarkers of, e.g., neurodegeneration (e.g., CSF total-tau and MRI). Based on this, we have made three predictions that we believe follow from the assumptions of the dynamic biomarker model. We argue that for each of these predictions, there are conflicting evidence

This is illustrated in Fig. 7. For example, annual rate of atrophy for hippocampus was about the double for the Aβ-negative MCI patients compared to the controls (about 2 % vs. about 1%). Thus, in these MCI patients, an AD-like pattern of atrophy was seen that could not be explained by amyloid levels.

This evidence is not conclusive because it is not given that all of these patients will go on to develop a clinical picture that fits with AD. Further follow-up examinations are needed, but the pattern of atrophy and the clinical symptoms were characteristic of what is seen in AD. However, a new study showed that an AD-like pattern of atrophy predicted conversion from MCI to AD even in patients negative for T-tau/Aβ42 [87]. This shows that AD-like atrophy can be detected in patients with normal CSF values of Aβ and that this atrophy is predictive of conversion to AD also in patients without abnormal Aβ values. According to the amyloid hypothesis and the dynamic biomarker model, MCI/AD patients will be Aβ positive before they show AD-like atrophy or cognitive/clinical symptoms. Contrary to this, it seems that abnormal Aβ is not a necessary condition for typical AD brain atrophy or clinical manifestation of AD, which violates the first two conditions described above. This has also been confirmed in cross-sectional studies, where morphometric differences between healthy elderly, MCI patients, and AD patients could not be explained by CSF levels of Aβ42 or tau [75], and levels of amyloid burden as quantified by PiB PET could not explain the contributions from hippocampal volume to memory function in healthy elderly and MCI patients [88].

One study found that PiB PET did not differ between controls and aMCI patients, while hippocampal volume did [89]. However, PiB PET differed between MCI patients and AD patients. This could be taken to indicate that atrophy is the early marker, distinguishing MCI patients from cognitively healthy controls, while plaque burden as quantified by PiB PET contributes to diagnostic accuracy later. Still, such results are interpreted differentially by different researchers within the field of neuroimaging. In a later study, the same group found that the annual change in PiB retention did not differ by clinical group (healthy elderly vs. aMCI vs. AD), while ventricular expansion, as a proxy for brain atrophy, did [90]. One interpretation of these results could be that PiB retention is a less sensitive predictor of clinical change, possibly because amyloid plaques may not be the most important factor of AD. An alternative interpretation, favored by the authors, is that the lack of PiB differences between the group and the large differences in ventricular expansion are caused by dissociation between the rate of amyloid deposition and the rate of neurodegeneration late in life, with amyloid deposition proceeding at a constant slow rate while neurodegeneration accelerates [90]. This

Table 1 Select recent key studies of Alzheimer's disease combining neuroimaging with other biomarkers discussed in the present paper

Study	Sample	Main measures	Main results
Becker et al. [96]	87 HC, 32 AD	PiB, MRI	Hippocampal volume and PiB differed between HC and AD
			PiB-positive healthy elderly showed thinner cortex (posterior cingulate/precuneus, lateral parietal, and prefrontal cortices), but not smaller hippocampal volume
			The relationship between PiB and thickness stronger in AD than HC
Bourgeat et al. [101]	92 HC, 32 aMCI, 35 AD	PiB, MRI (hippocampal volume)	Correlation between PiB in the inferior temporal region and hippocampal volume in PiB-positive HC (r=−0.59), but no difference in volume between PiB-positive and PiB-negative HC
	ABIL		No correlations found in other groups
Chetelat et al. [100]	44 HC, 49 sMCI, 22 aMCI, 34 AD ABIL	PiB, MRI (VBM)	PiB-positive sMCI patients had smaller hippocampal volume; the inverse relationship was observed in controls. There were no PiB-negative MCI and AD cases
Chetelat et al. [102]	45 HC, 49 sMCI, 34 MCI, 35 AD ABIL	PiB, MRI (VBM)	A relationship between PiB retention and global and regional brain volume in sMCI (highest r=−0.56), but not in HC, MCI, or AD
Chetelat et al. [88]	93 HC, 43 MCI	PiB PET, GM volume, memory score	Hippocampal volume and temporal beta-amyloid deposition provided independent contributions to memory deficits
Desikan et al. [91]	107 HC, 179 aMCI ADNI	Longitudinal MRI (entorhinal cortex), CSF $A\beta_{1–42}$, p-tau	A significant relationship between elevated entorhinal cortex atrophy rate and decreased $A\beta_{1–42}$ only with elevated p-tau
Fjell et al. [93]	71 HC	Longitudinal MRI (1 year), CSF $A\beta_{1–42}$	High correlation between 1 year atrophy and levels of $A\beta_{1–42}$ below a threshold level (<175 pg/mL), but not in areas vulnerable to early AD
Fjell et al. [75]	105 NC, 175 MCI, 90 AD	Longitudinal MRI (305 1 year, 176 2 years), CSF t-tau, $A\beta_{1–42}$, p-tau	CSF biomarkers could not account for group differences in morphometry but showed moderate relationships to atrophy in numerous brain areas
	ADNI		MCI patients with normal levels of $A\beta_{1–42}$ showed more atrophy than controls
			Morphometry predicted clinical change (CDR-sb) better than CSF biomarkers
Heister et al. [87]	192 MCI	Longitudinal MRI of medial temporal lobe, CSF t-tau, $A\beta_{1–42}$, p-tau, RAVLT	All risk factors (MRI, CSF, RAVLT) predicted conversion to AD
	ADNI		Combination of increased atrophy and RAVLT impairment gave highest risk (85% conversion vs. 5%)
			Medial temporal atrophy was associated with shortest dementia-free survival (15%)
Jack et al. [89]	20 HC, 17 aMCI, 8 AD	PiB PET, MRI (VBM), cognitive tests	PiB PET did not differ between HC and aMCI, but between the other groups
			Hippocampal volume differed between all groups
			Stronger correlations between cognitive performance and MRI than PiB
Jack et al. [90]	21 HC, 32 aMCI, 8 AD	Longitudinal PiB PET (1 year), ventricular expansion	No differences in PiB retention change between groups, and no correlation between PiB and CDR-sb or MMSE change
	ADNI		Differences in ventricular expansion between groups, correlations with CDR-sb (r=0.42) and MMSE (r=−0.52) change
Scheinin et al. [92]	9 MZ twins and 8 DZ, 9 HC	PiB	Cognitively preserved MZ, but not DZ, twins of cognitively impaired probands had increased PiB retention in the same areas as their impaired co-twins, i.e., in the temporal and parietal cortices, as well as posterior cingulate
Storandt et al. [46]	135 HC	PiB, MRI, longitudinal cognitive tests	29 participants were PiB positive
			PiB-positive participants had smaller volumes in typical AD areas, including hippocampal and temporal neocortex, as well as posterior cingulate
			PiB retention and hippocampal volume associated with longitudinal cognitive decline

The list includes the main studies discussed in the present paper and is not intended to be complete

HC healthy controls, *MCI* mild cognitive impairment, *sMCI* subjective MCI, *aMCI* amnestic MCI, *AD* Alzheimer's disease, *ADNI* data from the Alzheimer's Disease Neuroimaging Initiative, *ABIL* data from the Australian Imaging Biomarkers and Lifestyle Study of Aging, *CDR-sb* Clinical Dementia Rating—Sum of Boxes, *RAVLT* Rey Auditory Verbal Learning Test, *GM* gray matter, *VBM* voxel-based morphometry, *MMSE* Mini Mental Status Exam

interpretation is of course consistent with the data. On the other hand, there is nothing in the results that directly supports such a model. The problem is that the vast majority of studies have a design that cannot be used to address the

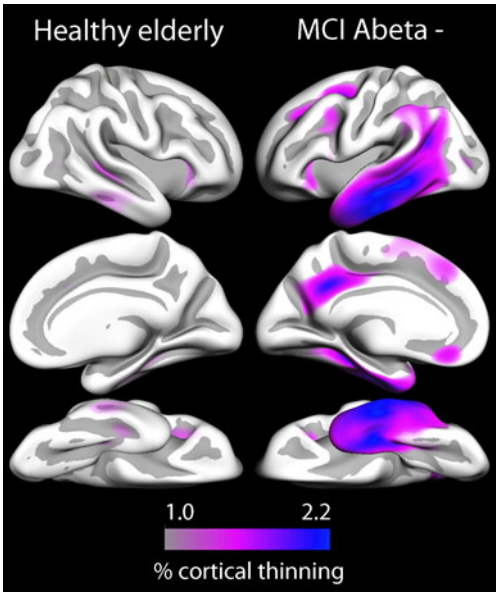


Fig. 7 Elevated rates of atrophy in Aβ-negative MCI patients. Annual atrophy in MCI patients with normal CSF levels of Aβ42 show is substantially higher than in healthy controls. Increased atrophy in this group is especially strong in typical AD areas, like the inferior and lateral temporal cortex, parts of entorhinal cortex, and the precuneus/posterior cingulate. This demonstrates that an AD-like pattern of atrophy can be seen in patients negative for Aβ. Data from Fjell et al. [75]

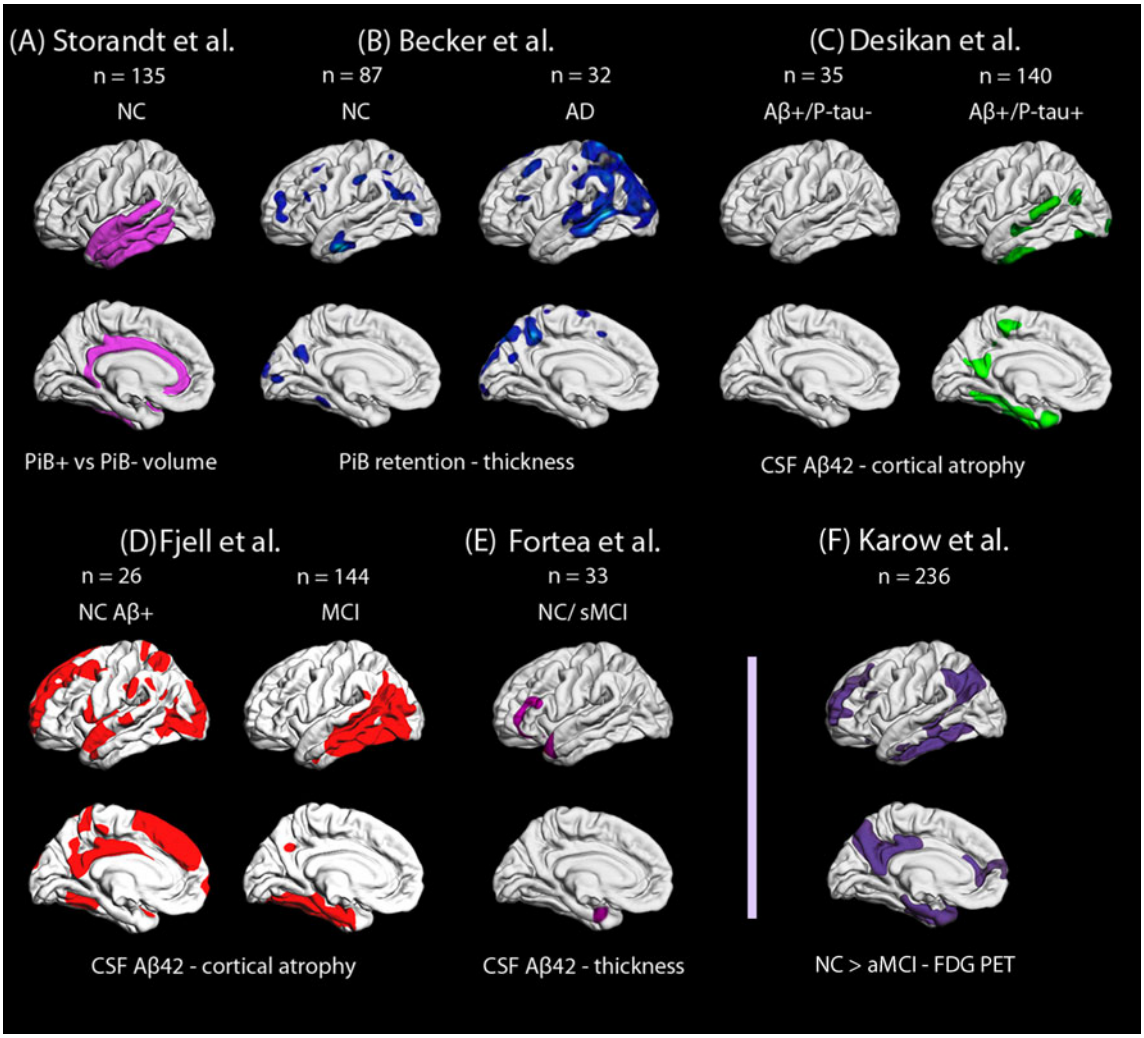
amyloid hypothesis on these premises because one would need follow-up studies spanning several years and maybe even decades. Since the rate of change in amount of Aβ is assumed to level off before any cognitive, clinical, or atrophic symptom, change in amyloid levels is expected to be a poor biomarker even in MCI patients. Thus, observations that rate of change in PiB retention is similar between healthy elderly and AD patients are in accordance with the amyloid hypothesis and the dynamic biomarker model on one hand and alternative models ascribing a less important role for Aβ on the other.

As described above, several researchers are beginning to speculate whether Aβ instead of being a major causal agent in development of AD, rather is a symptom or response protein to other pathological processes in the brain. A recent study found that accelerated entorhinal cortex atrophy was related to lower CSF levels of Aβ42 only in individuals with elevated levels of p-tau (related to tangle load), in a sample of healthy controls and MCI patients (see Fig. 8c) [91]. The same mechanism was also found for accelerated clinical decline. It is of course still possible that Aβ is the main causal factor, driving the changes in p-tau, which at the next level causes neurodegeneration and clinical decline. But the study at least demonstrates that Aβ levels alone are not sufficient to cause increased atrophy and clinical decline, in accordance with the observation that a substantial number of healthy elderly have elevated amyloid plaque burden without experiencing cognitive symptoms. Another study found that cognitively preserved monozygotic co-twins of cognitively impaired probands had increased PiB retention in the same areas as their impaired co-twins, i.e., in the temporal and parietal cortices, as well as posterior cingulate [92]. The authors argued that the dissociation between cognitive impairment and brain amyloidosis in monozygotic twins implied that environmental or acquired factors may modulate the relationship between brain amyloidosis and neurodegeneration.

Atrophy, Amyloid, and Cognition in Nondemented Elderly

Finally, an interesting question regards how atrophy in healthy individuals is predictive of later degeneration and to what extent this atrophy is related to Aβ. Aβ-related atrophy in cognitively asymptomatic controls positive for Aβ should be seen in areas known to be vulnerable very early in AD, i.e., the medial temporal lobe. If Aβ is predictive of atrophy in healthy individuals but the pattern of atrophy does not resemble that seen in AD, this will arguably fit less well with the amyloid hypothesis, which assumes that Aβ-positive individuals will develop AD. Over the last couple of years, several studies have explicitly focused on the relationship between biomarkers of Aβ and brain atrophy in cognitively healthy elderly. The results of these studies are important, but their interpretation varies greatly across authors. One objective for studying cognitively healthy controls is to detect subtle brain lesions and degeneration before cognitive and clinical symptoms. However, to be able to state that A occurs prior to B, it is necessary to observe both A and B. Often, however, Aβ levels and brain atrophy are studied (A), and the results are interpreted within the framework of pre-symptomatic dementia (B). However, it is not possible to make any deduction about whether A, i.e., elevated Aβ levels, reduced brain glucose consumption, or brain atrophy, precedes B, cognitive or clinical symptoms, without measuring B. Thus, it is important to distinguish the term "presymptomatic" from the terms such as "cognitively healthy" or "asymptomatic" because the former implies that symptoms eventually will arrive. This term should be restricted to those cases where follow-up examinations have established that symptoms actually have arrived at a later point. It may seem unnecessary to state this point, but "presymptomatic" is surprisingly often used to describe individuals for whom no follow-up examinations indicate that symptoms have ever arisen.

We studied the relationship between CSF levels of Aβ and atrophy longitudinally in cognitively healthy controls from the ADNI database [93] (see Figs. 4c and 8d). The results showed that Aβ was not related to atrophy before a certain limit of CSF level of Aβ42 (175 pg/mL) was reached. This limit was close to the mean CSF level of Aβ42 (164 pg/mL) in MCI in ADNI [94]. For the 26



participants (37%) crossing this limit, there was a high correlation between atrophy and CSF levels of Aβ42. For the rest of the participants (63%), no relationship between Aβ and atrophy existed. Further, there were no differences in scores on a memory test between the groups.

These results can be interpreted according to different models. Our belief is that the Aβ-atrophy relationships in the cognitively healthy in this study do not represent an early sign of degenerative processes that will end up in AD. The areas most vulnerable to atrophy in very early AD are medial, inferior, and lateral temporal cortex, as well as the hippocampus. However, atrophy in these areas was to a very moderate extent related to Aβ-levels in the Aβ-positive group of cognitively healthy elderly (see Figs. 4c and 8d). Thus, even though the typical distribution of amyloid plaques in the brain in preclinical AD patients does not cover the temporal lobes, we would expect to see more atrophy in these areas and a higher correlation with CSF levels of Aβ42. In MCI patients, the relationships between CSF levels of Aβ42 and atrophy are much stronger in the temporal lobe than any other place in the brain [75] (see Fig. 4d). This is also in line with a recent study showing that PiB retention in the temporal neocortex was a much better predictor of memory scores than global retention, both in groups of cognitively normal elderly, MCI patients, and cases with high neocortical Aβ [88].

Importantly, these and similar findings have been interpreted differently. For instance, four papers have interpreted the above-described Aβ-atrophy correlations in the cognitively healthy as indications of early AD [3, 95–97] and that the results support or are in accordance with the amyloid hypothesis. Thus, the same results are taken to support radically opposing views. Tosun et al. [98] analyzed the same cohort of ADNI participants with a different brain segmentation scheme and a different statistical approach and found correlations between low CSF levels of Aβ42 cortical thickness at baseline in widespread areas. Similar to our study [93], no effects were seen in the medial temporal lobe (including entorhinal cortex and hippocampus) in controls, while correlations in MCI patients showed the typical

◀ **Fig. 8** Overview of multiple studies of the relationship between Aβ, cortical thickness, volume, or atrophy. We identified five studies of the relationship between amyloid levels (PiB PET or CSF Aβ) and cortical thickness (baseline) or cortical atrophy (longitudinal). Common for these studies was the use of anatomically unbiased surface-based cortical analyses using FreeSurfer (surfer.nmr.mgh.hardard.edu). We extracted the effect sites from the published figures and projected them onto the same standard brain to allow visual comparison of the results. The *colors* of the effects were changed to aid discriminability between the different studies. The main conclusions are that Aβ levels are not related to cortical thickness/atrophy on cognitively healthy elderly in typical AD areas in the temporal lobe. In contrast, in MCI, the relationships are typically found in the temporal lobe and the posterior cingulate/retrosplenial cortex/precuneus. **a** Storandt et al. [46] contrasted cortical volume across a range of regions of interest (ROI) between cognitively healthy elderly who were amyloid positive (n=29) vs. negative (n=106) based on level of PiB retention. We have *color-coded* the ROIs showing significantly lesser volume in the PiB-positive individuals. No ROIs showed larger volume for PiB positive. **b**? Becker et al. [96] correlated PiB retention from posterior cingulate/precuneus with cortical thickness in 87 healthy elderly and 32 AD patients. The relationships were most extensive in AD but included parietal and cingulate regions in both groups, although the exact anatomical localization of effects differed across. Interestingly, no relationship between PiB retention and thickness was found in the medial temporal lobe, including the hippocampus. The results are shown at a threshold of $p<0.05$ (uncorrected), but the main clusters of effect survived Monte Carlo simulations. **c** Desikan et al. [91] correlated CSF levels of Aβ42 with cortical atrophy in healthy controls and MCI patients positive for Aβ42 but either negative for P-tau (n=35) or positive for P-tau (n=140) (diagnosis was used as covariate in the analyses), taken from the ADNI database. Only in the individuals that showed heightened P-tau levels in addition to being positive for Aβ was a relationship between CSF Aβ42 and atrophy found. Thus, in individuals with heightened levels of brain Aβ (i.e., lower levels of CSF Aβ42), Aβ is not sufficient to cause atrophy alone. In the Aβ+/P-tau+group, the relationships between Aβ and atrophy were found in typical AD areas, including the temporal lobe and posterior cingulate/retrosplenial cortex. **d** Fjell et al [75, 93] showed that CSF Aβ42 in healthy controls correlated with atrophy only in those (n=26) with low levels (CSF Aβ42<175 pg/mL), i.e., high brain levels. No relationships were found in the inferior and medial temporal lobe, indicating that the Aβ-related atrophy is not similar to the atrophy seen in preclinical stages of AD. In contrast, CSF Aβ42 correlates with atrophy in typical AD areas in a group of MCI patients (n=144). The sample was from the ADNI database. Please note that the analyses are identical to those presented in Fig. 4**c**, **d**, but the results are binarized and corrected for multiple comparisons across space (FDR<0.05). **e** Fortea et al. [95] correlated CSF Aβ42 with cortical thickness in a group of healthy elderly and patients with subjective MCI (sMCI). The relationships found in this mixed cohort were spatially restricted, but included an area overlapping the entorhinal cortex. Separate analyses of the healthy controls (n=17), excluding the patients with sMCI (n=16), showed no indication of a relationship in this area (even at an uncorrected p value level of <0.05). The authors thank Inge K Amlien for assistance in making the figure. **f** Karow et al. [115] compared glucose metabolism indexed by FDG PET between healthy elderly (n=80) and patients with amnestic mild cognitive impairment (aMCI) (n=156). The purple areas are those where the controls had >3% higher glucose metabolism than the aMCI patients. As can be seen, reduced metabolism is found in the inferior temporal lobe, both medially and laterally, medial parts of the parietal cortex (posterior cingulate/retrosplenial cortex/precuneus), and in the frontal lobes. No areas showed the opposite relationship (higher metabolism in aMCI)

AD-like pattern. These results were interpreted as indicating that "[…] CSF biomarker concentrations are associated with the characteristic patterns of structural brain changes in healthy elderly and mild cognitive impairment subjects that resemble to a large extent the pathology seen in AD. Therefore, the finding of faster progression of brain atrophy in the presence of lower $A\beta_{1-42}$ levels and higher tau levels supports the hypothesis that CSF $A\beta_{1-42}$ and tau are measures of early AD pathology." [98]. As seen, similar patterns of effects from neuroimaging studies can be taken to support radically opposing views on the role of Aβ. It is our opinion that results often are taken to support the amyloid cascade hypothesis in some form, even though the validity of these inferences sometimes can be questioned.

Studies of Amyloid Imaging and Atrophy

In addition to studies relating brain morphometry to CSF levels of Aβ42, a complementary line of studies are testing the relationship between PiB retention and morphometry. In a large cross-sectional study where PiB retention was correlated with cortical thickness and hippocampal volume both within a group of healthy elderly and a group of AD patients, it was found correlations in a pattern similar to that observed in mild AD [96] (see Fig. 8b). PiB-positive healthy elderly showed thinner cortex in scattered areas in posterior cingulate/precuneus, as well as lateral parietal and prefrontal cortices, but not hippocampal volume. The relationship between PiB and thickness were much stronger in the AD than the control group. As the PiB retention levels were higher in the AD group than the controls, these results are consistent with stronger relations between amyloid and thickness (as a proxy for atrophy) in groups with higher levels of amyloid. Since the study was cross-sectional, it is not possible to make inferences regarding temporal ordering of effects, and the conclusion can thus not be used to support or weaken the amyloid hypothesis or the dynamic biomarker model directly. However, both hippocampal volume and PiB retention differed between controls and AD patients, indicating that neither measure had stopped being "dynamic" even at the stage of full AD diagnosis, which is not in accordance with the dynamic biomarker model. Also, it is unknown whether the healthy controls will develop cognitive impairment in the future, and it is thus impossible to know whether the relationships seen are a sign of early pathological neurodegeneration or only "normal" age changes in cortical thickness [99].

In contrast to the results above, relationships between thickness or volume of brain areas vulnerable to early AD and PiB retention in cognitively healthy elderly have been found in other studies. One study found that PiB-positive participants had smaller volumes in typical AD areas, including hippocampal and temporal neocortex, as well as posterior cingulate [46] (see Fig. 8a). Since hippocampus

has only mild levels of Aβ binding, the authors speculated that volumetric reductions in these areas in PiB-positive cognitively healthy elderly could indicate pathological processes in addition to amyloid deposition [46] and that the temporal reductions were not necessarily directly caused by amyloid accumulation.

In a series of studies from the Australian Imaging Biomarkers and Lifestyle Study of Aging (AIBL) Research Group, PiB retention levels were related to hippocampal volume in healthy elderly, patients with subjective MCI (sMCI), amnestic MCI (aMCI), MCI, and AD. In one of these was a surprising discrepancy between healthy controls and sMCI patients observed in that while PiB-positive sMCI patients had smaller hippocampal volume, the inverse relationship was observed in controls [100]. The authors speculated that this could be caused either by a reactive response to Aβ, brain reserve, or a sampling issue with an underrepresentation of standard/low hippocampal volumes in the group of PiB-positive controls. The higher episodic memory scores in the PiB-positive group may speak against the reactive response theory.

In another study on the same cohort, a negative relationship between hippocampal volume and PiB retention in the inferior temporal region was found in PiB-positive healthy controls, while no relationships were found in a group of aMCI and AD patients [101]. In a third paper, a relationship was found between PiB retention and global and regional brain volume in the sMCI group, but not in healthy controls without memory complaints, MCI, or AD patients [102]. As can be seen, the relationship between amyloid load as indexed by PiB retention and brain volume is complex: In the AIBL study alone, it was found that PiB-positive healthy controls had larger volumes [100] but showed a negative relationship between volume and PiB retention values [101]. Further, a relationship between brain volumes and PiB retention in an overlapping sample was not found in a separate paper [102].

Thus, the relationship between PiB retention and hippocampal volume in healthy controls does not seem entirely clear. In sMCI, the picture from the AIBL study is more clear, with smaller hippocampi observed in PiB-positive than PiB-negative individuals [100] and naturally a negative correlation between PiB and brain volumes across a pooled sample of positive and negative individuals in this group [102]. In aMCI, MCI, and AD, a general lack of relationship between brain volumes and PiB is found, which is in accordance with the view that if amyloid is related to atrophy, this is restricted to early phases of the disease, likely at a presymptomatic stage [4]. However, most of the studies of PiB and brain volumetry in healthy controls have been conducted on cross-sectional MRI data and can therefore be used to draw inferences about volumetric differences and not atrophy directly. This is an important point, since it is possible that initial brain volume may be an important reserve factor, which may be protective against possible adverse effects of Aβ, and volume differences between groups thus cannot entirely be ascribed to atrophy.

Conclusion: How Does the Amyloid Hypothesis Fit with Neuroimaging Results?

As argued, the NIA-AA diagnostic guidelines and the dynamic biomarker model take as a starting point a view on amyloid as an early and likely initiating event in the cascade of detrimental processes that ultimately lead to AD. However, the results from the neuroimaging studies reviewed above leave us with a less clear picture. AD-like atrophy in patients with normal CSF Aβ42 values, high rate of conversion from MCI to AD in patients negative for Aβ, and significant relationships between Aβ and brain atrophy in areas not especially vulnerable to early AD in healthy controls positive for Aβ are all recent findings that are not easily accommodated into the canonical view of Aβ as the early and initiating event. Further, the dynamic biomarker model assumes that increases in amyloid levels, as indexed by PiB PET, level off before onset of atrophy and cognitive and clinical symptoms. The evidence for this is not compelling, with some studies finding similar rates of PiB retention between controls, MCI, and AD patients and others finding increased retention as a function of symptom severity. While there is some agreement that measures of brain atrophy are more closely related to cognitive and clinical symptoms, the case that this is caused by amyloid being a more upstream event is in our view not entirely compelling. Thus, we might be wise in reconsidering the role of amyloid as a very early event in AD and rather start looking for more upstream factors.

Alternative Theories: the Role of Amyloid Redefined?

Although the evidence reviewed above suggests that the view of Aβ as the main causal agent in AD could be ready for revision, it is beyond doubt that a series of neurobiological events in AD involve Aβ at some level. Understanding Aβ processing in sporadic AD is therefore an extremely important task. Aβ accumulation in AD may be more related to decreased clearance than increased production in the sporadic form of AD [103, 104], in contrast to evidence pointing to increased Aβ production in familial AD [105]. Several researchers also speculate that APP and possibly Aβ are damage response proteins rather than primary causal agents [27]. Thus, APP upregulation and Aβ deposition could be acute responses to for instance vascular damage. If the damage is chronic, these APP/Aβ responses could cause further lesions and dysfunction [27]. Castellani et al.

[28] suggest that amyloid pathology may be a host response to an underlying etiology. Promotion of polymeric structures may be a cellular survival technique with the purpose of inhibiting oligomeric toxicity. An implication of such a view is that targeting drugs on amyloid deposition will be unlikely to succeed because they will affect symptoms and not the real cause of the degeneration. Although a possible protective nature of Aβ needs to be explored further, it can at least be argued that oxidative stress precedes accumulation of Aβ in plaques, that neurons respond to oxidative stress by increasing Aβ production, and that the Aβ increase is associated with a consequent reduction in stress [106].

Another suggestion takes as starting point that Aβ is not over-expressed in sporadic AD, and a plausible explanation for the aggregation of Aβ in plaques may thus be that neurodegeneration affects the ability of the brain to keep the Aβ peptides soluble [34]. It can be speculated that healthy neurons produce a factor that inhibits Aβ aggregation and that compromised neurons produce lower levels of this hypothesized factor. This may in turn lead to aggregation of soluble Aβ. Such an explanation can account for the observed decrease in soluble Aβ in AD brains and stands in stark contrast to the transgenic mouse models where amyloidosis is driven by very high levels of Aβ, produced by over-expressed exogenous APP [34].

Mutations in PSEN1 are related to autosomal dominant AD. Even though this is a very rare form of AD compared to the sporadic form, it is often used as evidence for the amyloid cascade hypothesis, since PSEN1 mutations are related to abnormal levels of APP/Aβ. Still, it has been shown that mutations in PSEN1 cause neurodegeneration and memory loss that are independent of both APP and Aβ [107]. For instance, PSEN knockout mice have shown impaired hippocampal long-term potentiation and subsequent neurodegeneration and tau hyperphosphorylation [108]. This opens the possibility that PSEN1 mutations by themselves can trigger toxic events and that increased levels of Aβ and plaques may be secondary effects, less important to disease progression [16]. Thus, it is suggested that to understand the effects on AD neuropathology, one should focus also on other functions of presenilin besides its γ-secretase activity resulting in accumulation of Aβ42 [107].

In a recent symposium paper emanating from the 2010 Annual Meeting of the Society for Neuroscience, it was suggested that several amyloid-independent mechanisms in AD pathogenesis exist, including calcium dysregulation, proteolysis failure, altered cell signaling, oxidative stress, and neuroinflammation, all of which may play roles in neuronal dysfunction and neurodegeneration similar to those observed in AD [32]. While genetic studies of familial AD have been considered the strongest evidence supporting the amyloid hypothesis, it was pointed to the fact that the familial form of AD only accounts for ~3–5% of AD cases. And that even in the familial form, there is increasing evidence that even the FAD mutations in APP and presenilins can act via amyloid-independent mechanisms [32].

Even though these theories of the role of Aβ in sporadic AD need to be better explored and tested, they are important because they encourage researchers to look for even more upstream events in the cascade that eventually results in AD. Another aspect of Aβ that is mostly ignored in AD research is that amyloid may ultimately also have some useful biological functions. All humans produce Aβ, but most do not develop AD. Aβ and APP, may harm the brain in AD and possibly healthy aging, while being critical for normal brain development. Evidence has suggested that Aβ and APP are involved in synapse elimination [109] and neuronal cell body death and axonal degeneration [110], and it could be possible that these developmental mechanisms are "hijacked" in aging [110]. Thus, a more comprehensive theory of AD could take aging as the starting point and redefine the role of amyloid from the main causal event to one of several different degenerative processes.

The Main Risk Factor for AD: Aging

An important feature of AD is that its histopathological manifestations overlap substantially with normal aging. This phenomenon is generally not shared with other neurodegenerative conditions. This is very evident from the commonly used histopathological criteria for AD, e.g., the Consortium to Establish a Registry for Alzheimer's Disease [111] and the NIA-Reagan consensus criteria [112], where different amounts of neuritic plaques are required to reach a diagnosis for patients at different ages. Thus, two patients with the same plaque burden at different ages may be diagnosed differently [28]. Even though AD is distinguished from normal aging in terms of the type of cognitive changes [113] and the pattern of brain atrophy seen [99, 114], this underscores that at the neurobiological level, there are certain similarities. The fact that the main risk factor for AD is age indicates that any theory of AD should be able to account for the influence of age on the brain. Karl Herrup recently proposed a novel theory, taking as the starting point that the main risk factor for AD is age [49]. With higher age, the brain, like the rest of the body, is less capable of dealing with insults and other stress factors that a younger brain would have a better defense against. However, to progress from age-appropriate reductions in brain function and cognitive capabilities, an initiating injury needs to take place. This triggers a protective response among brain cells, normally a neuroinflammatory response. The crucial point of the theory is that age will increase the likelihood of failure of the normal homeostatic mechanisms, which prevent abruption of the response, even when the initiating injury is abated. Thus, according to this theory, it is the nature of

the response, not the nature of the injury, which is the crucial element in AD. A nice feature is that the role of amyloid in AD is integrated into the model, without serving as the main causal agent. Rather, the amyloid cascade is reconfigured as an amyloid deposition cycle: Aggregates of amyloid stimulate the immune response, which again will stimulate more amyloid production.

Noteworthy, the amyloid cascade theory and Herrup's age-based hypothesis both assume that at some early stage in the progression of the disease, the brain biology is altered in a fundamental way, setting off a sequence of events that cannot be prevented by eliminating the initial causal factor. According to the amyloid cascade hypothesis, especially as this is formulated in the dynamic biomarker theory of Jack et al. [4], once the amyloid cascade is initiated, it cannot be stopped by normalization of amyloid levels. Similarly, according to the age-based hypothesis, cell biology changes during the disease progression, so that the AD process is independent of the initiating injury. Thus, the neurobiology of early vs. late AD differs in fundamental ways and attempts to treat the chronic inflammation that will not transform the cells back to their normal state. Thus, both theories can account for the so far disappointing results of human AD drug trials.

Conclusion

The purpose of this paper is to show that a major part of contemporary human AD research, including neuroimaging studies, are biased toward the value of some version of the amyloid cascade hypothesis, as exemplified by the NIA-AA revised diagnostic guidelines and the recent dynamic biomarker model. PET and CSF biomarkers of brain amyloid levels tend to be regarded as markers of early and upstream events, while other biomarkers are seen as later and downstream events in the chain of pathological processes that eventually lead to development of AD. However, we have tried to show that there are serious problems with this view and that recent neuroimaging results are difficult to reconcile within the classical view of the role of amyloid. In our opinion, this calls for a new way of thinking about the full spectrum of pathogenesis, with less focus on single etiological factors, maybe in favor of a system-level approach [2].

Acknowledgments This work was supported by grants from the Norwegian Research Council to Kristine B Walhovd (grant nos. 177404, 186092, and 192663) and Anders M Fjell (nos. 175066 and 189507).

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