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New Tools for the Study of Alzheimer's Disease: What Are Biomarkers and Morphometric Markers Teaching Us?

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Abstract

Early detection is vital in the quest to develop a cure for Alzheimer's disease (AD), and CSF biomarkers (Aβ42, t-tau, p-tau) and MRI morphometry distinguish AD from healthy controls. Aβ42 and neurodegenerative biomarkers may precede clinical symptoms, but it is not clear whether AD invariably follows and whether neuropsychological tests are as sensitive. Aβ42 is related to plaque burden, which was assumed to be the main cause of AD. Evidence is now pointing to other forms of Aβ, for example, soluble Aβ oligomers, and it is possible that plaques are secondary rather than causative to neuronal damage. This makes it less obvious that CSF Aβ42 necessarily is the most potent marker. Atrophy has been regarded as a downstream event, but novel MRI analysis techniques detect atrophy at a stage where the cognitive reductions are small and possibly reversible, and MRI is superior to CSF biomarkers in the prediction of cognitive decline. The impact of biomarkers may be dynamic; changed Aβ42 is seen in cognitively normal, while atrophy causes decrements later. In conclusion, CSF and MRI biomarkers are extremely important, but it is not known whether they can distinguish events that will lead to AD from events that will not before cognitive reductions are measurable.

Keywords

Alzheimer's disease, amyloid, cognition, CSF biomarkers, early diagnosis, morphometry, MRI

Alzheimer's disease (AD) was first described by Alois Alzheimer at the beginning of the 20th century. AD is a terminal, but usually slow progressing, neurodegenerative disease, and no curative treatment exists. Diagnosis can be confirmed only by autopsy, and the defining characteristics are extracellular plaques of amyloid-β peptides and intracellular tangles of abnormally processed (hyperphosphorylated) tau protein. Clinically, the disease is manifested first through increasing problems with memory and spatial navigation and ultimately leads to both anterograde and retrograde amnesia, along with emotional instability, a complete loss of executive functions, and often a state of confusion or psychosis. The prevalence of AD increases manifold with advancing age, and so the rapidly aging population throughout much of the world will greatly increase the number of people who suffer from the disease. The current estimate of 26 million people worldwide is expected to double by 2030 and quadruple by 2050 unless preventive treatment is developed (Brookmeyer and others 2007; Jonsson and others 2006).

Even though we have no effective treatment to offer patients diagnosed with AD other than symptom treatment, good biomarkers are of vital importance in the quest to ultimately be able to prevent, cure, or at least stop the progression of the disease. Biomarkers can be used in clinical trials in the selection of patients and as outcome measures in intervention studies. In addition, good biomarkers also have the potential to improve our understanding of the pathogenesis of AD, which again may promote the development of therapeutic approaches. As AD in its advanced stages is associated with pervasive brain atrophy, it is impossible to imagine that we will ever have a treatment that can restore cognitive function in patients with advanced AD. Thus, it is necessary to develop biomarkers that are sensitive to AD pathology before the damage has gone too

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far—at a stage where the disease still could be prevented if proper treatments were available. This means that we will likely need biomarkers sensitive to AD pathology that precede clinical symptoms. CSF biomarkers and measures of brain atrophy derived from magnetic resonance imaging (MRI), that is, MR morphometry, are prime candidate biomarkers for early diagnosis and monitoring of disease progression. Brain atrophy, lowered CSF levels of amyloid beta (Aβ42), and heightened levels of the microtubule-associated proteins tau (t-tau) and hyperphosphorylated tau (p-tau) are found in mild cognitive impairment (MCI) and Alzheimer's disease (AD). MRI and CSF measures were thus suggested as supportive biomarkers for research diagnostic criteria for AD in a consensus paper (Dubois and others 2007).

In this article, we will review the research on the use of CSF biomarkers and MR morphometry in AD. First, we will go through the main neurobiological processes that the different biomarkers are assumed to reflect and describe how these are related to AD. Next, we will evaluate the status of these biomarkers for early detection and prediction of progression of the disease and also compare their predictive power in the diagnosis and prediction of cognitive change. Finally, we will discuss what these biomarkers can teach us about the pathophysiology of the disease itself. Especially, the relationships between the different biomarkers are complex, and we need a better understanding to better comprehend the mechanisms of the disease. We will only sporadically discuss positron emission tomography (PET) because compared to MRI, this method is more invasive, more expensive, and less accessible, and thus, it is less likely that it will find large-scale application in everyday clinical practice.

CSF Biomarkers in Diagnosis and Prediction of Alzheimer's Disease

The Amyloid Hypothesis

Depositions of extracellular plaques (Aβ42) and intracellular neurofibrillary tangles (tau) are believed to play causative roles in neurodegeneration in AD (Goedert and Spillantini 2006; Spires-Jones and others 2009). Especially, the amyloid cascade hypothesis has dominated much of the field of AD research. The specifics of this hypothesis vary, but its main tenet is that increased production or decreased clearance of Aβ peptides gives rise to a series of detrimental processes in the brain, which ultimately cause the disease (Fig. 1). It has been suggested that nerve cell degeneration is a downstream event from these Aβ-related processes (Goedert and Spillantini 2006), leading to the temporal and hippocampal changes measured by MRI (Arriagada and others 1992; Price and Morris 1999).

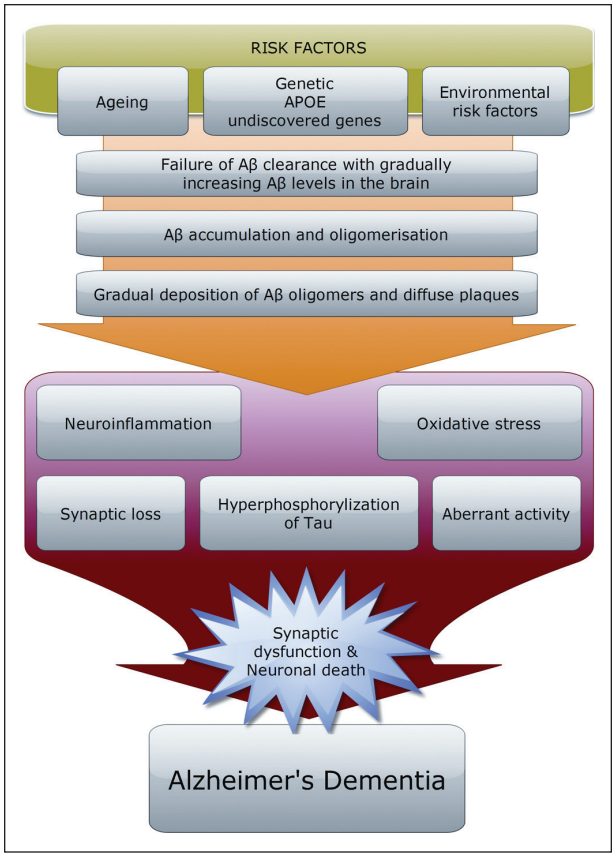

Figure 1. The amyloid cascade hypothesis. According to the amyloid cascade hypothesis, Aβ is the main causal event of Alzheimer's disease (AD). Processes related to the generation and/or clearance of Aβ will elicit a cascade of events eventually leading to brain atrophy and cognitive decline as manifested in AD. The exact mechanisms behind the role of Aβ in AD are yet not known, and so the different pathological events included in the figure must be regarded as candidates only. While formation of extracellular plaques due to increased levels of Aβ was believed to be a key to AD, the view that the Aβ-soluble oligomers play the lead pathogenic role in AD has become increasingly popular. The authors thank Inge K. Amlien for making the figure.

The major constituent of the amyloid plaques is the proteolytically derived product of amyloid precursor protein (APP) Aβ42. Aβ is produced from APP by sequential cleavage by β-secretase and γ-secretase along the amyloidogenic pathway and is secreted to CSF as a soluble peptide as part of the normal APP metabolism (Portelius and others 2008) (Fig. 2). Aβ is present in the brain in different isoforms, and the longest and most hydrophobic is Aβ42, consisting of 42 amino acids. Aβ42 aggregate more rapidly than other Aβ isoforms, and the CSF level of Aβ42 is inversely related to amounts of Aβ42 in the brain. CSF Aβ42 is by far the Aβ isoform that changes most in AD, and a reduction of about 50% is typically seen (Blennow

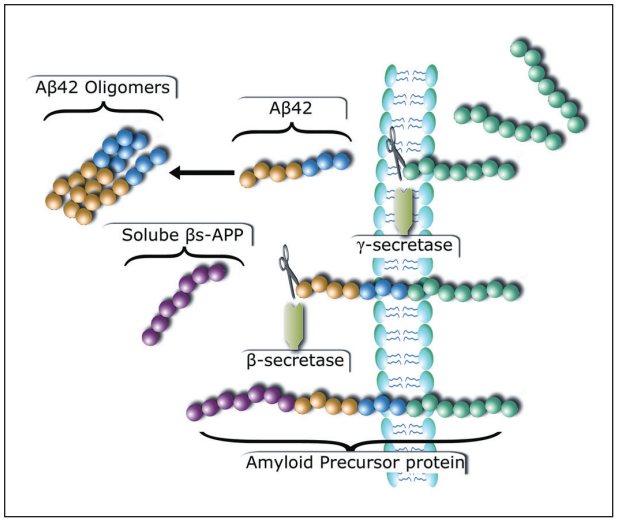

Figure 2. Generation of Aβ42 by cleavage of the amyloid precursor protein (APP). APP is a transmembrane protein and can be cleaved by the γ-secretase pathway, which is nonamyloidogenic, or the β-secretase pathway, which is amyloidogenic. β-secretase cleaves APP before the Aβ domain, and this releases the soluble β-APP (red circles). The remaining part of the APP (β–C-terminal fragment; β-CTF: yellow, blue, and green circles) is cleaved further by the γ-secretase complex, releasing the free Aβ peptide consisting of 40 to 42 amino acids (yellow and blue circles). The longer isoforms of 42 amino acids (Aβ42) are more hydrophobic and aggregate more rapidly than other Aβ isoforms, for example, Aβ40. The remaining APP (AICD; APP intracellular domain: green circles) is released into the cytoplasm. The authors thank Inge K. Amlien for making the figure.

and Hampel 2003). Some studies have found the reduction of the ratio of Aβ42 to the shorter forms Aβ1-40 and Aβ1-38 to be more pronounced than the reduction in Aβ42 alone (Portelius and others 2008). One overview paper reported that Aβ42 distinguished between AD and normal controls with a sensitivity of 89% and specificity of 90% (Blennow 2004). However, a reduced level of CSF Aβ42 is not a unique characteristic of AD, as this pattern is found in several neurological conditions.

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 are taken to indicate high levels of Aβ42 in the brain (Blennow and others 2006). This is supported by 2 lines of evidence. First, one study found CSF Aβ42 levels to correlate with amyloid neuropathology verified by autopsy (Strozyk and others 2003). Higher numbers of neuritic plaques in the neocortex and hippocampus were strongly correlated with lower CSF levels of Aβ42 obtained from the ventricles post mortem. Second, there is a strong relationship between CSF Aβ42 and Pittsburgh Compound-B (PiB) retention on PET. In one study, there was no overlap in CSF levels of Aβ42 between PIB-positive and -negative participants (Fagan and others 2006), while another study found correlations between PIB and Aβ42 in the range of –0.64 to –0.74 (Forsberg and others 2008). One study also gave evidence for a relationship between PiB-PET retention and insoluble Aβ peptide levels in vitro and a relationship between PIB retention levels and region-matched post-mortem measures of insoluble Aβ42 peptide levels confirmed by autopsy (Ikonomovic and others 2008). In sum, the few studies that have been conducted to validate the relationship between levels of CSF Aβ42 and plaque burden have yielded convincing results.

The original view of the proponents of the amyloid cascade hypothesis was that amyloid plaques were pathogenic. This position has less support today, mainly because plaque load does not correlate well with degree of dementia in humans, many patients with assumed AD and severely impaired memory show no plaques at post-mortem analysis, and plaques may be found in the elderly without dementia (Pimplikar 2009), even though it cannot be ruled out that the latter is related to preclinical manifestations of AD. Results from research using mouse models that express a human APP have shown memory deficits independently of both plaques and neuronal loss (Lesne and others 2006). Further, a recent study found that high anti-Aβ titers were related to clearance of amyloid from the brain, but progressive neurodegeneration was not prevented, cognition was not improved, and survival did not increase (Holmes and others 2008). Therefore, it has now been suggested that rather than the insoluble plaques, other specific forms of Aβ cause AD, for example, soluble Aβ oligomers (Zetterberg and others 2010). Reliable methods for measuring Aβ oligomers in biological fluids are needed to validate this hypothesis (Zetterberg and others 2010). Still, even though soluble Aβ42 may be more detrimental and toxic for brain function than the insoluble Aβ42 found in plaques, the plaques may act as Aβ42 sinks, thus hindering transport of soluble Aβ42 between the brain and CSF (Fagan and others 2006).

The amyloid hypothesis still has a strong position, even though insoluble plaques now are regarded as less likely to be the main cause of effect in AD. Pimplikar (2009) suggests that the amyloid hypothesis can be evaluated along 4 lines of evidence.

Genetics. Mutations in APP, presenilins 1 (PSEN1), and presenilins 2 (PSEN2) can account for familial AD, with more than 200 mutations identified (The Alzheimer Disease & Frontotemporal Dementias Mutation Database, under the guidelines of the Human Genome Variation Society [Horaitis and others 2007]). These mutations are responsible for 30% to 50% of autosomal dominant AD cases and tend to increase Aβ generation or 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 (Portelius and others 2008).

Still, the autosomal dominant AD cases sum up to only a small fraction of all AD cases, so it is possible that other genetic factors are responsible for the much more common sporadic AD. Further, it is convincingly shown that mutations in PSEN1 cause neurodegeneration and memory loss that are independent of both APP and Aβ (Neve 2008). For instance, PSEN knockout mice have shown impaired hippocampal long-term potentiation and subsequent neurodegeneration and tau hyperphosphorylation (Saura and others 2004). 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 (Pimplikar 2009). 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 (Neve 2008).

Pathology. Aβ plaques are a defining trait of AD pathogenesis. However, intracellular phosphorylated tau and fibrillary tangles seem more consistent with characteristic AD atrophy and the cognitive symptoms in early phases of the disease (Braak and others 1998). Medial temporal structures, that is, the 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 (Fyhn and others 2004; Scoville and Milner 1957). 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.

Cell biology. Fibrillar Aβ has been shown to induce apoptosis, neuronal cell death, and loss of synapses and dendrites when injected into both tissue cultures and living mouse brains (Pimplikar 2009). The major limitation of this line of research is that it is difficult to convincingly show that the in vitro results can be generalized to the in vivo brain tissue of humans with AD.

Animal studies. We do not yet have mice that develop all the AD-associated neuropathology seen in humans. Still, transgenic mouse models with AD-like lesions, including diffuse and neuritic plaque deposits, amyloid angiopathy, and amyloid-associated neuroinflammation, usually triggered by overexpression of APP mutations, have been useful in testing generation of Aβ and its effects on brain lesions (Radde and others 2008) and memory function (Ashe and Zahs 2010). However, it has been disappointing that therapeutic interventions have shown positive effects in mouse models but not in human trials (Pimplikar 2009). The fact that most mouse models of AD do not develop tau pathology and neurodegeneration indicates that these models are more useful for the study of amyloid than neurodegeneration in AD in general. In a recent review, Ashe and Zahs (2010) argued that transgenic mice expressing APP should be considered models of accelerated brain aging or asymptomatic AD and that the interventional efforts in these mice should be interpreted in the context of prevention. They argue that studies of soluble Aβ oligomers and soluble tau in disease pathogenesis support a model in which soluble Aβ oligomers trigger synaptic dysfunction, while formation of abnormal tau species leads to neuron death and cognitive decline.

It has been suggested that a major contribution of Aβ to the pathophysiology of AD is its synaptotoxic effects (Shankar and others 2008), related to a causal chain of events including inhibition of long-term potentiation (LTP), removal of glutamate receptors, and elimination of glutamate synapses (Zetterberg and others 2010). However, aggregated forms of Aβ in fibrils and plaques seem not to impact synaptic function (Shankar and others 2008), which may contribute to explain why some cognitively normal persons have high amounts of fibrillar Aβ in the brain. Zetterberg and others (2010) suggest that extended follow-up is needed to know whether these are protected from Aβ toxicity by effective sequestration of Aβ in inert aggregates or by other factors or whether they eventually will show cognitive reductions. It is also possible that changes in CSF levels of Aβ42 are secondary rather than causative to neuronal damage and that, for instance, increased vulnerability to oxidative and apoptotic insults can lead to Aβ42 aggregation (Lee and others 2006).

In an intensive longitudinal case study, it was suggested that the drop in CSF Aβ42 may occur soon after the beginning of diffuse amyloid depositions in the brain but before fibrillar amyloid β plaques are detectable by PiB (Cairns and others 2009). The authors speculated that substantial densities of diffuse plaques may be downstream to more toxic Aβ and can be associated with early symptomatic stages of AD. Elevated mean cortical binding potential for PiB is usually associated with low CSF Aβ42 (Fagan and others 2006), but it is likely that low CSF Aβ42 levels can occur in the absence of elevated mean cortical binding potentials for PIB. In sum, while it is vital to understand the role played by amyloid in AD, and the CSF level of Aβ42 is a potent biomarker in AD, the possibility that other agents may be even further up in the chain of causation should still be considered.

Tau Proteins

While CSF levels of Aβ42 are related to amyloid clearance from the brain, levels of tau in CSF reflect other pathogenic processes. Total tau (T-tau) is probably related to the intensity of the neuronal damage and degeneration

in the brain. A transient increase in CSF levels of T-tau is found in acute conditions such as stroke, and it has been demonstrated that the magnitude of increase correlates with the size of the infarct (Hesse and others 2000). In AD, degeneration is less intense, yielding a more moderate increase of CSF T-tau. T-tau is typically increased by a factor of 3 in AD patients compared to healthy controls. Ten prospective studies showed a sensitivity of 84% and specificity of 91% against normal age-matched controls (Blennow 2004). In contrast to this, P-tau does not reflect general neurodegeneration since increased CSF levels have so far only been found in AD. Instead, CSF P-tau seems to correlate with tangle load in the neocortex (Buerger and others 2006), suggesting that it is a marker for tau hyperphosphorylation and tangle formation, although various p-tau versions might behave differentially with regard to neurofibrillary pathology (Buerger and others 2007).

In a prospective study, it was found that AD patients with low levels of CSF Aβ42 and very high levels of T-tau and P-tau performed worse on cognitive tests compared to other patients and that they responded poorly to cholinesterase treatment and showed worse clinical outcomes over time (Wallin and others 2010). Andersson and others (2008) found increasing levels of P-tau during cognitive decline and conversion to dementia and suggested that P-tau may be useful as a longitudinal marker of the neurodegenerative process. Okonkwo and others (2010) found that all the tested CSF biomarkers were associated with decline in everyday function in MCI and that all but the T-tau/Aβ ratio were associated with functional decline in healthy controls. The authors argued that both tau and Aβ42 are associated with functional decline and development of AD in controls and MCI patients but that they are not predictive of further functional degradation in AD (Okonkwo and others 2010).

The study by Okonkwo and others (2010) was based on the The Alzheimer Disease Neuroimaging Initiative (ADNI) database. ADNI is a major research initiative aiming at validating and developing biomarkers for AD (http://www.adni-info.org/) and includes CSF measures, MRI, PET imaging, and cognitive testing of about 800 participants (200 healthy elderly, 400 MCI, and 200 AD). Trojanowski and others (2010) from the CSF biomarker core in the ADNI study recently published an overview of their ADNI CSF research and argued that Aβ42 was the single most sensitive biomarker for AD, with a sensitivity of 96.4%. However, a combination of Aβ42, T-tau, and the APOE e4 allele provided the best delineation of mild AD. Further, a pathological baseline CSF profile for T-tau/Aβ42 was detected in 33 of the 37 participants who converted to probably AD during the first year of the study. Thus, it appears that the 3 major AD CSF biomarkers all may aid in the early detection of the disease.

MR Morphometry in Diagnosis and Prediction of Alzheimer's Disease

MRI can be used to measure brain atrophy directly and is therefore a highly relevant method in studies of neurodegenerative conditions (Fig. 3). AD is associated with a range of structural brain changes that can be measured in vivo by MRI. These effects are especially prominent in a temporoparietal neural network involved in episodic memory function (Buckner and Wheeler 2001) and include the hippocampus (de Leon and others 1989), entorhinal, retrosplenial, posterior cingulate, and precuneus cortices (Du and others 2007; Fennema-Notestine and others 2009) (Fig. 4). Because of the pathophysiology of AD, with tangle formation in the medial temporal lobes (MTL) and episodic memory problems early in the disease, the MTL structures initially received most focus in neuroimaging studies of AD. However, as methods for testing structural effects throughout the brain have been improved, several independent studies have shown convincing evidence that atrophy can be identified in a number of different cortical and subcortical brain areas early in the disease. Primary and secondary sensory areas are relatively spared (Atiya and others 2003), and a study based on the ADNI database did not show significant differences between AD patients and healthy controls in the cuneus and the areas around the central sulcus (Fjell and others 2010a). Most other brain regions seem to be affected to a smaller or larger degree, as reviewed below.

MRI-based quantification of brain morphometry can be used to distinguish controls from MCI or AD patients. For instance, in a recent paper based on the ADNI database, Cohen *d* for the hippocampus was 1.75 for the comparison between controls and MCI and 2.57 for the comparisons with AD (Fjell and others 2010a) (Fig. 5). The effect sizes for CSF measures in the comparison between controls and MCI were similar to those reported in a recent meta-analysis (±0.92–1.05) (Schmand and others 2010) and somewhat higher for the comparison between controls and AD patients (±1.37–1.92) (Fjell and others 2010a). However, to be an early marker, it is important that MRI can be used to predict clinical change, that is, conversion to MCI or AD, and cognitive decline. Schmand and others (2010) identified 21 MRI studies of medial temporal lobe atrophy in normal controls or MCI patients who converted to MCI or AD. The weighted mean effect size was 0.75 (Hedges *d*), which by convention would constitute an intermediate or large effect. The effect size was lower than the weighted mean for only 7 of the studies because the effect size in the by far largest study, with more than 500 participants, was only 0.28. Methods used for acquiring and analysis of MR images have generally

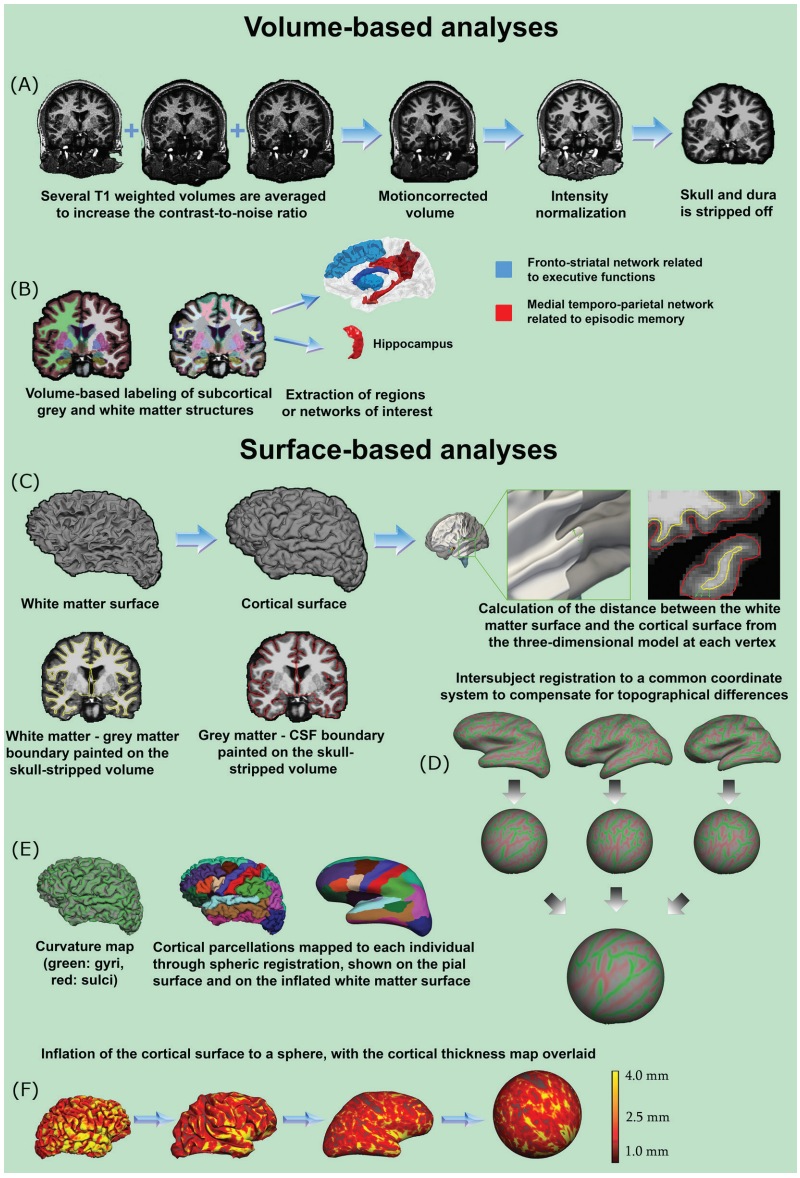

Figure 3. Quantitative MR morphometry. Several automated or semiautomated procedures for quantification of brain morphometry exist. One of the most popular is FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), freely downloadable from the Internet. Some basic features of this program package are illustrated. Panel A: In the first preprocessing steps, several T1-weighted MR scans are averaged and motion corrected to increase the ratio of the gray matter–white matter contrast to noise, the image intensity is normalized yielding homogenous values in similar tissue, and skull and dura are stripped off. Panel B: By whole-brain segmentation, a neuroanatomical label is assigned to each voxel (3-dimensional picture element) in the MR image. This is based on several sources of information, including probabilistic information automatically estimated from a manually labeled training set, and allows accurate quantification of a large number of subcortical and cortical brain structures. For instance, such procedures can be used to test specific hypotheses of effect of AD on various defined brain networks, for example, the medial temporoparietal network (red) related to episodic memory and known to be heavily affected in AD, and the frontostriatal network related to executive functions (blue), which seems to be substantially impaired also in healthy elderly. Panel C: Cortical thickness analyses are performed by reconstruction 3-dimensional models of the white matter surface and the brain (pial) surface and then calculating the distance between these surfaces (the mean of the shortest distance from each point of the white matter surface to the pial surface and from each point of the pial surface to the white matter surface). The folding pattern of the brain makes it necessary to reconstruct the surfaces in 3 dimensions to allow quantification of thickness. Panel D: Large interindividual variability in gross brain topography makes it difficult to compare the surfaces of individual brains point by point. This problem can be handled by inflating the individual brains to spheres, registering them to a template and taking variability of the sulcal patterns into account, and inserting a common coordination system. Panel E: Maps of curvature and the automated parcellation of the cerebral cortex, shown on the pial surface and on the inflated surface of the brain. Panel F: Cortical thickness shown in an individual participant, with gradual inflation of the brain surface allowing better visualization of thickness values buried within the sulci.

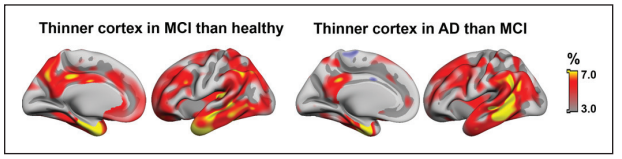

Figure 4. Effects of mild cognitive impairment and Alzheimer's disease on cortical thickness. Thinner cortices in MCI patients than healthy controls can be seen in widespread areas but are especially prominent in the medial and lateral temporal cortex, as well as in the posterior cingulate/retrosplenial cortex and inferior parietal areas/supramarginal cortex. Further effects are seen when AD patients are compared to MCI patients. The samples of patients used to generate the maps are derived from the Alzheimer Disease Neuroimaging Initiative (ADNI), which is a large multicenter research initiative building a freely available database of AD patients (http://www.adni-info.org/), and are described in depth elsewhere (Fjell and others 2010a).

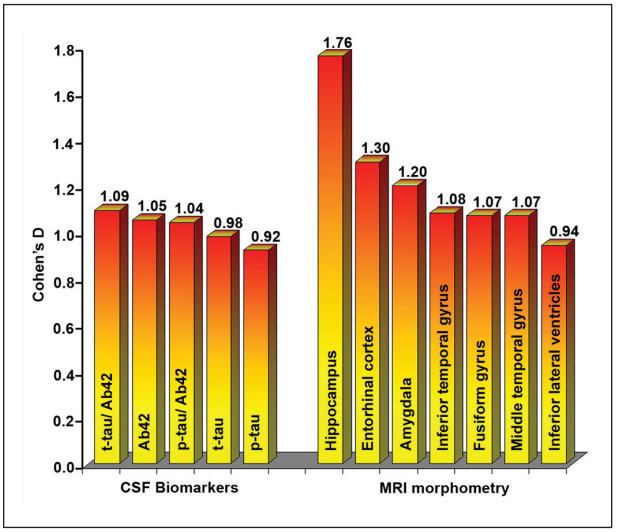

Figure 5. CSF biomarkers and MRI morphometry distinguish mild cognitive impairment from healthy elderly. Cohen *d* (the group difference divided by the pooled standard deviations) for the most used CSF biomarkers in AD and for the volume of selected brain structures. For all of these measures, Cohen *d* indicates large effect sizes. Data are taken from Fjell and others (2010a) and are based on the ADNI database.

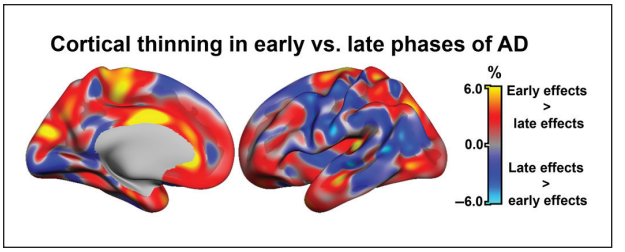

Figure 6. Cortical thinning in early versus late phases of Alzheimer's disease. Based on the cross-sectional maps from Figure 4, the differences in cortical thickness at each point of the surface between healthy controls and MCI patients were contrasted with the differences between MCI patients and AD patients. Red and yellow areas indicate that the differences between MCI and healthy patients are larger than the differences between MCI and AD patients, and blue-cyan indicates the opposite pattern. As can be seen, the medial and anterior lateral temporal effects are larger in early phases than in later phases. A similar approach, based on longitudinal data, was taken by McDonald and others (2009). The present figure confirms the pattern of larger early versus late effects for the anterior temporal lobe in that paper. Otherwise, the early > late effects pattern seen in the present figure is naturally much larger compared to what would be seen when longitudinal data are used since the thinner cortex seen in cross-sectional comparisons of MCI patients to healthy controls is a result of accumulated atrophy that has probably been going on for several years.

improved over the last few years, possibly yielding even higher effect sizes.

Several important studies have been published over the last 2 years. For instance, Bakkour and others (2009) 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. The effect was largest in the MTL. Based on the baseline scans, progression to mild AD could be predicted with 83% sensitivity and 65% specificity. Also, large studies have recently been published based on the ADNI database and from the group of Susan Resnick at NIH (Davatzikos and others 2009; Driscoll and others 2009). In one study, neocortical atrophy rates were compared between healthy controls, MCI patients with low scores on the Clinical Dementia Rating–Sum of Boxes scale (CDR-SB) (0.5–1.0), MCI patients with higher CDR-SB scores (1.5–2.5), and patients with early AD (CDR-SB ≥3.0) (McDonald and others 2009). For the hippocampus, annual atrophy rate was 0.86% for the controls, increasing to 1.94%, 2.39%, and 3.64% with higher CDR-SB. The same general pattern, although with lower rates of atrophy, was seen for several brain areas. The lateral, inferior, and medial parts of the temporal lobes were especially affected, with annual atrophy rates in AD of more than 3.0% in large areas of the temporal lobes, especially the inferior and middle temporal gyrus. Interestingly, however, when authors tested which areas showed atrophy increases in early versus late stages of the disease, while MTL stood out as the earliest marker, frontal and parietal areas showed relatively stronger increases in atrophy rates in later stages of the disease (Fig. 6).

Two general problems for the prospect of predicting AD from structural MRI data are first that the normal variation in brain structures is huge and second that the structural changes observed in healthy aging are also profound (Fjell and others 2009; Walhovd and others 2009). Thus, small baseline volume or high rates of atrophy in a specific brain structure may prove insufficient to distinguish

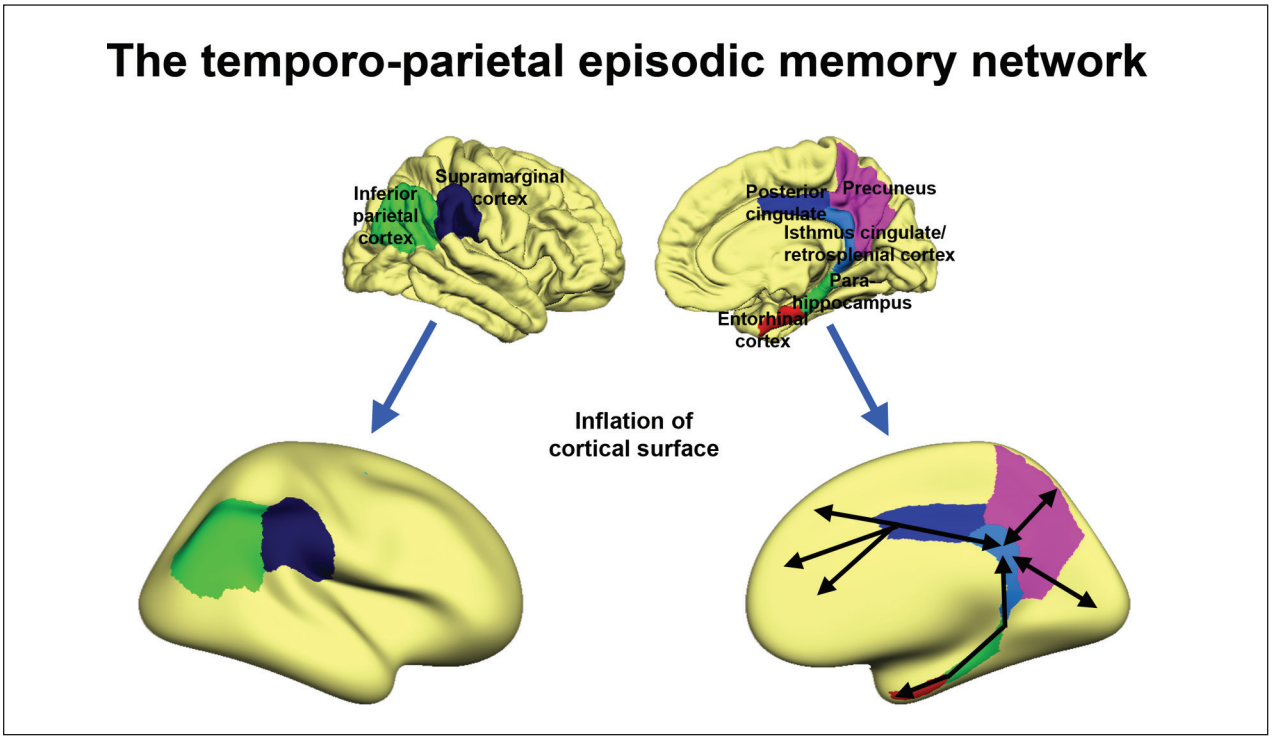

Figure 7. A temporoparietal network involved in episodic memory. Converging evidence points to the involvement of a temporoparietal network involved in episodic memory, overlapping with the default network. The different structures within this network are vulnerable to AD, and the atrophy here likely plays a vital part in the memory problems experienced by AD patients already in the initial phases of the disease. There are reciprocal connections from the precuneus (pink) to the posterior cingulate (dark blue) and the retrosplenial cortex (light blue) and to the inferior parietal lobule (light green), and further from the posterior cingulate and retrosplenial cortex to parahippocampal (light green), entorhinal (red), and hippocampal (not shown) areas, and further reciprocal connections extending anteriorly towards prefrontal areas. More detailed descriptions of these connections and the functions of the different areas can be found in Cavanna and Trimble (2006) and Vann and others (2009). Please note that the labels used in the figures are based on the parcellations automatically done by the FreeSurfer program, and the placement of the anatomical borders may certainly be subject to debate. Further, other structures could also have been included in such a network.

AD from normal aging. To overcome these problems, some researchers have tried to reveal patterns of brain change that may be more characteristic for AD than normal aging. These efforts have been promising. One study using unbiased linear stepwise regression analysis found that there was no overlap between the collection of brain structures that best distinguished AD patients from healthy elderly and the structures that best distinguished healthy elderly from young controls (Fjell and others 2010b). McEvoy and others (2009) used stepwise linear discriminant analysis to identify regions that best aided discrimination of healthy controls from AD patients in the ADNI database. 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. The results of this analysis were later applied to a group of MCI patients, and it was found that the presence of phenotypic AD atrophy at baseline was predictive of clinical decline and structural loss. In the group of MCI patients with this pattern of atrophy, 29% progressed to probable AD in 1 year compared to 8% of the other patients. The same general conclusion was drawn by an independent group of researchers using high-dimensional pattern classification on an overlapping sample (Fan and others 2008). In a longitudinal study spanning 10 years, Driscoll and others (2009) found that even though all investigated brain volumes declined in normal aging, the participants converting to MCI in the course of the study showed a unique pattern of structural vulnerability reflected in accelerated atrophy in whole brain volume, CSF volume, temporal gray matter, and orbitofrontal and temporal association cortices, including the hippocampus. Thus, the use of multiple brain areas seems to be a promising approach in the prediction of cognitive and clinical change and structural degradation over time. Empirical and theoretical works along such lines have also converged on a medial-temporal-parietal network of brain structures related to episodic memory function, where substantial AD-related atrophy is seen (Fig. 7). This network overlaps greatly with the default or resting state network.

Comparisons of MRI and CSF Biomarkers in Prediction and Monitoring of Change

As argued above, a good biomarker should be able to predict disease progression before substantial irreparable neurological damage is manifested. If amyloid is the major causal event in AD, this gives hope that changes in CSF levels of Aβ may be sensitive to AD in its earliest phases. However, if amyloid is a downstream event, this hope is less likely to be warranted. T-tau is likely related to neuronal damage and degeneration in the brain, but it is still possible that changes in CSF T-tau levels can be found in early disease phases. A challenge to the use of T-tau for early diagnosis, however, is that the CSF level of this protein is substantially elevated in a number of other conditions, including healthy aging. Thus, it is possible that atrophy as quantified by MRI is an upstream event compared to the CSF biomarkers or that they are both caused by some other events even further up in the chain of causation. This does not imply that the MRI cannot be a sensitive marker of pathological processes early in the disease. By use of state-of-the-art methods for analyzing MRI data, even minute changes can be reliably detected, for instance, changes in cortical or hippocampal volume of less than 0.5% (Holland and others 2009). It is conceivable that the sensitivity of such techniques is high enough to allow intervention at a stage where the cognitive consequences of the neurodegenerative processes are small and maybe even reversible. Thus, even though MR morphometry is restricted to detecting atrophy, this does not imply that MR cannot be used as an early, presymptomatic marker of AD-related pathology.

Based on existing knowledge about the neurobiological mechanisms behind changes in CSF biomarker levels or brain atrophy in AD, it is not possible to state with certainty whether CSF biomarkers or MRI morphometry have the best potential to be the earliest marker of cognitive and clinical decline in AD. However, we can look at the existing evidence and compare the power of each of the biomarkers in the prediction of decline in cognition and clinical status, as well as rates of atrophy. The literature that directly compares the predictive power of CSF biomarkers and MRI measures of brain structure is unfortunately not very coherent. Discrepant results may not only be related to differences in samples studied but also to the sensitivity of the approach taken, perhaps especially in MR morphometry, where different procedures may yield partly different results (Tisserand and others 2002). In the meta-analysis of longitudinal studies described above, the weighted mean effects sizes of CSF biomarkers ranged from 0.91 to 1.11, while the corresponding number for atrophy in the medial temporal lobe was 0.75 (Schmand and others 2010). Interestingly, however, memory performance had an effect size of 1.06. Thus, the authors concluded that CSF biomarkers and MRI biomarkers were not very sensitive to preclinical AD and did not outperform memory performance. As pointed out by the authors, if these biomarkers are to detect incipient brain disease that will lead to dementia long before the first symptoms arise, the prognostic accuracy of these biomarkers would need to be clearly superior to measures of behavioral symptoms (Schmand and others 2010).

In other recent studies using the ADNI database, there is a tendency for MRI measures to outperform CSF biomarkers in the prediction of clinical and cognitive change. Vemuri and others (2009a, 2009b) compared the predictive power of CSF biomarkers and structural MRI with regard to 2-year changes in Mini-Mental Status Examination (MMSE) and Clinical Dementia Ration–Sum of Boxes (CDR-sb). They found that MRI (ventricular volume) changed significantly over 1 year in healthy elderly, MCI patients, and AD patients, while the only significant change in biomarker levels was seen for T-tau in healthy controls. A measure of atrophy, the so-called Structural Abnormality Index (STAND), was a better predictor of subsequent functional change (CDR-SB and MMSE) than CSF biomarkers, but both provided information about future functional change even after adjusting for baseline cognitive performance (Vemuri and others 2009a). In another ADNI study, it was found that combining MR morphometry and CSF biomarkers yielded superior diagnostic accuracy of AD patients compared to controls, while MRI and PET measures were more predictive of clinical change than CSF measures (Walhovd and others 2010). Actually, even though the CSF measures added to the diagnostic accuracy at baseline, they did not predict 2-year clinical decline in MCI. These results are in accordance with an independent study by Sluimer and others (2010), where whole-brain atrophy rate quantified by MRI was associated with change in MMSE, but changes in the CSF biomarkers were not. Kohannim and others (2010) used machine learning to diagnose groups and predict clinical change in the ADNI sample and found that MRI generally was a more important predictor than CSF biomarkers. Jack and others (2009) did not use CSF measures but found that PiB retention was not significantly related to 1-year changes in CDR-sb or MMSE, while ventricular expansion correlated with both. In a final independent study, it was found that hippocampal volume and cortical thickness generally were better predictors of learning and episodic memory than CSF biomarkers, especially better than Aβ, also in MCI patients (Fjell and others 2008). Thus, there are several recent studies, based on the ADNI material and independent studies, indicating that MRI is more closely associated with clinical and cognitive change in MCI and AD than

CSF biomarkers, although some studies indicate that the combination may increase the predictive accuracy further (de Leon and others 2006; Sluimer and others 2010; Vemuri and others 2009b; Walhovd and others 2010).

Jack and others (2010) have proposed a model of dynamic biomarkers of the AD pathological cascade, incorporating the evidence pointing to the poor abilities of CSF biomarkers to predict functional and cognitive decline in AD. A main aspect of the model is that the impact of the different biomarkers is dynamic across the progression of the disease, and the same biomarkers are not important both early and later in the development. Accordingly, the impact of Aβ42 on brain atrophy is early in the disease, and the influence is then reduced as the patient approaches an AD diagnosis. This fits with a study by Mormino and others (2009), where it was concluded that the direct substrate of memory impairment in AD was hippocampal atrophy as quantified by MRI, not depositions of Aβ measured by PiB imaging. According to the model proposed by Jack and others (2010), Aβ does not exert a direct influence on cognitive function but will initiate a cascade of events that includes atrophy as measured by MRI, which probably is the most direct causal agent for memory loss and other cognitive decline. Thus, Aβ42 will be an inferior predictor of cognitive decline compared to MRI in MCI or at least AD but is more likely to be an early, presymptomatic marker of an ongoing disease process in the brain. As CSF Aβ42 levels will remain relatively stable from the MCI stage and onwards, changes in this biomarker are less relevant to monitor when the MCI diagnosis has been reached. In accordance with this, Jack and others (2009) found that PiB retention did not show larger 1-year changes in AD or MCI than in healthy controls in the ADNI study. Rabinovici and Jagust (2009) speculate that by the time patients are at the MCI stage or the mildest stages of AD, other pathological processes that are independent of fibrillar Aβ may already be in motion and that the therapeutic window for antiplaque interventions may already be closed.

The latter model should draw attention to a related and important issue, which is the question of how closely related the different CSF biomarkers and MRI-derived measures of brain structure and atrophy are. A relationship between CSF biomarker levels and hippocampal volume or atrophy has been shown in vivo (de Leon and others 2006; Fjell and others 2008; Hampel and others 2005). One ADNI study found hippocampal atrophy to be related to Aβ42 but not to tau (Schuff and others 2009), while another ADNI study found Aβ42 to be related to ventricular expansion (Chou and others 2009). Temporal atrophy rates were found to be related to tau and to the tau/Aβ42 ratio in 14 AD patients but not in 26 MCI patients from ADNI (Leow and others 2009). Also based on ADNI data, it was found that P-tau and P-tau/Aβ42 correlated weakly but significantly (r = –0.20 and –0.22, respectively) with right hippocampal volume in the AD group, while no significant correlations were found in the control or MCI group (Apostolova and others 2010). Sluimer and others (2010), in an independent study, did not find any correlation between Aβ42 and whole-brain atrophy rate in a sample of controls, MCI patients, and AD patients when the tests were adjusted for age, sex, and diagnosis. Surprisingly, higher levels of P-tau were mildly related to a lower whole-brain atrophy rate in the AD group. Change in MMSE was related to brain atrophy but not change in CSF biomarker levels. Thus, there appear to be relatively modest relationships between CSF biomarker levels and MRI measures of brain atrophy.

Fjell and others (2010a) used the ADNI study to address the question of whether CSF biomarkers are upstream events compared to MRI morphometry. They found that CSF biomarker levels in MCI could not account for group differences in brain morphometry at baseline but that CSF biomarker levels showed moderate relationships to longitudinal atrophy rates in numerous brain areas, not restricted to medial temporal structures (Fig. 8). However, CSF biomarkers were not more predictive of atrophy than baseline morphometry. Interestingly, MCI patients with levels of Aβ42 comparable with controls and of p-tau lower than controls still showed more atrophy than the controls. Thus, low levels of CSF Aβ42 do not seem to be a prerequisite for higher atrophy rates in MCI. In addition, morphometry predicted clinical change (in CDR-sb) better than did CSF biomarkers. These results indicate that morphometric changes in MCI and AD are probably not secondary to CSF biomarker changes, at least not in a subgroup of the patients, and that the 2 types of biomarkers yield complementary information. Within the model proposed by Jack and others (2010), one may speculate that atrophy independent of CSF Aβ42 levels is a sign that the disease is already at a stage where the role played by Aβ is less important and that other mechanisms are driving brain atrophy, leading to progressive loss of cognitive functions.

In a study related to the above described one, the same group found that levels of CSF Aβ42 below a certain empirically established threshold value were strongly related to brain atrophy in healthy controls (Fjell and others 2010c). Above this cut off, there were no significant relationships between CSF Aβ42 and rate of atrophy. The low Aβ42 group also showed tendencies for slightly more atrophy than the high group, but the 2 groups had indistinguishable memory performance. These results indicate that Aβ42 is related to atrophy only in a subgroup of cognitively normal elderly (about one third) but that significant atrophy is seen in healthy elderly with normal levels of CSF Aβ42. Thus, Aβ42 is unlikely to be a driving

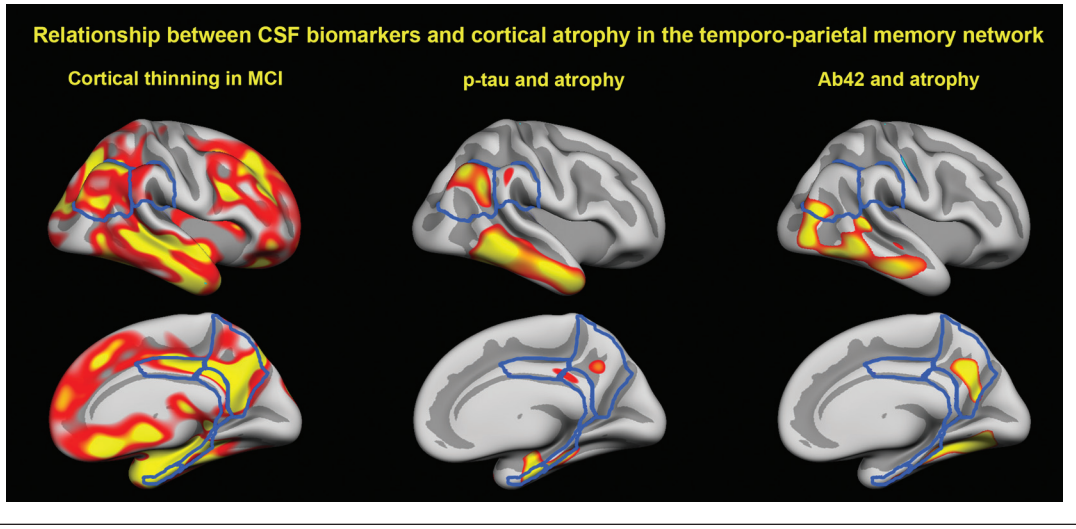

Figure 8. Relationship between cortical atrophy and CSF biomarkers in mild cognitive impairment. The temporoparietal network illustrated in Figure 7 is projected onto semi-inflated models of the right hemisphere. Left panel: Significantly thinner cortex in MCI patients than healthy controls is illustrated with yellow and red colors. As can be seen, all areas of the temporoparietal network are affected, especially the medial regions. Middle panel: Correlations between levels of p-tau and rate of atrophy in MCI patients from ADNI. Right panel: Correlations between levels of Aβ42 and rate of atrophy in MCI patients from ADNI. As can be seen, there is some overlap between the network and the areas showing correlations between CSF biomarker levels and atrophy, especially in the medial temporal cortex for p-tau. However, CSF biomarker levels generally seem at least as closely related to areas outside the network, for example, lateral temporal areas. All data are from Fjell and others (2010a).

force of atrophy in most cognitively normal elderly. The participants were followed for 2 years, but without even longer follow-up intervals, it is not possible to decide whether the normal controls with low Aβ42 levels eventually will develop AD. According to Jack and others (2009), the estimated average time taken to move from a negative to a positive PiB scan result is 23.8 years. Thus, substantially longer follow-up examinations are needed to decide on the significance of the low Aβ42 correlations in the cognitively healthy controls. However, the Aβ42 atrophy correlations were not strongest in the regions most affected early in AD, and the memory scores at baseline and after 1 year were normal. It can be argued that as Aβ42 is more diffusively spread out in the brain, one would not expect correlations with atrophy in the typical AD regions to be stronger than correlations with atrophy in other regions. However, as the earliest signs of atrophy as evidenced by MRI and by neuropsychological examinations are typically in the temporal lobes, it is certainly possible that the atrophy related to Aβ42 in other parts of the brain in the healthy controls is not of an AD-like character.

Also, research should focus on further development of novel biomarkers based on CSF samples and MRI. For instance, a recent study measured levels of 151 novel analytes from ante-mortem CSF samples from AD patients, patients with other neurodegenerative dementias, and cognitively normal subjects who had been followed longitudinally with repeated examinations (Hu and others 2010). The main conclusion was that AD was best distinguished from non-AD cases by a combination of traditional AD biomarkers and novel biomarkers. Six of the novel biomarkers (C3, CgA, IL-1α, I-309, NrCAM, and VEGF) also correlated with severity of cognitive impairment at CSF collection, and altered levels of IL-1α and TECK were associated with subsequent cognitive decline in 38 longitudinally followed MCI patients. Thus, enrichment of the collection of CSF biomarkers could aid in early detection, increase our understanding of the neurobiological mechanisms involved, and ultimately contribute to the development of better therapeutical interventions.

For MRI, diffusion tensor imaging (DTI) studies have shown that the white matter microstructure of MCI and AD patients is affected to a substantial degree and that this affection is at least partly independent of gray matter atrophy and Wallerian degeneration (Salat and others 2008). Since DTI is not yet an established AD biomarker, we have not included it in this review. Also, recent efforts focusing on the intensity of the MR signal in T1-weighted scans are promising and may add further to the possibility of using MRI as a tool for early detection of AD (Westlye and others 2010). Much more research is needed, but a

great advantage of this method is that quantification of signal intensity does not require extra scanning in that regular MRI sequences can be used. Further, as intensity measures are not related to morphometry, they are probably more sensitive to the microstructure of brain tissue than regular thickness and volume analyses and may thus constitute an even earlier marker of neurodegenerative processes than morphometric markers.

Thus, CSF and MRI biomarkers are extremely useful in research. CSF measures are applied in clinical settings in several countries, while the potential of MRI morphometry is increasingly often used. While both classes of biomarkers can be used to aid diagnosis and prediction of disease progression and conversion, MRI morphometry seems more appropriate as a marker of disease progression and predictor of cognitive and clinical change in MCI and AD groups. More normative studies are needed for MRI to fulfill its diagnostic potential also in clinical settings. Still, we know too little about the relationships between these biomarkers and the development of the disease, which neurobiological mechanisms each of them are sensitive to, and how to best utilize the information that these biomarkers give us in aiding presymptomatic diagnosis and intervention.

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