Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

Review

Structural imaging in early pre-states of dementia ☆

Charles D. Smith *

Alzheimer's Disease Center, Sanders-Brown Center on Aging, University of Kentucky, USA
Department of Neurology, University of Kentucky, USA
Magnetic Resonance Imaging Spectroscopy Center, Chandler Medical Center, University of Kentucky, USA

ABSTRACT

In this review focus is on structural imaging in the Alzheimer's disease (AD) pre-states, particularly cognitively normal (CN) persons at future dementia risk. Findings in mild cognitive impairment (MCI) are described here only for comparison with CN. Cited literature evidence and commentary address issues of structural imaging alterations in CN that precede MCI and AD, regional patterns of such alterations, and the time relationship between structural imaging alterations and the appearance of symptoms of AD, issues relevant to the conduct of future AD prevention trials. This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative disease.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

Interpretation of structural imaging in normal persons depends critically on beliefs concerning the individuals being imaged. Clarity in key general terms is needed before proceeding with a review of this topic, particularly because the same term may be used in both a theoretical and a practical sense in the literature without distinction. Cognitive normality, for example, may denote concepts of a particular range of expected behaviors attributed to brain performance together with theoretical factors contributing to variability in this performance. In practice cognitive normality may be assessed using interviews that probe relevant behaviors based on clinical knowledge and experience, or defined by scores on cognitive tests [1–3].

The mutual interaction between the theoretical and practical sense of cognitive normality (CN) in persons being imaged is revealed in its application to aging [4]. Is CN the ideal preservation of adult brain performance at any time point, in which case psychometric test norms might be independent of age, or should CN include acknowledgement of universally observed declines with age, particularly in certain domains such as processing speed, and hence interviews and cognitive tests should somehow adjust for age [5]?

A second general term relevant to the interpretation of structural imaging in cognitively normal persons at risk of AD is atrophy.

Atrophy as a medical concept refers to the reduction of brain substance relative to a presumed prior healthy normal state, and in addition implies that this reduction is an effect of disease rather than from a normal process, e.g., pruning due to developmental changes during puberty. Some studies are designed to assess longitudinal change and thus define an atrophy rate, but cross-sectional studies have to make an assumption of comparability with the normal control group when referring to atrophy [6].

A second issue related to atrophy is uncertainty in the *apportionment* of structural (e.g., volume, thickness or shape) differences between: (1) longstanding effects of brain development or prior injury, (2) ongoing alterations due to aging or to disease processes that are not primary to the study, and (3) the focus of the study, in the current instance risk of clinical AD. By clinical AD is meant the expression of the underlying pathophysiology of AD in the form of memory or other symptoms. Developmental endowments, life experiences or specific activities such as exercise could both protect the individual from clinical AD and subtly influence brain structures, e.g., by increasing cortical thickness, thus decreasing risk of AD even though they have no direct connection to AD pathophysiology [7]. The essence of the problem is whether one is "finding the beginning or predicting the future" [8]. However, the issue of apportionment is often not explicitly considered in the literature.

Finally, the general term "risk of AD" needs to be qualified by being specific about the time interval over which risk is defined. It is important to recognize the observation period of individual imaging studies because if they are short, there is little time for the underlying biology of AD to express itself, whereas if it is long, there is greater likelihood of cognitive decline or AD expression but also greater

---

* Room 62, MRISC (Davis-Mills Building) Chandler Medical Center, 800 Rose Street Lexington, Kentucky, 40536-0098, USA. Tel.: + 1 859 323 1113; fax: + 1 859 323 1068.
E-mail address: csmith@mri.uky.edu.

effects of competing risks, such as co-morbid cardiovascular disease. Likewise with the term "prediction", but that term is avoided herein.

This review will attempt to be mindful of the general terms CN, atrophy and AD risk as described above, while addressing the following questions: (1) Are there structural imaging alterations in CN that precede MCI and AD?, (2) Is there a regional pattern of such alterations and does this pattern provide insight into AD pathophysiology?, and (3) How long before symptoms of AD appear do structural alterations occur? A context for addressing these questions is provided first in terms of a simple model and a brief description of brain structural alterations in aging.

2. Conceptual model for AD pathology and expression

A basic framework for this article is illustrated in Fig. 1. In this simple model, the basic assumptions are that: (1) underlying AD neuropathology accumulates in many CN persons years before any cognitive symptoms or even measurable declines in cognitive testing occur, (2) the brain has intrinsic neural mechanisms that compensate for injury due to AD neuropathology (ADN) at all stages, e.g. by synaptic remodeling, and (3) the human brain has inborn, developmental and learned sources of cerebral reserve that may offset the

cognitive effects of injury, or, inversely, specific liabilities to the effects of ADN.

To clarify the framework, more needs to be said about "underlying AD pathology". Here the essence of AD pathology is taken to be the coupling between amyloid and tau. In this view beta-amyloid is not necessarily in the form of an accumulation (as in plaques) particularly in the earliest stages [9], but it must be present and coupled to abnormal tau for there to be AD pathology. This coupling could be mediated through, for example, prion protein [10,11]. Accumulations of both amyloid and tau are the evidence this coupling has occurred, and indicate the severity of the process and likely the duration. Atrophy is taken as evidence of synaptic and neuronal loss or shrinkage. These changes are accompanied by widespread tau aggregates within the affected region. The amount of amyloid in a region does not always correspond with atrophy—in this framework that is determined by the strength of the coupling with tau (the signature of an underlying process of synaptic and neuronal degeneration).

Neuropathologically amyloid alone is not sufficient. Most radionuclide-label imaging only assesses amyloid, so the coupling to tau is only a presumption. There is a strong correlation between tau measured in CSF and (decreased) CSF amyloid and (increased) brain amyloid. So while not perfect, the amyloid-tau relationship is
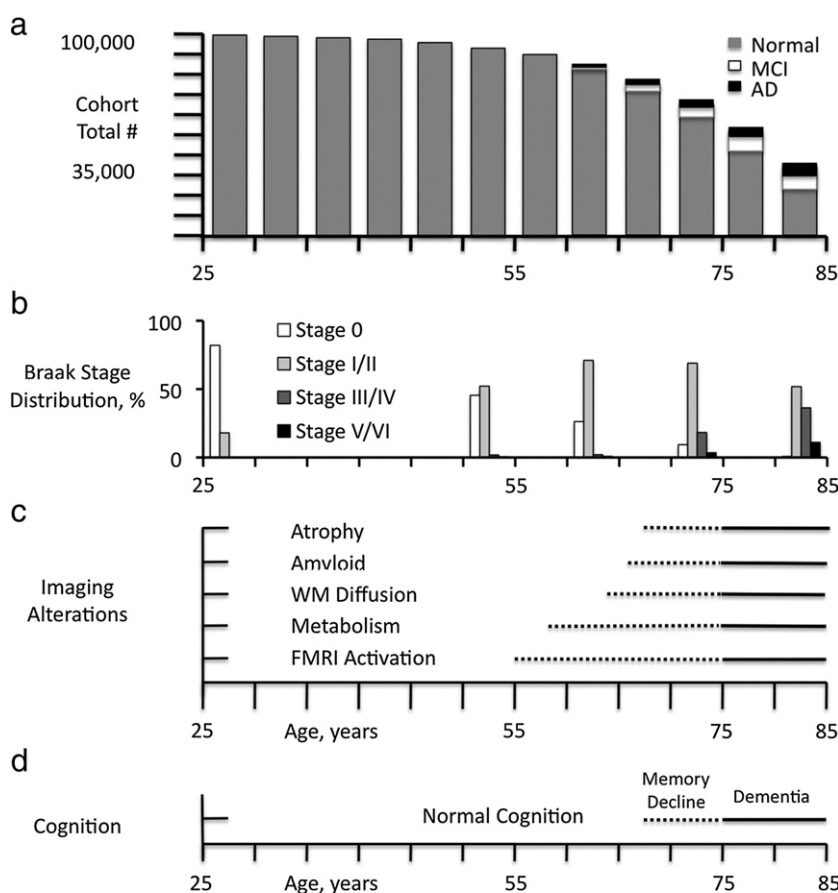

Fig. 1. Simple model of the AD timecourse (modified from [17]). a. Illustration of a statistical cohort of 100,000 persons beginning at the age of 25 years, with bar height representing the expected remaining population at each 5-year interval to age 85 based on the US census [88,89]. Each bar divided into proportionate parts representing the expected number of persons with AD (black) or MCI (white), or who remain normal (gray), based on US population model estimates [89,90]. The incidence of MCI and AD, and overall death rate accelerate after age 55. b. Percentage of Braak stages over the same age range based on Braak [89,91,92]. c. Conceptual diagram of the appearance of different image features by modality and age in a nominal cohort of persons who develop symptoms of AD at age 75 years, based on results in the current literature [17]. Dotted lines represent the variable appearance in individuals of the first detectable image changes within each modality, some of which may precede symptoms by several years. Solid lines represent the more certain appearance of alterations near the time symptoms appear (within a few years). The character and distribution of image alterations may change over time, e.g., in functional MRI activation, a subtlety not captured in this simplified diagram. d. In the nominal cohort, memory decline within the normal range of scores becomes detectable by sensitive tests and longitudinal assessment, later associated with a complaint noticed by a patient and outside observers, but without functional decline. Differences in rate of decline within the normal range may be dissected out using imaging and other biomarkers of AD neuropathology. These differences could result in a re-definition of CN.

strong. However, combined amyloid-tau labels such as FDDNP (2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethyli-dene)malononitrile ([(18)F]FDDNP)) may in the future prove better markers of AD pathology than amyloid-only agents [12]. Tau alone may be present in other conditions, but it is the coupling with beta-amyloid that is distinctive of AD pathology. Whether a decoupling might occur later in the process wherein further neurodegeneration becomes autocatalyzing is unknown.

Within this framework the mere presence of AD-like brain pathology by itself doesn't provide enough information to predict later dementia. It could be that the rate of accumulation is low, at least low enough to be successfully compensated, or that factors leading to an acceleration of the AD neuropathologic process are absent. Additional evidence that detected AD pathology is causing brain dysfunction may be needed in early cases, e.g., subtle cognitive impairment or at least decline, or brain network disruption detected by functional studies. However, it is reasonable to assume that the more pathology that is present, the more likely it is to be predictive of later AD, and that the absence of pathology is prognostically favorable [13].

Alzheimer's disease occurs in late life and thus in an environment of multiple competing causes of death (Fig. 1a). The earliest Alzheimer's disease neuropathology (Fig. 1b; nominal age range 55–65 years) occurs in middle adulthood, accompanied by "compensa-tory" imaging functional changes (Fig. 1c) but unaccompanied by brain volume loss on imaging or by diminished cognitive performance (Fig. 1d; [14]). As age and ADN increase (nominal age range 65–75 years), compensatory functional changes accompany early region-al brain atrophy associated with increasing global amyloid and regional tau accumulation. This stage represents the borderland between CN and early cognitive changes (memory decline ± MCI). Subsequent symptoms of cognitive impairment represent a critical point beyond which functional alterations, brain atrophy, and cognitive performance continually worsen (nominal age in this diagram 75 years). Functional losses in addition to compensations, increasing atrophy, and diminishing cognitive performance ensue in diagnosed clinical AD [15–17].

3. Structural imaging in aging

Well-characterized, longitudinally followed cognitively normal per-sons undergo brain volume losses with age, emphasizing the need for carefully selected age-matched controls in cross-sectional structural studies [18–20]. Only longitudinal studies can confirm baseline normal individuals who develop cognitive decline, MCI or AD at some future time. Retrospectively removing from analysis baseline structural scans from CN subjects who later develop MCI or AD could reduce effects of subtle disease-related volume losses, on the assumption these scans could skew regional volume distributions for CN [21]. Even when this step is taken, age-associated volume reductions are still observed. Gray matter volume reductions with age are generalized, without the relatively selective regional medial temporal, lateral temporal and parietal reductions characteristic of AD. Selective volume reduction with age also occurs in the deep frontal white matter and genu of the corpus callosum [21,22]. In one recent study cortical thickness was reduced predominantly in primary sensorimotor regions, but did not correlate with cognitive performance, whereas white matter integrity (assessed by fractional anisotropy) was reduced in genu of corpus callosum and in frontal white matter, and correlated with deficits of "cognitive control" in 38 CN elders [23].

Gray matter volume is not a static property and is potentially modifiable in aging. Erickson et al. found that vigorous levels of baseline physical activity (operationalized as blocks walked per week) were associated with increased cortical volume, particularly in premotor and prefrontal regions, 9 years later [24]. Gray matter volume increases are seen in aging even after short exercise interventions [25]. The main caveat to these studies is the possibility

that disease associated with brain volume losses biases toward non-participation in exercise.

Studies of hippocampal function (using cerebral blood pool volume measurements, CBV) suggest that losses with aging, including memory decline, may occur in the subiculum and dentate nucleus, whereas entorhinal functional changes are more specifically associ-ated with disease [26], particularly AD. Diabetes may be associated specifically with dentate gyrus functional decreases, hippocampal ischemia with CA1 decreases, and more generalized ischemia both with CA1 and subiculum sector decreases [27]. A structural study of hippocampal formation subfields in subjects carefully screened for vascular risk and diabetes demonstrated an age-related reduction in subiculum volume commensurate with global gray matter reductions, but relative preservation of other hippocampal segments (CA1 and dentate subfields; [28]). These results are consistent with the pattern of subfield changes associated with specific pathologies and with aging seen in CBV-based studies.

Involutional age-related erosion of brain reserve and mild cognitive decline appears to be a fact of life in brain aging [16]. However, more sensitive methods for evaluating gray and white matter structure, and finer resolution of these methods to the level of individual gray matter nuclei and subfields, are now demonstrating subtle structural alterations that can be apportioned to specific co-morbid pathologies. As discussed further on, risk factors for pathologies, e.g., maternal family history of AD, may be associated with alterations in gray matter in CN aged subjects. Thus, apportion-ment of structural alterations between aging involution and under-lying pathologies may soon be placed on a better scientific footing. Finally, effects of intervention such as exercise show that the aging brain may demonstrate plastic re-growth detectable as structural change.

4. Structural imaging in MCI

MCI is defined as a mild but definite decline from previous cognitive ability, confirmed by a reliable observer, and substantiated by deficits on neurocognitive testing [29–31]. Generally structural MRI studies have demonstrated decreased size of the hippocampal formation in MCI, by rating techniques [32] and in both region-of-interest [32–36] and voxel-based volumetric studies [32,37–41]. Studies are mixed regarding the presence of more global gray matter reductions in MCI compared to CN, e.g., in frontal and parietal regions [32,42,43]. Older adults who have memory complaints but do not meet formal criteria for MCI may nonetheless show similar gray matter reductions [32,44].

A recent study based on subjects from the landmark Alzheimer's disease Neuroimaging Initiative (ADNI) demonstrated that structural imaging data added significantly to the prediction of AD in patients with amnestic MCI [45]. The study used a modified version of freesurfer software [46] to compute cortical thickness and volumes from salient regions in subjects comparing CN and AD at baseline and over time using discriminant analysis. The discriminant functions were then used to compute risk scores for the MCI subjects. Subjects with high percentile scores were much more likely to convert to AD (odds ratios of 7.2 for highest vs. lowest percentiles for baseline scans, increasing to 12.0 when one-year longitudinal change was included in the analysis).

5. Structural imaging in CN persons at risk of AD

5.1. Overview

This section refers to imaging studies characterizing the brain in cognitively normal (also denoted by CN in context) subjects with the goal of characterizing risk for MCI or AD (cf. Fig. 1). Studies have operationalized CN by using expected cognitive test scores as they must,

as discussed in the Introduction. But this approach may not answer the question of whether the subjects "truly" have CN from an evolving theoretical point of view based on the neurobiology of AD, because there is always a better cognitive test, clinical interview, or longitudinal follow-up method for assessment of cognitive decline that might yet detect a subtle difference. This is a practical problem only if this potential difference would alter treatment or prevention, an important unresolved issue. Despite uncertainty, if risk stratification in defined CN subjects could be accomplished with reasonable accuracy using structural imaging, then interventions might be made to slow the progress of ADN or to enhance intrinsic brain compensatory mechanisms before symptoms, perhaps entirely preventing or at least delaying these symptoms [47,48]. This consideration motivates the search for structural, and other, biomarkers of AD in CN persons.

5.2. Brain structure and amyloid

The issue of defining CN mentioned in the Introduction has a specific application to presumed pre-state Alzheimer's disease (AD), because it has been found that brain amyloid accumulation is correlated negatively with memory scores in CN, although the scores are in the normal range [49]. Nonetheless, cognitive differences in general were not found between the 20–30% of CN with positive amyloid scans and the remainder with amyloid negative scans [13,50]. In a group of 95 CN subjects, 32 were found to have elevated ^{11}C-PIB amyloid brain labeling (PIB-positive; 34%). Again there were no cognitive differences or mean hippocampal volume differences between PIB-positive and PIB-negative CN, but there was a negative correlation between hippocampal volume and inferior temporal PIB retention in the former group [51]. Other recent studies have demonstrated decreased volume [52] or cortical thickness [53] in regions associated with early AD pathology (hippocampus, temporal neocortex, anterior and posterior cingulate) in CN subjects with increased amyloid burden. It was structural loss and not amyloid burden that correlated with cognitive performance in these studies, a finding that can be interpreted within our framework as the result of amyloid coupling to synaptic and neuronal degeneration associated with abnormal tau.

These findings suggest that in its early stages amyloid accumulation may not be associated with cognitive alterations but rather with subtle asymptomatic structural volume loss, implying ongoing brain injury that is somehow compensated. Evidence that structural alterations are associated with cognitive performance in CN subjects with increased amyloid burden, and amyloid burden with subsequent cognitive decline, suggests that this state of compensation is not long-lived [52]. The reverse conclusion, that amyloid accumulation is the consequence of volume loss, is less likely because there was no correlation of between brain volumes and amyloid burden in the frontal lobes, for example [51]. Nonetheless, amyloid accumulation correlating with hippocampal volume was located exclusively in local inferior temporal regions immediately upstream of the entorhinal cortex and hippocampus, not in other neocortical regions (Fig. 2).

Amyloid positive subjects are CN in one practical sense but not necessarily in a theoretical sense, because there is evidence of an underlying disease process, a process excluded from the concept of aging, which might cause the observed disease biomarker correlations with memory scores or with brain volumes. In this gray area lies the borderland between very early mild cognitive impairment (MCI) and CN aging.

5.3. Longitudinal structural studies

Annual rates of ventricular expansion have shown an increase in baseline CN subjects who received a clinical diagnosis of MCI within an average of 2.3 years, with an apparent acceleration of ventricular
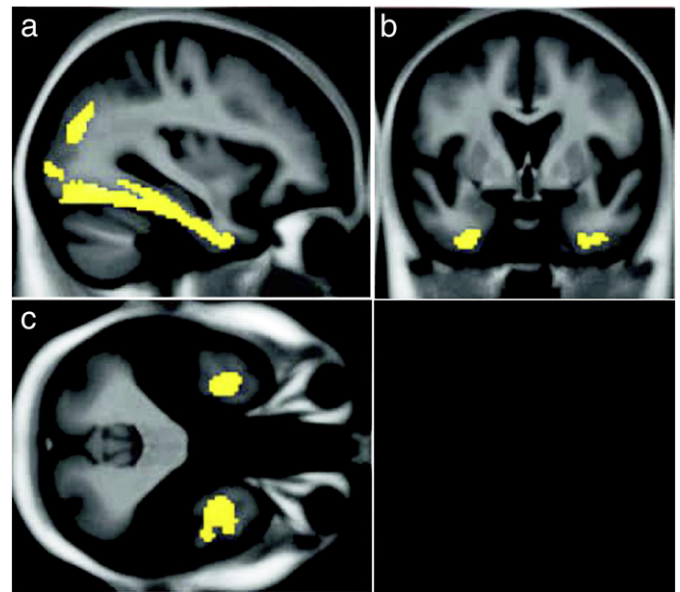

Fig. 2. Voxelwise negative correlation between amyloid burden in normal subjects with elevated global ^{11}C-PIB binding and hippocampal volume (r = −0.6, p = 0.02 using inferior temporal region). This relationship was not seen in subjects with MCI or AD, or in other brain regions outside of the inferomedial temporal lobe and parieto-occipital junction. Views: a—sagittal; b—coronal; c—axial.
With permission from [51].

volume expansion rate in the two-year lead-up to MCI diagnosis [51,54]. In a second study with 3.4 years follow-up from the last structural scan, ventricular expansion rate was associated with subsequent MCI diagnosis [55]. Volume loss rate in whole brain, hippocampus and entorhinal cortex was not associated with MCI conversion in this study, but regional medial temporal boundary shift atrophy rate has been associated with this conversion in over 6 years of observation [56].

Because the earliest ADN involves the entorhinal cortex, amygdala, hippocampus and other medial temporal structures, early atrophy in these regions could predict normal subjects who will later develop MCI or AD [57–61]. Medial temporal (particularly entorhinal) baseline volume also predicted decline on tests of delayed memory in CN subjects imaged at baseline and followed for 3.8 years [61,62].

An unexpected and significant early finding in the ADNI study was that temporal lobe atrophy predicted subsequent cognitive decline even in baseline cognitively normal participants in that study [41,61]. It has since been found that rate of atrophy in medial temporal structures in these subjects was associated with cognitive decline assessed by logical memory and AVLT tests [61,63]. These studies have been supplemented by analyses demonstrating that cortical thinning can be detected over 1 year in normal subjects, particularly in temporal and prefrontal regions [64]. These reductions were not confined to subjects with low CSF beta-amyloid levels, a marker of potential AD neuropathology, but in subjects with levels below a threshold, a correlation with cortical thinning was evident [65].

A longitudinal general community study of 511 nondemented subjects demonstrated that reduced global, hippocampal and amygdalar volumes at baseline were predictive of dementia within an average of 6 years [66], with the rate of volume change serving as an independent predictor [66,67]. Another recent study on 136 longitudinally-followed normal subjects undergoing a baseline structural scan demonstrated that volume in a combined region identified from these scans using VBM (anteromedial temporal and left angular gyrus gray matter; Fig. 3a) predicted MCI within 5 years with 76% accuracy. Predictive accuracy increased to 87% by combining volume in the combined region with a cognitive measure, raw Wechsler Memory

Scale score [66,68,69]. A study using a subset of these subjects for manual medial temporal tracing further supported these results [70].

A second potential structural signature of AD was found in a collection of cortical thickness measures in two independent groups of CN subjects using a retrospective comparison between subjects who developed AD versus groups of 25 control subjects who remained normal over the same observation periods of 7.1 (7 converters) and 11.1 (8 converters) years [71]. The sample sizes are relatively small and thus findings are prudently viewed as preliminary. The regions for cortical thickness comparison were established from previous studies of AD. Although medial temporal lobe (MTL), temporal pole, and superior frontal gyrus thickness was significantly less in CN to AD converters, averaging MTL with six additional region thickness values appeared to add further predictive power. The additional regions were inferior temporal, angular gyrus, supramarginal gyrus, superior parietal, precuneus, and middle frontal gyrus regions segmented in

freesurfer. High cortical thickness in some of these regions could have been protective for conversion to AD, because the conversion rate in 18% of subjects with this signature was zero (Fig. 3b).

5.4. Structural studies in CN involving genetics

Normal subjects with a maternal history of AD (+FHm) have demonstrated decreased cortical volumes compared to subjects with a paternal AD history or no family AD history, mainly in frontal regions [72,73]. Gray matter loss over 2 years in +FHm, however, displayed a somewhat different pattern, incorporating the dorsal frontal lobes but also the precuneus and inferotemporal cortex. A maternal inheritance influence on both earlier cortical development and later degenerative change is one explanation for these findings.

Apolipoprotein E (APOE) is a cholesterol carrier linked with cardiovascular disease and late-onset AD [74], particularly through the influence of the epsilon-4 allele on age of AD onset. Cognitive decline in CN APOE epsilon-4 carriers diverges from that of non-carriers before age 60 years according to one model based on longitudinal observation of approximately 5 years [75]. APOE allele status was not found to add to risk of future cognitive impairment in CN subjects over an observation period of 6 years when medial temporal volume, walking speed and logical memory II baseline scores were included in the analysis [76]. Increased amyloid burden has been associated in a dose-dependent manner with the epsilon-4 allele [77] in CN subjects. Reduced gray matter density in the right medial temporal lobe and in the frontotemporal cortex has been reported in CN carriers of a single epsilon-4 allele [78]. These findings suggest that APOE risk in CN subjects has proxies through amyloid accumulation and tissue loss in gray matter areas known to harbor neuropathology early in AD.

Familial Alzheimer's disease (FAD) involving single autosomal dominant gene mutations with early-onset dementia has been studied to provide insights into the far more common sporadic, polygenetic disease late-onset Alzheimer's disease (LOAD). Mutations in the amyloid precursor protein (APP) gene on chromosome 21 are quite rare. One study of presymptomatic APP V717G mutation carriers demonstrated slight baseline left hippocampal volume difference compared to controls with a rapid hippocampal volume loss (4.8% per year, n=3) as symptoms appeared over 2 years [79]. These subjects retrospectively had lower than expected global or memory scores despite normal day-to-day function and absence of reported memory decline. For comparison in a later study in the same family using a global brain volume technique, median global annualized volume change was 0.2%/year in 26 matched controls, 0.1%/year in 23 at-risk carriers who remained well, and 1.5%/per year in 5 who became symptomatic within 2 years of baseline scan [80]. These findings suggest the timeline for structural alterations in FAD due to APP mutations may be compressed compared to LOAD, with accelerated brain losses occurring in parallel with asymptomatic cognitive decline on testing, and the appearance of symptoms at an early age.

Of the three known FAD genes, the presenillin-1 (PSEN1) gene on chromosome 14 harbors the most common mutations. A study of six CN PSEN1 mutation carriers gathered from four families found increased cortical thickness in precuneus and parietotemporal regions approximately 10 years before expected symptoms, whereas symptomatic subjects demonstrated diffuse cortical thinning, including areas of increase found in asymptomatic subjects [81]. Other studies in FAD demonstrate cortical thinning in the precuneus at 4.1 years prior to symptoms, and at 1.8 years in the posterior cingulate in mutation carriers [82]. Thus the full trajectory of structural change in CN persons at risk of FAD is incomplete, and might include a very early phase of cortical swelling or enlargement.

A large family harboring the E280A PSEN1 mutation has been identified in Columbia, South America and characterized from the earliest, pre-symptomatic stages through dementia, serving as a
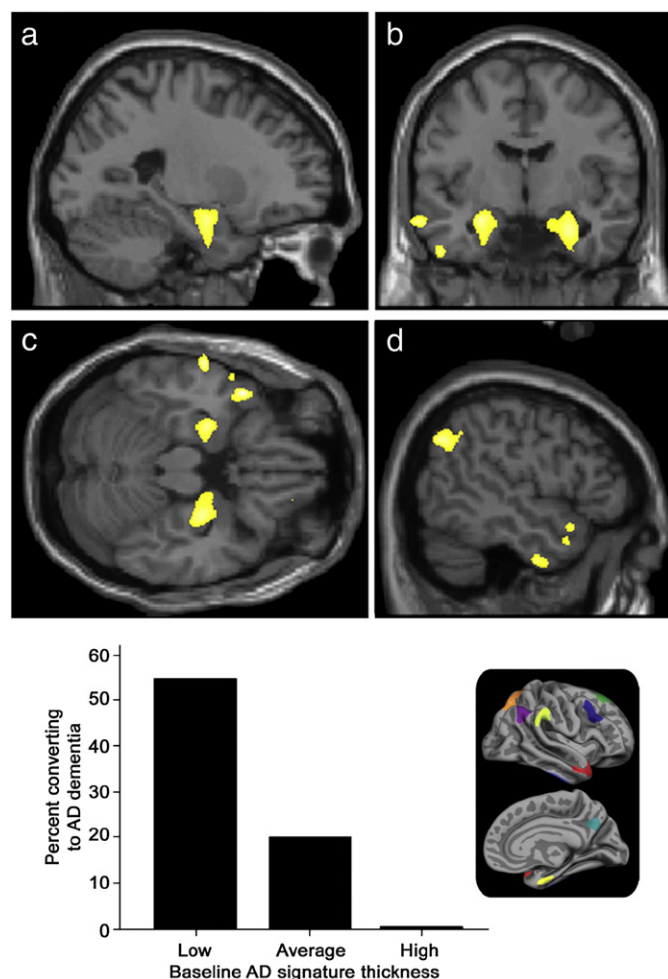

Fig. 3. Brain structural alterations in cognitively normal persons at risk of MCI or AD. a. Volume within a template identified by retrospective classification of baseline scans in CN subjects demonstrating a region of significantly reduced gray matter volume at baseline in those who later developed MCI within 5 years (yellow-white color scale). Views: a and d—sagittal; b—coronal; c—axial. Prediction accuracy of volume within this brain region alone was 76%, and 87% when combined with psychometric data (with permission from [21]). b. Decreasing rates of conversion from CN to AD over the observation period by average baseline cortical thickness, averaged across nine regions of interest, classified as *low* (1 SD below the entire cohort mean), *average* (within 1 SD of the mean), and *high* (1 SD above the mean—the rate was zero in this group). Regions of interest were selected by finding significant differences in cortical thickness between AD and CN in a prior study (inset left, nine color-coded regions projected on partially inflated brain surface image). Retrospective classification of baseline scans in CN subjects allowed calculation of thickness differences between baseline CN who developed AD vs. those who remained CN.
With permission from [71].

model for sporadic AD [83–85]. Structural studies in this large kindred (449 identified mutation carriers) have not yet been reported but will be extremely important because these subjects are likely to participate in clinical prevention trials in the near future. Family members who are PSEN1 carriers have a cognitive phenotype that parallels LOAD, a decade time scale for evolution of symptoms from earliest cognitive alterations, and certainty of dementia. In contrast, LOAD has no model that can approach the predictive power of an autosomal dominant mutation in patient selection for prevention trials [82,86]. Thus, in addition to the great medical significance of prevention in this particular family, there are many important implications of a successful prevention trial in this kindred for the worldwide family of the AD-at-risk.

6. Summary and future directions

In summary, responses to the three questions posed at the beginning of this review are:

(1) *Are there structural imaging alterations in CN that precede MCI and AD?* Approximately half of normal persons harbor Braak stage I–II neurofibrillary pathology by age 55 years, approximately 20 years before nominal onset of AD at 75 years (Fig. 1b). The neuropathologic burden increases progressively with age thereafter, at least in many persons. The exact manner of this progression is however unknown—whether it is linear, stuttering in bursts, or accelerating at some time. These unknowns become more important as we focus attention on AD neuropathology in CN subjects. Structural alterations in CN are observable well before dementia onset, and, when these alterations involve gray matter, may be associated with subtle cognitive decline in groups of clinically normal persons. Gray matter losses during this pre-state are also associated with fibrillary amyloid burden in the brain assessed by imaging or CSF studies, but these losses are more likely related to the amyloid coupling to abnormal tau than to amyloid per se. White matter diffusion changes are observed perhaps even earlier in interhemispheric and intrahemispheric long association tracts (cf. companion review on white matter neuroimaging in this issue).

(2) *Is there a regional pattern of such alterations and does this pattern provide insight into AD pathophysiology?* The most consistent finding is a decrease in medial temporal volume well before clinically symptomatic stages (MCI or AD). However cortical thinning has been detected in other regions in CN subjects, particularly the temporal and parietal neocortex. Gray matter atrophy appears in areas where AD neurofibrillary pathology is known to be heaviest, and is correlated both globally and locally with amyloid burden. Under our framework this association is mediated by the coupling between amyloid and abnormal tau, the latter representing the marker for synaptic and neuronal shrinkage and loss. For example, CN individuals with increased global amyloid burden demonstrate strong correlation between regional amyloid burden in the inferolateral temporal lobe and hippocampal atrophy. Thus structural imaging in gray matter, by itself, only confirms gross shrinkage of neurons and neuropil in a pattern consistent with expected local AD neuropathology. When marked by the detection of amyloid globally and locally, the strength of the inference underlying AD neuropathology associated with abnormal tau increases. Insight into how this coupling might come about is not forthcoming from these findings alone.

White matter alterations in association fibers appear to involve large stretches of the neocortex, but a more detailed review appearing elsewhere in this volume qualifies this conclusion. Early work suggests that white matter alterations may be reporting on altered axonal–myelin signaling interactions, perhaps an earlier indication of underlying AD neuropathology than gray matter atrophy.

(3) *How long before clinical symptoms of MCI or AD appear do structural alterations occur?* Approximately 5–10 years for gray matter atrophy, and perhaps longer for white matter diffusion alterations. This estimate suggests that interventions to prevent AD will need to begin early indeed, before the expected onset of even the earliest symptoms of cognitive impairment. One understudied area of structural imaging is the analysis of dynamic compensatory change (e.g., due to exercise or intensive educational activity) or components of cerebral reserve such as cortical thickness that may confer resistance to the effects of aging, AD, and co-morbid pathologies. Measures to enhance compensation for the presence of existing early AD neuropathology is an underexplored area of research in AD.

Many other questions regarding AD neuropathology in CN remain, some of which can be addressed with structural imaging. The answers are important for the rational consideration of AD prevention. The data presented here and elsewhere in this volume are sufficiently convincing that, for the purposes of including *and excluding* potential participants in clinical prevention trials, a combination of: (a) amyloid/FDDNP imaging [12,52] or CSF [87] and (b) a structural MRI pattern signature [67,68,71] would enhance the efficiency and speed of these trials. In a long-term trial, even expense might be reduced.

Conflict of interest

The author has no financial or ethical conflict of interest with regard to the content of this manuscript.

Acknowledgements

References

[1] R.J. Caselli, A.C. Dueck, D.E. Locke, C.R. Hoffman-Snyder, B.K. Woodruff, S.Z. Rapcsak, E.M. Reiman, Longitudinal modeling of frontal cognition in APOE {varepsilon}4 homozygotes, heterozygotes, and noncarriers, Neurology 76 (2011) 1383–1388.

[2] W.P. Goldman, J.L. Price, M. Storandt, E.A. Grant, D.W. McKeel Jr., E.H. Rubin, J.C. Morris, Absence of cognitive impairment or decline in preclinical Alzheimer's disease, Neurology 56 (2001) 361–367.

[3] R.T. Linn, P.A. Wolf, D.L. Bachman, J.E. Knoefel, J.L. Cobb, A.J. Belanger, E.F. Kaplan, R.B. D'Agostino, The 'preclinical phase' of probable Alzheimer's disease. A 13-year prospective study of the Framingham cohort, Arch. Neurol. 52 (1995) 485–490.

[4] A.M. Fjell, K.B. Walhovd, Structural brain changes in aging: courses, causes and cognitive consequences, Rev. Neurosci. 21 (2010) 187–221.

[5] T.A. Salthouse, Selective review of cognitive aging, J. Int. Neuropsychol. Soc. 16 (2010) 754–760.

[6] C.R. Jack Jr., M.M. Shiung, J.L. Gunter, P.C. O'Brien, S.D. Weigand, D.S. Knopman, B.F. Boeve, R.J. Ivnik, G.E. Smith, R.H. Cha, E.G. Tangalos, R.C. Petersen, Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD, Neurology 62 (2004) 591–600.

[7] Y. Stern, What is cognitive reserve? Theory and research application of the reserve concept, J. Int. Neuropsychol. Soc. 8 (2002) 448–460.

[8] R. Mayeux, S.A. Small, Finding the beginning or predicting the future? Arch. Neurol. 57 (2000) 783–784.

[9] H. Braak, K. Del Tredici, The pathological process underlying Alzheimer's disease in individuals under thirty, Acta Neuropathol. 121 (2011) 171–181.

[10] D.B. Freir, A.J. Nicoll, I. Klyubin, S. Panico, J.M. Mc Donald, E. Risse, E.A. Asante, M.A. Farrow, R.B. Sessions, H.R. Saibil, A.R. Clarke, M.J. Rowan, D.M. Walsh, J. Collinge, Interaction between prion protein and toxic amyloid beta assemblies can be therapeutically targeted at multiple sites, Nat. Commun. 2 (2011) 336.

[11] J. Lauren, D.A. Gimbel, H.B. Nygaard, J.W. Gilbert, S.M. Strittmatter, Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers, Nature 457 (2009) 1128–1132.

[12] M.N. Braskie, A.D. Klunder, K.M. Hayashi, H. Protas, V. Kepe, K.J. Miller, S.C. Huang, J.R. Barrio, L.M. Ercoli, P. Siddarth, N. Satyamurthy, J. Liu, A.W. Toga, S.Y. Bookheimer, G.W. Small, P.M. Thompson, Plaque and tangle imaging and cognition in normal aging and Alzheimer's disease, Neurobiol. Aging 31 (2010) 1669–1678.

[13] V.L. Villemagne, K.E. Pike, G. Chetelat, K.A. Ellis, R.S. Mulligan, P. Bourgeat, U. Ackermann, G. Jones, C. Szoeke, O. Salvado, R. Martins, G. O'Keefe, C.A. Mathis, W.E. Klunk, D. Ames, C.L. Masters, C.C. Rowe, Longitudinal assessment of Abeta and cognition in aging and Alzheimer disease, Ann. Neurol. 69 (2011) 181–192.

[14] C. Reitz, A.M. Brickman, T.R. Brown, J. Manly, C. DeCarli, S.A. Small, R. Mayeux, Linking hippocampal structure and function to memory performance in an aging population, Arch. Neurol. 66 (2009) 1385–1392.

[15] A.D. Smith, Imaging the progression of Alzheimer pathology through the brain, Proc. Natl. Acad. Sci. U.S.A. 99 (2002) 4135–4137.

[16] C.D. Smith, Mild cognitive impairment is too late: the case for presymptomatic detection and treatment for Alzheimer's disease, Cogn. Sci. 3 (2007) 127–177.

[17] C.D. Smith, Neuroimaging through the course of Alzheimer's disease, J. Alzheimers Dis. 19 (2010) 273–290.

[18] C.D. Good, I.S. Johnsrude, J. Ashburner, R.N. Henson, K.J. Friston, R.S. Frackowiak, A voxel-based morphometric study of ageing in 465 normal adult human brains, Neuroimage 14 (2001) 21–36.

[19] Y. Taki, R. Goto, A. Evans, A. Zijdenbos, P. Neelin, J. Lerch, K. Sato, S. Ono, S. Kinomura, M. Nakagawa, M. Sugiura, J. Watanabe, R. Kawashima, H. Fukuda, Voxel-based morphometry of human brain with age and cerebrovascular risk factors, Neurobiol. Aging 25 (2004) 455–463.

[20] A.F. Fotenos, A.Z. Snyder, L.E. Girton, J.C. Morris, R.L. Buckner, Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD, Neurology 64 (2005) 1032–1039.

[21] C.D. Smith, H. Chebrolu, D.R. Wekstein, F.A. Schmitt, W.R. Markesbery, Age and gender effects on human brain anatomy: a voxel-based morphometric study in healthy elderly, Neurobiol. Aging 31 (2006) 1122–1131.

[22] Y.C. Wu, A.S. Field, P.J. Whalen, A.L. Alexander, Age- and gender-related changes in the normal human brain using hybrid diffusion imaging (HYDI), Neuroimage 54 (2011) 1840–1853.

[23] D.A. Ziegler, O. Piguet, D.H. Salat, K. Prince, E. Connally, S. Corkin, Cognition in healthy aging is related to regional white matter integrity, but not cortical thickness, Neurobiol. Aging 31 (2010) 1912–1926.

[24] K.I. Erickson, C.A. Raji, O.L. Lopez, J.T. Becker, C. Rosano, A.B. Newman, H.M. Gach, P.M. Thompson, A.J. Ho, L.H. Kuller, Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study, Neurology 75 (2010) 1415–1422.

[25] S.J. Colcombe, K.I. Erickson, P.E. Scalf, J.S. Kim, R. Prakash, E. McAuley, S. Elavsky, D.X. Marquez, L. Hu, A.F. Kramer, Aerobic exercise training increases brain volume in aging humans, J. Gerontol. A Biol. Sci. Med. Sci. 61 (2006) 1166–1170.

[26] S.A. Small, W.Y. Tsai, R. DeLaPaz, R. Mayeux, Y. Stern, Imaging hippocampal function across the human life span: is memory decline normal or not? Ann. Neurol. 51 (2002) 290–295.

[27] W. Wu, A.M. Brickman, J. Luchsinger, P. Ferrazzano, P. Pichiule, M. Yoshita, T. Brown, C. DeCarli, C.A. Barnes, R. Mayeux, S.J. Vannucci, S.A. Small, The brain in the age of old: the hippocampal formation is targeted differentially by diseases of late life, Ann. Neurol. 64 (2008) 698–706.

[28] R. La Joie, M. Fouquet, F. Mezenge, B. Landeau, N. Villain, K. Mevel, A. Pelerin, F. Eustache, B. Desgranges, G. Chetelat, Differential effect of age on hippocampal subfields assessed using a new high-resolution 3 T MR sequence, Neuroimage 53 (2010) 506–514.

[29] C. Flicker, S.H. Ferris, B. Reisberg, Mild cognitive impairment in the elderly: predictors of dementia, Neurology 41 (1991) 1006–1009.

[30] R.C. Petersen, R. Doody, A. Kurz, R.C. Mohs, J.C. Morris, P.V. Rabins, K. Ritchie, M. Rossor, L. Thal, B. Winblad, Current concepts in mild cognitive impairment, Arch. Neurol. 58 (2001) 1985–1992.

[31] R.C. Petersen, J.E. Parisi, D.W. Dickson, K.A. Johnson, D.S. Knopman, B.F. Boeve, G.A. Jicha, R.J. Ivnik, G.E. Smith, E.G. Tangalos, H. Braak, E. Kokmen, Neuropathologic features of amnestic mild cognitive impairment, Arch. Neurol. 63 (2006) 665–672.

[32] J. Golomb, M.J. de Leon, A. Kluger, A.E. George, C. Tarshish, S.H. Ferris, Hippocampal atrophy in normal aging. An association with recent memory impairment, Arch. Neurol. 50 (1993) 967–973.

[33] M. Grundman, D. Sencakova, C.R. Jack Jr., R.C. Petersen, H.T. Kim, A. Schultz, M.F. Weiner, C. DeCarli, S.T. DeKosky, C. van Dyck, R.G. Thomas, L.J. Thal, Brain MRI hippocampal volume and prediction of clinical status in a mild cognitive impairment trial, J. Mol. Neurosci. 19 (2002) 23–27.

[34] J. Pantel, B. Kratz, M. Essig, J. Schroder, Parahippocampal volume deficits in subjects with aging-associated cognitive decline, Am. J. Psychiatry 160 (2003) 379–382.

[35] B.C. Dickerson, D.H. Salat, J.F. Bates, M. Atiya, R.J. Killiany, D.N. Greve, A.M. Dale, C.E. Stern, D. Blacker, M.S. Albert, R.A. Sperling, Medial temporal lobe function and structure in mild cognitive impairment, Ann. Neurol. 56 (2004) 27–35.

[36] C.R. Jack Jr., R.C. Petersen, Y.C. Xu, S.C. Waring, P.C. O'Brien, E.G. Tangalos, G.E. Smith, R.J. Ivnik, E. Kokmen, Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease, Neurology 49 (1997) 786–794.

[37] G. Chetelat, B. Desgranges, V. De La Sayette, F. Viader, F. Eustache, J.C. Baron, Mapping gray matter loss with voxel-based morphometry in mild cognitive impairment, Neuroreport 13 (2002) 1939–1943.

[38] G.B. Karas, P. Scheltens, S.A. Rombouts, P.J. Visser, R.A. van Schijndel, N.C. Fox, F. Barkhof, Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease, Neuroimage 23 (2004) 708–716.

[39] C. Pennanen, C. Testa, M.P. Laakso, M. Hallikainen, E.L. Helkala, T. Hanninen, M. Kivipelto, M. Kononen, A. Nissinen, S. Tervo, M. Vanhanen, R. Vanninen, G.B. Frisoni, H. Soininen, A voxel based morphometry study on mild cognitive impairment, J. Neurol. Neurosurg. Psychiatry 76 (2005) 11–14.

[40] J.T. Becker, S.W. Davis, K.M. Hayashi, C.C. Meltzer, A.W. Toga, O.L. Lopez, P.M. Thompson, Three-dimensional patterns of hippocampal atrophy in mild cognitive impairment, Arch. Neurol. 63 (2006) 97–101.

[41] X. Hua, A.D. Leow, N. Parikshak, S. Lee, M.C. Chiang, A.W. Toga, C.R. Jack Jr., M.W. Weiner, P.M. Thompson, Tensor-based morphometry as a neuroimaging biomarker for Alzheimer's disease: an MRI study of 676 AD, MCI, and normal subjects, Neuroimage 43 (2008) 458–469.

[42] A. Duarte, S. Hayasaka, A. Du, N. Schuff, G.H. Jahng, J. Kramer, B. Miller, M. Weiner, Volumetric correlates of memory and executive function in normal elderly, mild cognitive impairment and Alzheimer's disease, Neurosci. Lett. 406 (2006) 60–65.

[43] L.G. Apostolova, C.A. Steiner, G.G. Akopyan, R.A. Dutton, K.M. Hayashi, A.W. Toga, J.L. Cummings, P.M. Thompson, Three-dimensional gray matter atrophy mapping in mild cognitive impairment and mild Alzheimer disease, Arch. Neurol. 64 (2007) 1489–1495.

[44] A.J. Saykin, H.A. Wishart, L.A. Rabin, R.B. Santulli, L.A. Flashman, J.D. West, T.L. McHugh, A.C. Mamourian, Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI, Neurology 67 (2006) 834–842.

[45] L.K. McEvoy, D. Holland, D.J. Hagler Jr., C. Fennema-Notestine, J.B. Brewer, A.M. Dale, Mild cognitive impairment: baseline and longitudinal structural MR imaging measures improve predictive prognosis, Radiology 259 (2011) 834–843.

[46] N. Makris, J. Kaiser, C. Haselgrove, L.J. Seidman, J. Biederman, D. Boriel, E.M. Valera, G.M. Papadimitriou, B. Fischl, V.S. Caviness Jr., D.N. Kennedy, Human cerebral cortex: a system for the integration of volume- and surface-based representations, Neuroimage 33 (2006) 139–153.

[47] Z.S. Khachaturian, D. Barnes, R. Einstein, S. Johnson, V. Lee, A. Roses, M.A. Sager, W.R. Shankle, P.J. Snyder, R.C. Petersen, G. Schellenberg, J. Trojanowski, P. Aisen, M.S. Albert, J.C. Breitner, N. Buckholtz, M. Carrillo, S. Ferris, B.D. Greenberg, M. Grundman, A.S. Khachaturian, L.H. Kuller, O.L. Lopez, P. Maruff, R.C. Mohs, M. Morrison-Bogorad, C. Phelps, E. Reiman, M. Sabbagh, M. Sano, L.S. Schneider, E. Siemers, P. Tariot, J. Touchon, B. Vellas, L.J. Bain, Developing a national strategy to prevent dementia: Leon Thal Symposium 2009, Alzheimers Dement. 6 (2010) 89–97.

[48] E.M. Reiman, J.B. Langbaum, P.N. Tariot, Alzheimer's prevention initiative: a proposal to evaluate presymptomatic treatments as quickly as possible, Biomark. Med. 4 (2010) 3–14.

[49] E.C. Mormino, J.T. Kluth, C.M. Madison, G.D. Rabinovici, S.L. Baker, B.L. Miller, R.A. Koeppe, C.A. Mathis, M.W. Weiner, W.J. Jagust, Episodic memory loss is related to hippocampal-mediated {beta}-amyloid deposition in elderly subjects, Brain 132 (2008) 1310–1323.

[50] C.R. Jack Jr., V.J. Lowe, M.L. Senjem, S.D. Weigand, B.J. Kemp, M.M. Shiung, D.S. Knopman, B.F. Boeve, W.E. Klunk, C.A. Mathis, R.C. Petersen, 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment, Brain 131 (2008) 665–680.

[51] P. Bourgeat, G. Chetelat, V.L. Villemagne, J. Fripp, P. Raniga, K. Pike, O. Acosta, C. Szoeke, S. Ourselin, D. Ames, K.A. Ellis, R.N. Martins, C.L. Masters, C.C. Rowe, O. Salvado, A.R. Group, Beta-amyloid burden in the temporal neocortex is related to hippocampal atrophy in elderly subjects without dementia, Neurology 74 (2010) 121–127.

[52] M. Storandt, M.A. Mintun, D. Head, J.C. Morris, Cognitive decline and brain volume loss as signatures of cerebral amyloid-beta peptide deposition identified with Pittsburgh compound B: cognitive decline associated with Abeta deposition, Arch. Neurol. 66 (2009) 1476–1481.

[53] J.A. Becker, T. Hedden, J. Carmasin, J. Maye, D.M. Rentz, D. Putcha, B. Fischl, D.N. Greve, G.A. Marshall, S. Salloway, D. Marks, R.L. Buckner, R.A. Sperling, K.A. Johnson, Amyloid-beta associated cortical thinning in clinically normal elderly, Ann. Neurol. 69 (2011) 1032–1042.

[54] N.E. Carlson, M.M. Moore, A. Dame, D. Howieson, L.C. Silbert, J.F. Quinn, J.A. Kaye, Trajectories of brain loss in aging and the development of cognitive impairment, Neurology 70 (2008) 828–833.

[55] C.R. Jack Jr., M.M. Shiung, S.D. Weigand, P.C. O'Brien, J.L. Gunter, B.F. Boeve, D.S. Knopman, G.E. Smith, R.J. Ivnik, E.G. Tangalos, R.C. Petersen, Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnestic MCI, Neurology 65 (2005) 1227–1231.

[56] H. Rusinek, S. De Santi, D. Frid, W.H. Tsui, C.Y. Tarshish, A. Convit, M.J. de Leon, Regional brain atrophy rate predicts future cognitive decline: 6-year longitudinal MR imaging study of normal aging, Radiology 229 (2003) 691–696.

[57] J.A. Kaye, T. Swihart, D. Howieson, A. Dame, M.M. Moore, T. Karnos, R. Camicioli, M. Ball, B. Oken, G. Sexton, Volume loss of the hippocampus and temporal lobe in healthy elderly persons destined to develop dementia, Neurology 48 (1997) 1297–1304.

[58] C.R. Jack Jr., M.M. Shiung, S.D. Weigand, P.C. O'Brien, J.L. Gunter, B.F. Boeve, D.S. Knopman, G.E. Smith, R.J. Ivnik, E.G. Tangalos, R.C. Petersen, C.R. Jack Jr., M.M. Shiung, J.L. Gunter, P.C. O'Brien, S.D. Weigand, D.S. Knopman, B.F. Boeve, R.J. Ivnik, G.E. Smith, R.H. Cha, E.G. Tangalos, R.C. Petersen, Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnestic MCI, Neurology 65 (2005) 1227–1231.

[59] S. Adak, K. Illouz, W. Gorman, R. Tandon, E.A. Zimmerman, R. Guariglia, M.M. Moore, J.A. Kaye, Predicting the rate of cognitive decline in aging and early Alzheimer disease, Neurology 63 (2004) 108–114.

[60] L.G. Apostolova, L. Mosconi, P.M. Thompson, A.E. Green, K.S. Hwang, A. Ramirez, R. Mistur, W.H. Tsui, M.J. de Leon, Subregional hippocampal atrophy predicts Alzheimer's dementia in the cognitively normal, Neurobiol. Aging (2008).

[61] R. Schlosser, M. Hutchinson, S. Joseffer, H. Rusinek, A. Saarimaki, J. Stevenson, S.L. Dewey, J.D. Brodie, Functional magnetic resonance imaging of human brain activity in a verbal fluency task, J. Neurol. Neurosurg. Psychiatry 64 (1998) 492–498.

[62] W. Jagust, A. Gitcho, F. Sun, B. Kuczynski, D. Mungas, M. Haan, Brain imaging evidence of preclinical Alzheimer's disease in normal aging, Ann. Neurol. 59 (2006) 673–681.

[63] E.A. Murphy, D. Holland, M. Donohue, L.K. McEvoy, D.J. Hagler Jr., A.M. Dale, J.B. Brewer, Alzheimer's Disease Neuroimaging Initiative, Six-month atrophy in MTL structures is associated with subsequent memory decline in elderly controls, Neuroimage 53 (2010) 1310–1317.

[64] A.M. Fjell, K.B. Walhovd, C. Fennema-Notestine, L.K. McEvoy, D.J. Hagler, D. Holland, J.B. Brewer, A.M. Dale, One-year brain atrophy evident in healthy aging, J. Neurosci. 29 (2009) 15223–15231.

[65] A.M. Fjell, K.B. Walhovd, C. Fennema-Notestine, L.K. McEvoy, D.J. Hagler, D. Holland, K. Blennow, J.B. Brewer, A.M. Dale, Brain atrophy in healthy aging is related to CSF levels of Abeta1-42, Cereb. Cortex 20 (2010) 2069–2079.

[66] T. den Heijer, M.I. Geerlings, F.E. Hoebeek, A. Hofman, P.J. Koudstaal, M.M. Breteler, Use of hippocampal and amygdalar volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly people, Arch. Gen. Psychiatry 63 (2006) 57–62.

[67] T. den Heijer, F. van der Lijn, P.J. Koudstaal, A. Hofman, A. van der Lugt, G.P. Krestin, W.J. Niessen, M.M. Breteler, A 10-year follow-up of hippocampal volume on magnetic resonance imaging in early dementia and cognitive decline, Brain 133 (2010) 1163–1172.

[68] C.D. Smith, H. Chebrolu, D.R. Wekstein, F.A. Schmitt, G.A. Jicha, G. Cooper, W.R. Markesbery, Brain structural alterations before mild cognitive impairment, Neurology 68 (2007) 1268–1273.

[69] C.D. Smith, H. Chebrolu, W.R. Markesbery, J. Liu, Improved Predictive Model for Presymptomatic Mild Cognitive Impairment and Alzheimer's Disease, Neurological Research 30 (2008) 1091–1096.

[70] S.B. Martin, C.D. Smith, H.R. Collins, F.A. Schmitt, B.T. Gold, Evidence that volume of anterior medial temporal lobe is reduced in seniors destined for mild cognitive impairment, Neurobiol. Aging 31 (2010) 1099–1106.

[71] B.C. Dickerson, T.R. Stoub, R.C. Shah, R.A. Sperling, R.J. Killiany, M.S. Albert, B.T. Hyman, D. Blacker, L. Detoledo-Morrell, Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults, Neurology 76 (2011) 1395–1402.

[72] R.A. Honea, R.H. Swerdlow, E.D. Vidoni, J.M. Burns, Progressive regional atrophy in normal adults with a maternal history of Alzheimer disease, Neurology 76 (2011) 822–829.

[73] R.A. Honea, R.H. Swerdlow, E.D. Vidoni, J. Goodwin, J.M. Burns, Reduced gray matter volume in normal adults with a maternal family history of Alzheimer disease, Neurology 74 (2010) 113–120.

[74] D.L. Sparks, Coronary artery disease, hypertension, ApoE, and cholesterol: a link to Alzheimer's disease? Ann. N. Y. Acad. Sci. 826 (1997) 128–146.

[75] R.J. Caselli, A.C. Dueck, D. Osborne, M.N. Sabbagh, D.J. Connor, G.L. Ahern, L.C. Baxter, S.Z. Rapcsak, J. Shi, B.K. Woodruff, D.E. Locke, C.H. Snyder, G.E. Alexander, R. Rademakers, E.M. Reiman, Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect, N. Engl. J. Med. 361 (2009) 255–263.

[76] S. Marquis, M.M. Moore, D.B. Howieson, G. Sexton, H. Payami, J.A. Kaye, R. Camicioli, Independent predictors of cognitive decline in healthy elderly persons, Arch. Neurol. 59 (2002) 601–606.

[77] E.M. Reiman, K. Chen, X. Liu, D. Bandy, M. Yu, W. Lee, N. Ayutyanont, J. Keppler, S.A. Reeder, J.B. Langbaum, G.E. Alexander, W.E. Klunk, C.A. Mathis, J.C. Price, H.J. Aizenstein, S.T. DeKosky, R.J. Caselli, Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease, Proc. Natl. Acad. Sci. U.S.A. 106 (2009) 6820–6825.

[78] H.A. Wishart, A.J. Saykin, T.W. McAllister, L.A. Rabin, B.C. McDonald, L.A. Flashman, R.M. Roth, A.C. Mamourian, G.J. Tsongalis, C.H. Rhodes, Regional brain atrophy in cognitively intact adults with a single APOE epsilon4 allele, Neurology 67 (2006) 1221–1224.

[79] N.C. Fox, E.K. Warrington, J.M. Stevens, M.N. Rossor, Atrophy of the hippocampal formation in early familial Alzheimer's disease. A longitudinal MRI study of at-risk members of a family with an amyloid precursor protein 717Val-Gly mutation, Ann. N.Y.Acad. Sci. 777 (1996) 226–232.

[80] N.C. Fox, E.K. Warrington, M.N. Rossor, Serial magnetic resonance imaging of cerebral atrophy in preclinical Alzheimer's disease, Lancet 353 (1999) 2125.

[81] J. Fortea, R. Sala-Llonch, D. Bartres-Faz, B. Bosch, A. Llado, N. Bargallo, J.L. Molinuevo, R. Sanchez-Valle, Increased cortical thickness and caudate volume precede atrophy in PSEN1 mutation carriers, J. Alzheimers Dis. 22 (2010) 909–922.

[81] W.D. Knight, L.G. Kim, A. Douiri, C. Frost, M.N. Rossor, N.C. Fox, Acceleration of cortical thinning in familial Alzheimer's disease, Neurobiol. Aging 32 (2011) 1765–1773.

[83] F. Lopera, A. Ardilla, A. Martinez, L. Madrigal, J.C. Arango-Viana, C.A. Lemere, J.C. Arango-Lasprilla, L. Hincapie, M. Arcos-Burgos, J.E. Ossa, I.M. Behrens, J. Norton, C. Lendon, A.M. Goate, A. Ruiz-Linares, M. Rosselli, K.S. Kosik, Clinical features of early-onset Alzheimer disease in a large kindred with an E280A presenilin-1 mutation, Jama 277 (1997) 793–799.

[84] N. Acosta-Baena, D. Sepulveda-Falla, C.M. Lopera-Gomez, M.C. Jaramillo-Elorza, S. Moreno, D.C. Aguirre-Acevedo, A. Saldarriaga, F. Lopera, Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study, Lancet Neurol. 10 (2011) 213–220.

[85] Y.T. Quiroz, A.E. Budson, K. Celone, A. Ruiz, R. Newmark, G. Castrillon, F. Lopera, C.E. Stern, Hippocampal hyperactivation in presymptomatic familial Alzheimer's disease, Ann. Neurol. 68 (2010) 865–875.

[86] J.L. Cummings, R. Doody, C. Clark, Disease-modifying therapies for Alzheimer disease: challenges to early intervention, Neurology 69 (2007) 1622–1634.

[87] L.M. Shaw, H. Vanderstichele, M. Knapik-Czajka, M. Figurski, E. Coart, K. Blennow, H. Soares, A.J. Simon, P. Lewczuk, R.A. Dean, E. Siemers, W. Potter, V.M. Lee, J.Q. Trojanowski, Qualification of the analytical and clinical performance of CSF biomarker analyses in ADNI, Acta Neuropathol. 121 (2011) 597–609.

[88] D.L. Hoyert, H.-C. Kung, B.L. Smith, Deaths: Preliminary Data for 2003 National Vital Statistics Reports, 53, 2005.

[89] B.G. Knight, M. Silverstein, T.J. McCallum, L.S. Fox, A sociocultural stress and coping model for mental health outcomes among African American caregivers in Southern California, J. Gerontol. B Psychol. Sci. Soc. Sci. 55 (2000) P142–P150.

[90] J.A. Yesavage, R. O'Hara, H. Kraemer, A. Noda, J.L. Taylor, S. Ferris, M.C. Gely-Nargeot, A. Rosen, L. Friedman, J. Sheikh, C. Derouesne, Modeling the prevalence and incidence of Alzheimer's disease and mild cognitive impairment, J. Psychiatr. Res. 36 (2002) 281–286.

[91] H. Braak, E. Braak, Frequency of stages of Alzheimer-related lesions of different age categories, Neurobiol. Aging 18 (1997) 351–357.

[92] T.G. Ohm, H. Muller, H. Braak, J. Bohl, Close-meshed prevalence rates of different stages as a tool to uncover the rate of Alzheimer's disease-related neurofibrillary changes, Neuroscience 64 (1995) 209–217.