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Imaging the Alzheimer Brain

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Abstract

This supplement to the Journal of Alzheimer's Disease contains more than half of the chapters from The Handbook of Imaging the Alzheimer Brain, which was first presented at the International Conference on Alzheimer's Disease in Paris, in July, 2011.

While the Handbook contains 27 chapters that are modified articles from 2009, 2010, and 2011 issues of the Journal of Alzheimer's Disease, this supplement contains the 31 new chapters of that book and an introductory article drawn from the introductions to each section of the book.

The Handbook was designed to provide a multilevel overview of the full field of brain imaging related to Alzheimer's disease (AD). The Handbook, as well as this supplement, contains both reviews of the basic concepts of imaging, the latest developments in imaging, and various discussions and perspectives of the problems of the field and promising directions.

The Handbook was designed to be useful for students and clinicians interested in AD as well as scientists studying the brain and pathology related to AD.

1: Imaging the Alzheimer Brain: The Pathology and Pathophysiological Bases of Alzheimer's Disease: Implications for Advancing Diagnostic Imaging

Milan Sanchez M, Hippocampal Network Alterations in Alzheimer's Disease and Down Syndrome: Basis From Structure to Therapy [1].

Cohen et al., Cerebrospinal fluid biomarkers of neurodegenerative and ventricular changes in the elderly (see: [2]).

On November 3, 1906, in a presentation for the South-West German Society of Alienists (the term used at that time for superintendents of insane asylums) in Tübingen, Germany, Alois Alzheimer, presented a paper entitled “Über eine eigenartige Erkrankung der Hirnrinde” (“regarding a peculiar disease of the cortex”). In this paper, he described for the first time a constellation of symptoms in a 51 year-old woman that was associated at autopsy with several new neuropathological changes. This patient initially showed suspiciousness of her husband, and then soon developed a rapidly increasing memory impairment, disorientation, and further paranoia with progressive agitation. Clinically, the most severe disturbance was in her ability to encode information, immediately forgetting things after clearly perceiving them. The condition progressed to utter bewilderment with complete disorientation to time and place, leading to a terminal state after 4.5 years. The original description of her brain included both macro and microscopic pathology. Although postmortem examination showed generalized atrophy of the brain, there was no macroscopic focal degeneration. Upon preparation of tissue samples, neuritic plaques, neurofibrillary

tangles (NFTs), neuropil threads, and reactive gliosis were evident and appeared to be occurring with the deposition of a “pathological metabolic substance in the neuron” [3, 4].

The modern era of interest was ushered in when in 1968 Blessed, Tomlinson, and Roth linked the common, progressive dementia found in the elderly to the same type of pathology described originally by Alzheimer [5]. Today, the disease originally described by Alzheimer in a younger individual is no longer unique or infrequent. The incidence of AD has progressively increased with the great extension of longevity in most parts of the world over the last 100 years [6]. Now, AD is the most common cause of dementia, and reported as the sixth leading cause of all deaths in the United States (Centers for Disease Control (CDC) mortality data, 74,632 deaths attributed to AD in 2007). However, by another analysis, AD is now associated with more deaths than heart disease (in 2007, the CDC reported 2,423,712 total deaths and 616,067 deaths related to heart disease, 25.4% of all US deaths, but at the same time, the Alzheimer's Association estimated that 5 million individuals had AD in the US, with an 8 year life expectancy, leading to the calculation that 625,000 deaths would be AD-related, which is 25.8% of all deaths). According to the World Health Organization (WHO), in 2008, there were more than a half million deaths in the world attributed to AD, a number still greatly underestimating the occurrence of AD. These already grim figures do not take into account the psychological and social burdens of AD. Overall, AD patients are more likely to have mental health conditions, neurological conditions, cognitive disorders, cerebrovascular disease, diabetes with acute complications, and injuries resulting in annual costs for AD patients being 34% higher than for matched controls [7]. Individuals with AD have higher healthcare costs and utilization than demographically-matched Medicare beneficiaries and even after adjusting for comorbid illnesses sustain more emergency room visits and inpatient admissions [8]. As the US population ages, AD rates are expected to quadruple over the next 50 years [9]. In order to diminish or even sustain the current level of the devastating worldwide social and economic impact of AD, there is an urgent need to further our understanding and expedite research and development on all aspects of AD.

Thanks to enormous advances in science, engineering, and technology in recent decades, new imaging methods have been developed. The purpose of the Handbook of Imaging the Alzheimer Brain and this supplement of the Journal of Alzheimer's Disease is to present the developments and advances in numerous imaging modalities that are currently being used to increase our understanding of the pathophysiological basis of AD and drive us toward new therapies for this complex brain disorder. The chapters of this collection clearly show that multiple imaging systems are now available for helping understand, diagnose, and treat AD.

Understanding the Pathological Basis of AD

The fundamental pathological changes in AD are senile plaques (SPs), both primitive and neuritic, and neurofibrillary pathology (NP), which includes both NFTs and neuropil threads (see [10]). The SPs are thought to progress from a primitive to a neuritic form which is composed of several pathological entities including aggregated extra-cellular amyloid-beta (A β) protein, inflammatory glial cells, and pathological neurites containing hyper-phosphorylated microtubule-associated protein tau [11, 12]. The NP is primarily inside neurons and composed principally of paired-helical filaments (PHFs) which are composed of hyper-phosphorylated tau [12, 13]. The relationship between these two pathological entities, SPs and NP, is not fully understood. The neuropil threads (probably composed the same as pathological neurites) are inside dendrites and linked from the neuropil through dendritic shafts to the neuronal cell bodies which contain the NFTs [14]. These fundamental pathological entities are thought to begin their formation long before the first psycho-social symptoms appear [15]. A core concern in understanding AD has been the question of the nature, origin, and development of AD pathology. There have been two schools of thought concerning the development of AD pathology, one that has focused on the amyloid

pathology [16] and another that has considered the neurofibrillary pathology to be the fundamental problem [15]. Resolution of the relationship between these components may lead to the understanding of AD that has so far eluded research.

The New Perspective on the Continuum of AD

A new perspective has been developing in the AD field, that there must be consideration for the earliest developments of pathological changes associated with this disease. The pioneering discovery in this direction was from the Nun Study, which showed the linguistic ability evident in the writing in women in their early 20's could be associated with their later development of AD-related dementia [17]. This finding is complemented by recent pathological studies which have found that A β decreases in the spinal fluid likely occur as early as the fourth decade of life [18] and pathological findings of neurofibrillary pathology in individuals in their third decade [15]. Further AD-related changes can even be found in the entorhinal cortex of children [19]. This new perspective has led to the recent division of AD into preclinical [20], mild cognitive impairment [21], and dementia [22], with a particular focus on biomarkers and brain imaging [23]. Now AD can be seen as a continuum [24] that is influenced by factors early in life, including genetics [25, 26] and education [27]. The purpose of the Handbook and this supplement is to present the numerous modalities that are currently being used to estimate the degree of AD pathology in the brains of living individuals who are at risk for developing dementia or have already suffered from the impairments caused by this pathological condition. Conceptualizing the continuum of AD is likely to provide greater understanding of this disease and help to advance diagnosis and the quest for prevention and treatment.

Defining the Critical Areas of AD Study

A central theme of the Handbook and this supplement is the imaging of the brain along the continuum of AD, from young individuals who have early AD changes or have developed a predisposition, through early signs of cognitive impairment, through mild to profound dementia. Associated issues include genetic factors and environmental events that predispose an individual to develop A β or NP as well as the associated dementia.

Neurofibrillary pathology (NP)—Neurofibrillary pathology relates to the severity of dementia. The selective appearance of neurofibrillary changes in specific regions of the brain [28] and its progression through the brain [15] correspond closely to the distribution of loss of perfusion [29] (Fig. 1) and metabolism (Sections 3 and 4 in this volume). The abnormalities of metabolism are seen prior to the development of dementia in association with the ApoE- ϵ 4 genetic factor [30, 31] (see below). Even though the neurofibrillary changes are closely related to dementia, they do not have a clear relationship to genetic factors. However, they do seem to be stimulated by at least one contributing environmental factor, head-trauma. A specific PET ligand, FDDNP is able to show the distribution of neurofibrillary pathology in humans (see Shin et al., in Section 3 of this supplement [32]).

Amyloid- β accumulation and neurofibrillary degeneration—A β plaques constitute an important aspect of AD pathology. While rare genetic mutations associated with the production of A β suggest an important role for A β in AD in the affected younger individuals (see Reiman et al., Section 8 of this supplement [33]), the relationship of A β to AD in older patients has been less clear. AD is characterized by A β accumulation in the brain of affected individuals, and A β depositions are associated with the predisposition to dementia. However, A β depositions relate poorly to the severity of dementia, and neither A β accumulation nor the number of plaques has been clearly linked to the severity of cognitive dysfunction in AD (see [34]). The deposition of A β in the brain can now be imaged with PET ligands, such as 11C-labelled Pittsburgh-Compound-B (PIB) and 18F-labelled A β

ligands (florbetapir (18F-AV-45), flutemetamol (18F-GE067), florbetaben (18F-BAY94-9172), and 18F-FDDNP) (see Section 3 below and in this supplement).

Synaptic loss—Synapses are the dynamic infrastructures of cognitive processes. The anabolic production, maintenance, remodeling, and removal of these important entities are crucial for normal cognitive function [35]. Numerous studies have shown that AD is linked to a significant loss of synapses and synaptic markers in a variety of brain regions [36]. The loss of synapses is not only due to neuronal loss but also is linked to reduced number of synapses per neurons, likely related to the accumulation of hyperphosphorylated tau in dendrites [14]. Indeed compared with other pathological hallmarks of AD, the severity of synaptic loss correlates best with the severity of cognitive dysfunction in AD [36]. Excessive synaptic loss in the AD brain is associated with a cascade of pathological events, including hypofunction (decreased metabolism and blood flow), atrophy, and alteration in the chemical composition in various brain regions. For this reason, imaging modalities that can detect either structural (Section 2), metabolic (Section 3), functional (Section 4), electro-magnetoencephalographic (Section 5), axonal tract (Section 6), or chemical (Section 7) alterations in the brain are critical in detecting and assessing these pathological changes.

Neuronal loss and/or hypofunction of specific systems—In addition to significant volumetric and numeric loss of neurons in the cortex and hippocampus, AD is also characterized by a significant loss and dysfunction of subcortical neurons projecting extensively to the hippocampus and cortex (Section 1). These losses are some of the most critical early changes in the AD brain and may contribute to the development of pathology in the cerebrum. For example, degeneration of cholinergic neurons in the nucleus basalis of Meynert occurs early in the course of AD [37, 38]. Indeed, cholinergic drugs represent the most successful class of pharmaceuticals yet developed to treat AD [39]. Other neurotransmitter systems are also affected early in AD, including, the serotonin nuclei, particularly in the dorsal raphe nucleus, which may be affected significantly before any cerebral changes occur [40], and the noradrenergic neurons of the locus coeruleus (see Milan Sanchez M., in Section 1 of this supplement [1]). The selective vulnerability of these neurotransmitter systems to AD pathology, as well as the medial temporal lobe structures, likely relates to their involvement in neuroplasticity, basically the function of forming the substrates of new memories [41, 42]. The atrophy of the neurons of these neurotransmitter systems in AD and the loss of their trophic effects may specifically lead to degeneration and dysfunction in both hippocampus and cortex. These structural and functional changes in the hippocampus and cortex are easily detected by MRI and fMRI (Sections 2 and 4). Furthermore, the significant demise of neurons will also be reflected by the loss of extensive connections between these regions, which can be detected by EEG [43] (see Babiloni et al., in Section 5 of this supplement [44]) and DTI (Section 6).

Apolipoprotein E (ApoE) – the principle genetic factor associated with late-onset AD—The Apolipoprotein E (ApoE) polymorphism is the strongest genetic risk factor linked to the sporadic form of AD [25, 26]. Interestingly, ApoE-ε4 alleles increase the risk of AD in a dose dependent manner. Although the exact mechanism by which ApoE-ε4 alleles lead to increased risk of AD remains to be determined, a link to amyloid binding and neuroplastic mechanisms appears likely, particularly the constant high frequency of synapse creation and removal [26, 42]. Further, decreased neuronal activity related to ApoE-ε4 alleles is one of the most significant associations between any contributing factor and AD pathophysiology [45]. Indeed, abnormalities of metabolism are seen prior to the development of dementia in association with the ApoE-ε4 allele [30, 31]. Numerous studies have shown the link between ApoE-ε4 alleles and cerebral metabolic rate for glucose

(CMRgl) in brain regions including posterior cingulate, precuneus, parietal, temporal, and prefrontal brain regions in ApoE- ϵ 4 carriers [46] (Sections 3 and 4).

Metabolic disorders—The relationship of AD to the general status of cerebral metabolism is also of potential importance. Links to glucose metabolism and insulin mechanisms have been of considerable interest (see Section 10). There is also a potential link to fat metabolism and leptin (a protein hormone that is produced by fat cells and has effects in the brain) that is still under investigation [47]. Further, there are potential associations between risk and sex hormones. The relationship of AD to vascular factors is also of great importance (see Section 9).

Environmental factors, traumatic brain injury, and complex stimulation—While there are clearly genetic factors predisposing to the development of AD, there are numerous environmental factors that have been considered to have a possible relationship to AD causation. Questions of great interest in the Handbook and this supplement are which factors could be better studied through brain imaging and whether brain imaging can help to determine if the manipulation of those factors would lead to measurable alterations of the course of AD pathology development.

The relationship between repetitive brain trauma and progressive neurological abnormalities has long been established. Chronic traumatic encephalopathy seems to be a major contributor in cognitive dysfunction seen in athletes, particularly boxers and probably several other groups. Brain trauma may lead to significant atrophy of multiple brain regions including cortical and hippocampal areas and enlargement of ventricles. Microscopically, this condition is characterized by neuronal loss, gliosis, the occurrence of neurofibrillary degeneration, particularly in superficial cortical layer neurons, and tau-positive astrocytes [48]. Another recent finding is that combat veterans suffering from post-traumatic stress disorder (PTSD) have a two fold increase risk of dementia [49]. Of note, PTSD is also significantly associated with head trauma in this population [50, 51].

Environmental stimulation such as education [27] may decrease the risk of dementia. Further, as described by Forster et al., [52] and Rosen et al., [53] in Section 8 of this supplement, cognitive stimulation may have positive effects on dementia that can be measured by brain imaging techniques.

Identifying Biomarkers and Developing Early Detection Methods

The major genetic factor associated with AD in older individuals is the ApoE genotype. The variation in incidence between the ϵ 4/4 to ϵ 3/3 to ϵ 2/2 individuals potentially explains 95% of the causation of AD [26]. Recent data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) had initially suggested that CSF A β and tau levels were associated with the transition from “normal” to “MCI” (mild cognitive impairment) to “mild dementia”. However, re-examination of the data by genotype indicated that only the tau measures were associated with dementia, while the A β levels were associated with ApoE genotype [54]. Further, the initial association of A β to diagnosis turned out to be an artifact related to the small number of individuals with the ApoE- ϵ 4 allele in the normal group, an intermediate number in the MCI group, and a large number in the mild dementia group) (Tables 1, 2). Age was also a contributing variable in the ADNI data set (Table 3). Thus, ApoE genotype also appears to be the major factor associated with the development of dementia and the predisposing biomarkers in the population of the ADNI data set. This point is critical to understand because many studies that examine AD patients and compare their results to normal individuals do not address the issue of specific ApoE genotype and age, which

appears to be critical for the development of AD and for establishing the links leading to its causation.

There is a further problem with the ApoE genotype that should be mentioned here. While the ApoE protein is a cholesterol transport protein, it appears to bind to A β , with the ApoE- ϵ 4 protein binding most strongly to it (see [26, 42] for reviews). Such strong binding could explain why the ApoE- ϵ 4 individuals have lower A β in their cerebro-spinal fluid and more A β deposition in the brain. However, A β deposition in the brain has a high relationship to AD risk but not to AD dementia (see Section 3 of this supplement). Accordingly, there is a question of what the causal link is between A β and dementia. While A β is considered toxic, that toxicity may just be a normal aspect of neuroplasticity [42, 55–57]. It is the loss of synapses which is most closely associated with dementia [36], followed by the neurofibrillary pathology [5], with the neurofibrillary pathology likely leading to the synapse loss [14]. The question then is how A β predisposes to the neurofibrillary pathology, for example, through an effect on the tau protein [58, 59]. Alternatively, some associated factor, even an adjacent gene like Translocase of Outer Mitochondrial Membrane 40 homolog (TOMM-40) [60], which affects mitochondrial function, could affect the tau phosphorylation/de-phosphorylation balance.

Effective Methods of Evaluation of Therapies

Having access to methods that allow unbiased evaluation of different therapeutic strategies is an important aspect of developing a successful strategy for treating any disorder. Numerous therapeutic strategies, both invasive and non-invasive, have been used for the treatment of AD. These methods have focused either on reducing accumulation of specific proteins and/or elements, restoring the function of specific systems, increasing the function of neurons using trophic factors, or reducing the reaction of the brain to protein accumulation and toxicity. Although a few intervention strategies have shown promising effects and have reached advanced stages of clinical trials, the only FDA approved methods for countering cognitive dysfunction in AD are drugs that increase cholinergic tone through cholinesterase inhibition (tacrine, donepezil, galantamine, rivastigmine) and a drug that affects glutamate neurotransmission by modulating N-methyl-D-aspartate (NMDA) receptor activation (memantine). Advanced imaging methods have been instrumental in verifying the effects of different treatments in AD. Section 8 discusses important considerations for utilizing the developments in brain imaging to more effectively evaluate the benefit of treatments for AD.

The development of treatments for AD should begin with better understanding of the pathophysiology and more accurate assessments of the state and rate of progression of the disease. The earliest factors in the AD course are genetic (for example, see Reiman et al., [33] in Section 8 of this supplement), and the ApoE genotype appears to reflect a factor that is highly related to the predisposition to AD, though there have been no treatments yet that appear to block this predisposition. Since ApoE-related brain changes may be detected in childhood, interventions addressing this factor should begin very early in life (the best model may be the management of phenyl-ketonuria). The changes related to A β have been suggested to occur in middle adulthood [18], so therapeutic strategies that address A β would greatly benefit from brain imaging techniques that can detect A β –deposition at this middle phase of the disease. For therapies that target prevention of dementia progression (a later phase of the newly conceived AD continuum) early in its course, a greater focus on measuring atrophy, metabolism, and tau would be of most utility [61]. Recent data suggest that blocking tau hyperphosphorylation may be sufficient to prevent the progression to dementia [59]. Consequently, the brain imaging approaches most associated with neurofibrillary pathology would be of most relevance for assessing the benefits of therapies that target the transition from the state of normal cognitive function to dementia.

Future Directions of AD Research and Clinical Development

The concordance of the changes seen with pathological analysis, brain imaging, and neurocognitive testing indicate that the visualization of changes in the brain related to AD has progressed far, but discovering the cause of AD and developing appropriate interventions for cure and prevention have remained elusive. Future efforts will be needed to continue the incredible advances in neuroimaging (see Section 10). However, there needs to be more focus on the fundamental causative mechanisms leading to AD. In particular, advances in genetics need to determine the specific contributions of genetic factors to all of the pathological changes observed both biologically and psycho-socially. Since all adults with Down syndrome have AD pathology by age 40, there should be more emphasis on understanding the pathophysiological basis of Down syndrome which is considered a genetic model of AD. How numerous environmental factors affect AD progression from an apparently normal state toward dementia, likely beginning in childhood, also needs to be understood. Further refinements are also needed to improve the measurements of cognitive function to the point where cognitive measures accurately and precisely reflect the pathological changes seen in brain imaging and other biomarkers.

2: Structural Imaging (Bayley, Frisoni, Jack)

Thomann et al., Cognitive performance and its relation to brain morphology in MCI and AD (see: [62]).

Lehmann et al., Patterns of cortical thickness in pathologically-confirmed typical and atypical Alzheimer's disease (see: [63]).

Thomann et al., Volumetry of the olfactory bulb and tract: relation to medial temporal lobe atrophy and to cognitive performance in MCI and AD (see: [64]).

Fennema-Notestine et al., Presence of ApoE epsilon4 Allele Associated with Thinner Frontal Cortex in Middle [65].

Firbank et al., Alzheimer's disease and dementia with Lewy bodies can be differentiated by high resolution MR imaging of the hippocampus (see: [66]).

Oliveira et al., Automated Volumetric Methods to Detect Alzheimer's Disease (see: [67]).

Boccardi et al., Survey of Protocols for the Manual Segmentation of the Hippocampus: Preparatory Steps Towards a Joint EADC-ADNI Harmonized Protocol [68].

Tosun et al., Relationship Between CSF Biomarkers of Alzheimer's Disease and Rates of Regional Cortical Thinning In ADNI Data [69].

Brys et al., Quantitative Structural MRI And CSF Biomarkers in Early Diagnosis of Alzheimer's Disease (see: [70]).

Kerchner, Ultra-High Field 7T MRI: A New Tool for Studying Alzheimer's Disease [71].

Structural MRI provides a measure of the cerebral atrophy that is a central feature of AD. Atrophy in AD is a result of neurodegenerative processes involving dendritic pruning and loss of synapses, as well as neuronal cell body degeneration and death, with related loss of axons [14, 72]. A body of literature suggests that neurodegeneration in AD is a relatively late event, and is preceded by abnormalities in CSF, tau, A β , and FDG-PET [61]. While the rate of change of some of these other biomarkers may slow before the appearance of structural atrophy, abnormalities in neurodegeneration on MRI accelerate as clinical

symptoms appear, and then parallel cognitive decline. As a result, volumetric or voxel-based measures of brain atrophy retain a close relationship with cognitive performance across a broad range of AD severity, and rates of neuronal and synaptic loss indicated by brain atrophy correlate strongly with rates of concurrent cognitive decline [73]. In addition, the degree of atrophy correlates well with Braak staging at autopsy [74–76] and the topographic distribution of atrophy on MRI maps well onto Braak's staging of NFT pathology in patients who have undergone post-mortem staging [77]. Many of these themes are explored in the chapters of this Section.

For example, brain atrophy and its relationship to cognitive performance in patients with AD and MCI are examined in two articles by Thomann et al., (see: [62, 64]). AD is traditionally considered to be the prototypical “cortical” (limbic as well as neocortical) dementia which arises through degeneration of the cerebral cortex and is typically associated with severe memory loss. Thomann et al., (see: [62]) demonstrate that this may be an oversimplification, and that although recall and recognition in AD patients are indeed related to cortical atrophy in the bilateral medial temporal lobe and posterior cingulate, they are also related to degeneration in subcortical regions including the thalamus. The same group of researchers also identified reduced grey matter density in the olfactory bulb and tract suggesting that this brain region may provide a potentially useful marker of neurodegeneration in AD and MCI (see: [64]). One of the difficulties of diagnosing AD is that it shares many clinical symptoms with other types of dementia and the value of structural MRI in the diagnosis of AD is explored by several groups. For example, Lehmann et al., (see: [63]) show that although widespread cortical thinning occurs in AD, the specific pattern of thinning varies between patients with typical and atypical presentations of AD. However, thinning of the posterior cingulate is a distinctive feature in both typical and atypical cases of AD but not in frontotemporal lobar degeneration. Cortical thickness is also examined by Fennema-Notestine et al., [65] in relation to ApoE genotype in healthy middle-aged men. The ApoE- ϵ 4 allele is associated with significantly thinner frontal cortex in this group, which may help explain the greater susceptibility to AD in individuals with the ϵ 4 allele. Firbank et al. [66], examined the use of high resolution structural imaging of the hippocampus to differentiate between AD and dementia with Lewy bodies (DLB). They identified three structural abnormalities that differentiated AD from DLB and aged healthy subjects that included the subiculum, CA1, and a hypointense line between CA1 and CA3/4. Oliveira et al. [67], used image analysis algorithms in order to automatically discriminate between AD patients and controls using cortical thickness and volumetric data. Results demonstrated that this method could successfully distinguish between AD patients and controls (sensitivity = 93%; specificity = 85%). Although the patient sample size in this study was relatively small, this and other specialized statistical classification methods based on image analysis are promising techniques which have the potential to improve the diagnosis and monitoring of AD. Although automated procedures are increasingly used in the segmentation of structural images, manual segmentation remains the gold standard. However, as reviewed by Boccardi et al. [68], the results obtained by manual segmentation depends strongly on which protocol is used - and can result in up to 2.5-fold volume differences when evaluating hippocampal atrophy in AD. As a step in addressing this issue, Boccardi et al., [68] highlight some of the differences between 12 published protocols for hippocampal segmentation. The relationship between biomarkers of AD and rates of cortical thinning are also explored. It is known that patients with AD have reduced amyloid ($A\beta$ 1-42), elevated phosphorylated tau (p-tau) and elevated total tau in cerebrospinal fluid. Two groups (Tosun [69] et al., and Brys et al., see: [70]) both show that longitudinal rates of brain atrophy increase in the presence of lower $A\beta$ 1-42 levels and higher p-tau levels. Combining CSF biomarkers and structural imaging biomarkers significantly increases the overall predictive accuracy of conversion of MCI to AD and supports the hypothesis that CSF $A\beta$ 1-42 and tau are measures of early AD pathology. In this context, it should be noted that a long standing issue in AD is the

uncertain relationship between the senile plaque pathology associated with A β and the NP associated with tau. Recent data have suggested that the A β pathology is more closely associated with the ApoE genotype and the predisposition to AD and develops over decades, while the tau pathology is more closely related to cognitive function and develops over the course of dementia [18]. In view of this, the different time courses of these various biomarkers must be taken into account when using combined measures to estimate where an individual lies on the continuum of AD. Finally, new technologies are on the horizon for structural imaging in AD, including the routine use of ultrahigh field MRI. Kerchner [71] reviews two AD-related applications for 7T MRI: direct visualization of cortical plaques, and high resolution hippocampal imaging. Together, these tools promise to provide an ever greater insight for the diagnosis and treatment of AD.

3: Imaging of Cerebral Blood Flow, Metabolism, Amyloid Plaques and Neurofibrillary Tangles in AD (Furst & Sabri)

Weih et al., Nuclear Medicine Diagnostic Techniques in the Era of Pathophysiology-based CSF Biomarkers for Alzheimer's disease [78].

Sedaghat & Baloyannis, Unawareness of Cognitive and Behavioral Deficits in Alzheimer's Disease May Be Reflected By Functional Neuroimaging (see: [79]).

Alegret et al., Brain perfusion and neuropsychological deficits in Mild Cognitive Impairment and mild Alzheimer's disease (see: [80]).

Bastin et al., Neural correlates of controlled memory processes in questionable Alzheimer's disease (see: [81]).

Nobili et al., The value of SPECT in detecting Alzheimer-type neurodegeneration in mild cognitive impairment (see: [82]).

Mosconi et al., A tale of two tracers: Glucose metabolism and amyloid Positron Emission Tomography imaging in Alzheimer's disease (see: [83]).

Furst & Lal, Amyloid- β and glucose metabolism in Alzheimer's disease [84].

Barthel & Sabri, Florbetaben to trace beta-amyloid in the Alzheimer brain by means of PET [85].

Austin et al., Effects of Hypoperfusion in Alzheimer's Disease [86].

Shin et al., The Merits of FDDNP-PET Imaging in Alzheimer's [32].

Jensen et al., Research towards tau imaging [87].

This section provides an overview of the progress that has been made in the past decades in imaging AD pathology chiefly using techniques developed in nuclear medicine such as positron emission tomography (PET) and single photon emission tomography (SPECT). Together with new approaches also integrating magnetic resonance imaging (MRI) these techniques have focused on the detection and quantification of cerebral hypoperfusion, glucose hypometabolism and the hallmark pathological features of the disease, A β -SPs and neurofibrillary tangles (NFT).

A brief introductory review of existing imaging techniques in the context of AD diagnostics is provided in the article by Weih et al., [78]. This is followed by three articles from the

Journal of Alzheimer's Disease (Sedaghat et al., [79]; Alegret et al., [80]; and Bastin et al., [81]) illustrating the usefulness of imaging in detecting and exploring the neural correlates of cognitive deficits associated with AD pathology. Due to the failure of many clinical trials and the growing need for disease modifying drugs, Reiman et al., [33] (in Section 8) outline the Alzheimer's Prevention Initiative (API), an ambitious plan to target populations that are genetically at high risk for developing AD close to their expected onset of the disease with new drugs using imaging as outcome measures. Similarly, Tzimopoulou et al., (see: [88] from Section 8 of the Handbook) makes the case for the specific utility of fluorodeoxyglucose (FDG) imaging in multi-center clinical trials settings. The value of the more widely available SPECT in mild cognitive impairment and AD is discussed in Nobili et al., (see: [82]). A comprehensive comparison of the utility of FDG vs. the to-date most widely studied amyloid tracer Pittsburgh-Compound-B (PIB) is provided by Mosconi et al., (see: [83]) followed by a detailed comparison of the uptake patterns of the two tracers in AD, specifically in Furst & Lal [84]. Further, the current knowledge and future research activities for the 18F-labeled-amyloid-targeted PET tracer florbetaben are reviewed by Barthel & Sabri [85]. Austin et al., [86] discuss arterial spin labeling (ASL) a more recent MR-based alternative to measure hypoperfusion in AD. Finally the last 2 chapters of this section are focused on the challenges in imaging NFT pathology: Shin et al., [32] discuss this in the context of data of the only available compound capable of detecting both A β and NFTs, FDDNP, and points to the necessity for modification of current A β centered disease progression frameworks in order to accommodate these findings. In order to clearly distinguish the contributions of A β vs. NFT to AD pathology a tracer that is solely binding to NFT is urgently needed for future research. The specific difficulties in developing such an imaging agent are illustrated in the last article by Jensen et al., [87].

4: Current Advances in Functional Magnetic Resonance Imaging for Detecting Alzheimer's Disease (Adamson)

Sala-Llonch et al., Combining MRI modalities to study visual and default-mode networks in a-MCI (see: [89])

Bokde et al., Verbal Working Memory in Amnesic Mild Cognitive Impaired subjects: An fMRI study (see: [90])

Drago et al., Disease Tracking Markers for Alzheimer's Disease at the Prodromal (MCI) Stage [91]

Recent advances in imaging techniques have placed functional magnetic resonance imaging (fMRI) on the forefront for improving ways by which to identify individuals with very mild symptoms prior to dementia. Efforts are currently underway to revise the diagnostic criteria for AD with the goal being diagnosis prior to not only dementia but also MCI, including prodromal disease markers [91]. Such criteria will likely include results of monitoring the changes in functional brain activity particularly in the medial temporal lobe (MTL) as measured by fMRI. The MTL is the seat of episodic memory [92–94], including visuo-spatial memory [95], and the first site affected by AD [96]. Even at the preclinical stage, the hippocampus and the entorhinal and perirhinal cortices show AD-like pathology [97]. Many studies have provided evidence for neuronal changes that occur in the preclinical stage of AD, and fMRI may be a very useful technique to measure these changes *in vivo*. In the current section, we review recent fMRI studies in MCI, AD and pre-clinical AD.

Functional MRI in AD & MCI

Functional magnetic resonance imaging (fMRI) studies frequently focus on MTL subregions to capture activation patterns that are predictive of subsequent clinically significant decline

[98] and predictive of progression from MCI to AD [99]. A number of fMRI studies have identified alteration in task-related blood-oxygen-level-dependent (BOLD) response in not only medial temporal lobe (MTL) area but also in frontal regions in AD patients compared to controls [100]. The use of a variety of tasks addressing MTL involvement in various memory systems has led to wide-ranging results in AD and MCI groups (see [90]). For instance, both increased and decreased activations in temporal and frontal regions have been reported previously in mild AD patients [101, 102]. Some evidence also suggests that decreased hippocampus activity during encoding may be associated with increased frontal activity in mild AD patients. The latter is consistent with the idea that due to atrophy-related changes in MTL, other areas are recruited to perform the tasks at hand.

Results from studies in MCI have been very inconsistent possibly due to variations of cognitive impairment of the individuals at this stage. Decreased hippocampal activation, similar to AD patients, has been reported in MCI patients compared to controls during encoding and retrieval [103, 104]. In contrast, several studies investigating memory encoding with face, object, and word stimuli, have found increased activation in MCI compared to controls [105–107]. As mentioned earlier, these differences are likely due to the differences between subjects associated with the wide-range of severity of cognitive impairment in the MCI subjects studied based on the clinical dementia rating scale (CDR) and the numerous MCI definitions that have been developed and used in various studies. Some studies have used a more strict range allowing for only very mild cases to be included in a study. In addition to level of clinical impairment, the type of fMRI task used and other methodological differences also make a difference in the interpretation of results obtained in each study.

Whether there is increase or decrease in hippocampus activation in MCI and/or AD, fMRI can detect changes in the brain regions responsible for different memory systems that are associated with preclinical symptoms of AD. More recently, studies of resting state (non-task related fMRI) have provided evidence for the “default mode” network (DMN), comprised of medial parietal/posterior cingulate cortex, along with medial frontal and lateral parietal regions. This network is active during rest or when individuals are not engaged in a task. During a task, these regions show deactivation [108]. This DMN has been shown to be disrupted in AD by a number of recent studies [109–112]. Recently, Frings et al., [113] suggested that the lack of task-related deactivation in the precuneus, an important node in the DMN, is due to connectivity disruption in MCI and AD patients and may not be atrophy related. Evidence also links regions with amyloid deposition in AD to areas involved in the DMN [114]. Abnormalities in the DMN even appear in MCI (see: [89]).

Functional MRI Associated with APOE Genotypes

ApoE- ϵ 4 alleles increase the risk of developing late onset AD [26, 115, 116]. Carrying at least one ϵ 4 allele is a predictor of clinical progression from MCI to AD [117–119]. In cognitively normal populations, ApoE- ϵ 4-related differences in neuropsychological task performance have been detected before age 65 [120–123], although differences are typically modest [124]. The medial temporal lobe (MTL) is the seat of episodic memory [92–94], including visuo-spatial memory [95], and the first cortical sites affected by AD [96]. However, reports of ApoE- ϵ 4-related differences in brain structure, particularly in the MTL, are not consistent [125]. This inconsistency is especially problematic in cross-sectional studies, which have alternately revealed smaller and no differences in hippocampal volumes in ApoE- ϵ 4 carriers compared to non-carriers [120]. While it is possible that the impact of ApoE- ϵ 4 on hippocampal volume changes over time will turn out to be larger or more consistent than single-time point assessments, more immediate methods of assessing early indications of AD pathology are needed. Functional magnetic resonance imaging (fMRI) studies frequently focus on MTL sub-regions to capture activation patterns that are

predictive of subsequent clinically significant decline [98] and predictive of progression from MCI to AD [99]. Studying ApoE- ϵ 4-related hippocampal and MTL cortical activity differences during an episodic memory task may prove promising for evaluating the risk of AD associated with ApoE- ϵ 4 genotype in cognitively normal older adults.

Results from recent fMRI studies using episodic memory paradigms, however, have not been consistent in evaluating the ApoE- ϵ 4 risk for AD in cognitively normal older adults. Several studies followed the approach of measuring brain activity relative to fixation or rest periods. While an increase in MTL Blood Oxygen Level Dependent (BOLD) activity was reported in ApoE- ϵ 4 carriers using verbal paired-associate tasks [98, 126, 127]. A decrease was reported in ApoE- ϵ 4 carriers during spatial learning [128] and semantic categorization [129]. No ApoE- ϵ 4-related differences were reported during another paired-associate task [130]. Recently, Adamson et al., [131] reported that encoding-related activation during a perspective dependent spatial memory task in the hippocampus was significantly lower in carriers than non-carriers. These results have implications for fMRI studies that investigate the DMN (“default-mode” network) in middle-aged to older ApoE- ϵ 4 carriers to help evaluate AD risk in this otherwise cognitively normal population. The DMN is altered in cognitively normal older ApoE- ϵ 4 carriers similar to MCI and AD patients [112, 132–136]. Lustig et al., [111] reported that activation in medial parietal and posterior cingulate regions went from activation during a semantic judgment task to deactivation during fixation in young participants, but these regions were consistently activated in older adults with AD. Pihlajamäki et al., [136] provides evidence for the disruption of DMN along the continuum from normal aging to ApoE- ϵ 4 carriers to MCI and then AD. Recently, Fleisher et al., [132] reported no encoding-related activity differences in ϵ 4 carriers compared to non-carriers during a novel face-name pair task. Encoding-associated deactivations in the medial and right lateral parietal cortex are greater in non-carriers, similar to findings in AD studies. Fleisher et al., [132] also did a resting-state DMN analysis which revealed nine regions in the prefrontal, orbital frontal, temporal and parietal lobes that are different between ApoE- ϵ 4 carriers and non-carriers. Adamson et al., [131] report ApoE- ϵ 4 related differences (ϵ 4-carriers < non-carriers) in the orbital frontal and temporal lobe areas during encoding when compared to a non-MTL based control task. These areas are included in the DMN where resting state activity is reported to be different between carriers and non-carriers [132]. In addition, a previous study also reported the pattern of altered task-induced deactivations in ApoE- ϵ 4 carriers to be similar with the DMN [134]. It is possible that the ϵ 4-related difference in the previous studies is driven by preclinical atrophy in the hippocampus and surrounding areas. The underlying structural atrophy of these regions (hippocampal, surrounding MTL and orbital frontal lobe) may be the reason for the alteration in the DMN of ApoE- ϵ 4 carriers, MCI and AD as well as the reduction of encoding activity in ϵ 4 carriers compared to non-carriers in the Adamson et al., study [131]. Previous studies have shown that although elderly ApoE- ϵ 4 carriers show some atrophy in the MTL, there is no global brain atrophy [137–139].

In conclusion, fMRI is a promising technique that provides novel insights into the disease-related changes of cognitive systems during the course of AD. Despite its limitations, ranging from symptom severity and differences in task performances, fMRI is a unique tool that can provide answers for a disease which, to this day, can only be definitely diagnosed via autopsy. Combined with other emerging and state-of-the-art techniques, like Diffusion Tensor Imaging (DTI), perfusion MRI and amyloid based imaging, multi-modal imaging is the likely candidate to decipher the puzzle behind the development of early AD.

5: Electromagnetic Brain Mapping (Coburn, Olichney, Ashford)

Moretti et al., EEG changes are specifically associated with atrophy in amygdala and hippocampus in subjects with mild cognitive impairment (see: [140]).

Babiloni et al., Resting State Cortical Rhythms in Mild Cognitive Impairment and Alzheimer's Disease: Electroencephalographic Evidence [44].

Deiber et al., Working memory electroencephalographic patterns in subtypes of amnesic mild cognitive impairment (see: [141]).

Olichney et al., Cognitive event-related potentials: Biomarkers of synaptic dysfunction across the stages of Alzheimer's Disease [142].

Ashford et al., The topography of P300 energy loss in aging and Alzheimer's disease [143].

Verdoorn et al., Evaluation and tracking of Alzheimer's disease severity using resting-state magnetoencephalography [144].

Although studies of brain electrical activity have a long history in psychiatry and neurology, the advent of quantitative electroencephalography (qEEG) systems in the 1980 s introduced topographic mapping ("brain mapping") as a display option. This important development brought EEG and related techniques squarely into the domain of neuroimaging. Onto a standardized head or brain template (or more recently onto the subject's own brain MRI) could be mapped the raw voltages of EEGs, averaged voltages of Evoked Potentials (EPs) and Event-related Potentials (ERPs), frequency domain measurements of EEG amplitude and power deriving from fast Fourier transformations (FFTs), results of inferential statistical tests such as significance probability mapping (SPM), and a wide range of other quantitative data. Simultaneously the technique of magnetoencephalography (MEG), recording magnetic instead of voltage fields produced by brain activity, made its debut, introducing magnetic counterparts to EEGs, EPs, and ERPs. Application of these new techniques to dementia in general and AD in particular was rapid. There are two broad paradigms for studying brain electrical activity. In one, the EEG/MEG eavesdrops on the resting or idling brain while the subject sits quietly with his eyes open or closed. Verdoorn et al., [144] in this supplement present a vivid example of the use of the resting MEG to investigate AD. The other paradigm, subsuming EPs, ERPs and their magnetic equivalents, actively interrogates brain systems using external stimuli. In evoked potential (EP) studies auditory, visual, or other stimuli are used to drive the brain's sensory systems producing a sensory evoked potential containing a series of waves (components) corresponding to stages of cortical information processing. ERP studies elaborate on this framework by requiring the subject to perform a specific cognitive task related to the stimuli. The most common such task is the auditory oddball, in which the subject is instructed to ignore one class of stimuli (e.g., low pitch tones) but to respond to a second class of stimuli (e.g., high pitch tones). The brain responds with an ERP containing the familiar auditory sensory components followed by one or more new components (e.g., N200, P300) reflecting the additional information processing related to the cognitive task.

In many ways EEG offers an ideal method for assessing brain function. Its exquisite temporal resolution can track brain activity in the millisecond time domain characteristic of neuronal activity in the cortical substrate. It is entirely noninvasive and employs no ionizing radiation. It records both excitatory and inhibitory signals directly rather than secondary hemodynamic processes. It also is inexpensive. MEG offers these same advantages along with more precise spatial localization, although MEG systems are not in widespread clinical

use due to their size and the necessity of super cooling their superconducting sensors with liquid helium. In contrast, EEG systems are abundant and in many cases portable.

Another important advantage of EEG is that normative databases are available, allowing statistical comparison of a patient's brain activity with that of age-matched controls. The use of quantitative techniques and inferential statistics moves EEG analysis from the realm of qualitative clinical impressions into the realm of quantitative empirical assessment. Such comparison with healthy controls yields information about the degree of abnormality of the patient's brain activity recorded by each electrode. Some databases additionally offer comparison with known clinical conditions, allowing a statistically based multivariate "best fit" classification that can aid clinical diagnosis. EEG's poor spatial resolution is being overcome by the use of increasingly dense electrode arrays, from 20 a decade ago to as many as 256 today. MEG, in addition to having a theoretically better spatial resolution than EEG, has experienced a similar increase in the number of sensors.

It has long been known that the typical EEG in AD contains increased slow activity in the theta (4–8 Hz) frequency range and decreased fast activity in the beta (13–24 Hz) range over the broad regions of the temporal and parietal lobes sustaining high levels of tissue damage from the disease [145, 146]. More localized cortical damage resulting from strokes produces more focal theta, and in principle it should be possible to use this to identify individuals suffering from vascular dementia [147]. In practice however, this has been difficult to achieve using traditional univariate analysis techniques. Applications of multivariate techniques have shown more promise.

Quantitative EEG studies applying multivariate analysis to dementia have been reviewed extensively [148, 149]. Well-replicated studies have shown repeatedly that individual AD subjects and matched healthy controls can be classified into their appropriate groups on the basis of multivariate EEG analysis alone with accuracies as high as 80–90%. Furthermore, individual AD subjects could be discriminated from their nondemented depressed, alcoholic, or delirious, counterparts, and within the dementias AD subjects could be separated from those suffering from vascular or fronto-temporal dementia. However, such studies were performed using patients with established diagnoses and usually did not attempt to identify subjects in the earliest stages of a dementing process.

More recent work, reviewed in the Bablioni et al., [44] and Moretti et al., (see: [140]) articles in the Handbook and this supplement, greatly refines our understanding of the earliest frequency domain EEG changes in dementia. Subjects suffering from MCI were found to display several promising EEG markers. The markers not only distinguish between groups of MCI subjects and matched groups of healthy controls, but also between MCI sub-groups that will remain in MCI, progress to AD, or progress to non-AD dementia. It will be interesting to see whether these EEG markers, including integration with ApoE genotype, can be used to accurately classify individual subjects. If so, they could be employed as diagnostic aids and perhaps more importantly in a prognostic capacity. Additionally, the markers could serve as surrogate measures of disease progression, greatly aiding the development of new therapies.

The frequency domain changes seen in the EEG are paralleled by MEG changes. Verdoorn et al., [144] in this supplement document MEG differences between groups of AD patients and healthy controls, and additionally find several MEG markers that change over time in parallel with neuropsychological changes to track disease progression. As with EEG, the critical question is whether MEG markers derived from groups of subjects can be applied to individuals. If so, they offer great potential for early phase development of novel treatments.

Pritchard et al., [150] developed a new nonlinear mathematical method of analyzing EEG activity based on deterministic chaos theory, and derived a measure of brain activity they termed dimensional complexity. They then used dimensional complexity to study AD and found that not only did this measure reliably distinguish between groups of AD patients and groups of matched healthy controls [151, 152], but it also could reliably classify individuals as belonging to either of these two groups [146]. Direct comparison between standard frequency analysis and a combination of frequency analysis and dimensional complexity clearly showed the superiority of the combined technique. The use of nonlinear dynamic analysis has been limited by the availability of computational power. Indeed, those early studies required collaboration with the Supercomputer Computations Research Institute at Florida State University. But in the two decades since those seminal studies, rapid increases in computational power have allowed the analyses to be run on desktop computers, and nonlinear analysis has occupied a minor but important role in EEG research. Babilioni et al., [44], in this supplement, reviews some recent nonlinear dynamic findings regarding AD (e.g., the sparing of resting state posterior alpha EEG rhythms in AD patients with more severe ischemic changes in the white-matter).

Because AD involves widespread brain pathology and marked deterioration of cognitive functions one might expect changes in both EPs and ERPs, and both are seen. For example, the visual EP in response to a diffuse light flash contains a P2 component that has been found consistently to be delayed in groups of AD patients [145, 153–156]. This delay probably reflects damage to the cholinergic neurons in visual association areas of the cortex. Similarly, the ERP produced by AD victims during the oddball task typically contains a delayed P300 component, probably reflecting the additional processing time necessary for the damaged higher-order association areas of the cortex to perform the cognitive task. The amplitude of the P300 component is often found to be diminished in AD, presumably reflecting a reduced population of cortical pyramidal neurons involved in the cognitive oddball task. Unfortunately, neither the latency increase nor the amplitude decrease is sufficiently reliable to be of clinical value when assessing individual patients. In an effort to extract a more reliable P300 signal from the background noise, Ashford et al., [143], in this supplement, compute power and energy measures from the recorded P300 voltage record. Both derived measures appear to track age- and AD-related changes more closely than does the traditional voltage wave.

In this supplement, Olichney et al., [142] review prior ERP studies of AD, including P300 studies of attention and N400 studies of linguistic processing. Importantly, ERP studies can be designed to be sensitive to the cardinal features of AD. In this regard, recent work by Olichney and colleagues suggests that a Late Positive Component important for memory processes, sometimes termed the P600, may be particularly sensitive to the earliest stage of synaptic dysfunction during the ‘Pre-clinical’ (MCI) stage of AD. Olichney et al., [157] have demonstrated that two late ERP components (N400 and P600) are also promising in their ability to predict outcome in MCI. As with the EEG markers proposed by Babilioni et al., [44], an important question is whether ERP markers can accurately classify individual subjects during the MCI stage or even earlier. Recently proposed research criteria for pre-clinical AD [20] divided this entity into 3 stages based on the presence/absence of very mild cognitive deficits and synaptic dysfunction.

This supplement illustrates several applications of the EEG, ERP and MEG techniques to characterize synaptic/neuronal function and their earliest derailments in AD. Further research and validation of these measures are needed to test their clinical utility and cost-effectiveness and to determine which information is most complimentary to the results from other imaging modalities (e.g., MRI, PET) and other AD biomarkers.

6: Diffusion Tensor Imaging (Schuff)

Fellgiebel & Yakushev, Diffusion tensor imaging of the hippocampus in MCI and early Alzheimer's disease [158].

Friese et al., Detection of Alzheimer's disease with diffusion tensor imaging and deformation-based morphometry (see: [159]).

Canu et al., Mapping the structural brain changes in Alzheimer's disease: The independent contribution of two imaging modalities [160].

Haller et al., Diffusion tensor imaging (DTI) based individual prediction of cognitive decline in mild cognitive impairment using a support vector machine analysis (see: [161]).

Shu et al., Multiple diffusion indices reveals white matter degeneration in Alzheimer's disease and mild cognitive impairment: A tract-based spatial statistics [162].

Oishi et al., DTI analyses and clinical applications in Alzheimer's Disease [163].

Teipel et al., White matter microstructure in relation to education in aging and Alzheimer's disease (see: [164]).

Yassa, Searching for novel biomarkers using high resolution diffusion tensor imaging [165].

For many years, AD has been considered primarily a disorder of the gray matter of the brainstem, hippocampus, and cortex. Recently, a broader view has prevailed in which white matter changes are also seen to be relevant to assessing the AD process. The changing view arose to a large part from brain studies using diffusion tensor brain imaging (DTI), a variant of MRI, which provides a unique approach for the assessment of white matter. DTI captures the microstructural architecture of tissue by measuring the systematic directionality of water diffusion. The degree of diffusion directionality is usually expressed as fractional anisotropy (FA), which ranges theoretically from zero for isotropic diffusion to unity for diffusion exclusively along one direction [166]. It is now well established that FA is sensitive to changes in white matter integrity [167], although the biological underpinnings of FA alterations are not known in detail. Information from DTI can also be used for mapping fiber tracts and for studies of brain connectivity using the concept of tractography [168]. DTI has become the method of choice for studying alterations in white matter in normal aging as well as in a variety of neurological diseases. In AD research alone, roughly 100 DTI articles have been published in the past decade with a growing number of new reports appearing now every year.

The articles in this section of the Handbook and this supplement represent the status of current DTI research in AD and MCI and highlight the characteristics of white matter damage associated with AD. The article by Fellgiebel et al., [158] focuses on DTI studies of the hippocampus and associated limbic structures, which have received particular attention in AD research because of their critical role in memory processing and function. Several findings suggest that DTI-based indices of microstructural integrity of limbic structures might outperform conventional measures of macro structural volume loss as predictors of AD. The diagnostic utility of DTI in direct comparison to that of brain atrophy for AD is taken up directly in the article by Friese et al., (see: [159]). The feasibility of DTI as a biomarker for AD in clinical research settings and pharmacological trials is also discussed. Another perspective on using DTI and structural MRI together is presented in the article by Canu and colleagues [160], who aimed to identify the extent to which microstructural alterations and macrostructural atrophy provide independent information for the

characterization of AD pathology in a small group of diagnosed AD patients and healthy elderly controls. Their findings further expand the understanding of the topography of pathological changes in AD that can be captured with various MRI methods. The value of DTI for predicting cognitive decline from MCI toward dementia is investigated in the article by Haller et al., (see: [161]), using fractional anisotropy as a primary summary measure of DTI. The value of various other summary measures of DTI is addressed in the article by Shu et al., [162]. The different DTI measures are outlined and the sensitivity and interpretation of each measure is discussed in the context of detecting AD at an early stage. The potential translation of DTI research into clinical practice is critically examined in the article by Oshi et al., [163]. In addition, principles of DTI are reviewed and strategies for investigating white matter alterations are described. In the article by Teipel et al., (see: [164]), DTI is used to study associations between white matter integrity and education in the context of AD and brain reserve capacity. Finally, in the article by Yassa [165], a high resolution DTI method is reviewed to map the intricate structure of the perforant pathway, a connectional route linking the entorhinal cortex to the hippocampal formation and a target of early AD pathology.

DTI methods present novel and exciting opportunities but technical challenges remain. Taken together, the articles in this section demonstrate consistently that anisotropic diffusion of water in brain tissue measured by DTI is a highly sensitive probe to assess subtle disease processes in AD, not normally seen with conventional MRI contrast mechanisms. DTI holds great promise to become a useful clinical tool for early AD detection.

7: Magnetic Resonance Spectroscopy (Spielman)

Didic et al., Magnetic Resonance Spectroscopic Imaging detects metabolic changes within the medial temporal lobe in aMCI (see: [169]).

Westman et al., Resonance Imaging and Magnetic Resonance Spectroscopy for detection of early Alzheimer's disease [170].

The profound morphological changes that occur in the human brain in normal aging and neurodegenerative diseases have molecular, neurochemical, and cellular underpinnings as well as behavioral concomitants. Magnetic Resonance Spectroscopy (MRS) and Spectroscopic Imaging (MRSI) provide one of the few noninvasive *in vivo* investigative tools for deriving knowledge about the physiological processes of normal aging and the pathophysiological mechanisms by which AD causes dementia. As shown in the representative spectrum depicted in Fig. 2, proton-MRS (1H-MRS) permits visualization of a variety of markers of cellular integrity and function, including those of living neurons (N-acetyl compounds comprising mainly N-acetyl aspartate [NAA] and with contributions also from other N-acetyl compounds, especially N-acetyl aspartyl glutamate), glia (myo-Inositol [mI]), high-energy metabolic products (creatine [Cr]), cell membrane synthesis or degradation (choline [Cho]), plus less well resolved amino acids, including glutamate and glutamine). Table 4 contains a brief overview of the MR characteristics and bio- chemical roles of the most prominent MRS-detectable metabolites.

A large number of *in vivo* studies have been conducted documenting changes associated with AD, MCI, and other dementias [171–178]. These studies range from single voxel acquisitions, in which data are acquired from a single targeted volume of tissue, to multi-voxel MRSI studies, acquiring spectroscopic data from an array of voxels allowing the assessment of both spectral and spatial variations. Reduced NAA (or NAA/Cr ratios) and elevated mI (or mI/Cr ratios) have been the most consistent findings with respect to AD. Similar, though somewhat smaller effects, seen in individuals with MCI suggest that MRS may also have a predictive role in identifying early stage disease. However, to date, there

have been no published studies of ¹H-MRS in combination with confirmed diagnosis as assessed by histopathology at autopsy. Another important issue is the assessment of relationships with genetic (ApoE) and metabolic factors.

A summary of the current literature demonstrates MRSI is a powerful approach for addressing questions about the neurobiology and neurochemistry of the living human brain in health and disease and suggests that the MRS observable changes in AD are not merely an exaggeration of those seen in normal aging. The method is a safe, noninvasive technique ideal for longitudinal study, the essential design for characterizing aging and disease progression. Characterization of NAA, Cr, Cho, and mI, in particular, may provide a diagnostic tool, a monitor of disease progression, and insight into mechanisms of treatment response. Published data thus support the use of ¹H-MRS as an important adjunct to the clinical evaluation and diagnosis of dementia. The value of ¹H-MRS has been especially noteworthy for monitoring disease progression and identifying group effects for drug trials. However, the most valuable studies use MRS in conjunction with other imaging tools, such as structural MRI, for tissue segmentation and volumetric analysis, fMRI, and diffusion tensor imaging (DTI), in order to provide a multi-parametric assessment of brain tissue structure, function, and integrity. With the increasing availability of high-field scanners, which yield MRS studies with improved signal-to-noise ratios and increased spectral separation, the role of ¹H-MRS in the study of aging and dementia is anticipated to grow in the future.

8: Longitudinal Neuroimaging Measures: Windows into Progression of Disease and Potential Endpoints for Clinical Trials (Edland)

Reiman et al., Alzheimer's Prevention Initiative: A Plan to Accelerate the Evaluation of Presymptomatic Treatments [33].

Ashford et al., MR Spectroscopy for Assessment of Memantine Treatment in Mild to Moderate Alzheimer Dementia [179].

Förster et al., Effects of a 6-month cognitive intervention program on brain metabolism in amnesic MCI and mild Alzheimer's disease [52].

Rosen et al., Cognitive-training changes hippocampal function in mild cognitive impairment: A pilot study [53].

Tzimopoulou et al., Validation and Pilot Application of [¹⁸F]FDG-PET in Evaluation of a Metabolic Therapy for Alzheimer's Disease (see: [88]).

Zhang et al., An MRI brain atrophy and lesion index to assess the progression of structural changes in Alzheimer's disease, mild cognitive impairment, and normal aging: A follow-up study [180].

Ard & Edland, Power Calculations for Clinical Trials in Alzheimer's Disease [181].

This section explores the application of longitudinal imaging measures to studies of aging, AD, and AD treatments. Imaging allows highly focused assessment of specific aspects of disease effects, and many imaging measures are remarkably precise relative to clinical measures. For these reasons imaging measures hold great potential to characterize the natural history of disease and as endpoints for clinical trials. In the first chapter of this Section, Reiman et al., [33] explore the potential promise of imaging measures as endpoints for clinical trials and outline plans for large scale intervention trials. Feasibility is illustrated by four pilot clinical trials with novel interventions and imaging endpoints (Chapters 2

through 5). Ashford et al., [179] use magnetic resonance spectroscopy to assess the impact of memantine on mild to moderate AD. Förster et al., [52] use FDG-PET and Rosen et al., [53] use fMRI to assess the impact of cognitive interventions on brain function in early AD. Tzimopoulou et al., (see: [88]) describe a multicenter clinical trial using FDG-PET to assess the impact of rosiglitazone on metabolism in AD. The next two chapters review additional imaging measures. Olichney et al., [142] (section 5) reviews accumulating data on the response of event related brain potential (ERP) measurements to the progressive stages of AD, and Zhang et al., [180] describe the application of an MRI-based global atrophy and brain lesion index to AD. Finally, Ard and Edland [181] review statistical considerations relevant to planning clinical trials with imaging endpoints, and summarize the potential dramatic improvement in efficiency of clinical trial using those endpoints. Collectively, the chapters of this section suggest that longitudinal neuroimaging methods hold great promise to advance our understanding of AD and discover treatments for modifying the course of disease.

9: Vascular Co-morbidity and Alzheimer's Disease (Black & Rosen)

Knopman & Roberts, Impact of Vascular Risk Factors on Brain Structure (see: [182])

Gao et al., Complexity of MRI white matter hyperintensity assessments in relation to cognition in aging and dementia [183].

Bernardi et al., Late onset Alzheimer's disease with cerebrovascular lesions as a distinctive phenotype of the A β PP A713T Mutation in southern Italy (see: [184]).

Since the first description of dementia related to senile plaques and neurofibrillary changes by Alzheimer in 1907, there has been vacillation between thinking that most cognitive impairment in older individuals was related either to primary neurodegenerative disease or vascular insults. In the last few decades, there has been development of criteria for AD dementia and its underlying pathology and multi-infarct/vascular dementia, with the recognition that many elders harbor both conditions. Accordingly, while AD and vascular dementia have long been viewed as separate disorders, there is now a growing appreciation that vascular insults are an important comorbidity that contributes to disability in AD. Furthermore, these comorbid disorders may attack the same neural systems and synergize in disrupting cognitive functions.

Knopman & Roberts (see: [182]) describe various pathological processes that comprise the major vascular risk factors and review how they relate to AD, including hypertension, diabetes, hypercholesterolemia, and obesity. They also comment on population autopsy evidence suggesting that infarcts may be additive to AD pathology and accelerate its clinical expression as dementia. Quantifying ischemic lesions visible as hyperintensities on proton density/T2 weighted or FLAIR MRI provides an important means to study and understand, *in vivo*, the potential independent effects of covert infarcts in the deep nuclei and white matter lesions on cognition and expression of dementia in AD. Gao et al. [183] compare the sensitivity and utility of the major methods for quantifying these lesions. They test how well three expert rating scales, varying in complexity, compared to the results of automated, volumetric quantification in group classification of AD versus elderly controls, and in correlation to cognitive abilities. They find the scales to be highly correlated with each other and with the volumetrics, but the most complex rating scale and the continuous volumetric measures better predict cognitive function in different domains. Finally, Bernardi et al., (see: [184]) describe a form of early onset, familial AD in which an amyloid-protein precursor (A β -PP A713T) genetic mutation is associated with strokes, cerebral amyloid angiopathy, and AD pathology. This is important as it hints at mechanisms whereby AD and cerebrovascular disease may interact, as opposed to just being additive to each other. This

possible interaction may be occurring at the level of the microvasculature with capillary obliteration by amyloid deposition and toxicity, causing ischemia and oxidative stress that may further drive the amyloid cascade and tau hyperphosphorylation. Furthermore, periarteriolar deposition of A β -1-40, may interfere with amyloid clearance, now thought to be a major mechanism resulting in parenchymal amyloid accumulation in sporadic AD. This deposition can lead to microbleeds and macrohemorrhages and also infarction as described in the A713T mutation family reported by Bernardi et al., (see: [184]), illustrating that AD is under-recognized as a risk factor and direct cause of stroke. The chapters in this section clearly describe some of key issues in the relationship between vascular and parenchymal disease in the context of dementia and its relationship with brain degeneration in the elderly and particularly AD.

10: Neuroimaging in the Context of Alzheimer's Disease (Rosen & Kennedy)

Smith, Imaging in Alzheimer's Disease and Its Pre-States (see: [185]).

Mak et al., Discriminating Alzheimer's patients from cognitively normal older adults based on hippocampal volumes - voxel-based morphometry with DARTEL and standard registration versus manual volumetry (see: [186]).

Di Paola et al., Structural MRI investigation of neuroanatomy of Corpus Callosum in Alzheimer's Disease and Mild Cognitive Impairment (see: [187]).

Kaufman et al., Using an Eye Movement Task to Detect Frontal Lobe Dysfunction in Alzheimer's Disease (see: [188]).

Haller et al., Principles of classification analyses in mild cognitive impairment (MCI) and Alzheimer Disease [189].

Furney et al., Combinatorial markers of Mild Cognitive Impairment conversion to Alzheimer's disease -cytokines and MRI measures together predict disease progression [190].

The purpose of this section is to place the individual neuroimaging techniques in the larger context of how they can relate to one another and to the care and evaluation of patients with AD. The first article by Smith (see: [185]) in this section briefly summarizes the current status of the use of neuroimaging techniques in the context of early diagnosis of AD. As with most technologies, within the next few years many of the limitations we may admit to in this volume will likely have been addressed. However, it is essential that anyone using these techniques be aware of these limitations and appropriate uses. One current direction of development is to automate quantification of pathology. There are substantial advances being directed to make imaging techniques previously utilized only in select labs available to anyone with a computer and the resources to implement the analysis programs. Hippocampal volume decline is one of the most consistently reported imaging findings in AD so that a logical first approach in examining this process of using imaging in diagnostic decision making is to use hippocampal volume to discriminate diagnostic status between two obviously different populations, AD versus normal elderly. As with many techniques that extend clinical work, Mak et al., [186] begin with an expert manually defining hippocampal volume as the gold standard. They compare these results to some of the most commonly used, automated, approaches. A more extensive comparison of hippocampal volumetric techniques is also described in Boccardi et al., [68] earlier in this supplement.

Another fruitful approach is to compare a given structure using different imaging modalities, and this is particularly useful with respect to white matter regions. Di Paola et al., (see: [187]) review approaches to describing the integrity of the corpus callosum, a structure whose degeneration in AD is increasingly being studied, particularly in the context of vascular disease and AD [e.g., [191]]. The authors compare information from high resolution T1 images and diffusion methods to study Wallerian degeneration. Wallerian degeneration, or anterograde degeneration, is a process that occurs when an axon degenerates after damage disconnects it from a cell body. The importance of connectivity between brain regions is a direction in which the field of neuroimaging is moving and this article relates connectivity to the degenerative process of AD. Section 6 discusses DTI more fully.

Whereas many investigators compare various sources of clinical information with respect to diagnostic sensitivity and specificity, classification and support vector machine learning offer a way of integrating existing information to improve the accuracy of diagnosis. This section finishes with two papers on these techniques. The tutorial by Haller et al., [189] introduces classification in the context of discriminating MCI from AD patients. The paper by Furney et al., [190] provides an example of how this method can be applied to predicting conversion of MCI to AD and includes both CSF biomarkers and MRI.

The ultimate question a clinician needs to answer is how information from imaging can enhance clinical management. Neuroimaging of individual patients in everyday clinical care will not be useful unless it can improve what a clinician can do without it. Traditionally structural imaging and FDG-PET contribute to AD diagnosis by facilitating exclusion of alternative etiologies. The Handbook and this supplement describe several instances where imaging information has the potential to provide convergent information supporting early diagnosis. Examples of potentially useful techniques include ligands for amyloid and tau, pathognomonic patterns of FDG-PET hypometabolism (Section 3), and gross hippocampal volume loss (Section 2). Looking to the near future, of all the roles in clinical care, imaging is likely to have the biggest impact on early diagnosis and will be most helpful when combined with other sources of converging information [192, 193]. Early diagnosis has been the focus of most articles in this section. Classification techniques are a way of formalizing the process of integrating multiple sources of information including biomarkers, genetic risk, and other information. Ultimately the incremental value of early detection may be less dependent on the accuracy and sensitivity than whether there is a change in care as a result of early detection (i.e., treatment or avoidance of risk) to make it cost-effective.

Even when imaging data are not applied to the management of individual patients, they have the potential to assist in evaluating other components of care and diagnosis. To the extent that imaging can more sensitively measure brain integrity than existing techniques, novel treatments may be discovered because beneficial effects of treatments are not detectable with other methods. For example Section 8 applies imaging to evaluate the efficacy of pharmacologic and non-pharmacologic treatments. For investigators interested in conducting clinical research the discussion by Ard & Edland [181] on power calculations will be extremely valuable. Therefore, to the extent neuroimaging can serve to detect the effects of treatments in the development pipeline, such information can support early detection of cost-effectiveness, and treatments will become available more quickly and efficiently.

An alternative to using neuroimaging in diagnosis and evaluation of treatments is to assist in clinical decisions that limit the autonomy of patients in order to protect them from harm; however, this is unlikely to be feasible any time soon. One good example of a likely candidate for this use comes from the difficult clinical decision as to whether patients can manage their own financial affairs. This capacity in MCI patients has been related to angular

gyrus volume, measured by MRI, a region previously demonstrated to be important in math ability [194], and neuronal volume in the posterior cingulate cortex, measured by MRS [195]. This brain-behavior association may someday be used in the context of an early warning such that patients with a faster rate of change in this region may need special protections and monitoring to avoid financial predators who seek to exploit a developing vulnerability. In contrast, using neuroimaging to decide which MCI patients should lose driving rights is problematic. The processes and neural substrates of unsafe driving in AD are not well understood. Functional imaging studies that relate behavioral dysfunction to brain activation have the potential to indicate which brain regions underlie driving deficits; however, assessing driving in the MRI may not be comparable to assessing it in real life. In the typical MRI environment patients cannot talk or move a driving wheel but instead respond with minimal movement by pressing buttons. Remembering response mapping (e.g., left hand is yes and right hand is no) creates a dual task for patients that distorts and increases the complexity of the process an imager intends to study. The antisaccade task described by Kaufman et al., [188] in this section is an example of a task which is simpler for patients and which can be used as a measure of executive control. For example it is possible to assess whether the patient moves their gaze in a manner that suggests appropriate attention to traffic and street signs without requiring an artificial response modality. This interface has only been possible in the past few years due to innovations that made these devices MR compatible. Ultimately, however, there would need to be strong data to suggest imaging provided better prediction of driving safety than a road test.

The variety of neuroimaging techniques in all modalities have great allure with respect to their potential to improve diagnosis and care, and anyone who seeks to perform research with neuroimaging data has multiple new tools and resources to facilitate this work. The Alzheimer's Disease Neuroimaging Initiative (ADNI) and affiliated initiatives (European and Japanese ADNI's) have provided clinicians and imagers with acquisition protocols that are standardized across sites. The benefit is that there can be multi-site collaborations to increase statistical power and facilitate cross-site generalizability. Several investigators in this book have benefited from these initiatives. Because neuroimaging data are large, complex, and diverse, there needs to be a broad array of tools available to analyze them. The Neuroimaging Informatics Tools and Resources Clearinghouse (<http://www.nitrc.org/>) is a site from NIH which makes available neuroimaging software packages from a variety of modalities. This site contains reviews which advise all potential neuroimagers about the strengths and limitations of different software packages. For those clinicians who do not have resources to acquire their own data, there are multiple publicly available datasets. The ADNI data have been made available to researchers around the world and now there are MRI protocols for spectroscopy (Chapter 7), diffusion tensor imaging (Section 6), and arterial spin labeling (Austin et al., [86], Section 3) so this initiative is moving with the speed of innovation. In addition there are neuropsychological and biomarker data so that imaging data can be interpreted in context. Ultimately the prospects for neuroimaging to enhance clinical care are bright as researchers collaborate and clinicians become informed about innovations and advances.

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Fig. 1.

A single photon emission tomography (SPECT) analysis. Lateral view of the cortical surface (left side is on top). Scale indicates range for Pearson correlations with single decimal precision with “time-indexed” estimation of dementia severity in 30 probable AD male patients with a broad range of severity. Bottom graph shows relative frequency of each decimal range [29].

Fig. 2.
Typical human adult ^1H Brain spectrum.

Table 1
ADNI data on CSF biomarkers, mean±SD

	Tau	Aβ	P-Tau-¹⁸¹P
AD (<i>n</i> = 102)	122±58	143±41	42±20
MCI (<i>n</i> = 200)	103±61	164±55	35±18
Normal (<i>n</i> = 114)	70±30	206±55	25±15

$p < 0.0001$, for each of the 3 biomarker tests for AD vs. Normal and for MCI vs. Normal. For AD vs. MCI: $p < 0.005$, Tau; $p < 0.01$, A β ; $p < 0.01$, P-Tau-¹⁸¹P. Mann-Whitney test (ADNI data, 2008) (A β is 1-42).

Table 2
When the same data is analyzed by APOE genotype, different results are found, mean $\pm$ SD

APOE genotype	Normal	MCI	Mild AD
CSF A β levels			
33	212.4 $\pm$ 48.4	189.1 $\pm$ 59.8	168.8 $\pm$ 52.3
34	156.0 $\pm$ 47.8	148.4 $\pm$ 42.4	139.0 $\pm$ 27.2
44	126.0 $\pm$ 2.8	119.8 $\pm$ 23.5	116.2 $\pm$ 22.3
CSF P-Tau levels			
33	67.8 $\pm$ 26.9	83.6 $\pm$ 40.8	123.8 $\pm$ 68.6
34	81.8 $\pm$ 42.6	122.4 $\pm$ 72.7	113.3 $\pm$ 42.0
44	71.0 $\pm$ 2.8	110.6 $\pm$ 45.9	128.9 $\pm$ 53.1

<i>p</i> -value	
A β comparison	
33 vs. 34	<0.0001
33 vs. 44	<0.0001
34 vs. 44	0.08
Normal vs. MCI	0.57
Normal vs. Mild AD	0.15
MCI vs. Mild AD	0.20

<i>p</i> -value	
P-Tau comparison	
33 vs. 34	0.07
33 vs. 44	0.67
34 vs. 44	0.99
Normal vs. MCI	0.05
Normal vs. Mild AD	<0.01
MCI vs. Mild AD	0.06

APOE genotype	Normal	MCI	Mild AD
3/3	67 (72%)	82 (44%)	29 (31%)
3/4	24 (26%)	81 (44%)	42 (45%)
4/4	2 (2%)	22 (12%)	22 (24%)

Number of subjects (note more ϵ 4 alleles with higher grade of AD diagnosis).

Table 3
Ages of ADNI CSF subjects in each APOE genotype and subject group, mean±SD

APOE ϵ 4 genotype	Normal	MCI	Mild AD
3/3	75.8±5.0	75.4±8.4	76.3±8.6
3/4	75.8±6.0	73.9±6.7	75.6±6.6
4/4	77.0±1.4	72.2±6.0	69.8±7.0

Table 4
Commonly observed proton metabolites and their corresponding biochemical roles

Compound	Chemical shift	Biochemical role
N-acetyl aspartate (NAA)	2.0 ppm	NAA is only present in living neurons and is thus commonly used as a marker of neuronal density and viability (i.e., it is absent when neurons die or are absent). Note, the <i>in vivo</i> 2.0 ppm peak, while primarily comprised of NAA, actually contains contributions from several other N-acetyl compounds. For this reason the peak is sometimes labeled “NA” or “NAC”
Creatine (Cre)	3.0, 3.9	The Cre peak reflects the total creatine stores in cells (hence the common notation t Cr), and plays a primary role in maintaining the energy storage systems in cells. Cre levels tend to stay relatively stable in a variety of conditions and is thus often used as an internal standard for comparison to other metabolites. There are actual two peaks due to creatine, one at 3.0 and the other at 3.9 ppm (although the later peak is often lost due to water suppression).
Choline (Cho)	3.2	The bulk of the <i>in vivo</i> Cho peak comes from constituents of phospholipid metabolism of cell membranes. It has thus been used as a marker for cellular proliferation and density.
myo-Inositol (mI)	3.6	The biochemical role of myo-Inositol is not fully understood, though some have suggested it may be used as a glial cell marker, mI levels are relatively high in neonates, and it has also been observed to be elevated in Alzheimer's disease (along with decreased NAA).
Glutamine +Glutamate (Glx)	2.1–2.5	Glutamate is an excitatory neurotransmitter that play a critical role in the action of nerve cells in the brain. Glutamine plays a role in regulating neurotransmitter activities as well as in detoxification processes. These two metabolites resonate very close together and often cannot be separated at fields <3T (hence the common notation Glx to refer to the sum of these peaks).
Lipids (Lip)	0.9–1.4	Lipids, while common in many tissues in the body, are generally not MRS-detectable in the brain (lipids found in the brain are generally tightly bound and exhibit very short T2 relaxation times). Elevated lipids in the brain may reflect necrosis and cellular breakdown products. These signals can also obscure the measurement of lactate.
Lactate (Lac)	1.3	The signal due to lactate, which actually consists of two closely spaced peaks called a doublet, is an indicator of anaerobic metabolism. Normal brain tissue typically contains very low levels of lactate, and elevated lactate is usually an indicator of ischemia or hypoxia.