The Handbook of Neuropsychiatric Biomarkers, Endophenotypes and Genes

THE HANDBOOK OF NEUROPSYCHIATRIC BIOMARKERS, ENDOPHENOTYPES AND GENES

Volume 1: Neuropsychological Endophenotypes and Biomarkers

Volume 2: Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers

Volume 3: Metabolic and Peripheral Biomarkers

Volume 4: Molecular Genetic and Genomic Markers

Michael S. Ritsner
Editor

The Handbook of Neuropsychiatric Biomarkers, Endophenotypes and Genes

Volume 2

Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers

Springer

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Foreword

Common genetically influenced neuropsychiatric disorders such as schizophrenia spectrum disorders, major depression, bipolar and anxiety disorders, epilepsy, neurodegenerative and demyelinating disorders, Parkinson and Alzheimer's diseases, alcoholism, substance abuse, and drug dependence are the most debilitating illnesses worldwide. They are characterized by their complexity of causes and by their lack of pathognomonic laboratory diagnostic tests. During the past decade many researchers around the world have explored the neuropsychiatric biomarkers and endophenotypes implicated, not only in order to understand the genetic basis of these disorders but also from diagnostic, prognostic, and pharmacological perspectives. These fields have therefore, witnessed enormous expansion in new findings obtained by neuropsychological, neurophysiological, neuroimaging, neuroanatomical, neurochemical, molecular genetic, genomic and proteomic analyses, which have generated a necessity for syntheses across the main neuropsychiatric disorders. The challenge now is to translate these findings into meaningful etiologic, diagnostic and therapeutic advances.

This four volume collection of Handbooks offers a broad synthesis of current knowledge about biomarker and endophenotype approaches in neuropsychiatry. Since many of the contributors are internationally known experts, they not only provide up-to-date state of the art overviews, but also clarify some of the ongoing controversies, future challenges and proposing new insights for future researches. The contents of the volumes have been carefully planned, organized, and edited in close collaboration with the chapter authors. Of course, despite all the assistance provided by contributors and others, I alone remain responsible for the content of these Handbooks including any errors or omissions, which may remain.

The Handbook is organized into four interconnected volumes covering five major sections.

Volume 1 "Neuropsychological Endophenotypes and Biomarkers" contains 17 chapters composed of two parts emphasizing schizophrenia as a prototype. The first section serves as an introduction and overview of methodological issues of the biomarker and endophenotype approaches in neuropsychiatry and some technological advances. Chapters review definitions, perspectives, and issues that provide a conceptual base for the rest of the collection. The second section comprises chapters in

which the authors present and discuss the neuropsychological, neurocognitive and neurophysiological candidate biomarkers and endophenotypes.

Volume 2 "Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers", focuses on neuroanatomical and neuroimaging findings obtained for wide spectra of neuropsychiatric disorders.

Volume 3 "Metabolic and Peripheral Biomarkers", explores several specific metabolic and peripheral biomarkers, such as neuroactive steroid biomarkers, cortisol to DHEA molar ratio, mitochondrial complex, biomarkers of excitotoxicity, melatonin, retinoic acid, abnormalities of inositol metabolism in lymphocytes, and others.

Volume 4 "Molecular Genetic and Genomic Markers" contains chapters devoted to searching for novel molecular genetic and genomic markers in less explored areas. This volume includes an Afterword written by Professor Robert H. Belmaker.

Similarly to other publications contributed to by diverse scholars from diverse orientations and academic backgrounds, differences in approaches and opinions, as well as some overlap, are unavoidable. I believe that this collection is probably the first of its kind to go beyond the neuropsychiatric disorders and delve into the neurobiological basis for diagnosis, treatment, and prevention. The take-home message is that principles of the biomarker-endophenotype approach may be applied no matter what kind of neuropsychiatric disorder afflicts our patients.

The Handbook is designed for use by a broad spectrum of readers including neuroscientists, psychiatrists, neurologists, endocrinologists, pharmacologists, psychologists, general practitioners, geriatricians, graduate students, health care providers in the fields of neurology and mental health, and others interested in trends that have crystallized in the last decade, and trends that can be expected to evolve in the coming years. It is hoped that this collection will also be a useful resource for the teaching of psychiatry, neurology, psychology and mental health.

With much gratitude, I would like to acknowledge the contributors from 16 countries for their excellent cooperation. In particular, I am most grateful to Professor Irving Gottesman for his support of this project. His unending drive and dedication to the field of psychiatric genetics never ceases to amaze me. I wish to acknowledge Professor Robert H. Belmaker, distinguished biological psychiatrist, who was very willing to write the afterword for these volumes. I also wish to take this opportunity to thank my close co-workers and colleagues Drs. Anatoly Gibel, Yael Ratner, Ehud Susser, Stella Lulinski, Rachel Mayan, Professor Vladimir Lerner and Professor Abraham Weizman for their support and cooperation. Finally, I am forever indebted to my wife Galina Ritsner, sons Edward and Yisrael for their understanding, endless patience and encouragement when it was most required.

I sincerely hope that these four interconnected volumes of the Handbook will further knowledge in the complex field of neuropsychiatric disorders.

February, 2009

Michael S. Ritsner
Editor

Contents to Volume 2

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Part III
Neuroanatomical and Neuroimaging Findings

Chapter 18
Neuroimaging Biomarkers in Alzheimer's Disease

M.S. Chong and W.S. Lim

Abstract With the recent advances in treatment of Alzheimer's disease (AD) in the last decade, focus has shifted increasingly to accurate detection of earliest phase of the illness. This includes early Alzheimer's disease (AD) as well as the intermediate state between normal aging and established AD, is commonly known as mild cognitive impairment (MCI).

Clinical criteria alone are insufficient to accurately identify this at risk group of subjects and hence, biomarkers have been an area of intense research to see if they can supplement the clinical approaches. In recent years, neuroimaging has emerged as a useful biomarker in the diagnostic armamentarium of AD that serves the triple roles of early diagnosis, prediction of progression, and monitoring of disease progression.

In this chapter, we review the body of evidence on the use of neuroimaging biomarkers, alone and in combination, from the standpoints of diagnosis of early AD, predicting MCI conversion to AD and monitoring subsequent disease progression. We conclude with a discussion on the implications of these findings to the application of neuroimaging biomarkers in clinical and therapeutic trials.

Keywords Alzheimer's disease • early diagnosis • biological markers • magnetic resonance imaging • positron-emission tomography

Abbreviations AD: Alzheimer's disease; ADC: Apparent diffusion coefficient; APOE ε4: Apolipoprotein ε4; ASL-MRI: Arterial spin labeling; BOLD: Blood-oxygen-level-dependent; CDR: Clinical dementia rating; CBF: Cerebral blood flow; ^{11}C-PIB: ^{11}C-Pittsburg compound B; DBM: Deformation-based morphometry; DTI: Diffusion tensor imaging; DWI: Diffusion-weighted imaging; ERC: Entorhinal cortex; fMRI: Functional MRI; ^{18}F-FDDNP: 2-(1-{6-[(2-[^{18}F]fluroethyl)(methyl)amino]-2-napthyl}ethylidene)malononitrile; HC: Hippocampal; MCI: Mild cognitive impairment; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; MTL: Medial temporal lobe; PET: 2-[18F]fluoro-2-deoxy-D-glucose (FDG)-Positron Emission Tomograhy; SPECT: Single-photon emission computerized tomography; VBM: Voxel-based morphometry

Introduction

Given the rapid ageing of the population worldwide, global estimates of AD – generally considered to be the commonest subtype of dementia – are expected to increase from the current estimated 25–63 million in 2030, and by 2050, a staggering 114 million.[1] Over the last 2 decades in particular, significant but modest breakthroughs in pharmacological treatment of this devastating condition have occurred and presently, there is increasing conviction that intervention (especially disease modifying therapy) will have to be instituted at the earliest possible stage of the illness to confer the greatest benefit.

Currently, the diagnosis of prodromal AD is made using criteria which support a probabilistic diagnosis within a clinical context without added information from diagnostic biomarkers. Two commonly quoted approaches that have been validated and employed in interventional studies are the CDR[2] and MCI[3] (Fig. 18.1). MCI subjects have subjective features and objective evidence of cognitive impairment but of

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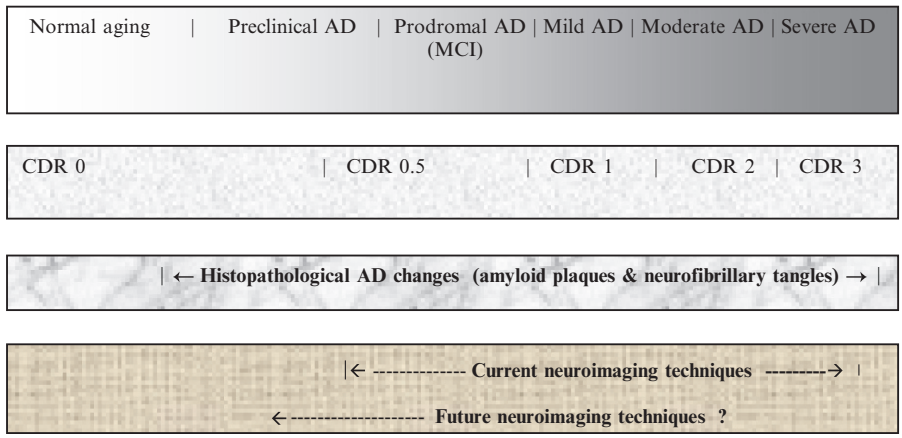

Fig. 18.1 Stages of cognitive impairment and neuroimaging methods (present and future)

MCI = Mild cognitive impairment
AD = Alzheimer's disease
CDR = Clinical Dementia Rating

insufficient degree to constitute dementia; they are at increased risk of progression to dementia, with conversion rates to clinical AD of approximately 12% annually and up to 80% at 6 years of follow-up.[4] However, this is an unstable construct where some MCI subjects will convert to clinical AD (MCI-converters) while others will not (MCI non-converters).[5]

Prevailing clinical criteria for MCI have low to moderate diagnostic accuracy in identifying MCI and in predicting progression to dementia.[6] The observation from neuropathological studies that the accumulation of AD pathology (β.-amyloid plaques and neurofibrillary tangles) precedes the onset of clinical disease by as long as 20–30 years,[7] suggests that functional and structural brain changes may occur prior to apparent clinical manifestations of cognitive impairment. This provides the impetus for the development of reliable biomarkers such as neuroimaging to complement clinical approaches in early diagnosis and predicting progression.

Whereas previously the primary purpose of neuroimaging was to rule out potentially reversible causes of cognitive impairment (such as space-occupying lesion or hydrocephalus), recent advances in the field of structural and functional neuroimaging have rendered neuroimaging as an important part of the diagnostic armamentarium of biomarkers for AD. This is reflected in the revised NINCDS-ADRDA criteria for diagnosis of AD,[8] which stipulates the need for at least one abnormal biomarker (which may include structural imaging with MRI or molecular imaging with PET) in the diagnosis of AD and its prodromal stages.

In our review, we will review evidence regarding the utility of neuroimaging biomarkers from the standpoints of diagnosis of early AD, predicting MCI conversion to AD and monitoring subsequent disease progression.

Structural Neuroimaging

Structural MRI

Medial Temporal Lobe Volumetry

MRI studies have documented that cortical atrophy occurs in a defined sequence with disease progression, in line with the predictable spatial pattern of neurofibrillary tangle accumulation seen at autopsy.[9] Atrophy of medial temporal structures, namely entorhinal cortex and hippocampus has been reported in mild AD patients[10,11] with subsequent volume reductions in other cortical regions with AD disease progression. Likewise, in MCI subjects, MTL atrophy has been consistently observed (Table 18.1).[12]

Longitudinal studies have shown decreased ERC[13–15] and HC volumes[16,17] at baseline to be predictive of MCI-converters. It has been argued that ERC atrophy might be a better predictor of AD progression than HC volume loss[14,17] while other studies have shown less clear-cut results. In a more qualitative manner, assessing MTL atrophy using a standardized visual rating scale[18–20] has also been shown to be predictive

Table 18.1 Neuroimaging biomarkers in predicting AD conversion in MCI patients

	Sensitivity/ Specificity	Accuracy
STRUCTURAL NEUROIMAGING		
Structural MRI		
• MRI volumetry[13–17] (ERC and HC atrophy)	Sn 50%, Sp 90%,	Ac81–85%[14,16,17]
• Visual rating scale (medial temporal lobe atrophy)[18–20]	Sn 70–78%, Sp 68–90%[19]	
• Brain atrophy rates (HC, ERC and Ventricular volume, whole brain)[21–23,102]		Ac 60.4%[102]
Voxel-based morphometry		
• Voxel-based morphometry[30–33]		
Deformation-based morphometry [35]		
• Multivariate deformation-based brain analysis		Ac 80%(CSF maps)
FUNCTIONAL NEUROIMAGING		
SPECT		
• SPECT[43–45] (↓ blood flow at cingulate, left frontal, inferior parietal, angular gyrus and precuneus regions)	Sn,Sp approx 80%[44]	Ac 84.4%[43]
FDG-PET		
• PET [49–51] (↓ glucose metabolism at 84%[49,51,99] temporoparietal region)	Sn 96.8%, Sp 58.8%, PPV48.1%, NPV 95.2% [51]	Ac 75 –
^{1}H MRS		
• Brain magnetic resonance spectroscopy (occipital cortex N-acetylaspartate/creatine ratio)	Sn 100%, Sp 75%, PPV 83%, NPV 100%,	Ac 88.7%[57]
fMRI		
• fMRI (↑recruitment of larger extent of right parahippocampal gyrus during encoding)[66]		
DWI		
• DWI (Apparent diffusion coefficient)[71]		
DTI		
• Elevated mean diffusivity in MCI-converters[81]		
MOLECULAR ADVANCES		
Amyloid imaging		
• Significantly higher ^{11}C-PIB retention[92]		
COMBINATION BIOMARKERS		
• SPECT and MRI volumetry[99]		
• Neuropsychological testing and PET		Ac 90–92.3%[49–51]
• APO-E and PET	Sn 100%, Sp 90%	Ac 94%[99–100]
• Neuropsychological testing and MRI volumetry		Ac 78.8%[101]
• CSF-tau and PET[102]		

Sn = Sensitivity; Sp = Specificity; Ac = Accuracy; ERC = entorhinal cortex; HC = hippocampal; DWI = diffusion-weighted imaging; SPECT = Single photon emission tomography; PET = Positron emission tomography; fMRI = functional Magnetic Resonance Imaging; DTI = Diffusion tensor imaging; APOE = apoliprotein E-4

of MCI-converters. From the standpoint of MRI brain atrophy rates, those of HC, ERC and whole brain were found to be greater among MCI-converters (3–7% change per year from baseline values compared to 0.4–3.7% change per year in non-converters).[21–23] Differences in longitudinal studies of brain atrophy rates between MCI-converters and normal aging over a period of up to 5 years have been demonstrated (Table 18.2).[21,22]

Automated Data-Driven Methods

With advances in technology, the focus has shifted in recent years from manual volumetric methods of regions of interest to automated data-driven methods, such as automated measurement of whole-brain volume over time,[24,25] as well as novel techniques such as voxel-based volumetry, deformation-based morphometry and analysis of cortical thickness.

Table 18.2 Longitudinal neuroimaging studies

Neuroimaging method	Years of follow-up	Results
MRI volumetry		
- Whole brain volume [24]	1.8 years	Normal control = −0.45% change/year Mild DAT = −0.98%/year
- Serial brain registered brain MRI [25] (Brain atrophy rate)	1 year	Normal control = −0.47%/year
- Hippocampal volume [11]	1–5 years	Normal control = −1.4%/year Normal converter = −3.3%/year MCI-stable = −1.8%/year MCI-converters = −3.3%/year AD-fast progressor = −3.0%/year AD-slow progressor = −3.6%/year
Entorhinal cortex colume [11]	1–5 years	Normal control = −2.9%/year Normal converter = −5.1%/year MCI-stable = −3.7%/year MCI-converters = −6.8%/year AD-fast progressor = −8.0%/year AD-slow progressor = −8.4%/year
Whole brain volume [11]	1–5 years	Normal control = −0.4%/year Normal converter = −0.8%/year MCI-stable = −0.4%/year MCI-converters = −6.8%/year AD-fast progressor = −0.6%/year AD-slow progressor = −1.4%/year
Ventricular volume [11]	1–5 years	Normal control = 1.7%/year Normal converter = 3.4%/year MCI-stable = 2.6%/year MCI-converters = 3.4%/year AD-fast progressor = 4.3%/year AD-slow progressor = 6.4%/year
Voxel-based morphometry		
- Medial occipitoparietal area [33]	3 years	
Positron Emission Tomography (PET)		
- Regional cerebral glucose metabolism (parietal, temporal, occipital, frontal, Posterior cingulate region) [53]	1 year	Differences comparing healthy controls with mild-moderate AD patients z-score = 3.82 – 6.61
Amyloid imaging (^{11}C-PIB)		
- PIB retention [94]	2 years	Relatively stable PIB retention in mild AD subjects

DAT = Dementia of Alzheimer type; MCI = Mild cognitive impairment; AD = Alzheimer's disease

(i) VBM

VBM is based on a low-dimensional spatial transformation of brain scans into a common reference space to get rid of global differences in brain size and shape; the remaining gray matter volume differences are parameters then driven into a voxel-based univariate statistic.

In both AD and MCI subjects, VBM consistently shows atrophy in the cortical grey matter in the MTL and lateral temporal and parietal association areas.[26–29] VBM has also been shown to have good predictive ability for MCI-converters with reduced gray matter density in the medial temporal, hippocampal, posterior cingulate and precuneus regions compared to non-converters.[30–32] A recent longitudinal study in mild AD subjects showed that VBM-derived medial occipitoparietal atrophy at baseline better anticipated the rate of progression over 3 years, compared with clinical and neuropsychological assessment.[33]

(ii) DBM

DBM transforms brain volumes at high resolution to a standard template to completely eliminate the anatomical differences between brains; the deformation fields then offer a multivariate vector field of localization information from which regional volume effects can then be extrapolated. Based on the pattern of spatial distribution involving HC, bilateral temporal, (L) fusiform gyri and posterior cingulate regions, Davatzikos et al.[34] reported good accuracy in differentiating MCI individuals from controls. Another study by Teipel et al.[35] also demonstrated good discrimination between MCI-converters and non-converters using multivariate deformation-based CSF and brain maps.

(iii) Other methods

By determining the thickness of the entire cortical mantle[36] automated measurements of cortical thickness have shown a high accuracy (>90%) in differentiating AD from controls. However, no data is available with regards to the use of cortical thickness in predicting AD progression in MCI subjects.

Hippocampal radial atrophy mapping technique by Thompson et al.[37] showed differences between AD and normal controls. Smaller HC and specifically CA1 and subicular involvement was associated with increased risk of AD progression in MCI subjects.[38]

Summary

MRI volumetry and brain atrophy rates have fairly good diagnostic and predictive value in MCI subjects. Longitudinal data on brain atrophy rates with disease progression are available and hence, can be used for monitoring disease progression in clinical trials. The limitations of structural neuroimaging as a biomarker include problems with the accurate delineation of regions of interest and lack of standardization of imaging and measurement techniques, making it difficult to compare data across the different institutions. The advent of automated data-driven innovations for structural imaging holds promise, although longitudinal data are still required.

Functional Neuroimaging

Functional Imaging

SPECT

Reduced CBF in the parietal, posterior cingulate and precuneus have been observed in early AD[39,40] and MCI subjects.[41,42] Using a combination of regional CBF at the cingulate, hippocampal-amygdaloid complex and the thalamus on SPECT, 84.8% of MCI-converters were identified.[43] Other studies showed decreased rCBF in the left frontal region,[44] left posterior cingulate gyrus,[42] inferior parietal lobe, angular gyrus and precuneus[45] to be similarly predictive.

FDG-PET

An AD-like pattern of cerebral glucose hypometabolism has been observed in MCI subjects,[46,47] and this is associated with elevated cerebrospinal fluid p-tau.[48] FDG-PET studies also reveal regional cerebral hypometabolism in the left temporo-parietal region,[49] right superior temporal region,[50] inferior parietal, posterior cingulate and medial temporal cortices[51] to be predictive of MCI-converters. Longitudinal FDG-PET studies show serial decline in glucose metabolism in the temporal, parietal, frontal and posterior cingulate regions. Using left frontal regions,[52,53] it is estimated that only 36 subjects per group would be required to show a 33% treatment effect in an adequately powered (80%) 1 year placebo-controlled trial.[53]

Proton MRS

MRS is a diagnostic technique measuring neuroaxonal injury by quantification of N-acetylaspartate/ creatine (NAA/Cr) ratio. There is evidence of differences in neuronal damage between AD, MCI and controls in a decremental manner in the whole brain, posterior cingulate and hippocampus.[54–56] The NAA/Cr ratio in the occipital cortex has been shown to reasonably predict MCI-conversion.[57] Currently there are no longitudinal data for MRS.

fMRI

Functional MRI studies that have been conducted in early cognitive impairment subjects (namely early AD and MCI subjects) show altered resting state networks[58,59] as well as decreased or delayed activations during task performances using BOLD response. However, the pattern is inconsistent and range from a decremental response from AD through MCI to normal controls,[60–62] to a compensatory increased activation in hippocampus[63–65] in MCI subjects. A study using fMRI showed that the MCI-converters recruited a larger extent of the right parahippocampal gyrus upon the encoding phase of memory testing,[66] reflecting a compensatory response to accumulating AD pathology. Currently, there are no longitudinal fMRI data available

ASL-MRI

Perfusion MRI using ASL-MRI uses magnetically labeled water protons as an endogenous tracer to denote an absolute temporal change in CBF. Its utility lies in the fact that it is able to obtain CBF maps repeatedly in short succession, thus enabling dynamic measurements of CBF. Resting ASL-MRI has shown decreased CBF in AD patients in the temporal, lateral and medial aspects of the frontal and parietal cortex compared to controls.[67] A study reported attenuated CBF in posterior cingulate, precuneus, bilateral inferior parietal gyri in AD compared to MCI subjects.[68] A recent ASL-MRI study of amnestic MCI subjects performing memory-encoding tasks reported significant regional cerebral hypoperfusion in the right precuneus and cuneus and an inability to modulate CBF in response to the functional task at hand.[69] There is currently no evidence with regards to prediction of AD progression in MCI subjects and longitudinal data.

DWI

Using DWI, HC ADC has been shown to be higher in AD and MCI subjects compared to controls.[70] The measurement of HC ADC improved the ability of HC measurements to predict MCI-converters.[71] There are currently no longitudinal data on serial progression for DWI.

DTI

DTI is an extended form of diffusion-weighted imaging of brain matter. Diffusion gradients are applied in several spatial directions to determine a multidimensional diffusion tensor. From these diffusion tensor measures of movement, directionality can then be derived. Fractional anisotropy measuring directionality of fibre tracts and mean diffusivity determining overall diffusivity are frequently employed parameters. The observation of widely distributed disintegration of white matter with a different pattern of degeneration from grey matter suggests that it might be an independent factor in AD progression.[72]

Comparing AD with normal subjects, DTI demonstrated white matter changes in the anterior temporal lobe,[73] uncinate fasciculus,[74] corpus callosum[75] as well as corticothalamic and thalamocortical radiations.[76] White matter changes are also seen in MCI subjects[77–79]; a study by Mueller et al,[77] reported superior accuracy compared to volumetric measurements in differentiating MCI subjects from normals. However, further studies are needed to determine the utility of white matter changes detected using DTI.[80] Fellgiebel et al.[81] demonstrated elevated left HC mean diffusivity at baselines in MCI-converters compared to MCI non-converters despite no differences hippocampal volumes and clinical performance. No data are currently available with regards to longitudinal progression.

Summary

FDG-PET appears to be the leading candidate among the functional neuroimaging modalities, with available evidence for MCI diagnosis, prediction of MCI-converters and longitudinal data in monitoring serial progression.

Among the newer MRI-based techniques, DTI appears to hold great promise as theoretically, microstructural alterations of the cerebral fibre system would predate volumetric changes. However, more data (especially on longitudinal progression) are needed before definitive recommendations can be made.

Molecular Advances

Amyloid Imaging

Advances in molecular imaging techniques have made it possible to visualize ß-amyloid in-vivo in Alzheimer patients by the use of small molecular ligands that bind with nanomolar affinity to amyloid and that enter the brain in amounts sufficient for imaging with PET.[82] Taking the cerebellum as the reference region, quantitative measures are used to analyze the generated PET images using either region-of-interest or voxel-based analysis to derive region-specific and global values of distribution volume ratio or binding potential.[83–85] Because positive scans can be seen in other forms of cerebral Aβ (e.g. cerebral amyloid angiopathy), concomitant AD pathology (e.g. dementia of Lewy body with amyloid pathology), and preclinical AD pathology (i.e. asymptomatic healthy control with cortical amyloid deposition), it is best not to equate amyloid deposition to clinical diagnosis from the outset but to think of PET amyloid tracer scans more fundamentally as a method to detect and quantify cerebral β-amyloidosis.[86]

PET amyloid ligands can be broadly divided into two groups: ^{11}C-based and ^{18}F- based. Table 18.3 summarizes the characteristics of two of the more widely studied compounds.^{11}C-PIB binds specifically to fibrillar Aβ with no demonstrable binding to neurofibrillary tangles, unlike ^{18}F-FDDNP which binds to both amyloid and tangles.[82] ^{11}C-PIB shows a greater magnitude of cortical binding, which allows PIB images to be visually read without quantification ($\kappa = 0.90$) and acquired with a shorter scanning time.[87] However, the short radioactive decay half-life of ^{11}C limits the use of ^{11}C-PIB to centers with an on-site cyclotron and ^{11}C radiochemistry expertise.[88] Rowe et al.[89] recently reported the results of a novel PET tracer, ^{18}F-BAY94–9172, which combines the characteristics of ^{11}C-PIB with the advantages of ^{18}F- based compounds.

Amyloid imaging studies in AD revealed increased cortical retention in the frontal, parietal and lateral temporal cortices, striatum and posterior cingulate, in accordance with the distribution of amyloid pathology previously documented in postmortem studies.[83,84,86] Recent studies in MCI subjects showed intermediate cortical binding compared with AD patients and controls.[90–91] Small et al.[91] reported that ^{18}F-FDDNP had better discriminatory ability for MCI compared with controls with FDG-PET metabolism and MRI medial temporal lobe atrophy (AUC: 0.95 vs 0.77 vs 0.64 respectively). MCI-converters had higher PIB retention in brain at baseline compared to MCI non-converters[92] and one study showing elevated PIB values in AD subjects compared to nondemented controls.[93] Intriguingly, there are consistent reports of positive scans in up to 23% of healthy elderly controls, with some of these subjects demonstrating cortical binding

Table 18.3 Differential properties of amyloid imaging modalities

	^{18}F-FDDNP	^{11}C-PIB
Properties		
Binding affinity	Aβ 40, NFT	Aβ 40, Aβ 42 (fibrillar)
Radioactive decay $T_{1/2}$	110 min	20 min
Scanning time	120 min	60–90 min 40 min if visual analysis
Increase in cortical Aβ binding (AD vs controls)	9%	40–80%
Available Evidence		
Diagnosis		
AD	Yes	Yes
MCI	Yes	Yes
Prediction of AD conversion in MCI	No	Yes
Longitudinal course	Limited 2-year data in MCI/healthy controls	Unchanged PIB retention after 2 years in mild AD

Aβ: β-amyloid; AD: Alzheimer's disease; ^{11}C-PIB: ^{11}C-Pittsburg compound B; ^{18}F-FDDNP: 2-(1-{6-[(2-[^{18}F]fluroethyl)(methyl) amino]-2-napthyl}ethylidene)malononitrile; MCI: Mild cognitive impairment; NFT: Neurofibrillary tangles

that was indistinguishable from AD.[84,90,91] Longitudinal follow-up is required to determine whether these asymptomatic controls with positive scans truly turn out to be preclinical AD cases.

In a 2-year longitudinal study using ^{11}C-PIB, there was no significant change in PIB retention compared to baseline despite a decline in cerebral glucose metabolism and cognition.[94] Stable PIB retention suggests that amyloid levels in the brain may reach a plateau early in the course of disease that precedes a decline in cerebral glucose metabolism and cognition.[82] Although there was an increase in ^{18}F-FDDNP binding at 2 years in three subjects who progressed, it is plausible that this may reflect binding to non-amyloid elements such as tau.[82,94]

Summary

To date, ^{11}C-PIB is the most extensively studied PET amyloid tracer. There is emerging evidence for amyloid imaging in the diagnosis of prodromal AD as well as predicting AD progression in MCI subjects. From the standpoint of clinical trials of anti-amyloid therapy, in-vivo amyloid imaging pre-treatment allows selection of patients with demonstrable cerebral Aβ loads; repeated imaging during ongoing treatment allows detection of decrease in insoluble Aβ load in response to amyloid-clearing drugs such as immunotherapy. However, the lack of serial change of ^{11}C-PIB with disease progression implies a limited role in monitoring the response to disease modifying drugs that act by halting amyloid deposition. Amyloid imaging needs to be more practically accessible and affordable before it can be transferable to the clinical diagnostic routine.

Combination Biomarkers

Recent studies have combined biomarkers to ascertain whether there is any added advantage in diagnostic and predictive performance compared with a single modality. We review the evidence for combination biomarker studies that involved neuroimaging.

Combination Neuroimaging Biomarkers

The addition of DTI fractional anisotropy and MRI HC volumetry improved the accuracy of diagnosing MCI and AD from normal controls compared to HC volumetry alone (63–74% and 78–91% for MCI and AD compared to controls respectively).[95] Kawachi et al.[96] reported that the accuracy of FDG-PET diagnosis of very mild AD was 89% and that of VBM-MRI was 83%, but in combination, the accuracy improved to 94%. A recent study noted the improved diagnostic classification using both ^{11}C-PiB and structural MRI (statistical parametric mapping and VBM) compared to either imaging methods in isolation.[97] For the identification of MCI-converters, a combination of both SPECT and MRI volumetry showed better discriminative performance than either used alone in predicting AD conversion.[98]

Combination of Neuroimaging with Other Biomarkers

In a study of MCI subjects, it was observed that the combination of impaired delayed recall and FDG-PET cerebral hypometabolism improved classification accuracy of MCI converters to 92.3% and MCI non-converters to 92.8%.[51] Various longitudinal studies involving MCI subjects also reported improved predictive accuracy with the combination of neuroimaging and other biomarkers: APOE ε4 genotype and FDG-PET[99,100]; episodic memory testing and MRI measures of ventricular and HC volumes[101]; cerebrospinal fluid tau and posterior cingulate hypoperfusion on SPECT.[102]

Conclusions and Future Directions

Recent unprecedented advances in the area of neuroimaging biomarkers in prodromal AD are in tandem with the growing emphasis on early diagnosis of the condition where disease-modifying therapeutic strategies are very likely to have a greater impact. Of particular relevance to the area of clinical trials of disease modifying therapy would be the availability of neuroimaging biomarkers with the discriminatory capacity to accurately diagnose MCI subjects and identify those at greatest risk of advancing to clinical disease; the ability to clearly indicate disease progression would enable the monitoring of treatment response.

In order for a diagnostic biomarker to be useful, certain criteria need to be met (see chapter 1 of this book, Ritsner, Gottesman). There is evidence

to support the use of MRI volumetry and FDG-PET biomarkers in the diagnosis of early cognitive impairment (MCI and early AD) with good sensitivity and specificity in differentiating pathological states (MCI and early AD) from normals as well as in predicting AD progression in at-risk MCI individuals. With regards to monitoring disease progression, the availability of reasonably good longitudinal normative data in age-matched controls supports the use of MRI volumetry and FDG-PET imaging. Using various techniques, brain atrophy rates and PET hypometabolism with disease progression exhibit a clinical effect of sufficient magnitude that can permit the use of fewer subjects in clinical trials of disease modification compared to using only anticipated changes on cognitive test scores. Recent advances in the various automated data-driven methods in structural neuroimaging can hopefully help to further improve the inter-rater reliability of volumetric data in multi-centre studies.

The most exciting development among the novel techniques is arguably the emergence of amyloid-specific imaging, which opens up new avenues for the evaluation of anti-amyloid therapy. Pre-treatment identification of scan-positive MCI subjects with demonstrable Aβ loads would permit the recruitment of smaller number of subjects and shorter observational periods. Comparison of pre-post treatment scans could provide an important surrogate outcome of the effectiveness of amyloid-clearing therapy. Mattis et al.[86] suggested that a twofold decrease in the test-retest variability, corresponding to 10–20% reduction in PIB retention post-treatment, should be sufficient to detect a reduced Aβ load. The diagnostic utility can potentially be extended to the presymptomatic histopathological AD group and allow the initiation of disease modifying therapy before extensive irreversible neuronal damage occurs (Fig. 18.1). However, practical issues relating to scan time, radioactive decay half-day, false positivity (e.g. cerebral amyloid angiopathy) and lack of longitudinal change (in the case of PIB imaging), need to be addressed.

Neuroimaging biomarkers should be used in combination with other biomarkers to produce the highest diagnostic and prognostic power necessary for accurate characterization of AD at its earliest stages. In addition, we strongly recommend the use of neuroimaging and other biomarkers to be supplemented by comprehensive clinical and neuropsychological assessment. The unexpected finding of greater brain volume loss despite better cognitive function among antibody responders in the phase II Aβ immunization trial[103] is a reminder that any treatment-related changes in biomarker levels should always be anchored to a comprehensive clinical evaluation that additionally incorporates cognitive, behavioral and functional measures.

A new multicenter AD research project called the Alzheimer's Disease Neuroimaging Initiative (ADNI) was launched in 2004 to identify neuroimaging measures and biomarkers associated with cognitive and functional changes in healthy elderly, MCI and AD subjects, encompassing clinical sites in United States and Canada.[104,105] This would hopefully address the issue of measurement variability via the development of optimized and standardized measurement protocols. It would also enable adequately powered trials to be conducted using the newer neuroimaging modalities which hold much promise such as functional imaging techniques (e.g. BOLD fMRI/ ASL-MRI), diffusion tensor imaging and amyloid imaging. With the newer neuroimaging techniques, it is foreseeable that the frontiers of diagnostic ability would move from established AD towards prodromal AD, and eventually even to preclinical AD (Fig. 18.1) where disease-modifying therapeutics would be able to target the disease at its earliest stage.

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