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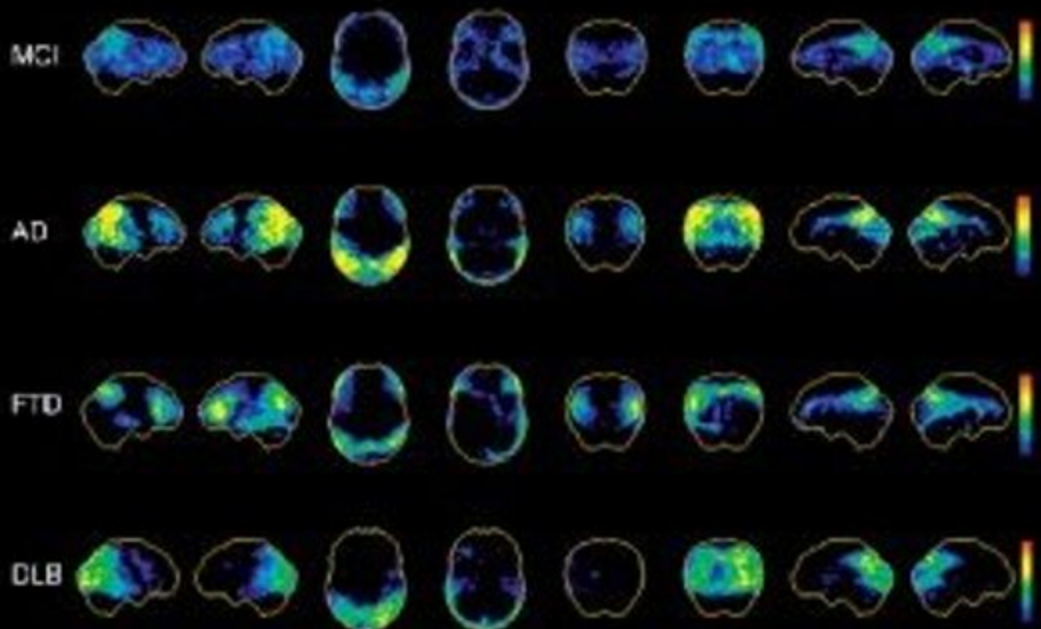

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CONTRIBUTORS

Numbers in parentheses indicate the pages on which the authors' contributions begin.

Katherine J. Bangen (81), Department of Psychiatry, School of Medicine, University of California, San Diego 92093, USA

Yvonne Bannon (1), Department of Psychiatry and Behavioral Medicine, University of South Florida, 3515 East Fletcher Avenue, MDC-14, Tampa, Florida 33613, USA

Lars Bertram (167), Neuropsychiatric Genetics Group, Department of Vertebrate Genomics, Max-Planck Institute for Molecular Genetics, Berlin 14195, Germany; and Genetics and Aging Research Unit, Department of Neurology, Massachusetts General Hospital, Charlestown, Massachusetts, 02129, USA

Mona K. Beyer (49), The Norwegian Centre for Movement Disorders; and Department of Radiology, Stavanger University Hospital, Stavanger, Norway

Mark W. Bondi (81), Veterans Affairs San Diego Healthcare System, San Diego 92161, USA; and Department of Psychiatry, School of Medicine, University of California, San Diego 92093, USA

Aimee Borazanci (245), Department of Neurology, Louisiana State University School of Medicine-Shreveport, Shreveport, Louisiana 71103, USA

Andrea C. Bozoki (185), Department of Neurology, Michigan State University, East Lansing, Michigan, 48824, USA

Maria T. Caserta (1), Department of Psychiatry and Behavioral Medicine, University of South Florida, 3515 East Fletcher Avenue, MDC-14, Tampa, Florida 33613, USA

Jody Corey-Bloom (81), Department of Neurosciences, School of Medicine, University of California, San Diego 92093, USA; and Veterans Affairs San Diego Healthcare System, San Diego 92161, USA

Turi O. Dalaker (49), The Norwegian Centre for Movement Disorders, Stavanger University Hospital, Stavanger, Norway; and Department of Neurology, Buffalo Neuroimaging Analysis Center, State University of New York at Buffalo, Buffalo, New York 14203, USA

Lisa Delano-Wood (81), Veterans Affairs San Diego Healthcare System, San Diego 92161, USA; and Department of Psychiatry, School of Medicine, University of California, San Diego 92093, USA

Jack C. de la Torre (35), Sun Health Research Institute, Center for Alzheimer's Research, Sun City, Arizona 85351, USA

Carol Di Perri (49), Department of Neuroradiology, IRCCS, C. Mondino, University of Pavia, Pavia, Italy; and Department of Neurology, Buffalo Neuroimaging Analysis Center, State University of New York at Buffalo, Buffalo, New York 14203, USA

Halim Fadil (245), Department of Neurology, Louisiana State University School of Medicine-Shreveport, Shreveport, Louisiana 71103, USA

Muhammad U. Farooq (185), Department of Neurology, Michigan State University, East Lansing, Michigan, 48824, USA

Francisco Fernandez (1), Department of Psychiatry and Behavioral Medicine, University of South Florida, 3515 East Fletcher Avenue, MDC-14, Tampa, Florida 33613, USA

Glen R. Finney (263, 283), Memory and Cognitive Disorders Program, University of Florida Department of Neurology, Gainesville, Florida 32610-0236, USA

Brian Giunta (1), Department of Psychiatry and Behavioral Medicine, University of South Florida, 3515 East Fletcher Avenue, MDC-14, Tampa, Florida 33613, USA

H. Randall Griffith (105), Department of Psychology; and Alzheimer's Disease Research Center; and Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama 35233, USA

Elhachmia Ait Ben Haddou (245), Service de Neurologie B et Neurogenetique, Hopital des Specialties, Rabat, Morocco

Jennifer C. Hanson (215), Drexel University College of Medicine, Mail Stop 423, Philadelphia, Pennsylvania 19107, USA

Jan A. den Hollander (105), Department of Medicine (Cardiology), University of Alabama at Birmingham, Birmingham, Alabama 35233, USA

Stephen L. Jaffe (151, 245), Department of Neurology, Louisiana State University School of Medicine-Shreveport, Shreveport, Louisiana 71103, USA

Amy J. Jak (81), Veterans Affairs San Diego Healthcare System, San Diego 92161, USA; and Department of Psychiatry, School of Medicine, University of California, San Diego 92093, USA

Anahid Kabasakalian (283), Memory and Cognitive Disorders Program, University of Florida Department of Neurology, Gainesville, Florida 32610-0236, USA

Roger E. Kelley (21), Department of Neurology, LSU Health Sciences Center, Shreveport, Louisiana 71103, USA

Elena Korniychuk (245), Department of Neurology, Louisiana State University School of Medicine-Shreveport, Shreveport, Louisiana 71103, USA

Carol F. Lippa (215), Drexel University College of Medicine, Mail Stop 423, Philadelphia, Pennsylvania 19107, USA

Francisco A. Luque (151), VA Neurology Service, Overton Brooks VAMC, Shreveport, Louisiana 71101, USA; and Department of Neurology, Louisiana State University School of Medicine-Shreveport, Shreveport, Louisiana 71103, USA

Uma Menon (21), Department of Neurology, LSU Health Sciences Center, Shreveport, Louisiana 71103, USA

Alireza Minagar (245), Department of Neurology, Louisiana State University School of Medicine-Shreveport, Shreveport, Louisiana 71103, USA

James M. Noble (133), Gertrude H. Sergievsky Center, and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain; and Department of Neurology, Columbia University Medical Center, New York 10032, USA; and Department of Neurology, Harlem Hospital Center, Columbia University College of Physicians and Surgeons, New York 10037, USA

Bradley J. Robottom (229), Department of Neurology, University of Maryland School of Medicine, Baltimore, Maryland 21230, USA

Nikolaos Scarmeas (133), Gertrude H. Sergievsky Center, and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain; and Department of Neurology, Columbia University Medical Center, New York 10032, USA

Mike R. Schoenberg (1), Department of Psychiatry and Behavioral Medicine, University of South Florida, 3515 East Fletcher Avenue, MDC-14, Tampa, Florida 33613, USA

Christopher C. Stewart (105), Department of Psychology, University of Alabama at Birmingham, Birmingham, Alabama 35233, USA

Jun Tan (1), Department of Psychiatry and Behavioral Medicine, University of South Florida, 3515 East Fletcher Avenue, MDC-14, Tampa, Florida 33613, USA

William J. Weiner (229), Department of Neurology, University of Maryland School of Medicine, Baltimore, Maryland 21230, USA

Christina E. Wierenga (81), Veterans Affairs San Diego Healthcare System, San Diego 92161, USA; and Department of Psychiatry, School of Medicine, University of California, San Diego 92093, USA

Mohamed Yahyaoui (245), Service de Neurologie B et Neurogenetique, Hopital des Specialties, Rabat, Morocco

Robert Zivadinov (49), Department of Neurology, The Jacobs Neurological Institute; and Department of Neurology, Buffalo Neuroimaging Analysis Center, State University of New York at Buffalo, Buffalo, New York 14203, USA

PREFACE

The significant increase in human longevity translates into a significant increase in the number of people with dementia around the globe. Due to its relentlessly progressive course and lack of any effective treatments, neurodegenerative dementing disorders pose an enormous economic and social burden on society as well as a great emotional burden. During the last two decades, our knowledge about molecular mechanisms of the various neurodegenerative dementias has grown remarkably, giving us unprecedented insight into the fundamental mechanisms of these incurable disorders.

This volume of the *International Review of Neurobiology* focuses on dementia and related diseases. The volume contains various chapters on pathogenesis, clinical features, genetics, neuroimaging and molecular pathogenesis of the neurodegenerative dementias. The first chapter by Caserta *et al.* addresses the very important topic of normal aging and highlights its salient features. The next three chapters discuss the role of cerebrovascular disease in cognition. First, Roger E. Kelley provides a comprehensive update on subcortical ischemic cerebrovascular dementia, and then J. C. de la Torre discusses the role of cerebrovascular and cardiovascular pathology in Alzheimer's disease. These two excellent chapters are followed by another detailed chapter by Dalaker *et al.*, explaining the neuroimaging of cognitive impairment in vascular disease. These authors provide our readers with the latest developments on this subject, highlighting recent advances in neuroimaging of cognitive decline caused by cerebrovascular disorders. The focus of this volume then switches to mild cognitive impairment (MCI), and the next three contributions cover various aspects of this significant clinical issue. Jak *et al.* discuss the role of neuropsychology and neuroimaging in better understanding of clinical subtypes of MCI. The next two chapters explore various imaging procedures used to study MCI. Griffith *et al.* discuss the role of proton MR imaging in the study of dementing disorders including MCI, and then Noble and Scarmeas provide readers with an interesting perspective on the application of PET imaging for the diagnosis of Alzheimer's disease and MCI.

The next section of this volume covers Alzheimer's disease and other progressive neurodegenerative dementias. First, Luque and Jaffe discuss the underlying molecular and cellular mechanisms of dementia of the Alzheimer's type. This interesting chapter is followed by another superb update on the genetics of Alzheimer's disease by Lars Bertram. The next three chapters discuss other neurodegenerative dementias. Bozoki and Farooq present an excellent discussion concerning the neuropsychology and neuroimaging of frontotemporal lobar degeneration.

Next, Lippa and Hanson give an update on Lewy body dementia. This extensive review is followed by Robottom and Weiner's chapter on the dementia in Parkinson's disease, presenting readers with the most recent findings on this subject.

The final section of this issue of the *International Review of Neurobiology* concentrates on important subjects which we as neurologists encounter on a daily basis. First, Minagar and colleagues discuss various causes of dementia in younger individuals and present the readers with a systematic approach for the diagnosis of this uncommon presentation. Then, Glen Finney and Anahid Kabasakalian discuss the pathogenesis and clinical features, as well as the diagnostic procedures for investigating normal pressure hydrocephalus and other reversible dementias.

In summary, various contributors to this issue of the *International Review of Neurobiology* have attempted to improve the readers' knowledge concerning a broad spectrum of dementing disorders. Each contribution provides the inquisitive reader with the latest developments in our understanding of that particular topic. The editor and the very knowledgeable contributors to this issue hope that this volume of the *International Review of Neurobiology* stimulates the readers' scientific curiosity and promotes basic and clinical research in the dementia.

Finally, I would like to acknowledge the excellent contributions of the various authors to this issue of the *International Review of Neurobiology*. Without their effort and dedication, compiling this volume would have never become a reality. I would also like to thank Ms. Narmada Thangavelu and Mr. Charles Prem Kumar Neelakandan from Elsevier for their time and effort expended to process and complete on this of the journal.

ALIREZA MINAGAR

NORMAL BRAIN AGING: CLINICAL, IMMUNOLOGICAL, NEUROPSYCHOLOGICAL, AND NEUROIMAGING FEATURES

Maria T. Caserta, Yvonne Bannon, Francisco Fernandez, Brian Giunta, Mike R. Schoenberg, and Jun Tan

Department of Psychiatry and Behavioral Medicine, University of South Florida, 3515 East Fletcher Avenue, MDC-14, Tampa, Florida 33613, USA

Brain aging is characterized by numerous physiological, structural, functional, and neurocognitive changes. The interplay of these various processes is complex and characterized by large interindividual differences. Although much is not understood about how we age, there are numerous studies detailing the nature of the changes in the brain as we age. This chapter will review some of the functional, neuropsychological, neuroimaging, and immunological processes known to occur in normal or "healthy" aging. Large epidemiological studies of older adults have shown health status in the elderly is a function of the negative consequences and impairment in functional performance caused by medical co-morbidities. Immunological function declines with age, such that adaptive immunity is reduced to previously encountered pathogens, and there is a weakened adaptive immune response to novel pathogens. Structural and functional neuroimaging studies of cognitively intact older adults have consistently shown volume loss and loss of white matter structural integrity, particularly in prefrontal cortex, which may be associated with cognitive decline. While data are incomplete, one consistent finding has been a decline in cognitive domains, such as arithmetic/numerical ability and perceptual speed. Alternatively, other cognitive functions such as verbal ability, word knowledge, and semantic memory remain

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quite preserved even to old age. Factors identified for healthy cognitive (brain) aging are multifactorial, and likely incorporate biological systems as well as cognitive reserve.

I. Introduction

The percentage of the population over age 65 is growing rapidly in the United States. In 2000, it was 12.4% and in 2050 it is projected to be 20.6% (Health, United States, 2005). Many people in this older age group are healthy but it is well known that functional disability increases with age. There are many theories of aging including "programmed aging" and the "wear and tear" theories. The former regards aging as being regulated by an internal clock and is seen as an extension of development, which is highly regulated and timed process. However, the interplay of disease, environment and genetics is evident not only in epidemiological studies of aging and longevity, but also in functional assessments of the elderly, and in such concepts as cognitive reserve and neural compensation.

Structural and functional imaging studies of intact older individuals have delineated specific areas where there is loss of brain volume and also a reduction in the lateralization of brain activity during cognitive performance in elderly individuals. However, not all of these changes are detrimental to maintaining performance levels and it is not yet clear which changes are precursors to further cognitive decline and which may be true compensatory mechanisms.

II. Epidemiology of Aging: Risks and Implications

Through the year 2000, approximately 35 million of people living in the USA were over 65 years. It is estimated that by 2050, this number will more than double to 82 million with 20% of the US population age 65 years or older (see Table I; Ferrucci *et al.*, 2008). With the life expectancy in old age increasing, and death rates reported to decrease, these numbers may be an underestimate of what is to come (Minino *et al.*, 2007). While older adults are generally healthy and independent and are active in various roles contributing significantly to their families and society, the increase in concurrent medical conditions causing excess morbidity and mortality as well as disability and decline in functional performance negatively impact a significant number of the elderly (Ferrucci *et al.*, 2008). Health status in the elderly is a function of the negative consequences and impairment in functional performance caused by medical co-morbidities.

TABLE I
ACTUAL AND PROJECTED GROWTH OF THE OLDER US POPULATION, 1900–2050 (MILLIONS)

		>65 Years		>85 Years	
Year	Total population (all ages)	Number	Percent of total	Number	Percent of >65 years
1900	76.1	3.1	4.1	0.1	3.2
1950	152.3	12.3	8.2	0.6	4.9
2000	276.1	34.9	12.6	4.4	12.6
2050	403.7	82.0	20.3	19.4	23.7

Note: This table from Ferrucci *et al.* (2008) is used with permission.

Any and all diseases occurring in the elderly cause excess disability and decrements in function in a variety of domains but mostly in independent function. For example, chronic health conditions such as hypertension, hyperglycemia, musculoskeletal disorders, coronary artery disease, cancer, and mixed states of anxiety and depression affect a significant number of the elderly (see Table II). By race and ethnicity these numbers vary among minority men and women when compared with that in White men and women. The proportion of these with cognitive impairment and dementing illness is also rising. Similarly, preexisting anxiety and depression may increase the risk of developing cognitive impairment (Backman, 2008; Loebach *et al.*, 2002).

In large epidemiologic studies such as the Canadian Study of Health and Aging, the authors evaluated the occurrence of an adverse event (symptom, sign, or disease), or the accumulation of a number of such co-morbid events, and modeled the events as a logistic function of chronologic age in a population (Graham *et al.*, 1999). In those who were cognitively normal, a linear relation between the log of the odds of events and chronologic age was present for the majority of symptoms and signs. Thus, the dynamics of aging are a complex process of accumulation of deficits (morbidity), whereby decline from some previously healthy level of synergistically associated symptoms and signs results in distinct patterns of disease.

But these studies are only part of the larger picture. It is a familiar epidemiologic concept that individuals vary not only in whether they develop a disease but also in the ages at which disease occurs and the rates at which pre-morbid changes progress to any specific disease. Available reports of genetic epidemiologic studies on diseases of aging are adding a new dimension—trait genomics—to assess the presence or absence of a disease (or occurrence of an adverse event) or evaluating the level of a given risk factor at one point in time (NIA Aging and Genetic Epidemiology Working Group, 2000). Moreover, two very specific types of age-specific traits are *survival traits* (the age at which a specified outcome has occurred or has not occurred) and *rate-of-change traits* (the rate at which individuals'

TABLE II
AGE-ADJUSTED[a] AND AGE-SPECIFIC MORTALITY IN THE UNITED STATES, 1950 AND 2004 AND PERCENT CHANGE

Cause of death	Age (years)	1950	2004	Change
Diseases of the heart				
Males				
	All ages	697.0	267.9	−61.6
	65–74	2292.3	723.8	−68.4
	75–84	4825.0	1893.6	−60.8
	85+	9659.8	5239.3	−45.8
Females				
	All ages	484.7	177.3	−63.4
	65–74	1419.3	388.6	−72.6
	75–84	3872.0	1245.6	−67.8
	85+	8796.1	4741.5	−46.1
Cerebrovascular disease				
Males				
	All ages	186.4	50.4	−73.0
	65–74	589.6	121.1	−79.5
	75–84	1543.6	402.9	−73.9
	85+	3048.6	1118.1	−63.3
Females				
	All ages	175.8	48.9	−72.2
	65–74	522.1	96.6	−81.5
	75–84	1462.2	374.9	−74.4
	85+	2949.4	1303.4	−55.8
Malignant neoplasms				
Males				
	All ages	208.1	227.7	9.4
	65–74	791.5	907.6	14.7
	75–84	1332.6	1662.1	24.7
	85+	1668.3	2349.5	40.8
Females				
	All ages	182.3	157.4	−13.7
	65–74	612.3	627.1	2.4
	75–84	1007.7	1023.5	1.6
	85+	1299.7	1340.1	3.1

Note: This table from Ferrucci *et al.* (2008) is used with permission.
[a]Data for "all ages" are age-adjusted using the US 2000 standard population.

characteristics change over a specified age interval). Many age-related conditions like dementing illness are likely to be highly polygenic, posing difficulties for identifying genes with these effects inclusive of the survival traits associated with longevity free of neurocognitive impairment. Moreover, there may well be a genotype that delays or accelerates onset of several diseases could affect disease expression and survival significantly. Thus, many important pathologies of aging

may be completely redefined in the era of neurogenomics. Recent neuroimaging findings substantiate the neurogenomics data by way of pathologic finding in age-related changes, such as vascular stiffening and loss of muscle mass that were considered "normal" aging until recently. Genetic factors may also influence not just physiologic functions at one time point but also their rates of change with age.

Thus, with the changing health status of the elderly population, there is an ever increasing role for epidemiology. Epidemiological studies will have a major impact on not just informing the public health entities on the impact on future demand for health services but also, in the era of neurogenomics, on prevention of cognitive decline and disease states such as AD.

III. Normal Aging and Functional Performance

The biophysiological changes that occur as part of normal aging can impact and limit functional performance in the elderly. The extent of impact to functional performance in the elderly is dependant on numerous factors, including cognitive status, physical disability, and medical illness (Njegovan *et al.*, 2001), as well as, emotional factors, quality of life, and numerous protective factors (Vaillant, 2002). The concept of expressing functional performance in terms of a person's ability to carry out routine activities of daily living (ADLs) was first introduced by Katz *et al.* (1963) and expanded by Lawton and Body (1969) to include more complex functions called instrumental activities of daily living (IADLs). ADLs include basic self-care activities such as bathing, dressing, eating, transferring, ambulation, and toileting: IADLs include shopping, managing finances, cooking, cleaning, and telephone use. The US Centers for Disease Control database tracks changes in functional performance in the elderly.

The association between cognitive impairment and functional performance has been studied extensively. A number of studies have demonstrated a relationship between cognitive status and functional performance independent of social, demographic, or medical factors (Hertzog and Wallace, 1997; Moritz *et al.*, 1995; Royall *et al.*, 2005). Predicting and measuring change in ADLs and IADLs with regards to advancing age has been the focus of many studies. Katz (1965) hypothesized that older persons with progressive cognitive decline lost ability to perform ADLs in the opposite order to which the skill(s) were acquired in childhood. Additionally, functional performance of IADLs was more likely to deteriorate prior to ADLs during the course of cognitive decline associated with pathological process. Although many studies have looked at changes in functional performance, and more specifically cognitive decline in the elderly with a disease process, few studies have looked at the correlation between normal physiological cerebral aging and cognitive decline (see below).

The Freedom House Study (Royall *et al.*, 2005) compared independence in IADLs to executive functioning in 547 non-institutionalized people (community dwellers) aged 70 and older. Royall's group concluded that decline in memory had no independent association with decline in functional performance, specifically IADLs. However, decline in executive function did correlate with a subject's ability to independently perform IADLs. Other studies have observed changes in functional performance led to changes in independence, socialization, self-perception, and quality of life (Keller *et al.*, 1999).

A. Quality of Life and Protective Factors

The term "successful aging" first appeared in medical journals in 1961 (Motta *et al.*, 2005). Today the term is used to describe the absence of significant disease and disabilities, maintenance of high levels of physical and cognitive function, and the preservation of social and productive activities (Motta *et al.*, 2005). The Harvard Study of Adult Development is considered the landmark study of adult development and has provided key predictors to "successful aging." This research followed 824 individuals from three separate prospective, longitudinal studies, selected as teenagers from various facets of mental and physical health, throughout their lives. The three groups consisted of 268 Harvard sophomores, a sample of 456 Inner City youths, and 90 women from Stanford—all selected as teenagers and followed throughout their lives. The research focused on (1) adaptation to stress, mental health, and defense mechanisms; (2) the effects of habits—especially alcoholism and affective disorders upon physical health and mortality; (3) the effect of childhood risk factors upon adult adaptation; (4) the unfolding of adult development; and (5) the natural history of alcohol and substance abuse (Valliant, 2002). Although the findings are numerous, key findings suggest the following factors predictive of healthy or "successful aging": being a non-smokers; adaptive coping styles, mature defense styles, and optimism; absences of alcohol abuse; maintaining a healthy weight; stable marriage or relationships; some physical activity; social engagement; and education. Education, including attainment and childhood intellectual ability, is also thought to provide a cognitive reserve in later life (Whalley *et al.*, 2004), protecting from cognitive decline associated with normal aging, as well as, cognitive decline associated to disease process.

B. Centenarians

The number of people living beyond the age of 100 is growing throughout the industrialized world (Motta *et al.*, 2005). Several studies of centenarians have been conducted to determine their level of independence, clinical condition, and

cerebral deterioration and whether centenarians are the prototype for "successful aging." The Italian Multicenter Study on Centenarians (IMUSCE) is one such study (Motta *et al.*, 2008). The IMUSCE was an epidemiological study which identified 1173 centenarians ranging in age from 100 to 109 years. A sub-sample of 346 centenarians was studied to determine the functional performance and cognitive status. The sub-sample was further divided into groups based on physical health and MMSE scores. True independence in all functional performance (IADLs) was seen in only six centenarians (1.7%): while 21 centenarians (6.1%) presented with slight dependence in functional performance. Additionally, 68 centenarians (19.67%) had only a moderate dependency in IADLs and 251 (72.6%) were severely dependent. Of the six independent functioning centenarians and the 21 centenarians with only slight dependence in IADLs, all have had significant changes in their level of social and productive activities, thus they cannot be considered prototypes of successful aging based on the current definition.

IV. T- and B-Lymphocyte Loss of Function in the Aging Immune System

With age, innate immunity progresses to a chronically active state secondary to exhaustion of the more evolutionary recent adaptive (specific) immune system (Franceschi *et al.*, 2007). This is in large part due to age-associated reduction of T-cells due to thymic involution (Aspinall 2000; Aspinall and Andrew, 2000; Linton *et al.*, 2005), as well as fewer bone marrow early progenitor B cells (Allman and Miller, 2005). In early life, naïve T-cells are activated by contact with antigens and then differentiate into effector or memory cells. Because the quantity of T-cells in healthy individuals is stable over the lifespan, peripheral T-cell turnover of preexisting populations in the thymus is required to replace cells to the system in relatively young individuals and to prime T-cells to new antigens (Fann *et al.*, 2005; Pawelec, 2005; Weng, 2006). Thus in the elderly there is an increase in the number of antigen-experienced cells and a decrease in the number of naïve T-cells in the circulation, which results in accumulation of incompetent memory lymphocytes (Cossarizza *et al.*, 1997). These cells likely clonally expand and became effector memory T-cells that were competent at one time, but then lost their antigen-specific function due to their age. This phenomenon is believed to be owed to life-long antigenic stress from immunosurveillance against persistent viruses (antigens), especially cytomegalovirus (CMV) (Solana *et al.*, 2006).

The net result of these age-associated phenomena are (1) reduced adaptive immunity to previously encountered pathogens and (2) weakened adaptive immune response to novel pathogens due to a reduction in the diversity of the antigen-recognition repertoire with age by approximately 10^8 in young adults to 10^6 in the elderly (Goronzy *et al.*, 2005). Moreover, $CD8^+$ T-cells in the elderly

display significantly decreased ability to secrete interferon-gamma (IFN-γ) when stimulated by cognate antigen in comparison to younger age groups (Ouyang *et al.*, 2003a,b). Also, naïve $CD4^+$ T-cells from old humans and mice show decreased responsiveness to TCR stimulation and altered profiles of cytokine production versus naïve $CD4^+$ T-cells from young hosts. Likewise, the helper function of naïve $CD4^+$ T-cells for antibody production by B cells is also decreased (Swain *et al.*, 2005). The decline in responsiveness of naïve $CD4^+$ T-cells is due to the chronologic age of the cells themselves, and not of the individual host (Swain *et al.*, 2005), suggesting that long-term maintenance of naïve $CD4^+$ T-cells through homeostatic cytokines may not have a positive impact on their function. Indeed, naïve $CD4^+$ T-cells that have undergone homeostatic cell divisions proliferate less and secrete less IL-2 in response to antigen than do naïve $CD4^+$ T-cells that have not undergone homeostatic division as is seen in the young (Swain *et al.*, 2005).

Unlike naïve lymphocytes, memory $CD4^+$ T lymphocytes are long lived and relatively competent with age. These antigen-experienced T-cells, when isolated from healthy elderly humans and healthy old mice, respond normally to antigen-induced proliferation *in vitro* (Kovaiou *et al.*, 2005) and those generated at a young age respond well to antigens over time. Conversely, naïve $CD4^+$ T-cells derived in old age respond poorly (Haynes *et al.*, 2005). Together, these studies point to an age-associated defect in memory $CD4^+$ T-cells which may originate from defects of aged naïve $CD4^+$ T-cells that have reduced clonal diversity and proliferation potential. Interestingly, changes of the ratio of memory to effector $CD4^+$ T-cell subsets with age have also been implicated in deficient adaptive immune responses to viral infections and vaccines (Kang *et al.*, 2004).

An additional important age associated defect in T-cell function is accumulation of $CD28^-CD8^+$ T-cells and the loss of naïve $CD8^+$ T-cells. These T-cells are absent in newborns while composing some 85% of circulating $CD8^+$ T-cells in the elderly. The accumulation of $CD28^-CD8^+$ T-cells was also shown in patients with viral infections such as CMV (Almanzar *et al.*, 2005). $CD28^-CD8^+$ T-cells may signify terminal differentiation from the $CD28^+CD8^+$ subset after repeated antigenic stimulation. Functionally, these cells have a reduced proliferative response to TCR stimulation but exhibit normal or even enhanced cytotoxic capacity and are resistant to apoptosis (Azuma *et al.*, 1993). Furthermore, several studies have demonstrated the virtual disappearance of naïve $CD8^+$ T-cells in the elderly associated with a significant increase in the proportions of differentiated effector memory and effector $CD8^+$ T-cells in comparison to younger individuals. Interestingly, most of these cells in the elderly do not have short telomeres. Taken together, these data suggest that, over the course of life, these T-cell populations have undergone a process of end-stage differentiation and that persistent infection with common pathogens, such as CMV, induces chronic stimulation of specific T-cells that leads to terminal differentiation to senescent cells with an altered

functional capability (Effros *et al.*, 2005; Fann *et al.*, 2005; Pawelec, 2005; Tarazona *et al.*, 2000). Further, it seems that clonal expansion of $CD28^{-}CD8^{+}$ T-cells seems directly responsible for increased infection rates and the common failed response to vaccines in the elderly (Almanzar *et al.*, 2005). Decreased adaptive immunity also involves changes in the B-cell repertoire not unlike those observed in the T-cell pool (Ghia *et al.*, 2000; Szbo *et al.*, 1999; Weksler, 2000). The quality of the humoral immune response is decreased with age owing to low serum immunoglobulin concentrations and low numbers of antigen-specific, immunoglobulin-secreting plasma cells. Further, antibody specificity, isotype and affinity changes are typical features of old age. For example, immunoglobulins produced in aged mice have lower affinity and are less protective versus those of young animals (Yang *et al.*, 1996). This may be secondary to aging's adverse effects on the germinal centre reaction in secondary lymphoid tissues (Zheng *et al.*, 1997) and leads to a diminished quantity of germinal centers in response to tetanus toxoid stimulation (Kraft *et al.*, 1987). The quantity of B cells also decreases in the elderly (Franchesci *et al.*, 1995). At the cellular level, alteration in immunoglobulin generation (through class switching) in B cells is observed in aged individuals (Frasca *et al.*, 2005), which may contribute to the decline of the adaptive immune response in the elderly.

V. Neuropsychology of Aging

The literature is replete with data indicating a broad spectrum of neuropsychological functions decline with normal aging (e.g., Craik and Salthouse, 2000; Woodruff-Pak, 1997). What is less clear is the line separating normal aging from cognitive dysfunction and dementia (e.g., Morris and Cummings, 2005; Morris *et al.*, 2001; Petersen, 2003; Raz, 1996, 2000). Various terms and criterion have been used to separate normal aging from abnormal, such as age associated memory impairment (AAMI; Crook *et al.*, 1986), aging-associated cognitive decline (Levy, 1994), benign senescent forgetfulness (Kral, 1962), cognitive impairment no dementia (CIND; Graham *et al.*, 1997), mild cognitive disorder (World Health Organization, 1978), mild cognitive impairment (MCI; Morris *et al.*, 2001; Petersen *et al.*, 1999), mild neurocognitive disorder (Gutierrez *et al.*, 1993), and questionable dementia (Hughes *et al.*, 1982), among others (see also Craik and Salthouse, 2000 for a review). Further complicating the division between normal and abnormal aging processes is the variability in neuropathological and neuropsychological functions between and within samples (e.g., see Craik and Salthouse, 2000; Woodruff-Pak, 1997 for reviews). A summary of neuropsychological changes associated with aging is provided below.

A. Changes in Neuropsychological Function in Normal Aging

It has long been recognized that some cognitive processes decline with age while others appear less affected, giving rise to the traditional dichotomy between the so-called "crystallized" abilities (e.g., accumulated knowledge and expertise) versus those termed "fluid" abilities (e.g., fluid reasoning, working memory, visuoperceptual abilities, processing speed, etc.) (e.g., Craik and Salthouse, 2000; Woodruff-Pak, 1997 for review). Within this framework, crystallized abilities have been considered generally stable with increasing age, while fluid abilities decline with increasing age, some thought to begin declining as early as in one's 20s (Babcock, 1930; Craik and Salthouse, 2000; Lezak, 1995; Wechsler, 1958; Woodruff-Pak, 1997 for review). Until recently, however, much of the previous knowledge regarding age-related cognitive decline have been criticized for lack of longitudinal data, with most derived from cross-sectional studies or other studies having small samples and/or short follow-up time frames (e.g., Baltes and Mayer, 1999; Hertzog *et al.*, 2003; Schaie, 1996).

Changes in normal aging are now being understood from longitudinal data from several sources, including the Berlin Aging Study (Baltes and Mayer, 1999), Mayo's Older Americans Normative Studies (MOANS; Ivnik *et al.*, 1992), Seattle Longitudinal Study (Schaie, 1996), and Victoria Longitudinal Study (Dixon and de Frias, 2004; Hertzog *et al.*, 2003). Combined, these studies provide longitudinal data of individuals beginning in participants' 20s up to 100 years old and beyond (e.g., Singer *et al.*, 2003). While data are incomplete, one consistent finding has been a decline in select cognitive domains beginning as early as the middle to late 20s. Alternatively, other cognitive functions remain quite preserved even to very old age (Singer *et al.*, 2003). Schaie (1994) found the average performances of arithmetic/numerical ability and perceptual speed beginning to decline at around age 25 years old. Alternatively, a general decline in performance on tasks of inductive reasoning, verbal ability, and episodic memory did not become apparent until the fifth or sixth decade of life. While episodic memory is known to decrease with age, some research suggesting as early as the third or fourth decade of life, other research suggests the decline may be much less precipitous and is gradual, at least until the seventh decade of life (Backman *et al.*, 2000). Similarly, Singer *et al.* (2003) found performance on tasks of processing speed, episodic memory, and verbal fluency declined from 70 to 100 years old. Alternatively, word knowledge has consistently demonstrated resilience to aging, remaining quite stable from one's 70s through 100+ years old (e.g., Lezak, 1995; Singer *et al.*, 2003). Executive functions (rapid problem solving, verbal fluency, inhibition, and flexibility) show early and considerable age-related declines (Mittenberg *et al.*, 1989; Parkin, 1996). Indeed, Mittenberg *et al.* (1989) found performance on neuropsychological tests of executive skills, thought to measure frontal lobe functioning, exhibited more age-related decline than other tests in a comprehensive battery. Further complicating

understanding age-related decline in cognitive function are data establishing individual variability in cognitive performance can vary considerably over 1–3 year time periods, although group level change tends to be more modest, at least to the sixth or seventh decades of life (e.g., Dixon *et al.*, 2004; Ivnik *et al.*, 1999). Recent data suggest increased individual variability in cognitive function predicts mortality (MacDonald *et al.*, 2008).

In summary, the cognitive decline observed in normal aging reflects the complex brain changes that occur with increasing age. The decline of cognitive abilities is a complex tapestry of selective areas of preservation while other interrelated areas decline all against a backdrop of biological and physical changes. Indeed, considerable research suggests two over-arching cognitive abilities that decrease with age, processing speed, and working memory, can account for a majority of variance in the age-related declines across a variety of cognitive skills (e.g., see Meyerson *et al.*, 1990; Mitchell, 1993; Salthouse, 1996). As an example, Hertzog *et al.* (2003) found deficits in episodic memory could be accounted for by declines in working memory and perceptual speed. Thus, declines in episodic memory, numerical ability/arithmetic, verbal fluency, and problem solving are, themselves, moderated by the decline in processing speed and working memory. It has been proposed that the decline in processing speed may be associated with the structural integrity of cerebral white matter, but rather than being linear, reflects a threshold phenomenon, in which age-related declines after white matter dysfunction exceeds a critical level (Boone *et al.*, 1992; DeCarli *et al.*, 1995; Raz, 2000).

B. Staving off Cognitive Decline

Aerobic exercise has shown to decrease cognitive morbidity in aging, but a more comprehensive picture including cognitive reserve and cognitive engagement is likely accounting for preventing cognitive morbidity (e.g., Milgram *et al.*, 2006; Stern, 2006). Research has also found older adults routinely use informal techniques to improve memory (e.g., increase use of external memory aides and organizational skills) in compensating for daily cognitive challenges (Dixon *et al.*, 2001). See discussion relating cognitive reserve to structural and functional neuroanatomy below.

VI. Imaging Studies in Aging

The changes that occur with aging in the brain are complex and are associated with large interindividual variability. There is, however, a pattern of selective loss and preservation delineated in numerous studies. The structural

and functional deterioration in specific brain areas is thought to be responsible for the reported cognitive decline that occurs with age while the substrates of "cognitive reserve" are less well defined.

Longitudinal studies using structural MRI from age 3 to 70 years old have shown an increase in cortical gray matter until, about, age 5 followed by a gradual decline in volume until age 70 (Pfefferbaum *et al.*, 1994). White matter growth accelerates during adolescence and then plateaus in the third decade. Several studies have indicated significant gray matter tissue volume loss (Blatter *et al.*, 1995; Brickman *et al.*, 2005; Sullivan *et al.*, 2004; Thompson *et al.*, 2003) while others have shown greater white matter loss in aging (Guttmann *et al.*, 1998; Jernigan *et al.*, 2001).

In general, brain atrophy has been reported consistently in aging and it is more pronounced in the frontal brain areas (DeCarli *et al.*, 1994; Raz *et al.*, 1997; Resnick *et al.*, 2003; Saloat *et al.*, 1999; Tisserand *et al.*, 2002). Other brain areas affected by aging are the temporal lobes with relative sparing of the parietal and occipital lobes (Bartzokis *et al.*, 2001; Good *et al.*, 2001; Raz *et al.*, 1997, 2005). The question of whether this loss is primarily due to gray matter or white matter volume loss remains controversial (see Sullivan and Pfefferbaum, 2007).

Although controversial, hippocampal volume is thought to remain relatively stable with age (Shamy *et al.*, 2006; Sullivan *et al.*, 1995, 2001, 2005) and remains intact in size in healthy elderly adults without concurrent hypertension (Raz *et al.*, 2005). There is age-related dilation of the temporal horns and this has been interpreted as hippocampal volume decline. It appears that volume loss and CSF expansion occur in diseases such as Alzheimer's, but not in normal aging. The relative resilience of hippocampal volume to aging makes hippocampal deviations from normal size a sensitive indicator of pathology, especially of the Alzheimer type.

Studies of normal aging have benefited immeasurably by the introduction of quantitative DTI, which has successfully revealed evidence of microstructural disruption of regional white matter even in regions appearing normal on volume imaging. MR diffusion-weighted imaging (DWI) and DTI allow quantification of microscopic water movement. In regions with few or no physical boundaries, such as CSF in the ventricles, water movement is random, that is, freely diffusing, and is therefore isotropic. By contrast, the path of a water molecule in white matter is constrained by physical boundaries, such as the axon sheath, causing the movement to be greater along the long axis of the fiber than across it and is anisotropic, typically measured as fractional anisotropy (FA) and ranging between 0 and 1 on a normalized scale (Pierpaoli and Basser, 1996). DTI is therefore sensitive to the detection of tightly packed fibers in locally parallel orientation, characterizing white matter tracts in the brain. One of the most robust findings regarding age-related differences in FA has been the finding of low FA in frontal white matter (Sullivan *et al.*, 2001). This finding has been supported by postmortem investigations and animal models of aging (for review see Sullivan and Pfefferbaum, 2007) and suggests that decreased brain white matter in older individuals may be a

consequence of myelin sheath changes and/or accumulation of fluid in fiber tracts. These types of changes may be reflected as increased white matter hyperintensities observed on T2-weighted MRI images in over 90% of older adults.

Beyond the structural changes summarized so far, there have been numerous functional imaging studies that have described cognitive changes with aging. These studies using positron emission tomography, PET, and functional magnetic resonance imaging, fMRI, have revealed how the neural correlates of different cognitive functions change as a function of aging. Most studies show a reduction in the lateralization of brain activity during cognitive performance in elderly individuals. For example, in a study utilizing word pair encoding, older adults showed weaker activity in several left prefrontal cortical (PFC) areas while several PFC regions showed increased activity (Anderson *et al.*, 2000). During episodic memory retrieval, age-related decreases were typically found in the right PFC and right parietal regions, while age-related increases in activation were found in left PFC as well as bilateral anterior cingulate and cuneus/precuneas regions (Anderson *et al.*, 2000; Cabeza *et al.*, 1997, 2002). Some investigators postulated that the age-related asymmetry reductions found in multiple studies reflect a compensatory mechanism. Older adults engage both hemispheres for tasks that younger adults usually use one hemisphere for, to compensate for neurocognitive deficits.

In a longitudinal study of 25 healthy older adults assessing changes in PET rCBF cerebral blood flow over an 8 year period among healthy older adults found no significant declines in verbal and figural recognition memory accuracy over an 8 year period (Beason-Held *et al.,* 2008). There were regional increases and decreases in brain activity were found over time in these individuals, particularly PFC regions. These data support the cross-sectional studies described previously where altered patterns of cerebral activity were found in old relative to young individuals and extend these findings to show that changing brain function continues throughout later life in cognitively stable individuals.

Although it is clear older adults demonstrate deficits relative to younger adults in various aspects of learning and memory by neuroimaging correlates, several studies have suggested there is differential susceptibility to age-related changes and dementia related to variables like education, IQ, and engagement in leisure activities (Gold *et al.*, 1995; Hultcsch *et al.*, 1999; Scarmeas *et al.*, 2001; Stern *et al.*, 1994). These studies provide epidemiological evidence for the presence of cognitive reserve (Stern, 2006). Cognitive reserve suggests individual differences in how tasks are processed might provide some protection against age-related changes or progressing brain pathology. Our understanding of how cognitive reserve might be reflected by brain networks is ongoing. Stern and his colleagues (2005) identified network activation changes which involve the right hippocampus, posterior insula, and right and left operculum as well as the inferior parietal lobe and association cortex, left posterior cingulated, and right and left calcarine cortex. Young individuals activation patterns in these networks were different

from older individuals performing the same task at the same level (Stern *et al.*, 2005). These authors suggest that cognitive reserve consists of two separate components: neural reserve and neural compensation. Neural reserve may result from innate differences and/or be modulated through life events such as educational experience. The substrate for this may be neural networks that are highly efficient or have greater capacity in the face of higher demand. Neural compensation on the other hand is defined as a change in neural network use such that different brain networks are used in a specific task, due to the physiological effects of aging or brain pathology. The study of the neural substrates of cognitive reserve is in its infancy, but imaging techniques assessing both functional and structural changes in the brains of older adults are progressing rapidly.

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SUBCORTICAL ISCHEMIC CEREBROVASCULAR DEMENTIA

Uma Menon and Roger E. Kelley

Department of Neurology, LSU Health Sciences Center,
Shreveport, Louisiana 71103, USA

It has become increasingly apparent, especially with the advent of MRI brain scanning, that a large number of patients develop signal intensity changes in the subcortical white matter and periventricular region as they age. This appears to be accelerated by risk factors for small vessel cerebrovascular disease such as hypertension, smoking, diabetes mellitus and hyperlipidemia. The major question becomes when such changes become clinically significant. It is obvious that subcortical lacunar-type infarction can be identified by the clinical presentation. For example, typical examples of so-called "lacunar syndrome" include pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, clumsy hand-dysarthria, and hemiataxia-hemiparesis. The issue becomes a measure of impact on functional ability. This is influenced by several factors. Baseline IQ and educational level, as well as expectations of age, certainly play a role. A person who develops cognitive impairment and long tract signs in their 50s or 60s is certainly going to be recognized as more impaired than an 80 year old individual who is retired and primarily is engaged in recreational activity. It would be expected that a person born with limited intellectual capacity and/or limited educational opportunity would be less likely to be identified as impaired than a person who has achieved substantial economic achievement through their innate talents.

The concept of tissue loss or lesion load becomes important when determining how pronounced the ischemic cerebrovascular changes translate into functional impairment. Correlative pathology may include cortical atrophy and ventricular

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dilatation. Loss of either cortical or subcortical tissue function is expected to be related to functional compromise. In addition, there are potential features such as the coexistence of small vessel cerebrovascular disease and Alzheimer's disease. Small vessel cerebrovascular disease might also play a contributing factor in patients susceptible to Dementia with Lewy Bodies or patients susceptible to fronto-temporal dementia or any other dementing process. Thus, the concept of tissue loss or lesion burden of disease becomes increasingly important as we recognize the potential for multifactorial issues, including genetic factors, to contribute to the phenotypic expression.

The relationships between cognitive impairment, dementia and subcortical vascular lesions are poorly understood. There have been several papers on the different aspects of cerebral insults and their impact on cognition, the various kinds of dementia and different methods of analyzing the impact of the various insults to the brain. This chapter is an attempt to review all pertinent information currently available on the poorly understood condition of "subcortical ischemic cerebrovascular dementia."

I. Terminology

It is felt that the term "Subcortical Ischemic Cerebrovascular Dementia" better describes the various categories of cognitive impairments related to ischemic changes in the brain which has been identified previously as Vascular Dementia, Vascular Cognitive Impairment or Disorder, Multi-infarct Dementia, and so on. However, there are no clear guidelines or accepted criteria for defining the complex category of SICD.

II. Various Classifications of ''Vascular'' Dementia

These are some of the commonly used criteria to define the dementia associated with vascular lesions in the brain (Wetterling, *et al.*, 1996):

1. DSM-IV Criteria for Vascular dementia
2. NINDS-AIREN criteria for the diagnosis of probable vascular dementia (Roman *et al.*, 1993)
3. ICD-10 research criteria (DCR-10) for dementia
4. Hachinski ischemic score

III. Cognition and Aging

Changes appear in the normal brain with aging which contribute to mental decline. It has been estimated that after the age of 65, 6.4% of patients show evidence of some cognitive impairment and this figure increases steadily with age (Ankri and Poupard, 2003). With aging, vascular lesions are seen commonly in the brain and opinions vary as to whether these lesions are clinically significant or not with regards to cognitive changes (Fig. 1). It has also been the subject of discussion about the location and volume of these lesions and whether that may have an impact on cognition.

Also with aging, the risk of vascular disease increases and the prevalence has been shown to be 0.3% during 65–69 years of age and as much as 5.2% at age 90 years (Chabriat and Bousser, 2006). The Rotterdam study showed that the prevalence of "vascular" dementia is higher in women, despite the higher incidence in men, because of increased longevity in women by 10 years (Lobo *et al.*, 2000).

Asymptomatic lacunar-type infarcts have been found to be present in 11–28% of normal elderly persons in multiple studies (Longstreth *et al.*, 1998; Price *et al.*, 1997; Vermeer *et al.*, 2003). Atrial fibrillation (Ott *et al.*, 1997) hormonal treatment (estrogen + progesterone) of women after age 65 (Shumaker *et al.*, 2003), diabetes mellitus (Leibson *et al.*, 1997) and smoking in persons above age 60 years (Juan *et al.*, 2004) have all been shown to have higher risk for "vascular" dementia.

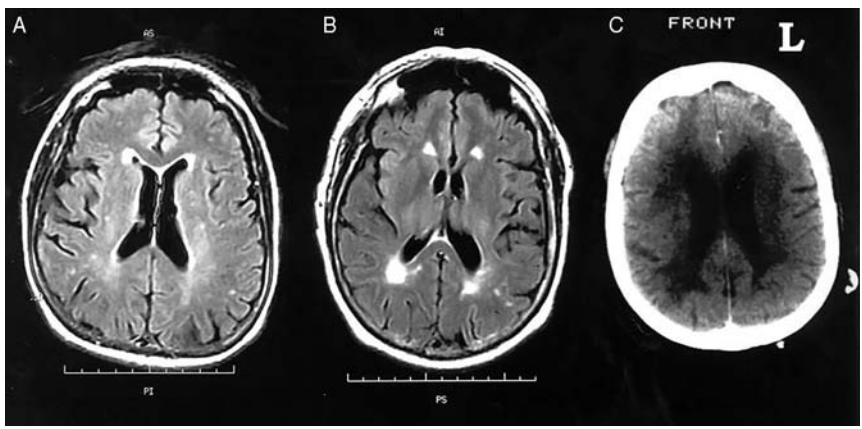

FIG. 1. Subcortical white matter hyperintensities, seen on FLAIR (transaxial) MRI brain scan, which demonstrates mild (A) and somewhat more advanced (B) periventricular findings. On noncontrast CT brain scan (C), there is prominent hypodensity in the periventricular region. These findings have been referred to as Binswanger's disease in the past, but more recently the term leukoaraiosis has been preferred because of the nonspecific clinical correlates of such findings.

Atrial fibrillation has also been shown to be an independent risk factor for cognitive impairment even in the absence of a stroke (Kilander *et al.*, 1998; O'Connell *et al.*, 1998). With the presence of hypertension, the greatest risk factor for stroke, the increased risk of cognitive impairment has been shown with different studies and patient cohorts (EVA Group, 1999; Launer *et al.*, 2000).

Stroke has been proved as a significant risk factor for cognitive impairment and dementia with as many as 25% of patients at 3 months and up to 50% within a year developing some degree of clinically significant cognitive impairment (Desmond *et al.*, 2002; Mackowiak-Cordoliani *et al.*, 2005; Tang *et al.*, 2004; Tatemichi TK *et al.*, 1994). A reported range of 25–80% of elderly subjects with dementia has Alzheimer's disease coexisting with the vascular lesions. This makes the assessment of pure cerebrovascular lesions difficult (Jellinger, 2008).

IV. Subcortical Strokes and Cognitive Impairment

It has long been believed that the small vessel or lacunar strokes in the white matter of the brain contribute minimally to the changes in cognition. However, a review of the NINDS-AIREN criteria (Roman *et al.*, 1993) demonstrates that it includes multiple basal ganglia and white matter lacunes and extensive periventricular white matter lesions on neuroimaging as causes of probable "vascular" dementia. Ischemic lesions in the brain can occur in various locations. However, with the current level and techniques of neuroimaging, it is not possible to visualize all the microinfarcts.

Areas of white matter ischemia, such as microinfarcts, often termed lacunes have been shown to be independent predictors of development of dementia (DeGroot *et al.*, 2000; Kovari *et al.*, 2004; Pasquier *et al.*, 2000; White *et al.*, 2002) particularly impairments with executive functions. Lacunes, when present in certain specific locations like the thalamus and basal ganglia, can cause cognitive disturbances (Fig. 2). Conversely, their presence in the deep white matter of the frontal, temporal, or parietal lobes does not seem to do so. Silbert *et al.* (2008) reported that an increase in total and periventricular white matter signal intensity changes, over time, correlates with progressive gait impairment while the progression of the total volume hyperintensity changes in the subcortical region is associated with memory decline in elderly subjects who are relatively intact from a cognitive standpoint.

The hippocampus is extremely sensitive to hypoperfusion which results in sclerosis. Both sclerosis and lacunes in the hippocampus can lead to decline in cognition (Bastos-Leite *et al.*, 2007; Fein *et al.*, 2000; Kril *et al.*, 2002) but this decline appears to be less than that seen in patients with Alzheimer's disease (Du *et al.*, 2002). Age appears to be the best and strongest predictor of the presence of white

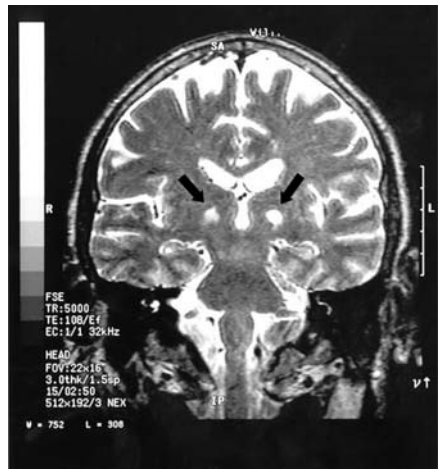

FIG. 2. Coronal T2-weighted MRI brain scan which reveals bilateral lacunar-type infarcts (arrows) in the thalamic region.

matter lesions in elderly subjects and whereas these white matter lesions maybe present in the elderly persons with normal cognitive function (Breteler *et al.*, 1994; Carey *et al.*, 2008; Liao *et al.*, 1997; Lindgren *et al.*, 1994; Longstreth *et al.*, 1996; Soderlund *et al.*, 2003; Ylikoski *et al.*, 1993), although elderly patients with dementia have been noted to have an increased load of lesions. There exists conflicting data as to whether these white matter lesions indeed contribute to cognitive decline. Some studies (Bracco *et al.*, 1993; Gold *et al.*, 2007; Schmidt *et al.*, 2002) were not able to find any definite evidence that these white matter lesions are responsible for the cognitive impairment in these subjects whereas some others including the subcortical ischemic vascular dementia (SIVD) program project (Chui, 2007; Mosley *et al.*, 2005; Prins *et al.*, 2005) have found that an increasing load of white matter lesions, over time, is associated with progressive cognitive decline (Fig. 3).

Price *et al.* (2005) report that despite the presence of white matter abnormalities, executive dysfunction is not seen until at least 25% of the white matter in the hemisphere is involved. Furthermore, when 50% of the hemisphere is involved, executive dysfunction exceeds the memory impairment. This forms the basis of research criteria proposed for subcortical vascular dementia (Erkinjuntti *et al.*, 2000). Understandably, there is no correlation between the MMSE score and white matter lesion load as the MMSE assesses the memory and cognitive functions and not the executive functions.

Carey *et al.* (2008) found that the presence of lacunes even when not producing any clinical deficits could cause decline in cognition and supports the view upheld by many others that in SIVD there is a disruption in the connecting pathways of the subcortical areas and the frontal cortex.

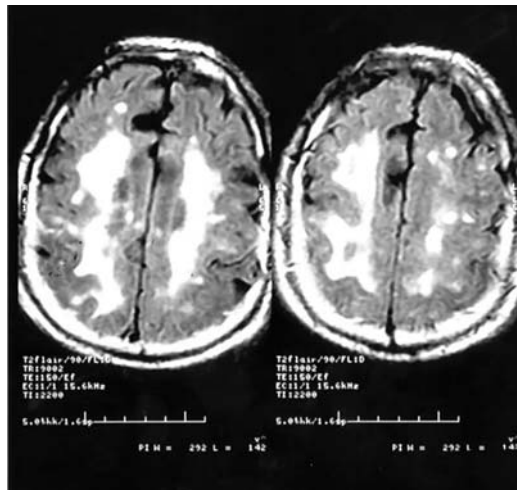

FIG. 3. Pronounced subcortical hyperintensities in the subcortical white matter, specifically the centrum semiovale, in a patient with progressive gait and cognitive impairment. This is a FLAIR (transaxial) MRI brain scan with two adjacent sections.

V. Pathophysiology of Cognitive Impairment in Subcortical Vascular Lesions

It has been proposed that various mechanisms contribute to impaired vascularity in the brain that occurs with age. Hypoperfusion related to atherosclerosis and arteriosclerosis, hypotension related to reduction in cholinergic effects, changes in the autonomic regulation of blood pressure, cortical hypometabolism, cardiac causes such as congestive heart failure with resultant systolic dysfunction and cardiac emboli and major surgical procedures have all been cited as causes for cognitive changes that occur in the older population (Baron *et al.*, 1986; Carey *et al.*, 2008; Nagata *et al.*, 2000; Roman, 2004).

The effects from the above-mentioned factors occur both in the cortical and subcortical areas. However, since the subcortical areas are mostly perfused by penetrating and deeper branches of the primary feeding arteries, the deleterious effects are most noticeable with increasing involvement of these vessels (Fig. 1). Age appears to be a significant contributing factor to the evolution of this process along with other risk factors for occlusive cerebrovascular disease. These are most readily detected as periventricular white matter lesions on neuroimaging, specifically MRI, in the elderly. It is also important to understand that all white matter lesions or hyperintensities seen are not infarcts and may potentially include causes such as astrocytic swelling as well as actual infarction (Sahlas *et al.*, 2002).

However, in a recent neuropathological study of these white matter hyperintensities (Young *et al.*, 2008), these lesions were associated with loss of vascular integrity which was interpreted to reflect a vascular origin.

It appears that any disruption in the limbic circuit, which has the anterior medial thalamus as the key component, results in memory impairment mainly involving the short term and working types (Carrera and Bogousslavsky, 2004; Swartz and Black, 2006).

Cholinergic factors have been cited as one of the possible mechanisms responsible for cognitive impairment, either causing hypotension from ineffective autonomic control related to aging or from disruption of the neurotransmitter pathways by ischemic lesions in the white matter. The treatment of Alzheimer's disease with cholinesterase inhibitors was based on the assumption that acetylcholine (Ach) is involved in memory and learning processes. Cholinergic pathways hyperintensities scale (CHIPS) developed by Bocti *et al.* (2005) provides a reliable rating scale based on white matter hyper intensities in the cholinergic pathways on MRI and their correlation to cognition in patients with Alzheimer's disease.

Whether the CHIPS scale can also be reliably used for patients with dementia from other causes as it relates to white matter ischemic lesions is not yet proved. *N*-acetyl aspartate (NAA) is a marker of neuronal integrity as measured with MRS and decreased levels are noted in the parietal and frontal cortices in subcortical ischemic cerebrovascular dementia (Capizzano *et al.*, 2000; Kattapong *et al.*, 1996; McKay *et al.*, 1996). It is thought that this correlates with the subcortical white matter lesions and supports the theory that altered metabolism plays a role in the pathogenesis.(Baron *et al.*, 1986; Nagata *et al.*, 2000) Another possible mechanism of subcortical ischemia causing cognitive deficit is interruption of the association fibers that connect the deep white matter with areas crucial for cognition (Chui, 2007). Tullberg *et al.* (2004) reported that there is an inverse relation between the glucose metabolism in the dorsolateral frontal lobe and the white matter lesion load, which supports this concept.

Altered cortical blood flow has been demonstrated with Xe-133 inhalation techniques and indicates that blood flow is primarily reduced in the ipsilateral fronto-parietal cortex with the presence of subcortical ischemic areas and reflects the subsequent changes noted in cognition and executive function (Hojer-Pederson and Friz-Peterson, 1989). Reduced volumes of the cortical gray matter and hippocampi have also been shown, by autopsy, in patients with subcortical ischemic cerebrovascular dementia (Chui, 2007; Schuff *et al.*, 2002).

Comparisons have also been drawn to the lesions of MS which also causes cognitive impairment with subcortical white matter lesions. Reduced magnetization transfer ratio (MTR) has been shown to correlate with myelin and axonal content in MS and also correlates with the level of cognitive impairment (Rovaris *et al.*, 2000, 2002; Schmierer *et al.*, 2004). Evaluation of the MTR in subcortical ischemic cerebrovascular dementia showed a reduction of MTR in the cortices (Leuchter

et al., 1994), again supporting the theory that remote effects in the cortices, resulting from possible disruption of the connecting tracts and circuits, may be responsible for the cognitive changes.

VI. Treatment and Prevention

Options for treatment of subcortical ischemic cerebrovascular dementia are presently quite limited. However, the overlap in pathological mechanisms between subcortical ischemic cerebrovascular dementia and Alzheimer's type dementia, with similar findings of subcortical white matter hyper intensities on MRI brain scan (Brickman *et al.*, 2008), suggests the potential for agents of some benefit in AD to be of similar benefit in subcortical ischemic dementia. Such agents include the cholinesterase inhibitors used in AD, vasodilators like nimodipine (a calcium-channel blocker) as well as some antioxidant agents. Results are somewhat favorable with the drugs used in AD and include donepezil, galantamine, and rivastigmine.

Donepezil showed significant improvement in two trials with a reduction in the cognitive decline over a period of 24 weeks (Black *et al.*, 2003; Wilkinson *et al.*, 2003) and galantamine showed some improved efficacy over placebo in another study over 12 months (Erkinjuntti *et al.*, 2002). Rivastigmine was also found to have some benefit in cognition, but this was in a relatively small open-label trial. The calcium-channel blocking agent nimodipine was tested in patients with "multi-infarct" dementia and, although initial observation appeared promising, subsequent studies were not (Pantoni *et al.*, 2000, 2005).

In view of the limited role of medications in treatment of subcortical ischemic cerebrovascular dementia, the focus is mainly on prevention. Prevention of this entity involves aggressive modification of the risk factors for stroke. Various studies have proved that control of hypertension results in a decrease in incidence of dementia up to 34% (Forette *et al.*, 1998; PROGRESS Collaborative Group, 2001; Tzourio *et al.*, 2003) and also a reduction in the incidence of stroke by as much as 35–44% (Chui, 2007). However, it is sobering to know that as many as 70% of Americans who have hypertension are unaware of their diagnosis and up to 60% are under-treated (Chobanian *et al.*, 2003). This places them at enhanced risk of stroke and other complications.

Control of other risk factors for stroke, such as diabetes mellitus, hyperlipidemia, atrial fibrillation, and so on, is also crucial for primary prevention (AHA/ASA Stroke Council, 2006). Evidence from various studies has shown the efficacy of antiplatelet agents in stroke prevention. However, there is not presently evidence-based support that the use of such agents translates into protection against dementia per se. However, by the same token, effective stroke prevention would be expected to lessen the contribution of cerebral ischemia to what might well be a multifactorial dementing process.

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CEREBROVASCULAR AND CARDIOVASCULAR PATHOLOGY IN ALZHEIMER'S DISEASE

Jack C. de la Torre

Sun Health Research Institute, Center for Alzheimer's Research, Sun City, Arizona 85351, USA

Presently, compelling evidence indicates that Alzheimer's disease (AD) is a vascular disorder with neurodegenerative consequences and should be treated as such. A substantial body of evidence including epidemiological, pharmacotherapeutic, and neuroimaging studies support the concept of AD as a vascular disorder or vasocognopathy that initiates as brain hypoperfusion, creating a neuronal energy crisis. The neuronal energy crisis provokes the cellular and molecular changes that characterize this dementia. In this brief review, the many vascular-related risk factors to AD including some that are preventable or amenable to treatment are discussed. Considerable human data now point in a new direction for guiding future research into AD. This new research direction should open a window of opportunity for decisive management and treatment of this devastating disorder.

I. Introduction

Cerebral energy supply can be interrupted after cardiac arrest or stroke, two conditions that result in global or local brain cell death. However, brain energy supply can dwindle slowly over long periods of time following non-fatal carotid artery stenosis or cardiac disease, two major disorders that result in brain hypoperfusion. Brain hypoperfusion (not an ischemic process) does not necessarily kill or damage nerve cells right away by significantly arresting energy nutrients delivered via the circulation but may chronically "gnaw" at nerve cells over a long period of time by destabilizing their normal function (Fig. 1).

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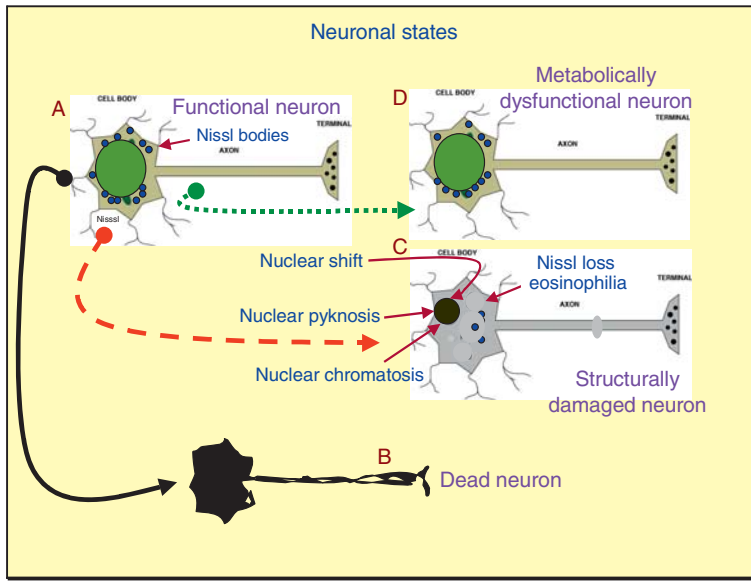

FIG. 1. Functional and pathological states deranging brain neurons resulting in degenerative processes. Healthy, functional neurons (A) can either (B) die (solid arrow), (C) undergo metabolic-structural damage (dashed arrow), (D) undergo metabolic only damage (dotted arrow). In the (C) state, intracellular damage can be assessed histologically by noting nuclear or cytoplasmic changes in organelles (chromatolysis, eosinophilia, nuclear shift, pyknosis, etc.). In the (D) state, bio-molecular markers reflecting neuronal distrenss are needed to evaluate extent of metabolic dysfunction. Neuronal metabolic dysfunction following chronic brain hypoperfusion is likely the first step in the pathologic pathway to cytostructural damage, atrophy, and death and how such dysfunction may explain cognitive disability, as in pre-clinical Alzheimer's disease.

Since cerebral hypoperfusion now appears to be a major precursor of Alzheimer's disease (AD) (Aguero-Torres *et al.*, 2006; Breteler, 2000; de la Torre, 2000, 2004a,b; de la Torre and Mussivand, 1993), the issue of glucose and oxygen availability and delivery via the circulation becomes a key element in the puzzle to understand the cellular-molecular cascade that leads to AD. The main reason to focus on glucose uptake and utilization by brain cells is that this molecule is the primary energy substrate for the brain which also consumes 20% of the total oxygen supply used by the body (Fig. 1A).

We became interested in the role of cerebral energy metabolism on AD in the early 1990s, when the subject was only of cursory, rare interest, following our series of experimental brain hypoperfusion studies and a review of the clinical dementia literature at the time (de la Torre and Mussivand, 1993). These experimental studies led us to propose the vascular hypothesis of AD as the likely cause of this disorder (de la Torre and Mussivand, 1993).

Since then, compelling evidence from a variety of clinical and basic studies has convince us that AD should be treated as a vasocognopathy (de la Torre, 2004) (a vascular-related, cognitive disorder) and we shall explore some of this evidence in our review here to determine whether proof of concept is met.

II. Risk Factors to AD

The most compelling evidence for a vascular connection to AD comes from independent epidemiological studies. Findings from the Rotterdam Study, the Kungsholmen project, EURODEM, FINMONICA, the PROCAM study, the Framingham study and the Honolulu-Asia study, among others, indicate that over two dozen risk factors, all vascular related, have thus far been recognized for AD (Table I) (Breteler, 2000; Aguero-Torres *et al.*, 2006; de la Torre and Mussivand, 1993). These epidemiological studies have led to the conclusion that most of the AD cases analyzed have a vascular involvement, and that pure dementia types (including vascular dementia) in older subjects constitute only a minority of dementia cases (Aguero-Torres *et al.*, 2006; Breteler, 2000). It is highly improbable that chance alone could explain the reduction of cerebral blood flow (CBF) induced by several dozen different risk factors found linked to AD (Table I). If indeed, a variety of vascular risk factors for AD exists and is highly important in promoting this dementia, then the question of the role of amyloid beta (Aβ) needs to be asked. Do risk factors eventually also promote the excessive production of Aβ in brain or does Aβ promote the varied risk factors? The second possibility seems rather unlikely due to the spectral nosology of each risk factor described thus far (Table I), so building on the assumption that vascular-dependent risk factors for AD *do* lower cerebral perfusion and eventually promote Aβ production, we have introduced the role of *critically attained threshold of cerebral hypoperfusion* (CATCH) (de la Torre, 2000). CATCH develops when a vascular risk factor or factors further diminishes cerebral CBF in an individual who already has developed declining cerebral perfusion due to advanced age and a poor vascular reserve. The reason is that CBF normally declines with age by about 21% from age 21 to 60 (Leenders *et al.*, 1990). Below this normal-age related CBF decline, a "CATCH brain blood flow level" can result from advancing age when it co-exists with one or more vascular risk factor as listed in Table I.

The speed at which CATCH is attained depends on the person's state of health, lifestyle, genetics, gender, diet, environmental exposure, and other confounding factors. Once CATCH is activated, energy hypometabolism and oxidative stress result from continuous brain hypoperfusion and from reduced glucose and oxygen delivery to neurons and glia (de la Torre, 2000) (Fig. 1B). The main reason for the high glucose/O_2 uptake in the normal brain is the massive amounts of ATP needed

TABLE I
SUMMARY OF FINDINGS FROM EPIDEMIOLOGICAL STUDIES (SEE TEXT) OF VASCULAR-RELATED RISK FACTORS TO ALZHEIMER'S DISEASE

Alzheimer's disease vascular risk factors
Brain-related risk factors
Aging
Ischemic stroke
Silent stroke
Head injury
Transient ischemic attacks
Migraine
Lower education
Hemorheologic abnormalities
Depression
Circle of Willis atherosclerosis
Heart-related risk factors
Congestive heart failure
Valvular disease
Hypertension
Hypotension
Thrombotic episodes
High serum homocysteine
Atrial fibrillation
Presence of ApoEε4 allele
Carotid atherosclerosis
Coronary artery bypass surgery
Peripheral risk factors
High serum cholesterol
High intake of saturated fat
Diabetes mellitus II
Hemorheologic abnormalities
Alcoholism
Smoking
Menopause

Highly prevalent conditions such as stroke, hypertension, atherosclerosis and heart disease are common precursors to AD.

to maintain neuronal signaling during active ion channel flux. Ion flux is the basis for propagation of action potentials and neurotransmission. Impaired brain energy production also upregulates the Aβ rate-limiting enzyme BACE1, thus promoting Aβ overproduction (Velliquette *et al.*, 2005) (Fig. 1B). Consequently, when mitochondrial function in neurons is disrupted by failing glucose/O_2 supply for energy production, rapid damage to brain cells occurs. Brain hypoperfusion is the pathogenic trigger that pushes the neuronal energy crisis and the cascade of molecular and cytopathologic changes that characterize AD (Fig. 2).

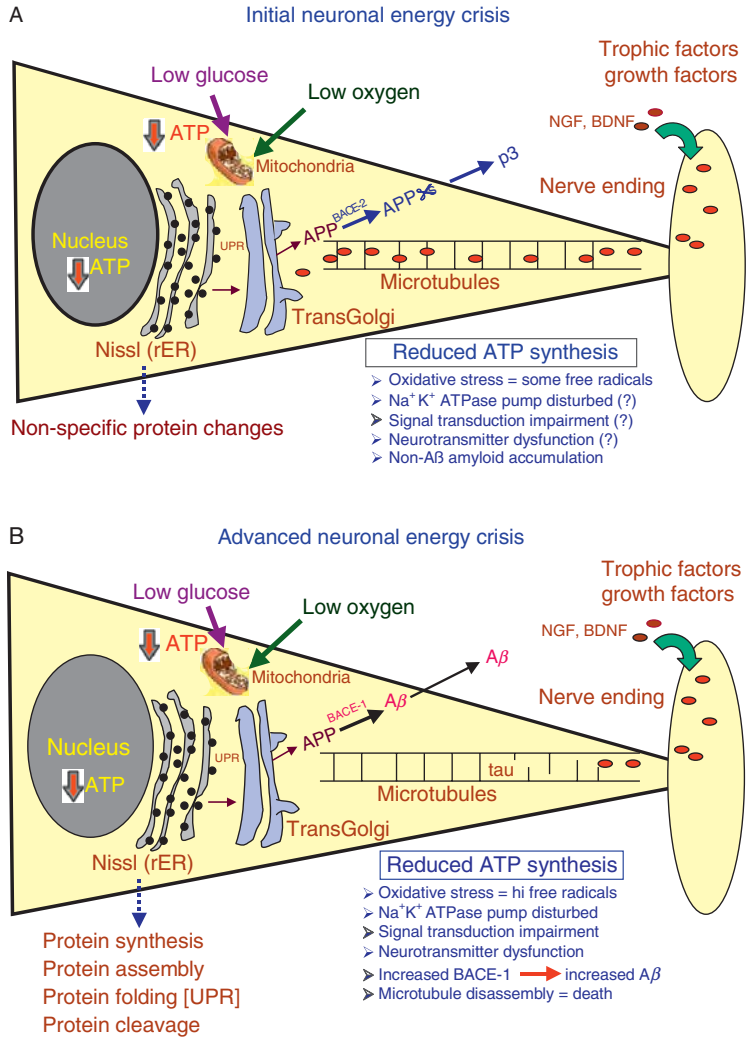

FIG. 2. (A) A fundamental principle in cell biology is seen by the use of chemical energy in the form of ATP derived from glucose/oxygen delivery to assemble, disassemble and alter protein structure. Since proteins work to keep a neuron healthy, defects in their synthesis, assembly, folding, or cleavage can impair the normal intracellular and extracellular secretory transport pathway and damage brain cells. Normal neuronal energy metabolism in the brain includes optimal ATP production by mitochondrial oxidative phosphorylation, RNA transcription and protein synthesis, cell signaling, neurotransmission, axonal transport of molecules between cytoplasm and nerve ending via microtubules. Normal brain has little or no Aβ accumulation. Following initial cerebral hypoperfusion, reduced ATP synthesis can result in non-specific protein and oxidative stress changes that may lead to MCI. Theoretically, overexpression of Aβ peptides and specific neurodegenerative pathology may be lacking.

Risk factors for AD are either the result of genetic susceptibility (e.g., carrying an ApoE ε4 allele) or environmental exposure of a person's health to an event that can introduce, accelerate, or further compromise cognitive dysfunction. At the present time, only environmental risk factor exposure is modifiable or preventable but in the future, genetic engineering of potential risk susceptibilities to AD could become a realistic therapeutic target for AD.

Vascular risk factors to AD as shown in Table I have been extensively reviewed (Aguero-Torres *et al.*, 2006; Breteler, 2000; de la Torre and Mussivand, 1993; Sjogren *et al.*, 2006; Sparks *et al.*, 2005) and only some recently reported risk factors will be briefly discussed here.

One example of a potentially modifiable vascular risk to AD of increasing research interest is hypercholesterolemia and dietary fat intake. A steady amount of research has confirmed a link between high levels of cholesterol and the development of AD (Sjogren *et al.*, 2006).

Hypercholesterolemia acts as a precursor of atherosclerosis, cardiovascular disease, and diabetes. For obvious reasons, high serum cholesterol levels have generated a rapid-growing market for lipid-lowering drugs prescribed to patients at risk of cardiovascular or cerebrovascular conditions. Statins that lower cholesterol levels have been suggested as useful in both prevention and treatment of AD but this conclusion needs further verification (Sparks *et al.*, 2005). The mechanism by which statins may provide a benefit against cerebrovascular disease including AD remains speculative and is likely multifactorial. In 1998, it was suggested, on the basis of murine studies, that the health benefits of statins did not merely aim at lowering lipids (Laufs *et al.*, 1998). Statins were shown to protect against injury by a mechanism involving the selective upregulation of endothelial nitric oxide synthase (Laufs *et al.*, 1998), the enzyme that generates nitric oxide in blood vessels and is involved with regulating vascular function. Further research along

(B) Persistent reduction of glucose and oxygen delivery to ischemic-sensitive neurons following *chronic* brain hypoperfusion leads to critical ATP depletion and promotes oxidative stress, reactive oxygen species and abnormalities in protein synthesis activating their disassembly, misfolding (generating unfolded protein response, UPR), and abnormal cleavage. Altered protein synthesis can subsequently form molecules that can ravage nucleic acids, protein kinases, phosphatases, lipids, and harm cell structure. ATP cutback also hastens ionic pump dysfunction, signal transduction breakdown, neurotransmitter failure, faulty cleavage of amyloid precursor protein (APP) leading to BACE-1 upregulation and Aβ overproduction and microtubule damage from tau hyperphosphorylation. Retrograde axonal transport (curved arrow) of trophic and growth factors (e.g., NGF, BDNF) essential for neuronal survival is diminished due to energy-starved motor protein deficiency. This *selective neuronal* energy crisis is caused by *blood flow supply not meeting cell energy demand* in highly active brain regions whose vascular reserve capability has reached a critical threshold. About 75% of ATP energy is used on signaling (action potentials, postsynaptic potentials, etc.). Reduced ATP synthesis is the precursor of the molecular cascade that leads to Alzheimer's disease (AD) and to the region-specific neurono-glial death pathway. Key: ↓ = reduction or loss; ⇣ = impaired reaction.

these lines has demonstrated that statins improve endothelial function, increase nitric oxide bioavailability, provide antioxidant properties, inhibit inflammatory responses, exert immunomodulatory actions, regulate progenitor cells, and stabilize atherosclerotic plaques (Endres *et al.*, 1998) and several studies have shown a benefit for statins in the treatment of AD (Wolozin *et al.*, 2000).

Another important modifiable risk factor to AD is metabolic syndrome (MeS). MeS is a cluster of factors that can lead to the development of cardiovascular disease. MeS is characterized by abnormal insulin, glucose, and lipoprotein metabolism as well as by hypertension and obesity (Grundy *et al.*, 2005). These factors are frequently found in people with either excess abdominal body fat or a decreased ability of the body to use insulin, which is known as insulin resistance (Grundy *et al.*, 2005).

MeS has been found to be associated with AD even when diabetic patients are excluded from analysis (Vanhanen *et al.*, 2006), suggesting that obesity associated with cardiovascular dysfunction or hypercholesterolemia is sufficient to initiate cognitive impairment that later can convert to AD. The number of people with MeS increases with age and is estimated to affect 40% of people beyond the age of 60. People with uncontrolled diabetes mellitus type 2 and those with heart disease or prone to stroke are most likely to develop MeS (Martins *et al.*, 2006).

Since obesity and lack of exercise are two conditions that can lead to MeS, correcting these by lifestyle changes that include a healthy diet and physical activity could help prevent or reverse MeS. The cardiovascular risk factors associated with MeS contribute to the development of atherosclerosis that can lead to a heart attack or a stroke. People with the MeS are also more likely to develop type 2 diabetes mellitus (Martins *et al.*, 2006). Insulin resistance is central to type 2 diabetes and is also implicated in the pathogenesis of AD (Vanhanen *et al.*, 2006). This has prompted ongoing clinical trials in AD patients to test the efficacy of improving insulin-like signaling with dietary omega-3 fatty acids or insulin-sensitizing drugs as well as by exercise regimens.

It is well established that hypertension can increase the risk of stroke and heart problems and decrease life expectancy (de la Torre, 2006). Many studies including the Framingham and the Honolulu-Asia Aging studies have implicated impaired cognitive function to hypertension in geriatric patients (Elias *et al.*, 1993). It has also been known for some time that hypertension in the elderly is a potential risk factor to AD (de la Torre, 2009). What is not clear is how hypertension increases the incidence of AD, particularly in those not-treated with antihypertensives. People with hypertension are six times more likely to have a stroke that can lead to AD (Ivan *et al.*, 2004). It is calculated that reducing the number of cases affected by stroke which are amenable to prevention or treatment, would have a major impact in lowering the incidence and societal costs of Alzheimer's disease which is now estimated to affect 25 million people worldwide.

A. Cardiovascular Disease

Some forms of cardiac disease that result in impairment of cardiac output or function with consequent reduction of cerebral perfusion have been found to increase AD risk (Alves and Busatto, 2006).

Since 20% of cardiac output goes to the brain and 80% of carotid artery flow goes to each ipsilateral middle cerebral artery, it is no surprise that vascular lesions of the gray and white matter are frequently associated with cardiac disease and carotid artery stenosis, both vasculopathies that can induce cognitive impairment and probably AD (Alves and Busatto, 2006; de Leeuw *et al.*, 2004; Ivan *et al.*, 2004; Miklossy, 2003).

Moreover, cerebral hypoperfusion can result in white matter lesions and cortical watershed microinfarcts in the absence of atherosclerosis or amyloid angiopathy (Miklossy, 2003), and may induce microinfarcts in the hippocampus prior to the onset of AD (de Leeuw *et al.*, 2004).

We firmly believe that AD onset can be delayed or possibly prevented if the heart can be kept healthy and brain hypoperfusion can be treated by restoring normal blood flow. The upshot would be a major research breakthrough in AD prognosis if either feat is successfully achieved. Consequently, diet, exercise, and management of many vascular risk factors amenable to treatment may be the key to significantly reducing the incidence of this dementia in the future.

B. Preclinical Detection of AD

The most important factor in developing a useful blueprint for AD treatment is identifying such candidates at the *preclinical* stage before any incapacitating cognitive damage has occurred. The reason is that once cognitive meltdown has begun (which implies serious neuronal damage and tissue atrophy), AD pathology may be most difficult to reverse or arrest.

Considering AD as a vascular disorder characterized by brain hypoperfusion, techniques that can detect regional CBF reduction during mild cognitive impairment (MCI), a condition often seen prior to AD, or even before any memory deficits are measured, will be crucial to predict AD candidates.

In our judgment, three of the most important neuroimaging tools to screen AD candidates before major clinical symptoms have developed are single-photon emission tomography (SPECT), injected [18F]fluorodeoxyglucose (FDG) using positron emission tomography (PET), and transcranial Doppler (TCD) ultrasonography. SPECT and TCD can detect with a good degree of sensitivity and specificy, persons showing regional brain hypoperfusion at the MCI stage, many who later convert to AD (Johnson *et al.*, 1998; Ruitenberg *et al.*, 2005).

Preclinical detection of AD as a group is now possible using FDG-PET although the technique is considerably more expensive and labor intense than SPECT or TCD. Individuals at risk of AD but who do not express any cognitive deficits show local hypometabolic reductions of the cerebral metabolic rate of glucose after FDG in brain regions that will later develop atrophy and neurodegeneration (de Leon *et al.*, 2001). Since measures of glucose metabolic rate and CBF are coupled (Silverman and Phelps, 2001), FDG-PET studies are proof of concept that regional brain hypoperfusion precedes Alzheimer clinical symptoms, Aβ production, and neurodegenerative changes. FDG-PET can also track AD progression (de Leon *et al.*, 2001).

Existing or developing coronary artery disease in the elderly patient may worsen age-related cerebral hypoperfusion in the elderly person (de la Torre, 2006). Most patients with ischemic heart disease will present themselves in general practice. Therefore, the community management of ischemic heart disease has already become increasingly important and the role of the primary care physician even more pivotal.

Inasmuch as normalization of diminished cardiac output from any cause may prevent or reverse MCI (a high risk for prodromal AD) (de la Torre, 2006, 2008, 2009), simple, safe, and reliable diagnostic screens should be applied to older patients in an effort to reduce the consequences of cardiac-to-brain related AD risk factors. We have recommended the use of cost-effective, safe, and reliable noninvasive tools such as echocardiography (Fig. 3) and carotid Doppler ultrasound to be used in the elderly individual found to complain of memory difficulties (de la Torre, 2008). Employment of noninvasive screening techniques using carotid artery ultrasound and echocardiography (CAUSE) (de la Torre, 2008, 2009) in the detection of medically or surgically correctable conditions that reduce heart or carotid artery blood flow to brain is anticipated to delay or prevent the progression to Alzheimer's or vascular dementia (VaD) in many of those affected. These office procedures involve no needles, no radiation, and no contrast agents that may cause allergic reactions.

Carotid artery ultrasound is a safe, cost-effective, and reasonably reliable way to determine the clinical action that may prevent potential or continuing cognitive decline. Such clinical action could significantly impact on the prevalence of incident dementia rate. Echocardiographic measurements can provide a relatively simple, safe, reliable, and cost-effective evaluation of impaired cardiac function that may indicate a dangerously reduced level of cerebral perfusion that can lead to AD.

Echocardiography is also useful in guiding therapy over time. This is possible by measuring the effect of therapy on multiple parameters of cardiac function, including diastolic filling and ventricular performance, two major determinants of preload and therefore of cardiac output (Ahmed *et al.*, 2007). These measurements have demonstrated considerable prognostic value in symptomatic and

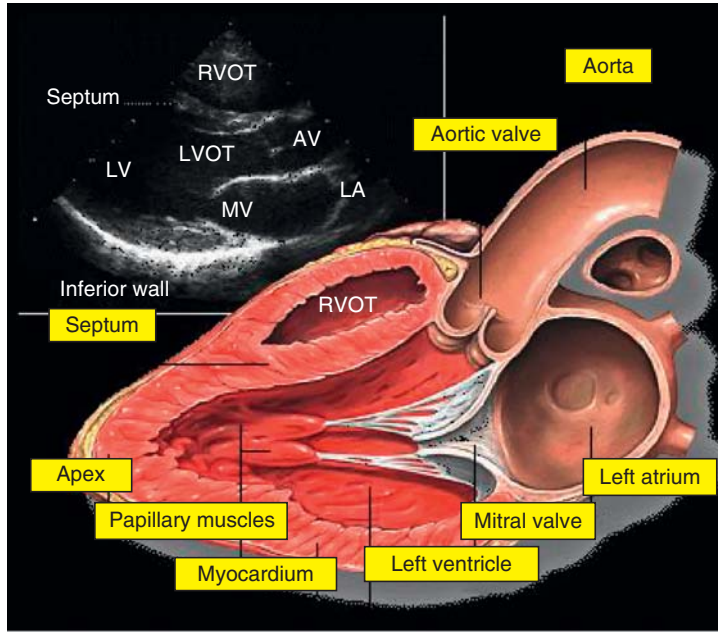

FIG. 3. Echocardiography image (top) is obtained by placing the ultrasound probe on the surface of the chest over the heart. Image shows all four chambers of the heart, useful for detecting chamber enlargement. Valvular disease, hypertension, arrhythmias, left ventricular function, ejection fraction, and cardiac output can be determined and measured. These cardiac measurements offer a noninvasive, cost-effective and reliable approach that can identify often correctable or treatable early lesions of the heart which may contribute to chronic brain hypoperfusion and possibly AD in the elderly patient with mild memory complaints. Key: RVOT = right ventricular outlet tract; LVOT = left ventricular outlet tract; LV = left ventricle; MV = mitral valve; LA = left atrium.

asymptomatic patients with either preserved or abnormal cardiac function (Ahmed *et al.*, 2007). Such techniques can generally rule out cardiac pathology and extracranial vessel disease. Cardiac pathology and extracranial vessel disease have been shown to be major contributors to cerebral hypoperfusion and stroke (Alves and Busatto, 2006) and their attrition may result in a significant impact on lowering the prevalence of Alzheimer's and VaD.

C. TREATMENT OF AD

There is presently no effective treatment for AD. Five drugs are available in the US market for prescriptive use in AD: Cognex (tacrine), Aricept (donepezil), Excelon (rivastigmine tartrate), Reminyl (galantamine hydrobromide), and

Namenda (memantine). The first four above act to slow the synaptic breakdown of acetylcholine, one of the neurotransmitters important in memory and learning. Reminyl also targets both AD and "mixed" dementia, that is, AD complicated by cerebrovascular pathology.

A fifth drug, memantine, is a relatively newer medication for the treatment of Alzheimer's disease that works ostensibly by antagonizing the *N*-methyl-D-aspartate receptors. Nonprescriptive treatments for AD in present use are nonsteroidal anti-inflammatory agents (NSAIDs), ginkgo biloba, estrogen, vitamin E, and prescriptive statins. All these treatments, whether prescriptive or over-the-counter, at best, provide only very modest control of symptoms generally at the early stages of AD and offer little to no cost-benefit ratio at the later stages of the disease (Loveman *et al.*, 2006). Their modest benefit to AD patients must be weighed against their frequent side-effects, particularly the anti-cholinergic agents which include nausea, vomiting, dizziness, headaches, and depression. Moreover, since most clinical trials on the effectiveness of these medicines were sponsored by industry or industry-paid researchers, a prominent shadow for positive bias has to be considered (Sismondo, 2008).

It should be noted that the common link binding practically all the medicines and therapies available or tested experimentally for AD so far is their ability to *mildly* increase cerebral perfusion (de la Torre, 2004b). However, since cerebral perfusion is only slightly improved, the beneficial effect of medicines such as those listed above is transient and limited. Interestingly, most of the products that improve AD symptoms also improve the symptoms of VaD. This activity by medicaments with differing pharmacokinetics and pharmacodynamics, lend additional support to the concept of brain hypoperfusion in AD and VaD and reinforce potential therapeutic targets aimed at patients who initially present with mild cognitive dysfunction and who display declining perfusion to the brain. New technologies, whose primary goal is to significantly increase cerebral perfusion in such patients, could delay, reverse, or prevent the neuropathological process that can lead to dementia.

III. Conclusions

There is now compelling evidence that Alzheimer's disease is a vascular disorder with neurodegenerative consequences and should be treated as such. A large body of evidence including epidemiological, pharmacotherapeutic, and neuroimaging studies support the concept of AD as a vascular disorder (a vasocognopathy; de la Torre, 2004a) that results in brain hypoperfusion and consequent neuronal energy crisis that provokes the cellular and molecular changes that characterize this dementia. Cerebrovascular and cardiovascular

conditions responsible for reducing carotid artery and cardiac blood flow to the brain may be crucial clues in better understanding the physiopathology of AD. This shift in thinking acknowledges the notion that current complacency on the state of the art has created the gridlock which ignores that something is wrong in our ability to clinically manage AD after a century of research. In this brief review, the many vascular-related risk factors to AD including some that are preventable or amenable to treatment are discussed. Considerable human data now point in a new direction for guiding future research into AD. A more data driven new research direction should open a window of opportunity that can lead to new technologies, create new subfields by revolutionizing the field of dementia and provide decisive management of this devastating disorder.

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NEUROIMAGING OF COGNITIVE IMPAIRMENTS IN VASCULAR DISEASE

Carol Di Perri,[*,†] Turi O. Dalaker,[*,§] Mona K. Beyer,[‡,§] and Robert Zivadinov[*,¶]

[*]Department of Neurology, Buffalo Neuroimaging Analysis Center, State University of New York at Buffalo, Buffalo, New York 14203, USA
[†]Department of Neuroradiology, IRCCS, C. Mondino, University of Pavia, Pavia, Italy
[‡]Department of Radiology, Stavanger University Hospital, Stavanger, Norway
[§]The Norwegian Centre for Movement Disorders, Stavanger University Hospital, Stavanger, Norway
[¶]Department of Neurology, The Jacobs Neurological Institute, State University of New York at Buffalo, Buffalo, New York 14203, USA

Cerebrovascular disease (CVD) is increasingly recognized as a common cause of cognitive impairment and dementia, alone or in conjunction with other neurodegenerative diseases, primarily Alzheimer's disease. The term vascular cognitive impairment (VCI) has been proposed as an umbrella term to recognize the broad spectrum of cognitive changes associated with vascular pathology, mainly characterized by executive impairment together with particular noncognitive features.

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Magnetic resonance imaging (MRI) has become the most important neuroimaging methodology for assessing and monitoring the pathological changes involved in the onset and progression of vascular neurological diseases. Conventional MRI sequences are usually not sufficient to provide full details about the different degrees of brain damage underlying vascular disorders. However, newer and more advanced nonconventional MRI techniques have the capacity to detect invisible brain damage that would otherwise not be detected. This review outlines some of the most important neuroimaging techniques commonly used in the diagnosis, assessment, and monitoring of cognitive impairment in vascular diseases. More detailed applications of these techniques, specifically for VCI, are discussed.

I. Introduction

A. Structural Brain Imaging

Although computed tomography (CT) is still important in many clinical settings, magnetic resonance imaging (MRI) is becoming the imaging method of choice, offering better tissue specificity and sensitivity with respect to relative pathology. Therefore, this section—which discusses structural imaging—will refer only to MRI studies.

1. *Conventional MRI Techniques*

T2-weighted imaging (WI) is highly sensitive in detecting vascular lesions. Upon gliotic transformation, that is, tissue scarring, these appear as local hyperintensities of T2 prolongation in the white matter (WM). There are different and various techniques for identifying T2 hyperintense lesions; among them, the most often recommended are conventional spin echo (CSE), turbo spin echo (TSE), and fluid-attenuated inversion recovery (FLAIR) (Zivadinov and Bakshi, 2004). FLAIR is a MRI sequence for optimized detection of brain parenchymal pathologic water content. It is particularly helpful in the evaluation of periventricular and cortical/juxtacortical lesions, where cerebrospinal fluid (CSF) may mask the visualization of these lesions on T2-WI (Zivadinov and Bakshi, 2004; Zivadinov and Cox, 2007). In the last decade, continuous technical improvements in MRI hardware and software have led to the development of new pulse sequences that are more efficient and sensitive. Among them, TSE or FSE, proton density (PD) and fast-FLAIR have already demonstrated their usefulness in a wide variety of neurologic diseases. Better lesion-to-CSF contrast is achieved with PD because of the relatively lower signal intensity of CSF on this sequence and improved lesion-to-tissue contrast. TSE showed greater sensitivity than CSE in detecting areas of T2 prolongation.

On noncontrast T1-WI, most ischemic lesions are iso- or hypointense in WM. T1-hypointense lesions are an important MRI metric of neurodegeneration in patients with different neurological disorders. They represent a more advanced pathological substrate of the lesions—mainly axonal loss, Wallerian degeneration, and gliotic changes (Zivadinov and Bakshi, 2004; Zivadinov and Cox, 2007).

Even though these techniques are highly sensitive to tissue damage, they are usually not capable of discerning among the possible different pathological origins of the damage (demyelinating, vascular, tumoral). Therefore, both in clinical and research practice, they have to be supplemented with the clinical history of the subject and, most of the time, with other newer nonconventional MRI techniques.

2. *Nonconventional MRI Techniques*

Magnetization transfer imaging. Magnetization transfer imaging (MTI) is an advanced MRI technique that has been widely used to evaluate characteristics and evolution of damaged tissue and normal appearing brain tissue (NABT). It is based on the interactions and energy exchange between protons that are unbound in a free water pool with those where motion is restricted due to binding with macromolecules (Horsfield *et al.*, 2003). MTI uses an off-resonance radio frequency (RF) pulse to saturate protons in macromolecules and water molecules that are bound to macromolecules and are normally not visible due to their very short T2* relaxation times. During pulse sequence acquisition, the saturated protons may enter the free pool of protons, primarily water, or may transfer their magnetization to free water protons. As a consequence, a decrease in the MRI-visible signal is produced in areas characterized by an abundance of macromolecules affected by magnetization transfer. Tissue damage is usually reflected by a reduction in this exchange of protons and thus a decrease in the magnetization transfer ratio (MTR). Decreases in MTR indicate a reduced capacity of free water to exchange magnetization with the brain tissue matrix with which the water comes into close contact. MTRs can be used to detect changes in the structural status of brain parenchyma that may or may not be visible with conventional MRI techniques. Therefore MTI enables semi-quantitative, reproducible characterization of tissue and pathologic entities which could substantially improve the specificity of MRI (Fig. 1).

Diffusion-weighted imaging. Diffusion-weighted imaging (DWI) and diffusion-tensor imaging (DTI) are advanced MRI techniques that allow the measurement of tissue water diffusion-related motion and, as a consequence, provide information about orientation of water motion within the tissue (Rovaris *et al.*, 2005). These techniques take advantage of the direction-dependent mobility of protons which is mainly due to the underlying structure of the brain tissue. The free, random diffusion is restricted by cellular boundaries in different directions to a varying degree, for example, diffusion along a myelinated nerve fiber is much easier than the diffusion perpendicular to it. Similarly, the apparent diffusion coefficient (ADC)

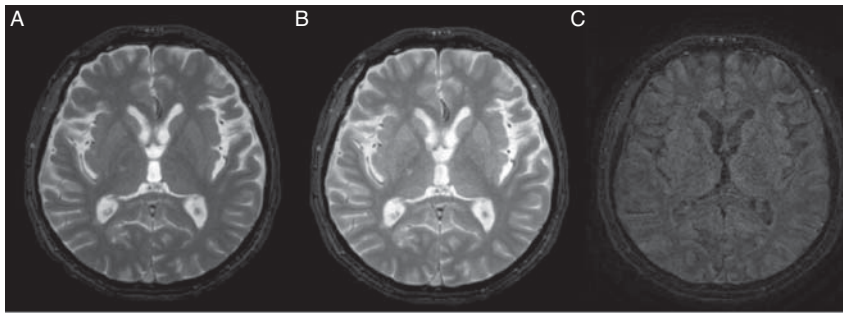

FIG. 1. Magnetization transfer imaging: sample scan with (A) and without (B) magnetic transfer pulse. A relative magnetization transfer ratio map (C) is generated.

is lower in highly structured tissues such as WM and gray matter (GM) than in pure water. ADC values depend on the orientation of the tissue relative to the measurement. Conventionally, the average ADC is calculated from three (DWI) or more than three (DTI) linearly independent directions that provide information on the overall diffusivity in the tissue. Pathological processes that modify tissue organization can cause abnormal water motion, thereby altering ADC values. Ischemic events can alter diffusion parameters of brain tissue *in vivo*, resulting in a decrease of water diffusivity measurable with different DWI and DTI indices. These measures include mean diffusivity (MD), fractional anisotropy (FA), entropy and subsequently tractography outcomes (Fig. 2). It is important to emphasize that, in most instances, very acute stages of ischemic events can be detected through this technique within the first hour of onset. On the other hand, such changes are often not recognized on other MRI sequences. The increased sensitivity of DWI in detecting acute ischemia is thought to be the result of the water shift restricting motion of water protons intracellularly (cytotoxic edema), whereas conventional T2-WI shows signal alteration mostly as a result of vasogenic edema. However, the exact origin of the decreased ADC measurements observed in early ischemia has not been fully established. The diminished ADC value also could be a result of decreased temperature in the malperfused tissues or a combination of all these factors (Busto *et al.*, 1987; Crain *et al.*, 1991).

Regardless of the cause, decreased apparent ADC is a very sensitive indicator of an early ischemic brain event at a stage when ischemic tissue remains potentially salvageable (Wolpert *et al.*, 1993).

Atrophy measures. The measurement of brain atrophy is of growing clinical relevance as a biomarker of the disease process, especially when correlated with other anatomical and functional information from conventional and nonconventional MRI. Various tools are available for semiautomatic evaluation of brain volume, longitudinal studies and intra-/intergroup cross-sectional analysis,

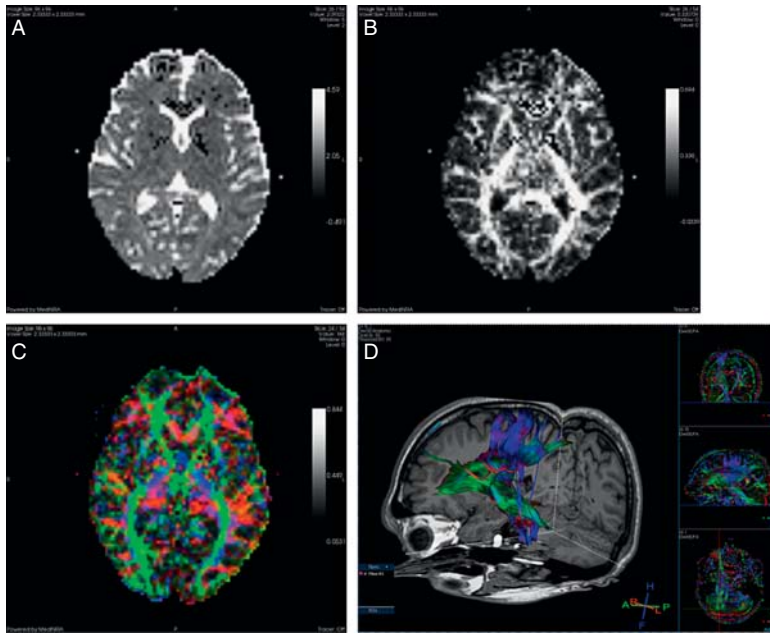

FIG. 2. Diffusion tensor imaging: Mean diffusivity (A), fractional anisotropy (B), and color-fractional anisotropy (C) maps are presented. The maps are defined as functions of the eigenvalues (i.e., the invariants of the diffusion tensor at each voxel); in the RGB (red-green-blue) FA map, the corresponding eigenvectors are also displayed through color coding. A streamline tractographic reconstruction (D) is displayed; fibers are reconstructed according to a linear algorithm following the direction of maximum FA until a threshold value is exceeded.

such as SIENA and SIENAX of the FSL library (http://www.fmrib.ox.ac.uk/fsl/), FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), and SPM (http://www.fmrib.ox.ac.uk/fsl/,http://www.fil.ion.ucl.ac.uk/spm/) (Fig. 3). Voxel-based analysis methods are of growing interest, giving the opportunity to perform local atrophy measurements and possibly displaying a stronger correlation with functional estimates. A high resolution 3D T1-weighted scan is necessary for the analysis and patient age, disease duration, total brain volume or any other presumably significant parameters are typically taken into account as covariates for the statistical analysis. A large subject cohort is indeed necessary for gaining sufficient statistical power, especially considering the sophisticated geometric preprocessing necessary for group analysis.

Atrophy is now proposed to be included as a secondary endpoint in longitudinal trials aimed at monitoring disease progression and therapy efficacy, as complementary information to conventional MRI in various diseases such as multiple sclerosis (MS) and Alzheimer's disease (AD) (Whitwell, 2008).

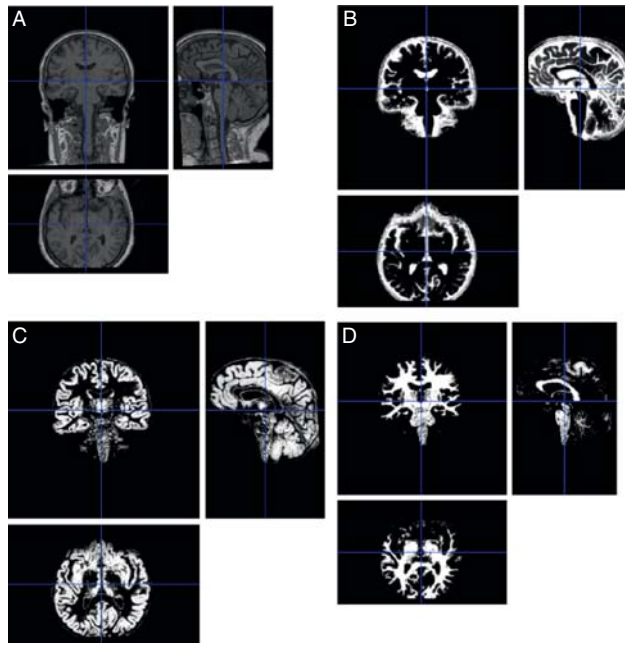

FIG. 3. Brain segmentation with statistical parametric mapping (SPM) software: (A) 3D-T1 image, (B) cerebrospinal fluid, (C) gray matter, and (D) white matter segmentation maps are displayed.

B. Functional Imaging

1. *Perfusion-Weighted Imaging*

Perfusion-weighted imaging (PWI) techniques are sensitive to microscopic levels of blood flow, defined as the amount of blood flowing into a voxel in a certain temporal span and measured in ml blood/min/gr tissue. This index may be altered in disease conditions and accurate monitoring is clinically relevant, improving our understanding of the pathophysiology of the disease.

With respect to other techniques that noninvasively investigate cerebral blood flow, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and xenon-enhanced computed tomography (Xe-CT), PWI shows some advantages by not using ionizing radiations, allowing a better spatial resolution and a better signal-to-noise-ratio (SNR). In addition, PWI is typically acquired over a short time, needing only a few extra minutes after a conventional MRI exam.

Contrast-enhanced relative cerebral blood volume (rCBV) is the most used perfusion imaging technique for parameter mapping. In this and other techniques, both the ready availability and the T2* susceptibility effects of gadolinium,

rather than the T1 shortening effects, make it a suitable agent for use in PWI. As long as the bolus transit through the tissue takes only a few seconds, high temporal resolution imaging is required to obtain sequential images during the wash-in and wash-out of the contrast material and for processing and calculation of hemodynamic maps (including mean transit time (MTT), time to peak (TTP), time of arrival (T0), negative integral (N1). An important neuroradiological indication for MRI is the evaluation of incipient or acute stroke via PWI and DWI. DWI can demonstrate the central effect of a stroke on the brain, whereas PWI visualizes the larger second ring delineating blood flow and blood volume. Echo planar and, potentially, echo volume techniques (such as PRESTO) together with appropriate computing power offer real time images of dynamic variations in water characteristics reflecting perfusion, diffusion, oxygenation, and flow; qualitative and in some instances quantitative maps of regional organ perfusion can thus be obtained (Fig. 4).

2. *Nuclear Medical Imaging*

The general principle behind nuclear medicine imaging is the following: a radioactive biologically active substance is chosen in such a way that its spatial and temporal distribution in the body reflects a particular body function or

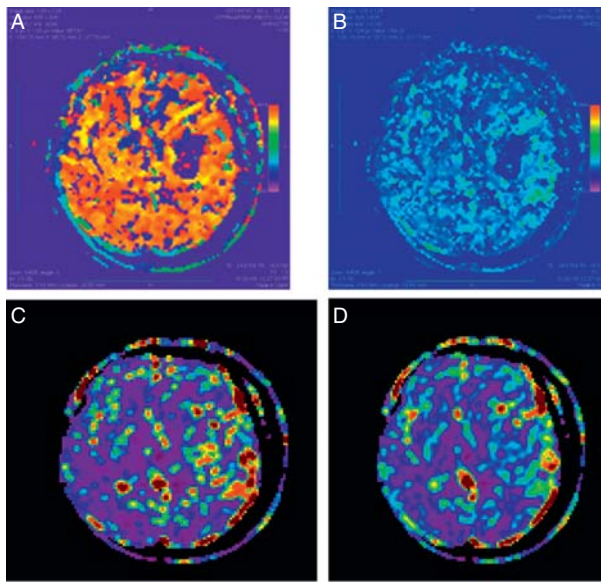

FIG. 4. Perfusion-weighted imaging (PWI): Time to peak (A), mean transit time (B), relative cerebral blood flow (C), and relative cerebral blood volume (D) maps are displayed. These and other possible maps that characterize entity and timing of tissue perfusivity are powerful and sensitive tools for summarizing the dynamic changes conveyed by PWI scans.

metabolism. To study the distribution without disturbing body function, only traces of the substance are administered to the patient.

The radionucleides (radioactive tracers) are unstable nuclei that decay by emission of gamma rays or positrons (followed by annihilation gamma rays). Distribution of the radioactive tracer is inferred from the detected gamma rays, trough instruments known as gamma camera, and mapped as a function of time and/or space. The most often used radionuclides are Tc-99 m in "single photon" imaging and F-18 in "positron" imaging (Saha, 2006).

Currently used nuclear neuroimaging techniques are SPECT and PET. They are both variations on the principle of gamma camera detection of emitted γ-rays. Tomographic reconstruction is used to construct three-dimensional images. Metabolic activity measures, receptor-binding studies, regional blood flow, and drug treatment response can be performed by using radiolabeled ligands. Some applications of PET include evaluation of stroke (blood clot or bleeding in the brain (Lovblad *et al.*, 1997; Sobesky *et al.*, 2005), study of dementia imaging (Silverman, 2004) and evaluation of brain tumors (Tian *et al.*, 2004).

The drawback of both SPECT and PET is poor spatial resolution. In some cases, PET may be more sensitive than SPECT, but PET scanners and tracers are much more costly than SPECT scanners and are often only available in the largest medical centers. A way of overcoming this limit, and thereby improving diagnostic accuracy, is to combine the SPECT and PET scanners with a multidetector computer tomography (MDCT) scanner. SPECT/CT and PET/CT combine a nuclear image with high-resolution structural CT images for accurate localization of lesions and physiological processes (Saha, 2006). Recently, combinations with MRI scanners have also been introduced to the radiological market.

Nuclear medicine imaging is an effective diagnostic tool in the early diagnosis, treatment, and prevention of numerous medical conditions. The main advantage of these techniques is their ability to show molecular function of pathological organs. This allows diagnosing of certain diseases and various medical conditions much sooner than with other medical imaging methodologies which provide mainly structural information about an organ or body part.

C. Metabolic Imaging

1. *Magnetic Resonance Spectroscopy*

In vivo magnetic resonance spectroscopy (MRS) offers information about the biochemistry of a selected brain tissue volume. This can represent surrogate markers for the pathology underlying the pathological process of different neurological diseases (Narayanan *et al.*, 2006).

MRS is a quantitative method of detecting nonaqueous proton signals that correspond to certain biological molecules in the brain. In most conventional and nonconventional MRI techniques, the MR signal originates from water protons and detailed images of the brain are created based on the different water content in various brain tissues. The hydrogen nuclei (protons) that are not in water (nonaqueous protons) are distributed throughout the hundreds of biologically significant molecules of the living brain. These molecular radio-signals are not visible on standard MR images because they are overwhelmed by the high signal derived from the aqueous protons. Each nonaqueous molecule has a unique radio-frequency specific to the chemical environment itself and distinct from the frequency of water protons. The amplitude or strength of these radio-frequencies is dependent on the concentration of the corresponding molecule in the volume of interest, each at its own radio-frequency position.

The most commonly used MRS technique we refer to, proton (1H) spectroscopy, measures the relative amplitude of the corresponding peak for each of several biological molecules by suppressing the signal from aqueous protons (Fig. 5). The best available and most important cerebral components that have been studied are *N*-acetyl aspartate (NAA), choline (Cho), creatinine(Cr)/phosphocreatinine (PCr), myoinositol and lactate. NAA is considered an *in vivo* marker of neuronal integrity and is often measured relative to Cr (which is thought to be unaffected by neurodegeneration). The NAA peak in an MR spectrum is a putative marker of neuronal and axonal integrity, and the Cho peak is largely a marker of cell-membrane turnover. Decreases in Cho usually represent inflammation and demyelinating processes, while decreases in NAA are markers of axonal and neuronal injury. On this basis, a reduction in the NAA peak is interpreted as representing neuronal/axonal dysfunction (Narayana, 2005) and an elevated Cho peak represents heightened cell-membrane turnover, as seen mainly in tumors. Therefore, MRS may provide unique information regarding metabolic changes in the CNS, evaluation of the pathogenesis, severity and progression of the neurological disease. Other metabolic peaks of increasing interest in the study of neurologic disorders are the glutamate/glutamine peak, representing a mixture of amino acids and bioamines used throughout the CNS as excitatory and inhibitory neurotransmitters (Vrenken *et al.*, 2005), and the myoinositol peak, representing a sugar-like molecule thought to be a marker of glial proliferation and now recognized for its importance in osmotic regulation of brain tissue (Narayana, 2005).

High-resolution ^{1}H MRS is expected to improve our understanding of the metabolic alterations that accompany ischemia, particularly those related to acid-base balance. ^{1}H MRS can depict an increase in lactate concentration and concomitant decrease in intracellular pH in the hyperacute ischemic stage when conventional MRI signal abnormalities are minimal.

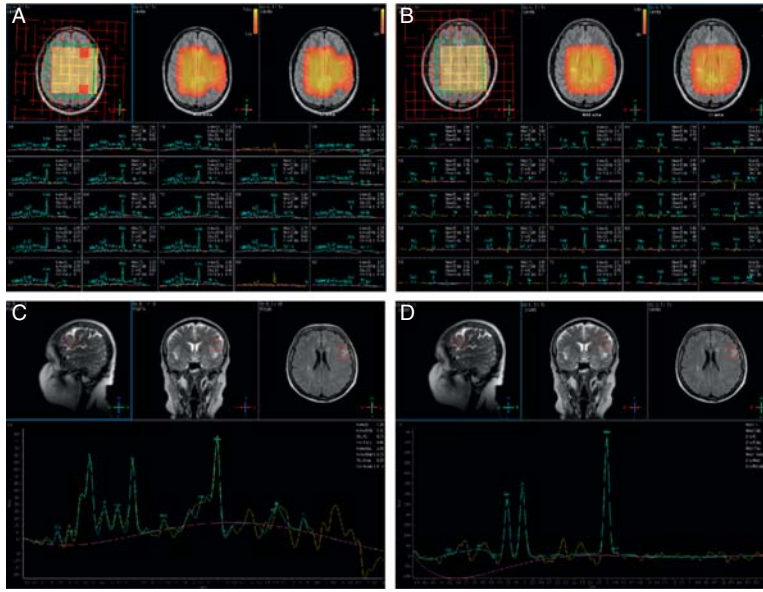

FIG. 5. Multi-voxel sMR: a TE = 25 ms (A) and TE = 144 ms (B) scan are reported with the fitted spectrum and estimated peak ratio reported for each voxel. A mixed Gaussian-Lorenztian peak shape was chosen for the fit as the most general. Single-voxel sMR: a TE = 25 ms (C) and a TE = 136 ms (D) scan are reported with the corresponding fit overlaid. The higher biochemical specificity of short TE scans is evident at the expense of the less accurate fit due to an irregular baseline and to peak overlap.

II. Vascular Cognitive Impairment

A. Terminology

After AD, CVD is recognized as the second most common cause of acquired cognitive impairment and dementia, alone or in conjunction with other neurodegenerative disorders (O'Brien, 2006).

Progress in the concept of vascular cognitive impairment (VCI) has been seriously limited by difficulties in finding agreement with respect to terminology. O'Brien *et al.* (2003) have proposed using VCI as an umbrella term, including all aspects and degrees of cognitive impairment resulting from vascular brain damage. Conversely, some authors favor regarding vascular dementia (VaD) and VCI as two different entities (Roman *et al.*, 2004). Although several definitions exist, both DSM-IV and ICD-10 require the presence of memory impairment as an absolute requirement, in addition to one or more other cognitive domains being affected. This has been largely criticized, since the presence of memory

impairment is known to be more prevalent in neurodegenerative disease, such as AD, than in CVD. The use of a term of dementia that does not require memory impairment and instead focuses on cognitive symptoms such as executive deficits (known to be affected more in CVD) would possibly solve this dilemma. For the purpose of this review, the term VCI will be considered to refer to all forms of mild to severe cognitive impairment associated with and presumed to be caused by CVD (O'Brien, 2006; O'Brien *et al.*, 2003).

B. Classification

The proposed classification by O'Brien *et al.* (O'Brien, 2006; O'Brien *et al.*, 2003) distinguishes between sporadic and hereditary disorders that represent the two main categories. The sporadic VCI is further divided into several clinical subtypes: post-stroke dementia (PSD), VaD, mixed AD and VaD (mixed dementia) and, finally, vascular mild cognitive impairment (VaMCI). The term VaD is again subclassified into multi-infarct dementia, subcortical ischemic vascular dementia (SIVD), strategic-infarct dementia, hypoperfusion dementia, hemorrhagic dementia, and dementia caused by specific arteriopathies.

1. *Classification of Sporadic Vascular Cognitive Impairment*

Sporadic VCI is a clinical-pathological entity which includes several different sporadic vascular disorders which are not yet fully defined, whose main feature is their contribution to cognitive impairment.

Post-stroke dementia. PSD includes all types of dementia that happen after stroke, irrespective of their cause (Leys *et al.*, 2005). Their prevalence is likely to increase in the future, because of the decline in mortality after stroke (Rothwell *et al.*, 2004) and the aging population. Community-based studies suggest that having a stroke doubles the risk of dementia (Leys *et al.*, 2005). PSD might be the result of vascular lesions, AD, WM changes or a combination of these. The causes of PSD differ among studies in relation to patient age, time after stroke, ethnicity and criteria used. The risk factors are in general the same as for most vascular disease (arterial hypertension, history of high cholesterol, diabetes, forms of heart disease). Stroke-related variables associated with an increased risk of PSD are stroke severity, cause, location, and recurrence (Leys *et al.*, 2005). Most studies have found that a more severe clinical deficit at onset is associated with a higher risk of PDS (Tatemichi *et al.*, 1992, 1990). The risk of PSD and its severity are not influenced by the type of stroke (ischemic or hemorrhagic) (Barba *et al.*, 2000; Linden *et al.*, 2004) (Fig. 6).

Vascular dementia. Multi-infarct dementia, also known as cortical vascular dementia, is the traditional term used for VaD and the consequence of multiple large cortical infarcts (Hachinski *et al.*, 1974). It is clinically characterized by a

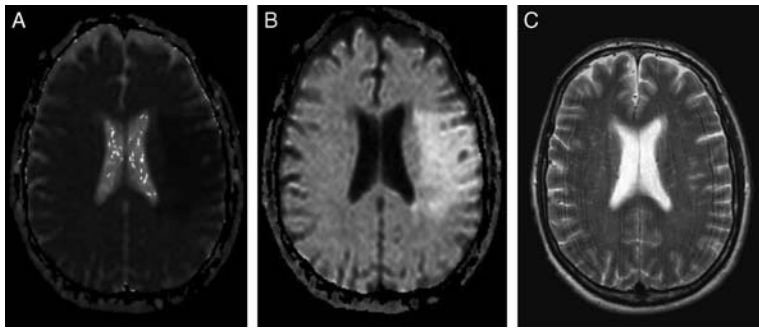

FIG. 6. Acute stage of left medium cerebral artery ischemic stroke: as shown on the images, the ischemic acute stage is visible on DWI-weighted images earlier than on conventional MRI: (A) ADC (B) eADC, and (C) conventional T2-weighted MRI scan.

relatively abrupt onset (days to weeks), a stepwise deterioration and a fluctuating course. It is related predominantly to large vessel disease and cardiac emboli events, being characterized by cortical-subcortical, arterial, territorial, and distal field infarcts (watershed areas).

Subcortical ischemic vascular dementia. SIVD is attributed to small-vessel disease and it is characterized by lacunar infarcts, ischemic WM lesions, and incomplete ischemic injury (Decarli, 2004; Wallin *et al.*, 2003). The clinical onset is variable (Babikian and Ropper, 1987) and the course is gradual, with or without acute deficits. The early cognitive syndrome of SIVD is characterized by a dysexecutive syndrome with slowed information processing. The dysexecutive syndrome includes impairment in goal formulation, organizing, planning, executing, and abstraction (Cummings, 1994). Memory loss is usually milder than in AD. In this subgroup of VaD, the onset is often more insidious and temporal relations between cognitive syndrome, brain imaging findings and vascular disease may not be clear (O'Brien *et al.*, 2003).

Hemorrhagic dementia. Hemorrhagic dementia is usually due to uncontrolled hypertension or vascular malformations, subarachnoid hemorrhage and intracerebral hemorrhage, with or without vasospasm. Due to the extent of the hemorrhage, patients often show additional neurological impairments such as sensorimotor changes or gait impairment. One of the most common causes of hemorrhagic dementia is subdural hemorrhage. Although it is primarily post-traumatic, considering it a vascular injury makes subdural hematoma a common and insidious cause of VCI in clinical practice (Starkstein *et al.*, 2005).

Much more common than epidural hemorrhages, subdural hemorrhages generally result from shearing injuries due to various rotational or linear forces (Maxeiner and Wolff, 2007). The disease is commonly seen in the elderly and in

alcoholics, who have evidence of brain atrophy. Cerebral atrophy increases the length the bridging veins have to traverse between the two meningeal layers (dura and arachnoidea), hence increasing the likelihood of shearing forces causing a tear. It is also more common in patients on anticoagulants, who can have a subdural hematoma with a minor injury. Chronic subdural bleeds can develop over a period of days to weeks, often after minor head trauma, though such a cause is not identifiable in 50% of patients. They may not be discovered until they present clinically months or years after a head injury and they are rather common in the elderly (Kushner, 1998) (Fig. 7).

Strategic-infarct dementia. It is characterized by focal, often small, ischemic lesions involving specific sites critical for specific higher cortical functions. Cortical sites more often affected are the hippocampal formation, angular gyrus and cingulate gyrus and thalamic infarcts (bilateral or monolateral).

Dementia caused by specific arteriopathies. Arteriopathies such as cerebral vasculitis, that is, acute or chronic inflammatory changes of small, medium, and large arteries or veins, can be cause of multiple ischemic lesions and lead to VCI. They are often accompanied by systemic signs of fever, malaise, and weight loss.

Some rare arteriopathies such as inflammatory arteriopathy (e.g., polyarteritis nodosa, temporal arteritis) and noninflammatory arteriopathy (e.g., moyamoya disease, fibromuscular dysplasia) can cause multiple infarcts and lead to vascular dementia as well. In cerebral amyloid angiopathy-associated vasculopathy, aneurysm formation and stenosis in the leptomeningeal and cortical vessels cause damage to the subcortical WM. In hereditary cystatin-C amyloid angiopathy, patients have recurrent cerebral hemorrhages before the age of 40 that can lead to dementia.

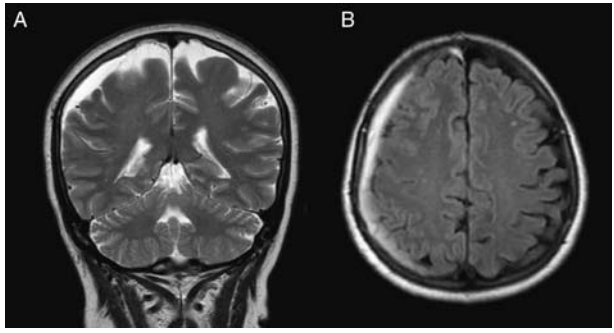

FIG. 7. Coronal and axial images of subdural hemorrhage on conventional MRI T2-weighted sequence (A and B).

Hypoperfusion dementia. Hypoperfusion due to large vessel or cardiac disease can affect the watershed areas of the brain and lead to vascular dementia. A correlation between systolic blood pressure reduction and cognitive decline in women, which was not accounted for by other factors, has been recently demonstrated (Zhu *et al.*, 1998). Baseline blood pressure was not found to be significantly correlated to cognitive decline with initial good cognition (Zhu *et al.*, 1998). It has also been suggested (Skoog *et al.*, 1998) that age-related changes in brain structure may contribute to the decrease in blood pressure in the very elderly, and that low blood pressure in dementia disorders is mainly a secondary phenomenon. Some researchers, therefore, have speculated that blood pressure reduction might be an early change in the dementing process, but further studies are necessary to clarify this aspect.

Mixed AD and VaD (mixed dementia). Mixed dementia has for a long time been underestimated as a common cause of dementia, particularly in the elderly. In fact, its diagnosis is still mostly a challenge. It has been shown that different vascular factors, including arterial hypertension and stroke, increase the risk of AD. Frequently, CVD coexists with AD (Decarli, 2004; de la Torre, 2004). This overlap is increasingly important in the elderly population since CVD is a potentially preventable and treatable cause of dementia. The actual relationship between AD and vascular pathology is still unclear. They may represent two independent co-occurring pathologies which happen to share risk factors (Decarli, 2004). However, accumulating evidence shows that vascular changes may actually stimulate or exacerbate the formation of AD pathology. For example, vascular disease might determine vessel wall thickening and reduce the efficiency of the perivascular drainage system, leading to a reduced rate of elimination of amyloid (Nicoll *et al.*, 2004) through the drainage system. Some of the most challenging clinical scenarios include VaD patients with an insidious onset or slow progression and AD patients with evidence of vascular lesions upon brain imaging. Given that reliable biological markers for recognizing AD and discerning it from mixed dementia do not yet exist, neuroimaging plays an important role as a potential marker. In fact, besides early episodic memory impairment and low concentrations of CSF peptides with high tau protein concentrations, early and significant medial temporal lobe atrophy on MRI and bilateral parietal hypoperfusion on SPECT are strongly suggestive of AD (Erkinjuntti, 2007).

Vascular mild cognitive impairment. VaMCI is a low degree of cognitive impairment resulting from CVD which does not meet the criteria for dementia. This entity has been relatively underestimated and understudied compared to the nonvascular pre-Alzherimer's (MCI) (Petersen *et al.*, 1999). However, recent studies have shown a higher percentage of VaMCI than VaD (Rockwood *et al.*, 2000) and a high tendency for converting into dementia in a relatively short time (Wentzel *et al.*, 2001).

2. *Hereditary Vascular Cognitive Impairment*

Understanding of the pathogenesis of vascular disease has improved greatly in recent years, and many molecular genetic conditions related to this symptom have been found. Among them, there is strong interest in cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL).

CADASIL is an inherited CVD due to mutations of the Notch3 gene at the chromosome locus 19p13. The clinical spectrum includes recurrent ischemic episodes, cognitive deficits, migraine and psychiatric disorders. The histopathological hallmark of CADASIL is accumulation of electron dense granules (GOM) in the media of arterioles. CADASIL was initially thought to be a rare disorder, but increasing numbers of families have been identified; therefore, it is likely that CADASIL is still largely underdiagnosed (Federico *et al.*, 2005). The course of the disease is very heterogeneous, even in the same family; some patients remain asymptomatic until their 70s, whereas others are severely affected from the age of 50 onward (Fig. 8).

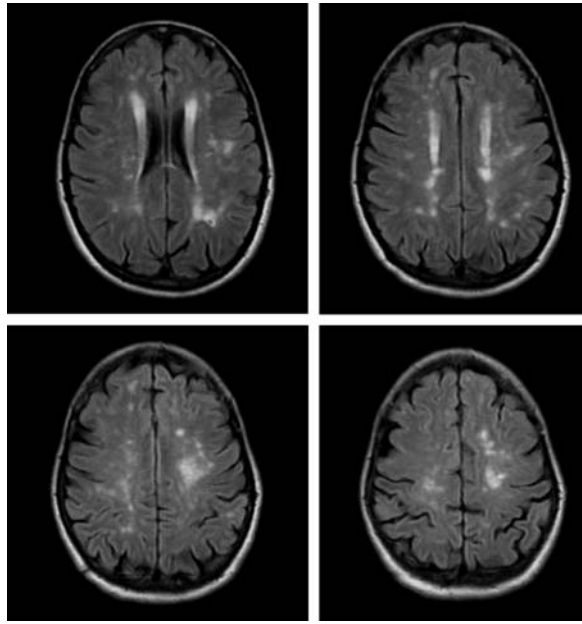

FIG. 8. Axial FLAIR sequence displays sample images of CADASIL MRI pattern of conventional MRI in a 32 y.o. patient.

C. Histopathology of VCI

Vascular disease produces either focal or diffuse effects on the brain and may cause cognitive decline. Focal CVD occurs mainly secondarily to thrombotic or embolic vascular occlusions. Common areas of the brain associated with cognitive decline are the WM of the cerebral hemispheres and the deep GM nuclei, especially the striatum and the thalamus. Hypertension is the major cause of diffuse disease and, in many patients, both focal and diffuse disease forms are observed together. The five most common pathological findings of VaD are white matter hyperintensities (WMH), macroscopic, lacunar and/or microscopic infarcts and microbleeds.

1. *White Matter Hyperintensities*

WMH, as revealed by MRI-histopathological studies, are associated with evidence of hypoxic tissue injury (Fernando *et al.*, 2006), with reduced capillary density not only in the lesions but also in normal-appearing WM (Brown *et al.*, 2007). However, smooth periventricular lesions directly adjacent to the ventricles of high T2 signal are considered by some researchers to be of nonischemic origin and consist of areas of demyelination, subependymal gliosis and discontinuity of ependymal lining (Fazekas *et al.*, 1993).

The most important risk factor for WMH is age, but other known risk factors are hypertension and decreased peak expiratory flow, elevated levels of glycated hemoglobin (Murray *et al.*, 2005), type 2 diabetes (Korf *et al.*, 2006) and cigarette smoking (Liao *et al.*, 1997).

2. *Macroscopic Infarcts*

Infarctions involving areas of major cerebral arteries may result in large territorial lesions with a variable amount of tissue loss. The infarcts develop in typical stages of gliosis with increased water content. The intensity of gliotic scarring is used in pathological studies to judge the degree and age of the infarction (Jellinger, 2007). Hypertension, diabetes, hypercolesterolemia, smoking, and heart disease are the most common risk factors for infarcts.

Multiple cortical infarcts are believed to be the neuropathological cause of multi-infarct dementia (Hachinski *et al.*, 1974). In multi-infarct dementia, the combined effects of different infarcts produce cognitive impairment by affecting neural networks. The cognitive impact of large complete infarcts depends on localization and the extent of the ischemic lesion.

3. *Lacunar Infarcts*

Lacunes (small infarcts in WM and deep GM structures with diameters ranging from 3 to 15 mm) (Jellinger, 2007), represent different stages of ischemic injury exhibiting loss of axons and myelin together with reactive changes (Ishii *et al.*, 1986). In pathological studies, they have been associated with cognitive

decline independent of other dementia pathology such as AD (Gold *et al.*, 2005). Some studies have reported that subcortical lacunes and multiple widespread infarcts are the most common morphologic substrates of VaD (Jellinger, 2007).

Lacunes in SIVD are typically located in the caudate, globus pallidus, thalamus, internal capsule, corona radiata, and in frontal WM (O'Brien *et al.*, 2003). Lacunar state is a condition in which numerous lacunae are present, which indicates widespread severe small-vessel disease. It is due to small-vessel disease affecting all the small vessels of the brain. The amount of lacunes has been found to be a significant predictor of cognitive status in the elderly and of executive dysfunction in patients 3 months after an ischemic stroke (van der Flier *et al.*, 2005; Vataja *et al.*, 2003).

4. *Microscopic Infarcts*

Recently, there has been increasing focus on the contribution of cortical microinfarcts (not visualized by current available neuroimaging techniques) to cognitive decline both in normal aging (Kovari *et al.*, 2004), VaD and mixed dementia (Gold *et al.*, 2007a). Cortical microinfarcts might be as strong a predictor of cognitive decline as is the presence of neurofibrillary tangles in AD (Gold *et al.*, 2007b).

5. *Microbleeds*

Microbleeds (MBs), characterized histopathologically by the presence of hemosiderin around small vessels (Fazekas *et al.*, 1999), display themselves in several ways, mainly as hypertensive arteriopathy or amyloid angiopathy (Fazekas *et al.*, 1999). MBs are often detected in demented individuals, such as patients with AD (Hanyu *et al.*, 2003), CADASIL (Dichgans *et al.*, 2002), subcortical vascular dementia (Won Seo *et al.*, 2007) or memory loss (Cordonnier *et al.*, 2006). Cordonnier *et al.* (2006) studied the prevalence of MBs in a large cohort of patients (772 patients) attending a memory clinic. They found that 65% of patients with vascular dementia exhibited MBs, vs 18% of AD patients, 20% of mild cognitive impairment patients, and 10% of patients with subjective complaints. The presence of MBs was associated with age, WMH, lacunar infarcts, and infarcts. This finding of a relatively high proportion of MBs in AD and mild cognitive impairment also provides further evidence for the involvement of vascular factors in neurodegenerative diseases such as AD.

D. Diagnostic Neuroimaging Criteria in VCI

Conventional imaging plays a central role in the diagnostic work-up in most vascular disorders. It is suggested that MRI should be incorporated as an essential part of clinical trials involving VCI (O'Brien *et al.*, 2003; Schmidt *et al.*, 2007), but the pulse sequences, techniques and clinical outcome to be used remain a matter of debate (Enzinger *et al.*, 2005; Schmidtke and Hull, 2005).

Of the available diagnostic criteria for VaD, only two of them, the NINDS-AIREN (Roman *et al.*, 1993) and the State of California AD Diagnostic and Treatment Centers (ADDTC) criteria (Chui *et al.*, 1992), require radiological findings of CVD in the form of infarcts or WMH.

E. Therapeutic Strategies

Therapeutic approaches can be divided into primary prevention (preventing the occurrence of CVD), secondary prevention (Fig. 9) (preventing the exacerbation of CVD), and symptomatic treatments (O'Brien, 2006).

Much is known about primary prevention, which mainly consists of preventing the vascular disease leading to VCI by reducing the above-mentioned risk factors (mainly hypertension, cigarette smoking, hyperlipidemia, etc.). However, the degree to which primary prevention can affect nonstroke-related damage and, in particular the development of WMH, is still mostly unclear. Secondary prevention consists mostly of preventing recurrent vascular episodes, mainly strokes, by the use of antiplatelet agents, carotid endarterectomy, anticoagulants for atrial fibrillation and decreasing blood pressure (O'Brien, 2006).

Regarding symptomatic treatments, several different trials have been undertaken, although they have been largely criticized, mainly because they have focused more on AD than VCI (the AD group is much bigger, and the effect on society would thus be more significant). One single study in VaD showed that aspirin yielded better cognitive outcomes for treated as opposed to untreated patients (Meyer *et al.*, 1989). Many studies suggest that cholinesterase inhibitors may prove beneficial in the treatment of VaD, both in cognitive and behavioral symptoms, as they already have in the management of AD (Erkinjuntti *et al.*, 2002; Pratt and Perdomo, 2002).

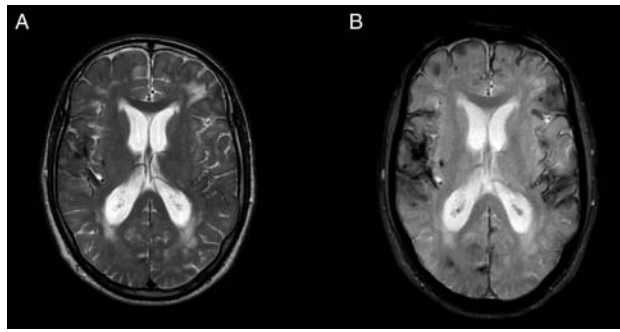

Fig. 9. T2w (A) and GRE axial images (B) in a case of amyloid angiopathy.

With respect to neuroimaging, such treatment effects would be especially interesting considering primary prevention strategies. The various neuroimaging techniques have, as shown below, been able to detect both established CVD as well as preclinical brain damage in healthy individuals possibly at risk. In this respect, neuroimaging may serve as an important tool of the future in attempts to reduce the prevalence of VCI.

III. Updates on Neuroimaging Techniques in VCI

A. Conventional Structural MRI

Conventional MRI techniques play an important role both for diagnosis and prognosis in VCI patients. Our knowledge of both incidental and disease-related findings has greatly increased during the last decades and allowed a better understanding of the pathological basis of VCI. However, VCI shows no pathognomonic imaging features. Infarct location often does not correlate with the cognitive profile, and neuroimaging can establish the chronology of lesions only with certain limits and cannot offer information about the relative contribution of neurodegenerative versus ischemic processes to the clinical presentation.

1. *White Matter Hyperintensities*

Apart from providing indications of ischemic lesions, MRI has, due to its widespread availability, resulted in increased recognition that WMH on T2-WI are common incidental findings in the brains of otherwise clinically healthy individuals (Fig. 10) (Enzinger *et al.*, 2006; Fazekas, 1989; Wen and Sachdev, 2004). In fact, epidemiological imaging studies show that WMH are extremely

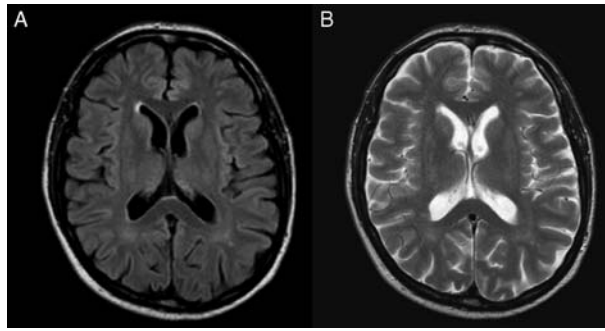

Fig. 10. Normal findings in healthy individuals on conventional MRI: (A) axial FLAIR image, (B) axial T2-weighted image.

common in the elderly (de Leeuw *et al.*, 2001; Liao *et al.*, 1997; Wen and Sachdev, 2004). In a population-based study, de Leeuw *et al.* (2001) showed that, of 1077 subjects between 60 and 90 years of age, only 5% had no WMH detectable on MRI. Other studies have shown up to 90% prevalence of WMH (Sachdev *et al.*, 2005). Most studies show that women have more WMH changes than men (de Leeuw *et al.*, 2001; Sachdev *et al.*, 2007; van den Heuvel *et al.*, 2004), while some others show contradictory findings (Wen and Sachdev, 2004).

Accumulation of WMH around the ventricles, also called leukoaraiosis, appears as a bright signal on T2-WI, indicating pathology involving increased water content and gliotic scarring in the WM of the brain. The FLAIR sequence is commonly used for detection of these WMH. Typical WMH in subcortical ischemic disease include extensive periventricular and deep WM signal abnormalities, usually located in the genu and anterior limb of the internal capsule, anterior corona radiata and anterior centrum semiovale (O'Brien *et al.*, 2003).

In nondisabled elderly living independently, age-dependent WMH have been recently reported as relating to both global cognitive dysfunction and various specific cognitive performances such as executive function, attention, and speed processing (Verdelho *et al.*, 2007). Despite evidence that age-related WMH influence cognitive status, some studies report that there is no such relationship, suggesting that MRI might be oversensitive when it comes to WMH, and that higher water content in the brain does not necessarily result in loss of function (Schmidtke and Hull, 2005). The association between WMH (especially low grade) and cognition in nondemented individuals is at the present time complex and not fully understood.

In subjects affected by VaD, the NINDS-AIREN criteria (Roman *et al.*, 1993) require that WMH involve at least 25% of total brain WM. In order to be significant, WMH must be diffuse and characterized by irregular periventricular lesions extending into deep WM, sparing areas thought to be protected from perfusion insufficiency (e.g., subcortical U-fibers and external capsule-claustrum-extreme capsule). Studies on the relationship between WMH in VaD and cognitive impairment have led to contradictory results (Cohen *et al.*, 2002; Fernando and Ince, 2004).This can be explained by the fact that the relationship between WMH and dementia might be driven by a threshold effect (Libon *et al.*, 2008; Wright *et al.*, 2008), which implies that a certain amount of WMH is needed to have clinical consequence. Once this threshold is reached, other factors might contribute more to cognitive impairment than WMH volume (Sweet *et al.*, 2003). In VaMCI patients, recent studies have also found an association between WMH volume and deficits on cognitive tests (Debette *et al.*, 2007; Sachdev *et al.*, 2006; Yoshita *et al.*, 2006), especially for executive dysfunction (Bombois *et al.*, 2007). Furthermore, periventricular WMH have been found to predict conversion to VaD and mixed dementia, but not to increase the risk of developing other dementias like AD, DLB, and fronto-temporal dementia (Bombois *et al.*, 2008).

2. *Macroscopic, Lacunar, and Microscopic Infarcts*

Cerebral infarction is focal brain necrosis due to complete and prolonged ischemia that affects all tissue elements, neurons, glia, and vessels. As previously described, they differ from each other with regards to their size and spatial location. The clinical consequences vary as well, depending on the size and location of the infarct, that is, a very small infarct in a core region such as the rolandic area can lead to pronounced deficits with very poor outcome, whereas a larger ischemic event in a not "eloquent" location can be of much less importance, that is, remain clinically silent. On conventional MRI such infarcts are seen as hyperintensities on T2-WI regardless of their cause, and they can be detected as soon as they enter into a subacute stage. For detecting the acute stage of an infarct and, therefore, the therapeutical possibilities of limiting the structural damage and neurological consequences, nonconventional techniques play a superior role.

The amount of lacunes has been found to be a significant predictor of cognitive status in the elderly (van der Flier *et al.*, 2005), in CADASIL disease (Liem *et al.*, 2007), as well as in the executive dysfunction of nondemented patients (Carey *et al.*, 2008) and in post-stroke patients (in the last ones in conjunction with temporal lobe atrophy, WMH volume, education, and Mini-Mental State Examination (MMSE)) (Vataja *et al.*, 2003). However, an earlier study found no association between either volume or localization of lacunes and cognition in SIVD (Fein *et al.*, 2000). The exact impact of lacunes on cognitive decline in SIVD is, therefore, not yet established and fully understood.

3. *Microbleeds*

In patients with lobar intracranial hemorrhage, cognitive decline has been shown to be more severe in subjects with larger numbers of MBs at baseline (Werring *et al.*, 2004). In a recent study, MBs appear to be primarily associated with global cognitive impairment even in subjects with no history of neurological disorder (Cordonnier *et al.*, 2006; Werring *et al.*, 2004).

4. *Hereditary VCI*

In hereditary VCI such as CADASIL, conventional MRI reveals extensive cerebral WM lesions, subcortical infarcts and MBs. CADASIL is characterized by WMH on T2-WI in the subcortical WM and basal ganglia. Two major types of abnormalities were first observed by Skehan *et al.* (1995) and later confirmed by other studies (Lesnik Oberstein *et al.*, 2003). The most striking findings were large confluent patches of high-signal change on T2- and proton density-weighted images present throughout the white matter, especially in the anterior part of the temporal lobes and the periventricular portion of the occipital lobes. Additionally, small linear and punctuate lacunes were detected, present not only

in the periventricular white matter but also in the brain stem, basal ganglia, thalamus, external capsule, and corpus callosum (Skehan *et al.*, 1995).

One of the main disabling symptoms of this disease is the cognitive impairment, providing CADASIL as a pure VCI entity. A recent study by Viswanathan *et al.* (2007) showed that, among the lesions observed on conventional MRI in CADASIL, the overall lacunar lesion burden seems to have the most important impact on cognitive function and disability. These findings suggest that preventive strategies to decrease the risk of lacunar lesions as observed on MRI may reduce disease-related impairment in CADASIL. These results suggest that lacunar lesions may also play a key role in disability and cognitive impairment in more common forms of small-vessel disease.

5. *Brain Atrophy*

Analyses estimating brain volumes have been widely used with respect to ischemic pathology. In normal aging, a large epidemiological study found that high WMH volume correlated with GM atrophy (Wen *et al.*, 2006). Medial temporal lobe atrophy (MTA) was recently demonstrated to predict cognitive status after stroke alone (Firbank *et al.*, 2007) or in conjunction with brain infarct, WMH volume, and the subject's educational level (Pohjasvaara *et al.*, 2000).

In CADASIL, atrophy is currently investigated as an additional important characteristic of the disease (O'Sullivan *et al.*, 2007; Peters *et al.*, 2006). Cerebral volumetric assessment might thus be an additional aspect in understanding the pathogenesis behind neuropsychiatric and neurobehavioral changes in ischemic brain diseases. A limitation to keep in mind is that brain atrophy might develop rather late in the course of some diseases and for the time being serves mostly to characterize the natural development of the pathology.

B. Nonconventional Techniques

1. *Diffusion-Weighted Imaging and Diffusion-Tensor Imaging*

Data from healthy individuals and patients with MCI and dementia, independent of their cause, converge on highlighting a positive correlation between cognitive performance and fractional anisotropy, and a negative correlation between cognitive performance and mean diffusivity (Kapeller *et al.*, 2004). Moreover, correlations between diffusional measurements and behavioral scores (e.g., side-alternating tapping speed) have been reported for normal individuals.

Diffusion tensor variants have also been previously shown to yield a better correlation with cognition than conventional MRI measures in VCI. DTI indices have been proved to correlate much more strongly with cognitive function than

WMH volume in patients with ischemic lesions. The correlation was strongest for diffusivity of normal appearing WM (NAWM), and remained significant after controlling for conventional MRI parameters, including brain parenchymal volume and T1 and WMH volumes. Regarding conventional measurements, brain volume predicted cognitive impairment best. Of special interest is the finding that DWI/DTI was able to detect specific pathology in NAWM, demonstrating the technique as a highly sensitive and early predictor of brain damage. This is in line with a pathological study combining postmortem MRI and histology (Brown *et al.*, 2007), and shows the great potential of newer imaging techniques. DWI might thus serve as a promising imaging technique for further knowledge about vascular changes in the brain not visible on traditional MRI scans and for exploring the mechanisms of cognitive dysfunction in these patients.

2. *Magnetization Transfer Imaging*

In many previous studies, WMH were not further evaluated than assessing the total volume of WMH based on T2-WI. As a result some studies show only correlations, if any, between the WMH volume on one hand and measures of cognitive function or risk factors on the other.

Recently, MTI has demonstrated that age-related WMH are quite heterogeneous despite their similar appearance on T2-WI, which is assumed to reflect histological differences in these lesions (Spilt *et al.*, 2006). Thus, by taking into account the heterogeneity of age-related WMH, both in terms of etiology and in terms of the severity of tissue destruction, a better understanding of the causes and consequences of these lesions and other tissue structure abnormalities leading to VCI can be obtained. This might explain previous contradictory findings on the clinical impact of WMH, since these lesions are not uniform.

C. Metabolic Imaging

1. *Magnetic Resonance Spectroscopy*

MRS has been shown to be superior to conventional MRI measurements in predicting cognitive decline after stroke. In a longitudinal study (Ross *et al.*, 2006), reduced frontal WM NAA/Cr and NAA appear to be useful predictors of cognitive decline over 12 months and 3 years in stroke/TIA and healthy aging, respectively. MRS may therefore play a useful role in the early investigation of individuals at increased risk of cognitive decline after stroke/TIA. Individuals identified to be at risk for cognitive decline may potentially benefit from early interventions. These MRS results were better predictors than hippocampal volume, whole brain or WMH volumes. As suggested by the authors, assessment of

frontal NAA/Cr ratio might serve as a possible biomarker for identifying patients at risk for cognitive decline after stroke/TIA.

D. Functional Imaging

Contrary to the case in neurodegenerative disorders, functional imaging has played a minor role compared to structural imaging in the investigation of cognitive impairment in CVD. Despite this, its use has been recently growing. It is therefore proposed by Nagata *et al.* (2007) that the old VaD criteria should be revised especially due to new insight brought by nuclear imaging techniques.

1. *Perfusion-Weighted Imaging*

Zimny *et al.* (2007) studied 64 patients with dementia with different degrees of cognitive impairment to assess the relationship between cognitive impairment according to the MMSE and values of CBF, CBV, and MTT obtained in perfusion CT (pCT). The results of this study showed that CBF and CBV calculated with pCT correlate with cognitive impairment in patients with dementia and thus may play a role in monitoring disease progression or therapeutic response (Zimny *et al.*, 2007). This may be a good setting for developing new studies using either pCT or perfusion MRI, the latter losing in spatial resolution but gaining in tissue specificity.

2. *SPECT and PET*

Functional imaging studies in VCI have mainly focused on cerebral metabolism and rCBF using techniques such as 18F-2-fluorine-2-deoxyglucose (FDG)-PET and perfusion SPECT. The pattern of altered brain metabolism is more variable in vascular disorders than in neurodegenerative, reflecting the heterogeneity of the lesions involved. Still, a few studies have found that functional nuclear imaging can distinguish VaD from differential diagnoses such as AD (Kerrouche *et al.*, 2006; Mielke *et al.*, 1994; Nagata *et al.*, 2000) and frontotemporal dementia (Lojkowska *et al.*, 2002). Functional imaging can be used to see the remote effect of different ischemic lesions on higher cerebral functions. In the past few years, radiotracer imaging has been used in many studies to address this issue.

For lacunar infarcts, Clarke *et al.* (1994) found that an isolated infarct in the left anterior nuclei of the thalamus in a patient with clinical amnesia was associated with reduced metabolism in the thalamus, amygdala, and posterior cingulate cortex. These are all regions known to be involved in memory functions. Another study found that not only symptomatic but also silent lacunes were associated with global reduction of brain glucose metabolism (Takahashi *et al.*, 2000).

PET and SPECT have also evaluated the effect of WMH on cerebral metabolism (Clarke *et al.*, 1994; Sultzer *et al.*, 1995; Takahashi *et al.*, 2000). In a FDG-PET study of subjects with no signs of neurological disorders, Takahashi *et al.* (2000) found that an increasing severity of incidental WMH, particularly

periventricular lesions, was associated with reduced cerebral metabolism. Furthermore, the periventicular lesions were associated with reduced performance on tests for attention and speed. An FDG-PET study (Sultzer *et al.*, 1995) investigated the effect of various ischemic subcortical lesions on cortical metabolism in patients with VaD. This study, with relatively few subjects and heterogeneity in lesion types, found that the type of subcortical pathology had a different influence on the amount of reduced metabolism in the cortex. In general, reduced metabolism was associated with the presence of WMH and lacunes. In addition, the severity of WM lesions correlated with anxiety, depression and overall severity of neuropsychiatric symptoms. Reed *et al.* (2004) performed a PET study investigating the impact of subcortical ischemic lesions on neuropsychological status in ischemic VaD, taking cerebral glucose metabolism, and both hippocampal and cortical atrophy, into consideration. The results showed that the functional impact of subcortical lesions, both lacunes and WMH, was strongest in the dorsolateral frontal cortex. The MRI pathology correlated with hypometabolism here and also with reduced executive function on neuropsychological tests. Hypometabolism and dysexecutive function was also associated with cortical atrophy, suggesting that this contributed to the clinical and imaging findings.

In SIVD, Yang *et al.* (2002) reported that, rCBF measured by SPECT showed a characteristic pattern with reduced metabolism in deep GM structures, superior temporal, and ventral subcallosal gyri. This pattern correlated with cognitive dysfunction. Taken together, the above studies suggest that vascular pathology may affect cerebral metabolism in a way that contributes to the cognitive dysfunction observed in VCI.

E. Correlations Between Imaging Findings and Pathology

Regarding ischemic changes in WM, lesion size is found to correlate with severity of pathologically confirmed tissue damage (Fazekas *et al.*, 1993). A recent combined neuropathological and MRI study found that both lacunes and WMH identified by imaging showed good correlation with CVD (Jagust *et al.*, 2008).

Nonconventional MRI techniques, such as DWI (O'Sullivan *et al.*, 2004), MRS (Ross *et al.*, 2006), and MTI (Spilt *et al.*, 2006), may increase both the sensitivity and specificity of detecting histopathological changes that are not seen by conventional MRI sequences.

IV. Conclusions

Neuroimaging plays an important role in the assessment of cognitive impairment in vascular disease. Conventional MRI findings have been extensively investigated and correlated with cognitive function in vascular patients.

Despite recent advances, many unsolved problems and questions remain to be answered. In fact, conventional MRI findings of WMH are unspecific and might not differentiate between various grades of histopathological damage. Higher field strength MRI (3 T and more) and newer nonconventional techniques can provide important contributions toward better understanding of the pathophysiology of the disease and the relation between vascular lesions and cognitive function. Functional imaging provides important knowledge about how the ischemic lesions affect brain activity and may help clarify the brain's plasticity- and receptor-dependent compensatory mechanisms in patients with a variety of neurological disorders, including vascular diseases. Nonconventional imaging goes beyond MRI-visible pathology, providing more information about subtle brain damage in VCI. Its results suggest that better understanding of the pathophysiological aspects of the disease may be obtained in the future. These techniques are unique tools for *in vivo* assessment of VCI and are useful in establishing diagnosis, monitoring disease activity, measuring therapeutic effect, and explaining the development of disability in the short and long term. They should be extensively taken into consideration for developing a new and more unified classification of VCI. Further studies are warranted to clarify the correlation between vascular brain damage and cognitive impairment.

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CONTRIBUTIONS OF NEUROPSYCHOLOGY AND NEUROIMAGING TO UNDERSTANDING CLINICAL SUBTYPES OF MILD COGNITIVE IMPAIRMENT

Amy J. Jak,[*,†] Katherine J. Bangen,[*] Christina E. Wierenga,[*,†] Lisa Delano-Wood,[*,†] Jody Corey-Bloom,[†,‡] and Mark W. Bondi[*,†]

[*]Department of Psychiatry, School of Medicine, University of California, San Diego 92093, USA
[†]Veterans Affairs San Diego Healthcare System, San Diego 92161, USA
[‡]Department of Neurosciences, School of Medicine, University of California, San Diego 92093, USA

The original conceptualization of mild cognitive impairment (MCI) was primarily as an amnestic disorder representing an intermediate stage between normal aging and Alzheimer's dementia (AD). More recently, broader conceptualizations of MCI have emerged that also encompass cognitive domains other than memory. These characterizations delineate clinical subtypes that commonly include amnestic and non-amnestic forms, and that involve single and multiple cognitive domains. With the advent of these broader classifications, more specific information is emerging regarding the neuropsychological presentation of individuals with MCI, risk for dementia associated with different subtypes of MCI, and neuropathologic substrates connected to the clinical subtypes. This review provides an overview of this burgeoning literature specific to clinical subtypes of MCI. Focus is primarily on neuropsychological and structural neuroimaging

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findings specific to clinical subtypes of MCI as well as the issue of daily functioning. Although investigations of non-amnestic subtypes using advanced neuroimaging techniques and clinical trials are quite limited, we briefly review these topics in MCI because these data provide a framework for future investigations specifically examining additional clinical subtypes of MCI. Finally, the review comments on select methodological issues involved in studying this heterogeneous population, and future directions to continue to improve our understanding of MCI and its clinical subtypes are offered.

I. Introduction

Mild cognitive impairment (MCI) is a clinical construct that describes individuals with mildly impaired performance on objective neuropsychological tests but relatively intact global cognition and daily functioning (Petersen *et al.*, 1999, 2001). MCI has been validated as qualitatively different from both normal aging and dementia (Petersen, 2004; Smith and Ivnik, 2003) and is a risk factor for the development of dementia. Because of its potential importance for early identification and intervention in those at risk for the development of dementia, the concept of MCI has received considerable research attention. However, the definition has evolved considerably over time. As originally proposed by Petersen and colleagues, MCI was characterized primarily as an amnestic disorder that represented an intermediate stage between normal aging and Alzheimer's dementia (AD) (Petersen *et al.*, 1999). More recently, broader conceptualizations of MCI have emerged that also encompass cognitive domains other than memory (Petersen and Morris, 2005; Petersen *et al.*, 2001). These characterizations delineate clinical subtypes that commonly include amnestic and non-amnestic forms, and that involve single and multiple cognitive domains (Manly *et al.*, 2005; Petersen and Morris, 2005; Petersen *et al.*, 2001; Tabert *et al.*, 2006) against the backdrop of intact daily functioning. With the advent of these broader classifications schemes, more specific information is emerging regarding the neuropsychological presentation of individuals with MCI, risk for dementia associated with different subtypes of MCI, daily functioning, and neuropathologic substrates connected to the clinical subtypes. The aim of this review is to provide an overview of neuropsychological, neuroimaging, functional, and treatment findings specific to clinical subtypes of MCI. In addition, methodological issues involved in studying this heterogeneous population and future directions to continue to improve our understanding of MCI and its clinical subtypes will also be highlighted and discussed.

II. Neuropsychological Presentation

It is certainly of great interest to determine factors placing individuals at highest risk for development of dementia so as to target them for early intervention. To this end, a better understanding of who is at risk for developing MCI may be an important first step. Presently, there are limited data about risk factors that correspond to conversion from cognitively normal to specific clinical subtypes of MCI; although, the existing evidence suggests that advancing age and lower education levels do place individuals at higher risk for MCI (Kryscio *et al.*, 2006), particularly for non-amnestic subtypes (Bickel *et al.*, 2006; Fischer *et al.*, 2007). For example, individuals with less than 9 years of education have an increased likelihood of isolated language and visuospatial deficits, as well as multiple domain amnestic MCI, whereas higher education was associated with increased chance of having isolated memory and executive impairments (Manly *et al.*, 2005). The presence of the apolipoprotein epsilon 4 allele (APOE $\varepsilon 4$) seems to more strongly influence transitions from normal cognition to amnestic MCI and influence conversion to multi-domain MCI to a lesser degree (Kryscio *et al.*, 2006).

More research attention has been paid to the neuropsychological presentation of MCI and use of neuropsychological testing to delineate distinct clinical subtypes (e.g., amnestic vs non-amnestic and single domain vs multiple domain). Even when stratified into clinical subtypes, MCI is still a heterogeneous concept. Complicating factors include widely differing neuropsychological tests and diagnostic criteria used across studies in arriving at the MCI classifications as well as inconsistency in how clinical subtypes are assigned. While Petersen advocated for four subtypes, including single and multiple domain amnestic MCI and single and multiple domain non-amnestic MCI, non-amnestic subtypes continue to receive less attention in the literature and multiple domain classifications often do not separate amnestic from non-amnestic presentations. Despite these challenges, some converging evidence about the presentation of distinct MCI subtypes is emerging.

Generally, multi-domain presentations seem to be more common than purely amnestic presentations (Alexopoulos *et al.*, 2006; Alladi *et al.*, 2006; Lopez *et al.*, 2003; Manly *et al.*, 2005; Rasquin *et al.*, 2005); although, some studies have identified single domains that are more common than multi-domains, and the non-amnestic type is as frequent as the amnestic (Busse *et al.*, 2006; Palmer *et al.*, 2008). Multi-domain MCI (mMCI) is the most common subtype in both stroke and memory clinic samples (Rasquin *et al.*, 2005). The prevalence of single domain amnestic MCI (aMCI) ranges from 0.5 to 8% (Bickel *et al.*, 2006; Das *et al.*, 2007; Di Carlo *et al.*, 2007; Jungwirth *et al.*, 2005; Lopez *et al.*, 2003), mMCI ranges from 0.5 to 16% (Bickel *et al.*, 2006; Busse *et al.*, 2003; Das *et al.*, 2007;

Di Carlo *et al.*, 2007; Jungwirth *et al.*, 2005; Lopez *et al.*, 2003), and single domain non-amnestic MCI ranges from approximately 3 to 15% (Bickel *et al.*, 2006; Busse *et al.*, 2003; Di Carlo *et al.*, 2007). There is only limited information on prevalence rates of multi-domain non-amnestic MCI, in which one group has identified less than a 5% prevalence rate (Bickel *et al.*, 2006). In addition to vastly different methodological approaches to defining MCI, the prevalence rates also differ due to varying sample origins, with hospital samples having generally higher prevalence rates across subtypes than community samples (Bickel *et al.*, 2006; Busse *et al.*, 2003). Presence of the APOE ε4 allele may also contribute to differing prevalence rates. Amnestic MCI presentations have a higher proportion of individuals with the apolipoprotein ε4 allele as compared to non-amnestic groups (Gabryelewicz *et al.*, 2007; Manly *et al.*, 2005; Whitwell *et al.*, 2007). Thus, if genetic risk is not determined, samples are likely to have differing proportions of individuals with the ε4 allele and, therefore, different prevalence rates.

Certainly the prevalence rates are impacted by the definition of MCI applied by each study. Basing amnestic subtype diagnoses on the presence of either verbal and/or visual memory deficits results in a larger proportion of individuals identified as amnestic MCI than just relying on verbal memory alone (Alladi *et al.*, 2006). Varying the cutoff score for defining impairment also alters diagnostic outcomes by up to 12%; use of a more stringent statistical cutoff for impairment (1.5–2.0 SD below normative expectations) increases positive predictive power compared to lower cut points (Busse *et al.*, 2003); although, a more liberal cutoff for impairment has been shown to have higher sensitivity and specificity for future development of dementia (Busse *et al.*, 2006). These sensitivity and specificity determinations are problematical; however, as they are based on a quite limited neuropsychological assessment.

Aside from the use in diagnosis and determination of objective cognitive deficits in MCI, additional neuropsychological findings may help differentiate MCI subtypes. Perhaps not surprisingly, Lopez and colleagues (2006) found that, compared to aMCI and normal cognition, mMCI was characterized by poorer language, psychomotor speed, fine motor control, and visuoconstructional functioning. What is of note is that, although the mMCI group had memory deficits, they were to a lesser degree than the deficits noted in the aMCI group (Lopez *et al.*, 2006). A substantial minority of the MCI cases did not have any memory impairment (Lopez *et al.*, 2006), further emphasizing that examining only amnestic subtypes fails to capture the full spectrum of possible cognitive declines associated with MCI.

Spatial navigation skills of those with multi-domain amnestic MCI tend to be more similar to spatial navigation skills of AD patients than to non-amnestic MCI subtype groups, with both the AD and multi-domain amnestic MCI groups impaired on virtually all portions of a spatial navigation task (Hort *et al.*, 2007). However, the multi-domain amnestic MCI group was generally more impaired

than other groups across all neuropsychological tests, so it is not clear that these spatial navigation difficulties occurred in isolation from the other impaired functions. Visuospatial skills specific to facial emotional processing have also been found to be intact in those with single domain amnestic MCI but impaired in those with multi-domain amnestic MCI, particularly in facial affect discrimination (Teng *et al.*, 2007).

III. Stability of Diagnosis

Multiple studies indicate that not all individuals diagnosed with MCI will decline and progress to a dementia diagnosis. In fact, a proportion of individuals appear to "improve" over time such that, at follow up, those initially identified as MCI are later categorized as cognitively normal. Anywhere from 20 (Fischer *et al.*, 2007) to 40% (Bickel *et al.*, 2006) of those with MCI appear to revert to the normal range upon retesting. Single domain classifications appear particularly susceptible to this instability, with single domain non-amnestic subtype often exhibiting the least stability over time (Bickel *et al.*, 2006; Busse *et al.*, 2006; Fischer *et al.*, 2007; Jak *et al.*, 2007). For example, one study reported that 50% of those with single domain MCI were normal upon later retesting whereas only 12% of those with multi-domain MCI "recovered" (Bickel *et al.*, 2006). Additional sources of instability in the MCI diagnosis can manifest via individuals changing MCI subtypes over time. Approximately 6% of those with MCI at baseline changed subtypes at follow up (Fischer *et al.*, 2007; Jak *et al.*, 2007). In contrast, over a 3-year interval, Zanetti and colleagues (2006) identified a more anticipated trajectory of their MCI cohort; all MCI subtypes either converted to dementia (about a quarter) or retained their MCI status (Zanetti *et al.*, 2006).

IV. Conversion to Dementia

Perhaps the largest amount of information exists on likelihood of conversion to dementia from various MCI clinical subtypes. Some evidence suggests that those with multi-domain amnestic MCI appear to be at greatest risk for future dementia (Di Carlo *et al.*, 2007; Palmer *et al.*, 2008; Tabert *et al.*, 2006), whereas others indicate that amnestic MCI places one at highest risk for conversion to dementia (Ravaglia *et al.*, 2006; Yaffe *et al.*, 2006). Amnestic MCI subtypes do seem to impart significant risk for future development of AD while multi-domain presentations may be more common in those who eventually develop vascular dementia (Fischer *et al.*, 2007; Rasquin *et al.*, 2005; Yaffe *et al.*, 2006; Zanetti *et al.*, 2006). Yaffe and colleagues (2006) found that, of those who progressed to AD,

76% were initially diagnosed with aMCI, 11% initially presented with single domain non-amnestic MCI, and 13% were initially identified as mMCI (Yaffe *et al.*, 2006). Conversely, of those who progressed to vascular dementia, 50% were initially diagnosed with aMCI, 8% had single domain non-amnestic MCI, and 42% had mMCI (Yaffe *et al.*, 2006). Rozzini and colleagues (2007) reported that, in a group of amnestic MCI individuals, poor global cognitive performance at baseline and worsening executive functioning, but not worsening memory performance, were associated with conversion to AD over a 1-year follow-up period. Those with non-amnestic multiple domain subtype appear more likely to convert to a non-AD dementia (Busse *et al.*, 2006), with the single domain non-amnestic MCI at particular risk to progress to a frontal dementia syndrome (Yaffe *et al.*, 2006). There are reports, however, in which detailed information about MCI subtypes does not add significant benefit in determining who may be at greatest risk for conversion to dementia (Maioli *et al.*, 2007; Ravaglia *et al.*, 2006; Rountree *et al.*, 2007).

V. MCI and Health Variables

Understanding any additional health factors that may be more prevalent in distinct MCI subtypes is also noteworthy as a way to further delineate risk profiles. For example, cardiovascular risk factors, presence of the apolipoprotein ε4 allele, mood symptoms, and parkinsonian symptoms have all been investigated in MCI subtypes. Recent research has shown that multi-domain or non-amnestic MCI subtypes may be more likely to have cardiovascular risk factors than either those with single domain amnestic presentations or those without MCI (Di Carlo *et al.*, 2007; Zanetti *et al.*, 2006). Mariani and colleagues (2007) found that those with single domain non-amnestic MCI had a higher frequency of ischemic heart disease, transient ischemic attack (TIA) or stroke, a higher Hachinski ischemic score, and more white-matter lesions on MRI compared to aMCI. Further, multi-domain and single domain amnestic subjects exhibited similar clinical characteristics; although, the multi-domain amnestic subtype did have a greater history of TIA/stroke (Mariani *et al.*, 2007). Amnestic MCI groups showed a higher prevalence of diabetes than controls whereas participants with non-amnestic MCI were more likely to have hypertension than were controls (Verghese *et al.*, 2008).

In contrast, Debette *et al.* (2007) found that white matter changes may play a role in cognitive decline in MCI as a whole, but they do not appear to be specific to either amnestic or non-amnestic clinical subtypes. Because their amnestic and non-amnestic characterizations were multi-domain, the authors found the rate of cognitive decline and the presence of periventricular hyperintensities was more prominent in those with baseline executive dysfunction (Debette *et al.*, 2007).

Mood symptoms also appear to be more common in those with multi-domain MCI relative to those with single domain amnestic presentations (Gabryelewicz *et al.*, 2007; Zanetti *et al.*, 2006). Additionally, higher depression ratings are linked to those whose cognitive symptoms progressed over the follow-up period (but not to the point of dementia) and to those who converted from MCI to dementia as compared to the stable group (Gabryelewicz *et al.*, 2007). Hallucinations and sleep disorders are more common in the non-amnestic than amnestic subtype (Rozzini *et al.*, 2008). Others have found, however, that mood symptoms are increased in MCI cohorts as compared to cognitively normal samples, but with no significant differences in mood symptoms emerging between specific MCI subtypes (Palmer *et al.*, 2007; Rozzini *et al.*, 2008).

Other health factors seem to be associated with MCI in general but are not necessarily specific to amnestic or non-amnestic presentations. For example, lower serum folate levels (Maioli *et al.*, 2007; Ravaglia *et al.*, 2006), history of atrial fibrillation (Ravaglia *et al.*, 2006), and higher serum HDL levels (Maioli *et al.*, 2007) contribute to increased likelihood of conversion from MCI to dementia, regardless of MCI subtype. Odor identification skills of MCI participants also fall in between those of AD and healthy control groups, and MCI subtypes did not differ on smell identification performances (Westervelt *et al.*, 2008).

Most conceptualizations of MCI exclude Parkinson's disease, given that the historical conceptualization has been of MCI as a precursor to Alzheimer's disease or other non-Parkinsonian dementias. In addition, the motor symptoms associated with Parkinson's disease often produce demonstrable changes in a person's activities of daily living (ADL), which confound its utility in the classification of MCI. Recently, however, there have been efforts to characterize the transitional period between normal cognitive function and dementia in Parkinson's disease (PD). The expanded clinical subtypes are particularly relevant to this effort given the difference in presentation between dementias of different origins. Data suggest that MCI in those with Parkinson's is predictive of future dementia in much the same way that it is for individuals with MCI without co-morbid PD. Non-amnestic subtypes are particularly prevalent in Parkinson's disease and the presence of MCI in individuals with Parkinson's disease does substantially raise one's risk of developing dementia as compared to those with PD and normal cognition (Janvin *et al.*, 2006). In contrast to AD, conclusions about amnestic subtypes of PD MCI are more difficult to draw given the low prevalence of this subtype. Boyle *et al.* (2005) found that those individuals with MCI had higher levels of parkinsonian symptoms (though not Parkinson's disease) than those who were cognitively normal. Verghese *et al.* (2008) found greater gait abnormalities in those with aMCI as compared to those with non-amnestic MCI or controls while others have noted that non-amnestic subtypes have higher rates of gait dysfunction than amnestic MCI (Boyle *et al.*, 2005). Those with mMCI may present with more extra-pyramidal features than those with aMCI (Zanetti *et al.*, 2006).

VI. Daily Functioning and MCI

Embedded in the controversy surrounding the establishment of specific diagnostic criteria for MCI, there is much debate regarding whether impairment in everyday activities should be included as a criterion. In its initial conceptualization, MCI guidelines required that functional abilities remain intact (Petersen *et al.*, 1999) as this specific criterion helped distinguish MCI from dementia. However, as Farias *et al.* (2006) note, cognitive and functional deterioration clearly occurs over the course of MCI since such change eventually leads to conversion to dementia for many individuals with MCI (e.g., Bruscoli and Lovestone, 2004; Petersen *et al.*, 1999). In light of this accumulating evidence, an international working group proposed modified criteria for MCI, which includes "preserved basic activities of daily living" and "minimal impairment in complex instrumental functions" (Winblad *et al.*, 2004, p. 243). Similarly, participants of the International Psychogeriatric Association Expert Conference on MCI did not require intact ADL/instrumental activities of daily living (IADL) as a criterion but, instead, defined MCI as "a syndrome defined as cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life" (Gauthier *et al.*, 2006, p. 1262).

Emerging information about the functional status of those with distinct clinical subtypes of MCI may shed additional light on the continuum of functional abilities spanning normal cognition to dementia. Supporting the notion that functional decline occurs on a continuum, several groups have reported that IADL decrements in MCI are intermediate to the subtle declines associated with normal aging and the frank impairments required for a dementia diagnosis (Farias *et al.*, 2006; Giovanetti *et al.*, 2008; Griffith *et al.*, 2003; Peres *et al.*, 2006).

Published reports comparing ADL and IADL performance between MCI individuals and their cognitively normal counterparts have demonstrated that those with MCI show greater IADL changes in areas including shopping, managing medications, and handling finances (Mariani *et al.*, 2008). In a study examining IADL performance across different MCI subtypes, Tam *et al.* (2007) reported that individuals with multiple domain MCI demonstrated impairment in IADL relative to both amnestic MCI participants and cognitively normal older adults. Corroborating this finding, Zanetti and colleagues (2006) demonstrated that individuals with multi-domain MCI performed more poorly on measures of ADL and IADL relative to amnestic MCI participants. In contrast, Farias and colleagues (2006) demonstrated that the MCI with memory impairment group showed somewhat more functional change relative to their MCI peers with no memory impairment and cognitively normal older adults. Similarly, Wadley and colleagues (2007) reported that amnestic, non-amnestic, and multiple domain MCI subgroups all demonstrated greater difficulty with IADL performance

compared to the cognitively normal group. However, unlike the other two MCI groups, individuals with non-amnestic MCI did not differ from the cognitively normal participants in terms of IADL performance. Notably, at least one study (Boeve *et al.*, 2003) did not find differences between amnestic MCI individuals and cognitively normal older adults in terms of functional abilities. However, it should be noted that the MCI participants who were included in this study were characterized as MCI based, in part, on intact ADL.

Farias and colleagues (2006) administered self-report and informant-based versions of the Daily Function Questionnaire (DFQ) and calculated a difference score by subtracting patients' DFQ from informants' DFQ. DFQ difference scores, which indicate a lack of awareness of deficits, were greater in demented individuals relative to their cognitively normal counterparts and MCI subtype groups (i.e., MCI with memory impairment and MCI without memory impairment). However, the difference scores did not differ between MCI groups and cognitively normal older adults. Based on these findings, Farias and colleagues (2006) argued that individuals with MCI do not underestimate functional changes as is often the case for demented individuals.

What seems clear from the above discussion is that changes in ADL and IADL are not uncommon across the spectrum of MCI; although, it remains to be determined whether many of these changes would be conceptualized as frank "deficits" or "impairments." Comparing the ADL and IADL changes of MCI to overt dementia groups would be helpful in determining cutoff criteria for impairment, or administering performance-based ADL and IADL measures with normative reference standards would also help to delineate whether such changes represent impairment.

VII. Neuroimaging

A. Structural MRI

In determining the clinical viability of the various clinical subtypes, many would assert that different subtypes should have distinct neuropathology or different courses of change in brain integrity. Certainly, structural neuroimaging provides a non-invasive way to begin to examine brain changes associated with MCI, and there is emerging evidence to support distinct neuropathological profiles in clinical subtypes of MCI. Whitwell *et al.* (2007) found that those with amnestic presentations (single or multiple domain) had greater gray matter atrophy in medial and inferior temporal lobes compared to controls. Those with multi-domain amnestic MCI additionally showed loss in posterior temporal lobe, parietal association cortex, posterior cingulate, anterior insula, and the

medial frontal lobe, a pattern of atrophy similar to that found in AD (Whitwell *et al.*, 2007). In support of this finding, Seo and colleagues (2007) reported that those diagnosed with single domain amnestic MCI showed cortical thinning in left medial temporal lobe (MTL) only, whereas those identified as multi-domain amnestic MCI showed cortical thinning in the left MTL, precuneus, and anterior and inferior basal temporal, insular, and temporal association cortices. The precuneus atrophy may be responsible for additional cognitive impairments present in the multi-domain MCI subtype and may suggest that the multi-domain presentations are a progression from single domain presentations since the areas of thinning noted in the multi-domain subtype encompassed all those in the single domain subtype and the extent of MTL atrophy was greater in the multi-domain versus the single domain subtype (Seo *et al.*, 2007).

In contrast, Becker and colleagues (2006) did not support the multi-domain subtype as the more advanced, transitional state between normal cognition and AD. They found that hippocampal volumes in those with multi-domain MCI were not statistically different from those of controls, but were significantly larger than both the amnestic MCI and AD groups (Becker *et al.*, 2006). Bell McGinty and colleagues (2005) found that the amnestic MCI group had greater volume loss in left entorhinal cortex and inferior parietal lobe as compared with multi-domain MCI. However, the multi-domain MCI group may exhibit their neuropathological changes in other areas, namely by smaller right inferior frontal gyrus, right middle temporal gyrus, and bilateral superior temporal gyrus as compared to amnestic MCI (Becker *et al.*, 2006).

Although the data are conflicting as to whether multi-domain subtypes necessarily have more extensive brain changes than single domain subtypes, current research does support the idea that different clinical subtypes of MCI have distinct neuropathology. Taken together, the available evidence suggests that those individuals with a more focal memory presentation have greater involvement of mesial temporal structures while those with more widespread deficits had greater involvement of association areas. Distinct MCI subtypes may represent different etiological paths to dementia, but the small sample sizes available in most of the imaging studies to date make conclusions tentative at best.

Other advanced imaging techniques hold promise to further clarify the nature and extent of brain changes associated with distinct clinical MCI subtypes though, to date, use of techniques such as functional magnetic resonance imaging (FMRI) and diffusion tensor imaging (DTI) has focused globally on MCI or on amnestic MCI, without significant investigation of non-amnestic subtypes. An overview of the use of these imaging techniques in MCI is provided, nonetheless, as this preliminary work is an essential framework for future examinations of clinical MCI subtypes.

B. Diffusion Tensor Imaging

A growing body of research suggests that white matter pathology contributes to age-related cognitive impairment and possibly potentiates the development of dementia (Raz and Rodrigue, 2006; Sullivan and Pfefferbaum, 2006). Although studies have generally shown white matter changes to be accelerated and more severe in AD (Pfefferbaum *et al.*, 2000; Rose *et al.*, 2006; Takahashi *et al.*, 2002), to date, few studies have employed DTI to examine early white matter changes in older adults with MCI with exceptionally limited focus on DTI-derived white matter changes in specific MCI clinical subtypes. Several studies have shown reduced fractional anisotropy (FA), a proxy of white matter integrity, in the posterior cingulum fibers, and this relationship seems to be stronger in the left versus right hemisphere (Fellgiebel *et al.*, 2005; Medina *et al.*, 2006; Rose *et al.*, 2006; Zhang *et al.*, 2007). Rose *et al.* (2006) demonstrated increased diffusivity in the entorhinal and parieto-occipital cortices, and decreased FA in the limbic parahippocampal white matter in patients with MCI. Moreover, Kantarci *et al.* (2005) was among the first to show that increased mean diffusivity of the hippocampus in amnestic MCI predicted future progression to dementia.

Several studies have shown decreased integrity in the posterior region of the corpus callosum (i.e., splenium) in those with MCI (Cho *et al.*, 2008; Delano-Wood *et al.*, 2007; Ukmar *et al.*, 2008), an area which is particularly sensitive to degenerative processes (Naggara *et al.*, 2006; Rose *et al.*, 2000; Takahashi *et al.*, 2002). Although some studies have shown changes in the frontal white matter of MCI patients (Bozzali *et al.*, 2002; Medina *et al.*, 2006; Naggara *et al.*, 2006), other studies have not identified any differences (Delano-Wood *et al.*, 2007; Head *et al.*, 2004; Medina *et al.*, 2006; Ukmar *et al.*, 2008). Although data are limited, results suggest a pattern of retrogenesis (Bartzokis, 2004), by which microstructural changes first occur in late-myelinating regions, spreading to early-myelinating regions only after the disease process has progressed beyond a particular threshold, which may initially manifest itself with the onset of MCI.

C. Functional MRI

Evidence to date indicates that functional brain decline precedes structural decline in prodromal dementia, including adults with MCI. Therefore, functional neuroimaging techniques may offer the unique ability to detect early functional brain changes in at-risk adults and identify the neurophysiological markers that best predict dementia conversion.

Given that AD neuropathology preferentially targets the MTL early in the course of the disease, thereby resulting in the hallmark episodic memory decline, and amnestic MCI is thought to represent prodromal AD, the majority of FMRI studies of MCI involve memory processing (particularly encoding) in amnestic samples. No known FMRI studies have been published focusing on other clinical subtypes of MCI. While several studies demonstrate increased blood oxygen level dependent (BOLD) response in the MTL (Dickerson *et al.*, 2004, 2005; Hamalainen *et al.*, 2007; Kircher *et al.*, 2007; Sperling, 2007), others report decreased MTL activity in MCI (Johnson *et al.*, 2006; Machulda *et al.*, 2003; Mandzia *et al.*, 2009). These discrepant findings have been interpreted as reflecting bimodal functional activity whereby less impaired MCI subjects show increased BOLD response in the hippocampus corresponding to a slight or moderate neuronal dysfunction, and more impaired MCI subjects demonstrate decreased BOLD response—similar to the levels observed in mild AD patients—as the cortical neuronal networks become more severely impaired with greater disease progression (Celone *et al.*, 2006; Dickerson *et al.*, 2004, 2005; Hamalainen *et al.*, 2007; Johnson *et al.*, 2006; Machulda *et al.*, 2003; Masdeu *et al.*, 2005; Petrella *et al.*, 2007a). However, this interpretation is primarily derived from cross-sectional studies and can only adequately be tested with longitudinal designs.

Few longitudinal FMRI studies of MCI have been reported. Although these studies are often limited by small sample sizes, they demonstrate promise for the use of FMRI to detect early AD. Those MCI patients who converted to AD showed a stronger relationship between brain activity in the left superior parietal lobe and the left precuneus during an angle discrimination task in the context of comparable performance (Vannini *et al.*, 2007). Similarly, despite equivalent memory performance, Dickerson *et al.* (2004) reported that MCI patients who subsequently declined during a 2.5-year follow-up period demonstrated increased right parahippocampal gyrus activity during picture encoding. In a more recent study, the same research group reported increased hippocampal activation predicted greater degree and rate of cognitive decline during a 6-year follow-up period, even after controlling for baseline level of impairment (Miller *et al.*, 2008).

Mandzia *et al.* (2009) reported that MTL activation during recognition was positively correlated with behavioral performance. However, unlike their healthy peers, MCI adults did not show a strong relationship between MTL activity during picture encoding and subsequent retrieval success, highlighting the complexity of the relationship between BOLD signal and effectiveness of encoding strategies. In contrast, Johnson *et al.* (2006) found reduced BOLD signal change in the right hippocampus during picture encoding and in the posterior cingulate during recognition of learned items in an amnestic MCI group despite comparable performance to their healthy peers. However, when activation corresponding only to successfully learned words was examined, an increase in hippocampal activity was seen, suggesting that an increase in MTL activity may support

successful memory encoding (Kircher *et al.*, 2007). Similarly, a positive correlation between extent of parahippocampal and hippocampal activation and memory performance was found in MCI but, in a paradoxical fashion, greater clinical impairment, was also associated with recruitment of a larger region of the right parahippocampal gyrus during encoding (Dickerson *et al.*, 2004). Data from Johnson *et al.* (2004) provided further evidence for hippocampal dysfunction in MCI, suggesting that adults with MCI do not habituate to increasingly familiar items in the same manner as healthy older adults who show expected reductions in BOLD response to repeated items over time.

Despite the prevalence of studies examining medial temporal cortex function supporting memory, other cortical areas have also been implicated in MCI. For example, a reduction in functional activity in the posterior cingulate cortex (PCC) during recognition and episodic retrieval of previously learned line drawings (Johnson *et al.*, 2006) and object working memory (Yetkin *et al.*, 2006), but not during self-appraisal (Ries *et al.*, 2007), has implicated this region in the memory retrieval difficulty seen in amnestic MCI. The degradation of PCC functioning in MCI is not surprising given that PET metabolic alterations in the temporoparietal cortices and in the posterior cingulate have been reported in MCI and AD (Desgranges *et al.*, 1998; Matsuda, 2001; Reiman *et al.*, 1996) as well as in nondemented young and middle-aged adults at genetic risk for AD (Petrella *et al.*, 2007b; Reiman *et al.*, 1996, 2004, 2005; Wolf *et al.*, 2003). Similarly, dedifferentiation in the retrosplenial cortex during the retrieval of recent versus remote autobiographical memories and during episodic versus semantic memory retrieval has been reported in amnestic MCI (Poettrich *et al.*, 2009), further implicating the medial posterior cortex in MCI. Additionally, the neural substrates of visual working memory (Yetkin *et al.*, 2006), self-appraisal (Ries *et al.*, 2007), and emotional working memory (Dohnel *et al.*, 2008) in MCI have also been examined, and generally implicate a greater number of cortical regions. However, results are varied and highlight the need for greater attention to other cognitive processes in MCI in order to more fully understand changes in cortical functioning that may signal impending cognitive decline.

VIII. Treatment

One motivation to better understand the heterogeneous concept of MCI and the risk it imparts for future development of dementia is to provide early interventions that could halt or at least slow progression of symptoms. To date, unfortunately, there are no FDA-approved therapies for MCI. Further, aMCI has received all the attention with regard to treatment trials with no trials investigating other distinct clinical subtypes of MCI. Of the existing treatment

TABLE I
CLINICAL TRIALS IN aMCI

Agent	*N*	Duration	Endpoint	Outcome
Donepezil	269	24 weeks	Symptoms	Negative
Donepezil/Vitamin E	769	3 years	AD	Partially positive
Rofecoxib	1200	2–3 years	AD	Negative
Galantamine	995	2 years	CDR 1	Negative
	1062	2 years	CDR 1	Negative
Rivastigmine	1018	3–4 years	AD	Negative

AD, Alzheimer's disease; CDR, clinical dementia rating.

trials in MCI, most have used a "progression to AD" design with the focus on slowing cognitive decline and delaying conversion to AD. As a whole, the trials have been disappointing with one possible exception, the Alzheimer's Disease Cooperative Study (ADCS)-sponsored trial (Petersen *et al.*, 2005) (see Table I).

The ADCS-sponsored study of Vitamin E and donepezil for MCI involved 769 subjects at 69 centers in the US and Canada over 3 years. There were three treatment arms: Vitamin E 2000 IU/day, donepezil 10 mg/day, and placebo. The primary trial endpoint was conversion to AD. Although conversion to AD favored donepezil at 1 year, there were no differences among groups with regard to conversion to AD at 3 years. However, possession of the APOE ε4 allele was noted to be associated with a threefold greater risk of conversion from aMCI to dementia and, thus, clearly an important predictor of progression. When the authors looked at the progression to AD for APOE ε4 positive participants by treatment group, they found that the effect of donepezil was greater in ε4 positive individuals and persisted for 2 years. While neither of the two active arms reduced the risk of progressing to AD over the entire 36 months, donepezil reduced the risk of progression to AD for the first 12 months in all subjects and up to 24 months in those who were positive for the APOE ε4 allele. No treatment effect was noted for Vitamin E.

Other treatment trials have been less promising for halting conversion from MCI to dementia over time. A large trial of rivastigmine, an acetylcholinesterase inhibitor, was a double blind, placebo-controlled trial of 1018 patients that had many of the same features as the ADCS trial, but was conducted in 14 countries using multiple languages and translations of the neuropsychological instruments (Feldman *et al.*, 2007). At baseline, arms were not well matched with regard to frequency of APOE ε4 genotype, which was 46% in the placebo arm but only 37% in the rivastigmine arm. The study also had a lower conversion rate than expected and had to be extended to 4 years; over that time, 21.4% of placebo treated, but only 17.3% of rivastigmine treated, subjects progressed to AD.

Although rivastigmine was favored, the results were not statistically significant, and secondary assessments were also not significant. Investigation of the efficacy of another acetylcholinesterase inhibitor, galantamine, also failed to reveal a significant effect of galantamine on conversion to dementia in those with MCI in either of two trials (Winblad *et al.*, 2008).

Finally, another large randomized, placebo-controlled, double-blind study examined the ability of the COX 2 inhibitor, rofecoxib, to delay disease progression in 1457 aMCI subjects (Thal *et al.*, 2005). Once again, there was a lower than expected annual rate of conversion to AD. Conversion to AD actually favored placebo in this trial but the authors dismissed the significance of this finding because the secondary cognitive measures did not corroborate the primary outcome.

In hindsight, several important factors likely influenced the results of these studies, including, perhaps first and foremost, the variable rate of progression from aMCI to AD. Sources of this variability likely include subject heterogeneity, with regard to impairment level, culture, language, and APOE $\varepsilon 4$ carrier status, in addition to even simple differences in implementation of enrollment criteria. MCI patients may show increased awareness of, or lower tolerability for, adverse events, resulting in higher discontinuation rates. Our current outcome measures may be insensitive; for example, the conversion design dichotomizes a continuous variable and most of the currently used efficacy measures follow an AD trial model of decline. Rather than decline, however, MCI patients may show improvement on cognitive measures, no matter which treatment group they are assigned to, because of at least some preservation in their ability to learn. Future MCI trials may benefit from less heterogeneous recruitment with stricter entry criteria and enriched populations, more sensitive cognitive and global outcome measures that reflect subtle impairments in complex activities, novel imaging outcomes, and longer trials.

IX. Conclusions

MCI remains a heterogeneous concept, though division of MCI into distinct clinical subtypes serves as a promising approach to better understanding MCI as a diagnostic entity and a risk factor for future cognitive decline. Evidence to date suggests that multi-domain amnestic presentations are more prevalent than either single domain amnestic or multi-domain non-amnestic presentations, though relatively little attention has been paid to the latter subtype. Converging neuropsychological, daily functioning, and neuroimaging data suggest that multiple domain presentations may place one at highest risk for future development of dementia. The current literature also supports that knowledge of subtypes of MCI informs the risk for future development of different types of dementia.

Though knowledge of MCI subtypes appears helpful in predicting risk of conversion to dementia, there remains a significant minority of individuals with MCI, particularly single domain subtype that may revert to normal cognition when followed over time. This instability in diagnosis as well as the varying prevalence rates, rates of conversion to dementia, and general oft-conflicting results in the literature, are likely due to ongoing challenges in operationalizing the diagnostic criteria for MCI. The methods for documenting objective neuropsychological impairment tend to be a particularly variable and ill-defined aspect of the MCI diagnostic process across studies (Portet *et al.*, 2006). There is little consensus about what neuropsychological tests (or how many) should be used to document objective cognitive impairment, what level of performance is considered cognitively impaired, how diagnostic criteria for different clinical subtypes of MCI are applied, what constitutes intact daily functioning, or about whether or not functional abilities should be included in the diagnostic decision-making regarding MCI. As this review highlights, the variable results in the current MCI literature clearly illustrate the importance of (a) understanding the criteria used to identify cognitive impairment in making the MCI diagnosis, (b) the value of using comprehensive neuropsychological assessment when diagnosing MCI subtypes, and (c) point to the need for further exploration of MCI subtypes, particularly non-amnestic presentations. Investigations and interventions targeting only amnestic subtypes are potentially missing a sizable number of individuals at risk.

Neuroimaging holds promise as a technique to better understand differences between distinct MCI subtypes although all of the above-mentioned methodological challenges together with small sample sizes and very limited attention paid to non-amnestic subtypes make drawing firm conclusions from the existing imaging literature challenging. To date, data do seem to support distinct neuropathology in the different clinical subtypes of MCI. However, there is still much overlap in structural imaging profiles and conflicting evidence making conclusions tentative at best. Advanced imaging techniques, such as DTI and functional MRI hold promise for detecting microstructural white matter damage or altered activation patterns in older adults prior to the manifestation of the full dementia syndrome. This early identification would identify the group in whom targeted therapies will likely have the greatest clinical impact (see Fagan *et al.*, 2005, for discussion). Overall, results from recent DTI studies indicate that white matter changes are evident in at-risk older adults and further validate the use of DTI to capture subtle, early white matter changes before significant atrophy is present. However, to date, very few studies have employed DTI in older adults with MCI, and even fewer have investigated the relationship between clinical subtype of MCI and white matter integrity.

Similarly, although FMRI techniques may prove to be instrumental in the early detection of AD, interpretation of current findings in MCI is complicated by

various methodological differences between studies. In general, functional changes in the MTL and posterior medial cortex appear to signal cognitive decline and dementia conversion. However, discrepant results across studies may be due to differences in diagnostic classification of MCI adults. Specifically, although the majority of studies reviewed classified their patients as amnestic MCI, it is likely that the patient sample represented a more heterogeneous group that may reflect different underlying neural pathology. This highlights the need for future research aimed at integrating behavioral performance with measures of functional activity that directly compare different MCI subtypes with these sophisticated neuroimaging techniques.

Finally, results of intervention trials to halt the progression of MCI have generally been disappointing. Future trials are needed that address both amnestic and non-amnestic presentations, employ more stringent entry criteria, use more sensitive cognitive and global outcome measures that reflect subtle impairments in complex activities, and include novel imaging outcomes.

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PROTON MAGNETIC RESONANCE SPECTROSCOPY IN DEMENTIAS AND MILD COGNITIVE IMPAIRMENT

H. Randall Griffith,[*,†,‡] Christopher C. Stewart,[‡] and Jan A. den Hollander[§]

[*]Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama 35233, USA
[†]Alzheimer's Disease Research Center, University of Alabama at Birmingham, Birmingham, Alabama 35233, USA
[‡]Department of Psychology, University of Alabama at Birmingham, Birmingham, Alabama 35233, USA
[§]Department of Medicine (Cardiology), University of Alabama at Birmingham, Birmingham, Alabama 35233, USA

With the anticipated increase in dementias due to the aging demographic of industrialized nations, biomarkers for neurodegenerative diseases are increasingly important as new therapies are being developed for clinical trials. Proton MR spectroscopy (^{1}H MRS) appears poised to be a viable means of tracking brain metabolic changes due to neurodegenerative diseases and potentially as a biomarker for treatment effects in clinical therapeutic trials. This review highlights the body of literature investigating brain metabolic abnormalities in Alzheimer's disease, amnestic mild cognitive impairment, frontotemporal dementia, vascular dementia, Lewy body dementia, and Parkinson's disease dementia. In particular, the review addresses the viability of ^{1}H MRS to discriminate among dementias, to measure disease progression, and to measure the effects of pharmacological treatments. While findings to date are encouraging, more study is needed in longitudinal patterns of brain metabolic changes, correspondence with changes in clinical markers of disease progression, and sensitivity of ^{1}H MRS measures to

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treatment effects. Such developments will hopefully benefit the search for effective treatments of dementias in the twenty-first century.

I. Introduction

The aging demographic of persons in the United States and other industrialized nations creates the prospect for a future major healthcare crisis from providing care to patients with dementia worldwide. Clearly, there is a great need for better treatments to emerge for these neurodegenerative illnesses within the next decade. A prime issue in clinical investigation of treating neurodegenerative diseases is the need for better markers of the disease process that can be used as measures of treatment efficacy (Mueller *et al.*, 2006). The current review focuses on proton magnetic resonance spectroscopy (^{1}H MRS) as a marker of metabolic brain changes in dementias and the potential for use as a biomarker in clinical trials. Findings are discussed from studies of Alzheimer's disease (AD), amnestic mild cognitive impairment (MCI), frontotemporal dementia (FTD), vascular dementia (VAD), Lewy body dementia (LBD), and Parkinson's disease dementia (PDD).

II. Metabolites in ^{1}H MRS

A comprehensive review of the development and technology of ^{1}H MRS is beyond the scope of the current review. Interested readers are referred to Ross and Bluml (2001). Although phosphorus (^{31}P), carbon (^{13}C), and fluorine (^{19}F) are all forms of MRS (Mueller *et al.*, 2006), ^{1}H MRS is the most frequently encountered subtype in the dementia literature due to its superior MR signal sensitivity, good spatial resolution, and its widespread availability (Jones and Waldman, 2004; Ross and Bluml, 2001). This review will thus focus exclusively on (Mueller *et al.*, 2006) ^{1}H MRS, and the metabolites commonly assessed in these studies. The following metabolites are mainly of interest in dementias (see Fig. 1).

N-acetyleaspartate. *N*-acetyleaspartate (NAA), which resonates at 2.02 parts per million (ppm), represents the largest proton metabolic concentration in the human brain after H_2O (Kwock, 1998; Valenzuela and Sachdev, 2001). NAA exists primarily within neurons, axons, and their processes, and has been implicated in several neuronal processes, including lipid and protein synthesis, mitochondrial functioning, and osmoregulation (Jones and Waldman, 2004). NAA is presumed to represent neuronal density or integrity based upon comparison of in vivo and in vitro studies (Cheng *et al.*, 2002; Valenzuela and Sachdev, 2001) and the prevalence of reduced NAA levels within a number of neuropathological conditions (Chen *et al.*, 2000). NAA may also serve as a marker of axonal metabolic fitness

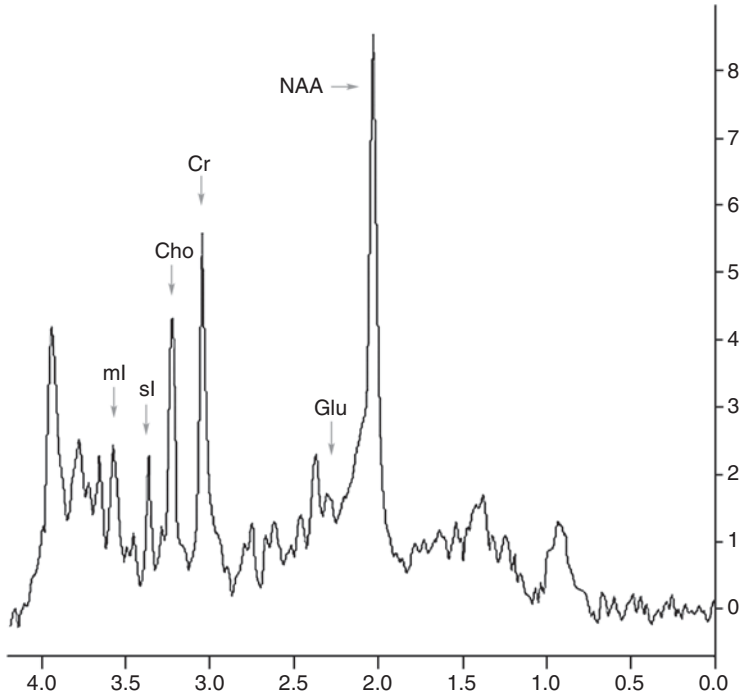

FIG. 1. Example spectra obtained from posterior cingulate gyrus at 3 T. mI, myo-Inositol; sI, scyllo-Inositol; Cho, Choline; Cr, Creatine; Glu, glutamate; NAA, *N*-acetyleaspartate.

(Valenzuela and Sachdev, 2001), as white and gray matter have comparable NAA levels and white matter NAA is reduced in white matter diseases (e.g., multiple sclerosis). Normalization of NAA levels in neurological disorders has been noted (e.g., following stroke); however, it remains unclear whether NAA "recovery" represents actual neuronal "recovery" or "regeneration" (Mueller *et al.*, 2006).

Choline. The Choline (Cho) peak (3.2 ppm) represents a combination of several choline-containing compounds, including free Cho, phosphorylcholine and glycerophosphorylcholine, and to a small extent acetylcholine (Firbank *et al.*, 2002; Valenzuela and Sachdev, 2001). Free Cho acts as a precursor to acetylcholine, while glycerophosphorylcholine is a product of breakdown of membrane phosphatidylcholine and acts as an osmoregulator (Firbank *et al.*, 2002). Cho is slightly more concentrated in white versus gray matter (Mueller *et al.*, 2006) and is likely present in glia. The Cho peak is often viewed as a marker of membrane turnover or inflammation in ^{1}H MRS studies (Mueller *et al.*, 2006).

Creatine. The Creatine (Cr) peak (3.0 ppm) is composed of creatine and phosphocreatine. Together, these metabolites buffer the energy use and energy storage of cells (Valenzuela and Sachdev, 2001). Cr is thought to exist primarily in glia and in neurons to a lesser extent (Firbank *et al.*, 2002) and is found in greater

concentrations in human gray versus white matter (Mueller *et al.*, 2006). Cr concentration is often used as an internal standard because it is considered to be relatively stable, showing slow increases with age (Firbank *et al.*, 2002; Valenzuela and Sachdev, 2001; however see Rosen and Lenkinski, 2007).

myo-Inositol. The myo-Inositol (mI) peak (3.56 ppm) represents the presence of myo-Inositol, a sugar alcohol that is similar in structure to glucose, and myo-Inositol phosphate (Valenzuela and Sachdev, 2001). These metabolites are located primarily in glia, where they are speculated to function as osmoregulators, intracellular messengers, and detoxifying agents (Valenzuela and Sachdev, 2001). mI is highly concentrated in gliosing lesions (Firbank *et al.*, 2002) and is one of the products of myelin breakdown (Rosen and Lenkinski, 2007). Thus, the mI peak is thought to represent an increase in glia density or an increase in glia size and associated brain inflammation (Brand *et al.*, 1993; Rosen and Lenkinski, 2007; Strange *et al.*, 1994; Valenzuela and Sachdev, 2001).

Scyllo-Inositol. The peak resonating at 3.342 ppm is thought to represent the presence of scyllo-Inositol (sI), a product of mI metabolism (McLaurin *et al.*, 2000). The neurobiological function of sI as differentiated from mI is unclear.

Glutamate-Glutamine. The GLX peak (2.1-2.4 ppm) represents both glutamate (Glu) and glutamine (Gln), which cannot be individually distinguished on 1.5 T (Mueller *et al.*, 2006) ^{1}H MRS but is more reliably distinguishable at 3 T (Kantarci *et al.*, 2003; Schubert *et al.*, 2004). Glu acts as the major excitatory neurotransmitter in the brain, and Gln is thought to play a role in the regulation and detoxification of glutamate (Valenzuela and Sachdev, 2001). Both Glu and Gln have been implicated in neuronal function, metabolism, and plasticity (Antuono *et al.*, 2001). Cycling between Glu and Gln is believed to account for approximately 80% of cerebral metabolism (Magistretti and Pellerin, 1999). Additionally, extracellular glutamate is excitotoxic and is now a target of treatment in neurodegenerative dementias (Riederer and Hoyer, 2006). However, the glutamate signal in brain (Mueller *et al.*, 2006) ^{1}H MRS is thought to primarily represent the intracellular compartment (Kickler *et al.*, 2007).

III. ^{1}H MRS Findings in Dementias

A. ^{1}H MRS Findings in Alzheimer's Disease

Dementia due to AD is the most common dementia affecting older adults (McMurtray *et al.*, 2006). The neuropathology of AD consists of amyloid plaques and neurofibrillary tangles that present in a characteristic pattern with early involvement of the medial temporal lobes and hippocampus, with subsequent spread to paralimbic and association cortical regions (Braak and Braak, 1991).

Definitive diagnosis of AD requires microscopic neuropathological examination and is most commonly made postmortem (Cummings *et al.*, 1998). Thus, the presence and pattern of cortical metabolic abnormalities are of potential clinical value in identifying the underlying neuropathology of AD and discriminating this disease from other dementias (Kantarci *et al.*, 2008).

Reduction in NAA is the most frequent ^{1}H MRS finding in AD (Adalsteinsson *et al.*, 2000; Chantal *et al.*, 2002; Christiansen *et al.*, 1995; Ernst *et al.*, 1997; Heun *et al.*, 1997; Parnetti *et al.*, 1997; Rose *et al.*, 1999; Schuff *et al.*, 1997; Watanabe *et al.*, 2002). Single voxel ^{1}H MRS studies of AD have consistently found reductions in NAA/Cr in the hippocampus/medial temporal lobe (Chantal *et al.*, 2002, 2004; Dixon *et al.*, 2002; Jessen *et al.*, 2000; Schuff *et al.*, 1997; Watanabe *et al.*, 2002) and other temporal lobe regions (Frederick *et al.*, 1997; Herminghaus *et al.*, 2003; Kantarci *et al.*, 2000; Parnetti *et al.*, 1997), and the midline parietal lobe/posterior cingulate (Antuono *et al.*, 2001; Griffith *et al.*, 2007a; Hattori *et al.*, 2002; Herminghaus *et al.*, 2003; Kantarci *et al.*, 2000, 2002b, 2003; Martinez-Bisbal *et al.*, 2004; Rose *et al.*, 1999), although two studies have failed to find abnormal NAA measures in this latter region (Waldman and Rai, 2003; Watanabe *et al.*, 2002). Findings of reduced NAA have also been seen in the temporal-parietal area (Chantal *et al.*, 2002; Ernst *et al.*, 1997; Parnetti *et al.*, 1996), occipital lobes (Kantarci *et al.*, 2000; Moats *et al.*, 1994; Shonk *et al.*, 1995; Waldman *et al.*, 2002; Watanabe *et al.*, 2002; Weiss *et al.*, 2003), and frontal lobes (Chantal *et al.*, 2002, 2004; Christiansen *et al.*, 1995; Herminghaus *et al.*, 2003; Parnetti *et al.*, 1997). In keeping with the emerging understanding of NAA as a marker for axonal viability as well as neuronal function (Valenzuela and Sachdev, 2001), some studies have found reduced NAA in parietal lobe white matter (Herminghaus *et al.*, 2003; Moats *et al.*, 1994) and subcortical white matter (Catani *et al.*, 2001; Hattori *et al.*, 2002; Heun *et al.*, 1997; Meyerhoff *et al.*, 1994), while others have not demonstrated this result (Catani *et al.*, 2002; Watanabe *et al.*, 2002). Studies using a whole brain spectral or multispectral approach have generally demonstrated reduced NAA in AD (Adalsteinsson *et al.*, 2000; Pfefferbaum *et al.*, 1999), which is mainly observed in posterior gray matter (Adalsteinsson *et al.*, 2000; MacKay *et al.*, 1996). Taken together, reports of widespread reductions in NAA are highly consistent with the known progression of neurofibrillary pathology of AD, which first is prevalent limbic cortical regions but then progresses to primary sensory-motor and visual cortices in more advanced stages (Braak and Braak, 1991).

A few studies to date have examined the pattern of changes in NAA over the course of one year in AD. Two such studies have pointed toward relative declines in NAA levels in AD patients (Adalsteinsson *et al.*, 2000; Kantarci *et al.*, 2007), while two others found no significant within-subjects declines (Dixon *et al.*, 2002; Jessen *et al.*, 2001) despite significantly lower NAA levels compared to older controls at both time points in one study (Dixon *et al.*, 2002). The indication

of these few longitudinal studies is that NAA is potentially sensitive to the progression of AD (Doraiswamy *et al.*, 1998; Kantarci *et al.*, 2007), although more studies are desirable.

Some studies in AD patients have detected abnormal measurements of Cho (Chantal *et al.*, 2002, 2004; Jessen *et al.*, 2000; Kantarci *et al.*, 2000, 2003; Lazeyras *et al.*, 1998; MacKay *et al.*, 1996; Meyerhoff *et al.*, 1994), although results have been inconsistent, with some studies finding reduced Cho levels in AD patients compared to controls (Chantal *et al.*, 2002, 2004; Jessen *et al.*, 2000; Kantarci *et al.*, 2000, 2003) and other studies finding elevated Cho levels (Lazeyras *et al.*, 1998; MacKay *et al.*, 1996; Meyerhoff *et al.*, 1994). A longitudinal study found that that Cho was elevated in AD patients versus older controls at baseline, but that the annualized rate of change in Cho did not differ between these groups (Kantarci *et al.*, 2007). The reasons for differences in Cho findings across studies are unclear. Cho elevations may be a consequence of increased membrane turnover secondary to neurodegeneration. Alternatively, Cho levels may increase secondary to increased membrane phosphatidylcholine catabolism, which may serve as a compensatory mechanism against chronically reduced acetylcholine levels in AD (Kantarci *et al.*, 2007). Abnormal Cho levels in AD may also be due to reduced choline acetyltransferase activity secondary to cholinergic agonist treatment (Griffith *et al.*, 2008c; Kantarci *et al.*, 2007). Alternatively, discrepant findings across studies may be due to variations in ^{1}H MRS methods, with studies using ^{1}H MRS sequences with longer echo times tending to find elevated Cho levels (Lazeyras *et al.*, 1998; MacKay *et al.*, 1996), while those with shorter echo times finding lowered Cho levels (Chantal *et al.*, 2002, 2004; Kantarci *et al.*, 2000, 2003). The location of the voxel of interest is also likely to account for differences, with decreased Cho detected in the posterior cingulate (Kantarci *et al.*, 2000, 2003) and medial temporal lobe (Chantal *et al.*, 2002, 2004; Jessen *et al.*, 2000), while increased Cho was detected in the posterior gray matter (Lazeyras *et al.*, 1998; MacKay *et al.*, 1996) and gray matter of the centrum semiovale (Meyerhoff *et al.*, 1994).

Studies have frequently found abnormal elevations of mI in AD patients, most often in the temporal-parietal area (Chantal *et al.*, 2002, 2004; Ernst *et al.*, 1997; Parnetti *et al.*, 1996), posterior cingulate gyrus/mesial parietal lobe (Griffith *et al.*, 2007a; Herminghaus *et al.*, 2003; Kantarci *et al.*, 2000, 2002b, 2003; Lazeyras *et al.*, 1998; Martinez-Bisbal *et al.*, 2004; Rose *et al.*, 1999; Waldman and Rai, 2003), parietal white matter (Herminghaus *et al.*, 2003; Moats *et al.*, 1994), and occipital lobes (Moats *et al.*, 1994; Shonk *et al.*, 1995; Waldman *et al.*, 2002). Abnormal mI levels are detected less often in the frontal lobes (Chantal *et al.*, 2002, 2004; Herminghaus *et al.*, 2003; Parnetti *et al.*, 1997) and subcortical regions (Catani *et al.*, 2001, 2002; Hattori *et al.*, 2002; Heun *et al.*, 1997) in AD, which is in agreement with the known regional distribution of AD neuropathology. One study performed at 3 T failed to detect mI differences in the posterior cingulate in AD patients (Hattori *et al.*, 2002), possibly due to higher magnetic

field inhomogeneity and susceptibility effects compared to 1.5 T (Kantarci *et al.*, 2003). A longitudinal study conducted at 1.5 T found no difference in annual rate of change in mI between AD patients versus older controls, although mI levels were elevated in AD patients at baseline (Kantarci *et al.*, 2007). Because of the robustness of findings involving decreased NAA and increased mI in AD patients, and because these two metabolites appear to represent independent markers of disease progression (Doraiswamy *et al.*, 1998), some researchers have used the ratio of NAA/mI to increase the sensitivity of ^{1}H MRS to metabolite changes in AD (Kantarci *et al.*, 2002b, 2003; Martinez-Bisbal *et al.*, 2004; Parnetti *et al.*, 1997; Rose *et al.*, 1999; Waldman and Rai, 2003; Weiss *et al.*, 2003). Reduced NAA/mI in AD versus healthy controls has been observed in the posterior cingulate (Kantarci *et al.*, 2002b, 2003), midline parietal lobe (Rose *et al.*, 1999), and frontal white matter (Parnetti *et al.*, 1997), but not frontal gray matter (Kizu *et al.*, 2004).

The majority of (Mueller *et al.*, 2006) ^{1}H MRS studies in AD have used Cr in the denominator of the metabolic ratio (Antuono *et al.*, 2001; Bartres-Faz *et al.*, 2002; Block *et al.*, 2002; Catani *et al.*, 2001, 2002; Chantal *et al.*, 2004; Christiansen *et al.*, 1995; Dixon *et al.*, 2002; Doraiswamy *et al.*, 1998; Ernst *et al.*, 1997; Frederick *et al.*, 1997; Hattori *et al.*, 2002; Herminghaus *et al.*, 2003; Heun *et al.*, 1997; Jessen *et al.*, 2000, 2001; Kantarci *et al.*, 2000, 2002b, 2003; Kattapong *et al.*, 1996; Lazeyras *et al.*, 1998; MacKay *et al.*, 1996; Martinez-Bisbal *et al.*, 2004; Meyerhoff *et al.*, 1994; Rose *et al.*, 1999; Schuff *et al.*, 1997; Shonk *et al.*, 1995; Waldman and Rai, 2003; Waldman *et al.*, 2002; Weiss *et al.*, 2003), due to its presumed invariance in brain disease (Valenzuela and Sachdev, 2001). Findings in AD have generally indicated no increases or decreases in Cr compared to controls (Ernst *et al.*, 1997; Pfefferbaum *et al.*, 1999; Schuff *et al.*, 1997). However, some have documented decreased Cr levels in AD patients versus normal controls in the left mesial temporal lobe, parieto-temporal cortex (Chantal *et al.*, 2002), and occipital lobe gray matter (Moats *et al.*, 1994).

The GLX peak has been investigated in a few studies of AD (Antuono *et al.*, 2001; Ernst *et al.*, 1997; Hattori *et al.*, 2002; Herminghaus *et al.*, 2003; Moats *et al.*, 1994), more recently with MRI scanners at field strengths other than 1.5 T (Antuono *et al.*, 2001; Hattori *et al.*, 2002). These studies have mostly reported reduced GLX levels in AD patients compared to controls in the posterior cingulate (Antuono *et al.*, 2001; Hattori *et al.*, 2002), occipital lobe (Moats *et al.*, 1994), and the dominant-hemisphere lateral temporal cortex (Herminghaus *et al.*, 2003), although two studies have failed to find GLX differences in patients with AD (Ernst *et al.*, 1997; Griffith *et al.*, 2008c).

Our group has performed one of the only studies to date systematically investigating sI in AD. We identified elevated sI/Cr in the posterior cingulate of AD patients, with MCI patients showing a trend toward elevation (Griffith *et al.*, 2007a); a prior study demonstrating raised concentrations of sI has been reported in the normal aging human brain (Kaiser *et al.*, 2005). The mechanism by which sI

elevations occur in AD is unclear, although given that sI is a breakdown product of mI metabolism, this finding may reflect the same processes involved in increased mI. sI agonist treatment has been recently shown to inhibit AD-like brain pathology in mice (Fenili *et al.*, 2007).

Utility of (Mueller *et al.*, 2006) ^{1}*H MRS for discriminating Alzheimer's disease from normal aging*: ^{1}H MRS has been used to discriminate AD patients from cognitively healthy older adults (Antuono *et al.*, 2001; Dixon *et al.*, 2002; Ernst *et al.*, 1997; Kantarci *et al.*, 2002b; MacKay *et al.*, 1996; Schuff *et al.*, 1997; Shonk *et al.*, 1995). Although an early study concluded that reproducibility and inter-rater error limited the utility of ^{1}H MRS as a clinical tool in AD (Heun *et al.*, 1997), several studies have since demonstrated that NAA can provide an adequate means of discriminating normal controls from AD patients (Antuono *et al.*, 2001; Schuff *et al.*, 1997; Shonk *et al.*, 1995) or improve discrimination of AD using structural neuroimaging variables (Dixon *et al.*, 2002; Ernst *et al.*, 1997; Kantarci *et al.*, 2002b; MacKay *et al.*, 1996). Among (Mueller *et al.*, 2006) ^{1}H MRS metabolite ratios, the NAA/mI ratio appears to best discriminate AD patients from normal controls (Kantarci *et al.*, 2007). The average accuracy of detecting AD with ^{1}H MRS is 87.75% (range 80-100%), and the average accuracy of identifying normal controls is 75.25 (range 73-78%) (Antuono *et al.*, 2001; Ernst *et al.*, 1997; MacKay *et al.*, 1996; Schuff *et al.*, 1997). Estimated sensitivity of ^{1}H MRS to AD is 83%, with a specificity of 95%, positive predictive value of 98% and a negative predictive value of 65% (Shonk *et al.*, 1995). Using a fixed specificity of 80%, one study reported a sensitivity of 82% for the NAA/mI posterior cingulate (Kantarci *et al.*, 2002b). An early longitudinal study that reported 70% correct classification of AD with ^{1}H MRS at baseline and 68% after 1 year for NAA of the left hippocampus (Dixon *et al.*, 2002). These results are consistent with a more recent longitudinal study examining the discriminatory value of NAA levels of the posterior cingulate in AD patients (Kantarci *et al.*, 2007).

^{1}H MRS and neurocognitive, psychological, and IADL measures in AD: Several studies have observed significant correlations between ^{1}H MRS and cognitive severity in AD as measured by a common mental status measure, the Mini Mental State Examination (MMSE) (Antuono *et al.*, 2001; Dixon *et al.*, 2002; Doraiswamy *et al.*, 1998; Ernst *et al.*, 1997; Heun *et al.*, 1997; Jessen *et al.*, 2000, 2001; Parnetti *et al.*, 1997; Rose *et al.*, 1999; Waldman and Rai, 2003); although, other studies have found no association between ^{1}H MRS and MMSE (Block *et al.*, 2002; Hattori *et al.*, 2002; Watanabe *et al.*, 2002). Fewer studies to date have investigated the relationships between other neurocognitive measures and ^{1}H MRS in AD. Pfefferbaum and colleagues (Pfefferbaum *et al.*, 1999) reported negative correlations of Cr with word recognition memory and negative correlations of Cho with face recognition memory. Chantal and colleagues (Chantal *et al.*, 2002) observed significant positive correlations between NAA of the left medial temporal lobe and verbal learning and recall. Negative correlations were detected between left

parieto-temporal cortex Cr and a confrontational naming measure, and right parieto-temporal cortex mI and a visual construction measure (Chantal *et al.*, 2002). One longitudinal study observed that in AD patients the annual percent change in NAA/Cr ratios was positively associated with annual change on a commonly used mental status measure, the Dementia Rating Scale (DRS), and negatively associated with change in a dementia severity rating scale, the Clinical Dementia Rating (CDR) (Kantarci *et al.*, 2007). These correlations were of comparable magnitude with correlations observed between the rate of change in MRI ventricular expansion and clinical progression measures (Kantarci *et al.*, 2007).

Other studies have investigated relationships between IADLs and ^{1}H MRS measures in AD. In a sample of mild AD patients, our group has demonstrated that NAA/Cr shows a positive correlation with a measure of financial abilities, while Cho/Cr showed a negative correlation with this same financial measure (Griffith *et al.*, 2007c). Antuono and colleagues (Antuono *et al.*, 2001) observed a significant correlation between GLX ratios from the posterior cingulate and an informant-report measure of daily activities in patients with AD, indicating more functional impairment as the GLX ratios decreased.

Postmortem neuropathologic correlates of in vivo ^{1}H MRS in AD: A recent study examined postmortem neuropathological correlates of antemortem ^{1}H MRS of the posterior cingulate and inferior precuneate gyri in healthy controls and in low- or high-likelihood AD, who were classified based on standard neuropathologic AD criteria (Kantarci *et al.*, 2008). The NAA/Cr, mI/Cr, and NAA/mI ratios differed between the low-, intermediate-, and high-likelihood AD groups after adjusting for age, sex, and time from ^{1}H MRS to death. Moreover, NAA/mI showed the strongest association with Braak neurofibrillary pathology staging, suggesting that NAA and mI provide complimentary information regarding the extent of disease involvement in AD patients. These results are consistent with a prior study reporting a correlation between postmortem ^{1}H MRS brain metabolite measures and neurofibrillary tangles and senile plaques in brain tissue of AD patients (Klunk *et al.*, 1998). Thus, antemortem ^{1}H MRS in patients with probable AD appears to be a sensitive marker of underlying AD neuropathology.

B. ^{1}H MRS Findings in Amnestic Mild Cognitive Impairment

Amnestic MCI has emerged as the diagnostic classification to denote the transitional phase between normal cognitive aging and AD (Petersen *et al.*, 2001). Diagnostic criteria for amnestic MCI include (1) subjective complaints of memory loss, preferably confirmed by an informant, (2) objective impairment on memory testing compared to age and educationally matched normative data, (3) otherwise normal performance on other cognitive tests, and (4) generally preserved activities of daily living (Petersen *et al.*, 2001). Individuals with MCI

progress to clinically probable AD more frequently than cognitively normal peers (Ganguli *et al.*, 2004; Petersen *et al.*, 2001), with a rate of 10-17% annual progression compared to a rate of 1-2% per year in the general older adult population (Ganguli *et al.*, 2004; Griffith *et al.*, 2006a; Petersen *et al.*, 1999, 2000, 2001; Storandt *et al.*, 2002; Tierney *et al.*, 1996).

Several cross-sectional (Mueller *et al.*, 2006) ^{1}H MRS studies have been performed to date in patients with amnestic MCI. Kantarci and colleagues (Kantarci *et al.*, 2000) examined metabolic ratios in the left temporal lobe, the posterior cingulate, and the medial occipital lobe of MCI and AD patients. Patients with MCI differed from controls only in significant increases of mI/Cr in the posterior cingulate; compared to AD patients, MCI patients had significantly lower cingulate mI/Cr ratios. The authors speculated that increased mI in MCI patients reflected very early pathological changes (possibly gliosis) preceding neuronal dysfunction, as would be indicated by decrements in NAA. Subsequent ^{1}H MRS studies in MCI patients have confirmed mI increases compared to controls in the posterior cingulate (Kantarci *et al.*, 2003; Rami *et al.*, 2007a), left hippocampus (Franczak *et al.*, 2007), and other brain regions such as the bilateral paratrigonal white matter (Catani *et al.*, 2001) and parieto-temporal cortex (Chantal *et al.*, 2004; Rami *et al.*, 2007a). Other studies, however, have not found differences between mI levels in AD and MCI (Catani *et al.*, 2001; Chantal *et al.*, 2004; Garcia Santos *et al.*, 2008; Kantarci *et al.*, 2003).

Other (Mueller *et al.*, 2006) ^{1}H MRS metabolic abnormalities in MCI patients include a significant increase of Cho in the right frontal cortex and posterior cingulate (Chantal *et al.*, 2004; Kantarci *et al.*, 2003), in addition to Cho and NAA decreases in the left medial temporal lobe (Chantal *et al.*, 2004). NAA decreases were also found in the right hippocampus in a small group of MCI patients (Franczak *et al.*, 2007) and were reduced in the posterior cingulate of MCI patients compared to controls, but not as severe as seen in AD patients (Kantarci *et al.*, 2003). In contrast, Ackl *et al.* (2005) detected equally reduced NAA/Cr in the hippocampus of MCI patients and AD patients, although posterior cingulate metabolic abnormalities were observed only in the AD patients. Other studies have not detected any NAA changes in MCI (Garcia Santos *et al.*, 2008; Kantarci *et al.*, 2002a). Thus, the cross-sectional data generally indicates that metabolic brain abnormalities in MCI are transitional between normal metabolism observed in healthy older adults and abnormalities seen in AD. The pattern of findings generally concurs with the known early neuropathology of AD (Braak and Braak, 1991; Markesbery *et al.*, 2006).

To our knowledge, only two studies have investigated longitudinal metabolic changes measured by ^{1}H MRS in MCI patients (Bartnik Olson *et al.*, 2008; Kantarci *et al.*, 2007). Kantarci and colleagues (Kantarci *et al.*, 2007) reported declines in NAA/Cr of the posterior cingulate in MCI and AD patients on scans occurring approximately 1 year apart. There was a similar rate of decline in NAA for MCI patients who converted to AD versus those patients who remained stable.

No changes were observed in mI/Cr. Interestingly, Cho/Cr levels declined in MCI patients who remained stable, suggesting to these authors that a compensatory cholinergic mechanism explained the stability of these non-converter MCI patients. This result appears consistent with the recent finding that MCI converters exhibited elevated Cho/Cr compared to non-converters at baseline (Rami *et al.*, 2007b). In a second longitudinal study, Bartnik Olson and colleagues (Bartnik Olson *et al.*, 2008) found increases of mI concentrations in the posterior cingulate gyrus occurring over an average interval of 11 months, but non-significant interval increases in NAA or Cho concentrations. Discrepant findings between these two longitudinal studies may be due to the fact that Bartnik *et al.* used a method to model spectral components to quantify metabolite levels, while Kantarci and colleagues used metabolic ratios as obtained automatically following acquisition on a General Electric (GE) scanner.

^{1}H MRS and neurocognitive measures in MCI: Kantarci and colleagues (Kantarci *et al.*, 2002a) performed correlations between a global measure of cognition (DRS) and a measure of auditory verbal learning (AVLT) with posterior cingulate ^{1}H MRS ratios of NAA/Cr, NAA/mI, and mI/Cr. All three ratios were significantly correlated with the DRS and to a lesser extent with the AVLT. Ackl and colleagues indicated that hippocampal NAA/Cr correlated with verbal fluency and confrontation naming, but interestingly not with memory, in a mixed MCI and AD group (Ackl *et al.*, 2005). Posterior cingulate ^{1}H MRS correlated with a wider range of cognitive measures. We very recently reported that visual executive function, as measured by clock drawing, was negatively correlated with mI/Cr in amnestic MCI patients (Griffith *et al.*, 2007b). Furthermore, mI/Cr ratios accounted for 26% of the variance in clock drawing scores after accounting for overall cognition, age, and other potential confounding variables through stepwise multiple regression analysis.

^{1}H MRS predictors of dementia in MCI: Studies have indicated that baseline NAA/Cr can predict subsequent progression, or "conversion," from MCI to AD with high sensitivity and specificity. A recent study indicated that baseline NAA/Cr of the occipital lobe was able to discriminate amnestic MCI converters from non-converters over a mean follow-up period of 3 years, with 100% sensitivity and 75% specificity (Modrego *et al.*, 2005). Another recent study reported that MCI patients who converted to dementia within a 1-year follow-up showed reduced NAA/Cr of the left paratrigonal white matter compared to stable MCI patients (Metastasio *et al.*, 2006). A third study concluded that NAA/Cr ratios in both the posterior cingulate gyrus and left occipital cortex predicted conversion with a sensitivity of about 80% and a specificity of about 70%. In general, these studies suggest that ^{1}H MRS may prove valuable in identifying patients with MCI who are at risk for dementia conversion, although participant selection issues limit the validity of the current studies, including the operational criteria for MCI (Modrego *et al.*, 2005) and extremely high conversion rates over 1 year (Metastasio *et al.*, 2006).

C. ^{1}H MRS Findings in Frontotemporal Dementia

FTD refers to a heterogeneous group of clinical syndromes involving progressive neurodegeneration of the frontal and/or temporal lobes, including gliosis, neuron loss, and vacuolation of surface cortical layers (Coulthard *et al.*, 2006; Ernst *et al.*, 1997).

Findings of metabolic profiles in FTD patients compared to controls have shown metabolic abnormalities in many brain cortical regions. One study investigated (Mueller *et al.*, 2006) ^{1}H MRS located in the temporal, frontal, and parietal lobes and found lower ratios of NAA/Cr in the temporal and frontal lobe voxels, in addition to an increased mI/Cr ratio in the frontal lobe voxel (Coulthard *et al.*, 2006). No ^{1}H MRS abnormalities were observed in the parietal lobes (Coulthard *et al.*, 2006). Other ^{1}H MRS studies suggest that the spatial distribution of brain metabolic abnormalities of FTD patients differs from that of AD patients. One such study found reduced NAA and Glx and increased mI in mid-frontal gray matter in FTD patients versus AD patients and healthy controls, whereas a trend toward significantly increased mI in the temporoparietal gray matter was observed in AD versus FTD patients (Ernst *et al.*, 1997; also see Mihara *et al.*, 2006).

Studies have reported the correspondence of ^{1}H MRS abnormalities with clinical and cognitive measures in patients with FTD, highlighting the clinical importance of these metabolic abnormalities. Clinical/functional measures (i.e., CDR and the MMSE) have been associated with NAA and mI in the frontal region and mI and Glx in the temporopartietal region in a group of FTD and AD patients and healthy controls (Ernst *et al.*, 1997). Rami *et al.* (2008) also reported associations of naming ability with NAA/Cr and Cho/Cr ratios in the left temporal pole, but not the left temporoparietal region, after controlling for MMSE scores across a sample of FTD, MCI, and AD patients, and heathy controls.

D. ^{1}H MRS Findings in Vascular Dementia

VAD results from one or a combination of cerebrovascular mechanisms that cause degenerative changes in the brain, including infarcts, white matter lesions, and resultant atrophy (Wiederkehr *et al.*, 2008). Diagnosis of VAD presents a challenge clinically due to its etiological heterogeneity, variable clinical manifestation, and co-occurrence with AD pathology (only 10% of dementia cases show pure vascular pathology on postmortem brain examination) (Holmes *et al.*, 1999; Jones and Waldman, 2004).

^{1}H MRS has revealed widespread brain metabolic abnormalities in VAD patients. In one study, Herminghaus *et al.* (2003) measured spectra from voxels in five brain regions: mid-parietal gray and white matter, mid-frontal gray and white

matter, and the temporal gyrus mixed gray/white matter. Compared to healthy controls, VAD patients exhibited global reductions in NAA/Cr ratios in all voxels, along with elevations in mI/Cr ratios in parietal gray and white matter, frontal white matter, and the temporal lobe, and elevations in Glx ratios in parietal gray matter and the temporal lobe. In another study, Kantarci and colleagues (Kantarci *et al.*, 2004) reported that in the posterior cingulate VAD patients had lower ratios of NAA/Cr, but normal ratios of mI/Cr and Cho/Cr, when compared with healthy controls. These studies suggest that VAD involves multiple neuropathological processes, even in regions distant from actual vascular pathology (Kantarci *et al.*, 2004), including neuronal dysfunction/loss, axonal damage, myelin loss, and gliosis (Jones and Waldman, 2004). Kantarci *et al.* (2004) have speculated that reductions in NAA in distal brain areas may be secondary to retrograde Wallerian degeneration caused from brain regions showing actual vascular neuropathology.

E. ^{1}H MRS Findings in Dementia with Lewy Bodies

The cardinal features of DLB include progressive cognitive decline, along with fluctuations in alertness and attention, persistent visual hallucinations, and spontaneous parkinsonian motor symptoms, including rigidity and the loss of spontaneous movement (McKeith *et al.*, 2005). Of note, DLB patients exhibit a striking reduction in cortical acetylcholine activity relative to AD patients (Tiraboschi *et al.*, 2000).

A relative paucity of ^{1}H MRS studies has examined patients with DLB, and their findings have been variable. Molina *et al.* (2002) initial study in this patient population found decreased NAA/Cr, Cho/Cr, and Glx/Cr ratios in DLB patients versus healthy controls in white matter from the left centrum semiovale, but did not find significant metabolite differences in gray matter from the midline parietal region. This study also found no correlations of any metabolite levels with clinical measures (age at onset and disease duration) or measures of cognitive and motor impairment, a result that is consistent with a prior neurochemical study which failed to find a relationship between reductions in acetylcholine activity and cognitive impairment in DLB (Tiraboschi *et al.*, 2000). In contrast, a more recent study found elevated NAA/Cr ratios in the left and right hippocampus in DLB patients versus controls but did not find group differences in Cho/Cr ratios, although their sample size was somewhat limited ($n = 8$ in both groups) (Xuan *et al.*, 2008). Kantarci *et al.* (2004) reported elevated Cho/Cr ratios in a voxel encompassing the posterior cingulate gyrus of DLB patients versus healthy controls, but did not find group differences in NAA/Cr or mI/Cr ratios.

The data on ^{1}H MRS findings in DLB are sparse and variable. In some respects, these variable findings are similar to those of postmortem pathological

studies on DLB, which have yielded inconsistent findings regard to neuronal loss in DLB (Cordato *et al.*, 2000; Gomez-Isla *et al.*, 1999). Moreover, methodological differences, including differences in symptom severity of patients, voxel placement, and (Mueller *et al.*, 2006) ^{1}H MRS acquisition parameters (e.g., short versus long echo time), may also account for some of the variable results across these studies.

F. ^{1}H MRS Findings in Parkinson's Disease Dementia

Dementia observed in patients with Parkinson's disease can manifest from a variety of clinical and neuropathological entities, including diffuse Lewy body pathology (Galvin *et al.*, 2006), AD (Galvin *et al.*, 2006), and isolated Lewy body pathology of the substantia nigra (Galvin *et al.*, 2006; Pletnikova *et al.*, 2005). A specific dementia in patients with Parkinson's disease, termed PD with dementia (PDD), involves the onset of a progressive dementing illness at least 1 year subsequent to the onset of the movement disorder (McKeith *et al.*, 2005). PDD is believed to be clinically (Benecke, 2003), cognitively (Aarsland *et al.*, 2003), neuropsychologically (Litvan *et al.*, 1991), and neuropathologically (Kovari *et al.*, 2003) distinct from that of patients with DLB (Benecke, 2003) and patients with AD and late motor complications (Dickson, 2000).

^{1}H MRS findings indicate that PDD patients exhibit abnormal brain metabolism as compared against healthy controls and nondemented PD patients. Initial ^{1}H MRS studies in PDD examined metabolite levels in the occipital cortex. These studies found reductions in NAA levels in PDD patients versus nondemented PD patients, but not healthy controls (Summerfield *et al.*, 2002), and elevations in lactate levels in PDD patients versus both nondemented PD patients and healthy controls (Bowen *et al.*, 1995), although similar lactate abnormalities have not been documented subsequently (Firbank *et al.*, 2002). More recent ^{1}H MRS studies by our group have investigated metabolism of the posterior cingulate gyrus, which shows neuropathological changes in postmortem PDD studies (Braak *et al.*, 2004) and abnormal blood flow (Osaki *et al.*, 2005) and dopamine transmitter alterations (Brooks and Piccini, 2006) in antemortem PDD imaging studies. Consistent with these post- and antemortem studies, ^{1}H MRS of the posterior cingulate gyrus in PDD has revealed reduced NAA/Cr ratios in PDD patients versus healthy controls (Griffith *et al.*, 2008a,c) and nondemented PD patients (Griffith *et al.*, 2008a), in addition to reduced Glu/Cr versus healthy controls (Griffith *et al.*, 2008c). Whereas lower NAA levels presumably reflect compromised functional integrity of neurons in the posterior cingulate gyrus and occipital lobe in PDD, lower Glu reductions could plausibly reflect other aspects of the PDD disease process, such as downregulation of glutaminergic cortical efferents from the basal ganglia to the posterior cingulate gyrus (Griffith *et al.*, 2008c).

Of note, ^{1}H MRS-derived NAA and Glu measures in the posterior cingulate gyrus appear to be able to discriminate PDD patients from nondemented PD patients. The NAA/Cr ratio has shown high sensitivity and reasonable specificity in correctly discriminating individuals with PDD from PD and healthy controls (Griffith *et al.*, 2008a). Moreover, both NAA and Glu levels have shown modestly strong correlations with mental status measures (MMSE and DRS scores) in PDD (Griffith *et al.*, 2008a,c). Future longitudinal ^{1}H MRS studies determining whether these brain metabolic abnormalities precede the clinical manifestation of PDD appear warranted.

G. Utility of ^{1}H MRS for Discriminating Among Dementias

Studies have sought to compare the sensitivity and specificity of brain metabolic profiles in discriminating among neurodegenerative dementias. Most all of these studies have compared patients with AD to another dementia, a question that is of clinical value given the high prevalence of AD (McMurtray *et al.*, 2006). Ernst and colleagues (Ernst *et al.*, 1997) found that FTD patients could be discriminated from AD patients and controls using a combination of NAA and Cr values from the mid-frontal and left temporoparietal region, with accuracy of detecting FTD of 92% and an accuracy of detecting AD of 82%. Shonk *et al.* (1995) indicated that NAA/Cr of the occipital lobe detected AD from FTD with a sensitivity of 82%, specificity of 64%, positive predictive value of 74% and a negative predictive value of 80%. Other studies have found no differences on (Mueller *et al.*, 2006) ^{1}H MRS between AD and FTD patients. For example, a recent study found reduced NAA/Cr levels and increased mI/Cr levels in the posterior cingulate gyrus in both FTD patients and AD patients when compared with healthy controls (Mihara *et al.*, 2006). Several other studies have found that metabolite concentrations did not differ significantly between FTD and AD patients (Garrard *et al.*, 2006; Kantarci *et al.*, 2004; Kizu *et al.*, 2004).

Other studies have attempted to distinguish between VAD and AD using ^{1}H MRS. Patients with VAD, when compared to patients with AD, show reduced NAA/Cr ratios in frontal gray matter and subcortical white matter, and elevated mI/Cr in frontal white matter (Herminghaus *et al.*, 2003; Kattapong *et al.*, 1996; Martinez-Bisbal *et al.*, 2004). In comparison, patients with AD show increased mI/Cr in the posterior cingulate gyrus (Kantarci *et al.*, 2004; Martinez-Bisbal *et al.*, 2004) and occipital lobe (Rai *et al.*, 1999; Waldman *et al.*, 2002), as well as increased Cho/Cr of the posterior cingulate (Martinez-Bisbal *et al.*, 2004), when compared with VAD patients. One study reported an 83% classification accuracy for AD and 71% accuracy for VaD using NAA measures from whole brain gray matter (MacKay *et al.*, 1996), while a second study comparing patients with

AD, VaD, MCI, and major depression reported that the NAA/mI ratio had an 81.5% sensitivity and 72.7% specificity for discriminating AD from the other groups (Martinez-Bisbal *et al.*, 2004).

We are aware of only two studies to date that have compared ^{1}H MRS across patients with Parkinson-spectrum dementias to patients with other dementias. Kantarci and colleagues (Kantarci *et al.*, 2004) reported that patients with DLB had normal NAA/Cr ratios when compared to patients with AD and patients with FTD; patients with DLB also had normal mI/Cr ratios compared to patients with FTD. No differences were observed between DLB patients and patients with VAD. Griffith and colleagues (Griffith *et al.*, 2008c) very recently reported that patients with PDD showed abnormally low Glu/Cr ratios when compared with patients with AD, while patients with AD showed a trend toward higher mI/Cr ratios when compared with patients with PDD. The Glu/Cr ratio was able to discriminate between AD and PDD at rates greater than chance. No studies to date that we are aware of have compared (Mueller *et al.*, 2006) ^{1}H MRS between patients with DLB versus patients with PDD, although both dementias show considerable clinical and neuropathological overlap (Galvin *et al.*, 2006).

H. Utility of ^{1}H MRS for Monitoring Treatment Effects in Dementias

A few studies have used ^{1}H MRS to assess responses to pharmacological treatment in AD patients. Krishnan *et al.* (2003) reported that NAA levels in subcortical gray matter and periventricular white matter increased following 12 weeks of therapy with donepezil, a cholinesterase inhibitor. Jessen and colleagues (Jessen *et al.*, 2006) observed changes in NAA/Cr, Cho/Cr and mI/Cr ratios associated with donepezil treatment; the ^{1}H MRS changes were also associated with improvement on the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), a commonly used measure of treatment effects in AD. In contrast, Bartha *et al.* (2008) found a decrease in NAA levels, along with a decrease in mI levels, in the right hippocampus following 16 weeks of donepezil treatment. In another study, 4 months of treatment with the cholinesterase inhibitor rivastigmine was associated with an increase in NAA/Cr in the frontal lobe in AD patients versus untreated AD patients; there was an association reported between the metabolite changes and modest clinical improvement in the treatment group (Modrego *et al.*, 2006). A study investigating the effects of treatment with xanomeline, a cholinergic agonist, have found associations between pre- and posttreatment changes in NAA/Cr, Cho/Cr, and mI/Cr ratios and changes in ADAS-cog scores (Frederick *et al.*, 2002). These studies suggest that ^{1}H MRS has the potential to monitor disease modifying treatment effects that are correlated with clinical outcome measures.

The ability of ^{1}H MRS to quantify therapeutic effects in dementias other than AD is unknown. One study investigated the effect of argatroban therapy, a potent selective thrombin inhibitor, on brain metabolite levels in peripheral arterial occlusive disease patients, two of whom were diagnosed with VAD (Kario *et al.*, 1999). Prior to argatroban therapy, patients with silent cerebrovascular disease had decreased NAA/Cr in the deep white matter. However, NAA/Cr ratios increased significantly in patients with silent cerebrovascular disease following argatroban therapy, accompanied by improved scores on the MMSE and improvements in activities of daily living in the two VAD patients. While this study highlights the potential importance of ^{1}H MRS in the monitoring of therapeutic effects, continued study in larger samples of VAD and with other therapeutic agents is clearly needed.

IV. Discussion

The use of ^{1}H MRS as a clinical investigative tool in neurodegenerative dementias has yielded a body of findings that could prove important for research into the causes and treatments of dementias. While there have been some methodological and technical advances in ^{1}H MRS over the years, there have been relatively consistent findings in studies of AD, providing evidence of the stability of this technique as a potential biomarker. The emergence of studies in other dementias, and comparative studies across dementias, has also proved worthwhile. Nonetheless, several important issues remain to be addressed.

Across ^{1}H MRS studies, some common findings have emerged that engender confidence in the interpretation of brain metabolic abnormalities in dementias. One such finding has been the nearly ubiquitous observation of reduced cortical NAA in almost all of the major dementing illnesses (with the notable exception of DLB in one study (Kantarci *et al.*, 2004)). Reduction in NAA has been observed in all major lobes of the brain as well as in the hippocampus. While NAA reduction is primarily observed in gray matter, white matter NAA abnormalities have also been reported. These results reify the interpretation of NAA as a marker of neuronal and axonal integrity in dementias. NAA ratios have also shown strong correspondence with postmortem neuropathology in AD (Kantarci *et al.*, 2008), presumably because higher levels of AD neuropathology correspond to greater loss of neuronal function. However, as reduced NAA is observed in dementias such as FTD, where there is no AD neuropathology, it is clear that NAA abnormalities are not specific effects of AD neuropathology alone, but are rather sensitive to any form of neuropathology that is detrimental to neuronal functioning. The use of NAA in combination with other ^{1}H MRS metabolites (such as mI) might improve the specificity of ^{1}H MRS to detect specific forms of

neuropathology (Kantarci *et al.*, 2008). An advantage of ^{1}H MRS is that data can be collected on several metabolites simultaneously, and thus can be used to determine metabolic profiles that could discriminate among dementias (Griffith *et al.*, 2008c; Kantarci *et al.*, 2004).

The sensitivity of ^{1}H MRS to detect dementias has been investigated in a few studies, showing generally good ability to discriminate between dementias and normally functioning individuals. However, ^{1}H MRS may hold the most promise as a means to identify earlier (preclinical) patients at risk for dementia, or completely asymptomatic individuals, who could then be the target for early intervention studies. The emerging body of findings in patients with amnestic MCI, some of whom progress to have clinically probable AD, indicates that ^{1}H MRS might be sensitive to the metabolic effects of neurodegenerative diseases prior to their clinical identification. An exciting area of development has been the identification of ^{1}H MRS abnormalities in patients who are at genetic risk of AD but who are otherwise completely asymptomatic, suggesting that brain metabolic abnormalities predate identification of cognitive deficits in these patients (Godbolt *et al.*, 2006). Cortical ^{1}H MRS changes that occur in patients with PD and no dementia (Griffith *et al.*, 2008b) resemble those reported in PDD patients (Griffith *et al.*, 2008c), suggesting that ^{1}H MRS may be helpful in determining risk of dementia in PD.

Longitudinal studies are slowly emerging to support the use of ^{1}H MRS as a means to track progressive brain metabolic changes. At least one study has demonstrated that ^{1}H MRS can be reliably obtained within the same participants at different time points (Rose *et al.*, 1999). A few longitudinal studies have been conducted to date in AD and MCI, although other dementias have not yet been investigated with longitudinal ^{1}H MRS. The findings of these longitudinal studies suggest that change in NAA corresponds well with change in clinical status of AD, and thus possibly could be used to measure disease progression with less error than is seen with clinical instruments such as the ADAS-cog (Mueller *et al.*, 2006). Some studies have employed ^{1}H MRS to measure treatment effectiveness in AD and shown links to modest cognitive improvement with improving metabolism. However, correspondence with clinical outcomes other than cognitive change, such as status of daily functional activities, is desirable to anchor ^{1}H MRS changes to real-world outcomes. Two cross-sectional studies have reported a correspondence between ^{1}H MRS and daily activities in AD (Antuono *et al.*, 2001; Griffith *et al.*, 2007c); these findings suggest that change in ^{1}H MRS would correspond to declines in complex daily activities. Clearly, a better understanding of the longitudinal course of brain metabolic abnormalities in dementias, and the associations of these metabolic abnormalities with cognitive and daily functional changes, is essential to pursuing ^{1}H MRS as a measure of treatment outcomes.

The search for viable biomarkers of dementing illnesses is critical for development of new treatments. Mueller and colleagues outlined their six criteria for a viable biomarker of treatment effects in patients with dementias: (1) links between the markers and treatment outcomes, (2) test-retest reliability; (3) sensitivity to desired stage of treatment; (4) link to the biomarker and amyloid burden, (5) non-invasiveness and tolerability; and (6) availability and cost (Mueller *et al.*, 2006). In considering ^{1}H MRS in light of these criteria, the current state of the literature suggests that several of the criteria are being approached. ^{1}H MRS appears to have some links to potential measurable outcomes, in that studies have reported associations with cognitive functioning and instrumental daily activities, as well as showing sensitivity to treatment effects. Test-retest reliability has been supported in at least one study, although interscan variability may not be at the desired level for reliable use in individual patients. Studies in ^{1}H MRS of preclinical dementias have shown that early metabolic changes are observable at the stage when treatment is most desirable (Petersen, 2004). ^{1}H MRS is arguably among one of the most widespread imaging modalities, in that many of the MRI scanners commercially available have the capability of collecting ^{1}H MRS data, although subsequent data processing and interpretation require expertise. In our experience, ^{1}H MRS is well tolerated in patients with mild to moderate stages of dementia as well as individuals with movement disorders.

The link of ^{1}H MRS with amyloid burden, one of the Mueller *et al.* (2006) criteria, is questionable. While amyloid deposition is clearly correlated with NAA and mI levels in patients with AD, abnormalities in these metabolites are also seen in non-amyloid neuropathologies such as FTD. ^{1}H MRS can likely play a role as a marker of neuronal integrity with sensitivity to a number of neuropathologies (i.e., Lewy bodies, tauopathies, cerebrovascular disease) rather than having a specificity to amyloid. Given that questions have arisen as to the key role that amyolid deposition plays in the dementing process in AD (Arends *et al.*, 2000; Dickson, 1997; Terry *et al.*, 1991), the importance of an amyloid biomarker over a biomarker of neuronal health is debatable.

Future directions in ^{1}H MRS of dementias should focus on developing stable and reliable longitudinal techniques and applying these to investigate longitudinal changes, especially in dementias other than AD as well as longitudinal comparative studies of AD with other dementias. Measuring correspondence of change on clinical and functional measures with changes in ^{1}H MRS measures is also needed. In addition, studies are needed to further investigate whether ^{1}H MRS measures are sensitive to medication effects, such as cholinesterase inhibitor use, in patients where these treatments are considered to be beneficial. The association of ^{1}H MRS measures with imaging of amyloid, such as comparison with the Pittsburgh B Compound PET procedure (Klunk *et al.*, 2004), would be beneficial. Lastly, as technological advances occur it would be worthwhile to expand from

single-voxel approaches to 2D and 3D ^{1}H MRS imaging to better understand the extent of ^{1}H MRS abnormalities in dementias. Such developments will hopefully prove to benefit the search for effective treatments of dementias in the twenty-first century.

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APPLICATION OF PET IMAGING TO DIAGNOSIS OF ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT[1]

James M. Noble*,†,‡ and Nikolaos Scarmeas†,‡

*Department of Neurology, Harlem Hospital Center, Columbia University College of Physicians and Surgeons, New York 10037, USA
†Department of Neurology, Columbia University Medical Center, New York 10032, USA
‡Gertrude H. Sergievsky Center, and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York 10032, USA

Alzheimer disease (AD) is the most common type of dementia and will become increasingly prevalent with the growing elderly population. Despite established clinical diagnostic tools, the workup for dementia among primary caregivers can be complicated and specialist referral may not be readily available. A host of AD diagnostic tests has been proposed to aid in diagnosis, including functional neuroimaging such as positron emission tomography (PET). We review the basis for FDG-PET and PiB-PET, as well as available operating statistics. From this we advise scenarios for use of PET in primary settings and referral centers, approach to its interpretation, and outline a clinical prediction model based on findings.

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I. Background

Dementia is a common disorder among the elderly, becomes more prevalent with advancing age, is typically medically refractory, reduces life expectancy, and diminishes quality of life for patients and their caregivers. Worldwide 600 million people are over the age of 60 and that number is expected to double by 2025 (UN, 2003). Of those over age 60, approximately 26 million people have dementia of any type (Wimo *et al.*, 2007), and as the population ages, this is projected increase to 80 million by the year 2040 (ADI, 2006). The costs of care are staggering, with a current annual worldwide health cost estimated at $300 billion (Wimo *et al.*, 2007).

Despite the high prevalence of dementia among the elderly, the diagnostic workup can be complicated, time consuming, and difficult to interpret, particularly in the primary care setting. In this manuscript, we will review the biologic basis of positron emission technology (PET) in the diagnostic workup of Alzheimer disease (AD) and its symptomatic prodrome, mild cognitive impairment (MCI), as well as outline current recommendations for use PET, and identify its main limitations to improve appropriate selection of patients.

A. Neurobiology of Alzheimer Disease

Abnormal accumulation of beta-amyloid (Aβ) peptide is widely believed to be the underlying mechanism of pathologic and clinical changes seen in AD (Cummings, 2004). Changes typically begin in the transentorhinal and entorhinal cortex as well as the hippocampus (Delacourte *et al.*, 1999), and thus earliest impairments occur with episodic memory deficits. Despite extensive neuropathologic changes, some patients may remain asymptomatic in a prodromal state of AD (Dubois *et al.*, 2007). Alternatively, some patients develop cognitive complaints and have objective cognitive impairment but no functional decline in level of activities of daily living, and these are classified as MCI (Petersen *et al.*, 2001). As disease progresses, other brain structures become involved, initially temporal cortex and later parietal and frontal association cortices, and finally primary motor and sensory cortices and the neocortex (Delacourte *et al.*, 1999). Symptomatically, patients progress from episodic memory loss to additional, progressive deficits in visuospatial and semantic abilities, mood and behavioral disorders, and an eventual vegetative state.

B. Epidemiology of Alzheimer Disease

Alzheimer disease (AD) is the most common type of dementia, representing 60–70% of all patients with dementia. The prevalence increases with age from approximately 3–5% for those under 75, 15–18% for those age 75–84 years, and

45% for those older than 85 years (Alzheimer's Association, 2008; Gurland *et al.*, 1999; Hebert *et al.*, 2003; Mayeux, 2003b). In the US alone, an estimated 5.2 million have AD in 2008 and this may increase to 13.2 million by 2050 (Alzheimer's Association, 2008). Sporadic AD represents 98% of all AD cases and is likely due to a complex interaction of environmental, vascular, and genetic risk factors (Mayeux, 2003a; Tang *et al.*, 1998).

The epidemiologic data for patients at risk for late onset AD are equally daunting. In the US alone, 25 million persons are over the age of 65 (18 million aged 65–74 years, 12 million aged 75–84 years, and 4 million aged 85 years and over) (He *et al.*, 2005). Before developing AD, many patients may transition through amnestic MCI (Petersen *et al.*, 2001), or memory complaints with commensurate objective neuropsychological test deficits, but without appreciable impact in general cognition or daily independent function.

MCI portends to a significantly increased annual risk of conversion to AD compared to others in their age group (Manly *et al.*, 2008; Petersen *et al.*, 2001). In a multiethnic urban American population, amnestic MCI (including single or multiple domain impairment) is prevalent in 3.8% of nondemented elderly aged 65–75 and in 6.3% of those over 75 years of age (Manly *et al.*, 2005). Overall, most studies suggest that MCI patients have an annual conversion rate (i.e., progression) to AD of approximately 10–15% per year (Morris *et al.*, 2001; Petersen *et al.*, 1999). Recently, age-stratified data from our center have suggested that of normal elderly individuals, the annual conversion rate from normal cognition to amnestic MCI is 1.1% of those aged 65–69 years, 2.1% aged 70–74, 2.2% aged 75–79, and 3.4% aged 80 years and above. Moreover, among those with amnestic MCI, the annual conversion rate to AD is 3.2% of those aged 65–69, 4.5% aged 70–74, 9.7% aged 75–79, and 11.1% aged 80 years and above (Manly *et al.*, 2008).

C. [^{18}F]2-Fluoro-2-Deoxy-D-Glucose

Positron emission tomography (PET) enables imaging of biological activity, and thus can identify abnormal biological activity in a host of diseases. Regional differences in brain glucose metabolism using PET have been explored in dementia, and [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG-PET) has become the most widely investigated radioligand since the first descriptions of cerebral metabolism in dementia over two decades ago (Benson *et al.*, 1981; Farkas *et al.*, 1982; Friedland *et al.*, 1983; Phelps *et al.*, 1982). Glucose hypometabolism identified in FDG-PET is thought to represent two findings: (1) local decreases in synaptic activity or synaptic dysfunction in neurons affected by Alzheimer type pathological changes and (2) decreased synaptic activity in regions receiving projections from these primary, diseased neurons (Friedland *et al.*, 1985; Hoffman *et al.*, 2000; Matsuda, 2007; McGeer *et al.*, 1986a,b, 1990a,b; Mielke *et al.*, 1996).

Thus, abnormalities in regional cerebral metabolism are thought to reflect the pattern of neuropathologic development of AD with early prominent AD changes in the medial temporal cortex and its projections to cingulate and parieto-temporal association cortices (Brun and Englund, 1986); although, all of these structures may become pathologically involved with disease progression (Braak and Braak, 1991).

Similarly, patients with MCI, with many in the earliest stages of AD change, may only have glucose hypometabolism in the medial temporal cortex (de Leon *et al.*, 2001; Nestor *et al.*, 2003). MCI patients with additional glucose hypometabolism in the parietal association cortex may be at greater risk for subsequent conversion to AD (Chetelat *et al.*, 2003; Mosconi *et al.*, 2004).

Despite the relatively lengthy history of FDG-PET in dementia, its clinical utility was not fully appreciated until relatively recently. The last American Academy of Neurology Practice Parameter for the diagnosis of dementia was released in 2001, at a time prior to any reports of PET operating statistics from large studies. In that report, PET was thought to "have promise for use as an adjunct to clinical diagnosis," but further studies were required "to establish the value that it brings to diagnosis over and above a competent clinical diagnosis." (Knopman *et al.*, 2001). Since then, several studies have been reported including one later that year, which included 284 patients undergoing dementia workup, with 138 having neuropathological diagnosis (Silverman *et al.*, 2001). The authors used a typical AD pattern of parietal and temporal hypometabolism, with or without frontal involvement, with a sensitivity of 94% (91/97; 95% CI, 89–99%) and a specificity of 73% (30/41; 95% CI, 60–87%) relative to neuropathologic diagnosis (Silverman *et al.*, 2001); other studies have found similar values of specificity and sensitivity of PET for AD, depending on comparisons with clinical or pathologic definitions of disease (Hoffman *et al.*, 2000; Patwardhan *et al.*, 2004).

In an attempt to clarify the sensitivity and specificity of PET, one meta-analysis of articles published through 2003 found significant faults in the generalizability of these studies overall (Patwardhan *et al.*, 2004). Namely, the authors noted that control patients may have dissimilar medical comorbidities, and that most of the studies were performed in specialty or tertiary referral centers, and may operate quite differently when used in primary care settings. Despite these limitations their best estimate suggested the summary sensitivity of PET was 86% (95% CI: 76–93%) and summary specificity was 86% (95% CI: 72–93%) (Patwardhan *et al.*, 2004), and subsequent individual studies have found similar results (Jagust *et al.*, 2007). Furthermore, in each of these studies, we cannot know whether individuals with an AD PET pattern, but without either clinical or pathologic correlate, would have eventually developed clinical AD. Thus, these patients may underestimate the specificity of FDG-PET (fewer false positives).

D. Pittsburgh Compound B-PET

Recent approaches to PET imaging in dementia have attempted to obviate the examination of glucose metabolism and its inherent limitations and focus on radioligands which bind with amyloid in the brain. One of the most promising and well studied of these ligands used amyloid binding dye thioflavin-T derivative [*N*-methyl-^{11}C]-2-(4′-methylaminophenyl)-6-hydroxybenzothiazole, better known as Pittsburgh Compound B (PiB)-PET, which binds to amyloid plaques and amyloid fibrils, but not neurfibrillary tangles. The first report of PiB-PET in humans suggested PiB affinity is generally inversely correlated with glucose metabolism on FDG-PET (Klunk, 2004) (e.g., regions with greater amyloid burden may be identified in regions with relative preservation of glucose metabolism); the highest degree of amyloid binding was associated with prefrontal cortex, and to a lesser degree in parietal, occipital, and temporal cortex (Klunk *et al.*, 2004; Mintun *et al.*, 2006). Subsequent studies have also suggested that relatively normal prefrontal glucose metabolism on FDG-PET despite high prefrontal amyloid binding on PiB-PET has led some to hypothesize additional mechanisms than just amyloid underlying neuronal dysfunction in AD (Edison *et al.*, 2007).

PiB binding has been demonstrated to be highly prevalent among larger studies of AD patients, and to a lesser degree but with a similar pattern among MCI patients (Kemppainen *et al.*, 2007). PiB binding may be present in as high as 22% of elderly individuals with healthy aging, and cortical PiB is significantly associated with episodic memory test performance among MCI and normal aged patients (Pike *et al.*, 2007), and facial and word recognition in all subjects (Edison *et al.*, 2007). One study of cognitively normal elderly and MCI subjects found no within-group relation between learning and memory testing and PiB binding (Jack *et al.*, 2008). To date, the relatively limited number of studies preclude definitive prediction of progression from MCI or a normal state to clinical AD based on PiB-PET, but MCI patients with an AD PiB-PET pattern may be more likely to progress to AD based on one study with relatively brief follow-up (Forsberg *et al.*, 2008).

Data regarding the sensitivity and specificity of PiB-PET in the diagnosis of AD is somewhat limited. One study found increased PiB binding in 89% of patients with clinically probable AD (Edison *et al.*, 2007); another found 100% sensitivity, with specificity dependent upon the age of the patient, ranging from 73 to 96% (Ng *et al.*, 2007). As with FDG-PET, the cause for the relatively low specificity (high false positives for AD) in some subjects is unclear, but could be related to several reasons. First, presymptomatic individuals could lead to false positive findings; autopsied brains of cognitively normal elderly can have pathologic AD changes in 25–67% of subjects (Crystal *et al.*, 1988; Morris *et al.*, 1996; Mortimer *et al.*, 2003; MRC-CFAS, 2007). Second, PiB amyloid binding is found in other cerebral amyloidoses including cerebral amyloid angiopathy (CAA)

(Lockhart *et al.*, 2007). Although the data are limited, the CAA pattern of PiB-PET signal may be distinguishable from AD; CAA may have a greater degree of occipital amyloid identified on PiB-PET than AD patients (Johnson *et al.*, 2007).

II. Application of PET to Primary and Specialty Care Settings

Given the data from these studies outlined above, it is worth considering the application and utility of PET in clinical practice. Prior to outlining the approach to its use, the current typical sequence leading to the workup and diagnosis of dementia bears review, to contextualize the potential role of PET within the diagnostic workup.

A. Diagnostic Workup of Dementia in Primary Care

For the workup of dementia patients, current recommendations for primary care physicians are to provide cognitive screens to only those with reported or suspected cognitive decline, or in the oldest old (Brodaty *et al.*, 1998; US Preventive Services Task Force, 2003). Without disease modifying treatment, the current ratio of benefit to harm of screening for dementia is unclear, and thus not recommended unless dementia is suspected (US Preventive Services Task Force, 2003). These practices may delay recognition relative to community screening programs (Barker *et al.*, 2005), but expanding current screening practices may be impractical for a busy primary care physicians, already conscious of cost concerns (Geldmacher, 2002). When concern for progressive cognitive impairment is raised in the primary care setting, one of several brief cognitive screening tests for dementia is often used. The best-studied cognitive screening tool is the Folstein Mini-Mental Status Examination (MMSE) (Folstein *et al.*, 1975; US Preventive Services Task Force, 2003), but scoring and interpretation may be somewhat dependent on education and age. If cognitive impairment is identified, other non-cognitive screening tests are recommend for the purposes of excluding uncommon causes non-degenerative cognitive decline (Knopman *et al.*, 2001). These tests include MRI (to rule out space occupying lesions, subclinical cerebral infarcts, and other conditions) and laboratory evaluations of thyroid function, vitamin B12 level, and syphilis serology. These tests have few limitations, are reproducible, and are relatively simple to perform and interpret by non-specialists.

Depending on individual practice, some primary care physicians may arrest the workup at this point and begin treatment. Others may refer to a specialist after screening, or even sooner—at the time of suspected cognitive impairment but

prior to screening laboratory evaluation. The current structure of diagnostic workup is likely impractical for every patient with probable AD to be seen by a specialist. Although data are limited, US community primary care physicians refer 44% of their patients to specialists for diagnosis or confirmation (Fortinsky *et al.*, 1995). In comparison, more than 80% of community primary care physicians in Germany and academic primary care physicians in Canada make specialist referrals, most often neurologists or physicians specializing in both psychiatry and neurology (Pimlott *et al.*, 2006; Riedel-Heller *et al.*, 1999). Potential dementia specialists include neurologists (on average, 4.5 neurologists serve 100,000 US population) (World Health Organization, 2005), gerontologists (2.4 per 100,000), and geriatric psychiatrists (0.5 per 100,000) (Wimo *et al.*, 2007); behavioral neurologists and neuropsychiatrists comprise a small minority of general psychiatrists and neurologists. Thus, any increase in referrals to specialists would likely overwhelm the current system.

The statistical rigor and cost-effectiveness of a non-selective community-based screen using most of these diagnostic tools has not been widely reported. It has been argued that FDG-PET can be a cost saving measure for the diagnosis of AD in geriatric populations, in comparison to a conventional workup of clinical evaluation and exclusion of potential mimicking diseases (Silverman *et al.*, 2002). However, this study considered the population of having 51% prevalent disease (Silverman *et al.*, 2002), which would only be applicable to a highly selected, screened population within a primary caregiver's office, or would require an unselected population with all patients over 90 years of age, based on current epidemiologic estimates.

B. Diagnostic Workup of Dementia in Specialty Care Settings

In contrast to screening tests used largely for exclusionary purposes, confirmatory tests used in the diagnostic workup of patients with dementia are typically used as sensitive measures to rule in a diagnosis in a patient with moderate to highly probable disease. These tests include initial clinical evaluation, often by a specialist, with supportive testing, decided on a case by case basis, including neuropsychological testing, cerebrospinal fluid markers, and functional imaging such as FDG-PET. Each of these is costly, time consuming and requires a large amount of manpower to complete (McMahon *et al.*, 2003). As noted elsewhere, the additional diagnostic benefit of these diagnostic tests when done in expert settings is unclear, and these tests may have greater potential diagnostic usefulness when the diagnosis is less certain, as may be the case in primary care settings (Knopman, 2001).

III. Appropriate Use of PET

Before delving into the statistics of available studies regarding PET, the use of sensitivity, specificity, and related statistical tools also bears brief review. From the Table I, *Sensitivity* = A/(A + C) is the probability of having a positive test result among all those with disease. The complement of sensitivity is the *false negative proportion* = C/(A + C). *Specificity* = D/(B + D) is the probability of having a negative test result among those without disease. Similarly, the complement of specificity is the *false positive proportion* = B/(B + D). Drawn from Table I are terms that are often cited to guide clinicians' use for practical matters, and perhaps incorrectly so: the predictive value terms. The *positive predictive value* = A/(A + B) is the probability of having the disease given a positive test result. Similarly, the *negative predictive value* = D/(C + D) is the probability of not having the disease given a negative test result. These predictive values are often applied incorrectly; their usefulness is dependent upon the prevalence of disease within a given population, which may be unknown to the clinician. Furthermore, if data are derived from case-control studies, the predictive value tools cannot be used unless an equal sampling fraction of controls is established, and this is often difficult.

In place of these predictive value tools, some have suggested using likelihood ratio statistics (Grimes and Schulz, 2005), but these have not become as widely reported, despite their relative ease of using an appropriate table or computer program. The benefit of the likelihood ratios is that they incorporate statistics regarding all disease states and test results, without depending on prevalence. Instead, using Bayesian statistics these ratios allow the user to apply a likelihood ratio to a pretest probability (either according to known disease prevalence or clinical probability based on additional data) to derive a posttest probability. Thus, again from Table I, the *Likelihood ratio for disease if test positive* = sensitivity/(1-specificity) and the *Likelihood ratio for disease if test negative* = (1-sensitivity)/specificity. One can also consider the likelihood ratio positive to be the ratio of true positives to false positives, and the likelihood ratio negative as the ratio of false negatives to true negatives. The likelihood ratios in and of themselves have little inherent meaning but become relevant when applying them to individual patients.

TABLE I
THE 2 × 2 TABLE

	Disease	No disease
Positive test result	A	B
Negative test result	C	D

Although the likelihood ratio calculations are relatively straightforward, their application can be exacted by using Bayesian statistics, but these can be perceived as cumbersome. An alternative strategy is the use of the likelihood ratio table (Fig. 1), or perhaps more simply by remembering a few important numbers (Grimes and Schulz, 2005). Here we present all three methods of practical application of likelihood ratios.

A. Using Likelihood Ratio Tables

When considering the FDG-PET meta-analysis outlined above (Patwardhan *et al.*, 2004), which identified the composite sensitivity = 86% and specificity = 86% for AD, then the Likelihood ratio positive = 0.86/(1−0.86) = 6.1 and the Likelihood ratio negative = (1−0.86)/0.86 = 0.16. Once these have been calculated, we then look to Fig. 1A, a typical likelihood ratio table. To use the likelihood ratio table, begin with the pretest probability at the left. Using a straightedge, tracing from the pretest probability through the likelihood ratio will derive the posttest probability. Presumably, a posttest probability will need to be sufficiently high or low to make a clinical decision. Arguably, given that tertiary referral centers may be correct in clinical AD diagnosis approximately 90%, then any posttest probability at or above this would be satisfactory; a suitable threshold value for a low likelihood posttest probability can be determined on a case by case basis but presumably should be less than 5%.

Consider an example of a 50% pretest probability, which could be prevalence of AD in a nonagenarian population (or alternatively a primary physician's clinical suspicion based on interview alone) and thus the pretest probability without further information or diagnostic tests. In this scenario, a positive FDG-PET with likelihood ratio positive = 6.1 would increase the posttest probability to about 90%, while a negative test result with likelihood ratio negative = 0.16 would decrease the posttest probability to 10%. Alternatively, we could consider a single, larger study of PET in AD as outlined above (Silverman *et al.*, 2001) which identified sensitivity = 94% and specificity = 73%, and thus a likelihood ratio positive = 3.5 and likelihood ratio negative = 0.08. Beginning with a 50% pretest probability, our posttest probability with a positive test increases to only about 70% while a negative test decreases the probability to about 5%.

Exploring the likelihood ratio table, one can clearly see that an uncertain pretest probability is the best scenario for use of a diagnostic tool with sufficiently high likelihood ratio positive (ideally over 10) or low likelihood ratio negative (ideally 0.1 or less). Very high or low pretest probabilities will not be appreciably affected, regardless of the likelihood ratio test characteristics (Grimes and Schulz, 2005).

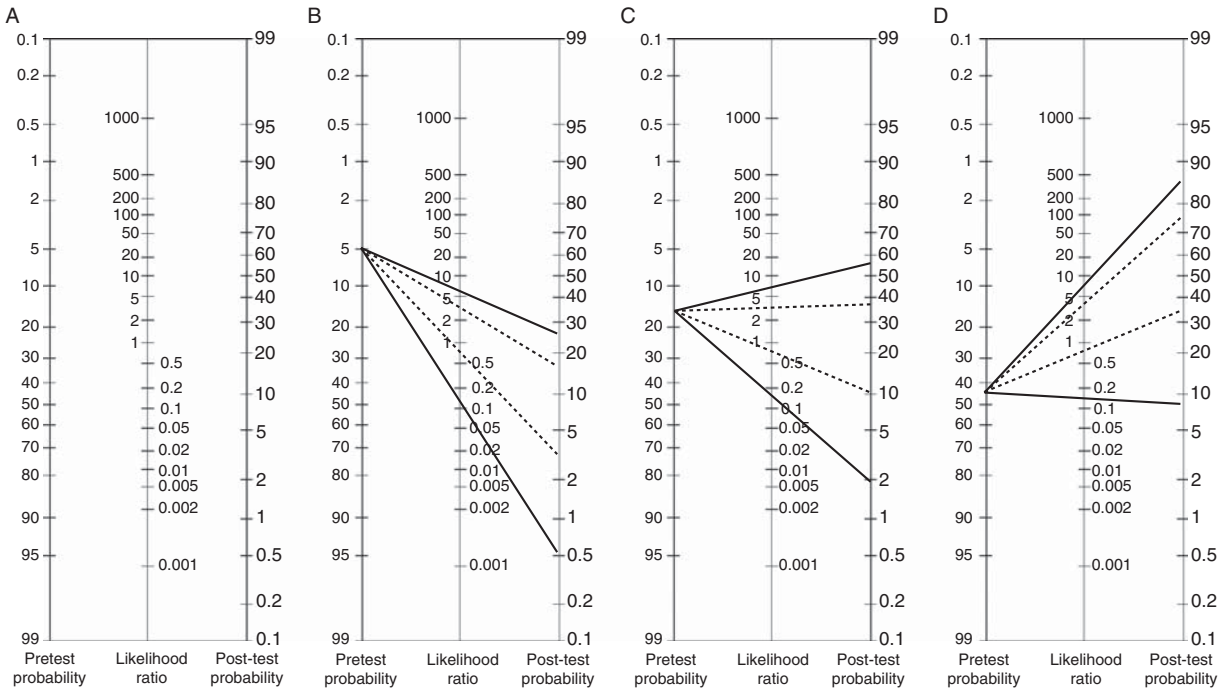

FIG. 1. Likelihood ratio tables of FDG-PET in the diagnosis of Alzheimer's disease in several age-stratified scenarios. (A) The likelihood ratio table. (B-D) Likelihood ratio tables for age stratified elderly populations, with pretest probability using only age-based prevalence statistics (Alzheimer's Association, 2008; Gurland *et al.*, 1999; Hebert *et al.*, 2003; Mayeux, 2003b). (B) Age less than 75 years (3–5% AD prevalence). (C) Age 75–84 years (15–18% AD prevalence). (D) Age 85 years and above (45% AD prevalence). Solid line: FDG-PET with sensitivity = 86% and specificity = 86% (Patwardhan *et al.*, 2004); (LR + = 6.1 LR− = 0.16). Dotted line: FDG-PET with sensitivity = 94% and specificity = 73% (Silverman *et al.*, 2001); LR + = 3.5 and LR− = 0.08. Figure (A) reprinted with permission from Elsevier (Grimes and Schulz, 2005).

Finally, in the Fig. 1B-D, we have applied the likelihood ratios derived from two studies of FDG-PET statistics (Patwardhan *et al.*, 2004; Silverman *et al.*, 2001) to visually demonstrate the utility of applying likelihood in several different scenarios. In this figure, we derived the pretest probability in each Fig. 1B-D from age-stratified prevalence statistics of AD (Alzheimer's Association, 2008; Gurland *et al.*, 1999; Hebert *et al.*, 2003; Mayeux *et al.*, 2003b) in an effort to demonstrate the utility of FDG-PET without additional screening or further workup. Clearly, the degree of certainty in diagnosis does not appreciably improve from this single test until applied to those older than 85 years of age.

B. Using a Likelihood Ratio "Mnemonic"

Should a likelihood ratio table not be immediately available, and if one chooses not to pursue the potentially difficult calculation steps outlined below, a simpler way has been suggested, requiring the user to remember a few numbers (Grimes and Schulz, 2005). Positive likelihood ratios 2, 5, and 10, approximately increase the posttest probability by 15% increments individually. That is, a likelihood ratio positive of 2 increases the posttest probability by an absolute difference of 15%, 5 by 30%, and 10 by 45%. Conversely, a likelihood ratio negative of 1/2 (0.5) decreases the posttest probability by an absolute difference of 15%, 1/5 (0.2) by 30%, and 1/10 (0.1) by 45%. Using this method considering one of the examples above, a likelihood ratio positive of 6.1 is similar to 5, which would increase a pretest probability of 50% absolutely by 30% to 80%. Similarly, a likelihood ratio negative of 0.08 is similar to 1/10 which would decrease a pretest probability of 50% absolutely by 45%, yielding a posttest probability of 5%, as estimated by the likelihood ratio tables. Overall, comparing this simplified methodology to the results above using the likelihood ratio tables, yields similar but less precise results.

C. Using Bayesian Calculations

Aside from using likelihood ratio tables or the mnemonic as suggested above, one can determine the exact posttest probabilities through a series of calculations, bearing in mind that pretest probabilities may be imprecise and based on clinical judgment. These calculations are

1. Calculate the pretest odds = pretest probability /(1-pretest probability)
2. Posttest odds = Pretest odds × likelihood ratio
3. Posttest probability = Posttest odds/(posttest odds +1)

Returning to the 50% pretest example using sensitivity and specificity for PET derived from the meta-analysis (Patwardhan *et al.*, 2004), for a positive test

Pretest odds = 0.50/(1−0.50) = 1 ("1:1 odds")
Posttest odds = 1 × 6.1 = 6.1
Posttest probability = 6.1/(6.1 + 1) = 86%

For a negative test

Posttest odds = 1 × 0.16 = 0.16
Posttest probability = 0.16/(1 + 0.16) = 14%

From this example we can see that the likelihood ratio table, menomnic, and calculations yield similar results for a test with 86% sensitivity and specificity, regarding a positive test result (posttest probability using the likelihood ratio table, 90%; mnemonic, 80%; calculation, 86%) and a negative test result (posttest probability using the likelihood ratio table, 10%; mnemonic, 5%; calculation, 14%).

D. Conclusions from Using the Likelihood Ratios for PET and AD

Based on these analyses, FDG-PET should be used only in a highly selected group of patients. Presumably, one would pursue a diagnostic workup until such a time that there is a high degree of certainty of either dementia or normal cognition. At this point FDG-PET should be reserved for patients having either (a) undergone an otherwise exhaustive diagnostic workup with a specialist in cognitive disorders or (b) partial workup with a primary care physician after having identified a cognitive disorder, but both yielding a still-uncertain diagnosis. This approach has been justified in expert centers attempting to distinguish ambiguous clinical cases of AD and frontotemporal dementia; FDG-PET changed the diagnosis in 26% of cases in which the examiner was uncertain or not completely confident in the diagnosis, versus 5% change of clinically certain cases after additional information provided by FDG-PET (Foster *et al.*, 2007). Current reimbursement practices in the United States reflect just such application of FDG-PET, and its use is restricted to consideration of a differential diagnosis of AD versus other neurodegenerative illnesses.

At this point, available data for either FDG-PET or PiB-PET in MCI are limited and preclude accurate derivation of a likelihood ratio test statistics. Neither study is currently indicated for suspected MCI patients, either as a diagnostic tool or as a prediction tool for progression. Should future studies reveal additional data regarding specificity and sensitivity of these imaging modalities, or any other MCI/AD diagnostic tool for that matter, one can apply such data to this formula and recapitulate this argument.

IV. Summary

Despite a relatively lengthy history of FDG-PET in the evaluation of dementia, it should still be used judiciously, and only in patients with a relatively uncertain cognitive diagnosis despite initial workup and evaluation, or if the etiology of their dementia is unclear. The use of FDG-PET as a blind screening tool is not recommended; although, screening in elderly at greatest risk for dementia (age $>$ 90) is worth considering. Newer PET radioligands such as amyloid binding tools (PiB among them) show promise as a future diagnostic tool, but are not commercially available at this time and cannot be recommended for routine use based on available data. FDG-PET, PiB-PET, and other supportive diagnostic tests may have greater roles in diagnosis and monitoring disease should be an era of disease-modifying therapies and prevention strategies for AD develop.

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THE MOLECULAR AND CELLULAR PATHOGENESIS OF DEMENTIA OF THE ALZHEIMER'S TYPE: AN OVERVIEW

Francisco A. Luque*,† and Stephen L. Jaffe*

*Department of Neurology, Louisiana State University School of Medicine-Shreveport, Shreveport, Louisiana 71103, USA
†VA Neurology Service, Overton Brooks VAMC, Shreveport, Louisiana 71101, USA

The pathogenesis of dementia of the Alzheimer's type (DAT) remains elusive. The neurodegeneration occurring in this disease has been traditionally believed to be the result of toxicity caused by the accumulation of insoluble amyloid-beta 42 (AB) aggregates, however recent research questions this thesis and has suggested other more convincing cellular and molecular mechanisms. Dysfunction of amyloid precursor protein metabolism, AB generation/aggregation and/or degredation/clearance, tau metabolism, protein trafficking, signal transduction, heavy metal homeostasis, acetylcholine and cholesterol metabolism, have all been implicated etiologically especially as to production of neurotoxic by-products occurring as a result of a specific process derangement. In this paper, these and other research directions are discussed as well as their implications for future therapies. The relationship of the proposed abnormal molecular and cellular processes to underlying genetic mutations is also scrutinized, all in an attempt to stimulate further insight into the pathogenesis of, and thus therapeutics for this increasingly prevalent disease.

I. Introduction

Over 100 years ago, Alzheimer described a patient with memory disturbance and a brain pathological picture which included miliary bodies (plaques) and dense bundles of fibrils (tangles). These observations remain the clinical and pathological hallmarks of dementia of the Alzheimer's type (DAT). DAT is

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the most common form of dementia and accounts for 50-60% of dementia presentations. Presently there are approximately 5.1 million patients in the USA with DAT; and it is estimated that in the next 20 years, there will be an additional 15 million cases. DAT incidence increases with age. Before age 60, the incidence is about 5%; but after age 85, it increases to 50%. The annual cost attributed to DAT in this country is $148 billion. The clinical symptoms of DAT include alterations of abstract thinking, skilled movements, emotional expression, executive function, and memory. The majority of DAT cases are sporadic, but around 10% are inherited. Autosomal dominant cases are related to mutations in the amyloid precursor protein (APP) (chromosome 21), presenilin 1 (PS1) (chromosome 14), and presenilin 2 (PS2) (chromosome 1) genes. Similar pathology with a dementing process often occurs in Down syndrome (trisomy 21).

The pathogenesis of DAT remains perplexing. Dysfunction in APP metabolism, Aβ42 (Aβ) degradation and clearance, signal transduction, tau metabolism, protein trafficking, acetylcholine and cholesterol metabolism, and homeostasis of heavy metals may be involved (Bertram and Tanzi, 2008). DAT neurodegeneration may be linked to dysfunction of the degradation process of Aβ or other proteins, or Aβ generation with production of toxic by-products may be responsible, and aggregate formation may be a benign phenomenon. On the other hand, Aβ aggregates may be primarily toxic interfering with the degradation of various proteins by interfering with chaperone function. Protein folding, protein-protein interaction, and protein membrane association are all thermodynamically driven processes utilizing enzymes known as chaperones. The importance of chaperones for proteosomal degradation has been corroborated in the endoplasmic reticulum (ER) where newly synthesized proteins that are abnormal or misfolded are removed by a quality control mechanism termed ER-associated degradation (Tai and Schuman, 2008; Zhang *et al.*, 2004).

II. Cellular Pathogenesis and Investigational Strategies

DAT histological brain changes are especially prevalent in the frontal and temporal lobes and include neuronal loss, extracellular deposition of Aβ as "senile plaques," and the intracellular accumulation of neurofibrillary tangles composed of microtubule-associated protein tau arrayed as paired helical filaments. One of the earliest neuropathological changes is the presence of a large number of reactive astrocytes at the site of Aβ deposition. Aβ deposition also leads to degeneration of the microvascular basement membrane and thus alteration in blood-brain barrier permeability (Berzin *et al.*, 2000) (Fig. 1).

As previously noted, it is unclear whether the process of formation and accumulation, precursors occurring during that process, the actual accumulated Aβ, and/or abnormal degradation initiates a series of neurotoxic events including

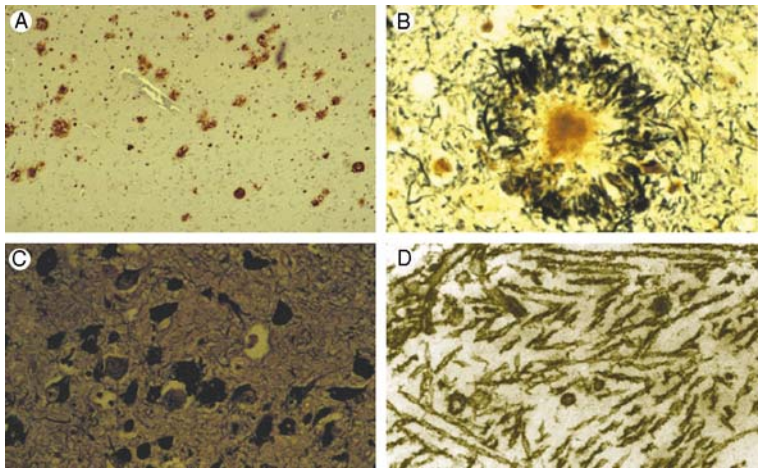

FIG. 1. Neuropathology of Alzheimer's disease. (A) Low power amyloid plaques, (B) high power amyloid plaque, (C) neurofibrillary tangles, silver stained, and (D) electron micrograph of neurofibrillary tangles composed of hyperphosphorylated tau (Courtesy of Sisodia and St. George-Hyslop, 2002; with permission from Nature Publishing Group).

hyperphosphorylation of tau that triggers neuronal dysfunction and cell apoptosis (the "amyloid cascade"). Although new ligands for positron emission tomographic (PET) imaging of Aβ *in vivo* (Pittsburgh Compound-B) are available, their diagnostic value is questionable due to this conundrum. However, the accumulation of amyloid plaques is the earliest feature that can be detected in presymptomatic individuals with a PS1 mutation or with trisomy 21. Although, it is not clear how Aβ specifically induces neurodegeneration, the accumulation of intracellular tau does appear to be neurotoxic.

It was originally thought that plaque formation occurred over long periods of time and long before the dementia became apparent. However, Meyer-Luehmann *et al.* (2008) using a DAT mouse model provided evidence that amyloid plaques form extremely rapidly, actually within 24 h, and their size and final characteristics stabilize within a week. In the early stages of the disease, microplaques can damage neighboring axons and dendrites within days. Among the features of the DAT degenerative process are damage to synaptic connections associated with accumulation of amyloid β oligomers, and neuritic dystrophy—the formation of tortuous neuronal elongations with eventual loss of selective groups of neurons. These processes have been strongly linked to DAT cognitive impairment.

Defects in axonal transport have been described in animal models of DAT including transgenic mice overexpressing APP, and those containing mutant PS1. However, the mechanism is not fully understood (De Vos *et al.*, 2008). Aβ appears

to disrupt the axonal transport of a variety of cargoes including mitochondria by associating with and thus damaging the mitochondria (Hiruma *et al.*, 2003; Manczak *et al.*, 2006). Mutant PS1 impairs axonal transport by causing a reduction in kinesin-I driven motility via interaction with glycogen synthase kinase-3β to produce phosphorylation of kinesin light chains with release of kinesin-I from membrane-bound organelles (Pigino *et al.*, 2003).

Disturbance of glutaminergic neurotransmission and consequent excitotoxicity has been implicated in the progression of DAT (Matos *et al.*, 2008). In DAT patients, increased glutaminergic excitotoxic activity appears to occur due to Aβ interference with glutamate uptake by astrocytes, leading to increased activation of NMDA neuronal receptors. Memantine is a noncompetitive NMDA receptor antagonist that appears to protect neurons from glutamate mediated excitotoxicity without interfering with the physiological NMDA receptor activation needed for cognitive functioning. Although there is no data showing memantine has a beneficial effect in mild DAT, this drug is well tolerated and may be a useful adjunct in moderate to severe disease defined as a mini-mental status exam (MMSE) score of less than 15.

Amyloid β aggregation disturbs the cellular proteosome by inducing oxidative stress with subsequent mitochondrial and proteosomal dysfunction (Hamacher *et al.*, 2007). Mitochondrial dysfunction appears to be an early causative event in neurodegeneration. Mutations of mitochondrial fusion GTPases, mitofusin 2, and optic atrophy 1, are neurotoxic and produce oxidative stress which disrupts the cable-like morphology of functional mitochondria. This causes impairment of bioenergetics, interfering with mitochondrial migration and triggering neurodegeneration (Knott *et al.*, 2008).

Sortilin related receptor (SorLA) belongs to a family of sorting receptors that mediate various intracellular processing and trafficking functions (Yamazaki *et al.*, 1996). SorLA/LR11 mediates re-internalization of APP, during which APP is transported from the cell surface to an endocytic compartment where it is cleaved into Aβ by β secretase and γ secretase. SorLA/LR11 is highly expressed in the brain and binds to ApoE and APP, sequestering APP in the Golgi apparatus and thus preventing APP generation into Aβ (Andersen *et al.*, 2006). In all studies to date, there is no consistent evidence of a SorLA association with DAT, possibly due to allelic heterogeneity. Studies *in vitro* suggest that SorLA expression is reduced in the brains of DAT patients, even in the preclinical state. SorL1-knockout mice show increase in brain Aβ level. Although there is convergence of data from genetic and biochemical studies, more data are needed to better evaluate this association.

Transferrin (TF) is a major circulating glycoprotein involved in the metabolism of iron and is highly expressed in the brain. Iron misregulation promotes neurodegeneration via generation of reactive oxygen species (ROS) (Brewer, 2007). Iron is increased in the brains of DAT patients where it is associated with plaques and tangles. Iron may play a role in the aggregation of hyperphosphorylated tau into insoluble paired helical filaments (Yamamoto *et al.*, 2002), and iron may also regulate

the translation of APP. Thus iron levels could modulate the generation of both plaques and tangles. Besides the binding of metals to Aβ, TF has been shown to modulate several physiochemical properties of Aβ including the rate of aggregation.

The ability of neurons to regulate the influx, efflux, and subcellular compartmentalization of calcium is compromised in DAT. This appears due to age-related oxidative stress, and impaired metabolism/accumulation of Aβ oligomers. Aβ can promote cellular calcium overload via oxidative stress and by forming pores in the membrane, rendering neurons vulnerable to excitotoxicity and apoptosis (Bezprozvanny *et al.*, 2008). Mutations of presenilin genes that cause early onset DAT also cause ER (endoplasmic reticulum) calcium overload by impairing the normal ER calcium leak-channel function of the presenilins. A perturbation in calcium homeostasis may be involved in early DAT by altering APP processing and thus Aβ production. Calcium activated neural proteinases (CANPs or calpains) are key enzymes in the intracellular signaling cascade and thus may mediate calcium dependent neural degeneration. Pharmacological modulation of the CANP system could be a potential therapeutic strategy in Alzheimer's disease (Saito *et al.*, 1993).

De Luigi *et al.* (2002) studied the presence of circulating cytokines and the ability of blood cells to release them in response to inflammatory stimuli in patients with different forms of dementia. A significant increase in circulating interleukin-1β was found in moderate DAT. Chronic inflammation as found in head trauma is an important risk factor for DAT, and the inflammatory process affects glial-neuronal interactions. The activation of the glial inflammatory process, either caused by genetic or environmental insults to neurons, produces glial derived cytokines and other proteins that results in neurodegeneration. Interleukin 1 is key in initiating and coordinating neuronal synthesis and in the processing of APP, resulting in the continuous deposition of Aβ. It also promotes astrocytic synthesis and release of inflammatory and neuroactive molecules such as S100β, which is a neurite growth promoting cytokine. This cytokine can stress neurons fostering neuronal cell dysfunction, causing apoptosis by increasing intraneuronal free calcium concentrations. This neuronal injury effect activates microglial cells which then overexpress inteleukin 1, thereby producing feedback amplification and self-propagation of this cytokine cycle (Griffin *et al.*, 1998).

III. Molecular and Genetic Studies Resulting in Therapeutic Strategies

Amyloid β is generated by endoproteolysis of the APP. This is achieved by cleavage of APP by a group of enzyme complexes: α, β, and γ secretases. Three enzymes with α secretase activity belong to the ADAM enzyme family (desintegrin and methaloproteinase enzymes): ADAM9, ADAM10, and ADAM17

(i.e., tumor necrosis factor converting enzyme). The β site APP cleaving enzyme-1 (BACE1), β secretase, is a type I integral membrane protein from the pepsin family of aspartyl proteases. Gamma secretase is an intramembranous complex of enzymes composed of presenilin 1 or 2, nicastrin, anterior pharynx defective-1, and presenilin enhancer 2, with the presenilin being the active site (Wolfe *et al.*, 1999; Yu *et al.*, 2000).

There are two pathways in the cleavage and processing of APP. One is non-amyloidogenic. APP is cleaved by α secretase at amino acid position 83, the carboxy terminus, producing a large amino terminal ectodomain (sAPPα). This is secreted into the extracellular medium where it is in turn cleaved by γ secretase producing a short peptide, p3. The cleavage by α secretase is in the middle of the APP region, and therefore there is no Aβ production. The amyloidogenic pathway leads to Aβ generation. Initially the β secretase cleaves at amino acid position 99, releasing sAPP β into the extracellular space. Meanwhile the C99 fragment stays in the membrane where it is cleaved by γ secretase between residues 38 and 43, liberating a peptide which is 40 amino acids in length (Aβ40). Only a small proportion (10%) composes the 42 residue, the Aβ peptide (Aβ42). Aβ is more hydrophobic and thus prone to form fibrils, and is abundant in senile plaques (Jarrett *et al.*, 1993; Martin, 1999; Suh and Checler, 2002; Younkin, 1998). Mutations in the APP gene linked to early-onset DAT produce a product that is preferentially cleaved to release Aβ 42 (Selkoe, 2001; Sisodia and St. George-Hyslop, 2002) (see Fig. 2).

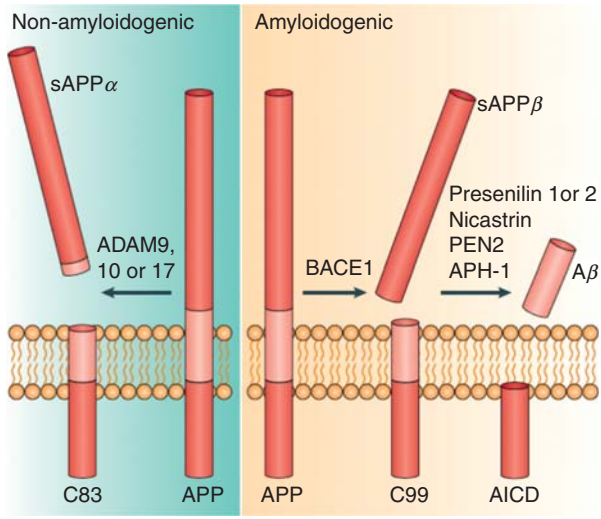

FIG. 2. Pathways in the cleavage and processing of APP (Courtesy of LaFerla *et al.*, 2007; with permission from Nature Publishing Group).

Presently, the major investigational therapeutic strategies are focused on inhibiting brain Aβ production, aggregation, and/or increasing Aβ brain clearance. Secretase modulators are being studied as Aβ production inhibitors based on the observation that Aβ production is abolished in BACE1 knockout mice and the DAT phenotype does not develop. BACE1 inhibitors have been developed to reduce brain Aβ accumulation in DAT transgenic mice. Rajendra *et al.* (2008) focused not only on inhibition of β secretase active site binding, but also on inhibiting the localized active enzyme at the subcellular level. He synthesized a membrane-anchored version of β secretase transition-state inhibitor by linking it to a sterol moiety. This targeted the inhibition of active β secretase found in endosomes, reducing the enzyme activity more readily than free inhibitor alone. Similarly γ secretase inhibitors specific to the APP cleavage site have been developed because of the concern of blocking γ secretase activity on other substrates such as the notch protein. Testing in transgenic mice is underway and appears successful in blocking the DAT phenotype, while inhibitors of Aβ accumulation show no effect on phenotype development again suggesting that effects of the process or the actual precursors may be the etiologic factors of DAT neurotoxicity (Schilling *et al.*, 2008).

Drugs that stimulate α secretase thus shifting the APP cleavage to a non-amyloidogenic pathway also reduce Aβ production. Among these, Bryostatin, a protein kinase C activator used for cancer treatment, increases α secretase activity and reduces Aβ accumulation in DAT transgenic mice models. Removal of Aβ by immunization is based on the observation that active immunization with fibrillar Aβ reduces Aβ deposition in DAT transgenic mice. In similar fashion, using a passive antibody technique against Aβ also reduces Aβ deposition. It is postulated that Aβ antibodies bind to Aβ plaques and induce Aβ clearance by microglia. However, a vaccine trial in humans was halted when 6% of patients developed encephalitis apparently due to T cell response to the C-terminus of the vaccine peptide. Presently monoclonal antibodies are being studied as well as nanobodies in attempts to increase Aβ clearance.

Inhibitors of Aβ fibrillization are among peptides that interfere with the assembly of Aβ into oligomers which eventually form protofibrils and fibrils. Two peptides have been shown to prevent the interaction Aβ-Aβ and Aβ-ApoE without inducing an immune response (Permanne *et al.*, 2002; Sadowski *et al.*, 2004). Glycosaminoglycans bind Aβ and can promote aggregation of Aβ. The drug NC-531 (Tramiprosate or Alzhemed) is a glycosaminoglycan mimetic designed to do the opposite and block Aβ aggregation. However, phase III clinical trials did not demonstrate a therapeutic effect for this compound. Scyllo-cyclohexanediol inhibits Aβ 42 fibril assembly, and tetracyclines as well as rifampin inhibit amyloid formation *in vitro*. Terenflurbil (Flurizan) is an allosteric modulator of γ secretase, inhibiting its activity. It is a stereoisomer of a nonsteroidal anti-inflammatory that does not have cyclo-oxygenase (COX) activity. Again however, a phase III trial failed to show clinical benefit.

Copper and Zinc ions can induce Aβ aggregation. The chelator, clioquinol (PBT-1), reduces brain deposition of Aβ in DAT transgenic mice. Clinical trials were stopped when compound impurities produced toxicity. However, PBT-2 (a second generation metal protein attenuating compound which does not contain iodine) is now undergoing clinical trial. In a DAT transgenic mouse model, preliminary results suggested improvement in a subset of cognitive measures, as well as reduction in cerebrospinal fluid and brain Aβ. Apomorphine and its derivatives promote the oligomerization of Aβ but inhibit the fibrillization. Structural activity demonstrated that 10, 11-dihydroxy substitutions in the D ring of apomorphine are required for the inhibitory effects. Methylation of these hydroxyl groups reduces the inhibitory potency. The ability of these molecules to inhibit Aβ formation appears to be linked to their tendency to undergo rapid auto-oxidation, suggesting that auto-oxidation products act directly or indirectly on Aβ and inhibit fibrillization. This paradigm offers the potential for designing more efficient inhibitors of Aβ amyloidogenesis *in vivo* (Lashuel *et al.*, 2002).

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce brain Aβ accumulation in DAT transgenic mice. This effect may be due to inhibition of COX or via direct effect on γ secretase. However, clinical trials with typical NSAIDs and COX-2 inhibitors (celocoxib and refecoxib) as well as other anti-inflammatories including prednisone and hydroxychloroquine, in established DAT showed no positive effects on cognition levels. It is postulated that this failure was due to the lack of ability to reverse already established pathology, and that the intervention has to be in the early stages of mild cognitive impairment (MCI). Statins also reduce brain Aβ accumulation in DAT transgenic mice. However, prospective studies showed no association between the use of statins and the risk of DAT development, nor were there any changes in CSF Aβ levels. Large, extended, randomized clinical trials are needed to determine if any benefit can be obtained with this drug class.

Nitric oxide may be involved in DAT neurodegeneration. By using redox proteomic techniques, 10 proteins have been associated with an increase of nitrotyrosine immunoreactivity in the brains of DAT patients. Of these proteins, α-enolase has been shown to be oxidized in the brains of DAT patients (Calabrese *et al.*, 2007; Castegna *et al.*, 2002). It is one of the subunits of enolase which catalizes the reversible conversion of 2-phosphoglycerate to phosphoenolpyruvate in glycolysis. This, in addition to the increase of nitration of the triosephosphate isomerase that interconverts dihydroxyacetone phosphate and 3-phosphoglyceraldehyde in glycolysis, may explain the altered glucose tolerance and metabolism seen in DAT patients. Neuropeptide h3 (a phosphatidylethanolamine-binding protein), hippocampal cholinergic neurostimulating peptide, and raf-kinase inhibitor protein have various functions in the brain. *In vitro*, they upregulate levels of choline acetyltransferase in cholinergic neurons following *N*-methyl D-aspartate (NMDA) receptor

activation. The activity of this enzyme is reduced in DAT patients. Together with cholinergic deficits, the nitration of neuropolypeptide h3 and the subsequent loss of neurotrophic action on cholinergic neurons of the hippocampus and basal forebrain may be part of the explanation of cognitive decline in DAT (Giacobini, 2003; Rossor *et al.*, 1982).

The polyphenolic molecule, curcumin, shows promise in reducing nitrosative brain injury and delaying the onset of neurodegenerative disorders. It is a strong antioxidant that inhibits lipid peroxidation intercepting and neutralizing ROS and reactive nitrogen species (RNS) and increasing haeme-oxygenase I expression in astrocytes and neurons. Dietary curcumin suppressed indicators of inflammation and oxidative damage in the brains of DAT transgenic mice (Butterfield *et al.*, 2002; Scapagnini *et al.*, 2006). However, antioxidants including vitamin E did not show any effect on the rate of progression of MCI to DAT in large studies. Drugs that reduce tau phosphorylation by inhibiting tau such as CDK5 (cyclin-dependent kinase 5) and GSK-3β (glycogen synthase kinase 3β) are being tested. Since tau phosphorylation results from the action of multiple kinases and phosphatases, these drugs may not effect normalization of tau phosphorylation.

Despite the identification of mutations in three genes associated with early-onset DAT (i.e., the APP, PS1, and PS2 genes) and one genetic risk factor for sporadic DAT (the gene for apolipoprotein E), our understanding of the pathological genetic mechanism remains elusive. There are additionally over 500 different gene candidates which may be involved in DAT pathogenesis, and at least 20 loci with modest but significant effects on the risk for this disease (Bertram and Tanzi, 2008). The APP gene is located at chromosome 21q21.3. Twenty-nine mutations in 78 affected families have been identified. These mutations are close to the β and γ secretase APP cleavage sites (Goate *et al.*, 1991). The PS1 gene is located at chromosome 14q24.3 and 166 mutations have been identified in 362 families. These mutations are associated with an increase in the Aβ42/Aβ40 ratio, and are located throughout the gene for the PS1 molecule where γ secretase complexing occurs (Sherrington *et al.*, 1995). PS2 localizes to chromosome 1q31-42. Ten mutations have been identified in 18 affected families. There is an increase in the Aβ42/Aβ40 ratio, similar to the effects of PS1 gene mutations. The mutations are found throughout the gene, and thus γ secretase complexing is affected (Levy-Lahad *et al.*, 1995; Rogaev *et al.*, 1995).

Roberson *et al.* (2007) studied a hybrid mouse expressing mutant APP and having the tau gene inactivated. The elimination of tau did not alter the accumulation of senile plaques but did prevent the memory loss, behavioral disturbances and sudden death associated with this DAT-like phenotype. The complete elimination of tau was not necessary, a reduction of 50% producing significant improvements. On the other hand, soluble Aβ assemblies cause memory loss and bind to dendritic spines. It would appear that soluble Aβ assemblies and not the precipitated senile plaques are the cause of impaired cognition, but

the exact mechanism remains ill-defined (Lacor *et al.*, 2004). Roberson appropriately sounded a note of caution in extrapolating mouse data into human pathophysiology in which other compensatory mechanisms may be playing a role (Avila *et al.*, 2004).

Bertram and Tanzi (2008) discussed 10 different selected genes potentially implicated in DAT. Angiotensin converting enzyme (ACE) has been shown *in vitro* to degrade naturally secreted Aβ and this could explain the increased risk of DAT in carriers of the ACE I allele; however, the relevance *in vivo* needs to be demonstrated. CH25H (cholesterol 25-hydrolase) which is responsible for the synthesis of 25-hydroxycholesterol, is a potent regulator of transcription of genes involved in cholesterol and lipid metabolism. There seems to be an association between variants of CH25H and DAT. One study (Papassotiropoulus *et al.*, 2005) suggested an increased DAT risk associated with a certain CH25H haplotype (containing the rs13500 risk allele) leading to an increase in CSF lathosterol (a metabolite precursor of cholesterol) as well as a higher brain Aβ load with lower levels of Aβ in the CSF of non-demented elderly subjects. Both CH25H and lipase A (LIPA) as well as APOE are involved in cholesterol metabolism, and Aβ production and clearance have been shown to be regulated by cholesterol. Drugs that inhibit cholesterol synthesis lower Aβ in cellular and animal models. Nicotinic acetylcholine receptors are widely expressed in the brain, and the β2 (CHRNB2) subunit is particularly abundant and forms a heteropentameric receptor ($\alpha 4\beta 2$) with the α4 subunit. The CHRNB2 gene which encodes the nAChR β2 subunit maps to chromosome 1q21. Two independent genetic association studies have investigated the potential involvement of this gene in DAT risk. Wu *et al.* (2004) found that Aβ directly inhibits the $\alpha 4\beta 2$ receptor complex, and that nicotine possibly by activating the NACHR can mitigate the toxic effects of Aβ, as well as influencing tau phosphorylation *in vitro* and *in vivo* (Oddo *et al.*, 2005).

Grb-2-associated binder 2 (GAB2) is a highly conserved scaffolding/adaptor protein involved in signaling pathways and in particular in the transduction of cytokine and growth-receptor signaling (Liu and Rohrschneider, 2002; Sarmay *et al.*, 2006). GAB2 is expressed ubiquitously, although in greatest amounts in white blood cells, the prefrontal cortex, and the hypothalamus. All 10 GAB2 gene single nucleotide polymorphisms (SNPs) showed significant association with DAT. A protective role is predicated for all the minor alleles. All 10 of the SNPs display a high LOD score ($\log_{10}$ ratio of probability data occurring if loci linked, to probability data occurring with unlinked loci), and therefore probably point to a single underlying signal effect. Of the 10 associated markers, only one, rsl1385600, is predicted to map within the coding region for GAB2 where it does not appear to produce a change in amino acid sequence. It has been suggested that changes in GAB2 expression could potentially affect glycogen synthase kinase 3 (GSK3)-dependent phosphorylation of tau, and thus formation

of neurofibrillary tangles. Moreover, growth factor receptor-bound protein 2 which binds GAB2 has been reported to bind tau, APP and PS1 and 2 (Nizzari *et al.*, 2007).

Laminins are intermediate filament proteins that are a component of the nuclear lamina. Alternative splicing produces two different isoforms, laminin A (LMNA) and C. Mutations in LMNA have been found to cause a number of different disorders. The LMNA gene maps 1.5 Mb distal to the CHRNB2 gene on chromosome 1, and close to the presumed DAT linkage region at 1q22-q25. Only one group has reported an association between variants of LMNA and DAT (Grupe *et al.*, 2007), the LMNA association ranked second in terms of genetic effect size of all non-APOE-4 related genes with an OR (odds ratio) of 1.35.

Macrotubule-associated protein tau (MAPT) is found in NFTs. The gene that encodes MAPT has been suspected of harboring disease causing mutations, but the search for such mutations in DAT has been unsuccessful. However, MAPT mutations were found to cause another form of dementia, frontotemporal lobar degeneration with parkinsonism linked to chromosome 17 (FTDP-17). Despite the lack of MAPT mutation associations in DAT, it is likely that tau dysfunction still contributes to an increased risk of developing DAT (Ballatore *et al.*, 2007).

Prion protein (PRP) is a membrane tethered glycoprotein that is highly expressed in all regions of the brain, mostly in neurons. Its physiological functions are not clear. Mutations of prion protein gene (PRNP) are a major determinant of familial and sporadic prion diseases such as Creutzfeldt-Jakob disease. Most prion diseases produce a rapidly progressive neurodenegeneration with spongioform brain changes and amyloid plaques that consist of misfolded PRP aggregates. There are more than two dozen different amino acid substitution mutations identified, which are transmitted in an autosomal dominant fashion with 100% penetrance. Aβ positive plaques in DAT brains often contain PRP deposits. Recent evidence from studies using APP-PRNP double transgenic mice suggests that PRP might actually promote plaque formation in DAT by increasing Aβ aggregation (Schwarze-Eicker *et al.*, 2005).

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ALZHEIMER'S DISEASE GENETICS: CURRENT STATUS AND FUTURE PERSPECTIVES

Lars Bertram

Neuropsychiatric Genetics Group, Department of Vertebrate Genomics, Max-Planck Institute for Molecular Genetics, Berlin 14195, Germany
Genetics and Aging Research Unit, Department of Neurology, Massachusetts General Hospital, Charlestown, Massachusetts, 02129, USA

Alzheimer's disease (AD) is a genetically complex disease whose pathogenesis is largely influenced by genetic factors. Three decades of intensive research have yielded four established AD genes (*APP*, *PSEN1*, *PSEN2*, *APOE*), and hundreds of potential susceptibility loci, none of which has been unequivocally shown to modify disease risk using conventional methodologies. The results of genome-wide association studies (GWAS) are now adding to an already vast and complicated body of data. To facilitate the evaluation and interpretation of these findings, we have recently created a database for genetic association studies in AD ("AlzGene"; available at http://www.alzgene.org). In addition to systematically screening and summarizing the scientific literature for eligible studies, AlzGene provides the results of allele-based meta-analyses for all polymorphisms with sufficient genotype data. Currently, these meta-analyses highlight over 20 different potential AD genes, several of which were originally implicated by a GWAS. First follow-up analyses in a large collection of over 1300 AD families reveal that—in addition to *APOE*—genetic variants in *ACE*, *CHRNB2*, *GAB2*, and *TF* show the most consistent risk effects across a wide range of independent samples and study designs. The chapter highlights these and other promising findings from the recent AD genetics literature and provides an overview of the powerful new tools aiding researchers today to unravel the genetic underpinnings of this devastating disease.

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I. Introduction: The Genetic Dichotomy of Alzheimer's Disease

Similar to many other adult-onset disorders, Alzheimer's disease (AD) shows a genetic dichotomy of cases with Mendelian inheritance ("simplex AD") versus cases governed by an array of different genetic and nongenetic risk factors ("complex AD"; Bertram and Tanzi, 2005; Tanzi, 1999). Simplex AD is rare (<5%) and usually shows an early (<65 years) or often times very early (<50 years) age of onset and, owing to its typical familial accumulation and inheritance pattern, is also known as "early-onset familial AD" (EOFAD). Currently, mutations in three genes are known to cause EOFAD, all leading to altered cerebral levels of the amyloid-β peptide (Aβ), the main constituent of senile plaques, and one of the neuropathological hallmarks of the disease (Tanzi and Bertram, 2005). The mutated genes leading to EOFAD are APP (amyloid precursor protein; Goate *et al.*, 1991), PSEN1 (presenilin 1; Sherrington *et al.*, 1995), and PSEN2 (presenilin 2; Levy-Lahad *et al.*, 1995; Rogaev *et al.*, 1995), and all three are intimately involved in the production of Aβ, which is liberated from APP via two enzymatic cleavage events, mediated by β- and γ-secretase. The latter is a protein complex consisting of various components, in which the presenilins form the γ-secretase active site. Even though EOFAD represents only a tiny fraction of all AD cases, the knowledge gained from uncovering its genetic underpinnings has been instrumental in our current understanding of the forces leading to AD across all onset ages and have corroborated the "amyloid hypothesis." This hypothesis posits that a dysregulation of the production/function of Aβ is the initiating event in the pathogenetic cascade eventually leading to neurodegeneration and dementia (Glenner and Wong, 1984; reviewed in Hardy and Selkoe, 2002; Tanzi and Bertram, 2005). Finally, many of the currently most promising therapeutic approaches in the AD field aim to directly intersect or reverse the pathological build-up of Aβ, which for the first time would allow a causal treatment of AD as opposed to the merely symptomatic options available to date.

Despite its relatively high heritability (Bergem *et al.*, 1997; Gatz *et al.*, 2006; Meyer and Breitner, 1998)—that is, the proportion by which phenotypic variation is determined by genetic variation—the genetic make-up of complex AD, which, owing to its later onset age ($\geq$ 65 years), is also known as "late-onset AD" (LOAD), has proved to be much more difficult to decipher. This is at least in part due to problems that generally aggravate epidemiological research in many neuropsychiatric diseases, for example, small genetic effect sizes and reduced penetrance of the involved genetic factors, a considerable degree of phenotypic variability and co-morbidity with other late-onset disorders, the lack of extended pedigrees for LOAD cases, and the absence of disease-specific biomarkers (Kennedy *et al.*, 2003). The identification of susceptibility genes is further

complicated by gene-gene interactions that are difficult to predict and model, and a sizeable but difficult to detect and measure environmental component. Notwithstanding these challenges, several chromosomal regions thought to harbor novel LOAD genes have been identified via whole genome linkage analyses, some, for example, on chromosomes 9, 10, and 12, overlapping across different samples (Bertram *et al.*, 2000; Blacker *et al.*, 2003; Ertekin-Taner *et al.*, 2000; Hamshere *et al.*, 2007; Kehoe *et al.*, 1999; Li *et al.*, 2002; Myers *et al.*, 2000; Pericak-Vance *et al.*, 2000). Furthermore, well over 1000 "candidate gene" studies—that is, studies that focus on certain genes based on some prior hypothesis regarding their potential involvement in the disease process—have been published over the past two decades claiming or refuting genetic association between putative AD genes and affection status and/or certain endophenotypes (Bertram *et al.*, 2007). Currently, nearly 150 AD genetic association papers are published each year, at increasing pace. However, with the exception of one genetic variant, the ε4-allele of the apolipoprotein E gene (*APOE*; Saunders *et al.*, 1993; Strittmatter *et al.*, 1993) none of these candidates has been proved to consistently influence disease risk or onset age in more than a handful of samples (Bertram and Tanzi, 2008). Instead, most studies of "novel AD genes" have been followed by a large number of conflicting reports, challenging prior claims that they may play an important role in contributing to disease risk. For geneticists as well as clinicians the growing number of (mostly conflicting) genetic association findings in AD has become increasingly difficult to follow, evaluate, and interpret.

II. Genome-Wide Association Studies in AD

An alternative to the traditional candidate gene approach is afforded by recent advances in large-scale genotyping technologies which now enable researchers to perform comprehensive and largely hypothesis-free genome-wide association studies (GWAS; Craddock *et al.*, 2008; McCarthy *et al.*, 2008). Four groups have reported the results of AD GWAS to date (Table I; Bertram *et al.*, 2008a; Coon *et al.*, 2007; Grupe *et al.*, 2007; Li *et al.*, 2008). The first (Grupe *et al.*, 2007) tested roughly 17,000 single nucleotide polymorphisms (SNPs) in or very near genetic coding regions ("cSNPs"). The only polymorphisms found to consistently associate with AD risk across the different samples were located in close proximity to *APOE*, and most likely reflect linkage disequilibrium (LD) with the ε4-allele. Although a number of additional loci were highlighted as potential AD genes by the authors, none showed the same consistency of effect or same level of statistical significance as the ε4-related variants. The second study (Coon *et al.*, 2007) tested ∼500,000 SNPs in roughly 1100 unrelated AD cases and controls.

TABLE I
OVERVIEW OF ALL PUBLISHED GWAS IN AD

GWA study	Design	Population	No. SNPs	No. AD cases (total)[a]	No. controls (total)[a]	"Featured" genes
Grupe *et al.* (2007)	Case-control	USA and UK	17,343	380 (1428)	396 (2062)	*APOE*, ACAN, BCR, CTSS, EBF3, GALP, GWA_14q32.13, GWA_7p15.2, LMNA, LOC651924, MYH13, PCK1, PGBD1, THEM5, TNK1, TRAK2, UBD*
Coon *et al.* (2007) and Reiman *et al.* (2007)	Case-control	USA, Netherlands	502,627	446 (861)	290 (550)	*APOE*, GAB2*
Li *et al.* (2008)	Case-control	Canada	469,438	753 (1071)	736 (985)	*APOE*, GOLM1, GWA_15q21.2, GWA_9p24.3*
Bertram (2008)	Family-based	USA	484,522	941 (2708)	404 (1242)	*APOE*, ATXN1, CD33, GWA_14q31,*

Modified after content on the AlzGene Web site (http://www.alzgene.org; current on October 31st, 2008). Studies are listed in order of publication date. "Featured Genes" are those genes/loci that were declared as "associated" in the original publication, note that criteria for declaring association may vary across studies.

[*] Indicates that surrogate markers were used for *APOE*.

[a]Numbers of "AD cases" and "controls" refer to sample sizes used in initial GWA screening, whereas "total" refers to initial sample plus any follow-up samples (where applicable); please consult AlzGene Web site for more details on these studies.

Again, with the exception of a single SNP in strong LD with *APOE*-ε4, no other genome-wide significant signals were observed. In a follow-up paper (Reiman *et al.*, 2007), the same group reported evidence of association with variants in the gene encoding GRB2-associated binding protein 2 (*GAB2*) on chromosome 11q14, which only became evident after their samples were stratified for *APOE*-ε4, that is, when AD cases and controls were divided into carriers and non-carriers of the ε4-allele. A third group (Li *et al.*, 2008) tested nearly ∼470,000 markers and reported association with variants in golgi membrane protein 1 (*GOLM1*) on chromosome 9q22 and two currently uncharacterized loci on chromosomes 9p and 15q. Finally, our own group (Bertram *et al.*, 2008a) recently reported the results of the first GWAS using family-based samples (∼1400 DNAs from over 400 families), as opposed the three previously summarized studies which were solely based on case-control datasets. Applying the same 500 K marker array as in Coon *et al.* (2007) and Li *et al.* (2008) we found—in addition to *APOE*-ε4—evidence for a number of potential AD loci (Table I). Although the findings from these first GWAS hold the promise of pinpointing novel pathways and mechanisms potentially important in AD pathogenesis, it will be important to await consistent replication by independent investigators.

While these and several of the forthcoming GWAS have the potential to significantly advance our understanding of the genetics and pathogenetic mechanisms of AD and other neurodegenerative disorders, it needs to be emphasized that in many ways genome-wide screens are actually not so different from conventional candidate gene association analyses. Both search for significantly different allele or genotype distributions or transmissions in subjects affected by the disease/phenotype as compared to presumably healthy individuals. The two approaches differ mostly on a *quantitative* level: instead of testing a few tens of markers (or less), GWAS simultaneously screen a few hundreds of thousands of markers (or more). The major *qualitative* difference between a GWAS and candidate gene analysis is that the former investigates the whole genome in a more or less unbiased fashion, whereas the latter only investigates a limited number of specific loci proved or thought to be involved in disease predisposition or progression (e.g., in AD many of these loci are involved in the production, trafficking, or removal of Aβ). On the downside and owing to their sheer number of polymorphisms tested, GWAS actually substantially compound the problem that has plagued genetic studies of complex phenotypes in the past, that is, to determine which of the many reported putative risk alleles are "real" as opposed to which merely reflect statistical artifacts. The first essential step in differentiating these two alternatives is to provide independent replication of the association (McCarthy *et al.*, 2008), just as for any result emerging from "old-fashioned" candidate gene analyses.

III. Systematic Field Synopsis and Meta-Analyses: The AlzGene Database

In an attempt to facilitate the interpretation of association findings regardless of the technology used for initial detection, we have recently created a publicly available database, "AlzGene" (http://www.alzgene.org), which systematically collects, summarizes and meta-analyzes all genetic association studies published in the field of AD, including GWAS (Bertram *et al.*, 2007). After thorough (and ongoing) searches of the available scientific literature, studies published in peer-reviewed journals that are available in English are included in the database. Key variables (such as ancestry, type of AD diagnosis, sample size, onset age, and genotype distributions) are extracted from the original publications. Furthermore, published genotype data from independent case-control samples are systematically meta-analyzed. Because this approach quantitatively synthesizes all of the published genotype data for each polymorphism, it facilitates the overall interpretation of association findings: rather than relying on the either "positive" (that is, statistically significant) or "negative" (that is, insignificant) outcomes of individual studies, it produces a summary risk estimate (called the odds ratio) that takes into consideration all data at once and accounts for within and between study variation.

Currently, AlzGene includes more than 1100 individual studies and showcases the results of over 200 individual meta-analyses. In these, more than 20 genes that are not related to the well-established *APOE*-ε4 allele show nominally significant risk effects (Table II). Interestingly, about one fourth of these were originally implicated by one of the four published GWAS, although independent replication by other groups is still lacking for most of these findings. As can be seen in Table II, the average allelic summary odds ratio (OR), for non-*APOE*-related effects are very modest (∼1.2 for "risk" alleles and ∼0.8 for "protective" alleles) compared to an OR of ∼3–4 for a single copy of the *APOE*-ε4 allele. These modest effect sizes are in good agreement with those found in other large-scale studies on the genetics of complex diseases (Allen *et al.*, 2008; Ioannidis *et al.*, 2001; Lohmueller *et al.*, 2003) and have important (and well known) implications for the design of future genetic association studies in AD, as sample sizes will need to be vastly increased to detect or exclude ORs of 1.25 or below with sufficient confidence. For instance, to detect an allelic OR of 1.25 with 80% power at a *P*-value of 0.05 sample sizes between ∼1400 and 6000 combined cases and controls are needed for disease allele frequencies ranging from 0.50 to 0.05, respectively (Bertram, 2008). Sample sizes need to be increased approximately fivefold to detect such modest effects with the same power at *P*-values below 5×10^{-8}, that is, one proposed threshold for declaring genome-wide significance (Hoggart *et al.*, 2008; McCarthy *et al.*, 2008).

TABLE II
ALZGENE "TOP RESULTS" (CURRENT ON OCTOBER 31ST, 2008)

Locus/Gene	Polymorphism	AlzGene OR (95% CI)[a]	*P*-value	No. AD	No. controls	No. Samples[b]	Ethnicity
APOE[c]	ε2/3/4	3.81 (3.38-4.29)	$<1 \times 10^{-30}$	2325	3574	23	CAU
CHRNB2	rs4845378	0.67 (0.50-0.90)	0.007	576	787	4	ALL
GAB2	rs10793294	0.69 (0.54-0.88)	0.0025	2073	1836	5	CAU
CH25H	rs13500	1.44 (1.08-1.93)	0.01	1549	1506	6	ALL
SORL1	SORL1-18ex26	0.70 (0.50-0.98)	0.04	743	913	3	CAU
CALHM1	rs2986017	1.42 (1.27-1.59)	1.2×10^{-9}	2043	1361	5	ALL
CST3	5′ UTR-157	1.28 (1.05-1.56)	0.02	804	571	3	CAU
ACE	rs1800764	0.79 (0.68-0.92)	0.002	818	747	4	CAU
PGBD1	rs3800324	1.25 (1.04-1.51)	0.02	2736	2964	6	ALL
MAPT/STH	rs2471738	1.24 (1.01-1.53)	0.04	1734	1411	6	ALL
SORCS1	rs600879	1.24 (1.04-1.48)	0.02	1361	1495	4	ALL
hCG2039140	rs1903908	1.23 (1.06-1.44)	0.007	1368	1497	4	ALL
TFAM	rs2306604	0.82 (0.72-0.94)	0.003	1059	792	5	ALL
IL1B	rs1143634	1.18 (1.03-1.34)	0.02	1011	1244	5	ALL
TF	rs1049296	1.18 (1.04-1.33)	0.01	1916	4058	9	ALL
TNK1	rs1554948	0.86 (0.80-0.93)	0.0002	2743	2984	6	ALL
LOC439999	rs498055	1.15 (1.03-1.29)	0.02	2787	2498	7	ALL
GAPDHS	rs4806173	0.87 (0.75-1.00)	0.05	1687	1775	4	ALL
DAPK1	rs4878104	0.88 (0.82-0.95)	0.002	2753	3036	7	ALL
PRNP	rs1799990	0.88 (0.81-0.96)	0.03	2280	2943	10	CAU
GWA_14q32.13	rs11622883	0.88 (0.80-0.97)	0.01	2685	2893	6	ALL
GALP	rs3745833	1.13 (1.00-1.29)	0.05	2739	2975	6	ALL

(*Continued*)

TABLE II (*Continued*)

Locus/Gene	Polymorphism	AlzGene OR (95% CI)[a]	*P*-value	No. AD	No. controls	No. Samples[b]	Ethnicity
LOC651924	rs6907175	0.89 (0.82-0.96)	0.005	2359	2522	6	ALL
NEDD9	rs760678	0.89 (0.81-0.97)	0.01	3452	3245	8	ALL
MTHFR	rs1801133	1.11 (1.02-1.21)	0.02	2887	4663	24	ALL
ENTPD7	rs911541	1.10 (1.01-1.21)	0.03	3429	3743	4	ALL
BDNF	rs6265	1.09 (1.02-1.18)	0.015	5299	4671	15	CAU
IL1A	rs1800587	1.09 (1.00-1.18)	0.04	5296	5321	25	ALL

List of loci, in descending order of genetic effect size, containing at least one polymorphism showing nominally significant (*P*-value ≤ 0.05) summary ORs in AlzGene on October 31st, 2008. To be considered as "Top Result," summary OR needs to be significant across samples from all ethnic backgrounds ("ALL") or in Caucasians only ("CAU"). Whenever nominally statistically-significant results are observed for both, that is, ALL and CAU, only the analysis that has the largest genetic effect size (OR deviating the most from 1) is reported here. Note that AlzGene is continuously updated, so results displayed online may differ from the results above; consult the AlzGene Web site for up-to-date numbers and additional meta-analyses in these and other loci (http://www.alzgene.org) (see also Table I).

[a]Summary ORs and 95% confidence intervals (CI) are based on random-effects allelic contrasts comparing minor versus major alleles at each polymorphism.,

[b]Number of samples refers to the number of independent case-control samples used in the meta-analyses; multiple samples may be reported in the same publication and are considered separately if they are independent, that is, non-overlapping. Samples overlapping across publications are only used once, usually by including the datasets with the largest number of available genotypes,

[c]Results are based on comparing $\varepsilon 4$- versus $\varepsilon 3$-alleles at this locus.

IV. Strengths and Limitations of the AlzGene Approach

The strengths of AlzGene are obvious: assuming that the literature searches, inclusion criteria, data management, and data analysis procedures actually provide a correct and exhaustive account of the available literature, AlzGene is the single most comprehensive resource for the status of genetics research in AD available to date. In our original data freeze (Bertram *et al.*, 2007) we could show that literature searches in AlzGene outperformed those of several other literature/genetics databases, and that the results of our meta-analyses were in very good agreement with estimates published previously in nearly two dozen individual papers. Similar observations were made in related database projects from our group (Allen *et al.*, 2008; Bagade *et al.*, 2006). Published meta-analyses, however, have one important disadvantage: by nature of their design, they run the risk of becoming outdated quickly, possibly as soon as new data from one or two additional studies are published. Provided that sufficient funding remains available, AlzGene does not have this caveat. Also, any meta-analysis in the database can be updated literally within days after the publication of novel data. Another strength of AlzGene is that it is not limited to meta-analyses on certain genes or networks of genes (e.g., those that are in the same pathway or gene family), but considers all published loci simultaneously, making the comparison of results across studies, genes, pathways, chromosomal regions, and so on extremely easy. Finally, as outlined above, all loci containing at least one polymorphism nominally significant by meta-analysis are separately highlighted on the database's homepage in a section called "Top Results." Thus, consulting this section of the AlzGene Web site will provide the user with a complete—and essentially real time—snapshot of the "most promising" AD candidate genes, based on the systematic evaluation of literally hundreds of individual studies and thousands of data points. As such, the "Top Results" list could help prioritize future genetic association studies (e.g., for further independent replication, or fine mapping), and guide functional genetics and molecular studies investigating the potential pathogenetic mechanisms underlying the genetic associations.

While AlzGene undoubtedly represents a leap forward in managing and displaying the data gathered within the domain of AD genetics research, its overall approach, too, comes with some strings attached. First and foremost, despite our comprehensive and systematic searches of the scientific literature, we cannot exclude the possibility that some AD association studies were overlooked or entered erroneously. This can be partly alleviated with the help of database users who are explicitly encouraged to alert the curatorial team of any errors or omissions, which will be fixed as soon as possible. Other limitations include our restriction to allele contrasts in the meta-analyses (which allows no inference of the true underlying mode of inheritance and is usually less powerful than genotype-based tests), the non-consideration of haplotype-based genotype data or

imputed single-locus genotypes (possibly missing important associations), the exclusive focus on "main effects" (and the inherent inability to account for gene-gene and gene-environment interactions), and the lack of adjustment for certain co-variates such as age or gender (which is impossible to do systematically without access to subject-level raw data). Further, protection from bias, in particular publication bias and other sorts of reporting biases, is particularly difficult to ensure or assess, and is likely to affect some of the meta-analysis results. Finally, the single most important caveat of the AlzGene approach is that the number of "true" associations is almost certainly going to be smaller than the number of nominally significant findings listed at any time on the AlzGene Web site (see also: Ioannidis, 2005; Wacholder *et al.*, 2004). This has a number of causes, including multiple testing, linkage disequilibrium among associated variants, undetected publication or other reporting biases, as well as study-level technical artifacts that may have gone unnoticed or may be impossible to detect. Furthermore, most of the "positive" meta-analysis outcomes currently do not reach very high levels of statistical significance (see Table II), only two attaining the threshold for genome-wide significance, for example, a *P*-value $\leq 5 \times 10^{-8}$. While this, too, could be due to a number of factors including small effect size and insufficient power even after combining all of the available data, it is important to emphasize that the possibility of a false-positive finding always exists, even for the highest ranked "Top Result." Eventually, genuine risk effects can only be "proved" by the accumulation of sufficient unbiased and high-quality genotype data (e.g., originating from case-control *and* family-based designs, see below) in favor of the presumed association in combination with functional genetics and biological evidence suggesting a direct biochemical effect of the associated variant (McCarthy *et al.*, 2008). Of course, such evidence can be difficult to come by. For instance, despite the unambiguous role of the *APOE-ε4* allele in increasing the risk for AD (see above), the precise mechanism underlying this association remains only poorly understood (Tanzi and Bertram, 2005). Notwithstanding these limitations, there is good reason to believe that the variants and loci highlighted in the "Top Results" section of AlzGene and related databases currently represent our best bets as to which of the hundreds of putative candidate genes might genuinely contribute to disease susceptibility and pathogenesis. As such, they probably warrant follow-up with high priority.

V. Assessment of Case-Control Associations Using Family-Based Methods

A first round of genetic follow-up of the most promising of these associations was recently completed in a number of projects from our group (Bertram *et al.*, 2008b; Schjeide *et al.*, 2009a,b). In particular, we assessed whether or not any of the AlzGene "Top Results" and/or any of the loci pinpointed by the two

high-density case-control GWAS (Li *et al.*, 2008; Reiman *et al.*, 2007) showed association in a total of four family-based datasets comprising nearly 4200 DNAs from over 1300 independent AD families. This was an important question as many of the investigated variants had been thoroughly tested across relatively large numbers of independent case-control datasets, but only a handful were also previously assessed in family-based samples, which may be genetically different from unrelated, population-based cases and controls. Family-based methods have the additional advantage of being robust against bias due to undetected population stratification and phenotype misspecifications (Laird and Lange, 2006), which may have affected some of the case-control meta-analysis results. After combining the results across all four datasets, we observed nominally significant association with variants in *ACE*, *CHRNB2*, *GAB2*, *TF*, and an as yet unidentified locus on chromosome 7p15.2 (Table III). Two of these loci, that is, *ACE* and *TF*, were also found to be associated with Aβ levels in CSF in an independent collection of AD cases and controls (Kauwe *et al.*, 2009). The independent convergence of (i) significant meta-analysis results across case-control samples, (ii) replication of these associations in AD family samples, and (iii) in the case of *ACE* and *TF*, a significant genotype-dependent correlation with one of the few established biomarkers in AD, strongly implies a genuine disease-risk modifying role of these loci, arguably more so than for any of the other hundreds of suggested AD candidate genes besides *APOE*.

Functionally, all of these potential new AD susceptibility loci are interesting and, if confirmed, may not only lead to a better understanding of the pathogenetic mechanisms driving neurodegeneration, but may also help to pinpoint novel treatment options for AD. *ACE* encodes angiotensin converting enzyme-1 (ACE-1), a ubiquitously expressed zinc metalloprotease that is involved in blood pressure regulation. Several epidemiological studies suggest that high mid-life blood pressure may increase the risk for AD in later life (Takeda *et al.*, 2008). More recently, ACE-1 activity has been reported to be increased in AD brains proportionately to parenchymal Aβ load (Miners *et al.*, 2008). The interpretation of ACE's role in AD pathogenesis is complicated by the observation that it is able to degrade naturally secreted Aβ *in vitro* (Hu *et al.*, 2001), which would predict an increased risk in individuals with reduced ACE-1 levels/activity, that is, opposite to what would be expected from the epidemiological data and the genetic association results. *CHRNB2* encodes the neuronal beta-2 nicotinic cholinergic receptor (β2nAChR). Nicotinic acetylcholine receptors (nACcRs) are widely expressed in the CNS, where the β2nAChR subunit is particularly abundant, forming hetero-pentameric receptors with β4nAChR subunits ($\alpha4\beta2$; Kalamida *et al.*, 2007). Pathologically, the reduction of nAChRs and the loss of cholinergic neurons in disease-relevant brain regions is one of the major neurochemical hallmarks of AD (Oddo and LaFerla, 2006), and several studies have suggested that an age-dependent decrease in protein and/or mRNA levels of the $\alpha4\beta2$-subtype (in particular β2nAChR) occurs in the cortex and hippocampus of healthy

TABLE III
ASSESSMENT OF CASE-CONTROL ASSOCIATIONS IN AD FAMILY DATASETS

				Case-control (AlzGene)		Family based (combined family datasets)			
Gene	SNP	Ethnicity	Model	OR (95% CI)	P-value	No. Fams	OR	χ^2	*P*-value[a]
ACE	rs4291	CAU	T vs. A	0.87 (0.76-0.99)	0.03	425	0.94	14.6	0.07
CHRNB2	rs4845378	ALL	T vs. G	0.67 (0.50-0.90)	0.007	170	0.79	17.4	0.03
GAB2	rs7101429	CAU	G vs. A	0.74 (0.59-0.93)	0.008	432	0.76	24.4	0.002
GWA_7p15.2	rs1859849	ALL	C vs. T	1.11 (0.97-1.29)	0.1	335	1.26	17.5	0.03
TF	rs104296	ALL	C2 vs. C1	1.18 (1.04-1.33)	0.01	295	1.17	21.1	0.007

Comparison of the association evidence of AlzGene "Top Results" (current on October 31, 2008) and family-based analyses (Schjeide *et al.*, 2009a,b). Note that the meta-analyses for rs1859849 in GWA_7p15.2 are currently only marginally significant (*P*-value 0.1), but were nominally significant at the time of genotyping in the Schjeide *et al.* (2009a) project. For up-to-date meta-analysis results on these variants, please consult the AlzGene Web site (http://www.alzgene.org). ALL = combining samples of all ethnic groups; CAU = combining samples of Caucasian ethnicity only; No. Fams = No. informative families; "OR" = summary odds ratio; "95% CI" = 95% confidence intervals.

[a]Test statistics are based on combining one-tailed *P*-values for each variant across all four samples using Fisher's combined probability test, which results in an 8 d.f. test. Single-locus analyses with variants in *ACE* only show marginally significant effects (*P*-value 0.07), while haplotype-based analyses yielded *P*-values <0.05 (see Schjeide *et al.*(2009a) for more details).

individuals (Tohgi *et al.*, 1998), which could be exacerbated in carriers of the AD risk allele. *GAB2* encodes GRB2-associated binding protein 2 (Gab2) which is a member of a family of evolutionarily highly conserved scaffolding/adapter proteins that are involved in multiple signaling pathways, and in particular in the transduction of cytokine and growth receptor signaling (Liu and Rohrschneider, 2002; Sarmay *et al.*, 2006). Gab2 is ubiquitously expressed, but is found at particularly high levels in white blood cells, prefrontal cortex, and hypothalamus. It was suggested that changes in Gab2 expression could potentially affect Gsk3-dependent phosphorylation of tau and the formation of neurofibrillary tangles (Reiman *et al.*, 2007). Moreover, growth factor receptor-bound protein 2, which binds Gab2, has been reported to bind both tau (Reynolds *et al.*, 2008), APP, and presenilin 1 and 2 (Nizzari *et al.*, 2007), and these interactions have been proposed to regulate signal transduction. *TF* encodes transferrin which is the major circulating glycoprotein involved in iron metabolism and is highly expressed in the brain. There is a vast body of literature suggesting that iron dysregulation promotes neurodegeneration, possibly via the generation of reactive oxygen species (Brewer, 2007). In AD, iron has been found to be increased in the brains of AD patients (Loeffler *et al.*, 1995), where it is associated with plaques and NFTs (Smith *et al.*, 1997). More recently, it was suggested that iron may also play a role in the aggregation of hyperphosphorylated tau into insoluble paired helical filaments, one of the core ingredients of NFTs (Yamamoto *et al.*, 2002). Thus it is conceivable, although not yet experimentally proved, that the AD-associated amino acid changing variant in *TF* (Pro570Ser) may interfere with all or some of these roles in AD pathogenesis. Finally, the *chromosome 7p15.2* association signal maps close to a predicted gene, NT_007819.514, encoding a protein of 358 residues, whose N-terminus exhibits a strong homology to a family of ubiquitin-like proteins, for example, human ubiquitin C. Thus, the predicted protein possibly plays a role in protein degradation.

Figure 1 summarizes the potential pathogenetic implications of these and several other of the currently most compelling AD susceptibility genes. Note that this summary represents only a snapshot of the presently available data, and that the set of genes thought to be involved in predisposing for LOAD today is likely going to change over time. For a more detailed review on the functional implications of these and other compelling AD candidate genes see Bertram and Tanzi (2008).

VI. Conclusions

Despite intensifying efforts to unravel the genetic underpinnings of AD, successes to date have been modest. This situation is expected to change dramatically with the advent of novel, genome-wide analysis tools that are becoming increasingly

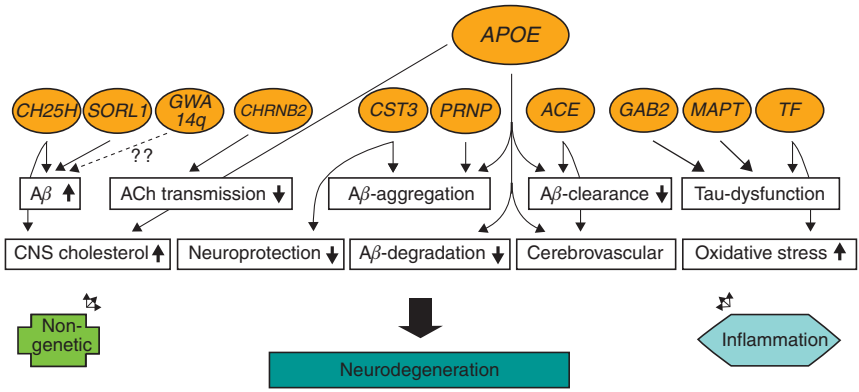

FIG. 1. *Potential pathogenetic roles of AD susceptibility genes.* Simplified summary of the potential pathophysiologic implications of the currently most promising AD susceptibility loci, including those of recent GWAS. Note that none of the genetic associations (except *APOE*) can be considered unequivocally established; the same is true for any of the proposed potential functional implications. Highlighted effects are likely further influenced by currently unknown gene-gene interactions and the contribution of nongenetic factors as well as inflammatory reactions (which themselves are likely genetically controlled). For didactic purposes, not all presumed or established functional implications have been indicated, for example, *GAB2's* role on APP metabolism via binding of Grb2. GWA 14q indicates GWAS locus identified by Bertram *et al.* (2008a). For a more detailed discussion of the potential role of these and other AD candidate genes see Bertram and Tanzi (2008).

popular, but it remains to be seen whether GWAS will live up to these expectations. In the interim, systematic bioinformatics approaches synthesizing the results from both candidate gene and genome-wide analyses will help researchers to keep track of the myriad of genetic association findings to come. One such approach, the AlzGene database, is now available, and already highlights a number of promising AD loci by means of systematic, unbiased meta-analysis.

As should be clear from the above discussion, AlzGene does not aim to deliver the *last* piece in the puzzle that AD genetic epidemiology research is trying to solve. Rather, it attempts to provide a tool that can help researchers of many disciplines decide which piece of the puzzle to try *next*. In the best case scenario, it will also help to sharpen the overall picture of the genetic forces driving AD predisposition and pathogenesis. Eventually, only the concerted efforts of genetics, genomics, proteomics, and clinical disciplines will give rise to new diagnostic and therapeutic targets that, hopefully in the not too distant future, will benefit the millions of patients afflicted with this devastating disorder.

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FRONTOTEMPORAL LOBAR DEGENERATION: INSIGHTS FROM NEUROPSYCHOLOGY AND NEUROIMAGING

Andrea C. Bozoki and Muhammad U. Farooq

Department of Neurology, Michigan State University, East Lansing, Michigan, 48824, USA

Frontotemporal lobar degeneration (FTLD) is a diagnostic term that encompasses three distinctly different syndromes, united by historic as well as pathologic commonalities. We briefly review the origins of the current classification scheme for diagnosing the three major subtypes—frontotemporal dementia, semantic dementia, and primary progressive aphasia, highlighting the differences between subtypes as well as from Alzheimer's disease (AD). We briefly examine current understanding regarding the histopathology and genetics of FTLD but note that there is a poor correspondence of these features with specific subtypes of FTLD. For clinicians and clinical researchers, this implicates the need for other diagnostic strategies. Neuropsychological and neurobehavioral testing currently offers the most sensitive and specific method for identifying subtypes, and discriminating FTLD from other forms of dementia. Multiple studies from the relevant literature

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are reviewed, highlighting those findings that are likely to be most valuable to physicians. Finally, we analyze some of the major findings from the large body of work on neuroimaging of FTLD, again focusing on those studies that potentially help discriminate FTLD subtypes or assist with the discrimination of FTLD from AD.

I. Introduction

Frontotemporal dementia used to be considered a rare disorder-one almost never seen by the average clinician. The typical patient with "Pick's disease" (PD) as it was known synonymously was about 65 years old, socially inappropriate, frequently hyperoral and became progressively more demented over a period of 5-7 years before dying.

In 1882, Arnold Pick described the clinical features of a patient with circumscribed lobar atrophy with an aphasic dementia. His initial cases had only gross examination without any histological data. The clinical pattern and its relation to focal atrophy were the basis of the syndrome. In 1911, Alzheimer described the now-characteristic hallmark inclusion bodies, called Pick's bodies. Other histological findings such as ballooned achromatic neurons (Pick cells), gliosis, and superficial cortical spongiform changes were also identified in these patients. These histopathological findings were associated with the circumscribed frontal and anterior temporal atrophy which Pick described in 1882, and the clinical syndrome came to be known as Pick's disease.

We have come a long way from these early findings. We now know that Pick's initial patients belong to a group of related dementias. The preferred term for this rather heterogeneous group is frontotemporal lobar degeneration (FTLD), and it is believed to be the second most common type of dementia in individuals younger than 65 years (Ratnavalli *et al.*, 2002). It remains clinically under-recognized both due to its frequent misdiagnosis as psychiatric disease or Alzheimer's disease (AD), as well as limited recognition of the different entities within the FTLD spectrum. Overall, estimated prevalence ranges from 6 to 12% of dementias (Kertesz, 2006).

Currently, FTLD is divided into three main subgroups; frontotemporal degeneration (FTD), primary progressive aphasia (PPA) (also referred to as progressive nonfluent aphasia; PNFA), and semantic dementia (SD) (Neary *et al.*, 1998). Each subtype of FTLD has distinguishing features and characteristic progression that help to distinguish it from "garden variety" AD. In addition, both neuropsychological testing and neuroimaging have extended the clinician's ability to distinguish FTLD from AD as well as other related dementias.

A. Diagnosis of FTLD

Clinically and pathologically, FTLD is distinct from AD, although the distinction is sometimes clinically challenging (Klatka *et al.*, 1996; Mendez *et al.*, 1993). A proportion of patients who meet the criteria for AD have FTLD confirmed at autopsy, occasionally co-occurring with AD pathology. A recent pathologic study examining the overlap of FTLD and AD clinical phenotypes described coexisting histopathological AD in almost one fourth of FTLD cases (Liscic *et al.*, 2007). Autopsy-proved FTLD cases, alone or in combination with AD, can meet the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) clinical criteria for AD during life (McKhann *et al.*, 1984; Snowden *et al.*, 2001), suggesting a lack of specificity in the criteria for both diseases. Despite these concerns (or perhaps because of them), several groups have put forward criteria for the clinical diagnosis of FTLD. The sophistication of these classifications and rating scales for FTLD has evolved since the 1980s.

B. Clinical Criteria

Gustafson and Nilsson (1982) studied 57 patients for differential diagnosis between dementias. They used three rating scales for identification of Alzheimer's disease, Pick's disease, and multi-infarct dementia. The rating scale for PD contained nine items, including assessment of early loss of insight, early signs of disinhibition, echolalia, mutism, and amimia.

Lund-Manchester groups (1994) published criteria in 1994 which required the presence of at least two of the following features: loss of personal awareness, strange eating habits, perseveration, and mood change. In addition, patients had to have one or more of the following: frontal executive dysfunction, reduced speech, and preserved visuospatial ability. Finally, the authors of the criteria cited several important supporting features, including onset before age 65, a family history of FTD, early urinary incontinence, motor neuron disease, and (in the late stages) akinesia, rigidity, and tremor.

Neary and colleagues (Neary et al., 1998) incorporated most of the above features and added some others. However, the authors subdivided patients into three separate clinical presentations: frontotemporal dementia (characterized primarily by personality change and disordered social conduct), PNFA (in which patients have difficulty with initiation but not comprehension of speech; see Section II.B), and semantic aphasia (distinguished by impaired understanding of word meaning and/or object identity). The general term FTLD was used to refer to any of the three syndromes.

ECAPD Consortium, 1998. The European Concerted Action on Pick's disease (ECAPD) was based on the review of 50 cases of pathologically verified disease for which adequate clinical, neuropsychological, and neuroimaging data were available. This resulted in the definition of provisional criteria for definite, clinically probable and clinically possible Pick's disease which emphasized the importance of impairment of language and praxic skills.

The Work Group on Frontotemporal Dementia and Pick's Disease (McKhann et al., 2001). An international group of clinical and basic scientists developed these consensus criteria in July 2000. Intended for clinicians rather than researches, these criteria were considerably simpler than the Neary criteria and lumped together all patients under the terminology of FTD, although the authors did note that patients would have either a "behavioral presentation" or a "language presentation."

C. Histopathology

Originally, Pick's disease was classified pathologically as type A (with Pick's bodies), type B (with only swollen neurons), and type C (with only gliosis) (Constantinidis *et al.*, 1974). However, in common usage, Pick's disease referred to patients with atrophy and disinhibition and Pick's bodies on histopathology. It resulted in the impression that Pick's disease was a rare entity and difficult to diagnose before autopsy. Later, it was found that patients with lobar atrophy only rarely have Pick's bodies and often do not show the typical histologic picture on autopsy (Constantinidis *et al.*, 1974). Therefore, the term FTLD came into use and a new label was given to clinical Pick's disease; those cases without the typical histologic picture were called frontal lobe degeneration (FLD) (Gustafson, 1987; Neary *et al.*, 1988). A similar clinical picture was described under the label of "dementia lacking distinctive histology" (DLDH) (Knopman *et al.*, 1990).

There are a few histological features including neuronal loss, gliosis, and superficial linear spongiosis, which are common to all histological subtypes of FTLD. Pick cells occur with variable frequency in all variants. These are called ballooned neurons because of their swollen appearance under light microscopy. These cells show neuronal achromasia and express phosphorylated neurofilaments. Spongiform changes are seen in layers II and III of the cortex. Various distinct features such as Pick's bodies, astrocyte plaques (common in Corticobasal Degeneration), tufted astrocytes (common in Progressive Supranuclear Palsy), and ubiquitin-positive tau-negative inclusions (common in Amyotrophic Lateral Sclerosis) known as motor neuron disease type inclusions or MNDI, have been described but can also occur with each of the FTLD variants and are non-specific. However, MNDI are found in more than half of the FTD cases on autopsy and

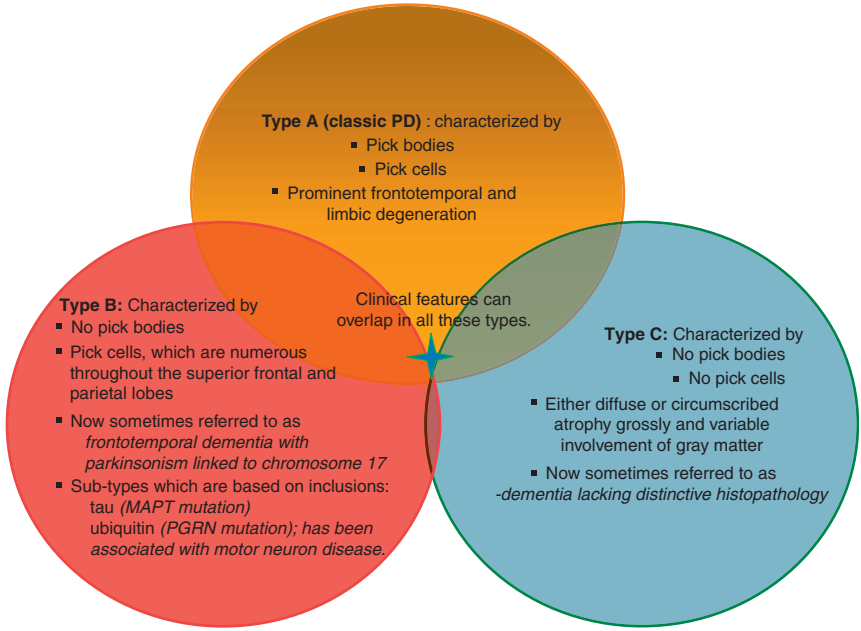

FIG. 1. Classification of Pick's disease based on histopathologic features. It is important to note that all three major clinical phenotypes have been documented with each of the pathologic subtypes.

now form the largest single pathological variety of Pick's complex (Hodges *et al.*, 2004; Kertesz *et al.*, 2005; Munoz *et al.*, 2003) (Fig. 1).

D. GENETICS

FTLD is a "presenile" dementia with a strong genetic component (Chow *et al.*, 1999; Stevens *et al.*, 1998). The first genetic correspondence, a linkage to chromosome 17 q21-22, was discovered in a large family with variable symptomatology of frontotemporal dementia, aphasia, parkinsonism, and amyotrophy (Wilhelmsen *et al.*, 1994). Later, the clinical features and pathology of 12 families resembling sporadic cases were described and the term "dominant inherited chromosomal 17-linked frontotemporal dementia with Parkinsonism" (FTDP-17) was accepted as a definite entity in a consensus conference (Foster *et al.*, 1997). The tau protein was suspected as the candidate gene for mutation and several tau mutations have been identified since then which occur only in familial cases (Hutton *et al.*, 1998). However, tau-positive pathology is not the only substrate of the disease, as the ubiquinated MNDI patients demonstrate (Hodges *et al.*,

2004; Jackson *et al.*, 1996). The phenotypic and pathologic variations of these mutations closely match sporadic disease and provide strong evidence for the cohesion of Pick's complex.

Like histopathology, genetic testing is also not specific for the subtypes of FTLD, with significant syndromic overlap within single mutation types. Tau protein mutations were first reported for the phenotypes of the FTDP-17 complex, which varied widely (some patients with parkinsonism, some with prominent aphasia, some with obvious amyotrophy. Several tau mutations have been discovered so far (Clark *et al.*, 1998; Hutton *et al.*, 1998; Spillantini *et al.*, 1998). Different tau mutations differently alter the biochemical properties of tau isoforms, but so far these mutations do not predict the clinical presentation. In addition, the tau protein is not abnormal in all forms of FTLD. The amount of hyperphosphorylated tau in FTLD can be low and sometimes even absent.

II. Classification of FTLD Subtypes and Their Features

A. Frontotemporal Degeneration

FTD is the most common diagnostic subgroup of FTLD; over half of FTLD patients fall in this category (Hodges *et al.*, 2003). FTD also has the earliest age at onset, often between 55 and 65, and almost never after age 75 (Johnson *et al.*, 2005; Rosso *et al.*, 2003). FTD is characterized by personality and behavioral changes. The initial manifestations can be subtle and difficult to diagnose beginning with apathy and disinterest which is often misdiagnosed as depression (Kertesz, 2003). These patients later develop lack of insight and disinhibition, impulsive and inappropriate behavior, poor financial judgment, changes in *libido* and inappropriate sexual behavior, blunting of appropriate behavioral response and at the extreme, self-destructive behavior (McKhann *et al.*, 2001). Their dietary habits may change, resulting in overeating or eating of only certain types of food. The overall appearance and personal hygiene of these patients is frequently affected as they show little personal concern for their actions. These patients can have problems with their memory, and formal memory testing can be abnormal, but they can track day-to-day events and do not have a typical amnestic syndrome (McKhann *et al.*, 2001). Frontal lobe functions are impaired in these patients but some can continue to perform well on formal measures of frontal tasks early in the disease course. Orientation and episodic memory is also relatively preserved; problems of forgetfulness are mainly due to inattention and poor organization of incoming information (Kertesz, 2003). Language is not affected early in the course of this disease; however, most patients eventually develop decreased verbal output and often progress to mutism in later stages (Kertesz, 2003).

B. Primary Progressive Aphasia or Progressive Nonfluent Aphasia

The term PPA was first used by Mesulam (1982) to describe a group of six patients who developed a slowly progressive aphasic disorder that "began in the presenium" (before age 65). These patients present with language difficulty characterized by a combination of word finding difficulties, abnormal speech patterns, decreased comprehension, and impaired spelling. In the early part of the disease these patients are able to perform their daily activities and have normal memory and visuospatial function. Mesulam's original description stressed the lack of a generalized dementia, and his criteria eventually included a stipulation that the patient's language difficulties should remain the only feature for at least 2 years before more generalized deficits develop (Weintraub *et al.*, 1990). Language deficits ultimately progress to mutism, however, these patients instead of developing a severe dementia in the advanced stages of their disease may have relatively preserved memory and can function well in the community, further helping to distinguish them from patients with AD (Kertesz, 2003). While the typical PPA patient does not have florid psychiatric features the way many FTD patients do, some can develop the behavioral problems seen in patients with other forms of FTLD in the later part of the disease and the distinction may become difficult in advanced cases, when both mutism and inappropriate behavior are seen.

C. Semantic Dementia

Snowden *et al.* described a distinct, fluent form of PPA that is different from the more common nonfluent type and called this semantic dementia (Snowden *et al.*, 1989). In this condition patients slowly and progressively lose the meaning of words; however, fluency remains intact and they are able to carry on a (somewhat empty) conversation. They have difficulty naming and comprehending even single nouns (Hodges *et al.*, 1992; Kertesz, 2003). These patients differ from the fluent aphasia of AD as they have relatively preserved episodic and autobiographical memory with a rather selective loss of semantic memory. These patients retain information that has immediate relevance to their environment or to their person; however, they lose the meanings of other common things. Some of these patients have visual agnosia (Kertesz, 2003). Patients with SD ultimately become nonfluent and even mute. They also develop behavioral problems in the later part of their disease.

We note that some authors categorize PPA and SD together as the language and aphasic variant of FTLD. In this nosologic schema, FTD represents the frontal variant of FTLD and PPA/SD together represent the temporal/parietal variant (Kertesz, 2003).

In addition, there is controversy regarding the separate existence of a fluent form of PPA distinct from both the more common dysfluent PPA and SD (Adlam *et al.*, 2006). In this schema, PPA is thought to present in both fluent and nonfluent forms. Some patients who meet the criteria for fluent PPA show nonverbal and verbal deficits in conceptual knowledge and other tasks that depend upon such knowledge, provided that the measures used allow for the vital impact of concept and typicality. If more emphasis is placed on the prominent language disorder, these individuals can be classified as fluent PPA; if more emphasis is placed on the multimodal pattern of deficits, these individuals can be seen as having SD.

III. Neuropsychological Assessment

A. Distinguishing FTLD from AD

1. *Comments Regarding the MMSE and FTLD*

Although neuropsychologists typically disdain the Folstein Mini Mental State Exam (MMSE; Folstein *et al.*, 1975) as being far too cursory to be useful, it is commonly used by clinicians as a screening tool for the presence of dementia and therefore worthy of comment in this chapter. The MMSE is heavily weighted toward verbal skills and gives relatively short shrift to executive processing. As such, compared with AD, it may underestimate dementia severity for FTD and overestimate it for PPA/SD. Clinicians are especially cautioned not to consider a normal-range MMSE score in a patient with suspected FTD as indicating the absence of disease. A recent study (Osher *et al.*, 2007) which compared FTD and PPA (but did not include AD), found that MMSE scores over time did correlate with changes on a measure of activities of daily living (the Activities of Daily Living Questionnaire or ADL-Q; Johnson *et al.*, 2004). However, PPA patients showed relatively greater declines, suggesting that the MMSE overestimates dementia severity for PPA patients but that the score may accurately measure functional impairment in FTD (Fig. 2).

2. *FTD*

Attempts to distinguish FTD from AD based only on neuropsychological testing have a long and controversial history. Numerous papers on this topic, spanning several decades, have failed to agree on whether it is possible to do this reliably. One group (Gregory *et al.*, 1997) failed to find differences between patient groups in memory, attention, language, and executive abilities, while another (Pasquier *et al.*, 1995) did not find any difference in letter and category verbal fluency (a frequently used bedside test for evaluating frontal lobe function).

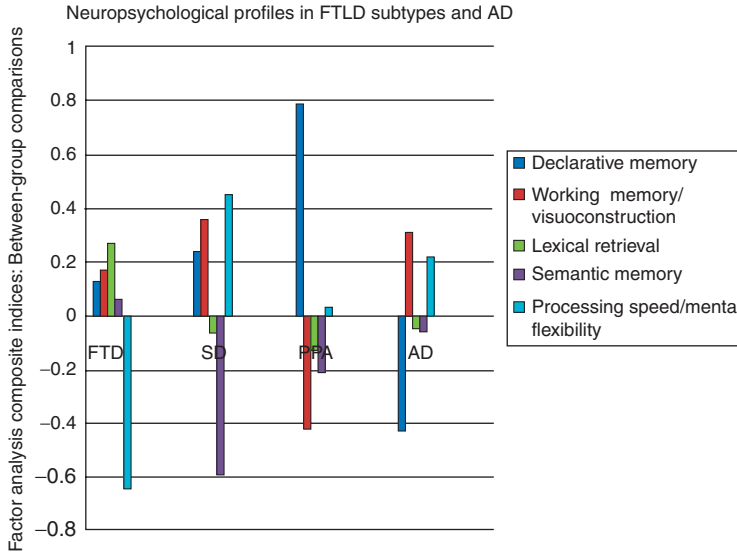

FIG. 2. Factor analysis of a multitest neuropsychological battery demonstrated five major cognitive factors. Between- and within-group analyses of the factors demonstrate that each patient group is associated with a specific profile of neuropsychological impairment, in which each group is significantly worse than the others on at least one factor (data from Libon *et al.*, 2007).

Conversely, several more recent studies have found the opposite; that a double dissociation between AD and FTD exists and can be identified with careful neuropsychological assessment. Perri and colleagues (2005) performed a stepwise discriminant analysis on a number of neuropsychometric variables and determined that subjects with AD were significantly worse on the Rey figure copy (a measure of visuospatial praxis) and significantly better on letter fluency than the FTD group, such that a combination of these two tests plus a measure of apathy (see Section IV) was sufficient to distinguish the two diseases with approximately 83% sensitivity and 82% specificity.

Also in 2005, a group from the UK (Thompson *et al.*, 2005), observing that patients with FTD tend to make different types of mistakes from those with AD, developed a way to assess qualitative performance and error types on their neuropsychometric battery. They found that "FTD patients displayed features associated with frontal lobe dysfunction, such as concrete thought, perseveration, confabulation, and poor organization, which disrupted performance across the range of neuropsychological tests." They advise that keeping track of the *types* and not just the number of errors made in performing neuropsychological tests can greatly enhance discrimination of these patient populations.

Nonetheless, while this chapter finds that FTD and AD can be discriminated neuropsychologically, they agree with the findings of the first two studies cited, that actual scores did not differ significantly between groups, especially on the classic tests of executive functioning. They attribute this to the idea that AD patients are failing at executive tasks "for non-frontal reasons." That is, executive tasks are complex and actually make demands on multiple cognitive domains (particularly memory and visuospatial abilities) that are weak in AD.

This is similar to the findings from the most recent group to weigh in on the matter. This year, a relatively large study (40 FTD, 77 AD, and 91 normal controls) (Giovagnoli *et al.*, 2008) was unable to find a significant difference between the patient groups with regard to executive functions. In this study, the AD patients were significantly more impaired than the FTD group in episodic memory, selective attention, visual perception, visuomotor coordination, and constructive praxis, whereas no differences were found in executive, intellective, and linguistic abilities between the two patient groups. Logistic regression analyses revealed that episodic memory significantly predicted the diagnosis of AD while no executive deficit was able to predict the diagnosis of FTD. The authors hypothesize that this may be due to a more widespread distribution of executive functions in the brain than is currently acknowledged, with other brain regions providing an extended network of functions that are interrelated with prefrontal cortex.

Another reason for the failure of some groups to find differences between FTD and AD may be that not all studies distinguished between FTD and SD in their samples; that is, they included both types of patients in their testing. Because FTD and SD overlap with AD deficits in very different ways, the net effect may have been to "cancel out" the differences between groups. This is the hypothesis of a study which in fact did find a double dissociation between AD, FTD and SD groups in their study (Perry and Hodges, 2000).

3. *PPA*

In contrast to the relatively difficult AD-FTD distinction neuropsychologically, distinguishing between AD and PPA is more straightforward. PPA patients maintain relatively normal episodic memory function—the hallmark decline of early AD, while developing progressively worsening language impairments. The original report on this clinical syndrome was published in 1982 by Mesulam, who reported on six patients with progressively worsening language impairment in the absence of dementia (Mesulam, 1982). Some years later, his lab published a follow-up study (Weintraub *et al.*, 1990) further characterizing three patients with sequential neuropsychological assessments. They demonstrated progressively worsening decline on measures such as the Token Test, sentence repetition and the Boston Naming test. Importantly, cognition was stable over time on measures such as spatial and temporal orientation, design recall, line orientation, and face

recognition. Another report on the longitudinal neuropsychological profile of PPA (Grossman *et al.*, 1996) concurred with the original description; they too found that individuals became progressively less fluent, naming and repetition declining over several years. Ultimately, their patients became mute. Grossman hypothesizes that the critical feature of PPA appears to be a grammatical impairment which interferes with speech production. This distinguishes them from SD, in whom speech may also appear nonfluent at times owing to word-finding pauses, as well as those with FTD who may have a paucity of speech output due to abulia or apathy.

4. *SD*

In 1975, Elizabeth Warrington described three patients with a combination of visual associative agnosia (difficulty recognizing objects based on their visual features), anomia, and impaired comprehension of word meaning (Warrington, 1975). The diagnostic term "Semantic Dementia" was coined by Snowden and colleagues, in their description of a different three patients in whom they found not only a progressive *fluent* aphasia (in contradistinction to the slowed, agrammatic and effortful speech characteristic of PPA), but also deficits in word comprehension and in knowledge of objects and people (Snowden *et al.*, 1989). That is, spontaneous speech is characterized by anomia in the context of relatively normal phonology and grammar. As the disease progresses, patients will more and more replace specific terms with more nondescript words such as "thing" or "that."

Neuropsychologically, the hallmark of SD is an associative agnosia and/or prosopagnosia (inability to recognize faces), coupled with a "loss of memory for words" which is quite different from the impairment of episodic memory seen in early AD. In addition, orientation to time and place, simple calculation and drawing skills are all preserved in SD. In the study by Perry *et al.* cited above, subjects with SD showed severe deficits in semantic memory (Pyramid Palm trees and the Graded Naming test) with preservation of attention and executive function, while the AD subjects had very little trouble on those same semantic memory tasks but were grossly impaired in episodic memory, as measured by the logical memory portion of the Wechsler Memory Scale-R and the Rey figure recall.

A final point of distinction between SD and AD regards the temporal gradient of their amnesia. In general, SD patients do not have a significant impairment of episodic or recent memory, but several authors have found that autobiographical memory for remote events can be significantly impaired in SD (Hou *et al.*, 2005; Nestor *et al.*, 2002). This is distinct from the relatively intact remote memories of most early AD patients, and speaks to the presumed extrahippocampal localization of the damage in SD. Overall, the consensus opinion seems to be that, like PPA, the neuropsychological profile of SD is sufficiently different from that of AD to make discrimination relatively straightforward on this basis alone.

B. Distinguishing FTLD Subtypes

Given how tricky it is to distinguish FTD from AD on the basis of neuropsychological testing alone, one might expect that the distinctions among the thee phenotypes of FTLD would be nearly impossible, yet this turns out not to be the case. The entities are sufficiently dissimilar to one another that it turns out to be more straightforward to tell them apart than to distinguish them from other dementias (i.e., AD or vascular dementia).

1. *FTD vs PPA*

In contrast to the relatively small distinction between executive processing deficits in AD vs FTD, those between FTD and PPA are considerable, as patients with PPA have essentially normal executive processing ability. PPA also seems to have more intact episodic memory function than FTD (Libon *et al.*, 2007), which is somewhat surprising because early FTD is not generally acknowledged to have significant declines in episodic memory function. Quite recently, Marra *et al.* published a study comparing both neuropsychological and neurobehavioral characteristics of 22 FTD and 10 PPA patients (Marra *et al.*, 2007). The latter results are given in Section IV. Their findings on the neuropsychological profiles corroborate the Libon *et al.* group's documentation of better (normal-range) scores on immediate and delayed recall measures and executive processing. In turn, their group of FTD patients did significantly better on letter fluency. Surprisingly, the two groups were about nearly equal on a test of category fluency (both groups performed poorly).

2. *FTD vs SD*

In addition to being dramatically worse on tasks that hinge on semantic knowledge, SD patients are also clearly worse than FTD patients on naming and other language-based tasks. An early study comparing FTD and SD (Hodges *et al.*, 1999) found that patients with SD were significantly worse on a category-fluency task, while being quite closely matched on the letter-fluency version of that task. The study by Libon *et al.* (2007) replicated this finding. In a related study, subjects with SD showed severe deficits in semantic memory with preservation of attention and executive function. Subjects with FTD showed the reverse pattern. The double dissociation in performance on semantic memory and attention/executive function clearly separated the temporal and frontal variants of FTD (Perry and Hodges, 2000).

3. *SD vs PPA*

The overarching difference between these two dementias neuorpsychologically is the difference between a pure speech/language impairment (PPA) and a relatively pan-modal agnosia (SD) which includes (but is not limited to)

language-based expression. In a recent review article on the distinctions between SD and PPA, Hodges and Patterson write the following: In SD, repetition is almost invariably perfect, but the definitions offered are either generalized and lacking in detail (e.g., "Hippopotamus, can you say that?," "Yeah, hippopotamus," "What is a hippopotamus?," "A big animal") or simply absent ("I think I've heard of a hippopotamus but I can't say what it is"). Patients with PPA typically show the opposite pattern (i.e., an advantage for defining over repeating these long words) (Hodges and Patterson, 2007).

In addition, and somewhat surprisingly, surface dyslexia (selective difficulty in reading words that have irregular pronunciation, such as "colonel" or "chamois") seems to be much more characteristic of SD than PPA. While both types of patients have difficulty with all verbal fluency tasks, PPA patients are comparatively worse at letter fluency than SD patients, while being indistinguishable from them on category-fluency (Libon *et al.*, 2007).

IV. Neurobehavioral Assessment

A. FTD

By far the most challenging of the FTLD subtypes to care for is the individual with FTD, also known as behavioral-variant FTD. This is due not to the cognitive impairment that develops, but to the challenging set of aberrant behaviors. Neuropsychiatric symptoms are usually the earliest manifestation of this subtype, and such patients are often referred to psychiatrists with working diagnoses of depression, bipolar disorder and even late-onset schizophrenia. Because the cognitive impairments early on are rather subtle, careful neuropsychological testing is necessary (as described in detail earlier) to determine that such individuals actually have a dementia rather than a purely psychiatric condition. Up until about 10 years ago, when these patients finally did get to the neuropsychologist, there was a paucity of instruments to delineate and quantify the often florid behavioral problems. Two efforts to better characterize these behavioral changes resulted in a measurement instrument called the frontal behavioral inventory (FBI), a 24-item questionnaire aimed at assessing the most commonly seen psychopathologies present in FTD (Kertesz *et al.*, 1997), and a shortened form of the Neuropsychiatric Inventory (Cummings *et al.*, 1994), called the NPI-Q (Kaufer *et al.*, 2000), which contains 12 items that must be assessed as to presence/absence and if present, the severity (mild, moderate, or severe).

The authors compared three groups of patients, those with FTD, those with AD and those with "depressive dementia" (aka pseudo- or psychodementia). They found that the FTD group scored much higher on the FBI then either

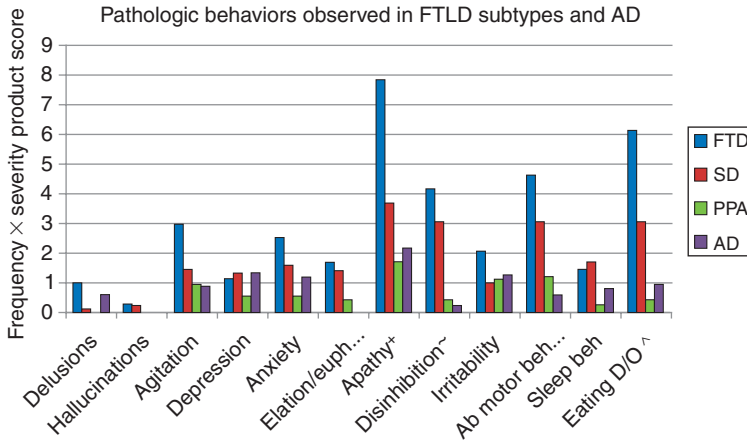

FIG. 3. Frequency of behaviors and mean frequency by severity product score for all individual Neuropsychiatric Inventory (NPI) behaviors across groups. Significant differences ($p < 0.05$) between groups are indicated by the special characters (data from Rosen *et al.*, 2006).

group of "controls." Individual item analysis showed loss of insight, indifference, distractibility, personal neglect and apathy as the most frequent negative symptoms, and perseveration, disinhibition, inappropriateness, impulsivity, and irresponsibility as the most significant positive symptoms. In their (admittedly small) group, using a cutoff score of 27 on the FBI resulted in only a single false positive.

The Marra *et al.* group which administered a large neuropsychological battery also compared AD, FTD, and PPA by use of the NPI-Q. They determined that aggression/agitation and apathy were both significantly more elevated in FTD than in either of the other two groups and concluded that, if a behavioral measure like the NPI-Q was included along with the neuropsychological evaluation, one could readily distinguish all three groups by their profiles—something that was nearly impossible based on the neuropsych data alone (Fig. 3).

B. PPA

Conversely, individuals with PPA have traditionally been considered to have little or no behavioral disturbances early on (Weintraub *et al.*, 1990), though more recent studies have demonstrated the evolution of neuropsychiatric symptoms, particularly after a few years of illness (Banks and Weintraub, 2008; Marczinski *et al.*, 2004). The earlier of these studies utilized the FBI and found that while initial evaluations failed to demonstrate scores above the cutoff value for PPA, by

the end of the third year the PPA group met criteria for FTD. The more recently published study by Banks and Weintraub uses the NPI-Q. This study, which compared individuals with FTD and those with PPA and divided the subjects into short-duration (<5 years) and long-duration (≥5 years) symptoms, found that the number of symptoms in long-duration PPA patients did not significantly differ from patients with FTD regardless of their disease duration. However, when comparing the short- and long-duration PPA patients, a trend toward decreased depression and increased disinhibition and nocturnal behavior was noted.

C. SD

Patients with SD are widely perceived by behavioral neurologists to have behavioral problems that are about midway on the continuum between FTD and PPA, however, formal investigations of behavioral deficits in SD have been rare. In 2001, Snowden and colleagues published a comparison of SD with both apathy-predominant and disinhibition-predominant FTD (Snowden *et al.*, 2001). Using semi-structured interviews, they found that a pervasive lack of emotional response was characteristic of FTD but in SD was limited to the capacity to show fear. They found a tendency toward social-seeking (preference for being with others), and somewhat exaggerated responses to sensory stimuli, in contrast to social-avoidance and reduced pain responses typical of FTD. Conversely, SD patients seemed to show more frequent compulsive repetitive behaviors such as clock-watching, adherence to daily routines and verbal stereotypies.

A few years later and utilizing the NPI rather than interviews, Rosen *et al.* compared SD with FTD and PPA. He measured the mean frequency by severity product score across all 12 behavioral domains and confirmed this empirically (Rosen *et al.*, 2006). In his *post hoc* comparisons between groups, he found similar degrees of elation/euphoria as the FTD group, but much less apathy (suggesting a generally more upbeat/outgoing profile than that of FTD). The SD group also had significantly more disinhibition and abnormal motor behavior than those with PPA. Furthermore, he found that these behavioral abnormalities increased in severity with disease duration in SD.

V. Neuroimaging of FTLD

Historically, structural neuroimaging of degenerative dementias has not played a critical role in diagnosis. Characteristic changes consist primarily of atrophy in certain regions, and this is often rather subtle in early stages of disease, although at later stages the atrophy can result in a "knife blade" appearance of the effected gyri

(Graff-Radford and Woodruff, 2007). The utility of brain imaging lay in determining whether additional neuropathology was seen (e.g., ischemia, subdural hematoma). The advent of sensitive, automated methods for quantifying regional atrophy has provided a new and better way to evaluate this distinguishing feature of FTLD. In addition, functional studies which are used to measure neurochemical breakdown products, regional cerebral blood flow or cerebral metabolism can help to diagnose FTLD at the earlier stages, and can distinguish FTLD from AD. Functional imaging with SPECT or PET can achieve a >90% sensitivity of detecting FTLD (Mendez *et al.*, 2007). It is also becoming possible to distinguish the different types of FTLD with these more advanced imaging techniques. Nonetheless, there is still a need for larger randomized studies to determine the sensitivity and specificity of functional imaging modalities in the diagnosis of FTLD, its phenotypes and their differential from other types of dementia especially AD.

A. Differentiation of FTLD from AD

1. *Structural and Volumetric MRI Studies*

Structural MRI and MR-volumetric analysis of different brain regions can help discriminate FTLD from AD. Structural MRI in patients with FTLD often reveals atrophy in the frontal and temporal lobes, which can be quite asymmetric. The ventricles may be enlarged and the head of the caudate may be atrophic. These findings vary depending on the stage of the disease. Initially, prominent mesial temporal lobe and hippocampal atrophy were demonstrated to be a key diagnostic finding on volumetric MRI studies in AD (Jack *et al.*, 1997), whereas selective frontal volume decreases were suggestive of FTLD (Fukui and Kertesz, 2000). Therefore, it was thought that simply measuring hippocampal volume would determine whether an individual had AD or FTLD. Unfortunately, more recent studies suggest that hippocampal/mesial temporal atrophy alone does not reliably distinguish AD from FTLD (Bocti *et al.*, 2006; Galton *et al.*, 2001). However, a severe or asymmetrical pattern of amygdala atrophy (along with hippocampal atrophy) suggests FTLD (Barnes *et al.*, 2006), as does a topographical pattern of atrophy involving the frontal lobes and anterior temporal regions (Bocti *et al.*, 2006). Directly comparing frontal versus temporal volume changes over time is another, and more sensitive approach to distinguishing disease states (Chan *et al.*, 2001a), though this approach requires two scans taken a year apart (Fig. 4).

2. *MR Spectroscopy*

Proton magnetic resonance spectroscopy (MRS) allows *in vivo* noninvasive estimation of brain metabolites. MRS analysis reveals peaks which correspond to different compounds and metabolites in brain tissue. Two of these compounds are

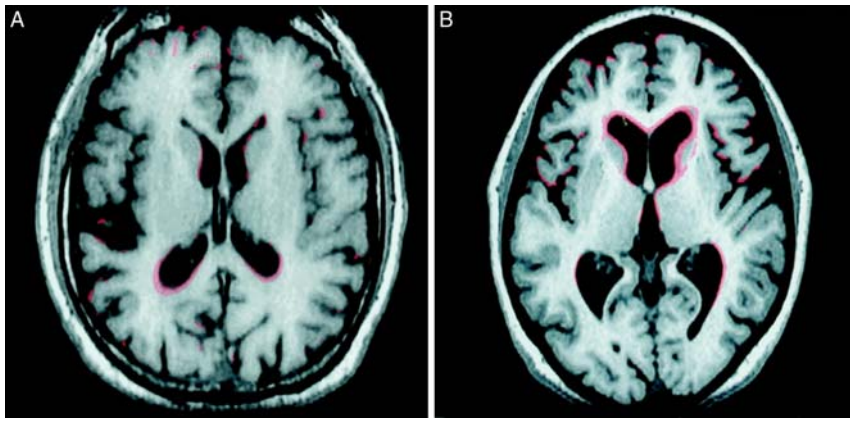

FIG. 4. Distribution of cerebral atrophy in a patient with AD (A) and frontotemporal dementia (FTD) (B). Both patients had similar interscan intervals (11 months) and annualized rates of global cerebral atrophy (approximately 4%). Areas of volume loss are highlighted in red. Note the generalized distribution of atrophy in AD and the preferential anterior volume loss in FTD (Reprinted from Neurology 57, Chan, D., Fox, N. C., Jenkins, R., Scahill, R. I., Crum, W. R., and Rossor, M. N. (2001a) with permission from Lippincott, Williams and Wilkins).

relevant in the work up of patients with dementia, *N*-acetyl aspartate (NAA) which is predominantly intracellular, and myoinositol (MI) which is predominantly found in glial cells. NAA is a marker of neuronal activity and MI is a marker of gliosis. MRS can help to differentiate FTLD from AD as these disorders are accompanied by relatively distinct neurochemical abnormalities. Ernst *et al.* found that patients with FTLD had a statistically significant increase in myoinositol (MI) and decrease in *N*-acetyl (NA) and glutamate in the frontal region, which was distinct from AD. The NA concentration in a frontal region of interest allowed the best discrimination of FTLD from AD and controls. In the temporoparietal regions, changes in MI concentration occurred prior to observable changes in NA concentration, indicating that glial proliferation may be more readily detected than neuronal loss in the early stages of FTLD (Ernst *et al.*, 1997).

3. *Positron Emission Tomography*

Functional imaging methods have significantly improved our ability to detect early changes and to distinguish neurodegenerative diseases. PET imaging has become the most commonly used and promising modality to differentiate FTLD from other dementia syndromes, including AD.

The cerebral metabolic rate of glucose in different areas of brain can be measured with ^{18}F-FDG PET, and the pattern of hypometabolic regions can be used to differentiate various types of dementia (Foster *et al.*, 2007; Ibach *et al.*, 2004; Silverman *et al.*, 2002). This metabolic decline occurs quite early in the

course of disease, making PET a relatively sensitive imaging tool for discerning both the presence and the type of neurodegeneration. In fact, the Centers of Medicaid and Medicare recently approved reimbursement of clinical ^{18}F-FDG-PET for the indication of distinguishing AD from FTLD. FTLD patients have prominent hypometabolism of the frontal and anterior temporal cortices as compared with AD patients who show decreased metabolism in the posterior cingulate and parietotemporal cortices (Diehl-Schmid *et al.*, 2007; Ishii *et al.*, 1998; Jeong *et al.*, 2005a; Mosconi *et al.*, 2008). PET statistical parametric mapping studies in patients with FTLD have shown hypometabolism in other areas of brain such as the anterior cingulate, uncus, insula, and subcortical regions including basal ganglia (Jeong *et al.*, 2005a). Moreover, hemispheric metabolic asymmetry is common in patients with FTLD (Garraux *et al.*, 1999; Jeong *et al.*, 2005a) (Fig. 5).

The novel PET tracer ^{11}C-PIB has a high affinity for fibrillar A-beta protein which is a pathological hallmark of AD and is not a part of the FTLD spectrum (Klunk *et al.*, 2003). Because of this, ^{11}C-PIB can help to discriminate AD from FTLD. Engler *et al.* conducted a study of 10 patients with FTLD using PIB. Eight of these FTLD patients showed significantly lower PIB retention as compared to

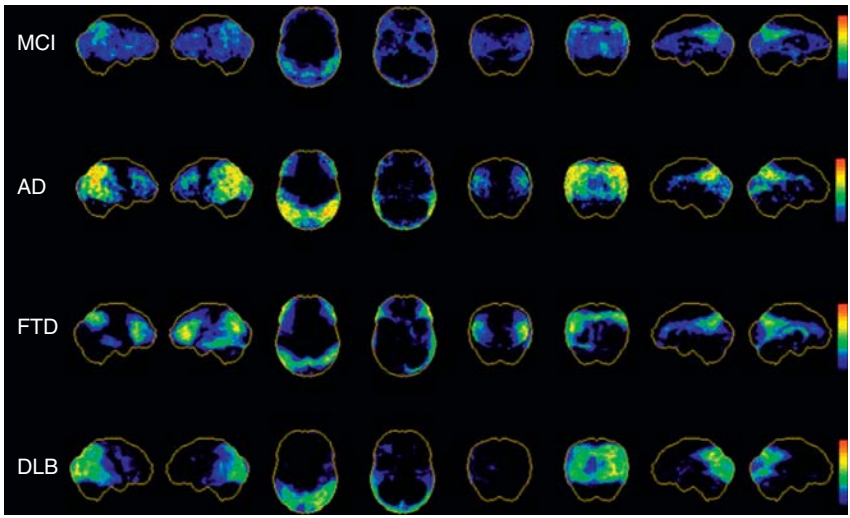

FIG. 5. Representative cortical ^{18}F-FDG PET patterns in NL, AD, DLB, and FTD. 3D-SSP maps and corresponding Z scores showing CMRglc reductions in clinical groups as compared with the NL database are displayed on a color-coded scale ranging from 0 (black) to 10 (red). From left to right: 3D-SSP maps are shown on the right and left lateral, superior and inferior, anterior and posterior, and right and left middle views of a standardized brain image (Reprinted by permission of the Society of Nuclear Medicine from Mosconi, L., Tsui, W. H., Herholz, K., Pupi, A., Drzezga, A., Lucignani, G., Reiman, E. M., Holthoff, V., Kalbe, E., Sorbi, S., Diehl-Schmid, J., Perneczky, R., *et al.* (2008)).

AD in different brain regions. In fact PIB uptake in these FTLD patients did not differ significantly from healthy controls in any region (Engler *et al.*, 2008).

Another novel PET tracer, which is relatively a small molecule, is called FDDNP. It is an *in vivo* chemical marker for cerebral amyloid and tau proteins. Initial FDDNP studies of FTD show binding in the frontal and temporal regions but not in the parietal regions suggesting that FDDNP labels regional tau tangles and thus can differentiate FTD from AD according to the binding patterns (Silverman *et al.*, 2002). However, these are preliminary studies and further pathological correlation and larger scale studies are warranted to confirm the utility of this promising modality in clinical practice.

4. *Single Photon Emission Computed Tomography*

Unlike FDG-PET, which is a marker of cell metabolism, SPECT is based on the brain uptake of a technetium 99m-based lipid-soluble radionucleotide (ethyl cysteinate dimer or hexamethylpropylene amine oxime) which stays within vascular channels and is therefore a marker of brain perfusion. It has been shown to differentiate FTLD from AD with high sensitivity. Charpentier *et al.* demonstrated that 100% of patients with FTLD and 90% of AD patients could be correctly classified by using a SPECT-image-derived algorithm that included analyzing regions of interest in frontal and temporoparietal lobes (Charpentier *et al.*, 2000). Sjogren *et al.* demonstrated the successful utility of SPECT in differentiating FTLD from other forms of dementia including AD using an anterior to posterior ratio of technetium uptake to classify these patients, with a sensitivity of 87.5% and a specificity of 78.6% (Sjogren *et al.*, 2000). Many investigators have also found that there is a reduction in tissue metabolism in the posterior cingulate cortex of patients with AD. Bonte *et al.* highlighted the significance of this "posterior cingulate sign" in the diagnosis of FTLD by using SPECT RCBF studies to distinguish AD from FTLD based on presence or absence of this sign (Bonte *et al.*, 2004).

B. Differentiation of Different Subtypes of FTLD

1. *Structural and Volumetric MRI Studies*

MRI studies can help differentiate subtypes of FTLD, as they exhibit different patterns of regional atrophy on volumetric analysis, although reported sensitivity and specificity of these techniques has varied greatly. Typically, FTD is associated with bilateral frontal atrophy, SD is associated with predominantly left anterior temporal lobe atrophy and PPA is associated with left perisylvian atrophy (Chan *et al.*, 2001b; Gorno-Tempini *et al.*, 2004; Rosen *et al.*, 2002). It has been shown that there is more frontal lobe gray matter atrophy in FTD compared with SD cases (Rosen *et al.*, 2002). Patients with SD show bilateral, typically asymmetrical,

atrophy of the anterior temporal lobes. As the disease progresses this degenerative process evolves caudally to the posterior temporal lobes or rostrally to the posterior, inferior frontal lobes, or both. Utilizing volumetric MRI methods, Chao *et al.* demonstrated that patients with SD had both white matter and gray matter atrophy in the temporal lobes, and that therefore adding temporal white matter volume to temporal gray matter volume significantly improved the discrimination between SD and FTD (Chao *et al.*, 2007).

Gorno-Tempini *et al.* in their voxel-based morphometry MRI study showed that all of their patients with PPA had atrophy of the left perisylvian region, anterior temporal lobes bilaterally and the basal ganglia bilaterally (Gorno-Tempini *et al.*, 2004). Their study also showed distinctive patterns for PPA, SD, and logopenic progressive aphasia. PPA was associated with left inferior frontal and insular atrophy, SD with anterior temporal damage and logopenic progressive aphasia with atrophy of left posterior temporal cortex and inferior parietal lobule (Gorno-Tempini *et al.*, 2004). Mummery *et al.* conducted a voxel-based morphometry study of SD patients and identified well-circumscribed regions of atrophy in individual patients including the bilateral temporal poles (left more than right), the left inferior temporal gyrus, the left middle temporal gyrus, the left amygdaloid complex, and the ventromedial frontal cortex (Mummery *et al.*, 2000). The degree of semantic deterioration correlated with the extent of left anterior temporal damage and not with that of adjacent ventromedial frontal cortex.

An excellent recent summary of the "triple dissociation" between the three subtypes of FTLD can be seen in the recent study by Schroeter, *et al.* (2007). This group undertook a large quantitative meta-analysis of 267 FTLD patients (and 351 control subjects) across 19 MRI and PET studies. Their results indicated specific neural networks for each of the three clinically defined subtypes that did not overlap. The study further related each subtype's clinical features to its neural substrate, demonstrating a close structure-function correlation for the diseases (Schroeter *et al.*, 2007) (Fig. 6).

2. *MRI Diffusion Tensor Imaging*

Historically, most neuroimaging studies have focused on gray matter changes in the brain, as FTLD has traditionally been regarded as a gray matter disease. More recently, white matter changes in FTLD have received some attention, both because there is a greater understanding of the interplay between gray and white matter degeneration, and because of the evolution of MRI diffusion tensor imaging, a technique that detects microstructural alterations in white matter by measuring the directionality of molecular diffusion. Borroni *et al.* found a difference in the pattern of white matter loss in early stages of frontal and temporal variants of FTD which might be helpful to differentiate these two variants of

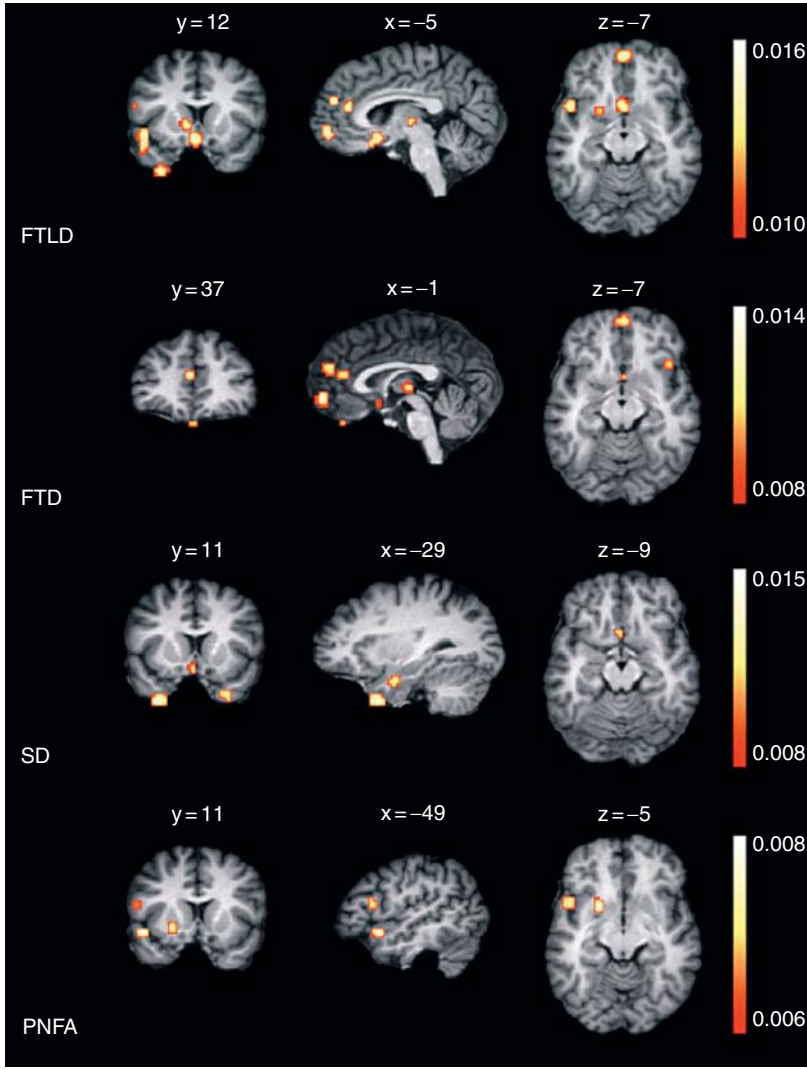

FIG. 6. Results of the quantitative meta-analyses (using activation likelihood estimates) for the three subtypes of FTLD individually, and for FTLD all subtypes pooled. Left side is left (Reprinted from NeuroImage 36(3), Schroeter, M. L., Raczka, K., Neumann, J., and Yves von Cramon, D. (2007) with permission from Elsevier).

FTLD (Borroni *et al.*, 2007). Another study using tensor-based morphometry has reported white matter atrophy in temporal lobes of patients with SD (Studholme *et al.*, 2004).

3. *MR Spectroscopy*

NAA and creatine (Cr) on MRS have been reported to differentiate not only AD from FTLD, but the different types of FTLD as well. Coulthard *et al.* performed a study on FTLD patients showing that MRS can reveal regionally selective abnormalities in patients with FTLD. MRS was performed on the temporal, parietal, and anterior cingulate cortices of five patients with established SD, and two patients with FTD. All the patients with FTLD had reduced NAA/Cr in frontal and temporal lobes and not in parietal lobes; however, the patients with FTD had increased MI/Cr in their cingulate cortices differentiating then from SD (Coulthard *et al.*, 2006).

4. *Positron Emission Tomography*

FDG studies in patients with SD have shown temporal cortical hypometabolism with the left temporal lobe often being more severely effected (Diehl *et al.*, 2004; Hodges *et al.*, 1999). Other studies in patients with PPA showed left temporal and perisylvian defects early in the disease course and parietal and frontal region abnormalities occurring later on (Chawluk *et al.*, 1986; Kempler *et al.*, 1990; Tyrrell *et al.*, 1990). Grossman *et al.* reported a group of patients with PNFA who had global left hemisphere hypometabolism and more specific hypometabolism in the left inferior frontal, superior, and middle temporal gyri (Grossman *et al.*). Nestor *et al.* conducted a study on patients with problem of progressive dysfluency using ^{18}F-FDG PET and analyzed with the technique of statistical parametric mapping. They identified seven patients with PPA who showed hypometabolism in several regions, most notably in the left anterior insula/frontal opercular region (Nestor *et al.*, 2003). They also assessed regional atrophy with MRI voxel-based morphometry and this analysis revealed only a small area of atrophy in the left peri-Sylvian region.

FTD can coexist with MND (FTD/MND) and the clinical features of this entity are somewhat different from FTD patients. Garraux *et al.* reported that FTD/MND showed hypometabolism in the bilateral frontal, anterior temporal lobes, and in putamen. When compared with FTD, FTD/MND patients had more hypometabolism in medial temporal regions (Garraux *et al.*, 1999). Another study by Jeong *et al.* showed that patients with FTD/MND showed glucose hypometabolism only in the frontal region, whereas most patients with FTD had hypometabolism in the frontal and temporal areas. Moreover, FTD/MND patients had a more symmetric pattern of hypometabolism than FTD (Jeong *et al.*, 2005b). In addition to the above findings, FTD/MND patients also had hypometabolism in the basal ganglia region and thalamus. A key finding from these studies was that asymmetric degeneration is not a feature of FTD/MND as compared to FTD which is well known for asymmetric hemispheric degeneration (Garraux *et al.*, 1999; Jeong *et al.*, 2005b).

5. *Single Photon Emission Computed Tomography*

SPECT has been shown to differentiate between the frontal and temporal variants of FTD (Perry and Hodges, 2000). Utilizing a region of interest approach, both Talbot and Newberg (Newberg *et al.*, 2000; Talbot *et al.*, 1995b) conducted SPECT studies and found hypoperfusion in bi-frontal and left temporoparietal region and in the left dorsolateral prefrontal cortex and left subcortical nuclei in patients with PPA. Neary *et al.* found hypometabolism confined to frontal lobes in patients with FTD/MND (Neary *et al.*, 1990). Another study by Talbot *et al.* using ROI analysis of SPECT mages found no significant differences between FTD and FTD/MND (Talbot *et al.*, 1995a).

VI. Summary

The accurate diagnosis of FTLD in all of its guises is very important for the development of new therapeutic options and disease modifying therapies. Clinical diagnosis is based on the recognition of all the core and necessary neurologic, neuropsychological, and neuropsychiatric features of FTLD. However, patients often lack all the core features at the initial assessment, and subtle personality or behavioral changes can be caused by a range of other disorders, making diagnosis difficult (Mendez and Perryman, 2002; Mendez *et al.*, 2007). Furthermore, there is no single hallmark genetic mutation or susceptibility locus that can be tested to provide the diagnosis in most cases. Therefore, careful neuropsychological *and neurobehavioral* assessment should be performed in all suspected cases to increase the reliability of discrimination between AD and FTLD, esp. FTD. Several authors have come to the same conclusion (Marra *et al.*, 2007; Perri *et al.*, 2005). Furthermore, neuroimaging plays a significant role in diagnosis, not only in excluding alternative pathologies, but as a positive, "rule-in" test in which the characteristic features of frontal and anterior-mid temporal atrophy and hypometaboloism should be evaluated. New and improved methods for evaluating these features are on the horizon, and adoption of a quantitative volumetric approach to MR as well as the addition of PET or SPECT to the clinical evaluation algorithm will add greatly to our diagnostic acumen.

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LEWY BODY DEMENTIA

Jennifer C. Hanson and Carol F. Lippa

Drexel University College of Medicine, Mail Stop 423, Philadelphia, Pennsylvania 19107, USA

Dementia is becoming increasingly prevalent since elderly patients are living longer due to the development of treatments for other diseases and conditions. The percent of our population over 60 is also increasing with the wave of aging baby boomers. Additionally, more individuals seek medical assistance for cognitive problems as visibility for treatments improves. This combination of factors results in the dementia syndromes becoming more common, causing physicians to encounter more patients with dementia as well as more caregivers of these patients.

Of dementia subtypes, Alzheimer's disease (AD) is the most common. Dementia with Lewy bodies (DLB) is thought to be the second most common subtype. DLB's typical symptoms include cognitive impairment, visual hallucinations, spontaneous parkinsonism, and fluctuating confusion. Supportive features include a variety of sleep disruptions that may occur before manifestations of dementia. Psychiatric symptoms include vivid visual hallucinations and depression. The clinical features of DLB are strikingly similar to those of dementia in Parkinson's disease (PD).

The underlying biology of DLB is complex, but the presence of alpha-synuclein containing Lewy bodies (LB) is a common factor. These inclusions also contain ubiquitin. PD dementia shares these pathological findings with DLB, as well as neural degeneration of the substantia nigra. DLB and dementia in PD may represent the same pathological process along a disease spectrum.

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Additionally, many DLB cases are also associated with beta-amyloid and tau-containing neurofibrillary tangles, features that are associated with AD. Frequently, AD patients are also found to have LB. The reason for this overlap is unknown. However, the greater the Alzheimer's pathology in DLB patients, the more the clinical features of DLB overlaps with AD.

In this chapter, we will review DLB including clinical, pathological, and radiological features as well as biomarkers and treatments.

I. Introduction

Dementia is defined as a syndrome of progressive cognitive impairment that interferes with daily function (DSM IV-TR, 2004). The cognitive areas involved include memory, language, abstract thinking, visuo-spatial skills, behavior, and personality. Alzheimer's disease (AD) is the most common dementia subtype, representing over half of all dementias. Dementia with Lewy bodies (DLB) is the second most common type of dementia at 20%, affecting 15–25% of elderly demented patients (McKeith *et al.*, 1996). Of those patients with Parkinson's disease (PD), 30% will develop dementia during the course of their illness (Emre *et al.*, 2007). Many more Parkinson's patients will experience some type of cognitive change. Table I compares the most common forms of dementia.

The four main components of the DLB syndrome are dementia, visual hallucinations, parkinsonism, and fluctuation of symptoms, particularly confusion. The cognitive decline associated with DLB includes pronounced variation in attention and alertness. Visual hallucinations are recurrent, consist of formed or detached figures and typically occur early in the disease course. The parkinsonian motor features include myoclonus, bradykinesia, rigidity, and less commonly tremors. Additional associated features include sleep anomalies, repeated falls, syncope, transient loss of consciousness, delusions that are often paranoid, urinary incontinence, and depression. DLB patients are sometimes oversensitive to neuroleptic agents, and use of such medication may precipitate a change in functional status.

DLB exhibits a clinical overlap with both the dementia of AD and the motor symptoms of PD. DLB is characterized by intracytoplamic proteinaceous inclusions called Lewy bodies (LB). These collections of alpha-synuclein (AS) plaques occur throughout the cortex and subcortical regions. Additionally, DLB has a loss of acetylcholine producing neurons similar to those seen in AD and a loss of dopaminergic neurons, as seen in PD.

This chapter will review DLB clinical and pathologic features, radiographic findings, biomarkers, and current treatment modalities.

TABLE I
COMPARISON OF THE MOST COMMON FORMS OF DEMENTIA

	Epidemiology	Pathology	Clinical features
Alzheimer's disease	Most common >65 years old	General cortical atrophy, especially in medial temporal lobe	Memory impairment
	Genetic susceptibility factors (mostly for late-onset)	Amyloid plaques in cortex	Difficulty in learning new information
	Autosomal dominant inheritance (more often present in early onset)	Neuritic plaques	Little fluctuation or hallucinations
		Neurofibrillary tangles containing tau and ubiquitin	Apraxia
		Amyloid angiopathy	Rigidity may be a late feature
Vascular dementia	>40 years old	Multiple infarcts—often in subcortical areas	Step-wise deterioration
	Risk factors:		May improve
	Hypertension	Fibrous and hyaline degeneration of small arteries	Pyramidal signs
	Smoking		
	Vascular disease		
	Other vascular risk factors	White matter infarction	Pseudobulbar palsy
Dementia with Lewy body (DLB)	Usually sporadic	General cortical atrophy; may be normal	Parkinsonism
	Often elderly, especially when cognitive presentations	Depigmentation of substantia nigra	Fluctuating mental state with slow processing, attentional, and visuo-spatial problems
		LB in limbic and cortical neurons; often brainstem LB	Visual hallucinations
		Amyloid deposits are common	Neuroleptic sensitivity
			REM behavioral disorder
Parkinson's disease dementia	30% of PD patients	Neuronal cell death in substantia nigra	Parkinsonism before onset of dementia
	Usually sporadic	LB in nigral neurons; often in limbic and cortical regions	Fluctuating confusion with similar features (attentional problems, slow processing) to DLB
			Visual hallucinations

II. DLB Clinical Features

In 2005, the DLB consortium issued its third report on the Current International Consensus Diagnostic Criteria for DLB (McKeith *et al.*, 2005). The central features necessary for a diagnosis of DLB include the presence of a dementia, fluctuating cognition, hallucinations, and parkinsonian symptoms. Numerous supportive features are commonly found in DLB patients, but are not necessary for the diagnosis.

As in AD, DLB patients have a progressive cognitive decline sufficient enough to interfere with normal social or occupational functioning (DSM IV-TR, 2004). However, in contrast to AD, the memory impairment of DLB may not be prominent in the early stages (McKeith *et al.*, 2005). The cognitive problems fluctuate with pronounced variation in attention and alertness. This feature is hard to monitor in clinical practice due to its difficulty to observe on a consistent basis. When they do appear, the deficits on tests of attention, executive function, and visuo-spatial ability in DLB are generally prominent (McKeith *et al.*, 2005). Subjects with DLB have better delayed memory and spared recall, but worse executive function and visuo-spatial abilities than patients with early AD. Such differences in visuo-spatial abilities can be demonstrated by the intersecting pentagons used as part of the mini mental-status exam. An example of this is shown in Fig. 1.

In DLB, the cognitive deficits represent both cortical and subcortical impairments, with greatest deficits being verbal fluency, visual perception, and performance tasks while there is preservation of confrontation naming, recognition, and short-term recall (Connor *et al.*, 1998; Mormont *et al.*, 2003; Walker *et al.*, 1997).

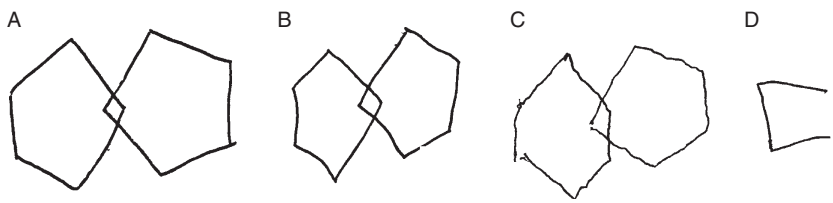

FIG. 1. Figure drawings of normal, Alzheimer's dementia, and Dementia with Lewy body (DLB) patients. Patient drawings demonstrate the visuo-spatial dysfunction in DLB patients compared with normal aging patients and AD patients. Image A is a model of connecting pentagons, normally used to test visuo-spatial function. The patient is asked to copy this image during the test. Image B shows a normal patient's response. Note that this image has five sides and that the adjacent sides intersect in both pentagons. Image C is drawn by an AD patient. This subject drew a hexagon rather than a pentagon. This is a cognitive error. Image D is from a patient meeting the criteria for probable DLB. There is marked loss of visuo-spatial relationships, and it is hard to tell what they are trying to copy.

Both DLB and Parkinson's disease dementia (PD-D) patients have more pronounced subcortical cognitive impairment profiles with less marked memory impairment than AD patients. However, those patients with a pattern of prominent cortical involvement have more severe memory impairment like that of AD (Janvin *et al.*, 2006).

Recurrent visual hallucinations are prominent and are typically well formed and detailed in DLB patients. Hallucinations of animals and people are common. They are usually frightening and it is difficult to convince the patient that they are not real. This may pose safety problems, as the patient will feel that they will be attacked or their home invaded. In contrast, visual hallucinations are uncommon in AD, particularly early in the disease course. Therefore, report of such vivid hallucinations in the context of dementia should alert the physician to the likelihood of DLB. LB concentrations in the posterior temporal lobes and amygdale, areas critical for emotion and visual processing, are associated with the presence of these hallucinations (Harding *et al.*, 2002). As such, it has been speculated that visual hallucinations are positive phenomenon, caused by an irritating effect of the LB in relevant areas.

The onset of parkinsonian symptoms occurs spontaneously in DLB. At the time of diagnosis, approximately 50% of DLB patients have extrapyramidal motor symptoms, with 75% developing them during some stage of the disease course (McKeith *et al.*, 1992b). Patients have postural instability, gait disorders that may be characterized by hunched posture and festination, and facial immobility (Burn *et al.*, 2003). Tremor may be present, but is not as prominent as in PD. The Unified PD Rating Scale can be used to monitor parkinsonian progression, but only for those symptoms that can be assessed in the face of dementia (Fahn *et al.*, 1987). Objective findings include tremor at rest, intention tremor, bradykinesia, rigidity, and facial expression. When compared to AD patients of a similar cognitive level, DLB patients have greater functional impairment due to the presence of extrapyramidal symptoms (McKeith *et al.*, 2005).

Many DLB patients have parasomnias. The most common is REM behavioral disorder (RBD) which often begins concurrently or after the onset of parkinsonism or dementia (Boeve *et al.*, 2007). It is marked by lack of muscle atonia in the presence of vivid dreams. In RBD that lack of muscle paralysis allows the patient to engage fully in the physical activities of the dream, resulting in vocalizations and sometimes wildly violent behavior. Patients are often unaware of the disorder, but bed partners may report it as a presenting symptom when asked. RBD is associated with daytime somnolence. It can be diagnosed by polysomnography which shows elevation in EMG tone during REM sleep and unusual movements during sleep (Fantini *et al.*, 2005).

DLB patients are notorious for their neuroleptic sensitivity, and reactions occur in 30–50% of DLB patients (Aarsland *et al.*, 2005b). Such neuroleptic

sensitivity reactions area characterized by sudden onset of impaired consciousness, acute confusion, psychotic episodes, and exacerbation of parkinsonian symptoms such as rigidity and immobility (McKeith *et al.*, 1992a). These reactions may even result in decreased survival within several days. A 2005 study by (Aarsland *et al.*, 2005b) demonstrated that there was a 58% frequency of neuroleptic sensitivity to olanzapine, with only 11% to clozapine and 6% to thioridazine. This confirmed previous studies that showed unacceptable safety profiles for some neuroleptics in LB dementias. Additionally, DLB patients are often activated by sedatives and awakened by sleep medications (Rogan and Lippa, 2002).

Other common findings in DLB include autonomic instability which results in orthostatic hypotension and urinary incontinence. Falls may be frequent, and can be the result of truncal ataxia or syncope. Hallucinations of other modalities, depression, and severe delusional symptoms may be present. Transient episodes of loss of consciousness occur and are often unexplained. Increased fluctuations of consciousness have been associated with increased thalamic and decreased occipital perfusion (O'Brien *et al.*, 2005).

III. PD-D

PD-D is a dementia syndrome that develops in the context of an established PD. PD-D has an insidious onset with slow progression, and is defined as having impairment in more than one cognitive domain representing a decline from premorbid level. The deficits present must be severe enough to impair daily life and the deficits must be independent of the impairment by motor or autonomic symptoms (Emre *et al.*, 2007). Such impairments may affect social functioning, occupational productivity, or personal care.

PD-D patients share many common deficits with DLB patients. PD-D patients demonstrate fluctuating impaired attention with difficulty in preforming tasks. Executive functions are impaired especially with tasks that require initiation, planning, and concept formation. Bradyphrenia is common. Visuo-spatial functions are impaired with problems of orientation, perception, and construction. Memory impairment is greatest in recalling recent events and new information, but memory can improve with cueing. Core language functions are preserved, but word recall and complex sentence comprehension may be limited. PD-D patients are often apathetic, with concomitant anxiety and depressive symptoms. Visual hallucinations are complex and include formed visions of people, animals, or objects. Delusions are often paranoid, and patients suffer from sleep disorders that result in daytime somnolence.

IV. DLB and PD-D

There is no clinical rational or pathological basis that determines a definite time interval between development of motor symptoms and onset of dementia in differentiating PD-D from DLB. In general, a diagnosis of PD-D should be made when dementia develops within the context of established PD, while DLB should be diagnosed when dementia occurs before or concurrently within 1 year of parkinsonism (McKeith *et al.*, 2005).

Often patients do not fit into either pattern above. Many times early cognitive change is recognized in patients with PD, or DLB patients present with parkinsonism at the same time as their cognitive symptoms. The neuropsychological profiles in DLB and PD-D share basic similarities with abnormalities in attention, executive function, visuo-spatial function, language function, memory retrieval, and behavior (Lippa *et al.*, 2007a,b). There is no symptom or sign that absolutely distinguishes DLB and PD-D, as both have fluctuating cognitive dysfunction, visual hallucinations, parasomnias, and autonomic dysfunction.

There are, however, some subtle differences that can be used to elicit a more precise diagnosis. DLB patients make executive function errors (Aarsland *et al.*, 2003), and have more hallucinations and psychosis than PD-D patients (Mosimann, 2006). DLB patients have fewer parkinsonian signs than PD-D patients and little resting tremor. The parkinsonism of DLB is more weighted with generalized slowing with postural and gait disturbances (Burn and McKeith, 2003). They also have greater symmetry of their motor features than PD-D patients. Additionally, adverse reactions to antipsychotic agents may be greater in DLB patients.

V. Pathology

Found in 50% of dementia patients (Hamilton, 2000; Lippa *et al.*, 1998), the main identifying pathologic feature of DLB is the LB. LB are spherical intracytoplasmic protein deposits around the nucleus and throughout the dendrite of subcortical and cortical neurons. They consist of filamentous protein granules composed of AS and ubiquitin, and are surrounded by a halo of neurofilaments. Widespread LB differentiate the LB dementias from other dementia subtypes. The number of LB present does not correlate strongly with either the duration or severity of the dementia (Harding *et al.*, 2001). However, the number of cortical LB is variably correlated with the severity of DLB (Samuel, 1996). When located in the temporal lobe, LB are associated with the visual hallucinations of DLB (Harding *et al.*, 2002).

AS is a synuclein protein primarily found in the neocortex, hippocampus, substantia nigra, thalamus, cerebellum, and with the highest proportion in the basal ganglia (Rockenstein *et al.*, 2001). Cortical-LB sites include the cingulate gyrus, entorhinal cortex, insular cortex, frontal cortex, and amygdale. AS is a small protein that shares a structural resemblance with apolipoproteins (Mukaetova-Ladinska *et al.*, 2006). It is a neuronal presynaptic protein found widely in the central nervous system (CNS). Normally a soluble and unstructured protein, it can aggregate to form the insoluble neurotoxic fibrils that characterize LB. Epitope mapping shows similar patterns in AD, DLB, and PD (Lippa *et al.*, 2001).

A 2007 study by Kramer found that small individual AS aggregates are more common than LB. These aggregates are located at presynaptic terminals, and result in almost a complete loss of dendritic spines at the postsynaptic areas (Kramer and Schulz-Schaeffer, 2007). Additionally, AS has been found to have a role in the reducing dopamine synthesis (Mukaetova-Ladinska *et al.*, 2006). Although the mechanism of AS activity is incompletely understood, it is clear that it plays a large and complex role in the pathogenesis of DLB.

There is no clear pathologic differentiation between DLB and PD-D. Both disease entities result in end-stage disease with diffuse brain involvement and clinical phenotypes that are nearly indistinguishable. However, there are subtle pathological differences that can be seen at autopsy. Neuronal loss in the substantia nigra is greater in PD-D than in DLB, while beta-amyloid patterns are more consistent in DLB. AS pathology is greater in the striatum in DLB than PD-D (Duda *et al.*, 2002). The AS aggregates into fibrils in LB and Lewy neurites in DLB, PD-D, and PD, with the LB being indistinguishable between the syndromes. AS is the primary protein in all the LB, and solubility and epitope studies show similar features of the AS among the syndromes (Baba *et al.*, 1998). This suggests that DLB, PD-D, and PD may represent different points on a continuum of LB disorders, with motor and nonmotor features reflecting the regional burden and distribution of pathology.

Most patients with DLB also have pathology typically seen in AD patients. LB and Lewy neurites occur in cortical and brainstem nuclei in association with cortical-amyloid plaques and neurofibrillary tangles (McKeith *et al.*, 2004). The degree of AD characteristics seen in DLB patients correlates with the amount of AD pathology, with the main components seen being beta-amyloid and tau. Tau aggregates are known to increase the formation of LB in susceptible brain regions, such as the amygdale (McKeith *et al.*, 2004). This finding has been noted in both DLB and AD patients, showing significant overlap between the two types of dementia with regard to pathological findings (Figs. 2 and 3).

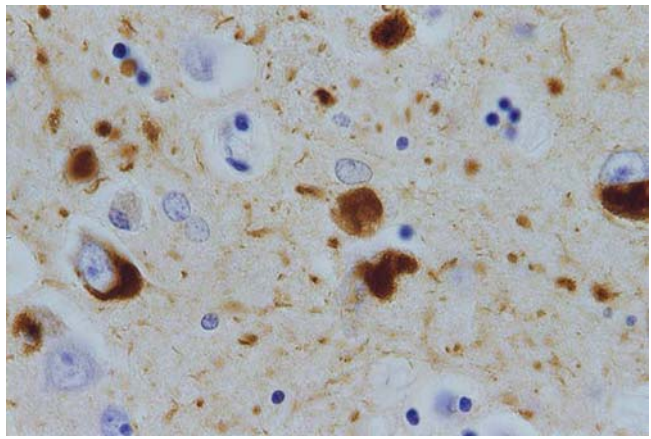

FIG. 2. Lewy bodies (LB) and Lewy neurites. This is a moderately high-power magnification of brain tissue from the amygdale of a patient with DLB. Tissue is stained with antibodies against alpha-synuclein (AS). It demonstrates numerous AS containing Lewy bodies and Lewy neurites.

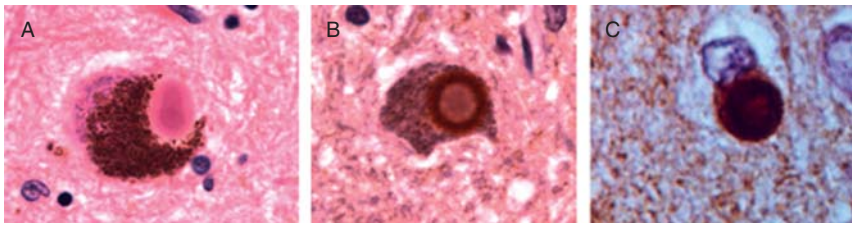

FIG. 3. High-power magnification images of LB. Image A is stained using a routine H & E stain. It shows the classical nigral LB with an eosinophilic core and clearer peripheral region. Note the neuromelanin pigment. Image B is a nigral LB from the same case, but stained with antibodies to AS. It demonstrates that AS is concentrated at the periphery of the LB (the clearer region on H & E stains). Image C shows a cortical LB stained with AS. These typically occur in smaller neurons, and they stain more uniformly with AS; cortical LB lack a halo.

VI. Genetics

In most cases, the LB diseases occur sporadically. Fully penetrate genetic causes for DLB are rare; however, there are likely additional genetic and environmental susceptibility factors that are still unidentified. There are a variety of genetic etiologies for dementia, with most being caused by abnormal CNS protein processing, expression, or aggregation. Many different types of cellular damage

cause aggregation of a variety of CNS proteins, and no single cause has been linked to dementias. Additionally, mutations causing dementia and Parkinsonism may lead to mixed or variable protein aggregates (Rajput *et al.*, 2006).

Genetic abnormalities in AS or other proteins that cause LB diseases are rare, but may lead to the cognitive or motor features of the disease. Dementia and parkinsonism are not always related to pathology; other genetic localizations may also lead to symptoms of parkinsonism and dementia. For example, some patients with tau mutations may have features of PD-D and DLB but lack LB, while others may have clinical and neuropsychological features that differ.

Factors determining the distribution of pathology in relation to the symptoms are incompletely understood. Schiesling *et al.* (2008) aptly stated that, "The identification of the first gene in familial Parkinson's disease (PD) only 10 years ago was a major step in the understanding of the molecular mechanisms in neurodegeneration. AS aggregation was not only recognized as a key event in neurodegeneration in patients carrying mutations in this gene, but it turned out to be the most consistent marker to define LB pathology also in nonheritable idiopathic PD." Numerous other genes have been found associated with PD, and many individuals with "idiopathic" forms may prove to carry susceptibility factors.

VII. Biomarkers

There are currently no highly sensitive clinical diagnostic criteria that distinguish DLB from other dementia subtypes with certainty, but this could be aided by biomarkers for DLB. Aarsland recently reviewed antemortem markers that aid in the diagnosis (Aarsland *et al.*, 2008). This study determined that, "The best evidence was for scintigraphy of the striatal dopamine transporter system using FP-CIT SPECT. Several small scintigraphy studies of cardiovascular autonomic function using metaiodobenzylguanidine SPECT have reported promising results. Studies exploring innovative techniques based on CSF have reported interesting findings for the combination of amyloid beta (abeta) isoforms as well as AS, and there are interesting results emerging from preliminary studies applying proteomic techniques." Other recent studies of modalities, including MRI scanning, SPECT, and EEG, were less useful for establishing a diagnosis in individual patients (Aarsland *et al.*, 2008). Of note, is the finding that DLB patients may show less medial temporal lobe atrophy on MRI when compared with the patients of AD (Lippa *et al.*, 1999). A large portion of future DLB research will be in field of identifying usable biomarkers to aid in clinical diagnosis.

VIII. Management

The treatment and management of DLB patients is complicated by their neuropsychiatric profile and extrapyramidal signs. Cognitive impairment must be addressed in the context of hallucinations, apathy, depression, and sleep disorders. Functional status is compounded by the increased morbidity of physical symptoms. Postural instability, continence, bradykinesia, syncope, falls, and autonomic instability worsen DLB functional impairment. All these factors must be considered when deriving a treatment program for the affected patient.

The management of DLB patients should focus on having an accurate diagnosis and identification of target symptoms that concern the patient and caregiver (Barber *et al.*, 2001). Nonpharmacological interventions such as physical and occupational therapy, community resources, and home care should be considered in addition to pharmacological interventions. Caregiver education is paramount because sometimes identifiable triggers for the patient's fluctuations can be identified.

Although there are no pharmacologic treatments aimed specifically at DLB, patient symptoms can be addressed by giving them the treatments for AD and PD. Medications should be kept to a minimum since adverse responses are not uncommon. In particular, traditional neuroleptics should be avoided, due to the high rate of severe neuroleptic sensitivity in DLB. Low-dose newer antipsychotic drugs are safer but sensitivity reactions have been documented and they should be monitored carefully (McKeith *et al.*, 2004).

DLB patients have greater cholinergic loss than AD patients (Perry *et al.*, 1994), and respond to cholinesterase inhibitors more effectively than AD patients (Samuel *et al.*, 2000). Significant improvement in fluctuating cognitive impairments, visual hallucinations, apathy, anxiety, and sleep disturbance are seen with cholinesterase inhibitors when used in the typical dose range for AD (McKeith *et al.*, 2004). Improvement of attention upon treatment was most notable in patients with visual hallucinations (McKeith *et al.*, 2004). Significant and extensive reduction in beta-amyloid deposits has been noted in DLB patients treated with cholinergic enhancers (Ballard *et al.*, 2007). Symptomatic response to cholinesterase inhibitors is comparable in PD-D and DLB, with neither having significant compromise of motor function (Burn and McKeith, 2003). Care should be used to monitor DLB patients for orthostatic hypotension when on cholinesterase inhibitors.

Dopaminergic therapy is the mainstay treatment for extrapyramidal symptoms in DLB and PD-D. The lowest effective level of levodopa should be used (McKeith *et al.*, 2004). Although the effectiveness in the LB dementias has not been extensively studied, the improvement of symptoms may be less than those seen in pure PD due to their additional intrinsic striatal pathology and dysfunction (Duda *et al.*, 2002).

Management of additional DLB symptoms is complicated. Depression is common in both DLB and PD-D and can be treated with selective serotonin reuptake inhibitors (McKeith *et al.*, 2005). RBD can be treated with clonazapam, melatonin, or quetiapine (Boeve *et al.*, 2004). Tricyclic antidepressants, low potency neuroleptics, antiparkinsonian anticholinergic drugs, and antispasmodics for bladder or gastrointestinal tract should be avoided in DLB and PD-D patients as they may not only worsen cognition and psychotic symptoms but may be associated with orthostatic hypotension (McKeith and Mosimann, 2004).

When treating dementia patients, physicians need to assess the individual needs of their patient. The safety and tolerability of pharmacologic agents should be considered, along with their risk of side effects and worsening of both motor and cognitive functioning in PD-D and DLB. It is also important to remember when treating these patients, that they are often frail and can clinically decompensate quickly in the face of minor infection, metabolic stress, or environmental changes. Physician should carefully review medications, reduce doses if possible, carefully search for infections, normalize patient environment, and introduce medications one at a time (Rogan and Lippa, 2002).

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DEMENTIA IN PARKINSON'S DISEASE

Bradley J. Robottom and William J. Weiner

Department of Neurology, University of Maryland School of Medicine, Baltimore, Maryland 21230, USA

Parkinson's disease is the second most common neurodegenerative illness diagnosed in the United States. Dementia is recognized as a common component of advanced Parkinson's disease (PD). In patients with early PD, cognitive changes occur and primarily reflect impairment in executive function. It is unknown if the early cognitive changes detected on neuropsychological testing in Parkinson's disease are predictive of the subsequent development of Parkinson's disease with dementia (PDD). Many patients with PD develop dementia characterized by a wide range of cognitive deficits distinct from those seen in Alzheimer's disease (AD). Neuropsychiatric problems frequently accompany PDD. This chapter reviews the epidemiology, clinical characteristics of early and late cognitive changes, pathology, neuroimaging, diagnosis, and treatment of PDD.

I. Introduction

In the 1817 monograph, "An Essay on the Shaking Palsy," James Parkinson wrote that "the senses and intellect remain uninjured" (Parkinson, 1817). PD is still diagnosed based on the motor features that Parkinson described (resting tremor, bradykinesia, rigidity), but it has become clear that cognitive changes and dementia in PD are common. The cognitive effects of PD are varied, ranging from subtle executive dysfunction in the early stages of illness to dementia in

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advanced PD. For the purpose of this chapter, cognitive changes in early PD will be defined as changes seen in patients with recent onset of disease (<5 years disease duration) or with mild motor symptoms (Hoehn and Yahr stages I or II). This chapter will review epidemiology of PDD, clinical features of early and late cognitive changes, pathology, neuroimaging, diagnosis, and treatment of PDD.

II. Epidemiology

Prevalence estimates of PDD vary widely, with recent studies showing a 19-78% prevalence of PDD (Biggins *et al.*, 1992; de Lau *et al.*, 2005; Emre, 2004; Hobson and Meara, 2004; Levy *et al.*, 2002c). Amongst the general population older than 65 years of age, prevalence of PDD is 0.2-0.5% (Aarsland *et al.*, 2005). Lack of diagnostic accuracy, difference in sampling methods, variability in study populations, and lack of clear diagnostic criteria may all contribute to widely varying prevalence. Estimates of incidence also indicate that PDD is common with rates varying from 42.6 to 112.5 per 1000 person-years (Aarsland *et al.*, 2001a; Hobson and Meara, 2004; Hughes *et al.*, 2000; Marder *et al.*, 1996). The relative risk for a PD patient to develop dementia is 5.1 compared to age matched controls (Hobson and Meara, 2004).

Risk factors for the development of dementia include older age at onset of PD, greater severity of neurologic symptoms, longer duration of PD, greater disability, and male sex according to a longitudinal study by Hughes *et al.* (2000). Similar findings were reported by Aarsland *et al.* (2001a), whose data show that baseline factors predictive of the development of dementia include age, Hoehn and Yahr score >2, and Mini-Mental State Examination score <29. Non-dopaminergic signs of motor impairment such as dysarthria, postural instability, and gait disorder may have a particular association with PDD (Levy *et al.*, 2000; Pillon *et al.*, 1989). Consistently reported risk factors for incident PDD include age and severity of parkinsonism (Levy *et al.*, 2002c). In a prospective study evaluating risk factors for incident dementia, Levy *et al.* (2002c) showed that the combination of older age and high severity of extrapyramidal symptoms confer a relative risk incident dementia of 9.7 compared to a PD population of younger age and low severity. In their study, it was necessary to have both older age and higher severity to have an increased risk of developing dementia.

Other risk factors for the development of PDD include cigarette smoking and family history of dementia. The finding that cigarette smoking increases risk of PDD is of particular interest (Ebmeier *et al.*, 1990; Levy *et al.*, 2002b), as there is a decreased risk of developing PD in cigarette smokers (Morens *et al.*, 1995). Family history of a first-degree relative with dementia is more common in patients with PDD (Marder *et al.*, 1990), including Alzheimer's disease (Marder *et al.*, 1999).

The association between family history of dementia and the development of PDD has led to a number of gene alleles being evaluated as risk factors for PDD. However, no conclusive evidence has been found (Rippon and Marder, 2005).

III. Early Cognitive Changes in Parkinson's Disease

Deficits in executive function are among the first cognitive changes demonstrable in early PD and may be present in a majority of patients with PD (Cooper *et al.*, 1991; Levin *et al.*, 1989). Intact executive functioning is necessary for cognitive tasks that require planning, anticipation, goal selection, and using feedback to guide behavior (Levin and Katzen, 2005). Patients may perceive these difficulties as bradyphrenia, or slowness of thought (Fahn and Jankovic, 2007). Deficits may be subtle and difficult to detect on standard memory testing such as the Mini-Mental State Examination. More in-depth neuropsychological tests such as the Wisconsin Card Sorting Task show a tendency toward perseverative errors (Canavan, 1989; Levin *et al.*, 1989). Abnormalities of set shifting and maintaining set can be demonstrated in early PD using Raven's Progressive Matrices (Farina *et al.*, 2000). The modified Tower of London task may also show difficulty with set shifting and maintaining the correct response set, even in early PD patients (Owen *et al.*, 1992). In Owen's study of non-medicated patients with PD, there were no differences in accuracy and initial thinking time, reinforcing that executive function deficit may be subtle. These early, subtle changes in executive function may not have clinical consequence. There are many early patients with high level professional and management positions.

Memory impairment occurs early in PD and may be related primarily to executive dysfunction leading to disruption of the memorization process (Levin and Katzen, 2005). Memory impairment in early PD is independent of dementia. Patients with PD perform comparably to controls on tasks of recall of unrelated words and spatial position (Taylor *et al.*, 1990). However, there may be deficits in the recall of semantically related words (California Verbal Learning Test), deficient source memory, and increased sensitivity to interference (Taylor *et al.*, 1990). PD patients are less likely to use strategies such as clustering that facilitate recall. Supporting the findings from Taylor's study, increased sensitivity to interference was also found in newly diagnosed PD patients by using the Brown-Peterson Distractor Task (Cooper *et al.*, 1993). Impaired inhibition is theorized to be the cause of PD patients' inability to maintain relevant information during distraction tasks (Kensiger *et al.*, 2003). These studies support the contention that memory impairment in early PD is related to executive dysfunction, causing a disruption in the necessary processes of sequencing and encoding new memories.

Patients with PD often complain of slowness of thought (Fahn and Jankovic, 2007), but this is hard to demonstrate in early PD. Many cognitive tasks have a motor component, so this must be accounted for in tests designed to evaluate processing speed in PD. One study comparing newly diagnosed, untreated PD patients with medicated PD patients and healthy controls found increased reaction time in both groups of PD patients. Based on their findings, the authors hypothesized that prolonged response time had a cognitive basis that was not dopaminergic (Jordan *et al.*, 1992). Cognitive processing time has been linked to the difficulty of the task. Early, untreated PD patients were compared to advanced, untreated PD patients and healthy control subjects. Untreated PD patients and controls performed similarly on simple reaction tasks; however, reaction time decreased with complex tasks (Zimmerman *et al.*, 1992). The authors concluded that the decision making process in PD patients is impaired when confronted with tasks that demand higher cognitive functioning. Zimmerman's findings of increasing reaction time in response to task complexity have been replicated by Cooper *et al.* (1994), who refer to the "cognitive-analytical" deficit which becomes apparent as cognitive complexity increases.

Visuospatial abnormalities are reported to be the most common deficits in PD, partly because of the wide range of abnormalities that are referred to as visuospatial (Levin and Katzen, 2005). Some of the more commonly tested visuospatial tasks which have shown abnormalities include facial recognition, spatial memory, spatial planning, visual attention, and visual orientation (Farina *et al.*, 2000; Levin, 1990; Postle *et al.*, 1997; Sharpe, 1990). In addition to difficulty with facial recognition, patients with PD also have difficulty recognizing emotional facial expressions (Dujardin *et al.*, 2004). Along with memory deficits in early PD, visuospatial deficits are also hypothesized to result from executive dysfunction leading to a failed integration of information (Levin and Katzen, 2005; Rippon and Marder, 2005).

Language ability is largely preserved in PD. The language deficits that do exist are subtle, consisting of hesitations at the beginning of speech (Illes, 1989), perseverative intrusions on word fluency tasks (Lees and Smith, 1983), and decreased categoric and letter fluency (Jacobs *et al.*, 1995; Levin *et al.*, 1989). There is no evidence for aphasia. The language deficits that are present appear to involve planning and execution of the motor aspect of language. These findings are suggestive of impaired executive function, a unifying factor in early cognitive changes in PD.

The cognitive changes observed in early PD are of uncertain significance. They are generally mild and detectable only on formal cognitive testing. There is no evidence suggesting that findings of executive dysfunction in the early stages of PD predispose a patient to developing dementia, although decreased performance on verbal fluency was predictive of development of dementia in a cohort of nondemented PD patients of longer disease duration (Levy *et al.*, 2002a).

Current evidence does not suggest that these findings are analogous to mild cognitive impairment and AD. Further research is needed to determine the significance of executive dysfunction in early PD.

IV. Clinical Features of Parkinson's Disease Dementia

Impairment of executive function is one of the earliest cognitive changes detectable in PD, and it is the core feature of PDD (Emre, 2003; Pillon *et al.*, 1996). The most prominent features of executive impairment include difficulty with problem solving, concept formulation, set shifting, and attention (Rippon and Marder, 2005). Performance of tests such as the Raven's Progressive Matrices and Wisconsin Card Sorting Test show impairment in PDD compared to controls or nondemented PD patients (Aarsland *et al.*, 2003; Litvan *et al.*, 1991; Noe *et al.*, 2004; Paolo *et al.*, 1996). In comparison to the most common cause of dementia, AD, PDD patients have more impairment on executive tasks (Litvan *et al.*, 1991). Other features distinguishing PDD from AD include decreased speed of information processing in PDD and a direct association between memory function and degree of executive impairment (Huber *et al.*, 1989b; Pillon *et al.*, 1993). PDD patients have difficulty switching set and maintaining attention (Girotti *et al.*, 1988; Noe *et al.*, 2004). Impaired attention in PDD is similar in severity to that seen in AD and dementia with Lewy bodies (DLB) (Aarsland *et al.*, 2003; Litvan *et al.*, 1991). However, attention may fluctuate more in PDD than AD (Ballard *et al.*, 2002). Perseverative errors are common and may be lessened by dopaminergic medication (Owen *et al.*, 1993). Cognitive reaction time and vigilance, both markers of attention, are impaired in PDD (Litvan *et al.*, 1991). Patients with PDD actually perform comparably to patients diagnosed with DLB on tasks of attention (Ballard *et al.*, 2002).

Memory impairment in PDD is characterized by a failure of retrieval rather than a failure to encode information (Emre, 2003). It is the presenting problem in 67% of patients with PDD, as opposed to DLB (94%) and AD (100%) (Noe *et al.*, 2004). Semantic and episodic memory is impaired, but benefit from cueing, reflecting that failure of retrieval rather than encoding is the primary problem (Rippon and Marder, 2005). Inability to effectively encode and retrieve information is thought to represent the effects of striatofrontal dysfunction (Pillon *et al.*, 1993). The primacy of the retrieval problem differentiates PDD from AD, where encoding is the primary problem (Stern *et al.*, 1993). The degree of memory impairment is probably less than that seen in AD (Emre *et al.*, 2007), and the increased burden of AD pathology in the hippocampus and temporal cortex may explain these differences (Pillon *et al.*, 1993).

Visuospatial deficits are common in PDD. Deficits may be present before a diagnosis of dementia can be made and consist of abnormalities in facial recognition, spatial memory, spatial planning, visual attention, and visual orientation (Farina *et al.*, 2000; Levin, 1990; Postle *et al.*, 1997; Sharpe, 1990). The deficits are thought to have both a perceptual and motor basis (Boller *et al.*, 1984). Compared to AD patients with a similar dementia severity, the visuospatial deficits of PDD are more severe (Huber *et al.*, 1989b; Mosimann *et al.*, 2004; Stern *et al.*, 1993). It is hypothesized that visuospatial deficits of PDD are mediated in caused in part by executive dysfunction (Levin and Katzen, 2005; Rippon and Marder, 2005).

Language deficits in PDD are varied. Aphasia is rare and should call into question the diagnosis of PDD (Emre *et al.*, 2007). Impaired verbal fluency is often seen before a diagnosis of dementia and is a common feature of PDD (Emre, 2003; Stern *et al.*, 1993). The severity of verbal fluency impairment is similar to that observed in AD (Cahn-Weiner *et al.*, 2002; Pillon *et al.*, 1993). Other features of language involvement include less content to speech, impaired naming, shorter phrase length, and dysarthria (Cummings *et al.*, 1988). Comprehension difficulties have also been noted, particularly with interpreting ambiguity and figurative language (Grossman *et al.*, 1992; Lewis *et al.*, 1998). When compared to the language deficits of AD, PDD patients display greater motor speech problems but fewer language problems (Cummings *et al.*, 1988).

Neuropsychiatric and behavioral symptoms are common in PDD, including psychosis, mood disturbance, and apathy. Psychosis in PDD is common, with hallucinations in 45–65% of patients and delusions occurring in 25–30% (Aarsland *et al.*, 2001, 2007; Fenelon *et al.*, 2000). Visual hallucinations occur twice as often as auditory hallucinations, and the visual hallucinations are usually complex, formed visions. The most common hallucination is of unknown people (Fenelon *et al.*, 2000; Mosimann *et al.*, 2006). The phenomenology is similar to that observed in DLB (Emre *et al.*, 2007). Delusions in PDD most often have a paranoid component, while the "phantom boarder" delusion is the second most commonly reported (Aarsland *et al.*, 2001b). Delusions and hallucinations may co-occur and lead to nursing home placement (Aarsland *et al.*, 2000).

Mood disturbances are not uncommon in PDD, with depression and anxiety being the most common. The frequency of major depression in PDD was 13% in one community-based study (Aarsland *et al.*, 2001b). While major depression was more common in PDD than AD, the prevalence of dysphoric mood was similar (Starkstein *et al.*, 1996). Anxiety often appeared with depression or dysphoric mood, and it was a common problem in PDD (Aarsland *et al.*, 2007; Menza *et al.*, 1993). PDD patients also have high rates of apathy, with apathy and depression being common comorbidities (23-54%) (Aarsland *et al.*, 2001b, 2007).

V. Pathology

The pathologic hallmarks of PD are Lewy neurites, thread-like bodies found in cellular processes, and Lewy bodies, found in neuronal perikarya (Pollanen *et al.*, 1993). The major component of these inclusion bodies is an aggregated form of α -synuclein. In PD, α-synuclein binds with other proteins to form insoluble Lewy neurites and Lewy bodies (Braak *et al.*, 2003). Pathological change in PD develops before the disease is symptomatic, and it is proposed to follow a predictable course (Braak *et al.*, 2003). The first sites thought to be affected are the dorsal motor nuclei of the glossopharyngeal and vagal nerves, the olfactory bulb, and the anterior olfactory nucleus. The sites involved differentiate PD from multiple system atrophy and possibly from DLB (Braak *et al.*, 2003; Galvin *et al.*, 2001). Pathological changes are hypothesized to proceed up the brainstem and through areas adjacent to the olfactory nucleus including piriform cortex and entorhinal cortex. As the disease spreads through the brainstem, the pars compacta of the substantia nigra becomes involved, leading to neuronal loss and the motor features of PD. According to this hypothesis, pathology is next found in the temporal mesocortex, and eventually spreads to multiple cortical areas including sensory association areas, premotor fields, primary sensorimotor cortex, and limbic structures including the amygdala and hippocampus (Braak *et al.*, 2003). Involvement of limbic structures and other cortical structures with Lewy body pathology may be the basis for PDD (Braak *et al.*, 2000); although, non-dopaminergic transmitter systems including noradrenergic, cholinergic, and serotonergic have been implicated (Rippon and Marder, 2005; Zgaljardic *et al.*, 2004).

Involvement of non-dopaminergic systems in the pathophysiology of PDD is supported by neuropathological studies. Neuronal loss in the locus ceruleus, a noradrenergic site, is more severe in PD patients with dementia than those without dementia (Chui *et al.*, 1986; Zweig, 1993). The degree of cell loss in the locus ceruleus correlates with neuronal loss in other areas including the nucleus basalis of Meynert, medial substantia nigra pars compacta, ventral tegmental area, and the burden of Lewy bodies in the anterior cingulate gyrus (Zweig, 1993). Cholinergic dysfunction is caused by involvement of the nucleus basalis of Meynert, with neuronal loss in PDD equal or greater to that seen in AD (Bohnen *et al.*, 2003). Involvement of the cholinergic system is thought to be the cause of decreased processing speed and contribute to the cognitive decline of PDD (Korczyn, 2001; Whitehouse *et al.*, 1983). Serotonergic loss in PDD is a result of neuronal loss in the dorsal raphe nuclei and is thought to account for some of the cognitive impairment of PDD (Jellinger, 1997; Zweig, 1993).

Concurrent AD pathology may further cognitive decline in PDD. Typical AD pathology including neurofibrillary tangles, neuritic plaques, and neuropil threads has been found more often in PDD than PD patients without dementia

(Braak and Braak, 1991; Paulus and Jellinger, 1991). In particular, there is a higher burden of cortical AD pathology found in PDD patients (Paulus and Jellinger, 1991). It has been hypothesized that Lewy body and AD pathology are triggered by a common cause, which would explain the correlation between the two (Apaydin *et al.*, 2002). Unlike the early involvement of sensory association areas seen in AD (Vermersch *et al.*, 1992), AD pathology found in PDD patients is found predominantly in frontal, temporal, and entorhinal cortices (Vermersch *et al.*, 1993). It seems likely that a combination of disrupted neurotransmitter systems, AD pathology, and Lewy body pathology all contribute to the clinical manifestations of PDD.

VI. Neuroimaging

Neuroimaging is not used routinely in the diagnosis of PDD. However, studies are available detailing common imaging findings of PDD in magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), positron emission topography (PET), and proton magnetic resonance spectroscopy (MRS). Early studies detailing results of MRI in PDD stated that there were no specific structural abnormalities that could be identified (Huber *et al.*, 1989a). More recently, preferential atrophy has been found in the substantia innominata (Hanyu, 2002), amygdala (Junque *et al.*, 2005), and hippocampus (Junque *et al.*, 2005; Laakso *et al.*, 1996). The degree of hippocampal atrophy is greater than would be seen in AD (Laakso *et al.*, 1996). Generalized atrophy is also present, and the rate of atrophy is greater than seen in PD patients without dementia (Burton *et al.*, 2005).

SPECT studies in PDD show a consistent pattern of bilateral temporal-parietal hypoperfusion, a pattern that is also seen in AD (Antonini *et al.*, 2001; Firbank *et al.*, 2003; Tachibana *et al.*, 1993). Using SPECT to track progression of dopaminergic degeneration demonstrates significant progressive loss that correlates to both motor impairment and dementia severity in PDD and DLB (Colloby *et al.*, 2005). The usefulness of SPECT as a diagnostic tool is limited due to its relative inability to distinguish PDD from other forms of dementia, and PET imaging shares a similar shortcoming. Studies of PET imaging in PDD show a pattern of bilateral temporal-parietal hypometabolism which cannot be reliably distinguished from AD (Goto *et al.*, 1993; Peppard *et al.*, 1992; Vander Borght *et al.*, 1997). Although PDD patients do appear to have a characteristic change of lower *N*-acetylaspartate levels in the occipital cortex on MRS (Summerfield *et al.*, 2002), MRS remains primarily a research tool and its clinical utility in differentiating PDD from other parkinsonian neurodegenerative disorders is unclear (Seppi and Schocke, 2005).

VII. Diagnosis

Prior to 1997, PDD was diagnosed according to DSM IV criteria, which were relatively nonspecific (Rippon and Marder, 2005). In 2007, the Movement Disorders Society created a task force which developed clinical diagnostic criteria for PDD. PDD is a slowly progressive dementia that develops with the context of established PD. There must be deficits in at least two of four core cognitive domains (attention, memory, executive, and visuospatial). The deficits must be severe enough to interfere with normal functioning. Behavioral features such as hallucinations, delusions, apathy, and changes in mood are frequently present but not necessary for diagnosis of PDD. The label of "possible PDD" is given to patients who do not have behavioral features, who have an atypical cognitive profile, or who have another abnormality which may explain the cognitive dysfunction (such as significant vascular disease, major depression, or a concurrent toxic/metabolic encephalopathy). A diagnosis of "probable PDD" requires a diagnosis of PD, a slowly progressive dementia defined by deficits in at least two of four core cognitive domains (attention, memory, executive, and visuospatial), and the presence of a behavioral feature (Emre *et al.*, 2007).

VIII. Treatment

There are no pharmacologic agents that have been developed specifically for the treatment of PDD. The agents that are currently used were first developed for AD and were subsequently studied in PDD. Randomized, double-blind, placebo controlled trials (RCTs) are limited in number and are confined to acetylcholinesterase inhibitors. Three small, RCTs of donepezil for treatment of PDD showed improvement in Mini-Mental State Examination of two points (Aarsland *et al.*, 2002; Ravina *et al.*, 2005) and improvement in the memory subscale of the Mattis Dementia Rating Scale (Leroi *et al.*, 2004). Overall the drug was well tolerated with few reports of increased parkinsonism. The overall benefit of donepezil is modest, and the American Academy of Neurology Practice Parameters state that donepezil "should be considered for the treatment of dementia in PD" (Miyasaki *et al.*, 2006). One large, RCT of rivastigmine was performed, and the results showed moderate improvements in dementia that were accompanied by worsening tremor in 10% of patients (Emre, 2004). Like donepezil, the AAN recommends that rivastigmine "should be considered for the treatment of dementia in PD" (Miyasaki *et al.*, 2006). Small, open label studies of tacrine and galantamine also report modest benefits on cognition (Aarsland, 2002; Hutchinson and Fazzini, 1996), but no RCTs of these agents have been performed. Memantine,

an NMDA antagonist used in the treatment of AD, has not been studied for the treatment of PDD.

Treatment of the neuropsychiatric or behavioral features of PDD may take a variety of approaches. The first strategy employed in the treatment of psychosis is to reduce the dose of those drugs which are least potent with respect to motor impairment (Fig. 1). Medications that are known to cause psychosis (e.g., dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, catechol-*O*-methyl transferase (COMT) inhibitors, amantadine) should be discontinued. If this is unsuccessful in resolving psychosis, then the daily levodopa dose should be reduced until unacceptable motor complications arise. If psychosis persists after reducing dopaminergic medications, then the addition of an antipsychotic medication may be necessary. The AAN Practice Parameters state that clozapine is "probably an effective treatment and improves psychosis" and quetiapine "possibly improves psychosis" in PD (Miyasaki *et al.*, 2006). Clozapine is the only antipsychotic that has been proved effective for psychosis in PD as both RCTs of quetiapine have failed to show benefit (Ondo *et al.*, 2005; Rabey *et al.*, 2007). However, quetiapine is often prescribed first because of the risk of agranulocytosis seen with clozapine. Other antipsychotics are not recommended because of their effects on motor function in PD. Open label trials of rivastigmine and donepezil have suggested that acetylcholinesterase inhibitors may be beneficial for psychosis in PDD

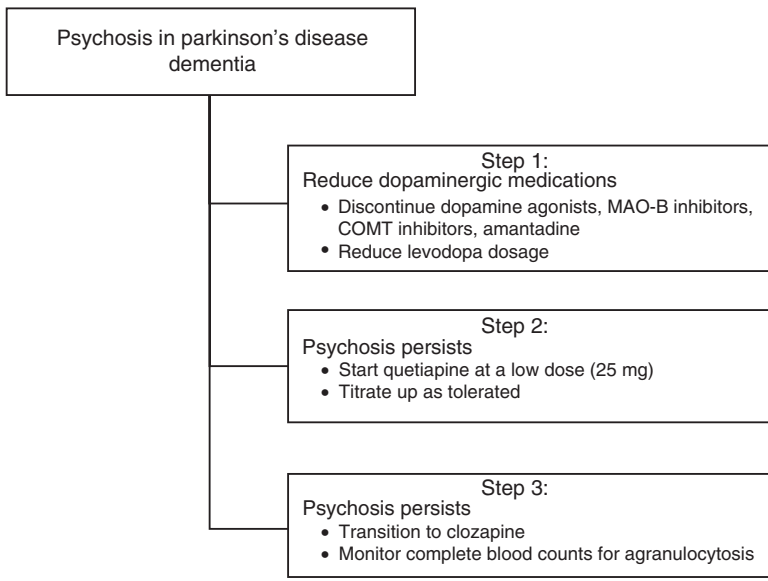

FIG. 1. Treatment of psychosis in PDD.

(Bergman and Vladimir, 2002; Reading *et al.*, 2001). One RCT of rivastigmine suggested that PDD patients with psychosis (visual hallucinations) may have greater cognitive benefit from rivastigmine than those without psychosis. The study was not powered to examine behavioral differences (Burn *et al.*, 2005). Acetylcholinesterase inhibitors may be a reasonable treatment option for psychosis in PD, though they do not have the proved efficacy of antipsychotic medications.

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EARLY ONSET DEMENTIA

Halim Fadil,* Aimee Borazanci,* Elhachmia Ait Ben Haddou,†
Mohamed Yahyaoui,† Elena Korniychuk,* Stephen L. Jaffe,* and Alireza Minagar*

*Department of Neurology, Louisiana State University School of
Medicine-Shreveport, Shreveport, Louisiana 71103, USA
†Service de Neurologie B et Neurogenetique, Hopital des Specialties, Rabat, Morocco

Dementia is characterized by a decline in cognitive faculties and occurrence of behavioral abnormalities which interfere with an individual's activities of daily living. Dementing disorders usually affect elderly individuals but may occur in individuals younger than 65 years (early-onset dementia or EOD). EOD is often misdiagnosed or its diagnosis is delayed due to the fact that it has a more varied differential diagnosis than late-onset dementia. EOD affects individuals at the height of their career and productivity and produces devastating consequences and financial loss for the patient's family as well as society. EOD is not uncommon and is diagnosed in up to a third of patients presenting with dementia. Most importantly, some of the causes of EOD are curable which makes the need for a specific and timely diagnosis crucial. The present chapter presents a systematic approach to the differential diagnosis of EOD and provides readers with the clinical and neuroimaging features of these disorders as well as important considerations for their diagnostic evaluation. Specifically, the nuances of assessing the history and examination are discussed with careful attention to the various methods of cognitive and behavioral evaluation. A step-wise approach to diagnostic testing is followed by a discussion of anatomical localization, which often aids in identifying specific etiologies. Finally, in order to organize the subject for

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the reader, the various etiologies are grouped under the general categories of vascular, infectious, toxic-metabolic, immune-mediated, neoplastic/metastatic, and neurodegenerative.

I. Introduction

Dementia is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), fourth edition (American Psychiatric Association) as a group of disorders which is characterized by the development of multiple cognitive deficits which include memory loss and dysfunction in at least another cognitive domain, severe enough to interfere with activities of daily living (ADLs). Other cognitive domains include executive function, language, praxis, and gnosis. While dementia is usually regarded as a disorder of old age (i.e., 65 and older) it can affect younger individuals under age 65. Early onset dementia (EOD) is not uncommon and has been reported in approximately one third of all patients presenting with dementia in developed countries, with a prevalence varying from 67 to 81/100,000 persons in the 45- to 65-year-old age group (Harvey *et al.*, 2003). McMurtray *et al.* (2006) reported EOD in 29.3% of 948 US veterans diagnosed with dementia in a memory disorders clinic. Its prevalence may be higher in less developed countries; 46.6% of 311 patients were found to have EOD in a Brazilian study (Fujihara *et al.*, 2004). EOD affects individuals during their most productive phase of life and has a devastating impact upon their families as well as a major economic impact upon society. In this chapter, we will review the diagnostic approach to EOD emphasizing the differential diagnosis, with the objective of presenting a paradigm which will aid in clinical recognition of curable subtypes.

II. Diagnostic Approach

The EOD diagnostic process consists of the following steps: obtaining the patient's history including interviewing a caregiver or a family member, and performance of a physical/neurological examination, formal cognitive assessment, laboratory testing, and neuroimaging. Important historical information includes the patient's age at onset of cognitive impairment; other associated neurological or systemic symptoms; the presence of co-morbidities (i.e., hypertension, diabetes mellitus, hyperlipidemia); dementia risk factors such as repetitive head trauma, alcohol abuse, or a family history of dementia; and the course of illness pattern (i.e., gradual in Alzheimer's disease versus stepwise in vascular

dementia). Interviewing a caregiver or a family member separately to obtain a more complete and accurate picture may provide useful diagnostic clues which they may not feel comfortable in disclosing with the patient being present. Moreover, patients may omit important aspects of their history because of poor insight into their illness or simply due to cognitive decline.

The neurological examination may provide significant findings further narrowing the differential diagnosis and directing the diagnostic work-up (Table I). For instance, the presence of focal findings such as corticospinal tract signs raises suspicion for stroke or a neoplastic process, while the presence of gait apraxia and sphincter incontinence suggests normal pressure hydrocephalus (NPH). Peripheral neuropathy may suggest B12 deficiency. Examination of other systems is also necessary to exclude the possibility of a multi-systemic process such as vasculitis, infection, metastases, or metabolic disorder (Table II). For example, the presence of a facial "butterfly" rash may suggest systemic lupus erythematosus; and uveitis may indicate sarcoidosis or Behcet's disease.

When dementia is suspected, a formal cognitive evaluation is necessary. Cognitive domains that need to be assessed are orientation, attention, language, memory, executive function, praxis, and visuospatial function. The most popular bedside cognitive test is the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975). As a practical bedside tool, the MMSE can be administered quickly. While the MMSE is highly sensitive and specific in detecting moderate to severe dementia, it remains an inaccurate tool for assessing mild dementia. Other limitations of the MMSE include restricted evaluation of executive function (i.e., limited to working memory) and inability to accurately assess non-educated patients. The clock-drawing test is another popular bedside test that can be administered in 5–10 min. It is used to evaluate mainly visuospatial, parietal lobe function as well as general executive functions of the frontal lobes. However, just like the MMSE, it lacks sensitivity for the diagnosis of mild dementia. To address the shortcomings of these tests, a number of more sensitive cognitive tests have been developed. Examples are the Addenbrooke's Cognitive Assessment (Mathuranath *et al.*, 2000), DemTect (Kalbe *et al.*, 2004), the Montreal Cognitive Assessment (Nasreddine *et al.*, 2005), and the Behavioral Neurology Assessment, short form (Darvesh *et al.*, 2005). Review of all these cognitive tests is beyond the scope of this article. However, it is important to mention that none is as extensive as neuropsychological testing which clearly determines the extent of cognitive dysfunction and establishes a neuropsychological profile. Often the disclosed pattern of cognitive decline can identify the EOD subtype.

At the end of the clinical evaluation, it may be useful to categorize the dementia into cortical, subcortical, or mixed types. Cortical dementia is clinically characterized by impairment of memory, language, gnosis, and praxis (i.e., Alzheimer's disease, Creutzfeld-Jakob disease). Subcortical dementia is characterized by less severe memory dysfunction, bradyphrenia, and executive dysfunction

TABLE I
NEUROLOGICAL SIGNS OR SYNDROMES AND CORRESPONDING POTENTIAL DIAGNOSES

Physical sign	Potential diagnosis
Papilledema	Brain tumor, subdural hematoma, hydrocephalus
Optic disc pallor	Multiple Sclerosis (MS), B12 deficiency
Blindness	Cerebrovascular disease, Alzheimer's disease (AD), Creutzfeld-Jakob disease (CJD)
Pigmentary retinal degeneration	Panthotenate kinase-associated neurodegeneration (PKAN)
Visual field defect	Cerebrovascular disease, Neoplasm, CJD
Kayser-Fleischer ring	Wilson's disease
Argyll Robertson pupil (reactive to accomodation but not to light)	Neurosyphilis
Optic neuritis	MS, Sarcoidosis, Lyme disease
Anosmia	Subfrontal meningioma, AD, Parkinson's disease (PD), Traumatic brain injury, Huntington's disease (HD)
Abnormal eye movements	Progressive supranuclear palsy (PSP), Corticobasal degeneration (CBD), Wernicke-Korsakoff syndrome, Whipple's disease, CJD, mitochondrial disorders
Parkinsonism	Dementia with Lewy bodies (LBD), PD, Vascular dementia (VaD), PSP, CBD, HD, Wilson's disease, PKAN, Dentatorubral-Pallidoluysian atrophy (DRPLA), Neuroacanthocytosis, CADASIL, Multiple system atrophy (MSA), Neuroferritinopathy
Myelopathy	Neurosyphilis, B12 deficiency, HIV, MS, spinocerebellar ataxia (SCA)
Pyramidal signs	Cerebrovascular disease, Brain tumors, Hydrocephalus, MS, AD, CJD, CBD, Leukodystrophies, Frontotemporal Dementia (FTD)
Alien hand	CBD
Myoclonus	CJD, AD, Subacute sclerosing panencephalitis (SSPE), CBD, LBD, Hashimoto's encephalopathy
Early onset incontinence	Hydrocephalus, Frontal lobe tumor, PSP
Bulbar signs	FTD (in association with Motor neuron disease)
Ataxia	Paraneoplastic syndromes, Whipple's disease, CJD, AIDS dementia complex, SCA, Wernicke-Korsakoff syndrome, PKAN, Mitochondrial disorders, Leukodystrophies, Lead poisoning
Peripheral neuropathy	B12 deficiency, paraneoplastic disorders, SLE, PKAN, Neuroacanthocytosis, SCA, Lead poisoning
Seizures	Cerebrovascular disease, Vasculitis, Neoplasms, Limbic encephalitis, AIDS dementia complex, Neurosyphilis, SSPE, Hashimoto's encephalopathy
Early gait disorder	Hydrocephalus, PSP, MSA, LBD

Reference: Cooper and Greene (2005).

TABLE II
NON-NEUROLOGICAL SIGNS OR SYNDROMES AND CORRESPONDING POTENTIAL DIAGNOSES

Physical sign	Potential diagnosis
Uveitis	Sarcoidosis, Behcet's disease
"Butterfly" facial rash	Systemic lupus erythematosus (SLE)
Dermatitis	Niacin deficiency
Macrocytic anemia	B12 deficiency

(i.e., Huntington's disease, Parkinson's disease). Certain conditions such as dementia with Lewy bodies (LBD) and corticobasal degeneration (CBD) cause a mixed type of dementia with both cortical and subcortical signs.

Recommended diagnostic studies include complete blood count, erythrocyte sedimentation rate, complete metabolic panel, thyroid profile, rapid plasma reagin, serum folate/vitamin B12 levels, ANA, urinalysis, urine toxicology, chest X-ray, and computerized assisted tomographic (CAT) brain imaging. Other investigations such as HIV serology, determination of angiotensin converting enzyme (ACE) level (serum/CSF), paraneoplastic antibodies, cerebrospinal fluid analysis, electroencephalography, and brain magnetic resonance imaging (MRI) will be directed by the history/physical examination and abnormal results of screening tests. Specialized tests such as slit lamp examination and genetic screening for certain hereditary disorders are considered if specific disorders are strongly suspected. At times, brain biopsy will be required. Functional neuroimaging including positron emission tomography (PET) with 2-fluoro-2-deoxy-D-glucose, single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI), even though not considered part of the routine work-up for dementia, may provide data to differentiate various types of neurodegenerative diseases.

III. Differential Diagnosis

A diagnosis of dementia cannot be established before excluding mental retardation, depression, and delirium. Mental retardation is excluded during history taking when the patient's level of cognition is determined to be deteriorating as compared to baseline. Depression may imitate dementia since it impairs concentration, and thus blocks effective data input and memory formation (i.e., pseudodementia). Depressive symptoms should be actively sought after during the interview with both the patient and family members. Occasionally, a detailed neuropsychological evaluation is required to differentiate dementia from depression. However, depression may coexist with dementia or even be one of the

clinical manifestations of the dementing illness. Delirium must also be excluded when evaluating a patient presenting with dementia. Delirium is defined as a transient acute confusional state with fluctuating level of consciousness and is considered to be a medical emergency with high risk of morbidity and mortality. Toxic and metabolic disorders are primary causes, and urgent medical investigation and proper treatment of the delirium are necessary. Additionally, a diagnosis of dementia cannot be established during a delirious state, even though demented patients are more prone to develop delirium.

Once the diagnosis of dementia is established, the specific etiology should be determined. Many underlying pathologies must be considered, and a systematic diagnostic approach is required. Vascular, infectious, toxic-metabolic, immune-mediated, metastatic/neoplastic, iatrogenic, and neurodegenerative problems can be etiologic and will be discussed in detail (Table III).

A. Vascular Diseases

Dementia related to cerebrovascular disease (initially termed "arteriosclerotic dementia," then "multi-infarct dementia," and later "vascular dementia" (VaD)) recently has been incorporated under the broader umbrella of "vascular cognitive impairment" (Bowler, 2005). Certain studies have found it to be the most common cause of EOD (McMurtray *et al.*, 2006), while others rank it as second to Alzheimer's disease (Harvey *et al.*, 2003; Shinagawa *et al.*, 2007). Clinically and neuropathologically, VaD represents a heterogeneous group of disorders which manifests with various neurological signs and behavioral syndromes as well as variable cognitive profiles depending on the location (cortical, subcortical, or mixed) of the vascular lesions. The underlying neuropathology is also variable and may be ischemic or hemorrhagic, focal or diffuse, and predominantly either cortical or subcortical. Based on these findings and other characteristics such as the size, location, and number of infarcts, multiple morphologic classifications exist (Jellinger, 2007). One classification system divides this type of dementia into large vessel disease (LVD) and small vessel disease (SVD). LVD, which is usually associated with atherosclerosis leading to classical multi-infarct encephalopathy, is the cause of only about 15% of VaD cases. SVD is the most common cause of VaD and comprises multiple subtypes such as strategic infarct dementia, Binswanger's syndrome, and hereditary vasculopathies.

Strategically located strokes in areas such as the thalamus, frontocingulate cortex, basal forebrain, hippocampus, caudate nucleus, and angular gyrus may cause dementia. For example, thalamic dementia secondary to bilateral ischemic infarction in the distribution of the paramedian thalamic arteries is a subcortical dementia characterized by marked apathy and impaired attention, as well as anterograde and retrograde amnesia. Typically, thalamic dementia occurs in a

TABLE III
DIFFERENTIAL DIAGNOSIS OF EARLY ONSET DEMENTIA

Vascular diseases	Metastatic/Neoplastic disorders
Cerebrovascular disease (multi-infarct state, strategic infarct dementia)	Brain metastatic disease
Binswanger's syndrome	Primary CNS lymphoma
Hereditary vasculopathies: (CADASIL)	Intravascular lymphoma
Infectious diseases	Lymphomatoid granulomatosis
HIV-associated dementia	Gliomatosis cerebri
Neurosyphilis	Iatrogenic disorders
Lyme disease	Alcohol related
Whipple's disease	Drug related
Subacute sclerosing panencephalitis	Bismuth toxicity
Neurocysticercosis	Lithium toxicity
Progressive multi-focal leukoencephalopathy	Mercury toxicity
Chronic meningitis	Arsenic toxicity
Toxic-metabolic disorders	Neurodegenerative diseases
Thyroid disease	Alzheimer's disease
Parathyroid disturbance	Dementia with Lewy bodies
Adrenal disease	Frontotemporal dementia,
Hepatic encephalopathy	Parkinson's disease
Renal failure and dialysis dementia	Progressive supranuclear palsy
B12, thiamine, niacin, folate deficiencies	Corticobasal degeneration
Porphyria	Huntington's disease
Leukodystrophies	Wilson's disease
Mitochondrial disorders	Neurofilament inclusion body disease
Electrolyte abnormalities	Pantothenate kinase-associated degeneration
Immune-mediated diseases	Neuroferritinopathy
Paraneoplastic syndromes	Neuroacanthocytosis
Multiple sclerosis	Miscellaneous disorders
Primary CNS angiitis	Traumatic brain injury (dementia pugilistica)
Systemic vascultides	Normal pressure hydrocephalus
Lupus cerebritis	Down syndrome (trisomy 21)
Hashimoto's encephalopathy	Obstructive sleep apnea
Nonvasculitic autoimmune inflammatory meningoencephalitis	

patient with multiple vascular risk factors such as hypertension and diabetes mellitus. It may also be observed in association with cocaine abuse. Subcortical microvascular leukoencephalopathy (also known as Binswanger's syndrome) was initially described by Binswanger (1894), and is clinically characterized by an insidiously progressive dementia in association with persistent hypertension. Brain imaging usually reveals multifocal and confluent lesions affecting the periventricular regions and/or deep white matter (Jellinger, 2007).

The most common hereditary cerebral angiopathy is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

(CADASIL). CADASIL is caused by mutations in the Notch 3 gene on chromosome 19q12. The Notch 3 gene encodes a receptor protein which is expressed on vascular smooth muscle cells and, when mutated, leads to formation of a non-amyloid, non-atherosclerotic microangiopathy. It is clinically characterized by the tetrad of migraine with aura, recurrent stroke, cognitive impairment leading to a subcortical dementia, and psychiatric manifestations.

B. Infectious Diseases

Dementia may occur in association with several infectious diseases, of which the most common ones are discussed below.

1. *HIV-Associated Dementia*

HIV-associated dementia (HAD) is the most devastating neurological complication of HIV infection consisting of a constellation of progressively disabling symptoms involving cognitive faculties, motor function, and behavior (Minagar *et al.*, 2008). AIDS patients with less serious degrees of cognitive and motor impairments not meeting the diagnostic criteria for dementia are diagnosed as HIV-associated cognitive/motor disorder (MCMD). The classical neuropsychological deficits in patients with HAD indicate dysfunction of frontal and subcortical circuits. HAD, as a predominantly subcortical dementia, presents with memory loss (mainly for retrieval of recorded information), psychomotor slowing, depression, and withdrawal from ADLs. Price and Brew (1988) developed the Memorial Sloan Kettering scale for HAD which classifies these patients as normal, mild, moderate, severe, and end stage (Table IV). Neuropathological findings in HAD consist of frontotemporal atrophy, and the presence of multiple small nodules (microglial nodules) containing macrophages, lymphocytes, and microglia scattered throughout the cerebral white matter, and the subcortical gray matter of the thalamus, basal ganglia, and brainstem. Brain imaging, particularly MRI with gadolinium, is necessary to exclude other causes of dementia which may imitate the HAD clinical picture. These other disorders in AIDS patients include toxoplasmosis, progressive multifocal leukoencephalopathy, cryptococcal infection, cytomegalovirus encephalitis, and CNS lymphoma. Brain MRI in patients with HAD reveals diffuse, non-enhancing, ill-defined areas of hyperintense signal in deep white matter along with cerebral atrophy, ventricular enlargement, and caudate region atrophy. Proton magnetic resonance spectroscopy (MRS) in HAD patients demonstrates increased myoinositol (indicating gliosis) and choline (indicating demeyelination) levels in gray and white matter along with decrease in levels of *N*-acetyl aspartate in gray matter (indicating neuronal/axonal loss). HAART treatment has been reported to have decreased the present incidence of HIV dementia (Sacktor *et al.*, 2003). However, HAD

TABLE IV
CLINICAL STAGING OF THE AIDS DEMENTIA COMPLEX

Stage 0 (normal)
Normal mental and motor function
Stage 0.5 (equivocal and subclinical)
Absent, minimal, or equivocal symptoms without impairment of work or capacity to perform ADLs. Mild signs (snout response, slowed ocular, or extremity movements) may be present. Gait and strength are normal
Stage 1 (mild)
Able to perform all but the more demanding aspects of work or ADLs, but with unequivocal evidence (signs or symptoms that may include performance on neuropsychological testing) of functional intellectual or motor impairment. Can walk without assistance
Stage 2 (moderate)
Able to perform basic activities of self-care, but cannot work or maintain the more demanding aspects of daily life. Ambulatory, but may require a single prop
Stage 3 (severe)
Major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all outputs) and motor disability (cannot walk unassisted, requires walker, or personal support, usually with slowing and clumsiness of arms as well
Stage 4 (end stage)
Nearly vegetative. Intellectual and social comprehension and output are at a rudimentary level. Nearly or absolutely mute. Paraparetic or paraplegic with urinary and fecal incontinence
Developed by Price and Brew at Memorial Sloan Kettering (Price and Brow 1988)

prevalence has actually risen due to the increasing number of infected subjects as a result of increased life expectancy.

2. *Syphilitic Dementia*

Syphilis is caused by *Treponema pallidum*, and worldwide is still a common disease. Certain factors such as poverty, illiteracy, and prostitution contribute to the prevalence of this infection with its tertiary stage dementia. Neurological manifestations of syphilis include meningoencephalitis and chronic vasculitis which can both cause stroke, tabes dorsalis, myelopathy, and dementia. Syphilitic dementia (which, since the advent of penicillin, is now a rare complication) occurs 20 years following the primary infection and presents with memory loss, apathy, seizures, dysarthria, and cortical deficits such as aphasia and apraxia. Examination of the serum and CSF demonstrates positive serology, and the CSF examination shows pleocytosis, elevated protein, and an increased IgG index.

3. *Subacute Sclerosing Panencephalitis*

Subacute sclerosing panencephalitis (SSPE) usually manifests itself several years after the primary measles infection and occurs in immunocompetent individuals. SSPE presents with gradual cognitive decline and behavioral abnormalities,

followed by myoclonus, ataxia, motor deficits, and spasticity. In its final stage, autonomic abnormalities and coma develop. The EEG is pathognomonic with periodic high-amplitude polyspike and sharp- and slow-wave complexes lasting 0.5–2 s. Neuropathological examination demonstrates patchy areas of demyelination and gliosis as well as the presence of Cowdry types A and B eosinophilic inclusions. There is no specific treatment for SSPE and preventive vaccination against measles virus remains the only way to avoid this complication.

4. *Prion Diseases*

The transmissible spongiform encephalopathies are an uncommon group of neurodegenerative diseases causing rapid onset dementia. This group of disorders is linked to abnormal metabolism of the prion protein. Prion diseases affect both human and animal hosts and remain invariably fatal. The transmissible agent is an abnormal isoform of the prion protein (PrP) which is designated as the protease resistant scrapie form (PrP^{sc}). The gene for the human PrP is located on the short arm of chromosome 20. Human prion diseases include Kuru, Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob disease (vCJD), Gerstmann-Strussler-Scheinker disease, and fatal familial insomnia. CJD which occurs worldwide can be acquired (iatrogenic), familial, or sporadic (sCJD). Acquired cases linked to iatrogenic transmission have been reported following corneal and dural graft transplantation. Variant CJD has been linked to bovine spongiform encephalopathy. sCJD which accounts for up to 85% of all cases of prion diseases is primarily a disease of older adults but can also affect young people. Patients with sCJD present with the triad of rapidly progressive dementia, myoclonus, and ataxia. Cognitive decline in these patients is manifested by poor concentration, difficulty with mental calculations, impaired abstract thought, aphasia, and apraxia, and can be associated with abnormal involuntary movements such as choreoathetosis (Eggenberger, 2007). Diagnosis of sCJD depends on the presence of rapidly progressive dementia associated with at least two of the following four findings: Myoclonus, visual manifestations or cerebellar signs, pyramidal or extrapyramidal signs, and akinetic mutism. The presence of bilaterally synchronous, periodic sharp waves or spikes against a slow background on the EEG, and elevated CSF levels of the 14-3-3 protein support the clinical diagnosis. Brain MRI of patients with sCJD may reveal the presence of bilateral hyperintense signals in the basal ganglia, corpus striatum, and thalamus, which are best observed on diffusion weighted images. In contrast to sCJD, patients with vCJD present primarily with psychiatric symptoms, and later in the course of disease develop dementia, ataxia, and involuntary movements. The T2-weighted MRI reveals abnormal hyperintense signals in the posterior thalamus (pulvinar sign) (Zeidler *et al.*, 2000).

5. *Lyme Disease*

Lyme disease is a systemic infectious disease caused by the spirochete, *Borrelia burgdorferi*, which is transmitted to the human host by the bite of the Ixodes tick. It predominantly affects the nervous system, skin, heart, and joints. The infection develops within a period of 3–32 days after tick bite with a characteristic acute rash, erythema chronicum migrans. About 15% of patients with Lyme disease develop neurological manifestations, which consist of lymphocytic meningitis, cranial neuritis, and radiculitis. The cognitive dysfunction in patients with Lyme disease is characterized by impaired executive function and attention. However, a clear dementia due to Lyme disease is infrequent. Depression, emotional lability, irritability and psychosis may also be present. CSF examination shows a pleocytosis with elevated protein levels and the presence of oligoclonal bands and Borrelia DNA; at times, T2-weighted and FLAIR MRI show increased signal in the white matter.

6. *Whipple's Disease*

Whipple's disease (WD) is a rare systemic infection caused by the bacterium *Tropheryma whipplei*. WD, which affects particularly middle-aged males, primarily involves the digestive system and most often manifests with weight loss, diarrhea associated with malabsorption, abdominal pain, lymphadenopathy, cardiomyopathy, hyperpigmentation, and hypotension. WD is responsible for primary neurological disorders in rare cases. The most common neurological manifestations include slowly progressive dementia (56%), supranuclear ophthalmoplegia, oculomasticatory myoryhthmia, oculofacioskeletal myorythmia, and myoclonus. The presence of periodic acid-Schiff (PAS) positive macrophages in biopsy specimens (jejunal) and the demonstration of "Whipple's bacilli" by electron microscopy are diagnostic of active WD. CSF polymerase chain reaction (PCR) analysis for detection of *T. whipplei* DNA is a very sensitive diagnostic technique, and the CSF protein may occasionally be elevated. Brain CT and MRI are often normal but may show cortical/subcortical atrophy, hydrocephalus, and mass lesions. All WD patients must be treated and monitored as if they have CNS involvement if CSF PCR results are positive, even if they are neurologically asymptomatic.

7. *Neurocysticercosis*

Cysticercosis is a zoonotic infectious disease caused by the parasitic tape worm *Taenia solium* which infests both pigs and humans. Cycticercosis is the most frequent parasitic infection of the human nervous system (neurocycticercosis). Neurocysticercosis (NCC) may be clinically asymptomatic or present with epilepsy, altered mental status, focal neurologic deficits, headache, hydrocephalus, and dementia (López *et al.*, 2008). Although the cognitive deficits in NCC have been recognized for a long time, they have been systematically evaluated only recently.

In a series of 90 patients with untreated NCC, Ramirez-Bermudez *et al.* (2005) found that 15.5% of patients developed dementia. Diagnosis of NCC rests on the clinical picture supported by CAT, MRI, and CSF analysis. On brain imaging, the presence of cyst-like lesions with a mural nodule associated with degenerative cysts and calcifications is typical features. Currently, the outcome for patients with NCC dementia is usually favorable with appropriate treatment.

C. Toxic-Metabolic Disorders

The most common toxic-metabolic causes of EOD include carbon monoxide poisoning, lead poisoning, arsenic intoxication, mercury poisoning, alcoholism, and adverse effects of prescribed medication, endocrine disorders such as hypothyroidism, uremia, B12 deficiency, hepatic insufficiency, and postirradiation syndrome. Dementia caused by specific etiologies such as B12 deficiency and hypothyroidism may be reversible with correction of the underlying problem. However, lead poisoning, which is common in children and rare in adults, can cause irreversible encephalopathy with cognitive decline. Arsenic poisoning may cause memory loss, and mercury intoxication may cause intellectual deterioration along with behavioral changes such as confusion and irritability. Alcoholism and alcohol-related dementia pose a significant burden to society. Alcoholic dementia which presents with progressive cognitive decline results from chronic alcohol abuse. Neuroimaging of these patients demonstrates cortical atrophy, subcortical white matter loss, and enlarged ventricles. Chronic use of certain centrally acting medications such as barbiturates may cause psychomotor retardation and cognitive impairment, usually reversible when the drugs are discontinued.

D. Immune-Mediated Disorders

1. *Multiple Sclerosis*

This group of dementing disorders includes multiple sclerosis (MS), CNS vasculitis, and Hashimoto's encephalopathy. MS is an immune-mediated neurodegenerative disorder of the human CNS which mainly affects young adults (Frohman *et al.*, 2006). The immunopathogenesis of MS is associated with activation of both the cellular and humoral arms of the immune system against specific CNS antigens (such as the myelin basic protein family), disruption of the blood-brain barrier, transendothelial migration of activated leukocytes into the CNS, and loss of the myelin/oligodendrocyte complex as well as neuronal/axonal degeneration. Up to 65% of patients with MS present with neuropsychiatric features and suffer from cognitive decline. In many patients with MS, cognitive decline and memory loss may be the predominant manifestations causing significant disability. Usually dementia occurs late in the course of MS; however, certain

authors have observed dementia as the initial manifestation. Cognitive decline which is generally associated with extensive white matter disease and cerebral atrophy (neuronal loss) presents with frontal executive dysfunction and memory loss. Based on MRI studies, cognitive impairment severity has shown correlation with both total lesion load and the severity of corpus callosal atrophy.

2. *Central Nervous System Vasculitis*

CNS vasculitis or CNS angiitis is a progressive inflammatory disease of the cerebral arteries, veins, or both which causes significant structural damage to the vessel wall resulting in thrombosis and thus ischemic infarction. CNS vasculitis is regarded as primary when the inflammatory process is limited to the nervous system. However, when a CNS vasculitic syndrome occurs in the context of an underlying autoimmune systemic disorder such as systemic lupus erythematosus or an infectious disease such as syphilis, it is classified as secondary. Clinically, CNS vasculitis manifests with headache, altered sensorium, seizures, hemiparesis or quadriparesis, cranial neuropathy, and dementia. The cause of primary CNS vasculitis remains elusive. However, massive activation of the immune system with migration of lymphocytes, plasma cells, and monocytes into the CNS, and their subsequent accumulation in the vascular walls of small arteries and veins (particularly in the leptomeninges) are significant features of its pathogenesis. Brain MRI reveals signal abnormalities on T2-weighted, FLAIR, and postcontrast sequences providing evidence of both white and gray matter involvement. Cerebral angiography may be diagnostic when a "vessel beading" pattern is observed; however, only meningeal/brain biopsy provides a definitive diagnosis.

3. *Hashimoto's Encephalopathy*

Hashimoto's encephalopathy (HE) refers to a presumably immune-mediated encephalopathy which is associated with elevated serum titers of antiperoxidase and antithyroglobulin antibodies. HE has been reported around the globe affecting all age groups, with females being more affected. This uncommon disorder manifests with fluctuating consciousness followed by cognitive decline and dementia. HE may have a relapsing course, and almost all cases respond favorably to high doses of corticosteroids (Mocellin *et al.*, 2007).

E. Neoplastic/Metastatic Disorders

Both primary and metastatic brain neoplasms may cause dementia, with location and the rate of tumor growth being the major severity determinants. Another etiology for development of cognitive impairment and dementia in the context of systemic malignancy involves a paraneoplastic mechanism. Paraneoplastic limbic encephalitis is the most common paraneoplastic syndrome and occurs in association with lung and breast cancer. Limbic encephalitis is

characterized by hallucinations, personality changes, epilepsy, and dementia and often precedes the diagnosis of systemic malignancy. Mesial temporal lobe involvement is common, however, other areas such as the hypothalamus and brainstem may be affected as well. Neuropathological features include the presence of infiltrating lymphocytes and neuronal loss in the hippocampus and cingulate gyrus.

F. Neurodegenerative Disorders

1. *Alzheimer's Dementia and Dementia with Lewy Bodies*

Alzheimer's disease (AD) is a progressive degenerative disorder and is usually associated with advanced age, but it can be a significant cause of EOD with a special relationship to Down syndrome. A number of studies have demonstrated that AD is a frequent cause of EOD (AD age of onset <65), accounting for 20–34% of patients. Neuropathologically, AD is characterized by the extracellular deposition of β-amyloid plaques and accumulation of intracellular neurofibrillary tangles. Clinical features of AD include memory impairment, language deterioration, and visuospatial deficits. There are no definite laboratory studies for the diagnosis of AD; although, CSF relative concentrations of tau and β-amyloid as well as amyloid quantification by PET are being investigated. Currently, three early onset AD genes with mutations affecting amyloid precursor protein, presenilin 1, and presenilin 2 and one late onset AD susceptibility gene for apolipoprotein E have been identified. Neuropsychological studies have indicated that there may be more cortical visuospatial function impairment in early onset AD than the late onset form, while PET and neuropathological examinations have suggested greater parietal lobe involvement in early onset AD.

DLB, which is the second most common cause of dementia after AD in elderly patients, is relatively uncommon in younger individuals. Neuropathological studies demonstrate the presence of neocortical Lewy bodies in up to 35% of demented elderly patients. The clinical manifestations of DLB are similar in young and elderly patients. DLB presents with cognitive decline without prominent early memory impairment, fluctuating cognitive ability, fully formed and detailed visual hallucinations, dysautonomia, and parkinsonian features including rigidity and bradykinesia, are typical findings. These patients also manifest excessive daytime drowsiness. Brain PET in patients with DLB reveals reduced metabolic activity in the posterior parietal cortex.

2. *Frontotemporal Lobar Degeneration*

Frontotemporal lobar degeneration (FTLD) is associated with focal degeneration of the frontal and temporal lobes, and after AD and DLB is the third most common cause of cortical dementia (Josephs, 2007). FTLD is a heterogeneous entity consisting of three dementing syndromes: frontotemporal dementia (FTD)

also known as frontal variant FTD (fv-FTD), semantic dementia (SD) (or temporal variant), and progressive non-fluent aphasia (PNFA). In addition to these three clinical forms, FTLD has been linked to CBD, progressive supranuclear palsy (PSP), motor neuron disease (amyotrophic lateral sclerosis), and apraxia of speech. FTLD typically affects individuals between 45 and 65 years of age; in up to 40% of cases, a positive family history may be identified. fv-FTD which is more common in males comprises up to 56% of FTLD cases and has the earliest age of onset (mean = 58 years). Patients with fv-FTD demonstrate behavioral abnormalities consisting of distractibility, decline in self-care, perseverant behavior, hyperorality, apathy, disinhibition, and language disturbance. Patients with SD develop a progressive loss of word knowledge and meaning. While speech fluency is retained, patients develop problems with word finding and have difficulty with naming and word recognition. These patients make speech errors which are typically characterized by circumlocution and overuse of generic words. In advanced cases, patients with SD may develop prosopagnosia. In patients with PNFA, the disease process commences insidiously with progressive deficits in speech or language. These patients have decreased word output and commonly exhibit difficulties with understanding grammar. Patients develop anomia but have relatively preserved memory and nonverbal cognition. Some of these patients may demonstrate upper-limb or orofacial apraxia. Word comprehension usually remains unchanged. Neuroimaging demonstrates left perisylvian atrophy.

3. *Corticobasal Degeneration*

CBD (also known as cortical-basal ganglionic degeneration) is a neurodegenerative disorder classified as a tauopathy, which presents with asymmetrical motor dysfunction having both parkinsonian and dystonic components, as well as postural tremor/myoclonus. Cortical features include aphasia, ideational and ideomotor apraxia, astereognosis and alien limb syndrome. Patients with CBD also display intellectual decline as well as frontal lobe release signs. Mean age of onset is 60 years, but onset may occur as early as 45 years. Neuropathological examination of the brain reveals intracellular filament accumulation consisting of microtubule-associated tau protein. PET and MRI studies have demonstrated symmetrical cortical and basal ganglion hypometabolism (McMonagle *et al.*, 2006). As a tauopathy, CBD has been linked to FTD and Pick's disease; however, its tau is hyperphosphorylated and makes unusual twisted filaments which share certain similarities with the paired helical filaments observed in Alzheimer's disease. The etiology and pathogenesis of CBD remain unknown and currently there is no specific treatment for this condition.

4. *Progressive Supranuclear Palsy*

PSP (or Steele-Richardson-Olszewski syndrome) is a progressive neurodegenerative disorder, which clinically manifests with rigidity, bradykinesia, postural instability, supranuclear ophthalmoplegia, pseudobulbar palsy, axial dystonia,

dysphagia, dysarthria, frequent falls, and dementia. PSP is frequently misdiagnosed as idiopathic Parkinson's disease (IPD). However, unlike IPD, tremor is uncommon. Neuropathologically, PSP is characterized by neuronal loss, gliosis, and the presence of neurofibrillary tangles, which are composed of paired helical filaments and straight filaments of tau protein. These neuropathological changes are observed in the substantia nigra, globus pallidus, superior colliculus, pretectal area, cerebellar nuclei, and substantia innominata. PSP affects males slightly more than females, and its onset is usually in the sixth decade (range: 45–75 years). Dementia is present in many cases and is characterized by bradyphrenia, apathy, depression, disinhibition, and progressive non-fluent aphasia. Brain PET reveals hypometabolism in the frontal lobe and anterior cingulate gyrus. MRI may show midbrain and superior cerebellar peduncle atrophy, which is disproportionate to the atrophy of the pons and cerebellum.

5. *Huntington's Disease*

Huntington's disease (HD) is an autosomal dominant progressive neurodegenerative disease which presents primarily with an irrepressible movement disorder, usually chorea, and various behavioral problems, evolving finally into severe dementia. Other motor presentations include bradykinesia, dystonia, imbalance, and speech abnormalities. HD results from an expanded and unstable CAG trinucleotide repeat, coding for a polyglutamine tract, in the IT15 gene, which is located on chromosome 4 (Huntington's Disease Collaborative Research Group, 1993). Dementia, which usually occurs after chorea and psychiatric symptoms have been present for several years, may precede chorea in about one fourth of cases. Psychiatric manifestations include irritability, mood lability, antisocial behavior, anxiety, delusional thought disorder, mania, obsessive behavior, and apathy. The exact cause of the progressive neurodegeneration in HD remains unknown; however, various hypotheses including free radical toxicity, glutamate toxicity, and abnormal caspase activity have been proposed. Brain MRI demonstrates prominent caudate atrophy with various degrees of cortical atrophy. DNA testing can establish the diagnosis. HD is progressive over a 15- to 25-year period, and most patients succumb to late stage disease complications such as infection.

6. *Idiopathic Parkinson's Disease*

IPD is a progressive neurodegenerative disease that affects about 1 million Americans usually over the age of 60, but onset at a much younger age in not unusual. The etiology of IPD remains poorly understood. Neuropathological examination has indicated that the pathogenesis of IPD is linked to degeneration of dopamine-generating neurons in the pars compacta of the substantia nigra. Other areas within the CNS where neuronal loss occurs in the course of IPD include pigmented brainstem nuclei, autonomic nuclei, and pyramidal cells in the pre-supplementary motor cortex. Currently, more than 11 autosomal dominant and

recessive genes have been linked to PD. IPD remains a clinical diagnosis, and its major clinical features include bradykinesia, resting tremor, limb rigidity, loss of corrective postural reflexes, and a gait disorder. Up to one-third of patients with IPD develop dementia which is characterized by significant impairment of executive functions, attention, concentration, working memory, and visuospatial function. Personality changes and behavioral disorders are common.

G. Miscellaneous Causes of EOD

1. *Traumatic Brain Injury*

Severe closed head trauma which is associated with coma may cause chronic cognitive impairment. In addition, repeated trauma to the head can have additive neuronal and axonal pathological effects producing cognitive decline and finally dementia. This form of dementia is often accompanied by dysarthria, akinesia, paranoia, depression, ataxia, and parkinsonism. EOD is particularly associated with traumatic brain injury secondary to motor vehicle accidents which predominantly involve young individuals.

2. *Normal Pressure Hydrocephalus*

Patients with NPH demonstrate gait apraxia, dementia, and urinary incontinence. Gait impairment, characterized by short-stepped and broad-based ambulation with clumsiness of foot placement, usually precedes other symptoms (Graff-Radford, 2007). Cognitive impairment varies in severity. Dementia in these patients consists of memory loss, bradyphrenia, frontal lobe executive dysfunction, and depression. A number of clinical reports have indicated a possible relationship between NPH and systemic hypertension. NPH, a communicating hydrocephalus which is objectively diagnosed by CSF flow/pressure studies, frequently responds to shunting, although dementia may not improve due to permanent neuronal damage.

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NORMAL PRESSURE HYDROCEPHALUS[1]

Glen R. Finney

Memory and Cognitive Disorders Program, University of Florida
Department of Neurology, Gainesville, Florida 32610-0236, USA

Normal Pressure Hydrocephalus first became recognized as a treatable, reversible disorder in the 1960s. The classic triad of magnetic apraxia, urinary incontinence, and dementia remain relevant into the 21st century as being the basis for symptomatic diagnosis and predicting potential benefit from ventriculo-peritoneal shunting, though they have been greatly augmented by the addition of modern neuroimaging, particularly MRI. Modern criteria recognize a wider range of diagnostic criteria, and new positive and negative prognostic indicators for treatment benefit have been discovered, though the mainstay remains initial drainage of a large volume of cerebrospinal fluid and monitoring for clinical improvement. Even with our advances in understanding both primary and secondary normal pressure hydrocephalus, diagnosis, management, and counseling remain challenging in this disorder.

[1]Also known as: Hakim-Adams Syndrome, Hakim's Disease, Hakim's syndrome, extraventricular obstructive hydrocephalus.

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I. History

For decades, students of neurology have been taught the mnemonic of "Wet, Wacky, and Wobbly" for the classic triad of symptoms seen in the entity primarily known as normal pressure hydrocephalus. Normal pressure hydrocephalus is a reversible dementia originally recognized only a little over a half century ago in the mid-1960s by neurosurgeon Solomon Hakim, M.D., Ph.D, with famed Massachusetts General Hospital neurosurgeons Robert G. Ojemann and William H. Sweet and legendary Massachusetts General Hospital neurologists Raymond D. Adams and C. Miller Fisher.

Solomon Hakim's first publication on the subject of Normal Pressure Hydrocephalus was in the form of his 1964 thesis at the Javeriana University School of Medicine in Bogota, Colombia (Hakim, 1964). He followed up on this work as a fellow at the Massachusetts General Hospital where in association with Raymond D. Adams he published the first peer reviewed report on symptomatic hydrocephalus with high normal pressures (Hakim and Adams, 1965), which was then followed by the groundbreaking paper, again in collaboration with Raymond D. Adams, and in addition C. Miller Fisher, Robert G. Ojemann, and William H. Sweet when they published the first peer reviewed paper on the subject of patients with symptomatic hydrocephalus but pressures that fell within the high normal range, and that could be treated by drainage of cerebral spinal fluid (Adams *et al.*, 1965). The initial three patients showed cerebrospinal fluid pressures of 150 mm H_2O, 160 mm H_2O, and 180 mm H_2O, thus the coining of the term normal pressure hydrocephalus due to the relatively normal pressures found on lumbar puncture. As noted by Raymond D. Adams himself, the idea of treatment of hydrocephalus by drainage of cerebrospinal fluid had been proposed as early as 1895 by Gartner (Adams, 1966), but it was the critical development of an autoclavable one-way shunt that allowed for a practical treatment for the entity of Normal Pressure Hydrocephalus. Solomon Hakim went on to a successful career in neurosurgery and continued to contribute to the art and science of treatment of hydrocephalus, even developing his own shunts starting in the early 1970s for the treatment of hydrocephalus (Hakim, 1973; Hakim *et al.*, 1973).

This early work in normal pressure hydrocephalus relied for work up on lumbar puncture, electroencephalogram, and pneumoencephalography to interrogate the central nervous system, but even then the classic clinical triad of alteration in mentation, gait disturbance, and incontinence was part of the diagnosis (Adams *et al.*, 1965).

A. History of Present Illness

It is important always to establish a good history in evaluating patients with cognitive disorders, and doubly so in the case of normal pressure hydrocephalus where history has a role in not just diagnosis but factor determination for likely response to treatment via shunting.

Onset is important, both for knowing if there were any precipitating factors that might indicate a secondary form of normal pressure hydrocephalus as well as other mimics of normal pressure hydrocephalus. Brain hemorrhage, brain surgery, head injury, and meningitis both recent and remote are identified risk factors for normal pressure hydrocephalus. Onset in idiopathic normal pressure hydrocephalus should be gradual, with slow worsening over time. Onset in secondary normal pressure hydrocephalus may actually be acute or subacute and found in relation with a suspected etiology around the time of onset, or like idiopathic normal pressure hydrocephalus, it may be gradual and have no close temporal relationship with the presumed original precipitating etiology. Secondary normal pressure hydrocephalus is more likely to respond to shunting than idiopathic normal pressure hydrocephalus (Black *et al.*, 1985; De Mol, 1985; Petersen *et al.*, 1985). Time of onset is also important for determining duration which is a factor in predicting possible improvement after shunting, with shorter duration suggesting more response to shunting.

It is also important to know the temporal order and duration of the presenting symptoms. Patients who had gait disturbances begin simultaneously or before the cognitive disturbance were more likely to respond favorably to shunting (Fisher, 1977; Graff-Radford *et al.*, 1989), but patients who have suffered from the dementia for more than 2 years are less likely to respond to shunting (Graff-Radford *et al.*, 1989; Petersen *et al.*, 1985).

Screen past medical history for possible congenital hydrocephalus that may have become significantly symptomatic only later in life. It is also important to screen medications that may have side effects similar to those seen in normal pressure hydrocephalus. In particular, be wary of patients who started with urinary incontinence and subsequently develop cognitive symptoms only after initiation of treatment for incontinence with an anticholinergic which can cause confusion.

It is also important to discern if the reason for urinary urgency or urinary incontinence is actually due to physical disability in gait disturbance making it difficult for the patient to reach the bathroom in a timely fashion. One should ascertain if the patient has a stress or urge incontinence, especially in older women who frequently suffer from stress urinary incontinence, which is not a neurogenic form of urinary incontinence but rather of a structural nature. In men, urinary frequency may be due to prostatic disease and this too should be screened for.

B. Past Medical History

As mentioned previously, it is important to find out if there is a history of previous insult to the central nervous system and surrounding environs which may be a precipitating factor for a normal pressure hydrocephalus or a mimic thereof. Most common include brain hemorrhage, brain surgery, head trauma, and meningitis. Obviously, these can be interrelated and you may find a complicated history of more than one of these occurring. Chronic subdural hemorrhages can be both a mimic of normal pressure hydrocephalus as well as a predisposing condition. It is important to screen for history of diseases or conditions that can mimic all or parts of the presentation of normal pressure hydrocephalus. Many primary neurodegenerative diseases can have similar sets of symptoms later in their course or can be negative indicators for likely response to shunting if occurring in the same patient. These diseases include Alzheimer's disease, frontotemporal lobar degeneration, Lewy body dementia, multisystems atrophy, Parkinson's disease, and progressive supranuclear palsy.

C. Medications

Anticholinergic drugs are often prescribed for urinary frequency or urinary incontinence. When urinary symptoms precede confusion and initiation of anticholinergic medications for the urinary symptoms precedes confusion, a high index of suspicion for medication effect must be held. It may take months off an anticholinergic medication to be certain that it is not clearly part of the dementia presentation in such patients.

II. Physical Examination

Two of the three cardinal features of classic normal pressure hydrocephalus, mental status and gait, are amenable to examination and therefore are the most important to be assessed, though the rest of the examination, particularly the neurological examination, can not be neglected as it may point to mimics of normal pressure hydrocephalus. Beyond the neurological examination, a musculoskeletal examination looking for mechanical hindrances to movement is the most important part of the non-neurological examination.

Cranial nerve examination should assess for possible mimics of normal pressure hydrocephalus. Funduscopic examination of the optic nerves may reveal papilledema which can point to other forms of hydrocephalus or other causes of raised intracranial pressure. Constriction of peripheral vision can be seen in such entities

and can raise the concern of the possibility of intracranial venous sinus thrombosis. Beyond the optic nerve, any other cranial nerve abnormality brings the diagnosis of an idiopathic normal pressure hydrocephalus into question as this can be an additional sign of significant raised intracranial pressures as in the false localizing signs of sixth nerve palsies, or sign of structural abnormalities in the posterior fossa such as in basilar meningitis, which might be an underlying etiology for a secondary normal pressure hydrocephalus. Ophthalmoplegia can indicate any number of other etiologies that may share some features with normal pressure hydrocephalus, including Wernicke-Korsakoff Syndrome, central nervous system Whipple's disease, and especially Progressive Supranuclear Palsy (particularly if there is restriction of down-gaze) which presents early with gait instability and may have cognitive impairment quite similar to that seen in normal pressure hydrocephalus.

Motor examination should demonstrate normal motor strength with no focal deficits. Focal weakness might point one away from normal pressure hydrocephalus and toward a more focal or multifocal etiologies like vascular damage. Tone may be normal or increased in normal pressure hydrocephalus, though asymmetric increased tone should bring up the possibility of Parkinson's disease, especially if accompanied by an asymmetric resting tremor.

Reflexes should be normal to mildly increased, again in a nonfocal pattern. Focal asymmetries in reflexes suggest the possibility of a different etiology. One may see frontal release signs (i.e., release of primitive developmental reflexes) such as a glabellar reflex, a rooting or suck reflex, a grasp reflex, facillatory paratonia (Mitgehen), and even bilateral Babinski signs can be found in some patients.

Sensory examination can be difficult to reliably obtain in this patient population, and many patients in the age group most susceptible to normal pressure hydrocephalus also suffer from a multifactorial vibratory sensory loss. Again, we cannot emphasize enough the importance of asymmetric sensory loss as indicating the possibility of a different or additional diagnosis than normal pressure hydrocephalus. There should be no Romberg sign (falling to one side when eyes are closed), otherwise a unilateral vestibular system abnormality may be contributing to gait disturbance.

Coordination examination may show truncal ataxia and abnormalities of fine motor activity that resemble ataxia or apraxia, particularly in the lower extremities. Frank tremor on examination can be seen but it is typically symmetric.

Gait examination, of course, is the most important portion of the examination in the case of normal pressure hydrocephalus. The most classic finding in idiopathic normal pressure hydrocephalus is a magnetic apraxia of gait, where the patient has difficulty with initiation and changes in trajectory of gait, and appears to be literally "stuck" to the floor. The degree of severity of magnetic apraxia can vary, with some patients only having subtle findings particularly on turns or transfers, whereas others may be so severe that they cannot even obtain the upright position. Unfortunately, it is not always the classic magnetic apraxia that is the form of gait disturbance that is manifest in the patient. A significant number of patients can

have a mixed magnetic/parkinsonian gait and in some individuals the gait can appear quite parkinsonian with no clear apraxia. Other forms of gait disturbances must be assessed for and ruled out. While gross testing of proprioception may be normal, many elderly patients even without normal pressure hydrocephalus or overt neurological impairment will have an unsteady gait due to diminution of multiple sensory modalities (e.g., vision, vestibular, vibratory) as well as general deconditioning of accessory musculature with decreased activity often seen in the elderly, particularly seen in deficits in righting reflex when patients get slightly off balance. A wide-based gait in frank loss of lower extremity sensation either due to a peripheral neuropathy or myelopathy impacting posterior columns also should raise doubts about the diagnosis of normal pressure hydrocephalus.

III. Laboratory Serologies

There is no specific blood test for normal pressure hydrocephalus and any laboratory serology work-up should be driven by history or examination findings suggestive of other possible etiologies. It is beyond the scope of this chapter to go into the laboratory work-up for these alternative etiologies in the differential diagnosis and direct the reader to the chapters on other forms of dementia, particularly reversible dementias, for further information.

IV. Neuroimaging

Imaging of the brain is absolutely necessary in the evaluation of the possibility of the diagnosis of normal pressure hydrocephalus. Finding signs of normal pressure hydrocephalus in the brain is often a subtle and difficult task, and for this reason we recommend against a computed tomography image of the brain for diagnosis as being to coarse grained and lacking in other qualities that are present in magnetic resonance imaging.

Where computed tomography of the brain can be useful is as a quick and inexpensive option in evaluation of already diagnosed and shunted normal pressure hydrocephalus patients in evaluating gross shunt failure and signs of increasing ventricular size. Radiography in the terms of a shunt series to establish position and patency of the shunt is also required, and ideally should be reviewed by a physician familiar with the evaluation of shunt patency. In more difficult cases repeat magnetic resonance imagery of the brain may also add useful information.

V. Modern Diagnostic Criteria

Relkin *et al.* (2005) criteria for probable and possible normal pressure hydrocephalus

A. Probable Idiopathic Normal Pressure Hydrocephalus

Diagnosis of probable idiopathic normal pressure hydrocephalus is based on:

1. Clinical history
2. Brain imaging
3. Physical findings
4. Physiologic criteria

1. Clinical history (corroborated by an informant)

- Insidious onset
- Onset after 40 years old
- Minimum duration of 3 months
- No secondary causes (e.g., head trauma, intracerebral hemorrhage, meningitis, etc.)
- Progresses over time
- No other neurological, psychiatric, or medical condition sufficient to explain the presenting symptoms

2. Brain imaging

Brain imaging study (CT or MRI) must be after onset and must show evidence of:

- Ventricular enlargement out of proportion to cerebral atrophy or not entirely attributable to congenital enlargement (Evans index >0.3 or comparable measure)
- No macroscopic obstruction of cerebrospinal fluid flow
- At least one of the following supportive features:
  - Enlargement of the temporal horns of the lateral ventricles not attributable to hippocampal atrophy
  - Callosal angle of 40° or more
  - Evidence of altered brain water content, including periventricular signal changes on CT and MRI not attributable to microvascular ischemic changes or demyelination
  - Aqueductal or fourth ventricular flow void on T2 MRI

- Other brain imaging findings:
  - Brain imaging study performed before onset of symptoms showing smaller ventricular size or without evidence of hydrocephalus
  - 48–72 h radionucleotide cisternogram showing delayed clearance of radiotracer over the cerebral convexities
  - Cine-MRI study or other technique showing increased ventricular flow rate
  - A single photon emission CT-acetazolamide challenge showing decreased periventricular perfusion that is not altered by acetazolamide

3. Clinical

By classic definition:

Findings of gait or balance disturbance must be present plus impairment in

- Cognition
- Urinary incontinence
- Or both

With respect to gait and balance, at least two of the following should be present and not entirely attributable to other conditions:

- Decreased step height
- Decreases step length
- Decreased cadence
- Increased trunk sway
- Widened standing base
- Toes turned outward on walking
- Retropulsion (spontaneous or provoked)
- En bloc turning (turning requires three or more steps for 180°)

With respect to cognition, there must be documented impairment (adjusted for age and education) or decrease in performance on a cognitive screening instrument (such as the Mini-Mental State Examination) or evidence of at least two of the following on examination that is not fully attributable to other conditions:

- Psychomotor slowing
- Decreased fine motor speed
- Difficulty dividing or maintaining attention
- Impaired recall, especially for recent events
- Executive dysfunction, such as impairment in multistep procedures, working memory, formulation of abstract/similarities, insight
- Behavioral or personality change

To document symptoms in the domains of urinary continence, either one of the following should be present:

- Episodic or persistent urinary incontinence and not attributable to urologic disorders
- Persistence of urinary incontinence
- Persistence of fecal incontinence

Or any two of the following be present:

- Urinary urgency as defined by perception of a pressing need to void
- Urinary frequency as defined by more than six episodes in an average 12-h period despite normal fluid intake
- Nocturia as defined by need to urinate more that two times in an average night

4. Physiologic

Cerebrospinal fluid opening pressure in the range of 5–18 mm Hg or 70–245 mm H_2O as determined by a lumbar puncture or other comparable procedure. Appropriately measured pressures that are significantly higher or lower are not consistent with a probable normal pressure hydrocephalus diagnosis.

B. Possible Idiopathic Normal Pressure Hydrocephalus

1. History

Reported symptoms may

- Have a subacute or indeterminate mode of onset
- Begin at any age after childhood
- May have less than 3 months of indeterminate duration
- May follow events, such as mild head trauma, remote history of intracerebral hemorrhage, or childhood and adolescent meningitis, or other conditions that in the judgment of the clinician are not likely to be casually related
- Coexist with other neurological, psychiatric, or general medical disorders but in the judgment of a clinician not be entirely attributed to these conditions
- Be nonprogressive or not clearly progressive

2. Brain imaging

Ventricular enlargement consistent with hydrocephalus but associated with either of the following (Figs. 1 and 2):

- Evidence of cerebral atrophy of sufficient severity to potentially explain ventricular size
- Structural lesions that may influence ventricular size

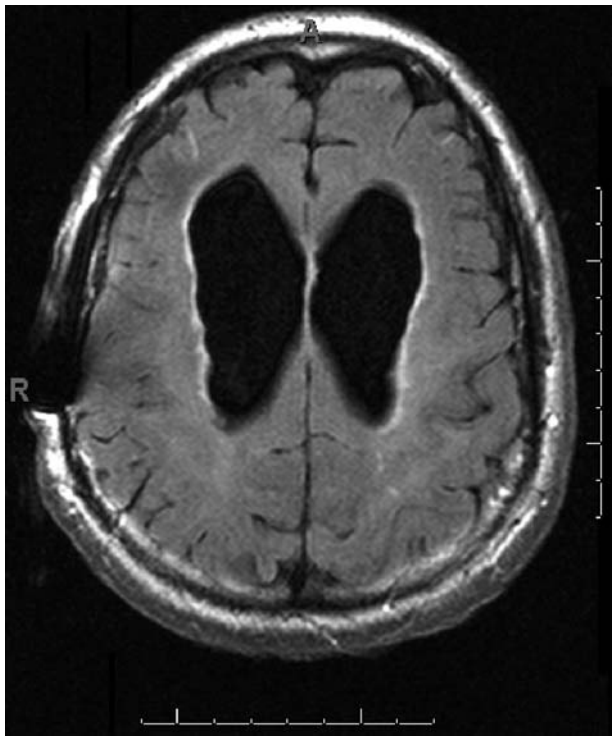

FIG. 1. Disproportionate enlargement of the ventricles.

3. Clinical
Symptoms of either

- Incontinence or cognitive impairment in the absence of an observable gait or balance disturbance
- Gait disturbance or dementia alone

4. Physiologic
Opening pressure not available or pressure outside the range of required for probable idiopathic normal pressure hydrocephalus.

C. Unlikely Idiopathic Normal Pressure Hydrocephalus

- No evidence of ventriculomegaly
- Signs of increased intracranial pressure, such as papilledema
- No component of the clinical triad of idiopathic normal pressure hydrocephalus
- Symptoms explained by other causes (e.g., spinal stenosis)

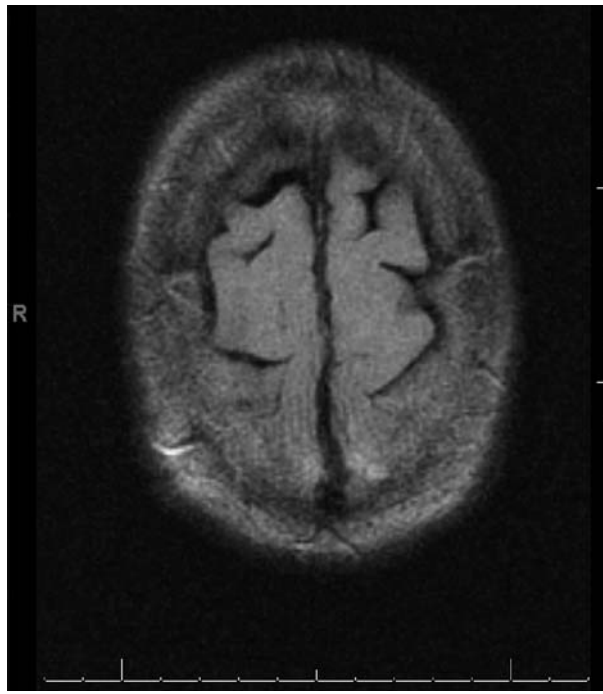

FIG. 2. Crowding of sulci at the calvarium.

Demographics:

Estimates of prevalence in small studies hover around 0.5% (Casmiro *et al.*, 1989; Trenkwalder *et al.*, 1995).

VI. Treatment

Treatment for normal pressure hydrocephalus is to establish a new route of drainage of cerebrospinal fluid from the central nervous system via a ventriculoperitoneal shunt. This invasive neurosurgical procedure has in the past had a high rate of complication, which in recent years has been somewhat ameliorated by the advent of rate-adjustable shunts. Complications of shunt surgery, other than the typical postoperative complications of any major surgery, include abdominal organ damage, intracerebral hemorrhage, subdural hematoma/hygroma, headache, hearing loss, oculomotor palsy, shunt infection, seizure, tinnitus. In addition, there can be shunt malfunction over time (Bergsneider *et al.*, 2005).

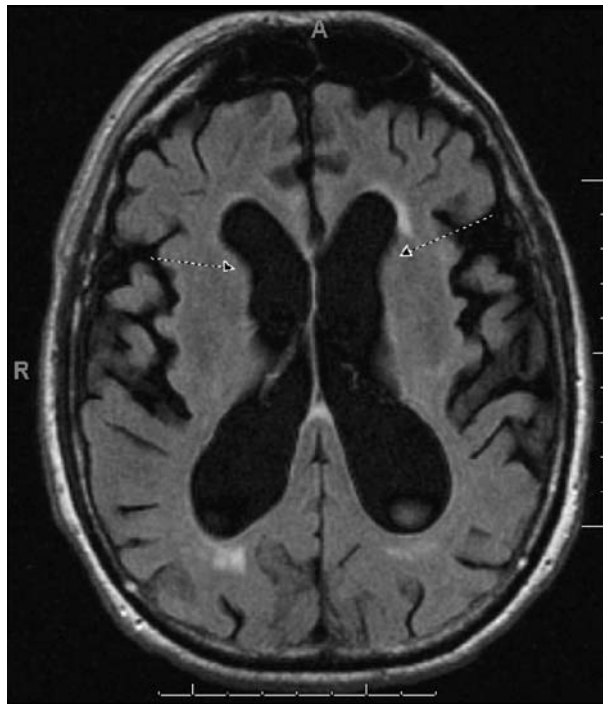

FIG. 3. Loss of curvature at the head of the caudate nuclei.

VII. Predictors of Response to Shunting in Normal Pressure Hydrocephalus

In his 2007 review of normal pressure hydrocephalus, Neill R. Graff-Radford of Mayo Clinic Jacksonville listed several positive and negative predictors for response to shunting in normal pressure hydrocephalus (Graff-Radford, 2007). Factors that favored clinical improvement included the form of normal pressure hydrocephalus being secondary to another etiology, if the gait disturbance appeared before the dementia portion of the syndrome, also if the deficit in cognition is modest. Lumbar procedure results that favored better outcomes were; a demonstrable clinical improvement, typically after removal of cerebrospinal fluid through a lumbar puncture or continuous lumbar drainage, Rcsf outflow of 18 mm Hg/mL/min or greater during continuous lumbar cerebrospinal infusion testing, and presence of B waves for 50% or greater of the time during continuous lumbar cerebrospinal fluid monitoring. Factors noted as negative predictors of response to shunting included moderate to severe dementia, dementia of duration greater than 2 years, if the cognitive impairment came before the gait abnormality, the presence of aphasia

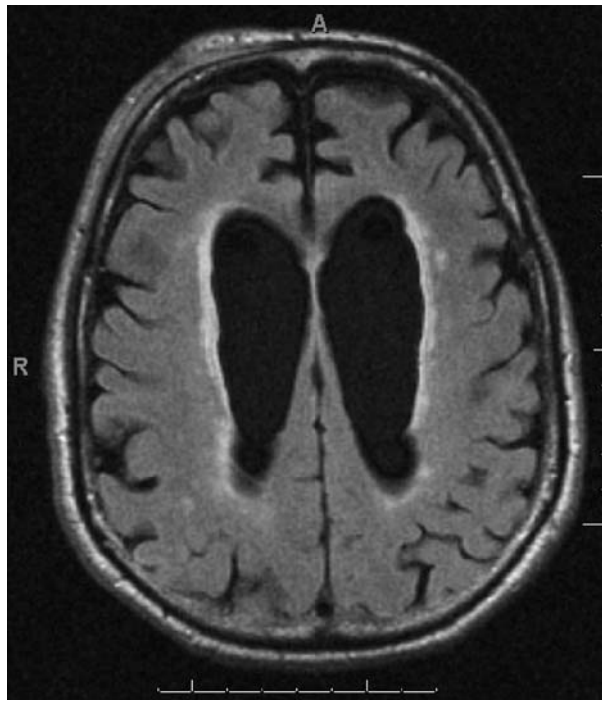

FIG. 4. Transependymal extravasation.

signs on examination, a history of alcohol abuse, significant white matter involvement on MRI, and diffuse cerebral atrophy.

Patients who have had symptoms of dementia greater than 2 years in duration are less likely to respond to shunting than those with a shorter course of dementia (Graff-Radford *et al.*, 1989; Petersen *et al.*, 1985). Duration of gait and urinary symptoms were not as useful (Graff-Radford *et al.*, 1989). Interestingly, alcohol abuse has been reported to be a poor prognostic indicator for response to shunting (De Mol, 1985).

VIII. Recent Work

In a small Japanese study (Akiguchi *et al.*, 2008) of patients with radiographic signs of normal pressure hydrocephalus and parkinsonism, both the parkinsonian symptoms and the radiographic signs, including white matter changes likely representing cerebrospinal fluid extravisation, were found to be somewhat

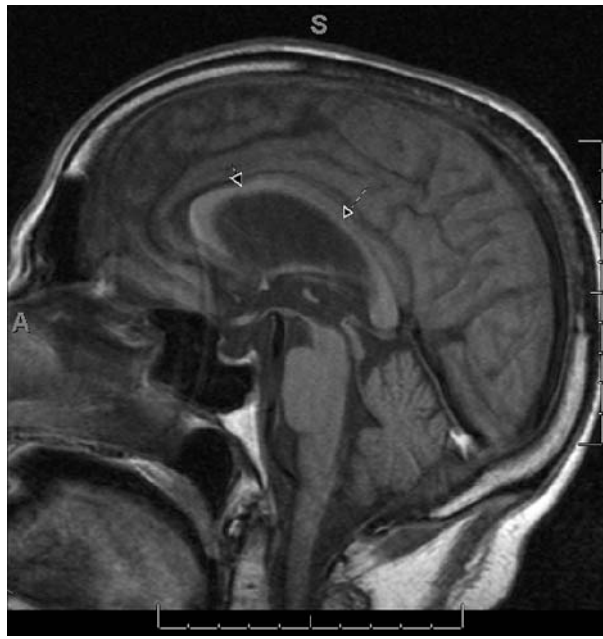

FIG. 5. Thinning of the corpus callosum.

reversible with shunting. In another small study it was discovered that patients with normal pressure hydrocephalus were more prone to have retrograde jugular flow during Valsalva maneuver (Kuriyama *et al.*, 2008). Attempts to find better diagnostic benchmarks for treatment responsiveness in normal pressure hydrocephalus continues, with one modest sized study from Norway suggesting a correlation with treatment response 1 year out from shunting for cerebrospinal fluid pressure pulsatility after lumbar infusion (Brean *et al.*, 2008), with cerebrospinal dynamics after shunting returning to a more normal nature in lumbar infusion after shunting (Petrella *et al.*, 2008). MRI measurement of CSF spaces at the high convexities and midline areas of the brain has shown reasonable ability to distinguish brains with normal pressure hydrocephalus (Sasaki *et al.*, 2008). Another small study identified the most common changes in gait between lumbar drainage responders and nonresponders to be walking speed, amount of steps in turning, and tendency toward falling (Ravdin *et al.*, 2008). One small but suggestive study that suggested the use of MRI cine (phase-contrast MRI) pre- and postlumbar drainage (at least 50 cc removed) could reliably identify patients who benefited from shunting from those who did not, with change in the peak flow velocity through the cerebral aqueduct after lumbar drainage suggesting amenability to shunting (Sharma *et al.*, 2008). In another small study using [(15)O]H(2)O

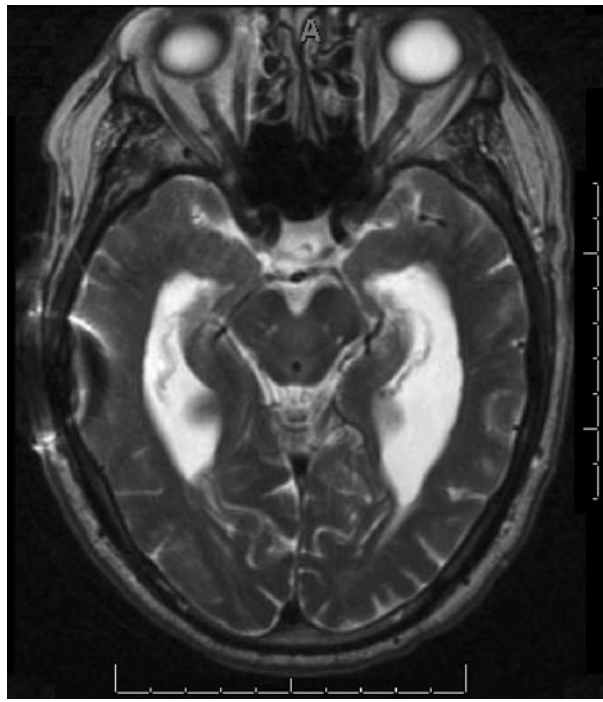

FIG. 6. Turbulent flow void (hypointense) in the cerebral aqueduct.

positron emission tomography the pre–versus postshunting change in regional blood flow in the mesial frontal lobes correlated with response to treatment (Klinge *et al.*, 2008). Perhaps one of the most important papers to come out recently retrospectively reviewed long term outcomes over 5–7 years after shunting for normal pressure hydrocephalus, and found that sustained improvement existed in ally symptoms, though sometimes this result had to be maintained by multiple shunt revisions (Pujari *et al.*, 2008). An autosomal dominant form of heritable normal pressure hydrocephalus with earlier onset essential tremor (essential tremor-idiopathic normal pressure hydrocephalus (ETINPH)) has been identified (Zhang *et al.*, 2008). The use of a spinal catheter or lumbar shunt in lieu of large volume lumbar tap is a recent trend, the most serious complication of which is infection, but this risk can be brought down to below 2% (1.8%) with use of proper antibiotic prophylaxis and clinical surveillance (Greenberg and Williams, 2008). There was a recent attempt at a unified rating tool for signs in idiopathic normal pressure hydrocephalus with relatively good inter-rater reliability (Kubo *et al.*, 2008). One factor not commonly taken into

account in shunt planning is intra-abdominal pressure which can impact shunt performance (Sahuquillo *et al.*, 2008). In the use of proton magnetic resonance spectroscopy, some suggestion was made of using NAA/Cr ratios to distinguish between idiopathic normal pressure hydrocephalus patients who have more neuronal dysfunction than destruction, with average ratio around 1.7 in external lumbar drainage responders compared to 1.5 in external lumbar drainage non-responders (Lenfeldt *et al.*, 2008). The nature of the urinary symptoms, namely incontinence, seen in normal pressure hydrocephalus, is mostly due to detrusor overactivity (Sakakibara *et al.*, 2007). In functional neuroimaging with positron emission tomography, decrease in oxygen metabolism in the basal ganglia was noted for patients with idiopathic normal pressure hydrocephalus (Miyamoto *et al.*, 2007). Work to develop cerebrospinal fluid biomarkers continues, with recent findings of utility in using neurofilament protein light (NFL), hyperphosphorylated tau (P-tau), and beta-amyloid (1–42) (Abeta42) to distinguish between idiopathic normal pressure hydrocephalus which had higher NFL, lower P-tau, and lower Abeta42 than controls, and subcortical vascular dementia which had higher NFL but normal P-tau and Abeta42 than controls (Agren-Wilsson *et al.*, 2007). Magnetic resonance imaging full-brain voxel-based morphometric analysis was used to again verify the impact of idiopathic normal pressure hydrocephalus on the caudate nucleus (DeVito *et al.*, 2007). A small study found that white matter lesions in patients believed to have normal pressure hydrocephalus correlated negatively with a positive outcome after shunting (Bugalho and Alves, 2007). In using functional neuroimaging to try to predict response to shunting three-dimensional single photon emission computed tomography showed that reduced regional cerebral blood flow in the basal frontal lobes and cingulated gyrus were potential predictors of shunt response in a small study (Murakami *et al.*, 2007). In a medium sized study with long term follow-up, continuous intraventuricular monitoring over a 48 h period, including an intraventricular steady-state infusion test, was used to select candidates for shunting and had a fairly high rate of improvement for gait disturbance around 96%, cognitive improvement and urinary improvement in the mid-70th percents, with sustainment of clinical improvement over years in all but three of the responders (Pfisterer *et al.*, 2007). One small study saw hypokinesia improve more than disequilibrium after shunting (Bugalho and Guimara, 2007). Normal pressure hydrocephalus patients display bradykinesia, increased resting tone, and difficulty with self-initiation of tasks, though improvement in these features after shunting is variable, but sometimes seen (Mandir *et al.*, 2007). Another moderate sized study compared outcomes using repeated lumbar punctures, lumbar drainage, or cisternography as screening procedures. Both thrice repeated high volume (30–40 cc) and continuous lumbar drainage (150–250 cc over 3 days) had fairly good rates of improvement in gait disturbance (88 and 91%, respectively) whereas cisternography only had 66% responders (Kilic *et al.*, 2007) (Figs. 3–6).

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REVERSIBLE DEMENTIAS

Anahid Kabasakalian and Glen R. Finney

Memory and Cognitive Disorders Program, University of Florida
Department of Neurology, Gainesville, Florida 32610-0236, USA

The causes of potentially reversible dementia syndromes are legion, as many perturbations of body chemistry can lead to dysfunction of higher cortical function, including the chemical interventions we call medication. It is vital for the cautious clinician to take a painstaking history to develop a differential diagnosis of potential causally related reversible phenomena. This, coupled with an extensive examination and a widecast net of serological, and when appropriate, cerebrospinal, electrophysiologic, and neuroimaging studies can increase the potential for discovering these mimics of the primary neurodegenerative dementias. While some cases of reversible dementia will be obvious from history and physical and only require a few confirmatory tests or even just a trial of treatment (or often, discontinuation of a suspect treatment), it is worthwhile to perform more extensive work-up in cases of dementia, as the costs to allowing our patients to remain in an incapacitated, possibly progressive, state of disability far outweigh the costs of ruling out reversible causes. This chapter provides a lengthy, though by no means exhaustive, review of etiologies and work-up for the currently recognized reversible dementias.

I. Introduction

Dementia is a loss of cognitive capacity usually associated with minimal effect on level of consciousness. Primary neurodegenerative dementias result from progressive, irreversible destruction of neurons in the brain, whereas, reversible dementias result from progressive but potentially reversible processes from a

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secondary etiology. The underlying etiologies of reversible dementias may be the same as those causing delirium except occurring over a much longer time frame and having a more indolent course. While in some cases, correction of the underlying etiology may reverse or halt the progression of the cognitive decline, in others a fixed deficit may remain due to permanent damage to the brain. Often, the degree of reversibility is unpredictable and can only be ascertained by treatment. An additional caveat lies in the tendency to assume irreversibility in patients who have cognitive impairments at baseline. It is important to remember that patients with a primary neurodegenerative dementia or a static encephalopathy can still develop reversible cognitive impairments, and in fact, are at greater risk for cognitive decline from systemic disturbances, infection, or medications (Moore and O'Keefe, 1999). Dementia or a history of any other brain damage, is, in fact, a primary risk factor for delirium. Other major risk factors for reversible cognitive impairment are age and multiple chronic diseases (Moore and O'Keefe, 1999). Finally, due to the protean nature of many illnesses, it is critical to keep an open mind and consider a broad differential when approaching the cognitively impaired patient. Reversible cognitive impairments may closely mimic characteristic features of neurodegenerative dementias, so care must be taken not to make hasty judgments based on impression without further investigation. The potential for treatable causes of dementia, thus places an onus on the physician to investigate demands investigation in cases of dementia, as allowing a further or continued deterioration of cognition when preventable is a disservice to the patient.

History: Patients with cognitive disorders are suspect historians. As such, a friend, family member, or caretaker plays the important roles of corroborator at minimum, though more often as surrogate historian. Dementia patients themselves are notorious for anosognosia (unawareness of their own deficits) and may be quite convincing at times in their denials of significant problems. Since the pattern of onset, progression and the circumstances surrounding cognitive decline can give important clues to possible etiology, historical details provided by healthy family, friends or caregivers are often invaluable. History taking should include baseline state, character of the impairment, rate of onset of change (gradual vs abrupt), course of the impairment since onset, for example, static, continual decline, fluctuating, or stepwise, associated symptoms and signs; and assessment of risk factors, for example, sick contacts, toxic exposures, recent changes in medications roughly corresponding in time with the onset. A complete list of medications must be obtained as iatrogenic etiologies are the most common cause of reversible dementias. Dates of initiation or changes in dosage of medications known to cause confusion, either primarily or secondarily may correspond with the onset of cognitive decline. A complete past medical history may reveal chronic diseases which if inadequately treated may lead to cognitive decline over time. Sometimes, a history from the remote past may prove relevant to the current complaint. A remote history of blood transfusions, unsafe sexual practices, or

intravenous drug use increases risk for blood-borne diseases, for example, HIV, syphilis, and hepatitis. History of immunodeficiency may point to indolent infections, for example, crytococcal meningitis (CM), though lack of such a history does not necessarily rule these opportunistic infections out. Remote history of head trauma may point to a chronic subdural hematoma. Social history is vitally important. Abuse of recreational substances such as alcohol, tobacco, and other intoxicants may cause cognitive decline or predispose the patient to several secondary etiologies. As above, IV drug use may lead to investigation of certain blood-borne diseases. Suspicion for substance abuse should not be omitted based on the patient's appearance. Well-dressed and groomed patients may use substances covertly. Nutritional habits may reveal unusual or poor diets predisposing patients to vitamin deficiencies, or more rarely, toxicities. Travel history to areas both in and outside of the country may reveal exposure to infectious diseases associated with a particular region to which an illness is known to be endemic, for example, the northeastern United States for Lyme disease or to Central America for neurocysticercosis. Family history of heritable medical conditions (or heritable risk) that might lead to cognitive decline may be prime targets for exploration of the patient's own cognitive decline.

Examination: Vital signs, while normal in most cases of indolent reversible dementias, may reveal an etiology, for example, extraordinarily high resting blood pressure may underlie a chronic hypertensive encephalopathy. An inspection of the skin surface can discover signs of infection, neurocutaneous abnormalities, signs of hepatic dysfunction, such as capet medusa, the spidery web of blood vessels on the surface due to portal hypertension, or evidence of vitamin deficiency, for example, pellagra. Orientation may be impaired in a myriad etiologies reflecting alteration of consciousness, most often affecting orientation to time and to place. Orientation to self is typically is spared in mild to moderate forms of altered mental status. Level of consciousness is typically normal in patients with primary neurodegenerative disorders, though Lewy body dementia can have a fluctuating level of consciousness. Unlike deliriums which overlap in differential diagnosis with forms of reversible dementias, reversible dementias tend to have relatively normal to slightly impaired level of consciousness, or at worst a fluctuating level of consciousness. This is most likely due to the indolent nature of these perturbations of consciousness which allow for a degree of compensatory function in arousal systems not seen in acute perturbation as seen in acute onset delirium. Attention level is often impaired in reversible forms of dementia and is one of the most common forms of disruption of mental status. Since higher cortical functions rely on a certain level of attention, a defect in this portion of the examination can cause disruption in numerous cognitive responses. Concentration is closely related to attention, but even when working memory and attention to stimuli may be adequate, concentration requires further executive function, a role of the frontal lobes, to keep the patient on task and tracking

progression of complicated tasks. Finger agnosia, left/right confusion, calculation, and agraphia without alexia form the elements of the Gerstmann Syndrome and localize to the angular gyrus of the dominant parietal lobe. The presence of a full Gerstmann Syndrome out of proportion to other cognitive impairments may indicate a degree of focality, especially if the findings are reproducible on examinations separated in time. Such focality in the examination tends to point away from more systemic disruptions like hormonal abnormalities and toward more direct lesions to the brain. Thought process and thought content can be a hint to possible etiologies. Hallucinations are more often seen in acute deliriums and in psychoses, but can be seen intermittently in any of the reversible dementias. Hallucinations can be in any sensory modality. Cranial Nerve Examination can include ophthalmologic examination for Keyser-Fleischer rings is particularly important when behavioral disturbances are accompanied by movement disorders, though it may require a slit lamp examination to be certain. Cranial nerve palsies may represent a basilar process such as neurosarcoidosis, tuberculosis meningitis, or carcinomatous meningitis, though these more often present with an acute or subacute presentation rather than a subacute to chronic course which is the hallmark of the reversible dementias. Patients with Whipple's disease (WD) can demonstrate supranuclear palsies and or an abnormal oculocephalic reflex. Speech may be dysarthric, or if there is specific cerebellar involvement, ataxic. Language is typically spared in systemic etiologies of reversible dementia, but can be abnormal in etiologies that have multifocal impact directly on the central nervous system. Motor features can include rigidity, tremors, multifocal myoclonus (drug intoxication), whole body myoclonus, psychomotor slowing may be observed in drug intoxication, hypothyroid, hyperactivity (hyperthyroid), asterixis is present in toxic metabolic conditions like uremia or hepatic encephalopathy. Reflexes may show delayed relaxation, as with hypothyroid, or be brisk, as with hyperthyroid.

Laboratory studies: Nutritional: B1 (thiamine), B3 (niacin), B6, B12, vitamin E, vitamin D, vitamin A, folate. Hematologic: blood cell count: for evidence of anemia, elevated or decreased leukocyte count, micro- and macrocytosis. Electrolytes: sodium, calcium, magnesium, phosphorus, 24 h excretion of sodium, potassium, calcium, magnesium, chloride, uric acid, inorganic phosphorus, glucose, creatinine. Metabolic: liver function tests (AST, ALT, Alkaline Phosphatase), ammonia, blood urea nitrogen, creatinine, amylase, lipase. Metals: ceruloplasmin, copper, 24 h copper excretion, arsenic, lead, iron, mercury, cadmium, aluminum, manganese. Hormonal: antithyropyroxidase antibody, antithyroid antibodies (Hashimoto's encephalitis), thyropyroxidase (TPO), parathyroid hormone (PTH), free T4, T3, thyroid stimulating hormone, cortisol (24 h), aldosterone, ACTH, prolactin, testosterone. Infection: lyme antibody titers, Syphilis tests (RPR, HATTS, TPPA, FTA), HIV, cryptococcus antibody, Whipple's disease

PCR. Protein: SPEP, UPEP, albumin, Cyclic AMP (plasma, urine, CSF). Paraneoplastic (Limbic encephalitis): anti-HU, anti-MA, anti-TA. Autoimmune: ASO (antistreptolysin antibody), ESR, RF, ANA, lupus anticoagulant assay (tissue thromboplastin inhibition, anticardiolipin antibody IgG, IgM), Anti-Ro(SS-A), anti-La (SS-B), antiribosomal ab, anti-Smith ab, anti-RNP, anti-dsDNA, C3 complement, C4 complement, perinuclear antineutrophil cytoplasmic autoantibodies (pANCA), cytoplasmic (cANCA).

II. Etiologies

Medications: Risk factors for cognitive impairment resulting from medications include age, premorbid brain pathology, renal insufficiency or failure, multiple chronic medical problems, previous adverse drug reactions, polypharmacy, and multiple prescribers (Canto and Korek, 1991; Hajjar *et al.*, 2003; Moore and O'Keefe, 1999; Trimble, 1987). Specific classes of medications are known culprits in reversible dementias; although others not typically associated with impairment are possible causes in some cases. Drug classes causing reversible dementia include anticholinergics, antiepileptics, tricyclic antidepressants, antihistamines, antipsychotics, hypnotics and sedatives, opiods, and amphetamines (Hajjar *et al.*, 2003; Moore and O'Keefe, 1999). While certain drugs are marketed specifically as anticholinergic medications (scopolamine, atropine, trihexiphenydyl, benztropine), other medications, including tricyclic antidepressants (Moore and O'Keefe, 1999), antipsychotics (Feinberg, 1993; Foy *et al.*, 1995; Moore and O'Keefe, 1999) and some antihistamines such as first generation H1 blockers, for example, benadryl, H2 receptor antagonists (Das *et al.*, 1990; Moore and O'Keefe, 1999) have significant anticholinergic properties. Valproate has been shown to cause reversible dementia in both elderly and young patients which may be associated with elevated ammonia levels (Beyenburg *et al.*, 2007; Zaret and Cohen, 1986). Reversible dementia has been reported with topiramate in an elderly patient. Other common medications described as causing reversible cognitive impairment include lithium dopaminergic, agents, opioids, especially meperidine digoxin, and beta-blockers (Miller and Jick, 1978; Moore and O'Keefe, 1999; Rogers and Bowman, 1990). Smith and Kocen (1988) describe two patients in whom lithium toxicity presented clinically in a manner indistinguishable from Creutzfeldt-Jakob encephalopathy, including the characteristic one-per-second periodic complexes on EEG. Antineoplastic agents may also impair cognition. Severe but reversible cognitive impairment has been reported with thalidomide which is used to treat multiple myeloma (Morgan *et al.*, 2003).

III. Nutritional Abnormalities

Vitamin B1 (Thiamine): Wernicke's encephalopathy, characterized by a triad of opthalmoparesis, ataxia, and confusion, results from thiamine deficiency. While most commonly associated with alcohol abuse, Wernicke's encephalopathy may be seen with dialysis, bariatric surgery, prolonged administration of IV glucose alone, high caloric administration of parenteral nutrition, hyperemesis gravidarum, and acute lymphoblastic leukemia (Nakajima *et al.*, 2006; Singh and Kumar, 2007; Ueda *et al.*, 2006). Thiamine is a water soluble vitamin which is absorbed by intestinal epithelium and stored in liver, brain, and skeletal muscle. Thiamine deficiency results in hemorrhagic encephalitis in the gray matter. In addition to the classic triad of symptoms, Wernicke's encephalopathy may present with nystagmus, polyneuropathy, myoclonus, convulsions, hypothermia, and shock (Ueda *et al.*, 2006). MRI may show dilatation of the third ventricle, atrophy of mamillary bodies, and damage to the medial thalamus (dorsal medial nucleus) and midbrain (periaquductal gray), caudate and putamen (Singh and Kumar, 2007; Ueda *et al.*, 2006).

Vitamin B3 (Niacin): Pellagra is characterized by dermatitis, dementia, diarrhea and without intervention, death. This condition may be observed with malnutrition, alcohol abuse, and gastric surgery. Pellagra has been observed in anorexia nervosa, in which it primarily presents with cutaneous manifestations. It is also observed in Hartnup disease, carcinoid syndrome, and with several medications thought to disrupt the vitamin B6-nicotinamide pathway, including antiepileptics (valproic acid, phenytoin, and diazepam), carbamezpine, phenbarbital, and hydantoins, INH, pyrazinamide, 6-mercaptopurine, 5-fluourouracil, azathioprine, chloramphenicol, ethionamide, and protionamide. The rash occurs in sun-exposed areas, consisting of round erytematous macules that evolve into blisters then become dry and scaly. Additionally there is glossitis and stomatitis.

Vitamin B12 (Cobalamin): There is controversy about whether a causal relationship exists between vitamin B12/cobalamin deficiency and cognitive impairment (Andres *et al.*, 2007; Chiu, 1996). However, Chiu (1996) concludes that literature review supports such a relationship and that "clinicians should assume that vitamin B12 deficiency can give rise to cognitive impairment ranging from memory defects to a potentially reversible dementia." Andres *et al.* (2007) take a less firm position but does note a higher incidence of cobalamin deficiency in association with several neurological impairments including dementia, Alzheimer's disease, and depression. Loikas *et al.* (2007) found that "undiagnosed vitamin B12 deficiency is remarkably common in the age," and others have "found a positive correlation between low levels of vitamin B12 and low MMSE scores among older patients. The question of reversibility is somewhat at issue and appears to be a function of the duration of the symptoms prior to

treatment. The main causes for vitamin B12 deficiency are pernicious anemia and food-cobalamin malabsorption, a syndrome characterized by the inability to release cobalamin from food or from its binding proteins, usually resulting from atrophic gastritis which stresses the urgency for prompt diagnosis and treatment (Andres *et al.*, 2007). Other risk factors and causes include male gender, age 75 years or more, refraining from milk products (Loikas *et al.*, 2007), blind loop syndrome, dietary deficiency, gastrectomy, surgical resection of the ileum, deficiency in the exocrine function of the pancreas in chronic gastritis, lymphomas, or tuberculosis (intestinal), Crohn's disease, Whipple's disease, and celiac disease (Andres *et al.*, 2007). Other neurologic manifestations of cobalamin deficiency include acroparesthesia (burning and painful sensations in the hands and feet), sensory ataxia, visual loss (due to optic neuropathy), autonomic dysfunction (e.g., sphincter dysfunction, impotence and orthostatic hypotension), loss of position and vibratory sensation, positive Romberg sign, brisk reflexes (Worrall and Worrall, 2005). Macrocytic anemia may not be present. MRI and CT may demonstrate white matter lesions that may be mistaken for changes due to hypertension or other metabolic causes (Sudo and Tashiro, 1998).

Vitamin D (Calcitriol): Although there are no significant data on the relationship between vitamin D and dementia, there are some findings supporting a positive relationship between vitamin D levels and cognitive performance. Przybelski and Binkley (2007) found a significant positive correlation between performance on MMSE and serum 25(OH) D. Studies of older adults found a positive relationship between low levels of vitamin D and poor cognition (Kipen *et al.*, 1995). Stuerenberg (1996) found that dementia associated with idiopathic hypoparathyroidism may be effectively treated with 1, 25-dihydroxy-cholecalciferol. Vitamin D homeostatis is also intimately related to PTH (Kipen *et al.*, 1995), and thus to the homeostasis of several other electrolytes known to affect cognition, particularly calcium (Shoback, 2008).

IV. Endocrine Disorders and Cognition

Overview: Endocrine disorders affecting cognition may result in derangements of other systemic parameters, for example, electrolyte or glucose homeostatis which then become symptomatic. Additionally, endocrine disorders may result from immune-mediated processes. Finally, endocrine related disorders of cognition may masquerade as other disorders. As such, we reiterate the need to search for reversible causes before arriving at a final diagnosis.

Thyroid: There is controversy regarding the effects of thyroid function on cognition (Dugbartey, 1998). The degree of reversibility of thyroid-related cognitive impairment varies, likely depending on underlying etiology and duration

before treatment. Hogervorst *et al.* (2008) found high TSH, as seen in those with hypothyroidism, was associated with low cognition, and normal TSH but high normal free T4 also is associated with poor cognition at baseline and clinically significant decrease at 2 year follow-up. With regard to etiology and reversibility, Whalund *et al.*, 2002 found "little evidence that hypothyroidism causes dementia, either reversibly or irreversibly." However, there are several cases in which treatment of both hypothyroid and hyperthyroid function (Fukui *et al.*, 2001) have restored cognitive function to different degrees (Bono *et al.*, 2004; Dugbartey, 1998; Mennemeier *et al.*, 1993). Etiologies for derangements in thyroid function may be clear, for example, thyroid cancer or treatment with radiation, or may require more investigation. Anti-thyroid receptor antibodies and antithyroid stimulating antibodies are found with Grave's disease, anti-TPO and antimicrosomal antibodies may be found in Hashimoto's encephalopathy. TSH, Free T4, T3 may all be normal in cases of autoimmune thyroid disease, particularly in Hashimoto's encephalopathy. Therefore, thorough investigation demands assessment for antimicrosomal and TPO in conjunction with the standard thyroid function tests (TFTs).

Hypercortisolemia: Selective memory impairment is seen in Cushing's syndrome. Results following surgery are equivocal with some studies demonstrating improvement in cognitive function and others not (Mauri *et al.*, 1993).

Parathyroid: PTH regulates the homeostatis of calcium, phosphate and vitamin D activation (Shoback, 2008). PTH released into the blood acts distally at the bone to increase release of calcium and phosphate into the blood and at the kidney to promote calcium resorption into the blood and phosphate excretion in the urine. In the kidney, PTH also facilitates the conversion of inactive vitamin D (25-hydroxycalciferol) to active vitamin D (1, 25-dihydroxycalciferol) which subsequently facilitates increased intestinal absorption of both phosphate and calcium.

Cognitive disturbances are seen in both hypo- and hyperparathyroidism (Adorni *et al.*, 2005; Chadenat *et al.*, 2008). Cognitive impairment associated with PTH is most often associated with derangements in free calcium (Shoback *et al.*, 2008), however, in at least one case of idiopathic hypoparathyroidism and normal calcium, dementia reversed following treatment with 1,25-dihydroxycalciferol (Stuerenburg *et al.*, 1996). In that same case, MRI had diffuse signal enhancement of the periventricular frontal and parietal white matter on T2 suggestive of edema that also resolved after treatment with vitamin D. In addition, magnesium depletion or excess may cause functional hypoparathyroidism (Shoback, 2008). Hypercalcemia may also result from activity of a PTH-like substance which may be produced ectopically by several tumor types. The most common cause of hyperparathyroidism is parathyroid adenoma. Additionally, hyperparathyroidism and Creutzfeldt-Jakob disease may be mistaken for each other (Chadenat *et al.*, 2008; Goto *et al.*, 2000). CT in hypoparathyroid will demonstrate intra parenchymal calcifications (Adorni *et al.*, 2005), and some

have noted, a positive correlation between the degree of calcification and the degree of cognitive loss and motor symptoms.

Electrolyte abnormalities: Alterations in mental status resembling dementia may result from electrolyte abnormalities, particularly sodium, calcium, and magnesium.

Disorders of calcium homeostasis: Hypocalcemia, in addition to presenting with cognitive dysfunction, may present with seizures, extrapyramidal signs, papilledema and elevated intracranial pressure, neuromuscular hyperreactivity, and cataracts (Stuerenburg *et al.*, 1996). Hypercalcemia may occur as a paraneoplastic condition, most often with lung and breast cancer, osteolytic metastases to bone, as well as in association with hyperparathyroidism. Activated vitamin D, 1,25 (OH)2D3 is normally suppressed when serum calcium levels are high. Elevated 1,25(OH)2D3 in association with hypercalcemia may be seen with granulomatous disease, non-Hodgkin's lymphoma, and other hematologic malignancies due to extrarenal production of 1,25(OH)2D3 (Clines and Guise, 2005). Increased suspicion for malignancy should be raised in patients greater than 50 years of age, or progressive pain for greater than 1 month with no relief with bed rest. Solid tumors may produce other humoral factors resulting in hypercalcemia, for example, IL-1, IL-6, TGF-alpha, TNF, and granulocyte-CSF (Clines and Guise, 2005).

Disorders of sodium homeostasis: In hypernatremia older patients are at increased risk of hyperosmolar states. One documented etiology for this is decreased fluid intake. Decreased thirst has been demonstrated in normal elderly adults. Elderly patients may be limited in their abilities to act on thirst due medical conditions limiting their mobility and making them dependent on others to bring them fluids. In hyponatremia, patients demonstrate lethargy, fatigue, sleep disturbance, muscle cramps, and headaches. Worsening of the condition may result in nausea, vomiting, confusion, seizures, coma, and death (Flicker and Ames, 2005).

Hepatic encephalopathy: A linear progression of cognitive decline is associated with severity hepatic dysfunction.

Chronic obstructive pulmonary disease (COPD): COPD complicated by hypoxemia is associated with cognitive impairments, and patients with COPD are shown to demonstrate anterior cerebral hypoperfusion and directly correlated with impairments on neuropsychological assessment (Incalzi *et al.*, 2003). In a recent literature review, Kozora *et al.* (2008) documented some improvement with traditional therapies, for example, continuous and intermittent oxygen therapy and comprehensive pulmonary rehabilitation. Even greater improvement was demonstrated following lung volume reduction surgery.

Renal failure: Patients with renal failure may develop dialysis encephalopathy syndrome post-dialysis, which had been proposed to result from aluminum toxicity (Flicker and Ames, 2005). Pre-dialysis, uremia may result in cognitive compromise. Neurologic exam may demonstrate asterixis.

Infectious causes of dementia: If there are rules about manifestations of reversible infectious causes of dementia, the first is that there are no rules. Most of these infections are protean, occur infrequently, are insidious in onset, and therefore, not the first things to come to mind in the face of progressive cognitive decline. Additionally, all can be lethal. Therefore, the diagnostician's rule must be to consider all the zebras until a definitive cause has been clarified.

Whipple's disease: Whipple's disease is a rare systemic disease caused by infection by *Tropheryma whippelii* in which any organ system may be affected, including the brain which may include alterations in cognition or behavior (Rossi *et al.*, 2004). The central nervous system may demonstrate infection in 50% cases at postmortem; however, neurological symptoms are observed in only 10–20% of cases. Due to the insidious nature of onset and protean manifestations of infection, diagnosis is often elusive. Whipple's disease has presented with symptoms associated with several neurodegenerative conditions, including progressive supranuclear palsy, hypersomnia, and frontotemporal dementia (Rossi *et al.*, 2004). Other neurologic symptoms may occur, including, but not restricted to a stroke-like syndrome, ophthalmoplegia, mystagmus, myoclonus, disturbed sleep pattern, ataxia, seizure, or symptoms of elevated intracranial pressure secondary to hydrocephalus (Marth and Raoult, 2003). In some cases, the impairment is reversible (Rossi *et al.*, 2004). Early suspicion and aggressive diagnostic work-up may identify cases earlier when treatment may be more effective. Nonneurologic symptoms which should raise suspicion for WD include gastrointestinal symptoms, especially weight loss and diarrhea suggestive of malabsorption. Other symptoms may include arthropathy and myalgias (Marth and Raoult, 2003). Labs abnormalities may suggest malabsorption with low albumin, elevated serum cholesterol, steatorrhea, vitamin deficiencies of B12, D, K, folic acid and beta-carotene. Acute phase reactants, for example, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be elevated. Additionally there may be lymphocytopenia, throumbocytosis, and hypochronic anemia (Marth and Raoult, 2003). Diagnosis of WD may be performed by PCR amplification of TW 16S rRNA in biological fluids and staining of CSF may demonstrate PAS staining of cellular material (Rossi *et al.*, 2004). Treatment may be with ceftriaxone, sulfamethoxazole, and trimethoprim, though streptomycin and rifampicin have also been used with success (Gerard *et al.*, 2002; Rossi *et al.*, 2004). For treatment of the CNS, antibiotics must cross the blood-brain barrier. Panegyres *et al.* (2006) suggest penicillin/streptomycin or cotrimoxazole over tetracycline as well as penicillin, cetriaxone, chloramphenicol, and quinolones. Extended treatment is the rule, though the disease can have a chronic relapsing course and the organism can remain in many tissues even with extended therapy (Marth and Raoult, 2003). In cases of CNS involvement, treatment should be discontinued only when results of the PCR of the CSF are negative (Gerard *et al.*, 2002). Imaging

of the brain in primary WD of the CNS may show single or multiple enhancing lesions (Panegyres *et al.*, 2006).

Crytococcal meningitis and meningoencephalitis: Crytococcal meningitis, usually thought of as an opportunistic infection in immunocompromised patients (Mitchell and Perfect, 1995) may occur in immunocompetent patients in whom diagnosis may be delayed or missed due to similarity of presentation to other dementias, the insidious nature of onset, lack of risk factors for opportunistic disease, and the lack of specific symptoms (Butler *et al.*, 2000; Lewis and Rabinovich, 1972; Vella Zahra *et al.*, 2004). The presence of focal symptoms which may occur from infarct (Luse, 1967) need not concur with the cognitive changes. Diagnosis of in immunocompromised patients presents further complication as immunocompromised patients may not have an inflammatory response in the spinal fluid. PCR is useful for identification. Imaging studies for CNS cryptococcal infection have shown deep white matter and basal ganglia lesions typically interpreted as lacunes, dilated Virchow-Robin spaces, pseudocysts, masses, hydrocephalus, and radiological meningitis, multiple ring enhancing lesions, brain edema, hydrocephalus, leptomeningeal enhancement, subdural effusions, basal ganglia infarcts, and leukoencephalopathy. Of note, imaging findings may persist long after effective treatment and should not be mistaken for active Cryptococcus (Hospenthal and Bennet, 2000).

Lyme disease: Infection of the brain by *Borrelia burgdorferi* (neuroborreliosis) may result in reversible cognitive impairment. However, cognitive impairments may persist despite treatment and in some cases progress to death. Lyme disease usually begins with a rash which is usually, but not always, consistent with erythema migrans. This may be accompanied by fatigue, headache, mild stiff neck, joint and muscle aches, and fever. Disseminated disease may follow weeks or months after initial exposure primarily involving neurologic, cardiac, or joint disease. Neuroborreliosis has a protean presentation and has been reported as presenting with a frontotemporal dementia syndrome associated with severe associated subcortical atrophy (Waniek *et al.*, 1995), normal pressure hydrocephalus (NPH) (Danek *et al.*, 1996), and nigrostriatal degeneration (Cassarino *et al.*, 2003) as well as a "Lyme encephalopathy," mild to moderate in severity affecting memory and learning, sometimes with subtle psychiatric symptoms or somnolence, but usually without focal neurological signs or abnormalities on MRI (Logigian *et al.*, 1997). Chronic cognitive deficits may persist posttreatment. Encephalomyelitis and encephalopathy are most often been seen as late manifestations of infection (Wormser *et al.*, 2006), with rare exceptions (Danek *et al.*, 1996). In untreated patients, encephalomyelitis is most often monophasic, slowly progressive, and primarily affecting white matter and may be confused clinically with an initial manifestation of multiple sclerosis (Wormser *et al.*, 2006). There is no "gold standard" method to accurately determine neuroborreliosis. CSF shows a lymphocytic pleocytosis, moderately elevated protein and normal glucose. Serology is performed first by ELISA or

immunofluorescence antibody, and when positive followed by a Western blot (Roos and Berger, 2007). Serologic tests may be negative during early infection (Roos and Berger, 2007). In the United States, the presence of anti- *B. burgdorferi* antibodies in the CSF has been sufficient for diagnosis; however, as antibodies can passively transfer from serum to CSF, some argue that this is inadequate proof of CNS infection (Roos and Berger, 2007). In patients with focal neurological deficits from Lyme infection, MRI may demonstrate white matter abnormalities visible on T2 imaging similar to those seen in multiple sclerosis, while patients without focal symptoms may show no abnormalities. Some cases have demonstrated findings consistent with NPH (Danek *et al.*,1996). Reversible hypoperfusion of frontal subcortical and cortical structures has been shown on SPECT (Logigian *et al.*, 1997). Alteration of white matter blood flow has been demonstrated in brains of patients with chronic Lyme disease who complain of cognitive problems. In adults, early infection may be preferentially treated with oral antibiotics, for example, doxycycline, amoxicillin, or cefuroxime for 14–21 days, with selected macrolides used as alternatives when preferred medications are not tolerated. Late infection in adults requires treatment preferentially with parenteral ceftriazone, or alternately with cefotaxime or penicillin (Wormser *et al.*, 2006). Antibodies may remain elevated in the CSF after treatment (Wormser *et al.*, 2006).

Syphilis: Neurosyphilis results from infection of the nervous system by the spirochete *Treponema pallidum*. As with other indolent infections in the nervous system, its manifestations are protean. Some propose that presentations of neurosyphilis have changed since the development antibiotics and the spread of HIV infection with more than half of the cases late presenting with "dementia or psychiatric/behavioral syndromes." Others found a similar proportion of dementia, delirium, and other neuropsychiatric manifestations, but also noted the typical pre-antibiotic presentations of stroke, spinal cord disease, and seizures. Authors caution against neglecting to test for syphilis even in cases where there is low suspicion. RPR may be falsely negative, especially in secondary and tertiary syphilis. The *T. pallidum* particle agglutination test (TP-PA) is a more sensitive serum test of exposure than RPR in syphilis. CSF VDRL is specific for neurosyphilis but not very sensitive (Timmermans and Carr, 2004). In the case of a negative VDRL, a negative result in a treponeme-specific FTA-Abs in the CSF, which is sensitive but not specific for neurosyphilis, may support a negative diagnosis (Timmermans and Carr, 2004). In patients with HIV, CSF analysis is recommended when the serum RPR is greater than or equal to 1/32 (Libois *et al.*, 2007), and CSF-FTA and %CSF B cells may be used for diagnosis when the CSF-VDRL is nonreactive.

HIV: While HIV dementia is typically irreversible, in the earlier phases of the disease, HIV-related neurocognitive impairment can be reversed by highly active antiretroviral therapy (HAART), though some degree of neuropsychological

deficit may persist even after HAART treatment. The most important predictor of response to treatment was the degree of neurocognitive impairment prior to initiation of treatment (Tozzi *et al.*, 2007). Therefore, it is important to have a low threshold of suspicion for possible HIV infection and to screen for it on a regular basis in subacute dementias. In one study, HIV cognitive impairment patients were found to have reduced markers of mature neurons and increased markers of gliosis in the basal ganglia and frontal white matter (Paul *et al.*, 2007), which correlates with the frontal subcortical dysfunction seen in HIV cases.

Cerebral manifestations of systemic inflammatory disorders: This category includes such diverse entities as Behcet's disease, hypereosinophilic syndrome, celiac sprue CNS vasculitis, Susac's syndrome, Lupus cerebritis, Sjogren's syndrome, Antiphospholipid antibody syndrome, and Neurosarcoidosis. A number of these inflammatory conditions are associated with vasculopathy of the CNS, by either inflammatory or coagulopathic mechanisms. In some cases, both of these mechanisms are observed. A number of mechanisms may be involved in CNS damage. In SLE, for example, CNS damage may "fibrinoid necrosis of small vessels, embolic large- and small-vessel infarction, coagulopathy, vasculitis, antineuronal antibodies and the effects of cytokines (Ovsiew and Utset, 2002). Antiphospholipid antibodies (aPLs) have been associated with hypercoagulability, recurrent thromboses, transient ischemic attacks and chorea. Some lupus anti-DNA antibodies may cross-react with NMDA receptor subunits and cause apoptotic cell death. These findings suggest that the integrity of the blood-brain barrier may be crucial in protecting against the development of cognitive impairment due to NMDA-binding anti-DNA antibodies in patients with lupus. Vasculitis may be limited to the CNS or may have associated systemic symptoms including fever, fatigue, weight loss, rash, neuropathy, or other organ involvement. Workup for vasculitis includes ESR, CRP, C3, C4, Ch-50, ANA, RF, anti-SSA, anti-SSB, p-ANCA, c-ANCA. Urine evaluation may demonstrate a hemolytic anemia. Lupus anticoagulant may occur independently of SLE and may present with progressive intellectual decline and has been shown to be reversible with immune-suppressive therapy. Labs may clarify the diagnosis. Sjogren's syndrome will usually be positive for ANA, SS-A (Anti-Ro), SS-B (Anti-La), though rarely both SS-A and SS-B may be negative. SLE may demonstrate a positive ANA, double-stranded DNA, Anti-Smith antibody. Celiac sprue may be diagnosed with positive antigliaden antibodies. SLE-cerebritis may demonstrate positive anti-ribosomal and antineuronal antibodies. MRI may show cerebral atrophy, gadolinium enhancing T2 hyperintiensities in gray or white matter which are more often subcortical than periventricular. All may demonstrate elevated ESR and CRP. In Sjogren's syndrome, MRI may demonstrate nonenhancing densities on T2 in periventricular and subcortical areas. Reversibility of cognitive impairment in inflammatory conditions is highly variable (Caselli *et al.*, 1991). Hypercoagulable states may result from antiphospholipid antibodies. Hyperviscosity syndromes

resulting from polycythemia or gammopathies, for example, Waldenstrom's macroglobulinemia may cause a rapidly progressive dementia due to cerebral ischemia (Schofield, 2005).

Toxic conditions: Lead exposure may occur via oral ingestion, skin or lungs. Risk factors include battery production, brass, bronze, or glass works, ammunition production, paint and pigment production, pottery making and other industrial exposures. Lead encephalopathy can cause seizures and coma. Mercury in the brain is associated with erythrism (aka Mad Hatter's Disease) presenting with nervousness and timidity, irritability, labile mood, ataxia, and some cognitive changes. Aluminum toxicity is associated with dysarthria, dysphagia, dyspraxia, and personality change. Cases of manganese, tin, and arsenic are also reported as causes of neurocognitive impairment. Lead, arsenic, and mercury also result in peripheral neuropathy. MRI may show calcification and increased signal on T2 weighted imaging in the periventricular white matter, basal ganglia, hypothalamus, and pons with lead poisoning. 24 h urine heavy metal for lead, arsenic, and mercury, bismuth, aluminum, lithium. 24 h urine for copper. Treatment is by chelation. Ethylendiamineteraacetic acid (EDTA) or dimercaptosuccinic acid is used to lower lead levels. Dimercaprol, or British Anti-Lewisite (BAL) and penicillamine are used for treatment of elemental and inorganic mercury, but not methylmercury. History taking should include questions industrial contact or symptoms which might reveal exposure to carbon monoxide or solvents. Though changes are most often not reversible per se, identification of the offending agent may prevent further decline (Schofield, 2005).

Paraneoplastic limbic encephalitis (PLE): PLE is an immune-mediated neurological complication of malignancy characterized by triad of short term memory impairment, complex-partial temporal lobe seizures, and psychiatric symptoms (depression, psychosis, or change in personality). They are most often associated with specific cancer types, which produce correspondingly specific autoantibodies, for example, small cell lung cancer (anti-HU, anti-MA 1, 2, CRMP/anti-CV2, N-type VGKC antibodies), testicular cancer (anti-MA 2 antibodies), thymoma (antivoltage-gated potassium channel (anti-VGKC) antibodies and breast cancer (N-type VGCC). PLE has a heterogeneous presentation mimicking many other neurologic or psychiatric conditions, and onset may be acute or insidious. Most often, PLE precedes the diagnosis of cancer; however, constitutional symptoms of weight loss, night sweats, or lab findings of elevated ESR may suggest the presence of cancer. PLE typically involves the anteromedial temporal cortex, hippocampus and amygdale, and may also include nearby limbic structures, that is, hypothalamus and insular cortex. MRI may show nonenhancing signal changes in the mesial temporal lobes. PLE may improve with treatment of the underlying cancer and some may respond to steroids. Some patients also respond to plasmapheresis or IVIG (Vernino *et al.*, 2007).

Autoimmune disease and the thyroid: Grave's disease and Hashimoto's thyroiditis are autoimmune-mediated conditions of the thyroid. Grave's disease often presents with neuropsychiatric and systemic symptoms. Labs demonstrate low TSH, elevated thyroid hormone levels and demonstration of anti-TSH receptor antibody (TSHR). While, memory and cognitive complaints are common in acute onset Grave's disease, they do not manifest on formal neurocognitive assessment and are believed to be manifestations of mood and somatic symptoms experienced by patients with Grave's, and symptoms resolve with treatment. Hashimoto's thyroiditis (aka corticosteroid-responsive encephalopath associated with evidence of thyroid autoimmunity (SREAT) is one of several conditions characterized by encephalopathy which responds to treatment with steroids (nonvasculitic autoimmune meningoencephalitis (NAIM), has a broad range of clinical presentations. Onset may be acute or insidious with measurable multiple neurocognitive and neuropsychiatric impairments sometimes accompanied by tremor, seizures, stroke-like events and systemic symptoms of fatigue, general malaise, reduced appetite and weight loss (Mocellin *et al.*, 2006; Vernino *et al.*, 2007). History may include generalized seizures, and neurologic exam may reveal frontal release signs, brisk reflexes, myoclonus, tremor, and ataxia. Lab evaluation for Hashimoto's thyroiditis includes anti-TPO antiobody and antithyroglubulin antibody (TG). Antimicrosomal antibodies may also be positive. Thyroid hormones may be normal and inflammatory markers, for example, CRP and ESR may be elevated and some patients may show elevated liver aminotranferase levels. CSF may show elevated protein with mild lymphocytic pleocytosis. Neuroimaging is usually normal, however some may show increased white matter signal and T2-weighted and FLAIR sequences and less commonly dural enhancement. Treatment is with steroids. Of note, though anti-TPO and anti-TG antibodies may be found in Grave's disease, anti-TSHR antibodies are not observed in Hashimoto's thyroiditis. In general, steroid-responsiveness may be the only diagnostic clue for an autoimmune encephalopathy when serologic work-up is not revealing. Leger *et al.* (2004) reported on a woman who presented with changes in personality and attention with minor associated involuntary movements. In this patient a PET scan was diagnostic, demonstrating hypermetabolism in the striatum and CSF exam demonstrated antistriatal antibodies. Steroid nonresponsiveness in cases suggests a paraneoplastic or neurodegenerative disease (Mocellin *et al.*, 2006).

Wilson's disease (aka hepatolenticular degeneration): An autosomal recessive disorder of copper metabolism, resulting in copper toxicity, primarily in the liver and brain. This presents with psychiatric and movement abnormalities including personality changes, depression, hyperactivity, dystonia, incoordination, and tremor. Laboratory assessment should include ceruloplasmin, serum copper, and liver function tests. Slit lamp exam should be performed to evaluate for Kayser-Fleisher rings in Descemet's membrane. Treatment is through chelation with trientine and supplementation of zinc. In cognitive assessment of treated

patients with Wilson's found a presentation is consistent with subcortical dementia, with increased reaction times, impairments in short term memory, selective attention and executive functions and suggested that cognitive impairments result from disturbances in the frontal-subcortical circuits (Flicker and Ames, 2005).

Dural arteriovenous fistula (DAVF): A reported structural abnormality associated with progressive cognitive decline is DAVF (Bernstein *et al.*, 2003; Hirono *et al.*, 1993). These lesions may present with severe and slowly progressive global cognitive impairment as the main derangement, though they may also occur in association with transient or focal neurological deficits or symptoms (Bernstein *et al.*, 2003; Hirono *et al.*, 1993). However, there may be essentially no focal signs or symptoms. Associated signs and symptoms may include pulsatile tinnitus which may be transient, headache, papilledema, gait disturbance, parkinsonism. Examination may also reveal a bruit over the skull, most often the mastoid. MRI may demonstrate diffuse white matter changes with high signal intensity on FLAIR, and DWI. MRA and conventional angiography may show flow reversal in the venous system in association with venous thrombosis and decreased perfusion of the associated parenchyma. The symptoms and imaging findings are thought to result from venous hypertension. In all cases reported here, selective embolization resulted in complete or near complete resolution of function (Bernstein *et al.*, 2003; Hirono *et al.*, 1993).

Normal pressure hydrocephalus: NPH may present with progressive impairment of gait, cognition in association with urinary incontinence. However, not all cases may have reversible findings. See the separate chapter on "Normal Pressure Hydrocephalus" for more details.

Psychiatric causes: Depression and dementia are frequently comorbid. However, nondemented patients with depression may demonstrate or complain of impairments in cognition, giving the impression of dementia, a condition termed "pseudodementia." Neuropsychological testing is considered the gold standard in distinguishing between the two, as patterns in demented versus nondemented depressed normal are identifiable. However, because dementia and depression may be comorbid, addressing the treatable depression component is crucial for a patient's maintaining the highest level of functioning. The reverse is also true, however. Pseudodementia in the elderly is identified as a risk factor for progression to dementia. Therefore, older patients presenting with depression should be fully evaluated for dementia. In addition to standard labs for screening of reversible dementias, a cortisol level should be assessed, as hypercortisolemia may be associated with depression in the elderly. Imaging studies may show white matter and subcortical gray matter hyperintensities in elderly patients with depression. Catatonia is characterized by three cardinal features; little or no spontaneous movement, mutism, and refusal to eat or drink. Catatonia is observed with many brain disorders, including depression, dementia, head trauma, encephalitis, focal brain lesions, and in response to psychotropic medications. Catatonia may be mistaken

for severe, end-stage dementia. When associated with medications, particularly neuroleptics, vital signs demonstrating elevated body temperature and tachycardia are clues to the diagnosis. In those cases, medications should be stopped and the patient may require dopamine agonists to reverse the effects of the original offending agents. Benzodiazepines may be needed. Monitoring of vital signs, renal function, and supportive care is indicated. In other cases, patients may respond to benzodiazepines. Refractory cases may respond to electroconvulsive therapy (Wright and Persad, 2007).

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