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Neuropsychological and neurobiological markers of the preclinical stage of Alzheimer's disease

Helenice Charchat Fichman[1], Rosinda Martins Oliveira[2] and Conceição Santos Fernandes[3]

1 - Pontifícia Universidade Católica, Rio de Janeiro, RJ, Brazil

2 - Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

3 - Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

Abstract

Dementia, especially Alzheimer's disease, has a high prevalence in the elderly population. Therefore, identifying individuals who are at a high risk for early diagnosis is crucial to allow both pharmacological and behavioral therapeutic interventions, which in some cases can delay the progression of dementia. This paper describes neuropsychological and neurobiological markers for the early diagnosis of Alzheimer's disease and presents the main risk factors, including neuropathological, neuroanatomical, neurofunctional, genetic, and neuropsychological. The literature shows that the combination of these markers is the best method for predicting Alzheimer's disease, years before its clinical manifestation. The most prevalent neurobiological and neuropsychological risk factors include (1) senile plaques and neurofibrillary tangles in the medial temporal lobe and cortical regions, (2) low concentrations of Aβ1-42 peptide and high concentrations of total tau protein and phosphorylated tau protein in cerebrospinal fluid, (3) reduced global cerebral volume, increased ventricular volume, and atrophy in the hippocampal formation and entorhinal cortex, (4) global reductions in cerebral metabolism and perfusion in the temporoparietal junction, temporal, parietal, and frontal lobes, hippocampal formation, and posterior cingulate cortex, (5) the presence of the apolipoprotein E ε4 allele, and (6) verbal anterograde episodic long-term memory impairment and executive dysfunction. The present review discusses the evidence for markers that identify individuals who are at a high risk of developing Alzheimer's disease and the importance of longitudinal studies in this context.
Keywords: dementia, Alzheimer's disease, neurobiological markers, longitudinal studies.

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Introduction

Ageing has direct consequences on public health systems and the economies of developing countries. In almost all countries, the proportion of people over 60 years of age is growing faster than any other age group (World Health Organization, 2009). Brazil has experienced one of the greatest accelerations of growth of the elderly population in the past several years (Argimon & Stein, 2005; Camarano, 2004; Ramos, Veras, & Kalache, 1987). By 2025, Brazil could rank sixth in the world in terms of its proportion of older people (Banhato, & Nascimento, 2007; Kalache, 1991; Kalache, Veras, & Ramos, 1987).

Dementia, especially Alzheimer's disease (AD), has a high prevalence in the elderly population (Lopes & Bottino, 2002; Nitrini et al., 2002; Oliveira, Duarte, Lebrão, & Laurenti, 2007; Prince, Acosta, Chiu, Scazufca, & Varghese, 2003). According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV-TR), AD is characterized by memory loss associated with other cognitive changes, including language disorders, an impaired ability to perform motor activities despite intact motor function, a failure to recognize or identify objects despite intact sensory function, a prejudice of executive functioning, and resulting impairments in daily living (American Psychiatric Association, 1994).

Considering this epidemiological and demographic background, identifying individuals at risk for dementia is crucial. Although still generating controversy and ethical discussions, the early diagnosis of dementia allows both pharmacological and behavioral therapeutic interventions, reduces stress levels for families, reduces the risks of accidents, extends autonomy, and avoids or delays the beginning of the dementia process in some cases (Anstey et al., 2008; Myers, Kluger, Golomb, Gluck, & Ferris, 2008; Ritchie, & Touchon, 2000). The identification of individuals who are at a greater risk of

Helenice Charchat Fichman, Departamento de Psicologia, Pontifícia Universidade Católica, Rio de Janeiro, Brazil. Rosinda Martins Oliveira, Instituto de Psicologia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil. Conceição Santos Fernandes, Departamento de Psicologia, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil. Correspondence regarding this article should be directed to: Helenice Charchat-Fichman. Phone: 22595447. Fax: 22595447. E-mail: hcharchat@uol.com.br

developing dementia prepares patients and their families for the possibility of the progression to dementia and thus allows them to plan future strategies. (Petersen et al., 2001).

The present paper discusses the possible neuropsychological and neurobiological markers for the early diagnosis of AD and defines the concept of mild cognitive impairment (MCI) as a transitional stage between normality and dementia in the ageing process. The objective of this review is to present the major neuropathological, neuroanatomical, neurofunctional, genetic, and neuropsychological risk factors for AD.

Mild cognitive impairment

There is intense debate about the concept of "normality" in the ageing process. During the past decade, several studies have suggested that the majority of elderly persons do not show cognitive decline (Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006; Petersen et al., 2009; Plassman et al., 2008; Hänninen, Hallikainen, Tuomainen, Vanhanen, & Soininen, 2002; Unverzagt et al., 2001). However, cognitive decline is observed among some individuals who will eventually develop dementia (Busse et al., 2006; Fischer et al., 2007; Petersen et al., 2009; Solfrizzi et al., 2006).

Different diagnostic entities and clinical concepts have been proposed to characterize the transition between normal ageing and the dementia process. The first clinical concepts sought to describe cognitive impairment, especially with regard to memory, within the limits of physiologically normal ageing (Crook, Bartus, Ferris, Whitehouse, Cohen, & Gershon, 1986; Kral, 1962; Levy, 1994; World Health Organization [WHO], 1993). These concepts were followed by other diagnostic systems for identifying individuals who are at risk for developing specific forms of dementia (Gauthier et al., 2006; Morris, 1993; Petersen, Smith, Waring, Ivnik, Tangalos, & Kokmen, 1999; Petersen et al., 2009; Reisberg, Ferris, De-Leon, & Crook, 1982; Winblad et al., 2004). These diagnostic system studies were the foundation for the contemporary concept of MCI.

Mild cognitive impairment was initially proposed as a prodromal condition for AD and emphasized memory impairment as a characteristic of that condition. The criteria for MCI included memory complaints (preferably corroborated by an informant), memory impairment documented according to appropriate reference values, essentially normal performance in non-memory-related cognitive domains, generally preserved daily living activities, and a lack of dementia (Petersen et al., 1999).

Subsequent revisions of the MCI concept resulted in a distinction between amnestic MCI (aMCI) and nonamnestic MCI (naMCI). Each of these MCI subtypes can be further divided into single and multiple domain classifications. Thus, the concept of MCI includes four subtypes: aMCI single domain (the main requirement of which is objective memory impairment but not deficits in other cognitive domains), aMCI multiple domain (the main requirement of which is objective memory impairment and deficits in at least one other cognitive domain), naMCI single domain (characterized by objective impairment in a single cognitive domain other than memory), and naMCI multiple domain (characterized by objective impairment in at least two cognitive domains other than memory (Petersen, 2004; Petersen et al., 2009; Winblad et al., 2004).

Epidemiological data from different countries have shown a prevalence rate of MCI in the range of 14% to 18% for individuals aged 70 years and older (Busse et al., 2006; Das et al., 2007; Di Carlo et al., 2007; Fischer et al., 2007; Ganguli Dodge, Shen, & DeKosky, 2004; Hänninen et al., 2002; Lopez et al., 2003; Manly et al., 2008; Palmer, Bäckman, Winglad, & Fratiglioni, 2008; Plassman et al., 2008; Petersen et al., 2009; Roberts et al., 2008; Unverzagt et al., 2001). Despite variations, the overall estimated incidence rates of nonspecific MCI have been in the range of 51 to 76.8 cases per 1,000 person-years. For the aMCI subtypes, the incidence ranges from 9.9 to 40.6 cases per 1,000 person-years. For the naMCI subtypes, the incidence is 28 to 36.3 cases per 1,000 person-years. The factors that increase the risk for MCI are higher age, lower education, and hypertension (Busse et al., 2006; Caracciolo et al., 2008; Chaves, Camozzato, Godinho, Piazenski, & Kaye, 2009; Luck, Luppa, Briel, & Riedel-Heller, 2010; Manly et al., 2008; Ravaglia et al., 2007; Solfrizzi et al., 2004; Tervo et al., 2004; Verghese et al., 2006).

Despite methodological diversity, epidemiological studies agree that individuals with MCI present a higher risk for developing dementia compared with the elderly population without cognitive impairment. The conversion rates to dementia range from 3% to 24% per year, depending on the sources of the samples (Busse et al., 2006; Farias, Mungas, Reed, Harvey, & De Carli,, 2009; Fischer et al., 2007; Petersen et al., 2009; Ravaglia et al., 2007; Solfrizzi et al., 2004; Tschanz et al., 2006). Studies that have enrolled participants from referral sources show higher conversion rates compared with those that address a population from an epidemiological perspective. However, in both cases, the rates were always elevated compared with the base incidence rates of dementia and AD of 1% to 2% per year (Petersen et al., 1999).

The clinical concepts of MCI that show higher conversion rates for AD probably are those that are more restrictive and include elderly persons with episodic memory deficits (Bäckman, Jones, Berger, Laukka, & Small, 2005; Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001; Petersen et al., 1999; Ravaglia et al., 2007; Tierney et al., 1996). Typically, aMCI shows a higher probability of conversion to AD and, to a lesser degree, vascular dementia, whereas naMCI is likely to show far more variability in terms of progression to various

forms of dementia (e.g., frontotemporal dementia and primary progressive aphasia; Busse et al., 2006; Fischer et al., 2007; Yaffe et al., 2006; Yaffe et al., 2011a; Petersen, 2004). Some individuals with MCI may show long-term stability with regard to cognitive deficits or even achieve normal standards over time (Loewenstein, Acevedo, Agron, & Duara, 2007).

Thus, the concept of MCI itself has low specificity and low predictive value. However, increasing the knowledge of the variability in the transition from normal ageing to dementia and the risk factors for dementia in MCI is very important.

Despite some differences among MCI studies in terms of criteria, study design, and samples, the results consistently point to the possibility of biologically and psychologically identifying very early signs of dementia long before it can be diagnosed.

Recent studies have investigated the possibility of making predictions of AD before the criteria for MCI are met. Very subtle delayed recall and losses in executive function were shown to predict a greater likelihood of developing AD within 5 years. This pre-MCI is also known as the subjective cognitive impairment (SCI) stage of AD (Reisberg & Gauthier, 2008).

Subjective cognitive impairment has complex relationships with depression and anxiety. Differences between SCI subjects and age-matched non-SCI controls were found in cognitive tests, hippocampal gray matter density, hippocampal volume, cerebral metabolism (Mosconi et al., 2008a), and urinary cortisol levels. These data suggest a continuum between SCI, MCI, and dementia. These studies supported the previous estimates of the duration of the SCI stage of approximately 15 years prior to the development of MCI (Reisberg & Gauthier, 2008).

Neuropsychological markers

Controversial results have been found about which cognitive functions and tasks are the best indicators of future dementia and the development of AD. The majority of studies found that episodic memory is an important predictive factor, but the results of other cognitive functions have been highly variable (Albert et al., 2001; Bäckman et al., 2005; Blacker et al., 2007; Bondi et al., 2008; Daly et al., 2000; Elias et al., 2000; Linn et al., 1995; Small, Fratiglioni, Viitanen, Winblad, & Backman, 2000; Tierney et al., 1996). Fabrigoule et al. (1998) suggested two main causes for these results: variability of pre-dementia periods (1 to 22 years) and colinearities of neuropsychological tests.

Many recent studies have investigated cognitive markers that predict dementia, especially with regard to AD (Bäckman et al., 2005; Blacker et al., 2007; Bondi et al., 2008). The results are consistent regarding the role of anterograde episodic memory during the pre-dementia stages of AD. In longitudinal studies, verbal associative learning tasks (e.g., California Verbal Learning Test, Rey Auditory Verbal Learning Test, Verbal Associated Pairs of Wechsler Memory Scale-Revised – WMS-R) have been able to differentiate groups of elderly subjects with subclinical cognitive impairment that converted to AD from groups who remained stable (Albert et al., 2001; Daly et al., 2000; Elias et al., 2000; Linn et al., 1995; Tierney et al., 1996). Tasks that assess immediate and delayed (20 to 30 min) free recall of new information have also proven to be useful for predicting AD, particularly when they use verbal information. The majority of studies indicate that verbal episodic memory is a major predictor for the conversion to AD in elderly persons with MCI (Albert et al., 2001; Linn et al., 1995; Meyer, Xu, & Thornby, 2002; Small et al., 2000; Tierney et al., 1996; Touchon & Ritchie, 1999).

Bozoki et al. (2001) demonstrated that normal elderly people with a higher probability of developing AD exhibited memory deficits associated with mild impairment in other cognitive functions. In this study, the authors investigated episodic memory, naming, digit repetition, verbal fluency, and visuo-constructive ability (Cubes of Wechsler Adult Intelligence Scale - WAIS-III). During a 2-year period, Tierney et al. (1996) studied 123 elderly persons with impairments in only memory and found that 29 of these subjects developed AD. The combination of free recall of a list of words (RAVLT) and the WMS-R mental control test (attention and working memory) differentiated the cases that converted to AD from those who did not convert to AD, with 75.9% sensitivity and 93.6% specificity. Albert et al. (2001) performed a similar study and showed that memory impairment (total learning in the CVLT and immediate recall in the visual reproduction subtest of the WMS-R) associated with executive dysfunction (i.e., execution time of trail making form B and the self-ordering task) was able to differentiate 80% of the patients with a CDR (Clinical Dementia Rating) value of 0.5 who converted to AD from those who remained stable.

Thus, impairment of the central executive of operational memory was also a predictive factor for conversion to AD. Central executive function includes selection, operation, and temporary storage of information during operation (Baddeley, 1995, 1996). When the central executive fails, deficits occur in the inhibitory control of interference, flexibility of thinking, and short-term memory (Albert et al., 2001; Daly et al., 2000; Tierney et al., 1996).

Another cognitive domain that has been suggested to be an important predictive factor for the conversion to AD in elderly persons with MCI is the functioning of semantic memory and abstract verbal reasoning. This cognitive domain consists of the capacity to access concepts, meanings, and information acquired during life (Squire, 1986; Tulving, 1995). The lower

performance of MCI patients who converted to AD, compared with those who did not, in verbal fluency tests for categories, similarities (WAIS), and naming by visual confrontation and the use of semantic cues in free recall tests provides clinical evidence of the contribution of semantic memory to the characterization of pre-dementia AD (Elias et al., 2000; Linn et al., 1995).

Elias et al. (2000) demonstrated the importance of combining episodic and semantic memory tests in a prospective 22 year study of the predictive factors of AD. By comparing two samples consisting of elderly persons who did not develop AD for at least 5 years and elderly persons who remained stable for at least 10 years, they found that only some tests successfully differentiated elderly persons who converted from those who did not convert. Learning tests, immediate recall, and abstract thinking were able to predict the development of AD in the elderly at least 5 years before the diagnosis could be made.

Other markers have been studied. Small et al. (2000) and Meyer et al. (2002) observed the role of time orientation in the MMSE (Mini Mental State Examination). Touchon and Ritchie (1999) showed that processing velocity measured by reaction time could predict the development of AD.

In summary, a detriment in verbal anterograde episodic memory is one of the main markers for the conversion to AD. Detriments in other cognitive domains, combined with memory impairment, contribute to the discrimination between elderly persons who convert to AD and those who remain stable. Evidence of executive dysfunction and decline of the semantic system characterizes the pre-dementia stages of AD.

Neuropathological markers for Alzheimer's disease

Neuropathological studies have shown that elderly persons with MCI, especially the amnestic form, present senile plaques and neurofibrillary tangles in the medial temporal lobe and cortical regions. The majority of aMCI patients show a neuropathological pattern similar to that observed in AD, but at an insufficient level that is considered by some authors as an incipient or pre-dementia stage of the disease (Bennett, Schneider, Bienias, Evans, & Wilson, 2005; Morris et al., 2001; Petersen et al., 2006; Price & Morris, 1999; Salmon et al., 2002).

Reflecting on the classic neuropathological features of AD, many MCI patients, especially those with an AD-like profile, present a so-called cerebrospinal fluid (CSF) "AD signature" (Wiltfang et al., 2005). They display low concentrations of Aβ1-42 peptide and high concentrations of total tau (T-tau) protein and phosphorylated tau (P-tau) protein (Hansson et al., 2006; Mattsson et al., 2009). These biomarkers are important predictors of AD and the progression from MCI to AD, with diagnostic accuracy higher than 80% (Andreasen et al., 2001; Diniz, Pinto Juñior, & Forlenza, 2008; Pereira et al., 2010; Riemenschneider et al., 2002; Shaw et al., 2009). Cross-sectional and longitudinal studies and recent advances in functional imaging techniques such as positron emission tomography (PET) have measured pathological signs of AD *in vivo*, with similar findings (Forlenza et al., 2010; Okello et al., 2009).

Brain structural and functional markers

Brain structural changes in AD mainly include a global cerebral volume reduction, increased ventricular volume, and atrophy in both the hippocampal formation and entorhinal cortex (Apostolova et al., 2006). The same pattern is considered an important diagnostic marker for MCI and risk factor for AD, with evidence from cross-sectional and longitudinal studies (Bottino et al., 2002; Du et al., 2001; Jack et al., 1997; Killiany et al., 2000). Although on a smaller scale than AD, gray matter loss may already be present in patients with MCI (Davatzikos, Xu, An, Fan, & Resnick, 2009; Seo et al., 2007; Singh et al., 2006), especially in those who later convert to AD. In these patients, gray matter loss occurs selectively in areas that have been shown to be compromised in AD (e.g., hippocampal and parahippocampal structures, posterior cingulate cortex, middle and inferior temporal gyri, posterior cingulate gyrus, precuneus, temporoparietal junction, and frontal cortex) (Davatzikos et al., 2009; Hämäläinen et al., 2007; Ridha et al., 2006; Ries et al., 2008; Tapiola et al., 2008; Trojanowski et al., 2010).

Functional neuroimaging data have corroborated pathophysiological and structural studies. Many MCI patients, particularly aMCI patients, exhibit metabolic and brain activation patterns similar to those found in AD, but to a lesser degree. These studies (i.e., using fluorodeoxyglucose PET [FDG-PET] and single-photon emission computed tomography) found global reductions in cerebral metabolism and perfusion in the temporoparietal junction, temporal, parietal, and frontal lobes, hippocampal formation, and posterior cingulate cortex in the range between healthy elderly subjects and patients with AD (Mosconi et al., 2008b; Nobili et al., 2008). Longitudinal studies also showed a similar pattern of functional brain changes that was more frequent in subjects with MCI who converted to AD (Chetelat et al., 2005; Fennema-Notestine, McEvoy, Hagler, Jacobsona, & Daleb, 2009; Mosconi et al., 2004; Ries et al., 2008).

Functional magnetic resonance imaging (MRI) studies found anomalous patterns of brain activation during an episodic memory task. Medial temporal (Johnson et al., 2004; Johnson et al., 2006) and bilateral (Petrella et al., 2006) frontal regions showed anomalous patterns of activation in MCI patients compared with cognitively healthy adults during the encoding phase of episodic memory tasks. Activity was also altered compared with

healthy subjects in medial parietal regions such as the posterior cingulate cortex, bilateral frontal regions, and left hippocampus during memory retrieval (Johnson et al., 2006; Petrella et al., 2006; Ries et al., 2008). These anomalies in activation correlated with performance in terms of episodic memory (Ries et at., 2008).

Functional MRI studies also showed alterations in activation of the medial frontal and parietal regions, regions related to self-awareness, in MCI patients. Although still controversial, these results are interesting because anosognosia to varying degrees is observed in AD. Moreover, longitudinal data indicated that MCI patients who lack accurate awareness are more likely to develop AD compared with those with more accurate awareness (Dickerson et al., 2005; Ries et al., 2008).

Genetic markers

The ε4 allele, a variant of the apolipoprotein E (ApoE) gene, is associated with changes in brain function and is a prominent genetic risk factor for non-familial and familial late-onset AD (Corder et al., 1993; Rao et al., 1996). The variations in the prevalence of the disease worldwide likely occur because of differences in the frequency of the ApoE ε4 allele. The disease is less common in Africa and India.

Despite the strong association between the e4 allele and AD, few studies have investigated the impact of ApoE ε4 status on cognitive performance in adults and elderly who do not meet the diagnostic criteria for AD. The results are still controversial about which cognitive functions are impaired (Jacobson et al., 2005; Rosen et al., 2005; Greenwood, Williams & Geary, 2005; Duchek et al., 2009) and about the age at which this impairment could be a marker for the precocious form of AD (Parasuraman, Greenwood, & Sunderland, 2002; Greenwood et al., 2005; Ramakers et al., 2008; Negash et al., 2009).

While still incipient and only based on studies that used experimental paradigms, more consistent findings have shown that non-AD ε4 allele carriers exhibit a decline in visuospatial attention (Negash et al., 2009; Greenwood et al., 2005), working memory (Wishart et al., 2006; Parasuraman et al., 2002; Greenwood et al., 2005), semantic access (Rosen et al., 2005), free recall and learning in episodic memory (Ramakers et al., 2008; Greenwood et al., 2005), and prospective memory (Driscoll, Howard, Prusky, Rudy, & Sutherland, 2005). Parasuraman et al. (2002) showed that the more evident effects of the ε4 allele on cognitive function occur in healthy individuals, effects that appear to dissipate in studies of the elderly. Performance, especially in visuospatial attention tasks, is qualitatively similar to that observed in AD. They claimed that visuospatial attention might be associated with the modulation of cholinergic receptors in the posterior parietal cortex. Wishart et al. (2006) used a working memory paradigm and fMRI and found higher bilateral activation of the frontal lobes, parietal medial regions, and prefrontal dorsolateral cortex in carriers of the ε4 allele.

Investigations of cognitive markers in individuals with the ε4 allele before they present symptoms of AD might help in the early diagnosis of this degenerative disease and might contribute to the development of methodologies for the detection of AD based on neuropsychological assessment models.

Multiple marker combinations

Several AD markers have been consistently shown to be present in most MCI cases and have been linked to a high probability of the conversion from MCI to dementia, especially from aMCI to AD. However, no single marker alone is able to predict which cases will convert to AD and which cases will not. To increase the predictive value and specificity, several studies have investigated a combination of risk factors (Devanand et al., 2008; Ries et al., 2008).

Generally, combinations of markers have shown more predictive and specificity power than isolated markers. In a cross-sectional and longitudinal study, Zhang, Wang, Zhou, Yuan, and Shen (2011) combined MRI, FDG-PET, and CSF biomarkers to classify MCI compared with healthy controls and achieved a combined classification accuracy of 76.4%, sensitivity of 81.8%, and specificity of 66%, whereas the best accuracy of an individual biomarker modality was only 72%. Moreover, 91.5% of MCI converters and 73.4% of MCI non-converters were correctly classified.

In a 3-year follow-up study, Devanand et al. (2008) found that combining five predictors (i.e., Informant report of functioning, Olfactory identification test, Selective immediate recall in a verbal memory task, MRI hippocampal volume, and entorhinal cortex volume) of 10% false positives (i.e., 90% specificity) had the highest sensitivity (i.e., 85.2%) compared with other combinations of these markers. This combination also had higher predictive power compared with other studies (e.g., combining MMSE/verbal recall measures with MRI hippocampal volume/medial temporal lobe atrophy or ApoE genotype), leading to moderately strong accuracy (65-84% correctly classified) in predicting the conversion to AD (Tierney et al., 1996; Visser et al., 2002).

Different markers might have more predictive value at different moments in the transition from MCI to dementia. Hinrichs, Singh, Xu, and Johnson (2011) proposed that at baseline neither neuropsychological measures nor imaging modalities have a strong ability to detect which subjects will convert to AD because cognitive and structural changes will be more marked later on, especially when the criteria for subject selection requires that they should be homogeneous in terms of cognitive characteristics. In their study, a

model based on all combined imaging modalities had a better AUC (area under curve) at baseline than the neuropsychological measures. Longitudinal imaging improved the model, suggesting that a significant portion of the neurodegeneration responsible for the subjects' conversion to AD occurs after the diagnosis of MCI.

Trojanowski et al. (2010) proposed a model for the temporal ordering of AD biomarkers in which Aβ amyloid biomarkers are the first to become abnormal. Subsequently, changes in neurodegenerative biomarkers become apparent (CSF tau, FDG-PET, MRI), and these are followed by the onset of clinical symptoms. The timing of these changes is variable among individual patients according to genetic and environmental factors that modulate an individual's resilience to progressive accumulations of AD pathologies.

Final considerations

This review presented the main neuropsychological, neuropathological, genetic, and brain neuroimaging markers of the early diagnosis of AD. The combination of these markers is the best method for predicting AD years before the clinical manifestations of the disease. The most predominant neurobiological and neuropsychological risk factors include (1) senile plaques and neurofibrillary tangles in the medial temporal lobe and cortical region, (2) low concentrations of Aβ1-42 peptide and high concentrations of T-tau and P-tau in CSF, (3) reduced global cerebral volume, increased ventricular volume, and atrophy in the hippocampal formation and entorhinal cortex, (4) global reductions in cerebral metabolism and perfusion in the temporoparietal junction, temporal, parietal, and frontal lobes, hippocampal formation, and posterior cingulate cortex, (5) the presence of the ApoE ε4 allele, and (6) verbal anterograde episodic long-term memory impairment and executive dysfunction. These markers allow the identification of individuals at a high risk for developing AD. The study of these individuals has resulted in the concepts of pre-MCI and MCI, and a better comprehension of these diagnostic concepts is crucial for the development of preventive therapeutic interventions. Longitudinal studies that use different combinations of neurobiological and neuropsychological markers for AD are likely to be the most productive in the coming years. The development of similar instruments and methodological approaches worldwide will provide a basis for the operational definition of this diagnostic entity (i.e., preclinical AD).

References

Albert, M.S., Villainy, R.J., Johnson, K., Tanzi, R.E., & Jones, K. (2001). Preclinical prediction of AD: relation between neuropsychological and neuroimaging findings. In K. Iqbal, S.S. Sisodia, & B. Winblad (Eds.), *Alzheimer's disease: advances in etiology, pathogenesis and therapeutics* (pp. 97-98). New York: John Wiley.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders*. 4th edition. Washington, D.C.: American Psychiatric Press.

Andreasen, N., Minthon, L., Davidsson, P., Vanmechelen, E., Vanderstichele, H., Winblad, B., & Blennow, K. (2001). Evaluation of CSF-tau and CSF-Aβ42 as diagnostic markers for Alzheimer disease in clinical practice. *Archives of Neurology*, *58*, 373-379.

Anstey, K.J., Cherbuin, N., Christensen, H., Burns, R., Reglade-Meslin, C., Salim, A., Kumar, R., Jorm, A.F., & Sachdev, P. (2008). Follow-up of mild cognitive impairment and related disorders over four years in adults in their sixties: the PATH Through Life Study. *Dementia and Geriatric Cognitive Disorders*, *26*, 226-233.

Apostolova, L.G., Dinov, I.D., Dutton, R.A., Hayashi, K.M., Toga, A.W., Cummings, J.L., & Thompson, P.M. (2006). 3D comparison of hippocampal atrophy in amnestic mild cognitive impairment and Alzheimer's disease. *Brain*, *129*, 2867-2873.

Argimon, I.I.L., & Stein, L.M. (2005). Habilidades cognitivas em indivíduos muito idosos: um estudo longitudinal. *Caderno Saúde Pública*, *21*(1), 64-72.

Bäckman, L., Jones, S., Berger, A.K., Laukka, E.J., & Small, B.J. (2005). Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. *Neuropsychology*, *19*(4), 520-531.

Baddeley, A. (1995). Working memory. In M.S. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 755-764). Cambridge, MA: MIT Press.

Baddeley, A.D. (1996). The fractionation of working memory. *Proceedings of the National Academy of Sciences of the United States of America*, *93*, 13468-13472.

Banhato, E.F.C., & Nascimento, E. (2007). Função executiva em idosos: um estudo utilizando subtestes da Escala WAIS-III. *PsicoUSF*, *12*(1), 65-73.

Bennett, D.A., Schneider, J.A., Bienias, J.L., Evans, D.A., & Wilson, R.S. (2005). Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. *Neurology*, *64*, 834-841.

Blacker, D., Lee, H., Muzikansky, A., Martin, E.C., Tanzi, R., & McArdle, J.J., Moss, M., & Albert, M. (2007). Neuropsychological measures in normal individuals that predict subsequent cognitive decline. *Archives of Neurology*, *64*, 862-871.

Bondi, M.W., Jak, A.J., Delano-Wood, L., Jacobson, M.W., Delis, D.C., & Salmon, D.P. (2008). Neuropsychological contributions to the early identification of Alzheimer's disease. *Neuropsychological Review*, *18*(1), 73-90.

Bottino, C.M., Castro, C.C., Gomes, R.L., Buchpiguel, C.A., Marchetti, R.L., & Neto, M.R. (2002). Volumetric MRI measurements can differentiate Alzheimer's disease, mild cognitive impairment, and normal aging. *International Psychogeriatrics*, *14*, 59-72.

Bozoki, A., Giordani, B., Heidebrink, J.L., Berent, S., & Foster, N.L. (2001). Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. *Archives of Neurology*, *58*, 411-416.

Busse, A., Hensel, A., Guhne, U., Angermeyer, M.C., & Riedel-Heller, S.G. (2006). Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology*, *67*, 2176-2185.

Camarano, A.A. (2004). *Os novos idosos brasileiros: muito além dos 60 anos*. Rio de Janeiro: IPEA.

Caracciolo, B., Palmer, K., Monastero, R., Winblad, B., Backman, L., & Fratiglioni, L. (2008). Occurrence of cognitive impairment and dementia in the community: a 9-year-long prospective study. *Neurology*, *70*, 1778-1785.

Chaves, M.L., Camozzato, A.L., Godinho, C., Piazenski, I., & Kaye, J. (2009). Incidence of mild cognitive impairment and Alzheimer disease in southern Brazil. *Journal of Geriatric Psychiatry and Neurology*, *22*, 181-187.

Chetelat, G., Landeau, B., Eustache, F., Mezenge, F., Viader, F., de la Sayette, V., Desgranges, B., & Baron, J.C. (2005). Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: a longitudinal MRI study. *Neuroimage*, *27*, 934-946.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L., & Pericak-Vance, M.A. (1993). Gene dose of apoliprotein E type 4 allele and the risk of Alzheimer's disease in late-onset families. *Science*, *261*, 921-923.

Crook, T., Bartus, R.T., Ferris, S.H., Whitehouse, P., Cohen, G.D., & Gershon, S. (1986). Age associated memory impairment: proposed diagnostic criteria and measures of clinical change: report of a National Institute of Mental Health work group. *Development Neuropsychology*, *2*, 261-276.

Daly, E., Zaitchik, D., Copeland, M., Schmahmann, J., Gunther, J., &

Albert, M. (2000). Predicting conversion to Alzheimer disease using standardized clinical information. *Archives of Neurology*, *57*, 675-680.

Das, S.K., Bose, P., Biswas, A., Dutt, A., Banerjee, T.K., Hazra, A.M., Raut, D.K., & Roy, T. (2007). An epidemiologic study of mild cognitive impairment in Kolkata, India. *Neurology*, *68*, 2019-2026.

Davatzikos, C., Xu, F., An, Y., Fan, Y., & Resnick, S.M. (2009). Longitudinal progression of Alzheimer's-like patterns of atrophy in normal older adults: the SPARE-AD index. *Brain*, *132*, 2026-2035.

Devanand, D.P., Liu, X., Tabert, M.H., Pradhaban, G., Cuasay, K., Bell, K., de Leon, M.J., Doty, R.L., Stern, Y., & Pelton, G.H. (2008). Combining early markers strongly predicts conversion from mild cognitive impairment to Alzheimer's disease. *Biological Psychiatry*, *64*, 871-879.

Di Carlo, A., Lamassa, M., Baldereschi, M., Inzitari, M., Scafato, E., Farchi, G., & Inzitari, D. (2007). CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. *Neurology*, *68*, 1909-1916.

Dickerson, B.C., Salat, D.H., Greve, D.N., Chua, E.F., Rand-Giovannetti, E., Rentz, D.M., Bertram, L., Mullin, K., Tanzi, R.E., Blacker, D., Albert, M.S., & Sperling, R.A. (2005). Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. Neurology, *65*, 404-411.

Diniz, B.S., Pinto Juñior, J.A., & Forlenza, O.V. (2008). Do CSF total tau, phosphorylated tau, and β-amyloid 42 help to predict progression of mild cognitive impairment to Alzheimer's disease? A systematic review and meta-analysis of the literature. *World Journal of Biological Psychiatry*, *9*, 172-182.

Driscoll, I., Howard, S.R., Prusky, G.T., Rudy, J.W., & Sutherland, R.J. (2005). Seahorse wins all races: hippocampus participates in both linear and non-linear visual discrimination learning. *Behavioural Brain Research*, *164*, 29-35.

Du, A.T., Schuff, N., Amend, D., Laakso, M.P., Hsu, Y.Y., Jagust, W.J., Yaffe, K., Kramer, J.H., Reed, B., Norman, D., Chui, H.C., & Weiner, M.W. (2001). Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *71*, 441-447.

Duchek, J.M., Balota, D.A., Tse, C.S., Holtzman, D.M., Fagan, A.M., & Goate, A.M. (2009). The utility of intraindividual variability in selective attention tasks as an early marker for Alzheimer's disease. *Neuropsychology*, *23*, 746-758.

Elias, M.F., Beiser, A., Wolf, P.A., Au, R., White, R.F., & D'Agostino, R.B. (2000). The preclinical phase of Alzheimer disease: a 22-year prospective study of the Framingham Cohort. *Archives of Neurology*, *57*, 808-813.

Fabrigoule, C., Rouch, I., Taberly, A., Letenneur, L., Commenges, D. Mazaux, J.M., Orgogozo, J.M., & Dartigues, J.F. (1998). Cognitive process in preclinical phase of dementia. *Journal of Neurology*, *121*, 135-141.

Farias, S.T., Mungas, D., Reed, B.R., Harvey, D., & DeCarli, C. (2009). Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. *Archives of Neurology*, 66, 1151-1157.

Fennema-Notestine, C., McEvoy, L.K., Hagler, D.J., Jr., Jacobsona, M.W., & Daleb, A.M. (2009). Structural neuroimaging in the detection and prognosis of preclinical and early AD. *Behavioural Neurology*, *21*(1), 3-12.

Fischer, P., Jungwirth, S., Zehetmayer, S., Weissgram, S., Hoenigschnabl, S., Gelpi, E., Krampla, A., & Tragl, K.H. (2007). Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology*, *68*, 288-291.

Forlenza, O.V., Diniz, B.S., Talib, L.L., Radanovic, M., Yassuda, M.S., Ojopi, E.B., & Gattaz, W.F. (2010). Clinical and biological predictors of Alzheimer's disease in patients with amnestic mild cognitive impairment. *Revista Brasileira de Psiquiatria*, *32*, 216-222.

Ganguli, M., Dodge, H.H., Shen, C., & DeKosky, S.T. (2004). Mild cognitive impairment, amnestic type: an epidemiologic study. *Neurology*, *63*, 115-121.

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R.C, Ritchie, K., Broich, K., Belleville, S., Brodaty, H., Bennett, D., Chertkow, H., Cummings, J.L., de Leon, M., Feldman, H., Ganguli, M., Hampel, H., Scheltens, P., Tierney, M.C., Whitehouse, P., & Winblad, B. (2006). Mild cognitive impairment. Lancet, *367*, 1262-1270.

Greenwood, K., Williams, T., & Geary, T. (2005). Nematode neuropeptide receptors and their development as anthelmintic screens. *Parasitology*, *131 Suppl.*, S169-S177.

Hämäläinen, A., Tervo, S., Grau-Olivares, M., Niskanen, E., Pennanen, C., Huuskonen, J., Kivipelto, M., Hanninen, T., Tapiola, M., Vanhanen, M., Hallikainen, M., Helkala, E.L., Nissinen, A., Vanninen, R., & Soininen, H. (2007). Voxel-based morphometry to detect brain atrophy in progressive mild cognitive impairment. *Neuroimage*, *37*, 1122-1131.

Hänninen, T., Hallikainen, M., Tuomainen, S., Vanhanen, M., & Soininen, H. (2002). Prevalence of mild cognitive impairment: a population-based study in elderly subjects. *Acta Neurologica Scandinava*, *106*, 148-154.

Hansson, O., Zetterberg, H., Buchhave, P., Londos, E., Blennow, K., & Minthon, L. (2006). Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurology*, *5*, 228-234.

Hinrichs, C., Singh, V., Xu, G., & Johnson, S.C. (2011). Predictive markers for AD in a multi-modality framework: an analysis of MCI progression in the ADNI population. *Neuroimage*, *55*, 574-589.

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

Jacobson, M.W., Delis, D.C., Lansing, A., Houston, W., Olsen, R., Wetter, S., Bondi, M.W., & Salmon, D.P. (2005). Asymmetries in global-local processing ability in elderly people with the apolipoprotein e-e4 allele. *Neuropsychology*, *19*, 822-829.

Johnson, S.C., Baxter, L.C., Susskind-Wilder, L., Connor, D.J., Sabbagh, M.N., & Caselli, R.J. (2004). Hippocampal adaptation to face repetition in healthy elderly and mild cognitive impairment. *Neuropsychologia*, *42*, 980-989.

Johnson, S.C., Schmitz, T.W., Moritz, C.H., Meyerand, M.E., Rowley, H.A., Alexander, A.L., Hansen, K.W., Gleason, C.E., Carlsson, C.M., Ries, M.L., Asthana, S., Chen, K., Reiman, E.M., & Alexander, G.E. (2006). Activation of brain regions vulnerable to Alzheimer's disease: the effect of mild cognitive impairment. *Neurobiology of Aging*, *27*, 1604-1612.

Kalache, A. (1991). Ageing is a third world problem too. *International Journal of Geriatric Psychiatry*, *6*, 617-618.

Kalache, A., Veras, R.P., & Ramos, L.R. (1987). The aging of the world population: a new challenge. *Revista de Saude Publica*, *21*, 200-210.

Killiany, R.J., Gomez-Isla, T., Moss, M., Kikinis, R., Sandor, T., Jolesz, F., Tanzi, R., Jones, K., Hyman, B.T., & Albert, M.S. (2000). Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. *Annals of Neurology*, *47*, 430-439.

Kral, V.A. (1962). Senescent forgetfulness: benign and malignant. *Canadian Medical Association Journal*, *86*, 257-260.

Levy, R. (1994). Aging-associated cognitive decline. *International Psychogeriatric*, *6*, 63-68 [erratum: *6*(2), 133].

Linn, R.T., Wolf, P.A., Bachman, D.L., Knoefel, J.E., Cobb, J.L., Belanger, A.J., Kaplan, E.F., & D'Agostino, R.B. (1995). The "preclinical phase" of probable Alzheimer's disease: a 13-year prospective study of the Framingham cohort. *Archives of Neurology*, *52*, 485-490.

Loewenstein, D.A., Acevedo, A., Agron, J., & Duara, R. (2007). Stability of neurocognitive impairment in different subtypes of mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, *23*, 82-86.

Lopes, M.A., & Bottino, C.M.C. (2002). Prevalência de demência em diversas regiões do mundo: análises dos estudos epidemiológicos de 1994 a 2000. *Arquivos de Neuropsiquiatria*, *60*, 61-69.

Lopez, O.L., Jagust, W.J., DeKosky, S.T., Becker, J.T., Fitzpatrick, A., Dulberg, C., Breitner, J., Lyketsos, C., Jones, B., Kawas, C., Carlson, M., & Kuller, L.H. (2003). Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1. *Archives of Neurology*, *60*, 1385-1389.

Luck, T., Luppa, M., Briel, S., & Riedel-Heller, S.G. (2010). Incidence of mild cognitive impairment: a systematic review. *Dementia and Geriatric Cognitive Disorders*, *29*, 164-175.

Manly, J.J., Tang, M.X., Schupf, N., Stern, Y., Vonsattel, J.P., & Mayeux, R. (2008). Frequency and course of mild cognitive impairment in a multiethnic community. *Annuals of Neurology*, *63*, 494-506.

Mattsson, N., Zetterberg, H., Hansson, O, Andreasen, N., Parnetti, L., Jonsson, M., Herukka, S.K., van der Flier, W.M., Blankenstein, M.A., Ewers, M., Rich, K., Kaiser, E., Verbeek, M., Tsolaki, M., Mulugeta, E., Rosén, E., Aarsland, D., Visser, P.J., Schröder, J., Marcusson, J., de Leon, M., Hampel, H., Scheltens, P., Pirttilä, T., Wallin, A., Jönhagen, M.E., Minthon, L., Winblad, B., & Blennow, K. (2009). CSF biomarkers and incipient Alzheimer disease in

patients with mild cognitive impairment. *Journal of the American Medical Association*, *302*, 385-393.

Meyer, J., Xu, G., Thornby, J. (2002). Longitudinal analysis of abnormal domains comprising mild cognitive impariment (MCI) during aging. *Journal of Neurologic Science*, 15, 201 (1-2), 19-25.

Morris, J.C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, *43*, 2412-2414.

Morris, J.C., Storandt, M., Miller, J.P., McKeel, D.W., Price, J.L., Rubin, E.H., & Berg, L. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. *Archives of Neurology*, *58*, 397-405.

Mosconi, L., De Santi, S., Brys, M., Tsui, W.H., Pirraglia, E., Glodzik-Sobanska, L., Rich, K.E., Switalski, R., Mehta, P.D., Pratico, D., Zinkowski, R., Blennow, K., & de Leon, M.J. (2008a). Hypometabolism and altered cerebrospinal fluid markers in normal apolipoprotein E E4 carriers with subjective memory complaints. *Biology Psychiatry*, *63*, 609-618.

Mosconi, L., Perani, D., Sorbi, S., Herholz, K., Nacmias, B., Holthoff, V., Salmon, E., Baron, J.C., De Cristofaro, M.T., Padovani, A., Borroni, B., Franceschi, M., Bracco, L., & Pupi, A. (2004). MCI conversion to dementia and the APOE genotype: a prediction study with FDG-PET. *Neurology*, *63*, 2332-2340.

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., Clerici, F., Caselli, R., Beuthien-Baumann, B., Kurz, A., Minoshima, S., & de Leon, M.J. (2008b). Multicenter standardized ^{18}F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. *Journal of Nuclear Medicine*, *49*, 390-398.

Myers, C.E., Kluger, A., Golomb, J., Gluck, M.A., & Ferris, S. (2008). Learning and generalization tasks predict short-term cognitive outcome in nondemented elderly. *Journal of Geriatric Psychiatry and Neurology*, *21*, 93-103.

Negash, L., Greenwood, P.M., Sunderland, T., Parasuraman, R., Geda, Y.E., Knopman, D.S., Boeve, B.F., Ivnik, R.J., Petersen, R.C., & Smith, G.E. (2009). The influence of apolipoprotein E genotype on visuospatial attention dissipates after age 80. *Neuropsychology*, *23*, 81-89.

Nitrini, R., Caramelli, P., Herrera, E., Jr., Bahia, V.S., Caixeta, L.F., Radanovic, M., Anghinah, R., Charchat-Fichman, H., Porto, Carthery, M.T., Hartmann, A.P., Huang, N., Smid, J., Lima, E.P., Takada, L.T., & Takahashi, D.Y. (2002). Incidence of dementia in a community-dwelling Brazilian population. *Neurobiology of Aging*, *23*(4), 241-246.

Nobili, F., Salmaso, D., Morbelli, S., Girtler, N., Piccardo, A., Brugnolo, A., Dessi, B., Larsson, S.A., Rodriguez, G., & Pagani, M. (2008). Principal component analysis of FDG PET in amnestic MCI. *European Journal of Nuclear Medicine and Molecular Imaging*, *35*, 2191-2202.

Okello, A., Koivunen, J., Edison, P., Archer, H.A., Turkheimer, F.E., Nagren, K., Bullock, R., Walker, Z., Kennedy, A., Fox, N.C., Rossor, M.N., Rinne, J.O., & Brooks, D.J. (2009). Conversion of amyloid positive and negative MCI to AD over 3 years: an ^{11}C-PIB PET study. *Neurology*, *73*, 754-760.

Oliveira, S.F.D., Duarte, Y.A.O., Lebrão, M.L., & Laurenti, R. (2007). Demanda referida e auxílio recebido por idosos com declínio cognitivo no município de São Paulo. *Saúde e Sociedade*, *16*, 81-89.

Palmer, K., Bäckman, L., Winglad, B., & Fratiglioni, L. (2008). Mild cognitive impairment in the general population: occurrence and progression to Alzheimer disease. *American Journal of Geriatric Psychiatry*, *16*, 603-611.

Parasuraman, R., Greenwood, P.M., & Sunderland, T. (2002). The apolipoprotein E gene, attention, and brain function. *Neuropsychology*, *16*, 254-274.

Pereira, F.S., Yassuda, M.S., Oliveira, A.M., Diniz, B.S., Radanovic, M., Talib, L.L., Gattaz, W.F., & Forlenza, O.V. (2010). Profiles of functional deficits in mild cognitive impairment and dementia: benefits from objective measurement. *Journal of International Neuropsychology Society*, *16*, 297-305.

Petersen, R.C., Smith, G.E., Waring, S.C, Ivnik, R.J., Tangalos, E.G., Kokmen E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology, 56*, 303–308.

Petersen, R.C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, *256*, 183-194.

Petersen, R.C., Doody, R., Kurz, A., Mohs, R.C., Morris, J.C., Rabins, P.V., Ritchie, K., Rossor, M., Thal, L., & Winblad, B. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology*, *58*, 1985-1992.

Petersen, R.C., Parisi, J.E., Dickson, D.W., Johnson, K.A., Knopman, D.S., Boeve, B.F., Jicha, G.A., Ivnik, R.J., Smith, G.E., Tangalos, E.G., Braak, H., & Kokmen, E. (2006). Neuropathologic features of amnestic mild cognitive impairment. *Archives of Neurology*, *63*, 665-672.

Petersen, R.C., Roberts, R.O., Knopman, D.S., Boeve, B.F., Geda, Y.E., Ivnik, R.J., Smith, G.E., & Jack, C.R., Jr. (2009). Mild cognitive impairment: ten years later. *Archives of Neurology*, *66*, 1447-1455.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology*, *56*, 303-308.

Petrella, J.R., Krishnan, S., Slavin, M.J., Tran, T.T., Murty, L., & Doraiswamy, P.M. (2006). Mild cognitive impairment: evaluation with 4-T functional MR imaging. *Radiology*, *240*, 177-186.

Plassman, B.L., Langa, K.M., Fisher, G.G., Heeringa, S.T., Weir, D.R., Ofstedal, M.B., Burke, J.R., Hurd, M.D., Potter, G.G., Rodgers, W.L., Steffens, D.C., McArdle, J.J., Willis, R.J., & Wallace, R.B. (2008). Prevalence of cognitive impairment without dementia in the United States. *Annals of Internal Medicine*, *148*, 427-434.

Price, J.L, & Morris, J.C. (1999). Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Annals of Neurology*, *45*, 358-368.

Prince, M., Acosta, D., Chiu, H., Scazufca, M., & Varghese, M. (2003). Dementia diagnosis in developing countries: a cross-cultural validation study. *Lancet*, *361*(9361), 909-917.

Ramakers, I.H., Visser, P.J., Aalten, P., Bekers, O., Sleegers, K., van Broeckhoven, C.L., Jolles, J., & Verhey, F.R.J. (2008). The association between APOE genotype and memory dysfunction in subjects with mild cognitive impairment is related to age and Alzheimer pathology. *Dementia and Geriatric Cognitive Disorders*, *26,* 101-108.

Ramos, L.R., Veras, R.P., & Kalache, A. (1987). Envelhecimento populacional: uma realidade brasileira. *Revista de Saúde Pública*, *21*, 211-224.

Rao, V.S., Cupples, A., van Duijn, C.M., Kurz, A., Green, R.C., Chui, H., Duara, R., Auerbach, S.A., Volicer, L., Wells, J., van Broeckhoven, C., Growdon, J.H., Haines, J.L., & Farrer, L.A. (1996). Evidence for major gene inheritance of Alzheimer's Disease in families of patients with and without apolipoprotein Ee4. *American Journal of Human Genetics*, *59*, 664-675.

Ravaglia, G., Forti, P., Montesi, F., Lucicesare, A., Pisacane, N., Rietti, E., Dalmonte, E., Bianchin, M., & Mecocci, P. (2007). Mild cognitive impairment: epidemiology and dementia risk in an elderly Italian population. *Journal of the American Geriatrics Society*, *56*, 51-58.

Reisberg, B., & Gauthier, S. (2008). Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. *International Psychogeriatrics*, *20*(1), 1-16.

Reisberg, B., Ferris, S.H., De Leon, M.J., & Crook, T. (1982). The Global Deterioration Scale for assessment of primary degenerative dementia. *American Journal of Psychiatry*, *139*, 1136-1139.

Ridha, B.H., Barnes, J., Bartlett, J.W., Godbolt, A., Pepple, T., Rossor, M.N., & Fox, N.C. (2006). Tracking atrophy progression in familial Alzheimer's disease: a serial MRI study. *Lancet Neurology*, *5*, 828-834.

Riemenschneider, M., Lautenschlager, N., Wagenpfeil, S., Diehl, J., Drzezga, A., & Kurz, A. (2002). Cerebrospinal fluid tau and β-amyloid 42 proteins identify Alzheimer disease in subjects with mild cognitive impairment. *Archives of Neurology*, *59*, 1729-1734.

Ries, M.L., Carlson, C.M., Rowley, H.A., Sager, M.A., Gleason, C.E., Asthana, S., & Johnson, S.C. (2008). Magnetic resonance imaging characterization of brain structure and function in mild cognitive impairment: a review. *Journal American Geriatrics Society*, *56*, 920-934.

Ritchie, K., & Touchon, J. (2000). Mild cognitive impairment: conceptual basis and current nosological status. *Lancet*, *355*, 225-228.

Roberts, R.O., Geda, Y.E., Knopman, D.S., Cha, R.H., Pankratz, V.S., Boeve, B.F., Rocca, W.A., & Petersen, R.C. (2008). Men are more likely to have mild cognitive impairment than women: the Mayo Clinic Study of Aging. *Neurology*, *70*(11 Suppl. 1), A225.

Rosen, V.M., Sunderland, T., Levy, J., Harwell, A., McGee, L., Hammond, C., Bhupali, D., Putnam, K., Bergeson, J., & Lefkowitz, C. (2005). Apolipoprotein E and category fluency: evidence for reduced semantic access in healthy normal controls at risk for developing Alzheimer's disease. *Neuropsychologia*, *43*, 647-658.

Salmon, D.P., Thomas, R.G., Pay, M.M., Booth, A., Hofstetter, C.R., Thal, L.J., & Katzman, R. (2002). Alzheimer's disease can be accurately diagnosed in very mildly impaired individuals.

Neurology, *59*, 1022-1028.
Seo, S.W., Im, K., Lee, J.M., Kim, Y.H., Kim, S.T., Kim, S.Y., Yang, D.W., Kim, S.I., Cho, Y.S., & Na, D.L. (2007). Cortical thickness in single- versus multiple-domain amnestic mild cognitive impairment. *Neuroimage*, *36*, 289-297.
Shaw, L.M., Vanderstichele, H., Knapik-Czajka, M., Clark, C.M., Aisen, P.S., Petersen, R.C., Blennow, K., Soares, H., Simon, A., Lewczuk, P., Dean, R., Siemers, E., Potter, W., Lee, V.M.Y., & Trojanowski, J.Q. (2009). Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Annals of Neurology*, *65*, 403-413.
Singh, V., Chertkow, H., Lerch, J.P., Evans, A.C., Dorr, A.E., & Kabani, N.J. (2006). Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease. *Brain*, *129*, 2885-2893.
Small, B.J., Fratiglioni, L., Viitanen, M., Winblad, B., & Backman, L. (2000). The course of cognitive impairment in preclinical Alzheimer disease: three- and 6-year follow-up of a population-based sample. *Archives of Neurology*, *57*, 839-844.
Solfrizzi, V., Colacicco, A.M., D'Introno, A., Capurso, C., Del Parigi, A., Capurso, S.A., Argentieri, G., Capurso, A., & Panza, F. (2006). Dietary fatty acids intakes and rate of mild cognitive impairment: the Italian Longitudinal Study on Aging. *Experimental Gerontology*, *41*, 619-627.
Solfrizzi, V., Panza, F., Colacicco, A.M., D'Introno, A., Capurso, C., Torres, F., Grigoletto, F., Maggi, S., Del Parigi, A., Reiman, E.M., Caselli, R.J., Scafato, E., Farchi, G., & Capurso, A. (2004). Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology*, *63*, 1882-1891.
Squire, L. (1986). Mechanisms of memory. *Science*, *232*, 1612-1619.
Tapiola, T., Pennanen, C., Tapiola, M., Tervo, S., Kivipelto, M., Hänninen, T., Pihlajamäki, M., Laakso, M.P., Hallikainen, M., Hämäläinen, A., Vanhanen, M., Helkala, E.L., Vanninen, R., Nissinen, A., Rossi, R., Frisoni, G.B., & Soininen, H. (2008). MRI of hippocampus and entorhinal cortex in mild cognitive impairment: a follow-up study. *Neurobiology of Aging*, *29*, 31-38.
Tervo, S., Kivipelto. M., Hanninen, T., Vanhanen, M., Hallikainen, M., Mannermaa, A., & Soininen, H. (2004). Incidence and risk factors for mild cognitive impairment: a population based three-year follow-up study of cognitively healthy elderly subjects. *Dementia and Geriatric Cognitive Disorders*, *17*, 196-203.
Tierney, M.C., Szalai, J.P., Snow, W.G., Fisher, R.H., Nores, A., Nadon, G., Dunn, E., & St. George-Hyslop, P.H. (1996). Prediction of probable Alzheimer's disease in memory-impaired patients: a prospective longitudinal study. *Neurology*, *46*, 661-665.
Touchon, J., & Ritchie, K. (1999). Prodromal cognitive disorder in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *14*, 556-563.
Trojanowski, J.Q., Vandeerstichele, H., Korecka, M., Clark, C.M., Aisen, P.S., Petersen, R.C., Blennow, K., Soares, H., Simon, A., Lewczuk, P., Dean, R., Siemers, E., Potter, W.Z., Weiner, M.W., Jack, C.R., Jr., Jagust, W., Toga, A.W., Lee, V.M., & Shaw, L.M. (2010). Update on the biomarker core of the Alzheimer's Disease Neuroimaging Initiative subjects**.** *Alzheimer's and Dementia*, *6*, 230-238.
Tschanz, J.T., Welsh-Bohmer, K.A., Lyketsos, C.G., Corcoran, C., Green, R.C., Hayden, K., Norton, M.C., Zandi, P.P., Toone, L., West, N.A., & Breitner, J.C. (2006). Conversion to dementia from mild cognitive disorder: the Cache County Study. *Neurology*, *67*, 229-234.
Tulving, E. (1995). Organization of memory: quo vadis? In S. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 839-847). Cambridge, MA: MIT Press.
Unverzagt, F.W., Gao, S., Baiyewu, O, Ogunniyi, A.O., Gureje, O., Perkins, A., Emsley, C.L., Dickens, J., Evans, R., Musick, B., Hall, K.S., Hui, S.L., & Hendrie, H.C. (2001). Prevalence of cognitive impairment: data from the Indianapolis Study of Health and Aging. *Neurology*, *57*, 1655-1662.
Verghese, J., LeValley, A., Derby, C., Kuslansky, G., Katz, M., Hall, C., Buschke, H., & Lipton, R.B. (2006). Leisure activities and the risk of amnestic mild cognitive impairment in the elderly. *Neurology*, *66*, 821-827.
Visser, P.J., Verhey, F.R., Scheltens, P., Cruts, M., Ponds, R.W., Van Broeckhoven, C.L., & Jolles, J. (2002). Diagnostic accuracy of the Preclinical AD Scale (PAS) in cognitively mildly impaired subjects. *Journal of Neurology*, *249*, 312-319.
Wiltfang, J., Lewczuk, P., Riederer, P., Grünblatt, E., Hock, C., Scheltens, P., Hampel, H., Vanderstichele, H., Iqbal, K., Galasko, D., Lannfelt, L., Otto, M., Esselmann, H., Henkel, A.W., Kornhuber, J., & Blennow, K. (2005). Consensus paper of the WFSBP Task Force on Biological Markers of Dementia: the role of CSF and blood analysis in the early and differential diagnosis of dementia. *World Journal of Biological Psychiatry*, *6*, 69-84.
Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.O., Nordberg, A., Bäckman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., de Leon, M., DeCarli, C., Erkinjuntti, T., Giacobini, E., Graff, C., Hardy, J., Jack, C., Jorm, A., Ritchie, K., van Duijn, C., Visser, P., & Petersen, R.C. (2004). Mild cognitive impairment-beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine*, *256*, 240-246.
Wishart, H.A., Saykin, A.J., Rabin, L.A., Santulli, R.B., Flashman, L.A., Guerin, S.J., Mamourian, A.C., Belloni, D.R., Rhodes, C.H., & McAllister, T.W. (2006). Increased brain activation during working memory in cognitively intact adults with the APOE e4 allele. *American Journal Psychiatry*, *163*, 1603-1610.
World Health Organization (1993). *The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research*. Geneva: World Health Organization.
World Health Organization (2009). Ageing (http://www.who.int/topics/ageing/en/; accessed September 21, 2011).
Yaffe, K., Petersen, R.C., Lindquist, K., Kramer, J., Miller, B. (2006). Subtype of mild cognitive impairment and progression to dementia and death. *Dementia and Geriatric Cognitive Disorders*, 22(4), 312-319.
Yaffe, K., Middleton, L.E., Lui, L.Y., Spira, A.P., Stone, K., Racine, C., Ensrud, K.E., & Kramer, J.H. (2011a). Mild cognitive impairment, dementia, and their subtypes in oldest old women. *Archives of Neurology*, *68*, 631-636.
Zhang, D., Wang, Y., Zhou, L., Yuan, H., & Shen, D. (2011). Multimodal classification of Alzheimer's disease and mild cognitive impairment. *Neuroimage*, *55*, 856-867.