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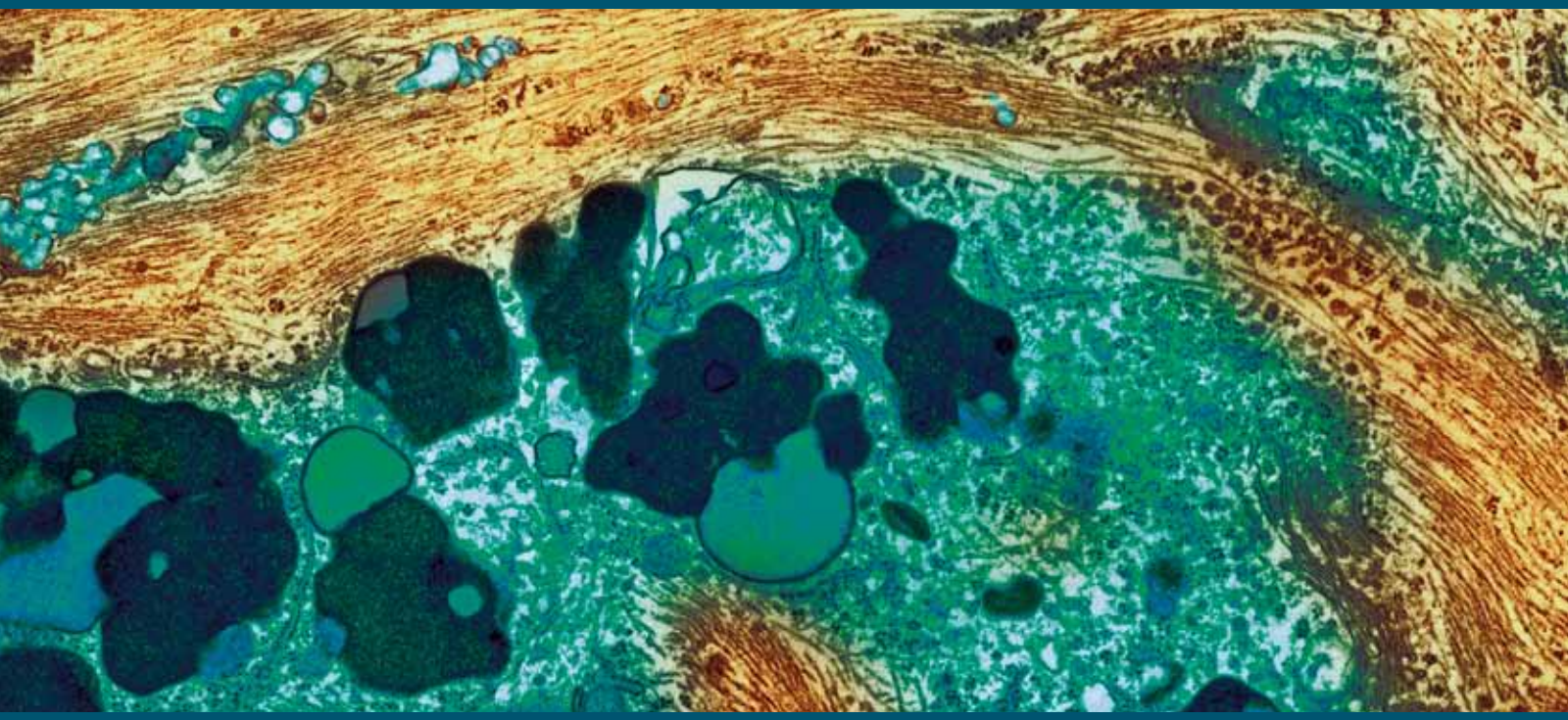
Mild Cognitive Impairment: Beyond Memory Dysfunction

Guest Editors: Andrea Tales, Antony Bayer, Štefan Krajcík, and Kurt A. Jellinger



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Editorial Board

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Editorial

Mild Cognitive Impairment: Beyond Memory Dysfunction

Andrea Tales,[1] Antony Bayer,[2] Štefan Krajčík,[3] and Kurt A. Jellinger[4]

[1] *School of Experimental Psychology, University of Bristol, 12a Priory Road, Clifton, Bristol BS8 1TN, UK*
[2] *Cochrane Institute of Primary Care and Public Health, School of Medicine, Cardiff University, Cardiff CF64 1AT, UK*
[3] *Geriatric Department, Slovak Medical University, Krajinska 91, 825 56 Bratislava, Slovakia*
[4] *Institute of Clinical Neurobiology, Kenyongasse 18, 1070 Vienna, Austria*

Correspondence should be addressed to Andrea Tales, andrea.tales@bristol.ac.uk

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Traditionally, mild cognitive impairment (MCI) has tended to be primarily characterised and diagnosed in relation to the integrity of amnestic function and thus studied accordingly. However, a more recent multidisciplinary and collaborative research approach has investigated a much wider range of cognitive, functional, structural, and behavioural integrity and is revealing an extensive and often complex range of characteristics in addition to memory dysfunction that differentiate MCI from healthy ageing. These may be of especial relevance when considering MCI as a potential prodromal stage of dementia.

Several papers in this special issue report novel and important findings with respect to the search for predictors of development of dementia in patients with MCI.

The paper by E. L. Abner et al. describes a new approach in the assessment of risk factors for dementia, including age, gender, education, apolipoprotein E status, family history of dementing illness, and baseline hypertension. Their results highlight the importance of objective criteria in MCI diagnosis.

I. Reinvang et al. report on how studies of genetic high-risk groups, using sensitive cognitive neuroscience paradigms, indicate the potential for differences in executive function to be a cognitive marker useful for tracking development of the pathophysiological changes of Alzheimer's disease (AD).

The paper by D. V. Moretti et al. reveals specific electroencephalographic (EEG) changes associated with atrophy of the hippocampus in people with MCI and AD, namely, that the increase of alpha3/alpha2 power ratio is correlated with atrophy of the hippocampus both in MCI and in AD patients, suggesting a possible diagnostic role of EEG markers.

In a comprehensive review, B. Ferencz et al. provide an overview of brain changes in early AD and MCI, together with evidence for recent advances in neuroimaging and genetic biomarkers and the importance of altered mitochondrial dynamics in the preclinical stages of AD.

D. P. Devanand et al. discuss the outcome of their detailed and novel study that uses clinical and magnetic resonance imaging (MRI) variables to compare predictor models for the transition to AD in patients with MCI.

Research priority has until relatively recently been directed to the amnestic type of mild cognitive impairment (aMCI). However, the paper by A. Poggesi et al. provides an important overview of the concept of vascular MCI and how it may signal the prodromal stages of vascular dementia or the presence of small vessel disease.

It is of course important to raise awareness of MCI within the public at large and also to determine the factors likely to encourage individuals to report a change in their memory to their general practitioner. C. Pires et al. highlight the importance of the type of memory complaint in determining whether an individual seeks medical attention and describe how forgetting the name of family members or friends is a particularly strong impetus for such contact.

Increasingly, studies are addressing the potential of MCI to adversely affect a wide range of factors that impinge upon an individual's quality of life. In the paper by G. Arsenault-Lapierre et al., the importance of stress in the lives of those with MCI and dementia is described, together with the finding that patients with MCI or dementia can display

anosognosia, which can preclude patients from accurately appraising their own level of stress.

Together these papers contribute to our further understanding of the concept of MCI and of its potential progression to dementia. All highlight the need to think beyond merely memory dysfunction in MCI and to continue to expand our knowledge in this important field of scientific and clinical research.

Andrea Tales
Antony Bayer
Štefan Krajčík
Kurt A. Jellinger

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Review Article

Executive Dysfunction in MCI: Subtype or Early Symptom

Ivar Reinvang,[1,2] Ramune Grambaite,[3] and Thomas Espeseth[2,4,5]

[1] *Center for the Study of Human Cognition, Department of Psychology, University of Oslo, 0316 Oslo, Norway*
[2] *Center for Advanced Study, Norwegian Academy of Science and Letters, 0271 Oslo, Norway*
[3] *Department of Neurology, Akershus University Hospital, 1478 Lørenskog, Norway*
[4] *Faculty Division of Psyciatry, Division of Mental Health and Addiction, Oslo University Hospital, 0407 Oslo, Norway*
[5] *Department of Biological and Medical Psychology, Faculty of Psychology, University of Bergen, 5020 Bergen, Norway*

Correspondence should be addressed to Ivar Reinvang, ivar.reinvang@psykologi.uio.no

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Mild cognitive impairment (MCI) may take several forms, and amnestic MCI (aMCI) has been recognized as an early stage of Alzheimer's Disease (AD). Impairment in executive functions including attention (eMCI) may be indicative of several neurodegenerative conditions. Executive impairment is frequently found in aMCI, it is significant for prognosis, and patients with eMCI may go on to develop AD. Recent studies have found changes in white matter integrity in patients with eMCI to be more sensitive than measures of cortical atrophy. Studies of genetic high-risk groups using sensitive cognitive neuroscience paradigms indicate that changes in executive function may be a cognitive marker useful for tracking development in an AD pathophysiological process.

1. Introduction

The diagnosis of MCI due to AD (the symptomatic predementia phase of AD) has been recently proposed by the National Institute on Aging and the Alzheimer's Association [1]. Diagnostic criteria include concern regarding a change in cognition, impairment in one or more cognitive domains, preservation of independence in functional abilities, and not demented. Within the generally accepted framework, clinical presentations may be in the memory (amnestic) or nonmemory domains [2].

Clinical studies of prodromal stages to AD tend to focus on persons with amnestic MCI (aMCI). Both the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Mayo clinic cohorts typify this population. In the Mayo clinical study of aging, persons in the age range of 70–89 years are enrolled, with 2/3 of the MCI group being aMCI [3]. ADNI [4] enrolls participants between ages 55 and 90, and mean age for the MCI group is 74.7 years. Researchers from the Mayo clinic proposed quantitative criteria for identifying MCI as a prodromal stage to Alzheimer's disease in 1999 [5]. They stressed the importance of memory impairment and proposed quantitative criteria specifying the level of memory deficit relative to global cognitive functioning. In ADNI, MCI is defined as a Clinical Dementia Rating of 0.5, and performance on the free recall measure of a neuropsychological memory test (Logical Memory II) is below a given threshold. Since the vast majority of the subjects characterized as aMCI will develop AD, aMCI may be defined as a prodromal condition of AD [6]. The pathophysiological basis and prognosis of nonamnestic MCI remains unclear, and the group is probably heterogenous [6, 7], including patients with frontotemporal dementia [8], Parkinson's disease [9], dementia with Lewy bodies [10], vascular dementia [11], and neuropsychiatric conditions (depression) [12]. Change in the frontostriatal network supporting executive functions may occur as a part of healthy aging [13, 14]. Thus, an MCI subgroup with isolated executive difficulties may be an extreme group of normal aging.

The objective of this paper is to review executive/attentional impairment as an important aspect of MCI or pre-MCI in terms of symptom manifestation and importance for disease progression. We will focus on recent research on MRI and genetic markers that may serve to further understanding of the pathophysiological processes underlying executive MCI (eMCI) and its relation to AD.

2. Executive Dysfunction in MCI

Attention and executive impairment are frequent and disabling symptoms in MCI when measured with neuropsychological tests ranging from simple processing speed tasks to tasks of complex problem solving. The distinction between clinical tests of attention and test of executive function is a fuzzy one and they are here treated as on the same continuum. There is no consensus on how executive function should be tested in clinical studies [15], and studies that take into consideration developments in cognitive psychology [16] find high frequency of executive impairment in both amnestic and nonamnestic MCI [17], with some subfunctions more affected than others.

Alzheimer's disease (AD) is the most common cause of dementia and accounts for approximately 60–70% of all dementia cases [18], and deficits of episodic memory are a cognitive hallmark of the disease [19]. Executive dysfunction is evident in the prodromal stage of AD [20–22] and appears predominantly in tasks requiring cognitive flexibility, inhibition, and self-monitoring [23]. There is evidence that the commonly reported impaired ability to perform two tasks simultaneously in AD reflects a specific deficit in dividing attention, rather than the result of a more general processing speed deficit [24]. According to the model of cognitive decline leading to AD presented by Perry and colleagues [25], executive problems appear after memory problems in time, but before typical parietal lobe symptoms (aphasia, visuospatial deficits). When executive dysfunction is present, it has a clear negative influence on ability to manage activities of daily living and may thus add to the risk of conversion from MCI to AD [26]. Predictive accuracy for conversion from MCI to AD for one set of cognitive variables (composed of episodic memory and processing speed measures) has been found to be as high as 0.86 (sensitivity, 0.76; specificity, 0.90) [27]. Gomar et al. [28] found that a test of executive function and assessment of baseline functional capacity predicted conversion from MCI to AD after 2 years better than biomarkers (MR and CSF).

3. Executive Nonamnestic MCI

Both aMCI and attention/executive MCI subtypes have been regarded as important predementia subtypes, at risk for AD [29]. While aMCI is usually defined as a prodromal, at-risk condition of AD [30], isolated executive dysfunction can be a prodromal stage for several neurodegenerative diseases. In cases of predementia AD, it is not clear if aMCI and eMCI may be two different categories/subtypes of AD or represent different phases of AD development.

If attention/executive MCI is not a distinct AD subtype, but an earlier stage of AD than aMCI, then aMCI should be expected to have executive/attentional deficits in addition to memory impairment. It has been reported that attention and executive functions may be impaired in the incipient stages of AD and may contribute to the observed memory deficit [31]. It has been argued that even patients defined as "pure" aMCI on screening tests may have executive impairment, when a comprehensive neuropsychological examination of executive cognition is performed [17].

The existence of nonamnestic attention/executive MCI has been recorded in several MCI studies [29, 32–37], where a comprehensive neuropsychological test battery has been utilized for classification purposes. The prevalence of attention/executive MCI will vary widely in different samples based on recruitment criteria and assessment methods but has been reported as from 3 to 15% [38]. In the sample studied by us [37] attention/executive MCI without amnestic deficit constitutes about 30% of the total MCI group, which on the whole is 10–15 years younger than the ADNI study group.

In a study of Johnson and colleagues [35], 31 older adults with pure executive MCI were identified. Of the 12 executive MCI patients who progressed clinically after two years, 2 converted to probable dementia with Lewy bodies, 10 retained the clinical diagnosis of MCI, and none reverted to normal. Patients with single domain executive MCI who progressed quickly over two years had more temporal lobe atrophy on MRI and slightly lower scores for visual memory recall when compared to the stable executive MCI patients, possibly suggesting that converters may be at their later stages of clinical progression. The executive MCI patients who progressed reported fewer dysexecutive symptoms than nonprogressors, while there were no differences in informant-rated dysexecutive symptoms and baseline performance on all four executive tests.

Nine subjects with pure attention/executive MCI were identified in the longitudinal study of Whitwell and colleagues [29]. In this study, almost 70% of MCI patients within an attention/executive subgroup progressed to dementia in the period of four years, suggesting that the group is at high risk of developing dementia. Three patients converted to dementia with Lewy bodies and three patients converted to AD dementia. The prognosis for other patients with isolated attention/executive dysfunction in the study of Whitwell and colleagues is not clear, but they may also convert to other dementias or remain stable over many years.

By using similar criteria for classification of subjects as those used in the study of Whitwell and colleagues, we have identified a bigger group of 23 nonamnestic attention/executive MCI patients [37]. A longitudinal followup will show how many patients will develop AD and other dementias.

4. Brain Imaging—MRI Morphometry and Diffusion Tensor Imaging

The attention and executive functions depend on distributed networks [39], encompassing both frontal and parietal associative cortices, as well as subcortical structures and white matter (WM) pathways [40]. The executive functions control and monitor task performance and depend critically on the frontal lobes. Three fronto-subcortical circuits (originating in the prefrontal cortex) have been identified as responsible for executive control functions, that is, the dorsolateral prefrontal cortex (working memory), the lateral

orbital cortex (inhibition), and the anterior cingulate cortex (response conflict) [41, 42].

Degeneration of the medial temporoparietal memory network is typical for AD [43]. Findings from functional imaging indicate that during prodromal AD, the brain network involving the dorsolateral prefrontal cortex and the anterior cingulate, is affected [44]. Alterations in these regions have been associated with impairments in executive functions [45]. While aMCI is characterized by medial temporal lobe affection [29], atrophy in the basal forebrain has been found to be characteristic for the MCI groups with isolated attention/executive deficits [29, 33].

Some studies have reported an association between prefrontal cortical changes and attention/executive impairment in MCI [29, 34, 46]. Significant cortical atrophy in frontal regions [47] has been found in predementia AD. It has been argued that prefrontal damage, in combination with cingulate damage, has predictive value for the conversion from MCI to AD [48]. Another recent study indicates that white matter (WM) pathology in AD is distributed in all lobes of the brain but it is most prominent in the frontal WM [49]. In addition to frontal WM changes, MCI patients may have WM changes in both anterior [50] and posterior [51] cingulate regions. The anterior cingulate region is regarded as belonging to a network responsible for executive control function while the posterior cingulate belongs to a memory network [52]. Thus, it has been hypothesized that the caudal portion of the anterior cingulate plays a major role in executive function abilities, primarily through its reciprocal connections with the prefrontal cortex [53, 54].

In our recent study on attention/executive MCI [37], we have demonstrated consistent relationships between neuropsychological function and the microstructural properties of the WM brain pathways measured by diffusion tensor imaging (DTI), as well as cortical-morphometric parameters. Executive impairment in MCI patients with unaffected memory performance has been associated with reduced WM tract integrity (increased radial diffusion (DR) and mean diffusivity (MD)) in frontal and cingulate regions and cortical thinning in caudal middle frontal region. We have found that WM DR/MD increases in frontal, cingulate, and entorhinal regions in patients with attention/executive MCI, but cortical thickness was not different from controls in any of the studied regions [37]. The findings may thus indicate that the relative importance of grey matter versus WM changes may differ at different stages of predementia cognitive impairment [55, 56].

Frontal and temporal WM diffusivity changes have been previously described in aMCI patients [57]. By using DTI to characterize executive networks in MCI, we found WM DR/MD changes in both the anterior and posterior cingulate regions in eMCI suggesting that both regions may contribute to attention/executive impairment in MCI [36]. The cingulate cortex projects into the striatum [42], and both the anterior and posterior cingulate cortices receive mediodorsal thalamic afferents [48], which are part of fronto-subcortical circuits, involved in executive function. Some attention/executive subfunctions correlated significantly with imaging findings in frontal and cingulate regions in the eMCI group, but no significant correlations were found in the controls. In attention/executive MCI, response inhibition was associated with WM DR/MD underlying the superior frontal cortex, and response inhibition/switching was associated with WM DR/MD underlying the superior frontal, rostral middle frontal, lateral/medial orbitofrontal, and retrosplenial cortices. Test scores for attention and divided attention were associated with the cortical thinning of the caudal middle frontal region. The study results thus support the results from previous MCI studies, where associations between prefrontal changes and attention/executive impairment have been reported [29, 34, 46]. In addition, the results confirm that cingulate changes are associated with executive impairment in MCI [48].

In one recent study [34], MCI patients with isolated executive dysfunction had cerebral hypoperfusion in bilateral middle frontal cortex, bilateral posterior cingulated, and the left precuneus relative to controls. Relative to aMCI patients, eMCI patients had hypoperfusion in the left middle frontal cortex, left posterior cingulate, and the left precuneus, supporting the existence of pathophysiologically distinct MCI subgroups.

In the study of Pa and colleagues [33], executive nonamnestic MCI subgroup had significantly less grey matter in the left dorsolateral prefrontal cortex compared with control subjects. The eMCI subgroup had less volume in the caudate nucleus compared with aMCI group, but the differences for prefrontal cortex in eMCI versus aMCI were not significant, which could be due to some reduction of prefrontal cortex volume in aMCI as well. In contrast, the aMCI patients had less volume in the right inferior parietal cortex, typical for AD, than eMCI. These neuroimaging findings also suggest that some of the eMCI patients may represent a distinct subgroup of MCI.

We have found increased entorhinal WM DR and MD in both patients with memory impairment and those with attention/executive dysfunction without objective memory impairment [37, 58], suggesting a common affection of regions known to show changes in early AD. Attention/executive MCI may be an earlier stage of AD than aMCI and the patients with nonamnestic attention/executive impairment may develop memory problems later. It is also possible that patients with attention/executive MCI may progress to non-AD dementias or AD with disproportionate neuropathology in the frontal cortex.

5. Nonmemory Findings Associated with Genetic Risk of AD

To study very early development of AD, neurobiological markers of high risk in asymptomatic individuals may be used. Sperling et al. [59] use the term AD-P to denote pathophysiological factors that are significant for the development of clinical AD (AD-C), but each factor in isolation does not cause AD-C. Candidates for markers may be molecular or genetic. Amyloid accumulation may be measured with positron emission tomography (PET) or with cerebrospinal fluid (CSF) analyses, but both are invasive and costly procedures that are not suitable for screening. Genetic risk

can be assessed relatively simply, and followup studies of healthy at risk populations are not prohibitively expensive although they have ethical problems.

Apolipoprotein E (APOE) and e4 allele carrier status confer a significant increase in risk of developing AD [60]. Recent studies of relative risk based on large samples [61] argue that the impact of APOE e4 on AD risk is similar to that of major genes in Mendelian diseases and comparable to genetic risk of breast cancer. Amyloid load in cognitively normal persons above age 60 correlates positively with APOE e4 [62]. In MCI patients PIB-positive PET scans are more frequent in APOE e4 carriers [63]. In patients with AD, progression of cerebral amyloid load is associated with e4 gene dose [64]. There is thus evidence that a major genetic risk factor for AD is associated with preclinical accumulation of beta amyloid, the most significant pathophysiological causal factor for developing AD. Greenwood et al. [65] have argued that in view of the complexity of APOE mechanisms affecting cognition, it would be misleading to view all cognitive effects of e4 as evidence of incipient AD, and they argue that in normal aging there is an accumulating effect of inefficient neural repair mechanisms associated with the e4 allele. These changes make the brain more vulnerable to pathological processes, including accumulation of amyloid beta 42 in AD, but do not cause this process to occur in all e4 carriers.

Severe cholinergic changes are found in advanced AD, with loss of cholinergic neurons and receptors [66, 67]. DeKosky et al. [68] found that cholinergic systems are upregulated in MCI individuals. The authors propose that the loss of this apparent compensatory response may mark the conversion of MCI to diagnosable AD. Recent evidence indicates that complex interactions between APOE e4 and cholinergic genes (BuChE) affect the conversion rate of MCI to AD [69] and that the level of beta amyloid accumulation in the brain is related to both APOE and cholinergic activity [70, 71]. Thus we see evidence of a negative interaction between APOE, beta amyloid accumulation, and cholinergic dysfunction.

There have been numerous studies of cognitive symptoms associated with APOE e4 carrier status in nondemented persons. Wisdom et al. [72] used a meta analysis of more than 2000 participants and found significant positive effect size for memory and global intellectual function. The effect sizes are moderate, and the studies are influenced by choice of methods, especially in nonmemory cognitive domains. Parasuraman and collaborators [73] have taken a cognitive neuroscience approach to study effects of genes involved in risk of AD (APOE) or mechanisms involved in cognitive deficit in AD (cholinergic genes—CHRNA4). They concluded that intact focusing and impaired disengagement of visuospatial attention may be linked to dysfunction in early AD of corticocortical networks linking the posterior parietal and frontal lobes. Greenwood et al. [74] found that healthy middle-aged adults without dementia who carry the APOE e4 allele show deficits in spatial attention and working memory that are qualitatively similar to those seen in clinically diagnosed AD patients. This finding is replicated in an independent sample by Espeseth et al. [75]. The findings support an association between APOE polymorphisms and specific components of visuospatial attention. Later studies have extended the findings to working memory measured by operation span [76]. Greenwood et al. [65] used an experimental paradigm measuring working memory for dot locations in a spatial array and found that accuracy was reduced in healthy e4 homozygotes, of mean age 57–60. Reinvang et al. [77] found that e4 carriers performed worse on letter-number span, another working memory task, and in addition on the Stroop color-word interference task. The groups did not differ in tasks of episodic memory.

Wishart et al. [78] studied cortical activation pattern in a working memory task and the e4 group showed greater activity during working memory in the medial frontal and parietal regions bilaterally and in the right dorsolateral prefrontal cortex. There were no regions in which the e3 group showed greater activation than the e4 group. By measuring event-related potentials (ERPs) while MCI patients 50–76 years of age worked on an experimental attention task (auditory three-stimulus oddball). Reinvang et al. [77] performed an event related potential (ERP) study with MCI patients and found attenuated N1 and N2 amplitudes in e4 carriers. In a follow up study with only normal controls covering the same age range working on the same auditory oddball task, e4 carriers also had reduced N1 amplitudes. Furthermore, N2 latency was longer for e4 carriers, and this latency predicted memory decline 3.5 years later, suggesting that attention-related functions may presage memory decline in those with elevated risk for AD [80]. The later component P3 has been shown to be associated with APOE in healthy controls. Irimajiri et al. [81] found reduced amplitude among healthy female e4 carriers in auditory task, and Espeseth et al. [82] found e4-related reduction of visual P3a amplitudes. Together, these findings indicate a potential clinical significance of individual differences in the attention-related ERP components N1, N2, and P3. These findings of APOE-related changes in attention are associated with APOE-related differences in brain structure. Espeseth et al. [83] found that healthy e4 carriers had thicker cortices than noncarriers in regions of the brain known to be involved in attentional function. However, an age by APOE interaction showed that this effect was specific for the middle-aged participants. The crosssectional data indicated that there might be an accelerated thinning of the cortex for e4 carriers, suggesting that the thicker cortex among the middle-aged might be associated with a dysfunctional process. Espeseth et al. [82] showed that cortical thickness in regions with significant carrier versus noncarrier diffrerences was negatively correlated with P3a amplitudes, suggesting that the increase in cortical thickness was indeed dysfunctional. Further support for this interpretation was presented by Fortea et al. [84, 85] who showed that while symptomatic PSEN1 mutation carriers had widespread cortical thinning compared to healthy controls, asymptomatic mutation carriers had thicker cortices, suggesting that high risk for AD may be associated with a temporary thickening of the cortex.

Cognitive functions are sensitive to interaction of APOE with other factors, including interaction with other genes. Espeseth et al. [75] and Reinvang et al. [86] have argued

that interaction (epistasis) of APOE and CHRNA4, a nicotinic receptor gene, influences function in the domains of attention and executive function. CHRNA4 has been shown to be related to attentional function in several studies [86–93]. The search for cognitive markers of very early AD, possibly predating amnestic MCI, should therefore take account of the cognitive neuroscience literature on the role of cholinergic systems in attention and executive function. Furthermore, tasks from cognitive neuroscience research that have proven to be related to specific cortical-subcortical activation patterns or neurotransmitter systems may in general be more sensitive to subtle cognitive changes than tests derived from clinical studies of advanced pathology.

6. Discussion

Problems of attention and executive function are common in MCI, and in patients with aMCI they are the most important additional symptom domain in multidomain aMCI. It is generally believed that in this group, executive deficit appears after memory impairment in the sequence of cognitive decline leading to full blown dementia.

Executive MCI may occur without memory impairment, and there is evidence that although etiology is heterogenous, a significant proportion of these patients develop AD. How large this group is in MCI samples varies and is dependent on several factors. The strong focus on memory problems as key symptom in early AD, and the wide normal variation in attention and executive function in aging, may indicate a high threshold for these patients to seek medical service. Our own data indicate that in a relatively young MCI population investigated with comprehensive neuropsychological testing, eMCI is a common variant. Attentional and executive dysfunctions may remain undetected even though a thorough neuropsychological examination is performed. Difficulties in dividing attention and manipulating remembered information may be reflected in everyday tasks, such as packing a bag, keeping track of conversations, or walking whilst talking [22]. Patients with executive MCI may show increased behavioral symptoms on questionnaires that specifically measure executive behaviors compared with aMCI and control subjects [33]. Knowing that decreased awareness of cognitive symptoms has been reported in some patients with MCI [94] and executive MCI [95], it may be helpful to ask other informants to rate executive symptoms of the patient.

Current conceptions of early MR changes emphasize hippocampal and cortical atrophy as the significant pathological event, closely linked with emergence of memory impairment [59, 96]. MR analysis yields sensitive measures of a range of pathognomonic events, and recent publications from our group and others indicate that reduced quality of the connectivity of brain networks may compromise cognitive function. This is true, both for the memory network of the brain, including posterior cingulate, and additionally for frontal networks. These networks are involved in both memory and nonmemory functions. Our studies and those of others indicate that in identifying the brain changes underlying eMCI one should emphasize fiber integrity as measures with DTI as well as frontal lobe cortical thinning.

In their report on the status of preclinical markers, AD Sperling and collaborators [59] use the concept of Alzheimer's Disease-pathophysiological process (AD-P) to denote different processes that may contribute to development of clinical Alzheimer's Disease (AD-C). Furthermore they point to studies combining biomarkers (of AD-P) with measures sensitive to very subtle cognitive decline as clearly needed. Large-scale longitudinal studies of biomarker-positive populations raise enormous problems in terms of ethics, costs, and logistics. We suggest that healthy APOE e4 carriers are a realistic and highly relevant study group. Subclinical genetic effects on MR-morphometry [83], DTI [97], and Default Mode [98] have been shown. Experimental cognitive studies have identified specific attention and executive subfunctions as sensitive to APOE allele variation. The paradigms need to be further developed and standardized for use in clinical/epidemiological studies. This development could be modeled on the effort to standardize cognitive neuroscience paradigms for application in schizophrenia research [99]. A great advantage is that they are suited for computerized administration and scoring, so that one may foresee study participants in a longitudinal study logging on to the internet and complete a set of standard tasks at regular intervals.

References

[1] M. S. Albert, S. T. DeKosky, D. Dickson et al., "The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimer's and Dementia*, vol. 7, no. 3, pp. 270–279, 2011.

[2] B. Winblad, K. Palmer, M. Kivipelto, V. Jelic, and L. Fratiglioni, "Introduction: mild cognitive impairment: beyond controversies, towards a consensus," *Journal of Internal Medicine*, vol. 256, no. 3, pp. 181–182, 2004.

[3] R. C. Petersen, R. O. Roberts, D. S. Knopman et al., "Mild cognitive impairment: ten years later," *Archives of Neurology*, vol. 66, no. 12, pp. 1447–1455, 2009.

[4] R. C. Petersen, P. S. Aisen, L. A. Beckett et al., "Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization," *Neurology*, vol. 74, no. 3, pp. 201–209, 2010.

[5] R. C. Petersen et al., "Mild cognitive impairment: clinical characterization and outcome," *Archives of Neurology*, vol. 56, no. 3, pp. 303–308., 1999.

[6] B. Dubois et al., "Revising the definition of Alzheimer's disease: a new lexicon," *The Lancet Neurology*, vol. 9, no. 11, pp. 1118–1127, 2010.

[7] B. Dubois, H. H. Feldman, C. Jacova et al., "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria," *The Lancet Neurology*, vol. 6, no. 8, pp. 734–746, 2007.

[8] H. J. Rosen, J. Lengenfelder, and B. Miller, "Frontotemporal dementia," *Neurologic Clinics*, vol. 18, no. 4, pp. 979–992, 2000.

[9] D. Aarsland, K. Brønnick, and T. Fladby, "Mild Cognitive Impairment in Parkinson's Disease," *Current Neurology and Neuroscience Reports*, vol. 11, no. 4, pp. 371–378, 2011.

[10] T. J. Ferman, B. F. Boeve, G. E. Smith et al., "REM sleep behavior disorder and dementia: Cognitive differences when compared with AD," *Neurology*, vol. 52, no. 5, pp. 951–957, 1999.

[11] M. Grau-Olivares and A. Arboix, "Mild cognitive impairment in stroke patients with ischemic cerebral small-vessel disease: a forerunner of vascular dementia?" *Expert Review of Neurotherapeutics*, vol. 9, no. 8, pp. 1201–1217, 2009.

[12] C. H. Wilkins, J. Mathews, and Y. I. Sheline, "Late life depression with cognitive impairment: evaluation and treatment," *Clinical Interventions in Aging*, vol. 4, no. 1, pp. 51–57, 2009.

[13] R. L. Buckner, "Memory and executive function in aging and ad: multiple factors that cause decline and reserve factors that compensate," *Neuron*, vol. 44, no. 1, pp. 195–208, 2004.

[14] D. Head, A. Z. Snyder, L. E. Girton, J. C. Morris, and R. L. Buckner, "Frontal-hippocampal double dissociation between normal aging and Alzheimer's disease," *Cerebral Cortex*, vol. 15, no. 6, pp. 732–739, 2005.

[15] D. R. Royall, E. C. Lauterbach, J. L. Cummings et al., "Executive control function: a review of its promise and challenges for clinical research—a report from the Committee on Research of the American Neuropsychiatric Association," *Journal of Neuropsychiatry and Clinical Neurosciences*, vol. 14, no. 4, pp. 377–405, 2002.

[16] A. Miyake, N. P. Friedman, M. J. Emerson, A. H. Witzki, A. Howerter, and T. D. Wager, "The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis," *Cognitive Psychology*, vol. 41, no. 1, pp. 49–100, 2000.

[17] J. Brandt, E. Aretouli, E. Neijstrom et al., "Selectivity of executive function deficits in mild cognitive impairment," *Neuropsychology*, vol. 23, no. 5, pp. 607–618, 2009.

[18] L. Fratiglioni, L. J. Launer, K. Andersen et al., "Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts," *Neurology*, vol. 54, no. 11, supplement, pp. S10–S15, 2000.

[19] G. M. McKhann, D. S. Knopman, H. Chertkow et al., "The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimer's and Dementia*, vol. 7, no. 3, pp. 263–269, 2011.

[20] M. Albert, M. B. Moss, D. Blacker, R. Tanzi, and J. J. McArdle, "Longitudinal change in cognitive performance among individuals with mild cognitive impairment," *Neuropsychology*, vol. 21, no. 2, pp. 158–169, 2007.

[21] P. Chen, G. Ratcliff, S. H. Belle, J. A. Cauley, S. T. DeKosky, and M. Ganguli, "Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented," *Neurology*, vol. 55, no. 12, pp. 1847–1853, 2000.

[22] J. D. Huntley and R. J. Howard, "Working memory in early Alzheimer's disease: a neuropsychological review," *International Journal of Geriatric Psychiatry*, vol. 25, no. 2, pp. 121–132, 2010.

[23] L. Traykov, A. S. Rigaud, P. Cesaro, and F. Boller, "Neuropsychological impairment in the early Alzheimer's disease," *Encephale*, vol. 33, no. 3, part 1, pp. 310–316, 2007.

[24] A. D. Baddeley, H. A. Baddeley, R. S. Bucks, and G. K. Wilcock, "Attentional control in Alzheimer's disease," *Brain*, vol. 124, no. 8, pp. 1492–1508, 2001.

[25] R. J. Perry, P. Watson, and J. R. Hodges, "The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: relationship to episodic and semantic memory impairment," *Neuropsychologia*, vol. 38, no. 3, pp. 252–271, 2000.

[26] D. R. Royall, E. C. Lauterbach, D. Kaufer, P. Malloy, K. L. Coburn, and K. J. Black, "The cognitive correlates of functional status: a review from the Committee on Research of the American Neuropsychiatric Association," *Journal of Neuropsychiatry and Clinical Neurosciences*, vol. 19, no. 3, pp. 249–265, 2007.

[27] M. H. Tabert, J. J. Manly, X. Liu et al., "Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment," *Archives of General Psychiatry*, vol. 63, no. 8, pp. 916–924, 2006.

[28] J. J. Gomar et al., "Utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to Alzheimer disease in patients in the Alzheimer's disease neuroimaging initiative," *Archives of General Psychiatry*, vol. 68, no. 9, pp. 961–969, 2011.

[29] J. L. Whitwell, R. C. Petersen, S. Negash et al., "Patterns of atrophy differ among specific subtypes of mild cognitive impairment," *Archives of Neurology*, vol. 64, no. 8, pp. 1130–1138, 2007.

[30] R. C. Petersen et al., "Current concepts in mild cognitive impairment," *Archives of Neurology*, vol. 58, no. 12, pp. 1985–1992, 2001.

[31] M. Storandt, "Cognitive deficits in the early stages of Alzheimer's disease," *Current Directions in Psychological Science*, vol. 17, no. 3, pp. 198–202, 2008.

[32] A. Nordlund, S. Rolstad, P. Hellström, M. Sjögren, S. Hansen, and A. Wallin, "The Goteborg MCI study: mild cognitive impairment is a heterogeneous condition," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 76, no. 11, pp. 1485–1490, 2005.

[33] J. Pa, A. Boxer, L. L. Chao et al., "Clinical-neuroimaging characteristics of dysexecutive mild cognitive impairment," *Annals of Neurology*, vol. 65, no. 4, pp. 414–423, 2009.

[34] L. L. Chao, J. Pa, A. Duarte et al., "Patterns of cerebral hypoperfusion in amnestic and dysexecutive MCI," *Alzheimer Disease and Associated Disorders*, vol. 23, no. 3, pp. 245–252, 2009.

[35] J. K. Johnson, J. Pa, A. L. Boxer, J. H. Kramer, K. Freeman, and K. Yaffe, "Baseline predictors of clinical progression among patients with dysexecutive mild cognitive impairment," *Dementia and Geriatric Cognitive Disorders*, vol. 30, no. 4, pp. 344–351, 2010.

[36] J. K. Johnson, B. A. Vogt, R. Kim, C. W. Cotman, and E. Head, "Isolated executive impairment and associated frontal neuropathology," *Dementia and Geriatric Cognitive Disorders*, vol. 17, no. 4, pp. 360–367, 2004.

[37] R. Grambaite et al., "Executive dysfunction in mild cognitive impairment is associated with changes in frontal and cingulate white matter tracts," *Journal of Alzheimer's Disease*, vol. 27, no. 2, pp. 453–462, 2011.

[38] A. J. Jak, K. J. Bangen, C. E. Wierenga, L. Delano-Wood, J. Corey-Bloom, and M. W. Bondi, "Contributions of neuropsychology and neuroimaging to understanding clinical subtypes of mild cognitive impairment," *International Review of Neurobiology*, vol. 84, pp. 81–103, 2009.

[39] P. A. Reuter-Lorenz and C. Lustig, "Brain aging: reorganizing discoveries about the aging mind," *Current Opinion in Neurobiology*, vol. 15, no. 2, pp. 245–251, 2005.

[40] F. Collette, M. Hogge, E. Salmon, and M. Van der Linden, "Exploration of the neural substrates of executive functioning by functional neuroimaging," *Neuroscience*, vol. 139, no. 1, pp. 209–221, 2006.

[41] R. Cabeza and L. Nyberg, "Imaging cognition II: an empirical review of 275 PET and fMRI studies," *Journal of Cognitive Neuroscience*, vol. 12, no. 1, pp. 1–47, 2000.

[42] J. L. Cummings, "Frontal-subcortical circuits and human behavior," *Archives of Neurology*, vol. 50, no. 8, pp. 873–880, 1993.

[43] R. L. Buckner and M. E. Wheeler, "The cognitive neuroscience of remembering," *Nature Reviews Neuroscience*, vol. 2, no. 9, pp. 624–634, 2001.

[44] M. P. Milham, K. I. Erickson, M. T. Banich et al., "Attentional control in the aging brain: insights from an fMRI study of the stroop task," *Brain and Cognition*, vol. 49, no. 3, pp. 277–296, 2002.

[45] G. Bush, B. A. Vogt, J. Holmes et al., "Dorsal anterior cingulate cortex: a role in reward-based decision making," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 1, pp. 523–528, 2002.

[46] J. Pa, K. L. Possin, S. M. Wilson et al., "Gray matter correlates of set-shifting among neurodegenerative disease, mild cognitive impairment, and healthy older adults," *Journal of the International Neuropsychological Society*, vol. 16, no. 4, pp. 640–650, 2010.

[47] A. M. Hall, R. Y. Moore, O. L. Lopez, L. Kuller, and J. T. Becker, "Basal forebrain atrophy is a presymptomatic marker for Alzheimer's disease," *Alzheimer's and Dementia*, vol. 4, no. 4, pp. 271–279, 2008.

[48] B. A. Vogt, *Cingulate Neurobiology and Disease*, Oxford University Press, New York, NY, USA, 2009.

[49] M. Sjöbeck, C. Elfgren, E. M. Larsson et al., "Alzheimer's disease (AD) and executive dysfunction. A case-control study on the significance of frontal white matter changes detected by diffusion tensor imaging (DTI)," *Archives of Gerontology and Geriatrics*, vol. 50, no. 3, pp. 260–266, 2010.

[50] M. M. Mielke, N. A. Kozauer, K. C. G. Chan et al., "Regionally-specific diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease," *NeuroImage*, vol. 46, no. 1, pp. 47–55, 2009.

[51] Y. Zhang, N. Schuff, G. H. Jahng et al., "Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease," *Neurology*, vol. 68, no. 1, pp. 13–19, 2007.

[52] R. L. Buckner, A. Z. Snyder, B. J. Shannon et al., "Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory," *Journal of Neuroscience*, vol. 25, no. 34, pp. 7709–7717, 2005.

[53] T. Arikuni, H. Sako, and A. Murata, "Ipsilateral connections of the anterior cingulate cortex with the frontal and medial temporal cortices in the macaque monkey," *Neuroscience Research*, vol. 21, no. 1, pp. 19–39, 1994.

[54] B. A. Vogt, P. B. Crino, and L. Volicer, "Laminar alterations in γ-aminobutyric acid(A), muscarinic, and β adrenoceptors and neuron degeneration in cingulate cortex in Alzheimer's disease," *Journal of Neurochemistry*, vol. 57, no. 1, pp. 282–290, 1991.

[55] C. R. Jack Jr., V. J. Lowe, S. D. Weigand et al., "Serial PIB and MRI in normal, mild cognitive impairment and Alzheimers disease: implications for sequence of pathological events in Alzheimers disease," *Brain*, vol. 132, no. 5, pp. 1355–1365, 2009.

[56] S. M. De la Monte, "Quantitation of cerebral atrophy in preclinical and end-stage Alzheimer's disease," *Annals of Neurology*, vol. 25, no. 5, pp. 450–459, 1989.

[57] L. Wang, F. C. Goldstein, E. Veledar et al., "Alterations in cortical thickness and white matter integrity in mild cognitive impairment measured by whole-brain cortical thickness mapping and diffusion tensor imaging," *American Journal of Neuroradiology*, vol. 30, no. 5, pp. 893–899, 2009.

[58] R. Grambaite, I. Reinvang, P. Selnes et al., "Pre-dementia memory impairment is associated with white matter tract affection," *Journal of the International Neuropsychological Society*, vol. 17, no. 1, pp. 143–153, 2011.

[59] R. A. Sperling, P. S. Aisen, L. A. Beckett et al., "Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimer's and Dementia*, vol. 7, no. 3, pp. 280–292, 2011.

[60] E. H. Corder, A. M. Saunders, W. J. Strittmatter et al., "Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families," *Science*, vol. 261, no. 5123, pp. 921–923, 1993.

[61] E. Genin, "APOE and Alzheimer disease: a major gene with semi-dominant inheritance," *Molecular Psychiatry*, vol. 16, no. 9, pp. 903–907, 2011.

[62] R. J. Caselli, D. Walker, L. Sue, M. Sabbagh, and T. Beach, "Amyloid load in nondemented brains correlates with APOE e4," *Neuroscience Letters*, vol. 473, no. 3, pp. 168–171, 2010.

[63] K. E. Pike, G. Savage, V. L. Villemagne et al., "β-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease," *Brain*, vol. 130, no. 11, pp. 2837–2844, 2007.

[64] T. Grimmer, S. Tholen, B. H. Yousefi et al., "Progression of cerebral amyloid load is associated with the apolipoprotein e ε4 genotype in Alzheimer's disease," *Biological Psychiatry*, vol. 68, no. 10, pp. 879–884, 2010.

[65] P. M. Greenwood, T. Sunderland, C. Lambert, and R. Parasuraman, "Effects of apolipoprotein E genotype on spatial attention, working memory, and their interaction in healthy, middle-aged adults: results from the National Institute of Mental Health's BIOCARD study," *Neuropsychology*, vol. 19, no. 2, pp. 199–211, 2005.

[66] P. Davies and A. J. F. Maloney, "Selective loss of central cholinergic neurons in Alzheimer's disease," *The Lancet*, vol. 2, no. 8000, p. 1403, 1976.

[67] P. J. Whitehouse, D. L. Price, and R. G. Struble, "Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain," *Science*, vol. 215, no. 4537, pp. 1237–1239, 1982.

[68] S. T. Dekosky, M. D. Ikonomovic, S. D. Styren et al., "Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment," *Annals of Neurology*, vol. 51, no. 2, pp. 145–155, 2002.

[69] R. Lane, H. H. Feldman, J. Meyer et al., "Synergistic effect of apolipoprotein E ε4 and butyrylcholinesterase K-variant on progression from mild cognitive impairment to Alzheimer's disease," *Pharmacogenetics and Genomics*, vol. 18, no. 4, pp. 289–298, 2008.

[70] T. Darreh-Shori, A. Forsberg, N. Modiri et al., "Differential levels of apolipoprotein E and butyrylcholinesterase show strong association with pathological signs of Alzheimer's disease in the brain in vivo," *Neurobiology of Aging*, vol. 32, no. 12, pp. 2320.e15–2320.e32, 2011.

[71] F. Bao, L. Wicklund, P. N. Lacor, W. L. Klein, A. Nordberg, and A. Marutle, "Different β-amyloid oligomer assemblies in Alzheimer brains correlate with age of disease onset and impaired cholinergic activity," *Neurobiology of Aging*, vol. 33, no. 4, pp. 825.e1–825.e13, 2012.

[72] N. M. Wisdom, J. L. Callahan, and K. A. Hawkins, "The effects of apolipoprotein E on non-impaired cognitive functioning: a meta-analysis," *Neurobiology of Aging*, vol. 32, no. 1, pp. 63–74, 2011.

[73] R. Parasuraman, P. M. Greenwood, J. V. Haxby, and C. L. Grady, "Visuospatial attention in dementia of the Alzheimer type," *Brain*, vol. 115, no. 3, pp. 711–733, 1992.

[74] P. M. Greenwood, T. Sunderland, J. L. Friz, and R. Parasuraman, "Genetics and visual attention: selective deficits in healthy adult carriers of the ε4 allele of the apolipoprotein E gene," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 21, pp. 11661–11666, 2000.

[75] T. Espeseth, P. M. Greenwood, I. Reinvang et al., "Interactive effects of APOE and CHRNA4 on attention and white matter volume in healthy middle-aged and older adults," *Cognitive, Affective and Behavioral Neuroscience*, vol. 6, no. 1, pp. 31–43, 2006.

[76] V. M. Rosen, J. L. Bergeson, K. Putnam, A. Harwell, and T. Sunderland, "Working memory and apolipoprotein E: what's the connection?" *Neuropsychologia*, vol. 40, no. 13, pp. 2226–2233, 2002.

[77] I. Reinvang, I. L. Winjevoll, H. Rootwelt, and T. Espeseth, "Working memory deficits in healthy APOE epsilon 4 carriers," *Neuropsychologia*, vol. 48, no. 2, pp. 566–573, 2010.

[78] H. A. Wishart, A. J. Saykin, L. A. Rabin et al., "Increased brain activation during working memory in cognitively intact adults with the APOE ε4 allele," *American Journal of Psychiatry*, vol. 163, no. 9, pp. 1603–1610, 2006.

[79] I. Reinvang, T. Espeseth, and L. Gjerstad, "Cognitive ERPs are related to ApoE allelic variation in mildly cognitively impaired patients," *Neuroscience Letters*, vol. 382, no. 3, pp. 346–351, 2005.

[80] T. Espeseth, H. Rootwelt, and I. Reinvang, "Apolipoprotein E modulates auditory event-related potentials in healthy aging," *Neuroscience Letters*, vol. 459, no. 2, pp. 91–95, 2009.

[81] R. Irimajiri, E. J. Golob, and A. Starr, "ApoE genotype and abnormal auditory cortical potentials in healthy older females," *Neurobiology of Aging*, vol. 31, no. 10, pp. 1799–1804, 2010.

[82] T. Espeseth, L. T. Westlye, K. B. Walhovd et al., "Apolipoprotein E ε4-related thickening of the cerebral cortex modulates selective attention," *Neurobiology of Aging*, vol. 33, no. 2, pp. 304–322.e1, 2012.

[83] T. Espeseth, L. T. Westlye, A. M. Fjell, K. B. Walhovd, H. Rootwelt, and I. Reinvang, "Accelerated age-related cortical thinning in healthy carriers of apolipoprotein E ε4," *Neurobiology of Aging*, vol. 29, no. 3, pp. 329–340, 2008.

[84] J. Fortea, R. Sala-Llonch, D. Bartrés-Faz et al., "Increased cortical thickness and caudate volume precede atrophy in psen1 mutation carriers," *Journal of Alzheimer's Disease*, vol. 22, no. 3, pp. 909–922, 2010.

[85] J. Fortea, R. Sala-Llonch, D. Bartrés-Faz et al., "Cognitively preserved subjects with transitional cerebrospinal fluid ß-amyloid 1-42 values have thicker cortex in Alzheimer's disease vulnerable areas," *Biological Psychiatry*, vol. 70, no. 2, pp. 183–190, 2011.

[86] I. Reinvang, A. J. Lundervold, H. Rootwelt, E. Wehling, and T. Espeseth, "Individual variation in a cholinergic receptor gene modulates attention," *Neuroscience Letters*, vol. 453, no. 3, pp. 131–134, 2009.

[87] T. Espeseth, T. Endestad, H. Rootwelt, and I. Reinvang, "Nicotine receptor gene CHRNA4 modulates early event-related potentials in auditory and visual oddball target detection tasks," *Neuroscience*, vol. 147, no. 4, pp. 974–985, 2007.

[88] T. Espeseth, M. H. Sneve, H. Rootwelt, and B. Laeng, "Nicotinic receptor gene chrna4 interacts with processing load in attention," *PLoS ONE*, vol. 5, no. 12, Article ID e14407, 2010.

[89] P. M. Greenwood, J. A. Fossella, and R. Parasuraman, "Specificity of the effect of a nicotinic receptor polymorphism on individual differences in visuospatial attention," *Journal of Cognitive Neuroscience*, vol. 17, no. 10, pp. 1611–1620, 2005.

[90] P. M. Greenwood, M. K. Lin, R. Sundararajan, K. J. Fryxell, and R. Parasuraman, "Synergistic effects of genetic variation in nicotinic and muscarinic receptors on visual attention but not working memory," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 9, pp. 3633–3638, 2009.

[91] P. M. Greenwood, R. Sundararajan, M. K. Lin, R. Kumar, K. J. Fryxell, and R. Parasuraman, "Both a nicotinic single nucleotide polymorphism (SNP) and a noradrenergic SNP modulate working memory performance when attention is manipulated," *Journal of Cognitive Neuroscience*, vol. 21, no. 11, pp. 2139–2153, 2009.

[92] G. Winterer, F. Musso, A. Konrad et al., "Association of attentional network function with exon 5 variations of the CHRNA4 gene," *Human Molecular Genetics*, vol. 16, no. 18, pp. 2165–2174, 2007.

[93] R. Parasuraman, P. M. Greenwood, R. Kumar, and J. Fossella, "Beyond heritability: neurotransmitter genes differentially modulate visuospatial attention and working memory," *Psychological Science*, vol. 16, no. 3, pp. 200–207, 2005.

[94] A. Vogel, S. G. Hasselbalch, A. Gade, M. Ziebell, and G. Waldemar, "Cognitive and functional neuroimaging correlates for anosognosia in mild cognitive impairment and Alzheimer's disease," *International Journal of Geriatric Psychiatry*, vol. 20, no. 3, pp. 238–246, 2005.

[95] J. K. Johnson, J. Pa, A. L. Boxer, J. H. Kramer, K. Freeman, and K. Yaffe, "Baseline predictors of clinical progression among patients with dysexecutive mild cognitive impairment," *Dementia and Geriatric Cognitive Disorders*, vol. 30, no. 4, pp. 344–351, 2010.

[96] C. R. Jack Jr., D. S. Knopman, W. J. Jagust et al., "Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade," *The Lancet Neurology*, vol. 9, no. 1, pp. 119–128, 2010.

[97] V. Heise, N. Filippini, K. P. Ebmeier, and C. E. Mackay, "The APOE epsilon 4 allele modulates brain white matter integrity in healthy adults," *Molecular Psychiatry*, vol. 16, no. 9, pp. 908–916, 2010.

[98] N. Filippini et al., "Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 17, pp. 7209–7214, 2009.

[99] C. S. Carter and D. M. Barch, "Cognitive neuroscience-based approaches to measuring and improving treatment effects on cognition in schizophrenia: the CNTRICS initiative," *Schizophrenia Bulletin*, vol. 33, no. 5, pp. 1131–1137, 2007.

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Review Article

Promising Genetic Biomarkers of Preclinical Alzheimer's Disease: The Influence of *APOE* and *TOMM40* on Brain Integrity

Beata Ferencz, Sari Karlsson, and Grégoria Kalpouzos

Aging Research Center, Karolinska Institutet-Stockholm University, Gävlegatan 16, 113 30 Stockholm, Sweden

Correspondence should be addressed to Beata Ferencz, beata.ferencz@ki.se

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Finding biomarkers constitutes a crucial step for early detection of Alzheimer's disease (AD). Brain imaging techniques have revealed structural alterations in the brain that may be phenotypic in preclinical AD. The most prominent polymorphism that has been associated with AD and related neural changes is the Apolipoprotein E (*APOE*) $\varepsilon 4$. The translocase of outer mitochondrial membrane 40 (*TOMM40*), which is in linkage disequilibrium with *APOE*, has received increasing attention as a promising gene in AD. *TOMM40* also impacts brain areas vulnerable in AD, by downstream apoptotic processes that forego extracellular amyloid beta aggregation. The present paper aims to extend on the mitochondrial influence in AD pathogenesis and we propose a *TOMM40*-induced disconnection of the medial temporal lobe. Finally, we discuss the possibility of mitochondrial dysfunction being the earliest pathophysiological event in AD, which indeed is supported by recent findings.

1. Introduction

Alzheimer's Disease (AD) is one of the leading causes of dementia today and it poses an immense societal challenge as the prevalence is expected to continue to rise [1]. This makes it imperative to identify early preclinical changes in AD with high accuracy, in order for intervention strategies to yield effective outcome and to allow affected individuals to partake in an active treatment plan [2–5]. AD is characterized by early pathological changes in the brain, including senile plaques, neurofibrillary tangles, synapse, and neuronal loss. Neurofibrillary tangle formation may initiate in subcortical nuclei such as the dorsal raphe and locus coeruleus, prior to spreading to transentorhinal regions [6, 7]. Findings also support that pathological changes in AD commence in the medial temporal lobe (MTL) [8–10], primarily in the entorhinal cortex (ERC) and hippocampus (HC) [11–13], which undergo initial gray matter (GM) loss. Recently, attention has also been directed towards the impact of pathological mechanisms on white matter (WM), as up to 50% of AD cases present with global WM deterioration in neuropathological examinations [14, 15]. The temporal succession of GM and WM changes in preclinical AD remains to be determined; so far there is support for both primary and secondary WM changes within the MTL [16, 17].

MCI is regarded as a prodromal state of AD, where individuals present with subjective memory complaints and/or objective memory impairment, but are still intact in daily life and do not meet current AD diagnostic criteria [2, 18, 19]. Amnestic type MCI (aMCI), where memory impairment is considered predominant, has been proposed as a solution for the diagnostic heterogeneity of the overall MCI criteria. The construct of MCI allows for the clinical assessment of prodromal AD, where early interventions could have a beneficial effect [20]. While promising, this therapeutic window is hampered by the fact that not all individuals with MCI convert to AD (6–25%), and almost half return to normal cognitive health within the first year of followup [2, 21]. Moreover, caveats remain regarding MCI and its clinical usefulness, signifying that the most beneficial use of the MCI criteria is by combination with other structural, functional, neuropsychological, genetic, and pathological biomarkers [22]. These

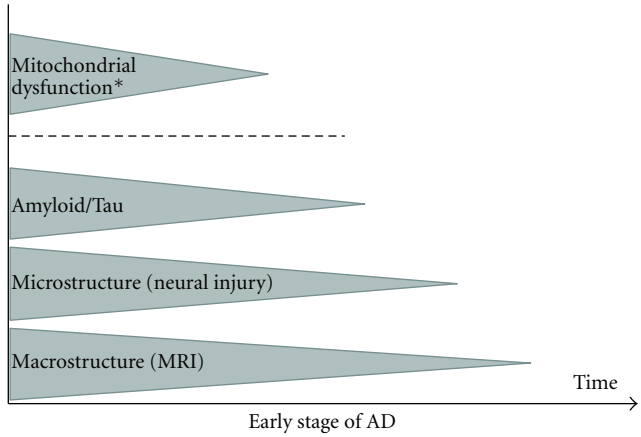

Figure 1: Timeline of potential biomarkers in Alzheimer's disease. Prior to clinical diagnosis of AD, beta-amyloid (Aβ) aggregation, micro- and macrostructural changes are thought to take place in a timewise fashion (adapted from [23]). *Recent research points to a shift in the biomarker timeline, with mitochondrial dysfunction being primary in the pathophysiological cascade of AD, eventually leading to micro- and macrostructural changes in the AD brain.

biomarkers were recently placed into a hypothetic biomarker timeline by Jack and colleagues [23], who proposed that the pathological cascade in AD commences with amyloid and tau pathology, followed by neural injury and dysfunction and finally structural alterations (see Figure 1). Furthermore, they hypothesize that β-amyloid deposition and the following cascade occur earlier in Apolipoprotein (*APOE*) ε4 carriers. Recent findings have shown brain and cognitive changes up to 10 years prior to the diagnosis of AD, indicating that the combination of biomarkers may provide an alternative timeline [23–25]. A growing body of literature has emphasized the association between genetic and structural brain biomarkers, with imaging quantitative traits within the MTL being a more objective outcome than clinical diagnosis alone. The MTL may act as a mediator between genetic polymorphisms and the clinical expression of AD, indicating the advantage of combined genetic and brain integrity biomarkers [26, 27].

APOE is one of the primary AD polymorphisms, associated not only with risk and age of onset, but also brain integrity in AD [3, 28, 29]. Due to its Linkage Disequilibrium (LD) with *APOE*, Translocase of outer mitochondrial membrane 40 (*TOMM40*) was previously thought to have minimal influence on the risk of AD [30, 31]. Nevertheless, it is now established that *TOMM40* influences onset of AD [31–37]. The *TOMM40* gene holds promising biomarker properties due to its negative impact on downstream apoptotic processes within the mitochondrial system via possible amyloid beta (Aβ) interplay [30, 38, 39]. Recently the mitochondrial cascade hypothesis has received increasing support, proposing that mitochondrial dysfunction is the key pathological mechanism in AD, influencing brain structures known to be vulnerable in AD [40, 41]. We intend to extend these theories by presenting the mitochondrial disconnection model, an adapted model for mitochondrial involvement in preclinical AD. We also suggest a timeline shift in the biomarker realm, away from the amyloid hypothesis, towards early and primary mitochondrial involvement in the pathophysiology of AD (see Figure 1). The implication of mitochondrial dysfunction in AD is currently supported by genetic and neuropathological research [30, 39, 41] and has the possibility to shed light on the primary biological insult in the disorder, as well as to provide a new therapeutic window for AD [42, 43].

The present paper focuses on recent advances in neuroimaging and genetic biomarkers for preclinical AD. After an overview of structural brain changes in early AD, we discuss the influence of *APOE* and *TOMM40*, in an effort to approximate the primary pathological cascade in AD. The mitochondrial disconnection model is an extension of previous findings and is suggested as a workable hypothesis from which the influential role of mitochondria on AD can be assessed.

2. Structural Brain Changes in Early Alzheimer's Disease

The consensus in the literature is that there is a long preclinical phase of AD, with cognitive as well as structural brain changes commencing years before clinical diagnosis of the disorder [23, 24, 44]. Indeed, significant brain atrophy can be observed in healthy individuals who will subsequently develop MCI or AD, in comparison to stable controls, within the bilateral medial and lateral temporal lobes, orbitofrontal cortex, posterior cingulate, and precuneus [24]. Interestingly, these preclinical changes correspond to the pattern of GM alterations seen in diagnosed AD [15, 45], demonstrating that early AD type pathology is present prior to clinical symptoms [24, 46].

Both MCI and AD have characteristic influence on structures in the brain, thereby making them dissociable from nonpathological aging [45, 47]. Imaging studies have been able to confirm the Braak staging of neuropathology in AD by showing early structural changes within the MTL (more particularly the ERC and HC), prior to spreading to adjacent cortices [10, 13, 48–50]. Looking closer at the HC, the lateral CA1 subfield is the most vulnerable in MCI and AD while GM loss in the subiculum is associated with nonpathological age-related changes, denoting region-specific changes within the HC in AD [51]. Moreover, several studies have indicated that the rate of atrophy within the MTL is faster for those who convert from normal aging to MCI as well as from MCI to AD in comparison to those who remain stable [52–54]. This shows that not only atrophy, but also the rate of atrophy in the HC over time could serve as a potential biomarker of preclinical AD. Structural changes in mild-to-moderate AD also occur in areas that are strongly connected to the MTL, such as the retrosplenial cortex, posterior cingulate, precuneus, and lateral posterior parietal regions [55, 56]. These findings have been confirmed in individuals with MCI, where medial and lateral temporal as well as parietal atrophy was evident in individuals who converted from MCI to AD, in comparison with those who remained stable [57].

Although the progression of WM alterations in the brain is still unclear, damage to WM pathways within the MTL can

be detrimental according to the "disconnection hypothesis," stating that deterioration of WM tracts leads to subsequent disconnection of the brain's circuitry [11, 58]. Not only might there be an overall disconnection, but a specific isolation of the HC that may result from reduced WM integrity within the MTL, mainly in the parahippocampal area, cingulum, fornix, uncinate fasciculus, and perforant pathway [59–61]. Moreover, an alteration in the WM of the precuneus, closely interconnected with the MTL, has also been observed, resulting in the isolation of the hippocampus [59]. Researchers debate the sequential order of GM and WM deterioration in preclinical AD and the Wallerian degeneration hypothesis stipulates that loss of WM integrity is secondary to GM changes. In line with this hypothesis, research has shown GM atrophy to be more efficient in distinguishing between AD patients and healthy controls. More specifically it has been observed that right-sided hippocampal GM loss is a better predictor of diagnostic status of AD than measures of WM integrity [8]. Recently, this hypothesis was supported in a study where primary GM degeneration in the HC was followed by Wallerian degeneration of WM within the interammonic commissure, a pathway connecting the left and right hippocampi [12]. Also similarly, Villain and colleagues found HC atrophy to be followed by loss of WM integrity in the uncinate fasciculus and cingulum bundle, which was corroborated by metabolic alterations in connected cortical areas, demonstrating a significant disruption in connectivity [61]. By contrast, WM deterioration has also been observed in the absence of primary GM changes [60, 62]. For example, in individuals with MCI and AD, loss of WM integrity has been seen in the perforant pathway in absence of GM atrophy [63]. Alteration of the perforant pathway, which connects the ERC and the HC and constitutes a gateway to the limbic system, may contribute to early and likely initial disconnection of the MTL in preclinical AD [60].

WM changes in small pathways of the brain, such as the perforant pathway, are still arduous to discern with the current available neuroimaging techniques. This is particularly important in preclinical AD where the areas implicated are small WM pathways within the MTL. Moreover, the lack of longitudinal studies renders it difficult to determine the temporal order of GM and WM changes in the brain. It has been pointed out that it is disadvantageous to consider the WM changes in the brain in a dichotomized fashion [16, 17]. Instead, a balanced view has been proposed where the temporal order of structural changes in the brain is dependent on the retrogenesis of the specific structure [16, 64]. For instance, in late myelinating pathways connected to the MTL such as the inferior longitudinal fasciculus, primary loss of WM integrity is thought to be of major influence. In early myelinating pathways such as the cerebral peduncles, posterior limb of internal capsule, and forceps major on the other hand, WM degeneration is considered secondary to GM loss. However, it has been proposed that within each brain area, depending on its retrogenetic development, there is a ratio between primary and secondary WM degeneration, possibly explaining why the temporal order of GM and WM changes in early AD has been difficult to ascertain [16].

3. *APOE* and Preclinical Alzheimer's Disease

While research in the genetic field has been fraught by small effect sizes and difficulty in replicating findings, *APOE* has remained a robustly replicated susceptibility gene for AD [42, 65, 66]. Located on chromosome 19, *APOE* translates into three common allelic variations $\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$ [67], the $\varepsilon 4$ being strongly associated with risk of developing AD [28, 68, 69]. Furthermore, the $\varepsilon 4$ allele has been associated with decreased memory functioning, processing speed, and loss of GM and WM integrity [70–74]. The $\varepsilon 4$ allele also modulates risk of progression from MCI to AD. In effect, a recent meta-analysis demonstrated that the presence of one or two $\varepsilon 4$ alleles increased the risk of MCI conversion to AD up to four times. However, *APOE* as a risk factor has low predictivity and sensitivity values as a diagnostic test for AD, leading to the conclusion that *APOE* genotyping has limited value as a diagnostic tool in clinical practice [75–77].

APOE appears to play an essential role for lipid metabolism within the Central Nervous System (CNS) and allelic variations of the gene are thought to modulate neural repair, lipid homeostasis, oxidative stress, and Aβ deposition [43, 68]. As lipids are abundant in the brain and essential for myelination of axons, it comes as no surprise that APOE, being the main cholesterol transport lipoprotein, appears to play an essential role in maintaining brain integrity [78]. Although the mechanism behind the influence of APOE on the brain is not fully elucidated, the protein appears to govern the efficiency of cholesterol delivery to neurons. Particularly, the presence of an $\varepsilon 4$ allele reduces the delivery of cholesterol, consequently disturbing lipid homeostasis within the CNS and triggering a cascade leading to the formation of amyloid depositions [79]. The combined amyloid cascade hypothesis [80] and APOE lipid recycling cascade models [81] promote a disturbance in lipid homeostasis as a source for AD pathology [82]. While the amyloid cascade hypothesis has been prominent throughout the last two decades, it was initially based on studies with rare autosomal dominant variants of AD and had pathophysiological shortcomings [83]. Indeed, widespread amyloid deposition is present in AD, but there is no consensus regarding the finite pathophysiological burden of amyloid in the brain and it has been argued that amyloid aggregation is a downstream process in AD not related to clinical manifestation of the disorder [84]. While *APOE* may influence the amyloid cascade in AD, other neuropathological aspects of the polymorphism have been highlighted, including influence on neuronal repair mechanisms and maintenance of synaptic connections [43]. One way of increasing the predictability of the *APOE* polymorphisms is by combining genetic and structural brain biomarkers [27, 73].

4. *APOE* and Structural Integrity

Extensive research has been done on the genetic influence of *APOE* polymorphisms on brain changes in preclinical AD (Table 1). Support for the influence of *APOE* on AD-like changes within the brain comes from a Genomewide Association Study (GWAS) on neuroimaging phenotypes in a mixed sample of MCI and AD individuals [85]. The authors

found *APOE* to be one of the top ten genetic markers to influence overall imaging phenotypes. Espeseth and colleagues [86] demonstrated a modulatory effect of *APOE* polymorphism on cortical thickness in healthy middle-aged adults. Carriers of an $\varepsilon 4$ allele showed accelerated cortical thinning in specific regions known to structurally deteriorate in normal aging but also in AD such as prefrontal regions, parahippocampal cortex, and adjacent occipitotemporal areas (fusiform and lingual gyri), but not the HC. Others have found more region-specific influence of *APOE* on MTL areas [29, 87, 88]. This effect appears to be left lateralized with the $\varepsilon 4$ influence on HC volume [89]. The majority of findings converge towards a significant impact of *APOE* polymorphism on GM integrity within the MTL, mainly the HC.

Further, evidence for the influence of *APOE* on the MTL comes from longitudinal studies on MCI and conversion to AD (see Table 1). These have found that there is a genetic influence of *APOE* not only on hippocampal GM loss, but also on the rate of atrophy of the HC [88, 94]. Support for the specific influence of *APOE* $\varepsilon 4$ in MCI has been shown, as aMCI individuals have been found more likely to have smaller hippocampi and be carriers of at least one $\varepsilon 4$ allele than nonamnestic MCI individuals [94]. Also, MCI *APOE* $\varepsilon 4$ carriers express AD-type structural alterations such as atrophy in MTL regions (ERC and HC). Those with MCI and an $\varepsilon 4$ allele who convert to AD also show atrophy in frontal and parietal cortices [48, 95]. Progressive MCI $\varepsilon 4$ carriers show global AD-type structural changes years before clinical diagnosis of AD [95]. However, *APOE* $\varepsilon 4$ does not predict conversion from MCI to AD, while ERC volume reduction at baseline does [48]. Hence, it appears that while *APOE* may influence structural integrity in areas that are vulnerable in the preclinical stages in AD, *APOE* polymorphism has limited predictive value on the conversion to AD. The latter finding may, however, be biased by limited sample sizes. Thus, future studies combining structural, genetic and cognitive biomarkers in larger samples may show enhanced predictability.

Given its hypothesized role as the brain's main lipid transporter [79], *APOE* impacts WM integrity in preclinical AD [99]. Several studies have confirmed both widespread and localized WM changes throughout the brain in relation to *APOE* polymorphism in healthy samples (see Table 1). Persson and colleagues [97], for instance, demonstrated an impact of *APOE* $\varepsilon 4$ on the WM integrity of the posterior corpus callosum and HC in healthy younger and older individuals, possibly reflecting preclinical signs of AD. Their findings are supported by recently published data showing that the presence of an $\varepsilon 4$ allele exacerbates age-related WM changes [73]. Moreover, it seems that late myelinating regions are more susceptible to age-related loss of integrity in $\varepsilon 4$ carriers, leading to progressive disconnection of the brain in *APOE* $\varepsilon 4$ carriers [96].

In conclusion, influence of *APOE* on GM structural integrity has been consistently demonstrated in areas associated with preclinical AD. By contrast, little is known about the genetic influence of *APOE* on WM changes in AD and whether these changes are occurring sequentially or in a balanced retrogenetic fashion.

5. *TOMM40* and Preclinical Alzheimer's Disease

Missing heritability is increasingly debated in the literature, as current genetic findings are not able to explain the full extent of the genetic contribution to complex diseases such as AD [65, 100, 101]. While larger sample sizes in GWAS are suggested as a remedy for missing heritability, others suggest that the answer resides in genetic polymorphisms that are in LD with current known ones [65, 102–104]. *TOMM40* is becoming increasingly acknowledged as a prominent AD gene [31–37]. In LD with *APOE*, *TOMM40* could hold part of the missing heritability that we are searching for in our efforts to map the genetic influences in AD. Moreover, taking *TOMM40* into consideration may contribute to a better understanding of the early and primary pathophysiological cascade that takes place in the preclinical phases of the disorder. This hypothesis is supported by the fact that *TOMM40* asserts its influence on mitochondrial survival, a process increasingly highlighted in the pathogenesis of AD [31, 105, 106]. Mitochondrial dysfunction has been associated with several pathological processes in AD, including brain hypometabolism, synaptic pathology, accumulation of Amyloid Precursor Proteins (APP), and Aβ influx to the cell [38, 39, 41]. Mitochondria have recently been implicated in more complex signaling cascades, oxidative stress, and apoptotic processes, indicating that mitochondria are not merely a powerhouse of the cell, rather they appear to govern cell death [107]. The notion of mitochondrial dysfunction in aging and neurodegeneration is not new. In fact, malfunctioning mitochondrial systems have been observed in premature aging [105, 108] as well as neurodegenerative disorders such as AD [40, 109, 110], Parkinson's and Huntington's disease [105] and appear to have an early and causal influence on pathological processes in the brain. Damage in mitochondria may exert a specific influence on the pathophysiology of AD through interplay with Aβ and its precursor, the APP [111].

Mitochondria play an essential role in providing energy to cells and are abundant in the neurons and synapses of the CNS. Containing an outer and inner membrane, the organelle is essential for the production of adenosine triphosphate (ATP), which is the energy source of all cells [112]. The outer mitochondrial membrane contains the translocase of outer mitochondrial membrane pore subunit (Tom40). The Tom40 channel forming subunit is one of the primary pores via which proteins can readily enter the mitochondria. The pore is governed by the *TOMM40* gene and is essential for mitochondrial survival as the majority of proteins that enter the mitochondria pass through here [107, 113]. In AD specifically, it has been hypothesized that mitochondria exert neurotoxic influence by allowing the influx of Aβ to the cell via the Tom40 import pore. Passage of Aβ through the Tom40 import pore increases Reactive Oxygen Species (ROS) within the organelle. This increase is detrimental for mitochondrial survival and energy production (ATP), ultimately resulting in apoptotic processes of the cell [38, 111, 114]. Further ROS precipitating events include the accumulation of APP in mitochondrial import pores. This

Table 1: Genetic influence of *APOE* and *TOMM40* on cerebral structural integrity.

Author	Population	Method	Structural integrity	Conclusion
			Alzheimer's Disease	
			APOE	
Pievani et al. 2011 [29]	Across *APOE* ($\varepsilon 4$) $n = 28$	Volumetry region based	Smaller HC in *APOE* $\varepsilon 4+$	$\varepsilon 4+$ carriers have greater atrophy in the HC.
Bendlin et al. 2010 [90]	Across *APOE*($\varepsilon 4$) & family history of AD $n = 136$	DTI whole brain	*Parental history of AD* Reduced FA in cingulum, tapetum, uncinate fasciculus, HC, and adjacent WM No main effect of *APOE* on WM, but interaction with family history where family history and $\varepsilon 4+$ induced reduced FA	While no main effect of *APOE* was observed onDTI measures, parental history of AD was associated with reduced WM integrity in brain areas deteriorated in AD, which in turn interacted with *APOE*.
Pievani et al. 2009 [91]	Across *APOE* ($\varepsilon 4$) $n = 29$	Volumetry whole brain	*APOE* $\varepsilon 4+$ Significant atrophy in Bil temporal lobes, occipital lobes, retrosplenial, and posterior cingulate Highest GM reduction >20%: entorhinal cortex, anterior temporal pole, superior and middle temporal gyrus, ventral, and dorsal occipital cortex *APOE* $\varepsilon 4+$ *versus* $\varepsilon 4-$ Global GM reduction comparable (RH: 14 versus 15%; LH: 16 versus 17%) $\varepsilon 4+$ more atrophy in medial and lateral temporal lobes, and right occipital pole	After assessing the whole cortical mantle, greater susceptibility of the MTL area was found in *APOE* $\varepsilon 4$ carriers.
Filippini et al. 2009 [92]	Across *APOE* $\varepsilon 4$ $n = 100$	Volumetry whole brain	*Additive model* GM reduction in Bil MTL (HC, amygdala, parahippocampal gyrus), fusiform cortex, and orbitofrontal cortex *Genotypic model* Partially overlapping with additive, extending from posterior MTL to inferior lateral temporal cortex	Dose-dependent decrease in medial and anterior temporal lobe volume per allelic ($\varepsilon 4$) load. Variable regional association indicating that *APOE* works differently on mechanisms of disease expression.
Barber et al. 1999 [93]	AD across *APOE* $\varepsilon 4$ $n = 25$	Visual scoring MTL atrophy WM HI	No significant differences between $\varepsilon 4+$ and $\varepsilon 4-$ on MTL atrophy, WM HI	*APOE* does not modulate white and gray matter in AD. While *APOE* influences risk of AD it appears not to modulate pathological processes after diagnosis.
			TOMM40	
Potkin et al. 2009 [27]	AD ($n = 229$) Healthy Controls ($n = 194$)	Volumetry region-based GWAS on HC QT	Case-control analysis identified *APOE* and a new risk gene *TOMM40* at 10^{-6} (10^{-11} at a haplotype level between *APOE* & *TOMM40* rs11556505) 25 SNPs were associated with QT HC, including *APOE*	*APOE* has an effect on brain atrophy independent from overrepresentation in AD. A novel risk gene, *TOMM40*, was found to be associated with AD.
			Mild Cognitive Impairment	
			APOE	
Spampinato et al. 2011 [88]	Stable versus Progressive MCI ($n = 55$) across *APOE ($\varepsilon 4$)*	Volumetry whole brain Longitudinal	*Progressive APOE$\varepsilon 4+$* 1 year prior to diagnosis: GM atrophy in right temporal lobe, HC, insula 1 year FU: GM atrophy Bil HC, parietal, insula, caudate *Stable APOE$\varepsilon 4+$* 1 year FU GM atrophy Bil insula, temporal lobe	*APOE$\varepsilon 4+$* converters show early GM loss 1 year prior to diagnosis, and atrophy progresses in $\varepsilon 4+$ converters to AD. However, some MTL atrophy is present in *APOE* $\varepsilon 4+$ nonconverters, reflecting nonlinear effects of *APOE* $\varepsilon 4$.

Table 1: Continued.

Author	Population	Method	Structural integrity	Conclusion
He et al. 2009 [94]	MCI across *APOE* $n = 153$	Volumetry region based Cross-sectional	*Amnestic MCI* Significantly reduced HC volume	Amnestic MCI individuals are more likely to have MTL atrophy and to be carriers of an *APOE ε4* allele.
Tapiola et al. 2008 [48]	Stable versus Progressive MCI across *APOE* $n = 60$	Volumetry region based Longitudinal	*Progressive APOE ε4+* Reduced HC and ERC volume	While significant atrophy was seen within the MTL in *APOE ε4+* carriers with progressive MCI, the presence of an ε4 allele did not predict conversion to AD.
Hamalainen et al. 2008 [95]	Stable versus Progressive MCI ($n = 56$) across *APOE* (ε4)	Volumetry whole brain Longitudinal	*Progressive APOE ε4+* Atrophy left inferior frontal gyrus, intraparietal sulcus *Stable APOE ε4+* Atrophy right amygdala, anterior HC	*APOE ε4+* converters display global AD-like atrophy in frontal and parietal cortices in comparison to ε4−, 2.5 years prior to diagnosis of MCI.
Shen et al. 2010 [85]	*APOE* $n = 818$	Volumetry whole brain GWAS Freesurfer QT: 56 areas VBM QT: 86 areas	***APOE & TOMM40*** *APOE* rs 429358 (ε4 dependence) associated with whole brain Freesurfer (15 regions) and VBM (4) phenotypes at 10^{-6} significance *TOMM40* rs2075650 associated with Freesurfer (5) at 10^{-7} significance *Freesurfer phenotypes* *APOE* associated with widespread phenotypes *TOMM40* specifically associated with left and right hippocampi and left amygdala	While *APOE* is associated with widespread cortical AD-like changes, *TOMM40* appears to be associated mainly with MTL phenotypes. Both *APOE* and *TOMM40* were found among the top 5 SNPs in the GWAS.
			Normal Aging (only cross sectional)	
Ryan et al. 2011 [73]	*APOE* $n = 126$ Age range 52–92	DTI region based	***APOE*** Significant differences in ADC and FA with increasing age in frontal WM, lateral parietal WM, centrum semiovale, genu and splenium of CC, temporal stem WM These age-related differences in WM integrity were more prominent in ε4+	*APOE ε4* exacerbates age-related WM changes.
Zhang et al. 2011 [89]	*APOE* $n = 409$ Age range 70–90	Volumetry whole brain/region based	Reduced GM volume in left HC in *APOE ε4+* No significant differences in basal forebrain	Only left hippocampal volume was significantly reduced in *APOE ε4* carriers and no differences were observed in the basal forebrain area.
Espeseth et al. 2008 [86]	*APOE* ε4+ ($n = 37$) ε4− ($n = 59$) Age range 48–75	Volumetry whole brain	No group differences in total brain volume, GM volume, WM volume *Cortical thickness ε4+* Thicker cortex in bilateral occipital and occipito temporal areas, right parahippocampal gyrus and frontal areas	Thicker cortex in *APOE ε4+* was found in regions adjacent to those that show accelerated age-related decline, indicating that although well preserved now they may eventually show cortical thinning.
			Age related cortical thickness ε4+ Both ε4+ and ε4− have age-related thinning in occipital and insula, but ε4+ also show thinning of MTL	*APOE ε4* may accelerate thinning in areas that decline with aging (medial prefrontal, pericentral cortex) as well as areas susceptible to Aβ aggregation (occipitotemporal, temporal cortex).
Bartzokis et al. 2006 [96]	*APOE* $n = 104$ Age range 55–75	DTI region based	*APOE ε4+* showed steeper age-related decline in radial diffusivity in late myelinated regions frontal lobe and genu of the CC	Late myelinated frontal regions appear more susceptible to age-related breakdown in *APOE ε4+* carriers. This leads to progressive disconnection of cerebral networks in ε4 carriers and is supportive of an anterior-posterior WM degeneration gradient.

Table 1: Continued.

Author	Population	Method	Structural integrity	Conclusion
Persson et al. 2006 [97]	*APOE* $n = 60$ Age range 49–79	DTI region based	*APOE ε4+* show reduced FA in posterior CC, frontal fasciculus and HC	Supportive of previous findings of reduced FA in posterior CC, an area thought to be associated with AD pathology.
			TOMM40	
Johnson et al. 2010 [98]	*TOMM40* across *APOE ε3* $n = 117$ Age range 40–65	Volumetry whole brain	Dose-dependent increase in *TOMM40* poly-T length associated with reduced GM volume in ventral posterior cingulate and medial ventral precuneus	A subgroup of *APOE ε3* carriers with long poly-T length of the *TOMM40* gene show brain changes in areas associated with AD. This indicates independent influence of *TOMM40*.

ADC: Apparent diffusion coefficient; *APOE*: Apolipoprotein E; Bil: Bilateral; CC: Corpus Callosum; DTI: Diffusion Tensor Imaging; ERC: Entorhinal cortex; FA: Fractional Anisotropy; FU; Follow up; GWAS: Genome Wide Association Studies; GM: Gray matter; HC: Hippocampus; HI: Hyperintensities: LH: Left Hemisphere; MD: Mean Diffusivity; MTL: Medial Temporal Lobe; QT: Quantitative Trait; RH: Right hemisphere; SNP: Single Nucleotide Polymorphism (denoted rs); *TOMM40*: Translocase of outer mitochondrial membrane 40; WM: White matter.

accumulation of APP in import pores has been found in AD brains, mainly in the frontal cortex, HC, and amygdala and seen to vary with disease severity. Intriguingly, *APOE* ε3/ε4 carriers endorse the highest amount of mitochondrial APP, suggestive of a synergetic effect of mitochondrial dysfunction in the presence of *APOE* [39]. Furthermore, it has been shown that mitochondria have high intracellular Aβ accumulation in AD [114]. It has been pointed out that Aβ accumulation in mitochondria precedes extracellular Aβ deposition, which supports the role of mitochondria in the pathogenesis of AD [38]. Moreover, *TOMM40* has recently been associated with CSF biomarkers including $A\beta_{1-42}$, t-tau, and p-tau [115]. To this end, the mitochondrial cascade hypothesis is receiving increasing support throughout the literature, thereby demonstrating the implications of mitochondrial dynamics in the early pathophysiology of AD. The hypothesis postulates that mitochondrial dysfunction precedes amyloid insult to the brain and that mitochondrial injury is the primary source of pathology in AD [40, 116].

A recent neuropathological study, investigating the morphology of mitochondria in AD brains, confirmed the presence of mitochondrial pathology in brain areas typically associated with AD-type pathology [41]. Here mitochondrial alterations of shape and size were observed in AD, in comparison to healthy controls, in the neurons of the HC, neocortex, cerebellum, thalamus, pallidum, red nucleus, and locus coeruleus. As these assessments were conducted in postmortem AD brains, they more likely represent late pathophysiological changes in AD. However, these findings are suggestive of morphological changes in mitochondria, possibly acting causally in the pathogenesis of AD. While mitochondrial morphological changes were not limited to the HC [41], one would expect to see preclinical morphological changes in the MTL, based on previous findings of mitochondrial- induced oxidative stress in preclinical dementia [110] as well as findings of Aβ and mitochondrial interplay [114].

Further support for mitochondrial involvement in AD comes from genetic studies involving the *TOMM40* gene. Primarily Roses, and colleagues, the same group that discovered the influence of *APOE* on AD [28], have been able to demonstrate an association between a long poly-T repeat of the *TOMM40* gene with earlier age of onset of AD in *APOE* ε3 carriers [30]. The *TOMM40* poly-T length acts either dependently or independently of *APOE* in the pathophysiology of AD [117]. Moreover, studies focusing on Single-Nucleotide Polymorphisms (SNPs) have found an association between *TOMM40* and AD. A recent case-control study, comparing individuals with or without AD, showed a highly significant relationship between a *TOMM40* SNP (rs2075650) and AD. Interestingly, a haplotype of *TOMM40* rs2075650, rs11556505, and *APOE* rs429358 held a stronger association with AD than *TOMM40* rs2075650 alone [85], supporting Roses and colleagues findings of a synergetic effect of *TOMM40* and *APOE* [30]. Moreover, a recent genetic association study suggested that protein transport across the mitochondrial membrane was implicated in the pathophysiology of AD, and that *TOMM40* is a likely contributor to this detrimental transmembrane process within the mitochondria [118].

Although genetic studies on mitochondrial involvement in AD are in their initial stages and replications are warranted, findings are supportive of previous postmortem, animal, and pathological studies in AD suggesting a significant involvement of mitochondrial dysfunction in AD.

6. *TOMM40* and Structural Integrity

Postmortem studies on mitochondrial morphology in the HC [41] and the presence of APP in mitochondrial import pores in the HC of AD patients [39] suggest that mitochondrial dysfunction may follow Braak staging of neuropathology [8], with degeneration commencing in the MTL. By assessing the mitochondrial influence on brain integrity in AD, this temporal association can be further evaluated. Current cross-sectional studies, focusing on the differential influence of *TOMM40* polymorphisms on the brain, offer promising insight to this link between genes and neuropathology in AD.

Johnson and colleagues [98] assessed the influence of *TOMM40* poly-T length on structural brain integrity and cognition among *APOE* ε3 carriers. Analyses were restricted

to areas known to be vulnerable in AD including the amygdala, HC, parahippocampal gyrus, posterior cingulated, and precuneus. *APOE* ε3 carriers were divided according to length variations of the *TOMM40* polymorphisms, homozygous short (SS), homozygous very long (VL), and heterozygotes (S/VL). *TOMM40* length variation was found to influence episodic memory, which strongly depends on HC integrity, exemplifying the genetic involvement of *TOMM40* on AD-type cognitive deficits. On the brain level, the poly-T length seems to influence the integrity of the medial ventral precuneus and posterior cingulate [98], which have been shown to be the site of early amyloid burden in AD [55]. This confirms previous findings, where the influence of *TOMM40* poly-T length on AD onset has been shown [31] and supports the notion of mitochondrial influence in areas of the brain that are vulnerable to AD. Hence, it appears that healthy middle-aged individuals, who are *APOE* ε3 homozygotes with a long poly-T of the *TOMM40* gene, show an AD-like profile with regards to cognitive performance as well as structural brain changes.

GWAS with HC volume as the phenotype supported the influence of the *TOMM40* gene on structural integrity of areas implicated in AD. The authors found that three *TOMM40* risk alleles (rs157580, rs2075650, and rs11556505) were overrepresented in the AD population as assessed by case-control analysis [27]. Shortcomings of focusing on one region in the brain were overturned, and a recent GWAS used whole brain imaging phenotypes in an attempt to understand the association between *TOMM40* and structural integrity [85]. Notably, this analysis resulted in a significant association of the *TOMM40* gene (rs2075650) with left amygdala and bilateral HC volume. Furthermore, comparison of healthy versus AD individuals revealed that *TOMM40* was among the top 5 SNPs associated with whole brain imaging phenotypes. This points to the selective influence of *TOMM40* on structural integrity in brain areas vulnerable to AD and supports previous findings of high APP burden in mitochondrial import pores in the HC and amygdala [85].

In an effort to examine the influence of *TOMM40* in an independent cohort, we used data from nondemented individuals (age range: 60–90 years), from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K) [119]. We assessed the genetic influence of the *TOMM40* (rs2075650) gene on GM volume of the HC and episodic memory performance [120]. We expected to observe an *APOE*-independent negative influence of *TOMM40* G (risk allele) on both cognitive performance and volume. Based on previous studies where *APOE*-independent *TOMM40* influence was assessed [117], we stratified our *TOMM40* sample across *APOE*. While we found no independent effect of *TOMM40* on HC or ERC volume per se, we did observe that the positive association between HC volume and episodic memory was driven by the presence of at least one *TOMM40* G allele in *APOE* ε4 carriers. This finding indicates that carriers of a *TOMM40* G allele may be more dependent on HC volume for accurate episodic memory performance. This study suggests alterations within the mitochondrial system in *TOMM40* G allele carriers, perhaps resulting in early morphometric alterations in mitochondrial shape and size. These alterations are not influencing structure, but rather the function of the HC, as assessed by episodic memory performance. It is possible that we are observing functional alterations at an early stage that are not yet accompanied by significant volumetric changes in aging. As the timeline shifts to neurodegeneration, these functional changes may result in substantial structural changes, supported by postmortem findings of morphometric alterations in the mitochondria of the HC in AD [41]. Further support is provided by *TOMM40* influence on brain integrity and cognition that are vulnerable in MCI and AD, as well as the overrepresentation of *TOMM40* risk alleles in AD population [27, 98]. Functional changes within the HC might therefore be a primary sign of mitochondrial degeneration in preclinical AD.

Overall, the studies that are available today point to a selective influence of *TOMM40* polymorphisms on structural changes in AD vulnerable areas such as the HC, precuneus and posterior cingulate cortex. To our knowledge, no studies have been conducted on the genetic influence of *TOMM40* on WM changes in the brain. While the majority of findings concerning *TOMM40* implicate GM changes, recent findings from our laboratory suggest that mitochondrial dysfunction might influence hippocampal functioning as well, as assessed using cognitive testing. These findings are supportive of a prominent mitochondrial dysfunction in AD and are promising for the utilization of mitochondrial biomarkers for the accuracy of early detection of preclinical AD.

7. The Mitochondrial Disconnection Model

As an attempt to recapitulate and expand on findings in the field, we propose the mitochondrial disconnection model (see Figure 2). This model is an adapted representation of the mitochondrial cascade in AD, and its downstream influence on structural brain changes. We propose that this cascade has a primary influence on GM structural integrity of regions of the MTL, leading to disconnection and isolation of the MTL as a result of deterioration of connecting WM tracts.

In the adapted mitochondrial disconnection model *TOMM40* acts via *APOE*-independent and -dependent pathways [31, 117]. Via *APOE*-independent pathways, *TOMM40* regulates Aβ influx to the mitochondria via the Tom40 outer membrane pore. This notion is in line with postmortem studies that have found APP lodged in the Tom40 channels [39] as well as genetic studies suggesting that protein transport across the mitochondrial membrane, that is governed by the *TOMM40* gene, is implicated in the pathophysiology of AD [118]. Via *APOE*-dependent pathways, there may be an interaction between *APOE* and *TOMM40*, which in turn may influence the Aβ influx. *APOE* is essential in the clearance and deposition of Aβ [79, 121–123] and has also been shown to increase extracellular Aβ availability [39, 43]. This increase in *APOE*-induced Aβ availability may allow for a larger proportion of Aβ to flow into the mitochondria via Tom40 import pores [117]. *APOE* ε3/ε4 carriers have the highest amount of mitochondrial APP, resulting in impaired mitochondrial functioning, suggestive of the importance of

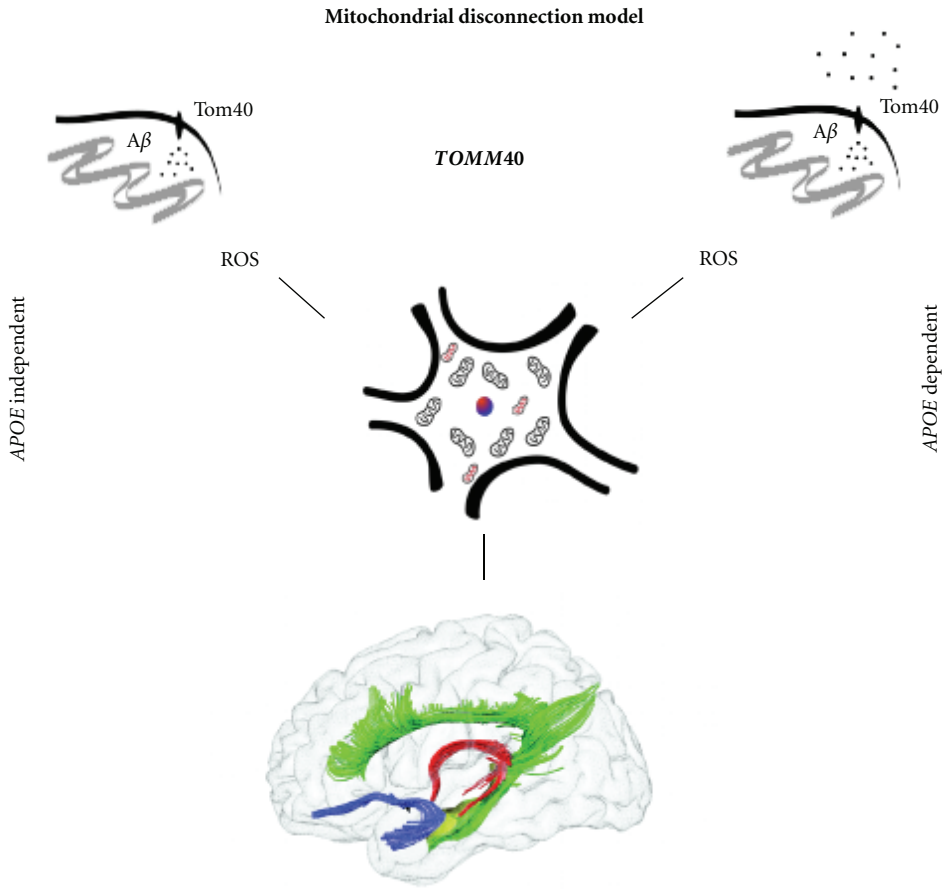

Figure 2: The mitochondrial disconnection model is an extension of the *TOMM40*-induced mitochondrial cascade in Alzheimer's disease (adapted from [31, 117]). *TOMM40* governs the Tom40 complex on the outer mitochondrial membrane, allowing the influx of amyloid beta (Aβ) into the organelle. *TOMM40* influence occurs either independently or dependently of *APOE*. Nevertheless, *TOMM40*-induced influx of Aβ to the cell starts downstream apoptotic processes via Reactive Oxygen Species (ROS), inducing cell death. We hypothesize that this results in early functional and structural alterations within the Medial Temporal Lobe (MTL), primarily in the hippocampus (yellow). Subsequent disconnection of the MTL, via deterioration of White Matter pathways such as the cingulum (green), fornix (red), and uncinate fasciculus (blue) follow. Disconnection of the MTL may induce secondary functional and structural alteration in distal areas possibly as a result of primary mitochondrial-induced cell death. (Brain graphic: courtesy of Michel Thiebaut de Schotten from the Natbrainlab, King's College, London, UK.).

mitochondrial dynamics, even in *APOE* $\varepsilon 3/\varepsilon 4$ carriers [39]. There is support in the literature for both *APOE*-independent and -dependent pathways. Moreover, the *TOMM40*-induced mitochondrial cascade is unlikely to be autonomous of *APOE*, considering that *APOE* and *TOMM40* are genetically linked via LD. Nevertheless, we propose that even in the *APOE*-dependent pathway, the role of *TOMM40* is primary, as it influences mitochondrial protein transport via the Tom40 import pore.

Irrespective of the pathway through which the mitochondrial cascade commences, the flow of Aβ into the organelle induces apoptotic processes. The latter functions by increasing ROS within the mitochondria and has detrimental effects on cell survival within the MTL. As neurons contain hundreds of mitochondria, apoptotic processes may occur in a gradient fashion and might not influence neuronal structure initially. Morphometric changes have been seen in the mitochondria of the HC in AD, but these take place in the later stages of the disorder [41]. It is possible that early *TOMM40*-induced mitochondrial changes likely influence HC function, rather than its volume, evidenced by the triad between *TOMM40*, HC volume, and episodic memory in our aforementioned ongoing study [120]. This points to the importance of combining genetic, structural, and cognitive biomarkers to assess preclinical AD, as structural brain changes alone might not be sufficient for early and accurate prediction of preclinical mitochondrial alterations in AD. We suggest that functional changes in the HC, as a result of early mitochondrial alterations, could be utilized as an additional biomarker for preclinical AD. A timeline of mitochondrial degeneration commencing with early functional changes followed by structural changes within the brain can be hypothesized.

Nevertheless, initial *TOMM40*-governed mitochondrial insult has been found to take place in the HC [85]. Based on previous findings that disconnection and isolation of the HC

plays an important role in the early pathophysiology of AD [59–61], we hypothesize that WM changes of directly HC-connected WM tracts including the fornix, cingulum, and uncinate fasciculus follow in the mitochondrial cascade (see Figure 2). Whether this occurs via primary Wallerian degeneration or balanced retrogenesis remains to be elucidated. WM changes have been shown to be both primary and secondary to GM alterations in AD. The balance between primary or secondary WM degeneration within a certain region may be dependent on the gradient of mitochondrial dysfunction within that area. This balance might not be the same throughout the brain, as mitochondrial dysfunction has been primarily observed in MTL structures such as the HC and amygdala [39]. Future longitudinal studies will have to discern the temporal order of events and whether WM changes in preclinical AD are dependent on mitochondrial dysfunction in the GM. Overall, a succession of mitochondrial dysfunctional events in the pathophysiology of AD is supported not only by our ongoing study, but also by studies showing mitochondrial damage in normal aging [124, 125]. The degree of how widespread mitochondrial injury is in the brain may be determined by the neurodegenerative status of the individual and may follow Braak staging of pathology. That would explain why we observe *TOMM40*-induced influence on structural integrity of areas implicated in the early stages of AD. Based on these findings, we propose that widespread GM atrophy, seen in the later stages of AD, results from mitochondria-induced MTL disconnection via corticolimbic pathways. Disconnection of the MTL may induce secondary functional and structural alteration in distal areas [61].

The proposed model is a representation of mitochondria-induced disconnection as an early and accurate biomarker for preclinical AD (see Figure 1). By this we expand on Jack and colleagues [23] dynamic biomarker timeline and propose that mitochondrial dysfunction initiates the pathophysiological cascade in AD. Findings in support of this timeline include the selective influence of *TOMM40* on AD onset, HC volume, and cognition over and beyond that of *APOE* alone [27, 31, 85]. Moreover, mitochondrial Aβ aggregation precedes extracellular Aβ aggregation [38] supporting the mitochondrial cascade hypothesis rather than the amyloid cascade hypothesis, as the primary event in the biomarker timeline of AD. However, Jack and colleagues [23] pointed out that Aβ depositions are also observed in asymptomatic individuals, suggesting that the amyloid pathological process might be part of the process of aging. While amyloid depositions precede the clinical outcome of AD, the high presence of Aβ in healthy individuals suggests that other factors are at play. Moreover, the amyloid cascade does not fall into line with the Braak staging of pathology, where tau pathology was proposed to precede amyloid aggregation and commence within more basal midbrain structures [6, 7]. It has been shown that both tau and amyloid have synergic effects on mitochondrial dysfunction [126], suggesting that a biomarker timeline based on mitochondrial pathology might be more accurate in AD and would reconcile with Braak staging of pathology that has been well supported by neuroimaging studies.

8. Conclusion

There is increasing evidence for a primary mitochondrial involvement in the pathophysiology of AD, as mitochondria have been found to regulate cell death. Several studies have highlighted the importance of altered mitochondrial dynamics in the preclinical stages of AD, as well as mitochondrial involvement in structural brain changes within the MTL. Perhaps more importantly, mitochondrial dysfunction appears to be primary to extracellular Aβ aggregation. These findings demonstrate the necessity to direct attention away from the amyloid cascade hypothesis towards the mitochondrial cascade hypothesis. Moreover *TOMM40* should be considered as a possible genetic modifier of the biomarker timeline in AD. The distinction between amyloid and mitochondrial cascades is not arbitrary with consideration to potential biomarkers and treatments of AD. While "mitochondrial protectors" as a potential treatment for AD are currently under investigation [116], further studies are needed in order to assess mitochondrial dynamics in preclinical AD. Genetic polymorphisms such as *TOMM40* have the potential not only to assess individuals at risk, but also to serve as biomarkers in combination with current known structural and cognitive ones. We propose the mitochondrial disconnection model as a means by which the mitochondrial dynamics can be assessed in preclinical AD.

Glossary

Allele:	One of two versions of a gene, an allele is a DNA coding that occupies a position on a given chromosome.
Amyloid cascade hypothesis:	Proposes that the primary pathogenic event in AD is alterations in Amyloid Precursor Protein (APP) leading to the aggregation of the amyloid beta (Aβ) peptide.
Diffusion tensor imaging (DTI):	Imaging acquisition that generates three-dimensional representation of the degree and direction of water diffusion (Brownian motion) in each voxel (tensor). Images are derived from computing 3 eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) within each tensor.
Fractional anisotropy (FA):	DTI measure derived from the ratio of eigenvalues in each voxel, providing information about the directionality of diffusion along a scale of 0 (isotropic diffusion) to 1 (anisotropic diffusion) where 0 represents completely random diffusion indicative of damaged along white matter fibers.
Freesurfer:	Software allowing assessment of volumetric and cortical thickness measures of the brain.
Genomewide association study (GWAS):	Study by which the whole genome within a population is assessed in an attempt to identify common genetic associations with diseases such as AD.

Linkage disequilibrium (LD):	Defines a genetic region that has had minimal recombination through ancestral history, making genes within such regions linked and dependent of each other.
Mean Diffusivity (MD):	A DTI measure derived from the mean of the three eigenvalues that reflects magnitude of water diffusion within a voxel, without providing directionality. Increased MD is an indicator of tissue degeneration.
Missing heritability:	The notion that a large proportion of the heritability of complex diseases such as AD remains unknown. Current GWAS have been able to identify genes with small effect sizes, leading us to ask where in the genome the remaining heritability is contained and why we cannot observe them with current techniques.
Mitochondria:	Are often referred to as the powerhouse of the cells, as they produce adenosine triphosphate (ATP), the main energy source of the cell. Mitochondria have an outer and inner membrane, with the outer being permeable via active import channels allowing the passage of proteins that are essential for ATP. Mitochondria are mainly independent organelles, as they contain their own DNA. While they are the major energy provider to the cells, they are also critical for cell survival, cell division, and neuronal death.
Mitochondrial cascade hypothesis:	Proposes that mitochondria are the primary source of pathology in AD, driving Aβ plaque and neurofibrillary tangle formation.
Radial diffusion:	Radial diffusivity ($\lambda_2 + \lambda_3$) represents perpendicular diffusion across fiber pathways. Reduced radial diffusion has been associated with myelin damage.
Reactive oxygen species (ROS):	A term that describes a variety of byproducts that are formed during the metabolism of oxygen, otherwise known as free radicals. In mitochondria they are formed as a result of respiration, and a disruption in this balance by increased ROS within mitochondria negatively influences cell survival.
Region of interest (ROI):	Imaging procedure that involves manual outlining of an a priori brain region for volumetric analysis.
Retrogenesis:	The hypothesis that brain areas that were early to develop are also the first to show AD-type pathology.
Single nucleotide polymorphism (SNP):	Stands for a difference in DNA sequence, occurring at a single nucleotide (A, T, C, or G) on a paired chromosome in an individual and denoted by RS (related sequence).
Translocase of outer mitochondrial membrane (TOM):	A major import channel on the outer mitochondrial membrane that allows for the influx of proteins to the intermembrane space of the organelle. Tom40 is the main component of this channel serving as the only channel by which proteins enter mitochondria.
Voxel Based Morphometry (VBM):	Automatic procedure that allows whole-brain voxelwise analysis of tissue density and volume.
Wallerian Degeneration:	Is a model for axonal degeneration. Initial neuronal damage is hypothesized to result in distal axonal degeneration.

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References

[1] L. E. Hebert, P. A. Scherr, J. L. Bienias, D. A. Bennett, and D. A. Evans, "Alzheimer disease in the US population: prevalence estimates using the 2000 census," *Archives of Neurology*, vol. 60, no. 8, pp. 1119–1122, 2003.

[2] R. C. Petersen, R. Doody, A. Kurz et al., "Current concepts in mild cognitive impairment," *Archives of Neurology*, vol. 58, no. 12, pp. 1985–1992, 2001.

[3] C. Qiu, M. Kivipelto, H. Aguero-Torres, B. Winblad, and L. Fratiglioni, "Risk and protective effects of the APOE gene towards Alzheimer's disease in the Kungsholmen project: variation by age and sex," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 75, no. 6, pp. 828–833, 2004.

[4] R. C. Petersen, "Clinical trials for early (pre-dementia) Alzheimer's disease: a case for mild cognitive impairment," *The Journal of Nutrition, Health and Aging*, vol. 14, no. 4, pp. 304–305, 2010.

[5] J. W. Anderson and M. Schmitter-Edgecombe, "Mild cognitive impairment and feeling-of-knowing in episodic memory," *Journal of Clinical and Experimental Neuropsychology*, vol. 32, no. 5, pp. 505–514, 2010.

[6] L. T. Grinberg, U. Rub, R. E. Ferretti et al., "The dorsal raphe nucleus shows phospho-tau neurofibrillary changes before the transentorhinal region in Alzheimer's disease. A precocious onset?" *Neuropathology and Applied Neurobiology*, vol. 35, no. 4, pp. 406–416, 2009.

[7] H. Braak and K. Del Tredici, "The pathological process underlying Alzheimer's disease in individuals under thirty," *Acta Neuropathologica*, vol. 121, no. 2, pp. 171–181, 2011.

[8] D. K. Johnson, W. Barrow, R. Anderson et al., "Diagnostic utility of cerebral white matter integrity in early Alzheimer's disease," *International Journal of Neuroscience*, vol. 120, no. 8, pp. 544–550, 2010.

[9] A. T. Du, N. Schuff, X. P. Zhu et al., "Atrophy rates of entorhinal cortex in AD and normal aging," *Neurology*, vol. 60, no. 3, pp. 481–486, 2003.

[10] H. Braak and E. Braak, "Neuropathological stageing of Alzheimer-related changes," *Acta Neuropathologica*, vol. 82, no. 4, pp. 239–259, 1991.

[11] N. Raz and K. M. Rodrigue, "Differential aging of the brain: patterns, cognitive correlates and modifiers," *Neuroscience and Biobehavioral Reviews*, vol. 30, no. 6, pp. 730–748, 2006.

[12] L. Serra, M. Cercignani, D. Lenzi et al., "Grey and white matter changes at different stages of Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 19, no. 1, pp. 147–159, 2010.

[13] C. Pennanen, M. Kivipelto, S. Tuomainen et al., "Hippocampus and entorhinal cortex in mild cognitive impairment and early AD," *Neurobiology of Aging*, vol. 25, no. 3, pp. 303–310, 2004.

[14] G. Bartzokis, J. L. Cummings, D. Sultzer, V. W. Henderson, K. H. Nuechterlein, and J. Mintz, "White matter structural integrity in healthy aging adults and patients with Alzheimer disease: a magnetic resonance imaging study," *Archives of Neurology*, vol. 60, no. 3, pp. 393–398, 2003.

[15] P. M. Thompson, M. S. Mega, R. P. Woods et al., "Cortical change in Alzheimer's disease detected with a disease-specific population-based brain atlas," *Cerebral Cortex*, vol. 11, no. 1, pp. 1–16, 2001.

[16] L. O'Dwyer, F. Lamberton, A. L. Bokde et al., "Using diffusion tensor imaging and mixed-effects models to investigate primary and secondary white matter degeneration in Alzheimer's disease and mild cognitive impairment," *Journal of Alzheimer's Disease*, vol. 26, no. 4, pp. 667–682, 2011.

[17] C. E. Sexton, U. G. Kalu, N. Filippini, C. E. Mackay, and K. P. Ebmeier, "A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease," *Neurobiology of Aging*, vol. 32, no. 12, pp. 2322.e5–2322.e18, 2011.

[18] C. Flicker, S. H. Ferris, and B. Reisberg, "Mild cognitive impairment in the elderly: predictors of dementia," *Neurology*, vol. 41, no. 7, pp. 1006–1009, 1991.

[19] R. C. Petersen, G. E. Smith, S. C. Waring, R. J. Ivnik, E. G. Tangalos, and E. Kokmen, "Mild cognitive impairment: clinical characterization and outcome," *Archives of Neurology*, vol. 56, no. 3, pp. 303–308, 1999.

[20] R. C. Petersen, R. O. Roberts, D. S. Knopman et al., "Mild cognitive impairment: ten years later," *Archives of Neurology*, vol. 66, no. 12, pp. 1447–1455, 2009.

[21] S. Gauthier, B. Reisberg, M. Zaudig et al., "Mild cognitive impairment," *Lancet*, vol. 367, no. 9518, pp. 1262–1270, 2006.

[22] B. Dubois and M. L. Albert, "Amnestic MCI or prodromal Alzheimer's disease?" *Lancet Neurology*, vol. 3, no. 4, pp. 246–248, 2004.

[23] C. R. Jack, D. S. Knopman, W. J. Jagust et al., "Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade," *The Lancet Neurology*, vol. 9, no. 1, pp. 119–128, 2010.

[24] M. Tondelli, G. K. Wilcock, P. Nichelli, C. A. De Jager, M. Jenkinson, and G. Zamboni, "Structural MRI changes detectable up to ten years before clinical Alzheimer's disease," *Neurobiology of Aging*, vol. 33, no. 4, pp. e825–e836, 2012.

[25] L. Bäckman, S. Jones, A. K. Berger, E. J. Laukka, and B. J. Small, "Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis," *Neuropsychology*, vol. 19, no. 4, pp. 520–531, 2005.

[26] J. L. Stein, X. Hua, J. H. Morra et al., "Genome-wide analysis reveals novel genes influencing temporal lobe structure with relevance to neurodegeneration in Alzheimer's disease," *NeuroImage*, vol. 51, no. 2, pp. 542–554, 2010.

[27] S. G. Potkin, G. Guffanti, A. Lakatos et al., "Hippocampal atrophy as a quantitative trait in a genome-wide association study identifying novel susceptibility genes for Alzheimer's Disease," *PLoS One*, vol. 4, no. 8, article e6501, 2009.

[28] A. D. Roses, "On the discovery of the genetic association of apolipoprotein E genotypes and common late-onset Alzheimer disease," *Journal of Alzheimer's Disease*, vol. 9, no. 3, pp. 361–366, 2006.

[29] M. Pievani, S. Galluzzi, P. M. Thompson, P. E. Rasser, M. Bonetti, and G. B. Frisoni, "APOE4 is associated with greater atrophy of the hippocampal formation in Alzheimer's disease," *NeuroImage*, vol. 55, no. 3, pp. 909–919, 2011.

[30] A. D. Roses, M. W. Lutz, H. Amrine-Madsen et al., "A TOMM40 variable-length polymorphism predicts the age of late-onset Alzheimer's disease," *Pharmacogenomics Journal*, vol. 10, no. 5, pp. 375–384, 2010.

[31] A. D. Roses, "An inherited variable poly-T repeat genotype in TOMM40 in Alzheimer disease," *Archives of Neurology*, vol. 67, no. 5, pp. 536–541, 2010.

[32] H. Li, S. Wetten, L. Li et al., "Candidate single-nucleotide polymorphisms from a genomewide association study of Alzheimer disease," *Archives of Neurology*, vol. 65, no. 1, pp. 45–53, 2008.

[33] R. Abraham, V. Moskvina, R. Sims et al., "A genome-wide association study for late-onset Alzheimer's disease using DNA pooling," *Biomedcentral Medical Genomics*, vol. 1, article 44, 2008.

[34] A. Grupe, R. Abraham, Y. Li et al., "Evidence for novel susceptibility genes for late-onset Alzheimer's disease from a genome-wide association study of putative functional variants," *Human Molecular Genetics*, vol. 16, no. 8, pp. 865–873, 2007.

[35] D. Harold, R. Abraham, P. Hollingworth et al., "Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease," *Nature Genetics*, vol. 41, no. 10, pp. 1088–1093, 2009.

[36] T. M. Feulner, S. M. Laws, P. Friedrich et al., "Examination of the current top candidate genes for AD in a genome-wide association study," *Molecular Psychiatry*, vol. 15, no. 7, pp. 756–766, 2010.

[37] C. E. Yu, H. Seltman, E. R. Peskind et al., "Comprehensive analysis of APOE and selected proximate markers for late-onset Alzheimer's disease: patterns of linkage disequilibrium and disease/marker association," *Genomics*, vol. 89, no. 6, pp. 655–665, 2007.

[38] M. Mancuso, V. Calsolaro, D. Orsucci et al., "Mitochondria, cognitive impairment, and Alzheimer's disease," *International Journal of Alzheimer's Disease*, vol. 2009, Article ID 951548, 8 pages, 2009.

[39] L. Devi, B. M. Prabhu, D. F. Galati, N. G. Avadhani, and H. K. Anandatheerthavarada, "Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction," *Journal of Neuroscience*, vol. 26, no. 35, pp. 9057–9068, 2006.

[40] R. H. Swerdlow, "Brain aging, Alzheimer's disease, and mitochondria," *Biochimica et Biophysica Acta*, vol. 1812, no. 12, pp. 1630–1639, 2011.

[41] S. J. Baloyannis, "Mitochondria are related to synaptic pathology in Alzheimer's disease," *International Journal of Alzheimer's Disease*, vol. 2011, Article ID 305395, 7 pages, 2011.

[42] N. L. Pedersen, S. F. Posner, and M. Gatz, "Multiple-threshold models for genetic influences on age of onset for Alzheimer disease: findings in swedish twins," *American Journal of Medical Genetics - Neuropsychiatric Genetics*, vol. 105, no. 8, pp. 724–728, 2001.

[43] R. W. Mahley, K. H. Weisgraber, and Y. Huang, "Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 15, pp. 5644–5651, 2006.

[44] L. Bäckman, "Memory and cognition in preclinical dementia: what we know and what we do not know," *Canadian Journal of Psychiatry*, vol. 53, no. 6, pp. 354–360, 2008.

[45] G. B. Karas, P. Scheltens, S. A. Rombouts et al., "Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease," *NeuroImage*, vol. 23, no. 2, pp. 708–716, 2004.

[46] C. D. Smith, H. Chebrolu, D. R. Wekstein et al., "Brain structural alterations before mild cognitive impairment," *Neurology*, vol. 68, no. 16, pp. 1268–1273, 2007.

[47] A. M. Fjell, K. B. Walhovd, C. Fennema-Notestine et al., "CSF biomarkers in prediction of cerebral and clinical change in mild cognitive impairment and Alzheimer's disease," *Journal of Neuroscience*, vol. 30, no. 6, pp. 2088–2101, 2010.

[48] T. Tapiola, C. Pennanen, M. Tapiola et al., "MRI of hippocampus and entorhinal cortex in mild cognitive impairment: a follow-up study," *Neurobiology of Aging*, vol. 29, no. 1, pp. 31–38, 2008.

[49] T. R. Stoub, M. Bulgakova, S. Leurgans et al., "MRI predictors of risk of incident Alzheimer disease: a longitudinal study," *Neurology*, vol. 64, no. 9, pp. 1520–1524, 2005.

[50] T. R. Stoub, L. deToledo-Morrell, G. T. Stebbins, S. Leurgans, D. A. Bennett, and R. C. Shah, "Hippocampal disconnection contributes to memory dysfunction in individuals at risk for Alzheimer's disease," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 26, pp. 10041–10045, 2006.

[51] G. Chételat, M. Fouquet, G. Kalpouzos et al., "Three-dimensional surface mapping of hippocampal atrophy progression from MCI to AD and over normal aging as assessed using voxel-based morphometry," *Neuropsychologia*, vol. 46, no. 6, pp. 1721–1731, 2008.

[52] T. R. Stoub, E. J. Rogalski, S. Leurgans, D. A. Bennett, and L. deToledo-Morrell, "Rate of entorhinal and hippocampal atrophy in incipient and mild AD: relation to memory function," *Neurobiology of Aging*, vol. 31, no. 7, pp. 1089–1098, 2010.

[53] I. Driscoll, C. Davatzikos, Y. An et al., "Longitudinal pattern of regional brain volume change differentiates normal aging from MCI," *Neurology*, vol. 72, no. 22, pp. 1906–1913, 2009.

[54] G. Chételat, B. Desgranges, B. Landeau et al., "Direct voxel-based comparison between grey matter hypometabolism and atrophy in Alzheimer's disease," *Brain*, vol. 131, no. 1, pp. 60–71, 2008.

[55] R. L. Buckner, A. Z. Snyder, B. J. Shannon et al., "Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory," *Journal of Neuroscience*, vol. 25, no. 34, pp. 7709–7717, 2005.

[56] A. M. Fjell, I. K. Amlien, L. T. Westlye et al., "CSF biomarker pathology correlates with a medial temporo-parietal network affected by very mild to moderate Alzheimer's disease but not a fronto-striatal network affected by healthy aging," *NeuroImage*, vol. 49, no. 2, pp. 1820–1830, 2010.

[57] G. Karas, J. Sluimer, R. Goekoop et al., "Amnestic mild cognitive impairment: structural MR imaging findings predictive of conversion to Alzheimer disease," *American Journal of Neuroradiology*, vol. 29, no. 5, pp. 944–949, 2008.

[58] A. M. Hogan, F. Vargha-Khadem, D. E. Saunders, F. J. Kirkham, and T. Baldeweg, "Impact of frontal white matter lesions on performance monitoring: ERP evidence for cortical disconnection," *Brain*, vol. 129, no. 8, pp. 2177–2188, 2006.

[59] D. H. Salat, D. S. Tuch, A. J. van der Kouwe et al., "White matter pathology isolates the hippocampal formation in Alzheimer's disease," *Neurobiology of Aging*, vol. 31, no. 2, pp. 244–256, 2010.

[60] P. Kalus, J. Slotboom, J. Gallinat et al., "Examining the gateway to the limbic system with diffusion tensor imaging: the perforant pathway in dementia," *NeuroImage*, vol. 30, no. 3, pp. 713–720, 2006.

[61] N. Villain, M. Fouquet, J. C. Baron et al., "Sequential relationships between grey matter and white matter atrophy and brain metabolic abnormalities in early Alzheimer's disease," *Brain*, vol. 133, no. 11, pp. 3301–3314, 2010.

[62] D. H. Salat, D. N. Greve, J. L. Pacheco et al., "Regional white matter volume differences in nondemented aging and Alzheimer's disease," *NeuroImage*, vol. 44, no. 4, pp. 1247–1258, 2009.

[63] M. P. Witter, "The perforant path: projections from the entorhinal cortex to the dentate gyrus," *Progress in Brain Research*, vol. 163, pp. 43–61, 2007.

[64] B. Reisberg, E. H. Franssen, S. M. Hasan et al., "Retrogenesis: clinical, physiologic, and pathologic mechanisms in brain aging, Alzheimer's and other dementing processes," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 249, no. 3, pp. 28–36, 1999.

[65] K. A. Frazer, S. S. Murray, N. J. Schork, and E. J. Topol, "Human genetic variation and its contribution to complex traits," *Nature Reviews Genetics*, vol. 10, no. 4, pp. 241–251, 2009.

[66] M. Gatz, C. A. Reynolds, L. Fratiglioni et al., "Role of genes and environments for explaining Alzheimer disease," *Archives of General Psychiatry*, vol. 63, no. 2, pp. 168–174, 2006.

[67] W. J. Strittmatter, A. M. Saunders, D. Schmechel et al., "Apolipoprotein E: high-avidity binding to β-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 90, no. 5, pp. 1977–1981, 1993.

[68] A. Saunders, M. K. Trowers, R. A. Shimkets et al., "The role of apolipoprotein E in Alzheimer's disease: pharmacogenomic target selection," *Biochimica et Biophysica Acta*, vol. 1502, no. 1, pp. 85–94, 2000.

[69] L. A. Farrer, L. A. Cupples, J. L. Haines et al., "Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis," *Journal of the American Medical Association*, vol. 278, no. 16, pp. 1349–1356, 1997.

[70] G. Bartzokis, "Acetylcholinesterase inhibitors may improve myelin integrity," *Biological Psychiatry*, vol. 62, no. 4, pp. 294–301, 2007.

[71] S. M. Hofer, H. Christensen, A. J. Mackinnon et al., "Change in cognitive functioning associated with ApoE genotype in a community sample of older adults," *Psychology of Aging*, vol. 17, no. 2, pp. 194–208, 2002.

[72] L. G. Nilsson, R. Adolfsson, L. Bäckman et al., "The influence of APOE status on episodic and semantic memory: data from a population-based study," *Neuropsychology*, vol. 20, no. 6, pp. 645–657, 2006.

[73] L. Ryan, K. Walther, B. B. Bendlin, L. F. Lue, D. G. Walker, and E. L. Glisky, "Age-related differences in white matter integrity and cognitive function are related to APOE status," *NeuroImage*, vol. 54, no. 2, pp. 1565–1577, 2011.

[74] B. J. Small, C. B. Rosnick, L. Fratiglioni, and L. Bäckman, "Apolipoprotein E and cognitive performance: a meta-analysis," *Psychology and Aging*, vol. 19, no. 4, pp. 592–600, 2004.

[75] G. M. McKhann, D. S. Knopman, H. Chertkow et al., "The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimer's and Dementia*, vol. 7, no. 3, pp. 263–269, 2011.

[76] R. Mayeux, A. M. Saunders, S. Shea et al., "Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease," *The New England Journal of Medicine*, vol. 338, no. 8, pp. 506–511, 1998.

[77] L. S. Elias-Sonnenschein, W. Viechtbauer, I. H. Ramakers, F. R. J. Verhey, and P. J. Visser, "Predictive value of APOE-ε4 allele for progression from MCI to AD-type dementia: a meta-analysis," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 82, no. 10, pp. 1149–1156, 2011.

[78] L. Jones, D. Harold, and J. Williams, "Genetic evidence for the involvement of lipid metabolism in Alzheimer's disease," *Biochimica et Biophysica Acta*, vol. 1801, no. 8, pp. 754–761, 2010.

[79] V. Hirsch-Reinshagen, B. L. Burgess, and C. L. Wellington, "Why lipids are important for Alzheimer disease?" *Molecular and Cellular Biochemistry*, vol. 326, no. 1, pp. 121–129, 2009.

[80] J. Hardy and D. Allsop, "Amyloid deposition as the central event in the aetiology of Alzheimer's disease," *Trends in Pharmacological Sciences*, vol. 12, no. 10, pp. 383–388, 1991.

[81] J. Poirier, "Apoliprotein E in animal models of CNS injury and in Alzheimer's disease," *Trends in Neurosciences*, vol. 17, no. 12, pp. 525–530, 1994.

[82] J. Poirier, "Apolipoprotein E and Alzheimer's disease. A role in amyloid catabolism," *Annals of the New York Academy of Sciences*, vol. 924, pp. 81–90, 2000.

[83] R. H. Swerdlow and S. M. Khan, "A "mitochondrial cascade hypothesis" for sporadic Alzheimer's disease," *Medical Hypotheses*, vol. 63, no. 1, pp. 8–20, 2004.

[84] R. J. Castellani, H. Lee, S. L. Siedlak et al., "Reexamining Alzheimer's disease: evidence for a protective role for amyloid-β protein precursor and amyloid-β," *Journal of Alzheimer's Disease*, vol. 18, no. 2, pp. 447–452, 2009.

[85] L. Shen, S. Kim, S. L. Risacher et al., "Whole genome association study of brain-wide imaging phenotypes for identifying quantitative trait loci in MCI and AD: a study of the ADNI cohort," *NeuroImage*, vol. 53, no. 3, pp. 1051–1063, 2010.

[86] T. Espeseth, L. T. Westlye, A. M. Fjell, K. B. Walhovd, H. Rootwelt, and I. Reinvang, "Accelerated age-related cortical thinning in healthy carriers of apolipoprotein E ε 4," *Neurobiology of Aging*, vol. 29, no. 3, pp. 329–340, 2008.

[87] D. Zhang, Y. Wang, L. Zhou, H. Yuan, and D. Shen, "Multimodal classification of Alzheimer's disease and mild cognitive impairment," *NeuroImage*, vol. 53, no. 3, pp. 856–867, 2011.

[88] M. Spampinato, Z. Rumboldt, R. J. Hosker, and J. E. Mintzer, "Apolipoprotein E and gray matter volume loss in patients with mild cognitive impairment and Alzheimer disease," *Radiology*, vol. 258, no. 3, pp. 843–852, 2011.

[89] H. Zhang, J. N. Trollor, W. Wen et al., "Grey matter atrophy of basal forebrain and hippocampus in mild cognitive impairment," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 82, no. 5, pp. 487–493, 2011.

[90] B. B. Bendlin, M. L. Ries, E. Canu et al., "White matter is altered with parental family history of Alzheimer's disease," *Developmental Neuropsychology*, vol. 35, no. 3, pp. 257–277, 2010.

[91] M. Pievani, P. E. Rasser, S. Galluzzi et al., "Mapping the effect of APOE ε 4 on gray matter loss in Alzheimer's disease in vivo," *NeuroImage*, vol. 45, no. 4, pp. 1090–1098, 2009.

[92] N. Filippini, A. Rao, S. Wetten et al., "Anatomically-distinct genetic associations of APOE ε4 allele load with regional cortical atrophy in Alzheimer's disease," *NeuroImage*, vol. 44, no. 3, pp. 724–728, 2009.

[93] R. Barber, A. Gholkar, P. Scheltens et al., "Apolipoprotein E ε 4 allele, temporal lobe atrophy, and white matter lesions in late-life dementias," *Archives of Neurology*, vol. 56, no. 8, pp. 961–965, 1999.

[94] J. He, S. Farias, O. Martinez, B. Reed, D. Mungas, and C. DeCarli, "Differences in brain volume, hippocampal volume, cerebrovascular risk factors, and apolipoprotein E4 among mild cognitive impairment subtypes," *Archives of Neurology*, vol. 66, no. 11, pp. 1393–1399, 2009.

[95] A. Hamalainen, M. Grau-Olivares, S. Tervo et al., "Apolipoprotein E ε 4 allele is associated with increased atrophy in progressive mild cognitive impairment: a voxel-based morphometric study," *Neurodegenerative Diseases*, vol. 5, no. 3-4, pp. 186–189, 2008.

[96] G. Bartzokis, P. H. Lu, D. H. Geschwind, N. Edwards, J. Mintz, and J. L. Cummings, "Apolipoprotein E genotype and age-related myelin breakdown in healthy individuals: implications for cognitive decline and dementia," *Archives of General Psychiatry*, vol. 63, no. 1, pp. 63–72, 2006.

[97] J. Persson, J. Lind, A. Larsson et al., "Altered brain white matter integrity in healthy carriers of the APOE ε 4 allele: a risk for AD?" *Neurology*, vol. 66, no. 7, pp. 1029–1033, 2006.

[98] S. C. Johnson, A. La Rue, B. P. Hermann et al., "The effect of TOMM40 poly-T length on gray matter volume and cognition in middle-aged persons with APOE epsilon3/epsilon3 genotype," *Alzheimer's & Dementia*, vol. 7, no. 4, pp. 456–465, 2011.

[99] R. Schmidt, H. Schmidt, J. Haybaeck et al., "Heterogeneity in age-related white matter changes," *Acta Neuropathologica*, vol. 122, no. 2, pp. 171–185, 2011.

[100] L. Bertram, M. B. McQueen, K. Mullin, D. Blacker, and R. E. Tanzi, "Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database," *Nature Genetics*, vol. 39, no. 1, pp. 17–23, 2007.

[101] W. Huang, C. Qiu, E. Von Strauss, B. Winblad, and L. Fratiglioni, "APOE genotype, family history of dementia, and Alzheimer disease risk: a 6-year follow-up study," *Archives of Neurology*, vol. 61, no. 12, pp. 1930–1934, 2004.

[102] J. Yang, B. Benyamin, B. P. McEvoy et al., "Common SNPs explain a large proportion of the heritability for human height," *Nature Genetics*, vol. 42, no. 7, pp. 565–569, 2010.

[103] T. B. Kirkwood, H. J. Cordell, and C. E. Finch, "Speed-bumps ahead for the genetics of later-life diseases," *Trends in Genetics*, vol. 27, no. 10, pp. 387–388, 2011.

[104] E. E. Eichler, J. Flint, G. Gibson et al., "Missing heritability and strategies for finding the underlying causes of complex disease," *Nature Reviews Genetics*, vol. 11, no. 6, pp. 446–450, 2010.

[105] M. T. Lin and M. F. Beal, "Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases," *Nature*, vol. 443, no. 7113, pp. 787–795, 2006.

[106] M. Mancuso, V. Calsolaro, D. Orsucci, G. Siciliano, and L. Murri, "Is there a primary role of the mitochondrial genome in Alzheimer's disease?" *Journal of Bioenergetics and Biomembranes*, vol. 41, no. 5, pp. 411–416, 2009.

[107] H. M. McBride, M. Neuspiel, and S. Wasiak, "Mitochondria: more than just a powerhouse," *Current Biology*, vol. 16, no. 14, pp. 551–560, 2006.

[108] A. Trifunovic, A. Wredenberg, M. Falkenberg et al., "Premature ageing in mice expressing defective mitochondrial DNA polymerase," *Nature*, vol. 429, no. 6990, pp. 417–423, 2004.

[109] R. H. Swerdlow and S. J. Kish, "Mitochondria in Alzheimer's disease," *International Review of Neurobiology*, vol. 53, pp. 341–385, 2002.

[110] R. Sultana and D. A. Butterfield, "Oxidatively modified, mitochondria-relevant brain proteins in subjects with Alzheimer disease and mild cognitive impairment," *Journal of Bioenergetics and Biomembranes*, vol. 41, no. 5, pp. 441–446, 2009.

[111] P. H. Reddy, "Amyloid beta, mitochondrial structural and functional dynamics in Alzheimer's disease," *Experimental Neurology*, vol. 218, no. 2, pp. 286–292, 2009.

[112] I. E. Scheffler, *Mitochondria*, John Wiley & Sons, Hoboken, NJ, USA, 2nd edition, 2008.

[113] A. D. Humphries, I. C. Streimann, D. Stojanovski et al., "Dissection of the mitochondrial import and assembly pathway for human Tom40," *Journal of Biological Chemistry*, vol. 280, no. 12, pp. 11535–11543, 2005.

[114] M. Manczak, T. S. Anekonda, E. Henson, B. S. Park, J. Quinn, and P. H. Reddy, "Mitochondria are a direct site of A β accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression," *Human Molecular Genetics*, vol. 15, no. 9, pp. 1437–1449, 2006.

[115] S. Kim, S. Swaminathan, L. Shen et al., "Genome-wide association study of CSF biomarkers A β1-42, t-τ, and p-τ181p in the ADNI cohort," *Neurology*, vol. 76, no. 1, pp. 69–79, 2011.

[116] M. Ankarcrona, F. Mangialasche, and B. Winblad, "Rethinking Alzheimer's disease therapy: are mitochondria the key?" *Journal of Alzheimer's Disease*, vol. 20, no. suppl.2, pp. S579–S590, 2010.

[117] L. Osherovich, "TOMMorrow's AD marke," *Science-Business eXchange*, vol. 2, no. 30, 1165 pages, 2009.

[118] M. G. Hong, A. Alexeyenko, J. C. Lambert, P. Amouyel, and J. A. Prince, "Genome-wide pathway analysis implicates intracellular transmembrane protein transport in Alzheimer disease," *Journal of Human Genetics*, vol. 55, no. 10, pp. 707–709, 2010.

[119] M. Lagergren, L. Fratiglioni, I. R. Hallberg et al., "A longitudinal study integrating population, care and social services data. The swedish national study on aging and care (SNAC)," *Aging and Clinical Experimental Research*, vol. 16, no. 2, pp. 158–168, 2004.

[120] B. Ferencz, S. Karlsson, G. Kalpouzos et al., "Differential influence of APOE TOMM40 on brain integrity and congnition: implications for biomarker potentialin Alzheimer's disease," in preparation.

[121] W. J. Strittmatter, K. H. Weisgraber, D. Y. Huang et al., "Binding of human apolipoprotein E to synthetic amyloid β peptide: isoform-specific effects and implications for late-onset Alzheimer disease," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 90, no. 17, pp. 8098–8102, 1993.

[122] D. A. Sanan, K. H. Weisgraber, S. J. Russell et al., "Apolipoprotein E associates with β amyloid peptide of Alzheimer's disease to form novel monofibrils. Isoform ApoE4 associates more efficiently than ApoE3," *Journal of Clinical Investigation*, vol. 94, no. 2, pp. 860–869, 1994.

[123] S. Ye, Y. Huang, K. Mullendorff et al., "Apolipoprotein (apo) E4 enhances amyloid β peptide production in cultured neuronal cells: ApoE structure as a potential therapeutic target," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 51, pp. 18700–18705, 2005.

[124] J. Miquel, A. C. Economos, J. Fleming, and J. E. Johnson, "Mitochondrial role in cell aging," *Experimental Gerontology*, vol. 15, no. 6, pp. 575–591, 1980.

[125] H. V. Remmen and A. Richardson, "Oxidative damage to mitochondria and aging," *Experimental Gerontology*, vol. 36, no. 7, pp. 957–968, 2001.

[126] A. Eckert, K. Schmitt, and J. Gotz, "Mitochondrial dysfunction - the beginning of the end in Alzheimer's disease? Separate and synergistic modes of tau and amyloid-beta toxicity," *Alzheimer's Research and Therapy*, vol. 3, no. 2, p. 15, 2011.

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Clinical Study

Risk and Determinants of Dementia in Patients with Mild Cognitive Impairment and Brain Subcortical Vascular Changes: A Study of Clinical, Neuroimaging, and Biological Markers—The VMCI-Tuscany Study: Rationale, Design, and Methodology

Anna Poggesi,[1] Emilia Salvadori,[1] Leonardo Pantoni,[1] Giovanni Pracucci,[1] Francesca Cesari,[2] Alberto Chiti,[3] Laura Ciolli,[1] Mirco Cosottini,[3] Alessandra Del Bene,[1] Nicola De Stefano,[4] Stefano Diciotti,[5] Maria Teresa Dotti,[4] Andrea Ginestroni,[5] Betti Giusti,[2] Anna Maria Gori,[2] Serena Nannucci,[1] Giovanni Orlandi,[3] Francesca Pescini,[1] Raffaella Valenti,[1] Rosanna Abbate,[2] Antonio Federico,[4] Mario Mascalchi,[5] Luigi Murri,[3] and Domenico Inzitari[1]

[1] *Department of Neurological and Psychiatric Sciences, University of Florence, Largo Brambilla 3, 50134 Florence, Italy*
[2] *Department of Medical and Surgical Critical Care, University of Florence, 50134 Florence, Italy*
[3] *Department of Neurosciences, University of Pisa, 56126 Pisa, Italy*
[4] *Department of Neurological and Behavioral Sciences, University of Siena, 53100 Siena, Italy*
[5] *Radiodiagnostic Section, Department of Clinical Physiopathology, University of Florence, 50134 Florence, Italy*

Correspondence should be addressed to Domenico Inzitari, inzitari@unifi.it

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Dementia is one of the most disabling conditions. Alzheimer's disease and vascular dementia (VaD) are the most frequent causes. Subcortical VaD is consequent to deep-brain small vessel disease (SVD) and is the most frequent form of VaD. Its pathological hallmarks are ischemic white matter changes and lacunar infarcts. Degenerative and vascular changes often coexist, but mechanisms of interaction are incompletely understood. The term mild cognitive impairment defines a transitional state between normal ageing and dementia. Pre-dementia stages of VaD are also acknowledged (vascular mild cognitive impairment, VMCI). Progression relates mostly to the subcortical VaD type, but determinants of such transition are unknown. Variability of phenotypic expression is not fully explained by severity grade of lesions, as depicted by conventional MRI that is not sensitive to microstructural and metabolic alterations. Advanced neuroimaging techniques seem able to achieve this. Beside hypoperfusion, blood-brain-barrier dysfunction has been also demonstrated in subcortical VaD. The aim of the Vascular Mild Cognitive Impairment Tuscany Study is to expand knowledge about determinants of transition from mild cognitive impairment to dementia in patients with cerebral SVD. This paper summarizes the main aims and methodological aspects of this multicenter, ongoing, observational study enrolling patients affected by VMCI with SVD.

1. Introduction

Dementia is one of the most disabling conditions affecting older people. The most frequent cause is Alzheimer's disease (AD) which is attributed to brain cortex degeneration. In Italy one-third of dementia cases are due to vascular dementia (VaD), a term that encompasses a few subtypes, among which subcortical VaD consequent to deep brain small vessel disease (SVD) is the most frequent [1]. Its pathological hallmarks are ischemic white matter changes, caused by hypoperfusion and lacunar infarcts [2]. These changes can progress over time silently, a profile similar to that occurring in AD. In the old brain degenerative and vascular changes may often coexist and possibly interact.

However, the exact mechanisms of such interaction are still incompletely understood [3]. Data suggest that vascular factors play a role also in AD [4]. How they contribute to both dementia types is a relevant issue, as they can be treated, favorably altering the progression of cognitive decline. In the neurovascular unit, vessels and cells, including neurons, closely interact, pointing to endothelial dysfunction as a key element for explaining neuronal damage associated with both subcortical VaD and AD.

The term mild cognitive impairment (MCI) defines a transitional state between normal ageing and dementia and is thought to anticipate dementia [5]. Subjects with MCI, compared to those without, progress to AD at a rate ten times greater [6]. Pre-dementia stages of VaD are also acknowledged: this condition is referred to as vascular mild cognitive impairment (VMCI) [7]. In the Canadian Health and Aging Study 46% of patients with VMCI developed dementia after 5 years [8]. Progression relates mostly to the subcortical VaD type. The determinants of this transition are not fully elucidated: it is not clear whether it is mainly driven by vascular, degenerative processes, or by their interaction. The increase in white matter changes and the accumulation of small infarcts proved to be associated with the cognitive decline [7]. Data show that brain atrophy is also associated with cognitive deterioration [9].

Phenotypic expression of subcortical VaD is variable. Variability is not fully explained by severity grade of lesions, as depicted by conventional MRI. This seems not enough sensitive in differentiating axonal loss and glia damage from intact structures. Furthermore, it does not provide pathophysiological details about changes ongoing in both parenchyma and vessels. Advanced techniques such as magnetization transfer, diffusion, and spectroscopy seem able to yield more in-depth information about the extent of tissue damage, its microstructural nature, and the underlying metabolic alterations [10]. Beside hypoperfusion, blood brain-barrier dysfunction has been also demonstrated in subcortical VaD [11, 12]. Since many factors associated with subcortical VaD are treatable, it seems of the utmost importance to expand the knowledge about determinants and mechanisms underlying the transition from VMCI to dementia. Estimating the relative weight of the predictive effect for each significant determinant (among the clinical, functional, imaging, and biological potential markers) of the transition may allow to evaluate the risk of dementia and to describe the risk-factor profile in individual patients with subcortical MCI, thus favoring tailored and appropriate preventive strategies.

During the last 10 years many clinical and functional outcomes in elderly patients with subcortical vascular changes have been investigated through a European multicenter collaboration called LADIS (leukoaraiosis and disability) Study [13]. The LADIS study, supported by the European Union, has been carried out in 11 European high-quality centers, coordinated by the Department of Neurological and Psychiatric Sciences of the University of Florence. Concerning the main study outcome, that is, transition to disability, results have shown that the risk of transition or death was more than twofold higher in patients with severe white matter changes compared to those with mild degrees [14]. Some vascular risk factors also predicted the transition. A review summarizing the LADIS main results has recently been published [15]. White matter changes also had an effect on cognitive decline and dementia. Cross-sectional baseline data analysis indicated that white matter changes and medial temporal lobe atrophy were independently associated with cognitive impairment [9]. At multivariable analysis, risk factors and the conventional MRI features were able to explain only part of the prediction of either disability or dementia [16]. It was thus decided to perform a new study, the VMCI-Tuscany Study, with the main aims of: (1) estimating the net and multivariable effect in predicting the transition from VMCI to dementia studying a large set of both conventional and nonconventional clinical, neuroimaging, and biological markers of SVD; (2) assessing the vascular and degenerative components in the determination of such transition, that is, their relative contribution and their possible interaction; (3) generating from the results of the multivariable predictive model a diagnostic algorithm able to determine the risk of transition in individual patients with VMCI with SVD.

2. Methods

The VMCI-Tuscany Study foresees the collaboration of the three university hospital centers in Tuscany: Florence, Pisa, and Siena (Department of Neurological and Psychiatric Sciences, University of Florence, Unit of Neurology and Neurophysiopathology, Azienda Ospedaliero-Universitaria Pisana, and Unit of Neurology and Neurometabolic Diseases, Azienda Universitaria Ospedaliera Senese) where the enrolment and assessment of patients with VMCI and SVD is actually ongoing. In order to reach the prespecified number of patients in the foreseen time period, the project has been promoted at all the regional, both neurological and geriatric, hospital units (Figure 2).

2.1. Inclusion Criteria. To be included, patients have to be classified as affected by VMCI with SVD according to the following criteria: (1) MCI defined according to Winblad et al. criteria [17], and (2) evidence on MRI of subcortical vascular lesions of moderate to severe degrees of white matter changes (WMC), according to the modified version of the Fazekas scale [13] (Figure 1). Each patient gives a written informed consent, and the study has been approved by local ethical committees.

2.2. Exclusion Criteria. Exclusion criteria are inability or refusal to undergo cerebral MRI, and inability to give an informed consent.

Sample size was estimated based on data about transition to dementia obtained in the LADIS Study. In the LADIS sample, patients with baseline mild cognitive impairment and moderate to severe WMC, had an annual rate of transition to dementia of 10%. Three hundred patients were considered the minimal number necessary to carry out multivariate analyses of potential predictors of transition to dementia.

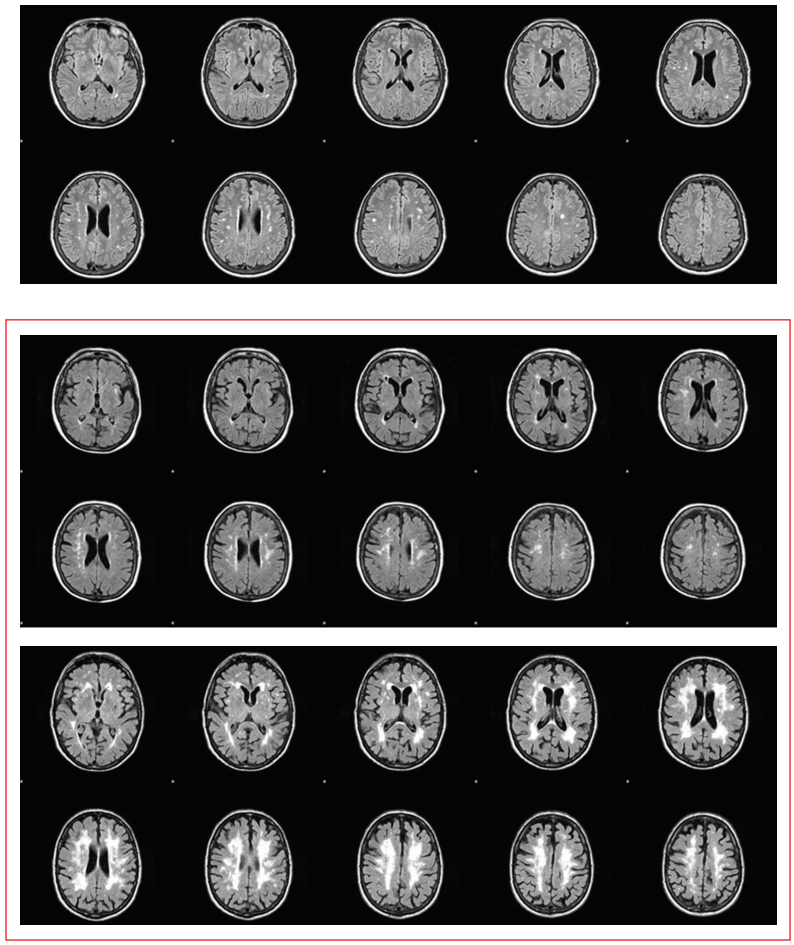

Figure 1: Cerebral white matter changes: examples of mild, moderate, and severe groups according to the modified Fazekas' scale. Only patients with moderate or severe degrees were included in the study.

2.2.1. Baseline Assessment. According to the study protocol, each patient enrolled undergoes an extensive clinical assessment and an MRI examination and permits the collection of blood samples for the determination of plasma biomarkers. Tables 1, 2, and 3 summarize main objectives and instruments for the clinical, neuroimaging, and laboratory assessments, respectively.

2.3. Clinical Assessment (Table 1). Social background and medical history are collected according to a structured and comprehensive questionnaire administered to the patient by trained personnel. This includes information on demographic characteristics, education (expressed as years of schooling), occupational status, longest job in life, marital status, living conditions, lifestyle habits (alcohol consumption, smoking, physical activity), and vascular risk factors. Furthermore, patients are specifically asked if they experience gait, memory, visual, or hearing problems, or bladder disturbances. Several other age-related comorbidities are assessed with the aim of controlling for their effect on the main study outcome. All possible medical information and records were collected and reviewed during the interview in order to reach or confirm the diagnosis of the diseases under investigation. If needed, contact with the family doctor can also be undertaken. All conditions were defined according to the currently most widely accepted criteria, selected after a systematic literature search. The whole set of criteria is reported in a specifically developed manual and distributed to all participating centers. Information is also collected about thyroid diseases, head injuries, falls in the last year. Data on family history of migraine, epilepsy, psychiatric disturbances, stroke, dementia, venous thrombosis, diabetes mellitus, hypertension, and hyperlipidemias are also recorded. Currently used drugs are registered in a structured way.

Blood pressure, weight, and height measurements are recorded, and a standard neurological examination is performed. The absence or presence of the following neurological examination abnormalities is assessed: upper motor neuron signs, extrapyramidal signs, cerebellar signs, cortical signs (language deficits and/or visual field abnormalities), pseudobulbar signs (hypophonia and/or dysphagia and/or dysarthria), and primitive reflexes (one or more of the following: grasp reflex, palmomental reflex, forced laughing and crying, snout reflex, glabellar tapping). Speed of finger taps (patient taps thumb with index finger in rapid succession

Figure 2: List of participating centers and personnel in the VMCI-Tuscany. *University of Florence*: (Coordinating Center): Domenico Inzitari (study coordinator), Rosanna Abbate, Manuela Bandinelli, Maria Boddi, Francesca Cesari, Laura Ciolli, Mirella Coppo, Alessandra Del Bene, Stefano Diciotti, Andrea Ginestroni, Betti Giusti, Anna Maria Gori, Mario Mascalchi, Serena Nannucci, Leonardo Pantoni, Marco Pasi, Francesca Pescini, Anna Poggesi, Giovanni Pracucci, Emilia Salvadori, Raffaella Valenti. *University of Pisa*: Luigi Murri, Ubaldo Bonucelli, Paolo Cecchi, Alberto Chiti, Mirco Cosottini, Giovanni Orlandi, Cristina Pagni, Gabriele Siciliano, Gloria Tognoni. *University of Siena*: Antonio Federico, Nicola De Stefano, Maria Teresa Dotti, Patrizia Formichi, Claudia Gambetti, Antonio Giorgio, Francesca Rossi, Laura Stromillo, Enza Zicari. *Tuscany region: Arezzo* (Paolo Zolo, Alessandro Tiezzi); *Empoli* (Elisabetta Bertini, Stefania Brotini, Leonello Guidi, Maria Lombardi, Stefania Mugnai, Antonella Notarelli); *Florence* (Laura Bracco, Massimo Cadelo, Renzo Cisbani, Luciano Gabbani, Guido Gori, Lorella Lambertucci, Luca Massacesi, Enrico Mossello, Marco Paganini, Maristella Piccininni, Francesco Pinto, Claudia Pozzi, Sandro Sorbi, Gaetano Zaccara); *Grosseto* (Tiziano Borgogni, Mario Mancuso, Roberto Marconi); *Lucca* (Monica Mazzoni, Marco Vista); *Livorno* (Giuseppe Meucci, Giovanna Bellini); *Massa Carrara* (Luciano Gabrielli); *Pisa* (Cristina Frittelli, Renato Galli, Gianna Gambaccini); *Pistoia* (Stefano Bartolini, Carlo Biagini, Veronica Caleri, Paola Vanni); *Prato* (Donatella Calvani, Carla Giorgi, Stefano Magnolfi, Pasquale Palumbo, Carlo Valente); *Siena* (Alessandro Rossi, Rossana Tassi, Stefania Boschi); *Viareggio* (Filippo Baldacci; Ubaldo Bonuccelli).

with widest amplitude possible) is assessed for each hand separately and scored as normal, mild slowing, moderately impaired, severely impaired, or barely able to perform the task (range 1 to 5). Gait and stance are coded as normal or abnormal. Concerning motor function, a standardized assessment is performed by means of the short physical performance battery (SPPB), and two additional simple measures of gait and balance, that is, gait velocity and single leg stance time, as already used in the LADIS study [18–20, 34].

Each patient is assessed by means of an extensive neuropsychological evaluation according to the specifically developed test battery. How the neuropsychological test battery was developed and the way it allows automation and standardization of the scoring procedures will be reported in a separate paper. In brief, the cognitive functions assessed include global mental functioning, orientation, memory, attention, executive functions, language, speed and motor control. The tests used are reported in Table 1 [21–30]. The geriatric depression scale (GDS) is used for the assessment of mood [31]. Functional status is measured by means of the activities of daily living scale and the instrumental activities of daily living scale [32, 33]: these 2 scales are addressed to the patient's caregiver, given the longitudinal design of the study and the possible transition to dementia of the patient.

In order to increase consistency and homogeneity in the assessments, all investigators participated to at least one training session and were provided with a specifically developed handbook with guidelines for the correct use of criteria and tools.

Table 1: Instruments for patients' assessment in the VMCI-Tuscany study protocol.

	Instruments/methods	References
Clinical assessment	Social background and medical history according to structured protocol	—
	Standard cardiovascular and neurological examination according to structured protocol	—
Motor performances	Short physical performance battery (SPPB)	[18]
	Single leg stance	[19]
	Gait velocity	[20]
Cognitive performances	Mini mental state examination (MMSE)	[21]
	Montreal cognitive assessment battery (MoCA)	[22]
	Rey auditory-verbal learning test	[23]
	Trail making test (A and B)	[24]
	Color word stroop test	[25]
	Symbol digit modalities test	[26]
	Visual search	[27]
	Phonemic and semantic fluency	[28]
	Rey-Osterrieth complex figure	[29]
	Short story recall test	[30]
Mood	Geriatric depression scale (GDS-15)	[31]
Global functioning	Activities of daily living (ADL) scale	[32]
	Instrumental activities of daily living (IADL) scale	[33]

2.4. MRI Examination (Table 2). Patients are examined on clinical 1.5 T system (Intera, Philips Medical System, Best,

Table 2: MRI protocol in the VMCI-Tuscany Study.

Sequences
(i) Axial high-resolution contiguous 3D T1-weighted images with isotropic voxels (MPRAGE sequence)
(ii) Axial T2-weighted images (FLAIR sequence)
(iii) Diffusion tensor imaging (DTI)
(iv) Functional MRI (motor or cognitive tasks)
(v) T2*-sensitive echo-planar imaging (EPI) sequence

Table 3: Plasma biomarkers under investigation in the VMCI-Tuscany Study.

Markers of endothelial function	von Willebrand factor, tissue factor, tissue factor pathway inhibitor, intercellular adhesion molecule-1 and count of the number of circulating endothelial progenitor cells by cytofluorimetric method using monoclonal antibodies anti-staminal cells markers (CD34 and AC133) and anti-endothelial cell markers (VEGFR2)
Polymorphisms associated with cerebral small vessels disease	Genes coding metalloproteases and their inhibitors, renin-angiotensin system components, genes coding endothelial nitroxide synthase
Pro- and anti-inflammatory molecules	interleukin-6, interleukin-1-RA, interleukin-8, interleukin-10, interleukin-18, and C-reactive protein

The Netherlands) with 33 mT/m gradients capability and a head coil with SENSE technology. After scout, the examination protocol includes a sagittal T1 weighted 3D T1-weighted turbo gradient echo sequence (repetition time (TR) = 8.1 ms, echo time (TE) = 3.7 ms, flip angle = 8°, inversion time (TI) = 764 ms, field of view (FOV) = 256 mm, matrix size = 256 × 256, 160 contiguous slices, slice thickness = 1 mm) axial FLAIR sequence (TR = 11000 ms, TE = 140 ms, inversion time (TI) = 2800 ms, FOV = 230 mm, matrix size = 320 × 216, contiguous slices, slice thickness = 5 mm), and axial single-shot echo planar imaging sequence (TR = 9394 ms, TE = 89 ms, FOV = 256 mm, matrix size = 128 × 128, 50 slices, slice thickness = 3 mm, no gap, NEX = 3; diffusion sensitizing gradients applied along 15 non-collinear directions using b value of 0 (b0 image) and 1000 s/mm^2) for DTI. A T2* weighted echo planar imaging sequence is used for the functional MRI. Details of such experiments are reported elsewhere.

2.5. Laboratory Analyses (Table 3). Tests for plasma biomarkers will be performed centrally, in Florence, Center for Thrombosis, after the collection of blood samples of all recruited patients will be completed. Laboratory investigations will then include the determination of those plasma biomarkers which, according to literature review, have been found to be associated with white matter changes. At the moment, the possible set of plasma biomarkers is composed of markers of endothelial function, polymorphisms associated with cerebral small vessels disease, and pro- and anti-inflammatory molecules (see Table 3 for details).

2.5.1. Follow-Up Assessment. The longitudinal design of the VMCI-Tuscany study encompass a clinical, functional, and neuropsychological assessment, according to the main study protocol already used at baseline, performed yearly after enrollment, for two years consecutively. The MRI assessment is performed at baseline and then repeated after two years, at the end of the study. This second MRI is planned with the aim of evaluating possible progression of both vascular and nonvascular lesions and of studying this progression in correlation with the evolution of clinical/functional deficits and the onset of dementia.

2.6. Outcome Measures. The main study outcomes will be the diagnosis of dementia and the occurrence of cognitive decline. Dementia diagnosis will be made according to DSM-IV criteria [35]. The diagnosis of vascular dementia will be made according to specific criteria [36]; the diagnosis of the main subtypes of vascular dementia will be performed for consensus according to clinical and neuroimaging characteristics. AD diagnosis will be performed according to the clinical research criteria [37]. Staging of dementia severity will be performed according to clinical dementia rating scale [38]. Cognitive decline will be evaluated as a decrease in the compound scores for each cognitive domain.

2.7. Data Management. Data collected in each center is entered into an electronic database on a specifically developed website (http://www.vmci-tuscany.it/). This allows the systematic and rapid control of completeness and online quality of data in real time.

3. Results

The study began on October 15, 2010. The first four months of the study have been dedicated to the preparation of all the study instruments and training of the participating personnel. During this first phase, the definitive project protocol has been established and shared by all the investigators, and the homogeneity of the clinical-functional and MRI sequences parameters have been tested across the three centres and investigators. The dedicated website for communications, storage of study instruments, and database for data collection has been created and is operative (http://www.vmci-tuscany.it/).

On February 15, 2011, the enrollment of patients was started. Up to now, eight months after the beginning of the study, 76 patients with moderate to severe WMC have been evaluated according to the entire study protocol. Mean age is 75.2 ± 7.4, 47 (62%) are males, and mean education, expressed as years of schooling, is 7.5 ± 3.9. Mean MMSE score is 26.6 ± 2.7, and mean MoCA score is 19.6 ± 5.0.

The end of the enrollment is scheduled for the end of 2012.

4. Discussion

The VMCI-Tuscany Study is one of the first longitudinal studies assessing determinants of the transition from a stage of mild cognitive impairment to dementia. For the first time the study will focus on a particular form of cerebrovascular disease as a cause of cognitive decline, that is, cerebral small vessel disease. Up to now, the study protocol showed a good feasibility and applicability in patients with VMCI and SVD. The first aim of the study is to investigate a large set clinical, neuroimaging, and biological markers of cerebral small vessel disease in predicting the transition from a stage of mild cognitive impairment to dementia. Secondly, the study will permit the assessment of the relative contribution, and possible interaction, of vascular and degenerative components in the determination of such transition. Last, but not least, final results of the multivariable predictive model will enable the generation a diagnostic algorithm able to determine the risk of transition to dementia in individual patients with VMCI and SVD.

Data from the literature show that the clinical and functional status in subjects with the same grade of WMC may be variable, suggesting the presence of "hidden" factors in determining the clinical picture [39]. Despite the known role of SVD in the determination of cognitive impairment, its net weight remains to be appreciated. For example it is known that some patients with similar visible SVD burden have different clinical outcomes, hinting at the presence of additional, uncovered aspects that may contribute to this transition. This uncovered aspect may relate to the same pathogenic process (SVD) but be undetected under routine assessment (e.g., conventional MRI) and instead be detected by new techniques [39]. The morphological alterations identified on conventional neuroimaging do not appear sufficient to explain the clinical-functional phenotype which is frequently variable for typology and severity also in presence of overlapping neuroimaging findings. A number of studies have investigated the association between white matter lesions extension, evaluated by means of visual scales or volume measurements, and functional, cognitive or motor disturbances, sometimes with inconsistent results. A limitation of these studies is that the signal alterations on conventional neuroimaging may be due to different degrees of parenchymal damage, from more or less severe axonal loss to a glia damage with intact nervous fibers. Conventional morphological neuroimaging is not able to provide details about pathophysiological processes within the cerebral parenchyma and vessels. Preliminary studies using advanced neuroimaging techniques such as magnetization transfer, diffusion, and spectroscopy have suggested the possibility to acquire more in-depth information about the microstructural tissue damage and underlying metabolic alterations and the association with the cognitive performances evaluating both white matter lesions revealed by conventional neuroimaging and normal-appearing white matter. However, such data have been obtained from small cross-sectional studies and without considering the influence of other frequently coexisting lesions such as lacunar infarcts and cortical atrophy.

Knowledge about determinants of the transition to dementia in patients with VMCI and SVD is essential to the identification of potential preventive and therapeutic targets, contributing to reduce the burden (on both the ethical and economical grounds) of disability in the elderly. This represents one of the greatest challenges for social and health systems in our ageing society. Moreover, results from the project may provide both health systems and professionals with a validated instrument (i.e., a diagnostic algorithm generated from the multivariable prediction models) for estimating the risk of transition to dementia in individual patients tailoring the appropriate preventive and therapeutic strategy. Finally, the multivariable prediction of the risk of cognitive decline and dementia in this population may represent an essential methodological background for designing and sample-sizing-controlled clinical trials in the selective clinical setting.

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References

[1] A. Di Carlo, M. Baldereschi, L. Amaducci et al., "Incidence of dementia, Alzheimer's disease, and vascular dementia in Italy. The ILSA study," *Journal of the American Geriatrics Society*, vol. 50, no. 1, pp. 41–48, 2002.

[2] L. Pantoni, "Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges," *The Lancet Neurology*, vol. 9, no. 7, pp. 689–701, 2010.

[3] K. M. Langa, N. L. Foster, and E. B. Larson, "Mixed dementia: emerging concepts and therapeutic implications," *Journal of the American Medical Association*, vol. 292, no. 23, pp. 2901–2908, 2004.

[4] J. C. de la Torre, "Cerebrovascular and cardiovascular pathology in Alzheimer's disease," *International Review of Neurobiology*, vol. 84, pp. 35–48, 2009.

[5] S. Gauthier, B. Reisberg, M. Zaudig et al., "International psychogeriatric association expert conference on mild cognitive impairment: mild cognitive impairment," *The Lancet*, vol. 367, pp. 1262–1270, 2006.

[6] B. C. Stephan, F. E. Matthews, K. T. Khaw, C. Dufouil, and C. Brayne, "Beyond mild cognitive impairment: vascular cognitive impairment, no dementia (VCIND)," *Alzheimer's Research & Therapy*, vol. 1, pp. 4–12, 2009.

[7] L. Pantoni, A. Poggesi, and D. Inzitari, "Cognitive decline and dementia related to cerebrovascular diseases: some evidence and concepts," *Cerebrovascular Diseases*, vol. 27, supplement 1, pp. 191–196, 2009.

[8] C. Wentzel, K. Rockwood, C. MacKnight et al., "Progression of impairment in patients with vascular cognitive impairment without dementia," *Neurology*, vol. 57, no. 4, pp. 714–716, 2001.

[9] W. M. van der Flier, E. C.W. van Straaten, F. Barkhof et al., "Medial temporal lobe atrophy and white matter hyperintensities are associated with mild cognitive deficits in non-disabled elderly people: the LADIS study," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 76, no. 11, pp. 1497–1500, 2005.

[10] C. Di Perri, T. O. Dalaker, M. K. Beyer, and R. Zivadinov, "Neuroimaging of cognitive impairments in vascular disease," *International Review of Neurobiology*, vol. 84, pp. 49–80, 2009.

[11] R. A. Charlton, F. Schiavone, T. R. Barrick, R. G. Morris, and H. S. Markus, "Diffusion tensor imaging detects age related white matter change over a 2 year follow-up which is associated with working memory decline," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 81, no. 1, pp. 13–19, 2010.

[12] G. Zuliani, M. Cavalieri, M. Galvani et al., "Markers of endothelial dysfunction in older subjects with late onset Alzheimer's disease or vascular dementia," *Journal of the Neurological Sciences*, vol. 272, no. 1-2, pp. 164–170, 2008.

[13] L. Pantoni, A. M. Basile, G. Pracucci et al., "Impact of age-related cerebral white matter changes on the transition to disability—the LADIS study: rationale, design and methodology," *Neuroepidemiology*, vol. 24, no. 1-2, pp. 51–62, 2005.

[14] D. Inzitari, G. Pracucci, A. Poggesi et al., "Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort," *British Medical Journal*, vol. 339, Article ID b2477, 2009.

[15] The LADIS Study Group, "2001–2011: a decade of the LADIS (leukoaraiosis and DISability) study: what have we learned about white matter changes and small-vessel disease?" *Cerebrovascular Diseases*, vol. 32, no. 6, pp. 577–588, 2011.

[16] A. Verdelho, S. Madureira, C. Moleiro et al., "White matter changes and diabetes predict cognitive decline in the elderly: the LADIS Study," *Neurology*, vol. 75, no. 2, pp. 160–167, 2010.

[17] B. Winblad, K. Palmer, M. Kivipelto et al., "Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment," *Journal of Internal Medicine*, vol. 256, no. 3, pp. 240–246, 2004.

[18] J. M. Guralnik, E. M. Simonsick, L. Ferrucci et al., "A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission," *Journals of Gerontology*, vol. 49, no. 2, pp. M85–M94, 1994.

[19] J. M. Guralnik, L. Ferrucci, E. M. Simonsick, M. E. Salive, and R. B. Wallace, "Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability," *The New England Journal of Medicine*, vol. 332, no. 9, pp. 556–561, 1995.

[20] C. R. G. Guttmann, R. Benson, S. K. Warfield et al., "White matter abnormalities in mobility-impaired older persons," *Neurology*, vol. 54, no. 6, pp. 1277–1283, 2000.

[21] M. F. Folstein, S. E. Folstein, and P. R. McHugh, "'Mini mental state'. A practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[22] Z. S. Nasreddine, N. A. Phillips, V. Bédirian et al., "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment," *Journal of the American Geriatrics Society*, vol. 53, no. 4, pp. 695–699, 2005.

[23] G. A. Carlesimo, C. Caltagirone, and G. Gainotti, "The mental deterioration battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment," *European Neurology*, vol. 36, no. 6, pp. 378–384, 1996.

[24] A. R. Giovagnoli, M. Del Pesce, S. Mascheroni, M. Simoncelli, M. Laiacona, and E. Capitani, "Trail making test: normative values from 287 normal adult controls," *Italian Journal of Neurological Sciences*, vol. 17, no. 4, pp. 305–309, 1996.

[25] P. Caffarra, G. Vezzadini, F. Dieci, F. Zonato, and A. Venneri, "A short version of the Stroop test: normative data in an Italian population sample," *Nuova Rivista di Neurologia*, vol. 12, no. 4, pp. 111–115, 2002.

[26] U. Nocentini, A. Giordano, S. Di Vincenzo, M. Panella, and P. Pasqualetti, "The symbol digit modalities test—oral version: italian normative data," *Functional Neurology*, vol. 21, no. 2, pp. 93–96, 2006.

[27] S. Della Sala, M. Laiacona, H. Spinnler, and C. Ubezio, "A cancellation test: its reliability in assessing attentional deficits in Alzheimer's disease," *Psychological Medicine*, vol. 22, no. 4, pp. 885–901, 1992.

[28] G. Novelli, C. Papagno, E. Capitani et al., "Tre test clinici di ricerca e produzione lessicale. Taratura su soggetti normali," *Archivio di Psicologia, Neurologia e Psichiatria*, vol. 47, pp. 477–506, 1986.

[29] P. Caffarra, G. Vezzadini, F. Dieci, F. Zonato, and A. Venneri, "Rey-Osterrieth complex figure: normative values in an Italian population sample," *Neurological Sciences*, vol. 22, no. 6, pp. 443–447, 2002.

[30] G. Novelli, C. Papagno, E. Capitani, M. Laiacona, S. F. Cappa, and G. Vallar, "Tre test clinici di memoria a lungo termine," *Archivio di Psicologia, Neurologia e Psichiatria*, vol. 47, no. 2, pp. 278–296, 1986.

[31] J. A. Yesavage, "Geriatric depression scale," *Psychopharmacology Bulletin*, vol. 24, no. 4, pp. 709–710, 1988.

[32] S. Katz, A. B. Ford, R. W. Moskowitz, B. A. Jackson, and M. W. Jaffe, "Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function," *Journal of the American Medical Association*, vol. 185, pp. 914–919, 1963.

[33] M. P. Lawton and E. M. Brody, "Assessment of older people: self-maintaining and instrumental activities of daily living," *Gerontologist*, vol. 9, no. 3, pp. 179–186, 1969.

[34] H. Baezner, C. Blahak, A. Poggesi et al., "Association of gait and balance disorders with age-related white matter changes: the LADIS Study," *Neurology*, vol. 70, no. 12, pp. 935–942, 2008.

[35] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, (DSM-IV), American Psychiatric Association, Washington, DC, USA, 4th edition, 1994.

[36] G. C. Roman, T. K. Tatemichi, T. Erkinjuntti et al., "Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop," *Neurology*, vol. 43, no. 2, pp. 250–260, 1993.

[37] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, and E. M. Stadlan, "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease," *Neurology*, vol. 34, no. 7, pp. 939–944, 1984.

[38] C. P. Hughes, L. Berg, W. L. Danziger, L. A. Coben, and R. L. Martin, "A new clinical scale for the staging of dementia," *British Journal of Psychiatry*, vol. 140, no. 6, pp. 566–572, 1982.

[39] A. A. Gouw, A. Seewann, W. M. van der Flier et al., "Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 82, no. 2, pp. 126–135, 2011.

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Clinical Study

Mild Cognitive Impairment: Statistical Models of Transition Using Longitudinal Clinical Data

Erin L. Abner,[1,2] Richard J. Kryscio,[1,2,3,4] Gregory E. Cooper,[1,2] David W. Fardo,[3,4] Gregory A. Jicha,[1,2,4] Marta S. Mendiondo,[1,2,3] Peter T. Nelson,[1,2,5] Charles D. Smith,[1,2,4] Linda J. Van Eldik,[1,2,6] Lijie Wan,[1,4] and Frederick A. Schmitt[1,2,7]

[1] *Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA*
[2] *Alzheimer's Disease Center, University of Kentucky, Lexington, KY 40536, USA*
[3] *Department of Biostatistics, University of Kentucky, Lexington, KY 40536, USA*
[4] *Department of Statistics, University of Kentucky, Lexington, KY 40536, USA*
[5] *Department of Pathology, University of Kentucky, Lexington, KY 40536, USA*
[6] *Department of Anatomy and Neurobiology, College of Medicine, University of Kentucky, Lexington, KY 40536, USA*
[7] *Department of Neurology, College of Medicine, University of Kentucky, Lexington, KY 40536, USA*

Correspondence should be addressed to Erin L. Abner, erin.abner@uky.edu

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Mild cognitive impairment (MCI) refers to the clinical state between normal cognition and probable Alzheimer's disease (AD), but persons diagnosed with MCI may progress to non-AD forms of dementia, remain MCI until death, or recover to normal cognition. Risk factors for these various clinical changes, which we term "transitions," may provide targets for therapeutic interventions. Therefore, it is useful to develop new approaches to assess risk factors for these transitions. Markov models have been used to investigate the transient nature of MCI represented by amnestic single-domain and mixed MCI states, where mixed MCI comprised all other MCI subtypes based on cognitive assessments. The purpose of this study is to expand this risk model by including a clinically determined MCI state as an outcome. Analyses show that several common risk factors play different roles in affecting transitions to MCI and dementia. Notably, APOE-4 increases the risk of transition to clinical MCI but does not affect the risk for a final transition to dementia, and baseline hypertension decreases the risk of transition to dementia from clinical MCI.

1. Introduction

Mild cognitive impairment (MCI) often refers to the clinical condition between normal cognition and probable Alzheimer's disease (AD). However, persons diagnosed with MCI may progress to non-AD forms of dementia, remain MCI until death, and in some instances recover to a normal cognitive state [1–3]. There has been considerable effort to refine diagnostic criteria, separate MCI into amnestic and nonamnestic subtypes, and identify the underlying etiologies of MCI [1, 4, 5]. However, whether MCI is a true precursor to dementia remains controversial [6–9] despite evidence of AD neuropathology in amnestic MCI [10, 11]. This is due in part to the description of "back transitions" (i.e., recovery to normal cognition) that have been reported in longitudinal studies [3, 9, 12, 13]. Although the long-term prognosis for such cases is unclear, patients with a Clinical Dementia Rating (CDR) global score of 0.5 often have AD pathology at autopsy regardless of back transitions to CDR global scores of 0 [14]. Back transitions are likely heterogeneous in origin and may be explained by misclassification of either the MCI or normal state, interclinician differences in application of diagnostic criteria, within-patient variability due to medical illness or psychosocial factors, or resistance to cognitive decline due to cognitive reserve [15–18].

In a previous study we investigated MCI as defined by cognitive test performance alone. Here, we have added a clinical consensus-based MCI state as defined by the Second International Working Group on MCI [1] and operationalized by the National Alzheimer's Coordinating Center

(NACC) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) [19, 20]. We now have sufficient data on this MCI state to assess it as risk factor for dementia. The purpose of this study is to describe our statistical model of longitudinal data in the context of studying MCI risks and to update our prior research with additional cognitive assessments and clinical diagnoses from a large longitudinal sample. Over 54% of the sample subjects now have a terminating event (i.e., we have 35 additional dementias and 69 additional deaths) compared to the 36% in the previous study. These additional events provide increased power to detect potential risks for transition including age, gender, education, APOE-4, family history of dementing illness, and baseline hypertension.

2. Methods

2.1. Subjects. Subjects in the current study are from the Biologically Resilient Adults in Neurological Studies (BRAiNS) at the University of Kentucky's Alzheimer's Disease Center (UK ADC), a longitudinal cohort of 1,030 individuals with ongoing recruitment established in 1989 [21]. Participants consent to extensive annual cognitive and clinical examinations as well as brain donation upon death. Exclusion criteria include age less than 60 years, active infectious diseases, neurological disorders, psychiatric disorders, disabling medical disorders, and dementing illness. Subjects included in the current study ($n = 554$) comprise those included in the previous report [22]. All subjects were cognitively intact at study entry. All research activities were approved by the University of Kentucky Institutional Review Board. Each participant gave written informed consent.

2.2. Cognitive Assessments. Annual cognitive test-based assessments taken on a cohort of initially cognitively normal subjects participating in the BRAiNS project are used to classify subjects into one of three states: normal, test-based amnestic MCI ($aMCI_{TB}$), or test-based mixed MCI ($mMCI_{TB}$) (Table 1). Classification of $aMCI_{TB}$ and $mMCI_{TB}$ has been described previously [22, 23]. Briefly, a classification of $aMCI_{TB}$ results from a poor score (as defined below) on at least one measure of episodic memory measure (Table 1). A classification of $mMCI_{TB}$ requires a poor score on at least one measure of language or executive function (Table 1) regardless of the $aMCI_{TB}$ classification status. A poor score is defined as at least 1.5 standard deviations (SD) below the age-adjusted mean, which is consistent with the Second International Working Group on MCI criteria [1]; normative values were derived from the baseline evaluations of the entire normal cohort.

Classification into clinical consensus-based MCI (MCI_{CC}) results from a diagnosis of MCI, which is determined according to the consensus guidelines on MCI developed by the Second International Working Group on MCI [1]. A diagnosis of MCI requires

(1) a cognitive complaint by the subject or informant, or evidence for longitudinal decline on cognitive test performance (at least 1.5 SD decline);

(2) generally intact global cognition;

(3) no or minimal functional impairment;

(4) not demented by DSM-IV criteria.

Additionally, MCI_{CC} is restricted to those individuals for whom a neurodegenerative etiology is suspected. The NACC diagnostic criteria designate patients with cognitive impairments but without a presumed degenerative etiology as "cognitive impairment, not MCI" [19]. Diagnosis of MCI_{CC} is based on a consensus team review by the examining physician, neuropsychologist, and the clinical research assistant administering the protocol [13]. This MCI_{CC} designation is equivalent in most respects to the new "MCI-Core Clinical Criteria" as defined by the National Institute on Aging-Alzheimer's Association Workgroup on Diagnostic Guidelines for Alzheimer's Disease [24]. The primary difference is that the new criteria allow the cognitive complaint in number one above to come from a skilled clinician rather than only the patient or informant. A dementia classification also results from a clinical consensus diagnosis of dementia (most often AD), which may be based on the dementia criteria of Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) [25], criteria of the Joint Working Group of the National Institute of the Neurologic and Communication Disorders and Stroke-AD and Related Disorders (NINCDS-ADRDA) [26], NINDS-AIREN criteria for vascular dementia [27], and the 2005 Dementia with Lewy bodies (DLB) Consortium revised criteria [28]. A diagnosis of MCI_{CC} or dementia supersedes a classification of normal cognition, $aMCI_{TB}$ or $mMCI_{TB}$ in our model.

Between their annual assessments, subjects may die or become demented, and these states are treated as completely absorbing competing states. MCI_{CC} is treated as a quasi-absorbing state, as subjects do not move backward to a transient state (i.e., normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$), but they may become demented or die.

For 19 subjects, review of the longitudinal record revealed apparent back transitions from MCI_{CC} to normal: nine subjects were diagnosed with MCI_{CC}, reverted to normal, and then reconverted to MCI_{CC}, three of whom eventually became demented; six subjects had a single diagnosis of MCI_{CC} between several diagnoses of normal cognition on either side; and four subjects had a single diagnosis of MCI_{CC} at their initial evaluation following the UK ADC's implementation of the NACC Uniform Data Set (UDS) cognitive and clinical testing protocol [19, 29] with all subsequent evaluations classified as normal. Review of each subject's complete study history revealed in all cases that the apparent back transitions were the result of underlying medical conditions, conflicting data from informants, or misclassification. Given that there are differences in the medical comorbidities (e.g., hypothyroidism, B_{12} deficiency) that can mimic MCI_{CC} in both research and general clinic settings (cf., [13]), "treatable" cases of MCI_{CC} were not considered to reflect neurodegenerative conditions. Similarly, a single diagnosis of "normal" in the midst of many years of MCI_{CC} diagnoses appears to reflect a temporary resolution of a neurodegenerative condition and so strains credulity.

Table 1: Criteria for state classification.

State	Definition
Normal cognition	No cognitive test score more than 1.5 standard deviations (SD) below the age-adjusted mean; absence of MCI_{CC} or Dementia (see below)
Test-based amnestic MCI ($aMCI_{TB}$)	At least one score more than 1.5 SD below the age-adjusted mean on the following measures of episodic memory: Wechsler Logical Memory, Benton Visual Retention Test (number correct or number of errors), a word list (Consortium to Establish a Registry in Alzheimer's Disease word list or California Verbal Learning Test) total learning score, delayed recall score, savings score, and the maximum recalled minus delayed recall score
Test-based mixed MCI ($mMCI_{TB}$)	At least one score more than 1.5 SD below the age-adjusted mean on the following measures of language and executive function: phonemic or category verbal fluency, Boston Naming Test (15-item), and Trail Making Tests A or B
Clinical consensus-based MCI (MCI_{CC})	A cognitive complaint by the subject or informant, or evidence for longitudinal decline on cognitive test performance (at least 1.5 SD decline); generally intact global cognition; no or minimal functional impairment; not demented by DSM-IV criteria; neurodegenerative etiology suspected
Dementia	Meeting DSM-IV criteria for dementia, or NINCDS/ARDRA criteria for possible or probable AD, or NINDS-AIREN criteria for possible or probable vascular dementia, or DLB Consortium criteria for Lewy body disease

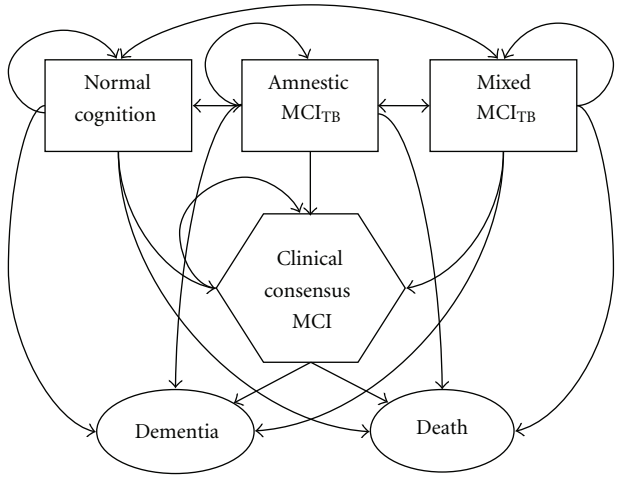

Figure 1: Flow diagram of transitions possible between subject visits. Normal cognition is the base state for transitions made from normal cognition, test-based amnestic MCI, and test-based mixed MCI; clinical consensus MCI is the base state otherwise.

Therefore, in light of the available evidence, the six normal to MCI_{CC} to normal cases and the four MCI_{CC} to normal cases were reclassified as never having MCI_{CC}, though they still might be classified $aMCI_{TB}$ or $mMCI_{TB}$, and the nine MCI_{CC} to normal to MCI_{CC} were reclassified as MCI_{CC} at every assessment after the first diagnosis of MCI_{CC}.

2.3. Statistical Analysis. The conditional distribution of the cognitive status at any assessment given the status at the prior assessment is assumed to have the Markov property. That is, the status at the current assessment depends only on the status at the prior assessment [30] and possibly other risk factors. A multistate Markov chain with three transient states (normal cognition, $aMCI_{TB}$, and $mMCI_{TB}$), one quasi-absorbing state (MCI_{CC}), and two absorbing states (death and dementia) was used to model the probability of maintaining the current state or moving to a different state at the next assessment (Figure 1). The Markov chain models the log-odds of transition between any two temporally adjacent assessments, here called the "prior state" and the "current state", versus remaining in or returning to a "base state" with a series of four random effects polytomous logistic regression models (i.e., one model for each transient state and one model for the quasi-absorbing state, MCI_{CC}).

The base state is normal cognition while a participant's prior state is normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$; once a participant has moved into MCI_{CC}, the base state then becomes MCI_{CC}. The model is additive, which means in practice that although we assume the risk factors are independent of the *prior state* (i.e., the effect of sex, e.g., is the same whether the prior state is normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$; there is no interaction between the covariates and the prior state), the estimated risk factor beta coefficients may depend on the *base state*. That is, the effect of sex, for

example, may vary with respect to a base state of normal cognition versus a base state of MCI_{CC}. To account for within-subject correlations, a normally distributed shared random effect due to Salazar et al. [31] was included in the model using PROC NLMIXED in SAS 9.2 (SAS Institute Inc, Cary, NC). The Quasi-Newton method is used to maximize the likelihood function, which due to the presence of the shared random effect is an integral approximated by an adaptive Gaussian quadrature with one quadrature point [32, 33]. Transitions to MCI_{CC} and dementia states are assumed to have occurred on the date of assessment as modeling assumptions do not permit the inclusion of interval censoring-type approaches. The model ignores any transitions among the transient states between regularly scheduled assessments. Statistical significance was set at $\alpha = 0.05$.

2.4. Covariates. Covariates of interest include age at assessment (centered at 78, the sample median), sex (1 = female, 0 = male), education (two levels: ≤12 years, >12 years), presence (1) or absence (0) of any copies of the APOE-4 allele, presence (1) or absence (0) of family history of dementing illness among first degree relatives, and presence (1) or absence (0) of hypertension at study entry. Hypertension status at entry was derived from participant responses to the question "have you ever been told by a doctor or nurse that you have high blood pressure?" Use of medications was also recorded; however, reported use of an antihypertensive medication did not supersede a participant's response of "no" since anti-hypertensives are used to treat other illnesses. Also included as covariates (when the base state is normal cognition) are two indicator variables for (1 = yes, 0 = no) $aMCI_{TB}$ and $mMCI_{TB}$; normal cognition is the reference category. Race was not included as a covariate because almost all of the included subjects (99%) are Caucasian.

3. Results

Study participants contribute an average of 10.8 annual assessments (median = 10 assessments, mode = 10 assessments) with the average time between assessments at approximately 13 months (Table 2). Approximately 87% of subjects who reported hypertension at baseline also reported taking at least one anti-hypertensive medication, whereas 15% of those who reported no history of hypertension reported taking at least one anti-hypertensive medication.

3.1. One-Step Transitions. Table 3 enumerates the one-step transitions associated with each arrow in Figure 1. The majority of transitions from $aMCI_{TB}$, which requires a poor score on a test of episodic memory, are back to normal cognition at the next visit (59.3%), and only 4.4% are transitions to MCI_{CC} or dementia. Mixed MCI ($mMCI_{TB}$), which requires a poor score on a test of executive function or language, appears more predictive of underlying impairment with 43.8% remaining $mMCI_{TB}$ and 7.1% transitioning to MCI_{CC} or dementia at the next visit. Entry into MCI_{CC} is a clear risk factor for transition to dementia since the majority of the transitions into the dementia state come from MCI_{CC} when compared to transitions into dementia from the other states. As previously stated, recovery from MCI_{CC} does not occur. We note that 13 of the 16 subjects who were MCI_{CC} and died without a dementia diagnosis have been autopsied. Of these, five had AD-type pathology insufficient for an AD diagnosis, two had mixed AD and vascular pathology, two had mixed vascular pathology (one with Lewy bodies and one with hippocampal sclerosis), two had hippocampal sclerosis, one had Parkinson's disease, and one had no histopathologic substrate for dementia (see also Reference [34]).

Table 2: Subject characteristics ($n = 554$).

Characteristic	Summary
Age at entry, y (mean ± SD)	72.7 ± 7.8
Female, %	64.3
Family history of dementia, %	41.3
At least one APOE-4 allele, %	30.0
>12 years of education, %	88.1
History of hypertension at entry, %	36.6
Hypertension treated with medication, %	86.5
Number of assessments (mean ± SD)	10.8 ± 4.5
Time between assessments, y (mean ± SD)	1.1 ± 0.4

3.2. Risk Factors. A number of risk factors alter the probability of transition to an MCI state (Table 4). Older age increases the risk of movement into $aMCI_{TB}$ ($P = 0.0006$) and $mMCI_{TB}$ ($P < 0.0001$). In addition, 12 (or fewer years) of education predicts transition to $mMCI_{TB}$ ($P = 0.0001$) but not $aMCI_{TB}$. Family history of dementia "protects" against transitions to $mMCI_{TB}$ ($P = 0.011$), and female sex is protective against entry into $aMCI_{TB}$ ($P = 0.013$). Classification as $mMCI_{TB}$ at the prior assessment is predictive of remaining $mMCI_{TB}$ rather than returning to normal at the next assessment ($P < 0.0001$).

Demographic risk factors for transition to the MCI_{CC} state (versus remaining in or returning to a normal state) are older age ($P < 0.0001$), presence of at least one APOE-4 allele ($P = 0.0053$), and high school education (12 years) or less ($P = 0.007$). Classification as either $aMCI_{TB}$ or $mMCI_{TB}$ at the prior assessment also increases the risk of transition to MCI_{CC} ($P = 0.0041$ for $aMCI_{TB}$, $P < 0.0001$ for $mMCI_{TB}$).

In the absence of MCI_{CC}, risk factors for dementia include older age ($P < 0.0001$) and the presence of at least one APOE-4 allele ($P = 0.0057$) (Table 4). A classification as $mMCI_{TB}$ ($P < 0.0001$) but not $aMCI_{TB}$ at the prior assessment also increases the risk of transition to dementia at the next visit. Risk factors for transition to death without dementia include older age ($P < 0.0001$) and self-reported hypertension at study entry ($P = 0.018$).

Participants in this sample who transitioned from MCI_{CC} to dementia ($n = 34$) did so in an average of 2.5 ± 1.5 years (median = 2.2 years), and those who transitioned from MCI_{CC} to death without an intervening dementia ($n = 16$) did so in an average of 2.7 ± 1.7 years (median = 3.4 years).

Table 3: One-step transition matrix (number of assessments [% of prior visit state]).

Prior visit	Current visit					
	Normal	Amnestic MCI_{TB}	Mixed MCI_{TB}	Clinical Consensus MCI	Dementia	Death
Normal	2192 (68.3)	478 (14.9)	385 (12.0)	34 (1.1)	19 (0.6)	100 (3.1)
Amnestic MCI_{TB}	448 (59.3)	148 (19.6)	108 (14.3)	23 (3.1)	10 (1.3)	18 (2.4)
Mixed MCI_{TB}	341 (33.0)	88 (8.5)	453 (43.8)	47 (4.5)	27 (2.6)	79 (7.6)
Clinical Consensus MCI				101 (66.9)	34 (22.5)	16 (10.6)

Table 4: Estimated relative risks and 95% confidence intervals for one-step transitions to test-based amnestic MCI ($aMCI_{TB}$), test-based mixed MCI ($mMCI_{TB}$), or clinical consensus MCI (MCI_{CC}) versus the base state of normal cognition (bolding denotes statistical significance).

Risk factor*	$aMCI_{TB}$ versus Normal	$mMCI_{TB}$ versus Normal	MCI_{CC} versus Normal
Age	**1.02 (1.01–1.04)**	1.07 (1.05–1.08)	**1.12 (1.09–1.15)**
Female sex (versus male)	**0.77 (0.62–0.95)**	1.01 (0.82–1.24)	0.71 (0.46–1.09)
Family history of dementia (yes versus no)	0.81 (0.65–1.00)	**0.76 (0.62–0.94)**	1.04 (0.66–1.64)
≥one APOE-4 allele (versus none)	1.04 (0.83–1.31)	1.12 (0.89–1.40)	**1.89 (1.21–2.95)**
≤12 years of education (versus >12 years)	1.24 (0.89–1.74)	1.79 (1.33–2.42)	**2.20 (1.24–3.91)**
History of hypertension (yes versus no)	0.95 (0.76–1.18)	1.04 (0.84–1.28)	0.79 (0.42–1.49)
$aMCI_{TB}$ at prior assessment (versus normal)	1.15 (0.91–1.45)	1.00 (0.77–1.29)	**2.28 (1.30–4.00)**
$mMCI_{TB}$ at prior assessment (versus normal)	0.76 (0.57–1.02)	**4.51 (3.63–5.61)**	**4.80 (2.94–7.81)**

* As risk factors do not depend on the prior state, covariate effects are the same regardless of whether transitions occur from a prior state of normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$.

Those cases that remain in the MCI_{CC} state ($n = 50$) have carried the diagnosis for an average of 4.1 ± 2.4 years (median = 4.2 years). Once a transition to MCI_{CC} has occurred, only history of hypertension at study entry appears to influence further transitions to dementia, or death without dementia, versus remaining in the MCI_{CC} state (Table 5). A participant who reported baseline hypertension is more likely to remain MCI_{CC} ($P = 0.037$) than to convert to dementia at the next visit: the yearly transition rate to dementia for those with hypertension at baseline is approximately 4.2% and 12.6% for those without hypertension at baseline.

4. Discussion

The addition of the MCI_{CC} state to the multistate Markov chain confirms the utility of cognitive testing in predicting true underlying cognitive impairment. Entry into $aMCI_{TB}$ and particularly $mMCI_{TB}$, both of which are determined solely by poor performance on cognitive assessment, increases the risk of a diagnosis of MCI_{CC} at the next visit versus returning to normal. These results highlight the importance of objective criteria in MCI diagnosis and emphasize the role of cognitive testing, particularly of language and executive function, in early detection. Notably, poor performance limited to tests of episodic memory ($aMCI_{TB}$) in this population can resolve to normal performance at the next annual assessment as much as 60% of the time and progress to MCI_{CC} just 3% of the time (Table 3). Poor performance on tests of language and executive function is somewhat more stable, returning to normal performance at the next annual assessment 33% of the time. While there is no question that MCI_{TB} predicts MCI_{CC}, these findings emphasize that clinicians who primarily rely on cognitive testing should obtain longitudinal followup before a diagnosis of MCI is given to the patient [35].

These findings reflect a novel analysis of risk factors for MCI and dementia based on the current NACC UDS criteria that are used across AD centers in the United States [19] and so represent a standardized diagnostic system in contrast to earlier analyses of MCI risk factors [36, 37]. Further, the comparison of two different sets of MCI criteria (MCI_{CC} versus MCI_{TB}) provides differing risk factors that could be of clinical use in patient care. This is best highlighted in our group's earlier comparison of patients diagnosed with MCI in a clinical research (i.e., the UK ADC BRAiNS cohort) as well as a memory clinic setting where only 9% of patients in the memory clinic had nonneurodegenerative causes for cognitive decline in contrast to 31% of the research clinic cases [13].

Risk factors for one-step transitions into MCI_{CC} include age, low education, prior classification as either $aMCI_{TB}$ or $mMCI_{TB}$, and the presence of at least one APOE-4 allele. APOE-4 is a known risk factor for AD, and although results for MCI have been mixed, a recent study of a nationally representative sample reported that APOE-4 was a reliable predictor of MCI versus normal cognition [38], and data from the Religious Orders Study reveal a 1.4-fold increased risk of MCI in persons with an APOE-4 allele [39].

It is clear that once an individual has transitioned to MCI_{CC}, the risk of dementia increases dramatically. In this sample, 38.5% of individuals with MCI_{CC} have transitioned to dementia (at an estimated overall rate of 12.6% per year) compared to 11.8% of individuals with no history of MCI_{CC} (at an estimated overall rate of 0.16% per year). However, common risk factors for dementia (i.e., age, sex, education,

Table 5: Estimated relative risks and 95% confidence intervals for one-step transitions to dementia or death without dementia versus the base state of normal cognition or clinical consensus MCI (MCI_{CC}) (bolding denotes statistical significance).

Risk factors* (normal is base state; no history of MCI_{CC})	Dementia versus normal	Death versus normal
Age	**1.19 (1.14–1.24)**	**1.18 (1.15–1.21)**
Female sex (versus male)	1.87 (0.95–3.68)	**0.68 (0.49–0.95)**
Family history of dementia (yes versus no)	1.66 (0.92–3.01)	0.82 (0.57–1.17)
≥one APOE-4 allele (versus none)	**2.33 (1.28–4.23)**	0.97 (0.67 –1.42)
≤12 years of education (versus >12 years)	0.75 (0.26–2.18)	1.33 (0.80 –.22)
History of hypertension (yes versus no)	0.79 (0.42–1.49)	**1.49 (1.07–2.08)**
$aMCI_{TB}$ at prior assessment (versus normal)	1.85 (0.82–4.21)	0.64 (0.38–1.08)
$mMCI_{TB}$ at prior assessment (versus normal)	**4.90 (2.58–9.30)**	**2.67 (1.88–3.79)**
Risk factors ($MCI_{CC}$is base state)	Dementia versus MCI_{CC}	Death versus MCI_{CC}
Age	1.05 (0.98–1.13)	1.03 (0.94–1.13)
Female sex (versus male)	1.75 (0.67–4.56)	1.15 (0.65–3.76)
Family history of dementia (yes versus no)	2.88 (0.95–8.72)	0.68 (0.15–3.03)
≥one APOE-4 allele (versus none)	0.69 (0.22–2.16)	2.33 (0.61–8.90)
≤12 years of education (versus >12 years)	0.97 (0.27–3.46)	0.55 (0.10–2.99)
History of hypertension (yes versus no)	**0.30 (0.10–0.93)**	0.70 (0.20–2.47)

* As risk factors depend only on the base state, covariate effects in the top half of the table are the same whether transitions occur from a prior state of normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$.

family history, and APOE-4) do not predict whether an individual will remain in MCI_{CC} or transition to dementia, or death without dementia, at the next visit. Similar results have been reported in studies that have examined risk factors for progression of cognitive impairment. Tschanz et al. [40] noted in the Cache County cohort that while female sex and age at onset were predictive of decline in Mini-Mental Status Exam (MMSE) scores, education was not related to rate of MMSE decline, and APOE-4 was related to earlier onset of impairment but not rate of MMSE decline. Fleisher et al. [41] reported that although APOE-4 did predict conversion from amnestic MCI to AD over a 36-month interval, it did not improve the predictive accuracy of their model (which included only neuropsychological test scores).

Participants who reported hypertension at baseline were significantly less likely to transition from MCI_{CC} to dementia at the next visit, which may indicate a primarily vascular rather than an AD or mixed AD and vascular etiology for MCI_{CC} in these patients. Several studies have shown that brain white matter changes are associated with cognitive decline in aging [42, 43] and that vascular changes exacerbate the cognitive decline associated with AD [44, 45]. Hoffman and colleagues [46] reported that autopsied subjects who took anti-hypertensive medications had significantly less Alzheimer-type pathology than either those with no history of hypertension or those with hypertension not treated by medication. However, the differences in risks for treated and untreated hypertension could not be assessed here due to the small number of cases of untreated hypertension in the sample.

As with $aMCI_{TB}$, $mMCI_{TB}$, and MCI_{CC}, older age increases the probability of a transition to a dementia state. Baseline hypertension plays no role in transitions to $aMCI_{TB}$, $mMCI_{TB}$, MCI_{CC}, or dementia (in the absence of MCI_{CC}), predicting only transitions to death (modeled as a competing risk for dementia). This result agrees with our previous research [23] even after four additional years of followup, as well as with the results of a recent meta-analysis, which found no increased risk of incidence of AD for either persons with hypertension or those taking anti-hypertensive medications [47]. We note that hypertension is a time-dependent risk factor as the participant's status may change during the course of followup. Availability of these time-dependent data is limited for many of the subjects in this sample; the study protocol did not call for annual assessment of health history until the implementation of the UDS in 2005.

All forms of MCI, and dementia as well, reflect a heterogeneous (and not completely understood) group of diseases including AD, hippocampal sclerosis, dementia with Lewy bodies, and vascular dementia [34, 48]. This heterogeneity may help explain the lack of significant predictors, other than baseline hypertension, from MCI_{CC} to dementia. We currently lack sufficient sample size to study these dementias as separate entities, but we have recently initiated work that will facilitate future research on which factors influence transitions into dementia subtypes. Similarly, MCI_{CC} is treated as a single entity here despite its well-documented heterogeneity [49] because we lack sufficient sample size to study the individual subtypes, and it is quite possible that risk factors for transitions to each subtype are different.

Limitations of the current study include that the final outcome for many of the included subjects is unknown as they continue to be followed longitudinally. Additional followup may change the results observed here, though they have face validity. The generalizability of the results is also somewhat limited due to the sample's demographic and geographic homogeneity, which would not be replicated in a population-based sample, and the nature of the longitudinal study, which requires brain donation at death. The volunteers are highly motivated and highly educated, and the

frequency of both family history of dementia and APOE-4 is higher than what would be observed in the general population. Biomarker data (i.e., blood, cerebrospinal fluid, and neuroimaging) are for the most part unavailable on these subjects, and studies that have investigated risk factors for transition from clinical MCI to dementia have largely been focused on biomarkers [50, 51]. Obtaining biomarkers is extremely expensive, however, and it has been reported that longitudinal neuropsychological testing data provides as good or better accuracy in predicting which clinical MCI cases will convert versus remaining stable [52]. Nevertheless, the recently published criteria for the diagnosis of MCI due to AD make extensive use of biomarker data [24], and this modeling technique will allow us to incorporate these data as they become available in the future.

Finally, a large portion of this University of Kentucky-based longitudinal cohort was not included in this study ($n = 476$). The decision to exclude all subjects not in the original study [22] was due to the fact that the model's power to detect risks is based on the number of events in the sample, not the number of subjects. The excluded subjects, who are relatively recent recruits with about four assessments on average, are unable to contribute events due to this abbreviated followup. Potential differences between included and excluded participants were assessed using standard parametric two-group comparisons. Included and excluded subjects compare favorably on distribution of sex, family history, APOE-4, history of hypertension at baseline, and time between assessments (data not shown). Although the excluded subjects were slightly older at baseline, the effect size is small (Cohen's $d = -0.05$). Excluded subjects also have lower education ($\chi^2 = 8.8$, 2 df, $P = 0.01$). That the excluded subjects are slightly older and less educated reflects that recruitment goals were changed in 2005 in order to enroll older participants with lower education, and all of the included subjects in the present model were recruited prior to 2005.

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References

[1] B. Winblad, K. Palmer, M. Kivipelto et al., "Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment," *Journal of Internal Medicine*, vol. 256, no. 3, pp. 240–246, 2004.

[2] B. Dubois and M. L. Albert, "Amnestic MCI or prodromal Alzheimer's disease?" *The Lancet Neurology*, vol. 3, no. 4, pp. 246–248, 2004.

[3] K. Ritchie, S. Artero, and J. Touchon, "Classification criteria for mild cognitive impairment: a population-based validation study," *Neurology*, vol. 56, no. 1, pp. 37–42, 2001.

[4] R. C. Petersen, "Mild cognitive impairment as a diagnostic entity," *Journal of Internal Medicine*, vol. 256, no. 3, pp. 183–194, 2004.

[5] R. C. Petersen and J. C. Morris, "Mild cognitive impairment as a clinical entity and treatment target," *Archives of Neurology*, vol. 62, no. 7, pp. 1160–1163, 2005.

[6] K. Palmer, L. Fratiglioni, and B. Winblad, "What is mild cognitive impairment? Variations in definitions and evolution of nondemented persons with cognitive impairment," *Acta Neurologica Scandinavica, Supplement*, vol. 107, no. 179, pp. 14–20, 2003.

[7] K. Palmer, L. Backman, B. Winblad, and L. Fratiglioni, "Mild cognitive impairment in the general population: occurrence and progression to alzheimer disease," *American Journal of Geriatric Psychiatry*, vol. 16, no. 7, pp. 603–611, 2008.

[8] A. Busse, M. C. Angermeyer, and S. G. Riedel-Heller, "Progression of mild cognitive impairment to dementia: a challenge to current thinking," *British Journal of Psychiatry*, vol. 189, pp. 399–404, 2006.

[9] S. Gauthier and J. Touchon, "Mild cognitive impairment is not a clinical entity and should not be treated," *Archives of Neurology*, vol. 62, no. 7, pp. 1164–1166, 2005.

[10] A. L. Guillozet, S. Weintraub, D. C. Mash, and M. Marsel Mesulam, "Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment," *Archives of Neurology*, vol. 60, no. 5, pp. 729–736, 2003.

[11] W. R. Markesbery, F. A. Schmitt, R. J. Kryscio, D. G. Davis, C. D. Smith, and D. R. Wekstein, "Neuropathologic substrate of mild cognitive impairment," *Archives of Neurology*, vol. 63, no. 1, pp. 38–46, 2006.

[12] M. Ganguli, H. H. Dodge, C. Shen, and S. T. DeKosky, "Mild cognitive impairment, amnestic type: an epidemiologic study," *Neurology*, vol. 63, no. 1, pp. 115–121, 2004.

[13] G. A. Jicha, E. Abner, F. A. Schmitt et al., "Clinical features of mild cognitive impairment differ in the research and tertiary clinic settings," *Dementia and Geriatric Cognitive Disorders*, vol. 26, no. 2, pp. 187–192, 2008.

[14] J. C. Morris and D. Fulling, "Early Alzheimer's disease. Diagnostic considerations," *Archives of Neurology*, vol. 45, no. 3, pp. 345–349, 1988.

[15] Y. Stern, "The concept of cognitive reserve: a catalyst for research," *Journal of Clinical and Experimental Neuropsychology*, vol. 25, no. 5, pp. 589–593, 2003.

[16] F. A. Schmitt, D. G. Davis, D. R. Wekstein, C. D. Smith, J. W. Ashford, and W. R. Markesbery, "'Preclinical' AD revisited: neuropathology of cognitively normal older adults," *Neurology*, vol. 55, no. 3, pp. 370–376, 2000.

[17] J. A. Mortimer, "Brain reserve and the clinical expression of Alzheimer's disease," *Geriatrics*, vol. 52, pp. S50–53, 1997.

[18] B. Schmand, J. H. Smit, M. I. Geerlings, and J. Lindeboom, "The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis," *Psychological Medicine*, vol. 27, no. 6, pp. 1337–1344, 1997.

[19] J. C. Morris, S. Weintraub, H. C. Chui et al., "The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer disease centers," *Alzheimer Disease and Associated Disorders*, vol. 20, no. 4, pp. 210–216, 2006.

[20] S. G. Mueller, M. W. Weiner, L. J. Thal et al., "Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative (ADNI)," *Alzheimer's and Dementia*, vol. 1, no. 1, pp. 55–66, 2005.

[21] F. A. Schmitt, M. M. C. Wetherby, D. R. Wekstein, C. M. S. Dearth, and W. R. Markesbery, "Brain donation in normal aging: procedures, motivations, and donor characteristics from the Biologically Resilient Adults in Neurological Studies (BRAiNS) project," *Gerontologist*, vol. 41, no. 6, pp. 716–722, 2001.

[22] R. J. Kryscio, F. A. Schmitt, J. C. Salazar, M. S. Mendiondo, and W. R. Markesbery, "Risk factors for transitions from normal to mild cognitive impairment and dementia," *Neurology*, vol. 66, no. 6, pp. 828–832, 2006.

[23] R. J. Kryscio, F. A. Schmitt, M. S. Mendiondo, and W. R. Markesbery, "Hypertension as a risk factor for transitions from normal to dementia or mild cognitive impairment," *Research and Practice in Alzheimer's Disease*, vol. 12, pp. 139–143, 2007.

[24] M. S. Albert, S. T. DeKosky, D. Dickson et al., "The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimer's and Dementia*, vol. 7, no. 3, pp. 270–279, 2011.

[25] *American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association, Washington, DC, USA, 4th edition, 1994.

[26] G. McKhann, D. Drachman, and M. Folstein, "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease," *Neurology*, vol. 34, no. 7, pp. 939–944, 1984.

[27] G. C. Roman, T. K. Tatemichi, T. Erkinjuntti et al., "Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop," *Neurology*, vol. 43, no. 2, pp. 250–260, 1993.

[28] I. G. McKeith, D. W. Dickson, J. Lowe et al., "Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium," *Neurology*, vol. 65, no. 12, pp. 1863–1872, 2005.

[29] S. Weintraub, D. Salmon, N. Mercaldo et al., "The Alzheimer's Disease Centers' Uniform Data Set (UDS): the neuropsychologic test battery," *Alzheimer Disease and Associated Disorders*, vol. 23, no. 2, pp. 91–101, 2009.

[30] P. J. Neumann, S. S. Araki, A. Arcelus et al., "Measuring Alzheimer's disease progression with transition probabilities: estimates from CERAD," *Neurology*, vol. 57, no. 6, pp. 957–964, 2001.

[31] J. C. Salazar, F. A. Schmitt, L. Yu, M. M. Mendiondo, and R. J. Kryscio, "Shared random effects analysis of multistate Markov models: application to a longitudinal study of transitions to dementia," *Statistics in Medicine*, vol. 26, no. 3, pp. 568–580, 2007.

[32] A. Skrondal and S. Rabe-Hesketh, "Multilevel logistic regression for polytomous data and rankings," *Psychometrika*, vol. 68, no. 2, pp. 267–287, 2003.

[33] SAS Institute Inc., *SAS 9.1.2 Help and Documentation: PROC NLMIXED*, SAS Institute Inc., Cary, NC, USA, 2000–2004.

[34] G. A. Jicha, E. L. Abner, F. A. Schmitt et al., "Preclinical AD Workgroup staging: pathological correlates and potential challenges," *Neurobiology of Aging*, vol. 33, no. 3, pp. 622.e1–622.e16, 2012.

[35] F. Portet, P. J. Ousset, P. J. Visser et al., "Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 77, no. 6, pp. 714–718, 2006.

[36] J. D. Fisk and K. Rockwood, "Outcomes of incident mild cognitive impairment in relation to case definition," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 76, no. 8, pp. 1175–1177, 2005.

[37] J. D. Fisk, H. R. Merry, and K. Rockwood, "Variations in case definition affect prevalence but not outcomes of mild cognitive impairment," *Neurology*, vol. 61, no. 9, pp. 1179–1184, 2003.

[38] C. J. Brainerd, V. F. Reyna, R. C. Petersen, G. E. Smith, and E. S. Taub, "Is the apolipoprotein e genotype a biomarker for mild cognitive impairment? Findings from a nationally representative study ," *Neuropsychology*, vol. 25, no. 6, pp. 679–689, 2011.

[39] P. A. Boyle, A. S. Buchman, R. S. Wilson, J. F. Kelly, and D. A. Bennett, "The APOE $\varepsilon 4$ allele is associated with incident mild cognitive impairment among community-dwelling older persons," *Neuroepidemiology*, vol. 34, no. 1, pp. 43–49, 2010.

[40] J. T. Tschanz, C. D. Corcoran, S. Schwartz et al., "Progression of cognitive, functional, and neuropsychiatric symptom domains in a population cohort with alzheimer dementia: the cache county dementia progression study," *American Journal of Geriatric Psychiatry*, vol. 19, no. 6, pp. 532–542, 2011.

[41] A. S. Fleisher, B. B. Sowell, C. Taylor, A. C. Gamst, R. C. Petersen, and L. J. Thal, "Clinical predictors of progression to Alzheimer disease in amnestic mild cognitive impairment," *Neurology*, vol. 68, no. 19, pp. 1588–1595, 2007.

[42] A. M. Brickman, I. B. Meier, M. S. Korgaonkar et al., "Testing the white matter retrogenesis hypothesis of cognitive aging," *Neurobiology of Aging*. In press.

[43] M. F. Elias, L. M. Sullivan, R. B. D'Agostino et al., "Framingham stroke risk profile and lowered cognitive performance," *Stroke*, vol. 35, no. 2, pp. 404–409, 2004.

[44] D. Mungas, B. R. Reed, W. G. Ellis, and W. J. Jagust, "The effects of age on rate of progression of Alzheimer disease and dementia with associated cerebrovascular disease," *Archives of Neurology*, vol. 58, no. 8, pp. 1243–1247, 2001.

[45] C. Regan, C. Katona, Z. Walker, J. Hooper, J. Donovan, and G. Livingston, "Relationship of vascular risk to the progression of Alzheimer disease," *Neurology*, vol. 67, no. 8, pp. 1357–1362, 2006.

[46] L. B. Hoffman, J. Schmeidler, G. T. Lesser et al., "Less Alzheimer disease neuropathology in medicated hypertensive than nonhypertensive persons," *Neurology*, vol. 72, no. 20, pp. 1720–1726, 2009.

[47] J.-W. Guan, C.-Q. Huang, Y.-H. Li et al., "No association between hypertension and risk for Alzheimer's disease: a meta-analysis of longitudinal studies," *Journal of Alzheimer's Disease*, vol. 27, no. 4, pp. 799–807, 2011.

[48] P. T. Nelson, G. A. Jicha, F. A. Schmitt et al., "Clinicopathologic correlations in a large Alzheimer disease center autopsy cohort: neuritic plaques and neurofibrillary tangles "do count" when staging disease severity," *Journal of Neuropathology and Experimental Neurology*, vol. 66, no. 12, pp. 1136–1146, 2007.

[49] T. F. Hughes, B. E. Snitz, and M. Ganguli, "Should mild cognitive impairment be subtyped?" *Current Opinion in Psychiatry*, vol. 24, no. 3, pp. 237–242, 2011.

[50] S. L. Risacher, A. J. Saykin, J. D. West, L. Shen, H. A. Firpi, and B. C. McDonald, "Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort," *Current Alzheimer Research*, vol. 6, no. 4, pp. 347–361, 2009.

[51] C. Misra, Y. Fan, and C. Davatzikos, "Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: results from ADNI," *NeuroImage*, vol. 44, no. 4, pp. 1415–1422, 2009.

[52] Y. Cui, B. Liu, S. Luo et al., "Identification of conversion from mild cognitive impairment to alzheimer's disease using multivariate predictors," *PLoS One*, vol. 6, no. 7, Article ID e21896, 2011.

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Clinical Study

Memory Complaints Associated with Seeking Clinical Care

Carolina Pires,[1] Dina Silva,[1] João Maroco,[2] Sandra Ginó,[1,3] Tiago Mendes,[1,4] Ben A. Schmand,[5] Manuela Guerreiro,[1,6] and Alexandre de Mendonça[1,7]

[1] *Dementia Clinics, Institute of Molecular Medicine and Faculty of Medicine, University of Lisbon, Avenue Prof. Egas Moniz, 1649-028 Lisbon, Portugal*
[2] *Superior Institute of Applied Psychology, Rua Jardim do Tabaco, 34, 1149-041 Lisbon, Portugal*
[3] *Santa Casa da Misericórdia de Lisboa, Largo Trindade Coelho, 1200-470 Lisbon, Portugal*
[4] *Psychiatry Department, Santa Maria Hospital, Avenue Prof. Egas Moniz, 1649-035 Lisbon, Portugal*
[5] *Faculty of Social and Behavioural Sciences, University of Amsterdam, 1018 vz Amsterdam, The Netherlands*
[6] *Laboratory of Language, Institute of Molecular Medicine and Faculty of Medicine, University of Lisbon, Avenue Prof. Egas Moniz, 1649-028 Lisbon, Portugal*
[7] *Laboratory of Neurosciences, Institute of Molecular Medicine and Faculty of Medicine, University of Lisbon, Avenue Prof. Egas Moniz, 1649-028 Lisbon, Portugal*

Correspondence should be addressed to Alexandre de Mendonça, mendonca@fm.ul.pt

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Diagnosis of mild cognitive impairment relies on the presence of memory complaints. However, memory complaints are very frequent in healthy people. The objective of this study was to determine the severity and type of memory difficulties presented by elderly patients who seek for clinical help, as compared to the memory difficulties reported by subjects in the community. Assessment of subjective memory complaints was done with the subjective memory complaints scale (SMC). The mini-mental state examination was used for general cognitive evaluation and the geriatric depression scale for the assessment of depressive symptoms. Eight-hundred and seventy-one nondemented subjects older than 50 years were included. Participants in the clinical setting had a higher total SMC score (10.3 ± 4.2) than those in the community (5.1 ± 3.0). Item 3 of the SMC, *Do you ever forget names of family members or friends?* contributed significantly more to the variance of the total SMC score in the clinical sample (18%) as compared to the community sample (11%). Forgetting names of family members or friends plays an important role in subjective memory complaints in the clinical setting. This symptom is possibly perceived as particularly worrisome and likely drives people to seek for clinical help.

1. Introduction

Since the original description of the disease by Alois Alzheimer [1], memory difficulties are considered the initial and the most prominent and typical symptom of Alzheimer's disease. More recently, the detection of elderly subjects with mild cognitive impairment and a high risk of progression to Alzheimer's disease also relies on the presence of memory complaints [2], and, in proposed revised criteria for prodromal AD, like the Dubois criteria [3], the report by patients or informants of memory decline remains part of the core diagnostic features. Memory complaints thus represent an important symptom in clinical practice.

On the other hand, when specifically asked for, people in the community frequently report memory difficulties. In fact, not only elderly but also young subjects may have an unfavourable opinion about their memory capabilities [4]. Using a formal scale, the subjective memory complaints scale (SMC; [5]), as much as 75.9% of people report at least minor complaints when answering to the first general question *Do you have any complaints concerning your memory*? (SMC1) [4]. The significance and clinical implications of the frequent report of memory difficulties in the community setting are not clear. In a meta-analysis, the presence of memory complaints was more frequent in cognitively impaired than in cognitively normal elderly subjects [6]. A systematic review

concluded that the subjective memory complaints appear to be associated with depressive symptoms and personality traits and may predict future cognitive decline [7]. A recent study found that self perceived memory complaints are an independent predictor of dementia [8].

In the present study, we analysed the severity and type of memory difficulties presented by patients who look for medical help in a memory clinic or hospital outpatient setting, as compared to the memory difficulties that subjects in the community report when specifically asked for. The same instrument, the subjective memory complaints scale, was applied in both samples. We tested the hypothesis that some types of memory complaints would be selectively reported by subjects in the clinical setting. The objective was to identify the memory complaints most prone to raise concern from the patients and their families and bring them to clinical care.

2. Methods

2.1. Patients. Subjects with cognitive complaints older than 50 years referred for neuropsychological evaluation at the Laboratory of Language Studies, Santa Maria Hospital, and a Memory Clinic, both in Lisbon.

2.2. Controls. Controls were volunteers older than 50 years attending a health itinerant unit that aims to screen and promote general health, a blood donor centre, a leisure centre for retired people, and a senior citizens college and university, all in the area of Lisbon.

2.3. Exclusion Criteria.

(1) presence of dementia (criteria of the American Psychiatric Association, DSM-IV-TR [9]), or MMSE score below the education-adjusted cutoff,

(2) neurological disorders (stroke, tumors, significant head trauma, and epilepsy), psychiatric conditions (including major depression), or uncontrolled medical illness (hypertension, metabolic, endocrine, toxic, and infectious diseases) able to interfere with cognition,

(3) psychoactive medications with possible influence on cognition,

(4) chronic alcohol or drug abuse,

(5) sensory deficits likely to interfere with assessment, and

(6) nonnative Portuguese speakers.

All participants gave their informed consent. The present study was approved by the local ethics committee.

2.4. Procedures. A semi-structured interview recorded clinical information, present and past medical conditions, psychiatric and neurological history, medication, social and familial status.

2.5. General Cognitive Assessment. The mini-mental state examination (MMSE; [10, 11]) was used for a general cognitive assessment. Participants with MMSE below education-adjusted values for the Portuguese population were excluded (<23 for less than 11 years of education, <28 for more than 11 years of education; [11]).

2.6. Assessment of Subjective Memory Complaints. Participants were assessed with the subjective memory complaints scale (SMC; [5, 12]). They were required to answer 10 individual items concerning difficulties in daily-life memory tasks, with total scores ranging from 0 (absence of complaints) to 21 (maximal complaints score). These items are considered representative of common memory complaints [5]. The SMC was always applied at the end of the clinical interview.

2.7. Assessment of Depression. For the assessment of depressive symptoms the geriatric depression scale (GDS; [13, 14]) was used. The version with 15 items was chosen.

2.8. Statistical Analysis. Statistical analyses were performed using IBM SPSS Statistics 19 for Windows (SPSS Inc., an IBM Company, Chicago, IL, USA). A probability value less or equal to 0.05 was assumed as statistically significant. Differences in the total SMC scores among the different community settings were tested with one-way ANOVA. Comparison of demographic and neuropsychological data between the participants in the community and in the clinical setting was done using Student's t test on quantitative variables and the Fisher's exact test on the nominal variable. Comparison of the SMC items and the SMC total score between participants in the community and in the clinical setting was performed with the Mann-Whitney U test. *Eta*-squared values were calculated for the individual SMC items to explain the total SMC score with ANCOVA, controlling for depression score and education years. The 95% confidence intervals for *eta*-squared values were obtained by nonparametric Bootstrap sampling ($k = 1000$) using the boot library in the R system software (v. 12.2.1, R Development Core Team).

3. Results

Eight-hundred and seventy-one nondemented subjects older than 50 years were included in the study, 581 recruited in the community, and 290 in the clinical setting. Participants in the clinical setting were more educated, had slightly lower MMSE scores, and presented more depressive symptoms than the participants in the community (Table 1).

All participants in the clinical setting had complaints at least in one SMC item, and 20 (3.4%) participants in the community reported no memory complaints (total SMC score = 0). Since no differences in the total SMC scores were found among the different community settings (health itinerant unit, blood donor centre, leisure centre for retired people, and senior citizens college and university), the results from community participants were pooled together.

Table 1: Characteristics of the participants.

	Community	Clinical setting	Statistical significance
Number of participants (n)	581	290	
Age [years, mean ± SD (range)]	67.4 ± 9.0 (50–92)	67.6 ± 8.6 (50–88)	$P = 0.679$*
Gender (female/male)	355/226	163/127	$P = 0.187$#
Education [years, mean ± SD (range)]	6.1 ± 4.1 (0–19)	10.7 ± 4.5 (2–18)	$\mathbf{P < 0.001}$*
MMSE [mean ± SD (range)]	28.0 ± 1.8 (23–30)	27.3 ± 2.0 (23–30)	$\mathbf{P < 0.001}$*
GDS [mean ± SD (range)]	3.5 ± 2.9 (0–14)	5.2 ± 3.4 (0–15)	$\mathbf{P < 0.001}$*

MMSE: mini-mental state examination; GDS: geriatric depression scale; *Student's t test; #Fisher's exact test.

Participants in the clinical setting had a higher total SMC score [10.3 ± 4.2 (1–21)] than those in the community [5.1 ± 3.0 (0–15)] (Figure 1), and this held true for almost all types of memory complaints (Table 2).

The only exception was the SMC7 item, *Did you ever lose your way in neighbourhood?* few subjects reporting this difficulty, both in the clinical setting (4.8%) and in the community (3.1%).

Analysing the weight of the different types of complaints to the global SMC score in the two groups, we found that SMC3, *Do you ever forget names of family members or friends?* contributed to only 11% of the total score variance in the community sample, and as much as 18% of the total score variance in the clinical sample (as shown in Figure 2, the 95% confidence intervals for the *eta*-squared values of SMC3 are separated). This was the item that contributed most to the total SMC score variance in the clinical group. In contrast, SMC1, which a general question about memory complaints, SMC6, *Do you ever have difficulties in finding particular words?*, and SMC 8, *Do you think more slowly than you used to?* contributed significantly less to the total SMC score in the clinical group.

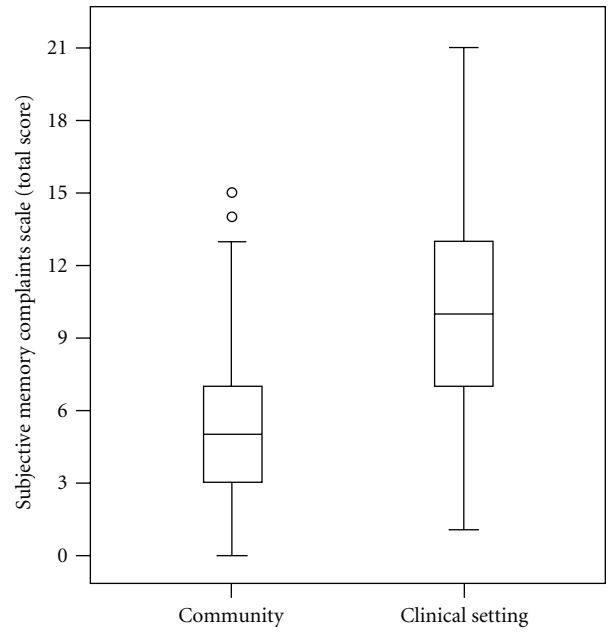

Figure 1: Total SMC scores in the community and in the clinical setting.

4. Discussion

Elderly patients who seek for medical help in a memory clinic or hospital outpatient setting reported more prominent memory difficulties as compared to the subjects in the community. Nevertheless, only 20 community participants reported to be completely free from memory difficulties (i.e., to say, had 0 in the SMC total score). The participants in the clinical setting scored higher in almost all SMC items, reflecting more problems in different types of memory complaints. The exception was item SMC7, about being lost in the neighbourhood, to which few participants answered positively, as found in previous studies [5]. Difficulties in spatial orientation in known places may well reflect the beginning of a dementing disorder like Alzheimer's disease. In a recent study, the complaining of difficulties on finding one's way around familiar streets was highly associated with objective cognitive impairment [15].

The hypothesis advanced in the present work, that some types of memory complaints would be selectively reported by nondemented elderly subjects in the clinical setting, as compared to the community, was confirmed. Forgetting names of family members or friends contributed more strongly

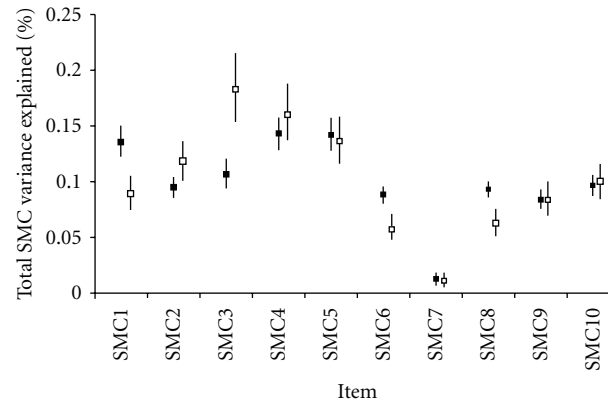

Figure 2: Percentage of the total subjective memory complaints scale (SMC) variance explained by each SMC item, controlling for depression score and education years. SMC: subjective memory complaints scale. *Eta*-squared values with 95% confidence intervals are shown. Black squares: community sample; open squares: clinical sample.

Table 2: Subjective memory complaints.

	Community mean ± SD	Clinical setting mean ± SD	Statistical significance*
(1) Do you have any complaints concerning your memory?	1.13 ± 0.70	2.05 ± 0.71	$\mathbf{P < 0.001}$
(2) Do other people find you forgetful?	0.36 ± 0.51	1.03 ± 0.69	$\mathbf{P < 0.001}$
(3) Do you ever forget names of family members or friends?	0.32 ± 0.54	1.15 ± 0.95	$\mathbf{P < 0.001}$
(4) Do you often forget where things are left?	0.78 ± 0.68	1.60 ± 0.91	$\mathbf{P < 0.001}$
(5) Do you often use notes to avoid forgetting things?	0.60 ± 0.61	1.22 ± 0.72	$\mathbf{P < 0.001}$
(6) Do you ever have difficulties in finding particular words?	0.48 ± 0.50	0.66 ± 0.48	$\mathbf{P < 0.001}$
(7) Did you ever lose your way in neighbourhood?	0.03 ± 0.17	0.05 ± 0.22	$P = 0.201$
(8) Do you think more slowly than you used to?	0.40 ± 0.49	0.84 ± 0.62	$\mathbf{P < 0.001}$
(9) Do your thoughts ever become confused?	0.45 ± 0.53	0.73 ± 0.67	$\mathbf{P < 0.001}$
(10) Do you have concentration problems?	0.52 ± 0.55	0.94 ± 0.70	$\mathbf{P < 0.001}$
Total SMC score	5.1 ± 3.0 (0–15)	10.3 ± 4.2 (1–21)	$\mathbf{P < 0.001}$

SMC: subjective memory complaints scale; *Mann-Whitney U-test
Scoring of items 1, 3, and 4: 0: no; 1: yes, but no problem; 2: yes, problem; 3: yes, serious problem.
Scoring of items 2 and 5: 0: no; 1: yes, sometimes; 2: yes, often.
Scoring of items 6 and 7: 0: no; 1: yes.
Scoring of items 8, 9 and 10: 0: no; 1: yes; 2: yes, serious problem.

to the global subjective memory complaints in the clinical setting. This memory difficulty is probably perceived as particularly worrisome, or more likely to impact on close interpersonal relationships. It is interesting that it is not just the problem with names that is involved because subjects in the clinical setting did not report more difficulties in finding particular words (item 6). The trouble with such a trivial task as remembering proper names of close people appears particularly disturbing. It is interesting that the neuronal basis for processing familiar proper nouns is different from other names and quite widespread, involving both cerebral hemispheres [16]. The perception of this type of memory complaint as worrisome is certainly justified since 20% percent of patients with early Alzheimer's disease report forgetting the names of relatives [17].

Factors other than the memory complaints themselves may of course influence whether elderly people seek for clinical help or not. The clinical participants were more educated, possibly with more awareness of the implications of memory problems and an easier access to clinical care. They also had more depressive symptoms, which could indeed drive their concern about memory problems. An association between depressive symptoms and reporting of memory complaints has been consistently found (see, for instance, [18, 19]). The influence of personality characteristics on the emergence of memory complaints was also emphasised [20]. A recent study, comparing patients in a memory clinic and non-help-seekers, found that beliefs about memory, as well as the presence of a close relative with dementia, were associated with the decision to seek help [21].

It must be recognized that in the present study the evaluation of memory complaints was based on a single scale, the subjective memory complaints scale. Although this scale has items considered representative of common memory complaints [5], the results may not necessarily be generalizable to other instruments of memory complaints evaluation [22].

In conclusion, the clinical diagnosis of mild cognitive impairment relies on the presence of memory complaints in subjects who seek for medical help. The present study suggests that both the global severity of memory complaints and the type of memory difficulties reported, particularly forgetting names of family members or friends, are associated with the clinical setting. Further research should clarify the reasons why some elderly people seek for medical help, and others do not, since important consequences for the screening of early cognitive decline in the community may ensue.

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References

[1] A. Alzheimer, "About a peculiar disease of the cerebral cortex," *Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin*, vol. 64, pp. 146–148, 1907.

[2] R. C. Petersen, G. E. Smith, S. C. Waring, R. J. Ivnik, E. G. Tangalos, and E. Kokmen, "Mild cognitive impairment: clinical characterization and outcome," *Archives of Neurology*, vol. 56, no. 3, pp. 303–308, 1999.

[3] B. Dubois, H. H. Feldman, C. Jacova et al., "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria," *Lancet Neurology*, vol. 6, no. 8, pp. 734–746, 2007.

[4] S. Ginó, T. Mendes, J. Maroco et al., "Memory complaints are frequent but qualitatively different in young and elderly healthy people," *Gerontology*, vol. 56, no. 3, pp. 272–277, 2010.

[5] B. Schmand, C. Jonker, C. Hooijer, and J. Lindeboom, "Subjective memory complaints may announce dementia," *Neurology*, vol. 46, no. 1, pp. 121–125, 1996.

[6] A. J. Mitchell, "The clinical significance of subjective memory complaints in the diagnosis of mild cognitive impairment and dementia: a meta-analysis," *International Journal of Geriatric Psychiatry*, vol. 23, no. 11, pp. 1191–1202, 2008.

[7] L. M. Reid and A. M. MacLullich, "Subjective memory complaints and cognitive impairment in older people," *Dementia and Geriatric Cognitive Disorders*, vol. 22, no. 5-6, pp. 471–485, 2006.

[8] A. Verdelho, S. Madureira, C. Moleiro et al., "Self-perceived memory complaints predict progression to Alzheimer disease. The LADIS study," *Journal of Alzheimer's Disease*, vol. 27, no. 3, pp. 491-8–498, 2011.

[9] American Psychiatric Association, *DSM-IV-TR*, APA, Washington, DC, USA, 4th edition, 2000.

[10] M. F. Folstein, S. E. Folstein, and P. R. McHugh, "Mini mental state. A practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[11] M. Guerreiro, A. P. Silva, M. A. Botelho, O. Leitão, A. Castro-Caldas, and C. Garcia, "Adaptation to the portuguese population of the mini-mental state examination," *Revista Portuguesa de Neurologia*, vol. 1, pp. 9–10, 1994.

[12] S. Ginó, M. Guerreiro, and C. Garcia, "Subjective memory complaints," in *Tests and Scales in Dementia*, Group for the Study of Brain Aging and Dementia, Lisbon, Portugal, 2nd edition, 2008.

[13] J. A. Yesavage, T. L. Brink, and T. L. Rose, "Development and validation of a geriatric depression screening scale: a preliminary report," *Journal of Psychiatric Research*, vol. 17, no. 1, pp. 37–49, 1982.

[14] J. Barreto, A. Leuschner, F. Santos, and M. Sobral, "Geriatric depression scale," in *Tests and Scales in Dementia*, Group for the Study of Brain Aging and Dementia, Lisbon, Portugal, 2nd edition, 2008.

[15] R. E. Amariglio, M. K. Townsend, F. Grodstein, R. A. Sperling, and D. M. Rentz, "Specific subjective memory complaints in older persons may indicate poor cognitive function," *Journal of the American Geriatrics Society*, vol. 59, no. 9, pp. 1612–1617, 2011.

[16] D. Van Lancker and C. Ohnesorge, "Personally familiar proper names are relatively successfully processed in the human right hemisphere; or, the missing link," *Brain and Language*, vol. 80, no. 2, pp. 121–129, 2002.

[17] C. Holzer and G. Warshaw, "Clues to early Alzheimer dementia in the outpatient setting," *Archives of Family Medicine*, vol. 9, no. 10, pp. 1066–1070, 2000.

[18] B. Schmand, C. Jonker, M. I. Geerlings, and J. Lindeboom, "Subjective memory complaints in the elderly: depressive symptoms and future dementia," *British Journal of Psychiatry*, vol. 171, pp. 373–376, 1997.

[19] T. Mendes, S. Ginó, F. Ribeiro et al., "Memory complaints in healthy young and elderly adults: reliability of memory reporting," *Aging and Mental Health*, vol. 12, no. 2, pp. 177–182, 2008.

[20] H. C. Comijs, D. J. H. Deeg, M. G. Dik, J. W. R. Twisk, and C. Jonker, "Memory complaints: the association with psychoaffective and health problems and the role of personality characteristics: a 6-year follow-up study," *Journal of Affective Disorders*, vol. 72, no. 2, pp. 157–165, 2002.

[21] C. S. Hurt, A. Burns, R. G. Brown, and C. Barrowclough, "Why don't older adults with subjective memory complaints seek help?" *International Journal of Geriatrics and Psychiatry*, vol. 27, no. 4, pp. 394–400, 2012.

[22] K. Abdulrab and R. Heun, "Subjective memory impairment. A review of its definitions indicates the need for a comprehensive set of standardised and validated criteria," *European Psychiatry*, vol. 23, no. 5, pp. 321–330, 2008.

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Clinical Study

Effects of Anosognosia on Perceived Stress and Cortisol Levels in Alzheimer's Disease

Genevieve Arsenault-Lapierre,[1] Victor Whitehead,[1] Sonia Lupien,[2] and Howard Chertkow[1]

[1] *Bloomfield Center for Research in Aging, Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada H3T 1E2*
[2] *Center for Studies on Human Stress, Fernand-Seguin Research Center, Louis-H. Lafontaine Hospital, Montreal, QC, Canada H1N 3V2*

Correspondence should be addressed to Genevieve Arsenault-Lapierre, genevieve.arsenault-lapierre@mail.mcgill.ca

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Anosognosia, or unawareness of one's own cognitive deficits, may cause issues when measuring perceived stress and cortisol levels in Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI). The goal of this study was to examine the effects of anosognosia on perceived stress and salivary cortisol levels in normal elderly (NE) adults, MCI individuals, newly diagnosed AD patients, and long-lasting AD patients, suspected to show more anosognosia. An anosognosia index for perceived stress was computed by subtracting the score on the Perceived Stress Scale measured in the participants and their relative. Cortisol levels were measured four times a day over two nonconsecutive days. Greater anosognosia for dementia correlated with greater anosognosia for perceived stress in the group as a whole. However, no correlation between cortisol levels and either anosognosia for dementia or perceived stress was observed. Our results suggest that measuring perceived stress in AD patients may be influenced by anosognosia.

1. Introduction

Cortisol is a hormone secreted when one faces a physical or a psychological stressor. As such, cortisol is conceived as a physiological marker of stress. When a stressor is perceived, the hypothalamo-pituitary-adrenal (HPA) axis is activated, the end product of which is the secretion of cortisol from the adrenal glands. Four psychological determinants have been shown to lead to the activation of the HPA axis and the secretion of cortisol: novelty, unpredictability, threat to self, and sense of loss of control [1]. Not everyone is sensitive to the same extent to each of these factors, but essentially, the more there are of these factors in any given situation, the more likely one will perceive the situation as stressful and the greater will be the secretion of cortisol [2].

Living with a diagnosis of Alzheimer's disease (AD) is especially stressful for the patients and their family and encompasses many, if not all, of the psychological determinants of a stress response. Indeed, in a review of qualitative studies on the impact of living with early dementia, Steeman and colleagues [3] reported that the "memory losses often threatens the patients' security, autonomy, and sense of being a meaningful member of society." The authors added that the memory losses interfering with coping strategies may cause "frustration, uncertainty, and fear." Similar conclusions were derived from a study by Clare and colleagues [4]. One would think that receiving the diagnosis of AD would trigger such a stress response. However, a group headed by Carpenter and colleagues [5] found that disclosure of AD diagnosis did not elicit significant increases on the Geriatric Depression Scale nor on the 20-item state version of the State-Trait Anxiety Inventory.

One important distinction in the field of human stress research is that to be stressful, a situation has to be perceived as such [6]. This brings us to an important limitation in the measurement of stress in AD, namely, the question as to whether AD patients are able to appraise their own level of stress. Patients with AD, and to some extent individuals with Mild Cognitive Impairment (MCI), often display anosognosia, or unawareness of their cognitive deficits [7–9].

The more the disease progresses, the more severe the anosognosia of the patients is [10]. It is therefore possible that AD patients and MCI individuals, unable to acknowledge their cognitive deficits, may also be unable to appraise their own stress.

Measures of perceived stress such as Cohen's 10-item Perceived Stress Scale (PSS-10) [11] have been used in the normal elderly (NE) population, and norms have been already established [12]. To our knowledge only one study has examined PSS-10 in AD patients. Wahbeh and colleagues [13] found that AD patients and their caregivers did not show significantly higher perceived stress compared to older adults. Consequently, norms have yet to be established for AD patients and individuals with MCI.

Higher cortisol levels have been found to correlate with increased perceived stress in some studies examining various populations [14, 15] but not in other studies [16–18]. Wahbeh and colleagues [13] have measured the association between cortisol levels and perceived stress in AD patients, and found a positive trend between cortisol levels measured at 30 minutes after awakening and the patients' scores on PSS-10. Although this result suggests that AD patients are able to appraise stressors with the concomitant increase of cortisol levels that is associated with this appraisal, it is not clear at this point in the literature whether the apparition of anosognosia that develops with the disease eliminates the association between perceived stress and cortisol levels in these populations. It is possible that with the progression of the disease over time, more anosognosia surfaces, counteracting the expected increase in cortisol levels of increasingly more advanced, and less insightful, AD patients.

There are many scales that measure anosognosia, such as the Anosognosia Questionnaire-Dementia (ANO) [19]. Like in most scales assessing anosognosia, the discrepancy between the scores of the participants and those of their relatives on a list of cognitive deficits items is used as an index of anosognosia for dementia. It would be interesting to look at a similar anosognosia index for perceived stress. To our knowledge, this has not been done or published in the literature before.

The goal of this study was to examine the effects of anosognosia on the psychological and physiological markers of stress in Alzheimer's disease. We wanted to examine this in a full cognitive spectrum of older adults, including healthy NE who have no anosognosia for dementia, MCI individuals who are expected to have lower levels of anosognosia for dementia, newly diagnosed AD patients, and AD patients who had the diagnosis for a longer period, thus suspected to show more anosognosia. We hypothesized that anosognosia for dementia should correlate positively with anosognosia for perceived stress and inversely correlate with cortisol levels.

2. Methods

2.1. Subjects. A convenience sample of 20 MCI individuals and 29 AD patients was recruited at the memory clinic of the Jewish General Hospital, Montreal, Canada. In addition, 20 normal elderly (NE) subjects without memory loss were recruited from the general population. Each participant underwent a battery of neuropsychological tests carried out by neuropsychologists or trained research assistants. CT scans were performed to rule out any organic cause of cognitive dysfunction. A diagnosis of MCI or AD was made by consensus at clinical meetings composed of neurologists, nurses, geriatricians, and neuropsychologists who attended to the patients.

Clinical criteria for MCI were those proposed by Petersen and colleagues [20]: (1) having subjective memory complaints, (2) small but measurable deficits (usually at least 1 to 1.5 standard deviations below norms) on neuropsychological tests adjusted for age and education, (3) lack of significant functional or social impairment, and (4) not meeting criteria for dementia. For a diagnosis of AD, the clinical criteria were those of the NINCDS-ADRDS [21]. We considered a participant to have newly diagnosed AD, labeled "new AD," if the diagnosis occurred within the past six months of testing; consequently, participants who have had AD for longer than six months were considered as having long-standing AD, hereafter labeled "old AD." The distinction from new AD and old AD is based on the fact that old AD patients are hypothesized to have higher anosognosia for dementia, and possibly for perceived stress, as well as to have more time to adjust to a new diagnosis of AD. Exclusion criteria were the presence of other organic or psychiatric disorder that could account for the cognitive deficits in MCI and AD patients, and the presence of any cognitive deficits in NE.

Each participant had to designate an individual in their immediate social circle (a friend, a spouse, a child, or a caregiver, hereafter referred to as a relative) to participate in the study. Medical charts reviews were carried out to determine the participants' medications that could affect cortisol and perceived stress ratings. Informed consent was received from every participant and their relative, and the protocol was approved by Research Ethic Board of the Jewish General Hospital, Montreal, Canada.

2.2. Anosognosia Index for Dementia (ANO). The Anosognosia Questionnaire-dementia (ANO), [19] was given to each participant. This questionnaire has been validated and consists of 30 items assessing one's memory, daily life, and behavioral and psychological symptoms on four-point scales. Both the participant's version and the relative's version of the questionnaire asked the same questions about the participant; the difference in the scores between these versions was then used as an index of anosognosia for dementia. The greater is the difference in the score of the AD patient and the relative on the scale, the greater is the anosognosia index assigned to the AD patient.

2.3. Anosognosia Index for Perceived Stress (PSS). The 10-item Perceived Stress Scale (PSS-10) [11] was administered to every participant and their relative. It constitutes one of the most widely used quantitative questionnaires on perceived stress and measures the stress perceived by an adult over the previous month. An index of anosognosia for perceived stress was devised by subtracting the score of the participant

from that of their relative, in a manner similar to how we obtained the index of anosognosia for dementia: PSS = PSS-10_{relative} − PSS-$10_{\text{participant}}$. About half of the participants and their relatives were given an incomplete version of the PSS-10 on the first visit (measurement error), resulting in two missing items for about 40% of the study sample, making comparisons with norms difficult. An adjusted score out of 10 was computed from the score out of 8 for every subject.

2.4. Salivary Cortisol Levels. Participants were instructed to collect four samples of saliva per day on two nonconsecutive days. The four samples were taken upon awakening, 30 minutes after awakening, at 2PM, and at bedtime and comprised passive drool collected in plastic tubes. The participants and/or caregivers were then instructed to write down the exact time, report any unusual event that might have occurred before the saliva collection, and rate the mood of the participant on a log sheet. We asked the participants and/or their caregivers to subsequently store the saliva samples in their freezer to prevent degradation until they could be collected for analysis. Radioimmunoassays were performed at the Douglas Institute of Mental Health, Montreal, Canada. Saliva measured for the four collection times were averaged across the two days, controlling for the day-to-day variation in cortisol secretion.

2.5. Procedure. The participants' and relatives' versions of both the anosognosia and the PSS-10 questionnaires were administered at the first home visit, along with the instructions for the salivary collection. About two weeks after the first visit, a second appointment was scheduled to pick up the saliva samples. At the same time the Mini-Mental State Evaluation (MMSE) [22] and Montreal Cognitive Assessment (MoCA) [23] were given to measure the cognitive function of the participants.

2.6. Statistical Analyses. Multiple analyses of variance (ANOVAs) and Pearson's correlations were carried out using SPSS version 16.0 (SPSS Inc., Chicago, IL).

3. Results

From November 2009 to January 2010, a total of 22 NE, 21 MCI individuals, 12 new AD patients (who received a diagnosis of AD within the past six months), and 16 old AD patients (who received a diagnosis of AD earlier than the past six months) and their relatives agreed to participate in the study. There were no differences in age, education, or gender between the participants included and the initial bigger cohort, nor between the participants for whom we have a perceived stress score out of 10 and those for whom we have a perceived stress score out of 8. We found very strong correlations between scores out of 10 and scores out of 8 for the participants on whom we had complete PSS-10 questionnaires ($r = 0.98$, $P < 0.01$, $n = 43$), suggesting that the two missing items for half of the sample had no major impact, allowing us to perform the intended analyses. One old AD participant was excluded from the analyses due to extreme levels of cortisol (more than 3 standard deviations above the mean for old AD group). A review of concomitant medications amongst participants revealed that more MCIs were on medication for diabetes than the other groups ($n_{\text{NE}} = 0$; $n_{\text{MCI}} = 5$; $n_{\text{newAD}} = 0$; $n_{\text{oldAD}} = 0$), whereas more AD patients (both new and old) were on sedatives/antidepressants ($n_{\text{NE}} = 1$; $n_{\text{MCI}} = 1$; $n_{\text{newAD}} = 4$; $n_{\text{oldAD}} = 5$) and acetyl cholinesterase inhibitors ($n_{\text{NE}} = 0$; $n_{\text{MCI}} = 0$; $n_{\text{newAD}} = 6$; $n_{\text{oldAD}} = 8$). There were no differences in demographics, anosognosia for dementia, anosognosia for perceived stress, or cortisol between the MCI who were on diabetic medications and those who were not. Similarly, there were no statistical difference in demographics, anosognosia for dementia, PSS-10, anosognosia for perceived stress, or cortisol between the AD who were on sedatives, antidepressants, and/or acetyl cholinesterase inhibitor and those who were not.

Table 1: Demographic information for the normal elderly, individuals with Mild Cognitive Impairement, newly diagnosed, and long-lasting Alzheimer's disease patients.

	NE	MCI	New AD	Old AD
Age	77.7 (1.3)	77.1 (1.3)	80.0 (0.8)	77.9 (1.4)
Education	15.2 (0.6)	15.9 (1.0)	13.1 (1.6)	13.9 (1.3)
Gender (M : W)*	9 : 13	14 : 7	7 : 5	14 : 2
MMSE*	28.7 (1.4)	27.8 (2.0)	26.0 (1.9)	20.1 (5.9)
MoCA*	27.2 (0.6)	23.5 (0.7)	19.1 (1.7)	14.8 (1.4)
PSS-10 adjusted				
Participant	7.6 (0.92)	12.6 (1.4)	8.8 (1.7)	10.2 (8.0)
*Relative**	9.3 (1.5)	11.3 (6.3)	15.1 (7.4)	19.2 (6.7)
ANO*	−0.5 (1.2)	1.0 (2.1)	10.9 (1.7)	19.2 (3.8)

This table represents the mean (standard error of the mean) and men to women ratio (M : W) for the 22 normal elderly (NE), 21 individuals with Mild Cognitive Impairment (MCI), 12 newly diagnosed Alzheimer's disease patients (new AD), and 17 long-lasting Alzheimer's disease patients (old AD). Age and education are in years. MMSE stands for Mini-Mental State Evaluation; MoCA stands for Montreal Cognitive Assessment, PSS-10 adjusted stands for 10-item Perceived Stress Scale out of 8, adjusted to a score of 10, as reported by the participants themselves, and as reported by their relatives; ANO stands for anosognosia for dementia score. *Denotes a significant group difference with a P-value less than 0.05.

The participants in the four groups were similar in age and education, but there were more women participants in the NE group compared to the other groups ($X^2_3 = 8.8$, $P = 0.03$). As expected, the groups differed in MMSE and MoCA scores (all $P < 0.01$). Demographic information is presented in Table 1.

There were no differences across the diagnostic groups in the level of perceived stress (PSS-10) as reported by the participants ($F_{(3,70)} = 2.5$, $P = 0.07$). There was a trend, however, mainly driven by MCI who reported higher perceived stress than the other groups (not significant). However, there were significant diagnostic group differences in the level of perceived stress (PSS-10) as reported by the relatives ($F_{(3,70)} = 7.3$, $P < 0.01$). Posthoc analyses showed that the relatives reported less stress for the NE participants

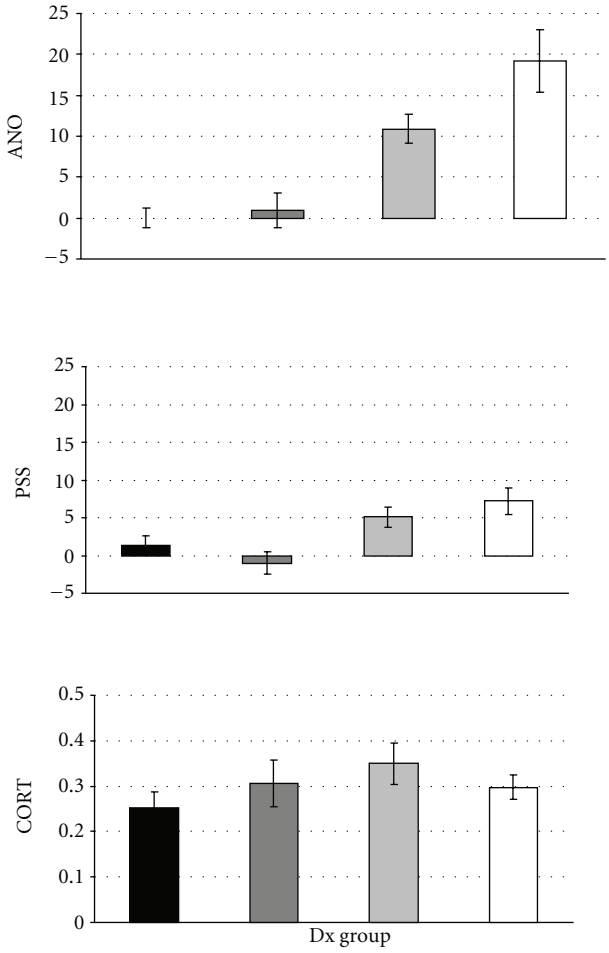

Figure 1: Scores on anosognosia for dementia, anosognosia for perceived stress, and cortisol levels in normal elderly, individuals with Mild Cognitive Impairment, newly diagnosed, and long-lasting Alzheimer's disease patients. These graphs represent the scores on anosognosia for dementia (ANO), anosognosia for perceived stress (PSS), and cortisol levels (CORT, in μg/dL) in 21 normal elderly (NE, black bars), 20 individuals with Mild Cognitive Impairment (MCI, dark grey bars), 12 newly diagnosed (new AD, light grey bars), and 17 long-lasting (old AD, white bars) Alzheimer's disease patients.

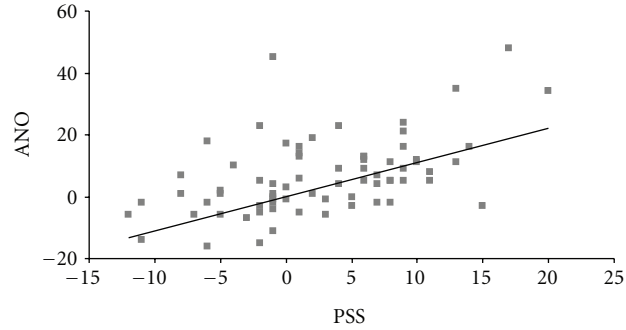

Figure 2: Relationship between anosognosia for dementia and anosognosia for perceived stress in normal elderly, individuals with Mild Cognitive Impairment, and Alzheimer's disease patients. This graph represents the lack of association between the scores on anosognosia for dementia (ANO) and on anosognosia for perceived stress (PSS) in all the subjects. PSS is calculated as a difference score on the PSS-10 as reported by the participants themselves versus the PSS-10 as reported by their relatives.

than for both new and old AD participants. In addition, the relatives reported less stress for the MCI participants than the old AD participants (all $P < 0.05$).

The ANOVAs revealed statistically significant group differences in the anosognosia index for dementia (ANO, $F_{(3, 67)} = 15.3$, $P < 0.01$). Post-hoc analyses, using Bonferroni's corrections, showed that the NE had lower anosognosia for dementia (ANO) than new AD ($P = 0.02$) and old AD ($P < 0.01$) and that, similarly, the MCI had lower anosognosia for dementia than new AD ($P = 0.04$) and old AD ($P < 0.01$). The ANOVAs revealed statistically significant group differences in the anosognosia for perceived stress (PSS, $F_{(3, 67)} = 6.15$, $P < 0.01$). Post-hoc analyses also revealed that NE ($P = 0.03$) and MCI ($P = 0.01$) had lower anosognosia for stress (PSS) than old AD. There were no group difference for cortisol level ($F_{(3, 63)} = 0.77$, $P = 0.51$). These results are presented in Figure 1.

To evaluate the association between the indices of anosognosia for dementia (ANO) and anosognosia for perceived stress (PSS), Pearson's correlations were carried out. We found a statistically significant positive correlation between the two scales across the groups ($r = 051$, $P < 0.01$, $n = 71$; see Figure 2) showing that greater anosognosia for dementia were associated with greater anosognosia for perceived stress. Carrying these analyses in the diagnostic groups independently, we found a positive correlation between the two scales in the NE only ($r = 0.98$, $P < 0.01$, $n = 22$). When we combined new and old AD together, we also found a positive correlation between the two indices of anosognosia ($r = 0.39$, $P = 0.04$, $n = 29$).

To evaluate the association between cortisol levels and the anosognosia indices for dementia and perceived stress, we performed Pearson's correlations across the diagnostic groups. We did not find any statistically significant correlations between cortisol levels and either the anosognosia index for dementia (ANO, $r = 0.10$, $P = 0.42$, $n = 64$) or the anosognosia index for perceived stress (PSS, $r = -0.11$, $P = 41$, $n = 64$).

4. Discussion

This study investigated whether a lack of insight of one's memory deficits correlates with one's lack of insight for perceived stress. Using targeted questionnaires, we found that an index of anosognosia for dementia correlated significantly with an index of anosognosia for perceived stress showing that measuring perceived stress in AD, and possibly in MCI individuals, may cause some problems due to the inability of AD patients and some MCI individuals to acknowledge their cognitive state.

Indeed, we found that AD patients, and more precisely AD patients who have been diagnosed for a longer period of

time, displayed more anosognosia for perceived stress than NE or MCI individuals. Similarly, both newly diagnosed and long-standing AD patients also showed greater anosognosia for dementia than either NE or MCI individuals. These results are similar to findings in the literature, where AD patients showed anosognosia for dementia [7–9], but not MCI individuals [24–27]. Although the difference between new AD and old AD was not significant in the anosognosia for dementia scale, our results indicated that with the disease progression and time, the severity of anosognosia for perceived stress, and to some extend for dementia, increased.

Surprisingly, we did not find group differences in cortisol levels. This contradicts numerous previous studies (including our own) that found differences between the cortisol levels of NE and AD groups [28–32], and between NE and MCI groups [32, 33]. The small sample size of this study, paired with the high variability of cortisol measurements across the days and seasons [32], almost certainly explains the failure to find statistically significant group differences.

Another goal for this study was to examine the relationship between anosognosia for dementia and perceived stress with physiological marker of stress, namely, cortisol levels. We did not find an association between cortisol levels and anosognosia for dementia, suggesting that anosognosia for dementia does not affect the levels of cortisol secreted by the participants. Interestingly, we did not find an association between cortisol levels and anosognosia for perceived stress. This adds to the body of literature that found no association of cortisol and perceived stress in various populations [16–18]. However, we did not find the expected group differences in cortisol secretion with progression of the disease, preventing us from driving more in-depth conclusions on the association, or lack thereof, between cortisol and anosognosia for dementia or perceived stress.

Beside the small sample size, a few limitations need to be addressed when interpreting our results. First, there were more women in the NE group compared to the other groups, especially when compared to AD patients. There exist gender differences in stress [34, 35], and there exist gender by age interaction effects on cortisol levels in response to a stressor [36]. Second, it is worth noting that more MCIs were treated for diabetes, and diabetic individuals have been found to secrete higher cortisol levels [37–39]. Third, and perhaps most importantly, more AD patients (both new and old) were on sedatives or antidepressants. These medications may affect the level of perceived stress and thus explain the relative anosognosia for perceived stress measured in these patients. The limited number of participants with up-to-date medication information, especially in the NE, prevented us from further conclusions regarding the effect of medications in this study. Finally, a subsample of the participants included in this study had incomplete PSS-10 questionnaires, where two items were missing. Although there was high correlation between the complete version and the incomplete versions in the individuals for which we had complete data, it remains difficult to assess whether the participants included in our study had scores within the norms for older adults as suggested by Cohen and Williamson [12]. When scores were adjusted to a total of 10, the means of the four groups (see Table 1) were within the suggested normal range (mean: 12.0 ± standard deviation: 6.3).

5. Conclusion

Despite these shortcomings, this study suggests that anosognosia for dementia has an impact on psychological markers of stress, but not on physiological markers of stress in Alzheimer's disease. It is necessary to replicate these findings in a larger sample while controlling for gender and, medications. However our results suggest that measuring perceived stress in AD patients may be influenced by the extent of anosognosia and consequently, caution should be taken when assessing association between perceived stress and cortisol levels in these populations.

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References

[1] C. Kirschbaum and D. H. Hellhammer, "Salivary cortisol in psychobiological research: an overview," *Neuropsychobiology*, vol. 22, no. 3, pp. 150–169, 1989.

[2] S. S. Dickerson and M. E. Kemeny, "Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research," *Psychological Bulletin*, vol. 130, no. 3, pp. 355–391, 2004.

[3] E. Steeman, B. D. De Casterlé, J. Godderis, and M. Grypdonck, "Living with early-stage dementia: a review of qualitative studies," *Journal of Advanced Nursing*, vol. 54, no. 6, pp. 722–738, 2006.

[4] L. Clare, J. Rowlands, E. Bruce, C. Surr, and M. Downs, "The experience of living with dementia in residential care: an interpretative phenomenological analysis," *Gerontologist*, vol. 48, no. 6, pp. 711–720, 2008.

[5] B. D. Carpenter, C. Xiong, E. K. Porensky et al., "Reaction to a dementia diagnosis in individuals with Alzheimer's disease and mild cognitive impairment," *Journal of the American Geriatrics Society*, vol. 56, no. 3, pp. 405–412, 2008.

[6] R. S. Lazarus and S. Folkman, *Stress, Appraisal, and Coping*, Springer, New York, NY, USA, 1984.

[7] A. Vogel, S. G. Hasselbalch, A. Gade, M. Ziebell, and G. Waldemar, "Cognitive and functional neuroimaging correlates for anosognosia in mild cognitive impairment and Alzheimer's disease," *International Journal of Geriatric Psychiatry*, vol. 20, no. 3, pp. 238–246, 2005.

[8] C. H. Y. Wong, L. C. W. Lam, V. W. C. Lui, H. F. K. Chiu, S. S. M. Chan, and C. W. C. Tam, "Subjective complaints and self-evaluation of memory test performancen in Questionable dementia," *International Journal of Geriatric Psychiatry*, vol. 21, no. 10, pp. 937–944, 2006.

[9] F. Galeone, S. Pappalardo, S. Chieffi, A. Iavarone, and S. Carlomagno, "Anosognosia for memory deficit in amnestic mild cognitive impairment and Alzheimer's disease," *International Journal of Geriatric Psychiatry*, vol. 26, no. 7, pp. 695–701, 2011.

[10] B. Reisberg, B. Gordon et al., " Insight and denial accompanying progressive cognitive decline in normal aging and Alzheimer's disease," in *Geriatric Psychiatry: Ethical and Legal Issues*, American Psychiatric Press, S. B. Washington, DC, USA, 1985.

[11] S. Cohen, T. Kamarck, and R. Mermelstein, "A global measure of perceived stress," *Journal of Health and Social Behavior*, vol. 24, no. 4, pp. 385–396, 1983.

[12] S. Cohen and G. Williamson, "Perceived Stress in a Probability Sample of the United States," in *The Social Psychology of Health*, S. Spacapan and S. Oskamp, Eds., pp. 31–67, Sage, Newbury Park, Calif, USA, 1988.

[13] H. Wahbeh, S. S. Kishiyama, D. Zajdel, and B. S. Oken, "Salivary cortisol awakening response in mild Alzheimer disease, caregivers, and noncaregivers," *Alzheimer Disease and Associated Disorders*, vol. 22, no. 2, pp. 181–183, 2008.

[14] W. B. Malarkey, D. K. Pearl, L. M. Demers, J. K. Kiecolt-Glaser, and R. Glaser, "Influenece of academic stress and season on 24-hour mean concentrations of ACTH, cortisol, and β-endorphin," *Psychoneuroendocrinology*, vol. 20, no. 5, pp. 499–508, 1995.

[15] J. C. Pruessner, D. H. Hellhammer, and C. Kirschbaum, "Burnout, perceived stress, and cortisol responses to awakening," *Psychosomatic Medicine*, vol. 61, no. 2, pp. 197–204, 1999.

[16] M. Van Eck, H. Berkhof, N. Nicolson, and J. Sulon, "The effects of perceived stress, traits, mood states, and stressful daily events on salivary cortisol," *Psychosomatic Medicine*, vol. 58, no. 5, pp. 447–458, 1996.

[17] L. Murphy, R. Denis, C. P. Ward, and J. L. Tartar, "Academic stress differentially influences perceived stress, salivary cortisol, and immunoglobulin-A in undergraduate students," *Stress*, vol. 13, no. 4, pp. 365–370, 2010.

[18] B. Garner, C. Phassouliotis, L. J. Phillips et al., "Cortisol and dehydroepiandrosterone-sulphate levels correlate with symptom severity in first-episode psychosis," *Journal of Psychiatric Research*, vol. 45, no. 2, pp. 249–255, 2011.

[19] R. Migliorelli, A. Teson, L. Sabe et al., "Anosognosia in Alzheimer's disease: a study of associated factors," *Journal of Neuropsychiatry and Clinical Neurosciences*, vol. 7, no. 3, pp. 338–344, 1995.

[20] R. C. Petersen, G. E. Smith, S. C. Waring, R. J. Ivnik, E. Kokmen, and E. G. Tangelos, "Aging, memory, and mild cognitive impairment," *International Psychogeriatrics*, vol. 9, no. 1, pp. 65–69, 1997.

[21] G. McKhann, D. Drachman, and M. Folstein, "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease," *Neurology*, vol. 34, no. 7, pp. 939–944, 1984.

[22] M. F. Folstein, S. E. Folstein, and P. R. McHugh, ""Mini mental state". A practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[23] Z. S. Nasreddine, N. A. Phillips, V. Bédirian et al., "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment," *Journal of the American Geriatrics Society*, vol. 53, no. 4, pp. 695–699, 2005.

[24] K. R. Greenop, J. Xiao, O. P. Almeida et al., "Awareness of cognitive deficits in older adults with cognitive-impairment-no-dementia (CIND): comparison with informant report," *Alzheimer Disease & Associated Disorders*, vol. 25, no. 1, pp. 24–33, 2010.

[25] M. D. Orfei, A. E. Varsi, C. Blundo et al., "Anosognosia in mild cognitive impairment and mild alzheimer's disease: frequency and neuropsychological correlates," *American Journal of Geriatric Psychiatry*, vol. 18, no. 12, pp. 1133–1140, 2010.

[26] E. Salmon, P. Ruby, D. Perani et al., "Two aspects of impaired consciousness in Alzheimer's disease," *Progress in Brain Research*, vol. 150, pp. 287–298, 2005.

[27] F. Clément, S. Belleville, and S. Gauthier, "Cognitive complaint in mild cognitive impairment and Alzheimer's disease," *Journal of the International Neuropsychological Society*, vol. 14, no. 2, pp. 222–232, 2008.

[28] K. L. Davis, B. M. Davis, and B. S. Greenwald, "Cortisol and Alzheimer's disease. I: Basal studies," *American Journal of Psychiatry*, vol. 143, no. 3, pp. 300–305, 1986.

[29] F. Masugi, T. Ogihara, K. Sakaguchi et al., "High plasma levels of cortisol in patients with senile dementia of the Alzheimer's type," *Methods and Findings in Experimental and Clinical Pharma-cology*, vol. 11, no. 11, pp. 707–710, 1989.

[30] K. Maeda, K. Tanimoto, T. Terada, T. Shintani, and T. Kakigi, "Elevated urinary free cortisol in patients with dementia," *Neurobiology of Aging*, vol. 12, no. 2, pp. 161–163, 1991.

[31] F. Giubilei, F. R. Patacchioli, G. Antonini et al., "Altered circadian cortisol secretion in Alzheimer's disease: clinical and neuroradiological aspects," *Journal of Neuroscience Research*, vol. 66, no. 2, pp. 262–265, 2001.

[32] G. Arsenault-Lapierre, H. Chertkow, and S. Lupien, "Seasonal effects on cortisol secretion in normal aging, mild cognitive impairment and Alzheimer's disease," *Neurobiology of Aging*, vol. 31, no. 6, pp. 1051–1054, 2010.

[33] K. Lind, A. Edman, A. Nordlund, T. Olsson, and A. Wallin, "Increased saliva cortisol awakening response in patients with mild cognitive impairment," *Dementia and Geriatric Cognitive Disorders*, vol. 24, no. 5, pp. 389–395, 2007.

[34] A. Baum and N. E. Grunberg, "Gender, stress, and health," *Health Psychol*, vol. 10, no. 2, pp. 80–85, 1991.

[35] P. McDonough and V. Walters, "Gender and health: reassessing patterns and explanations," *Social Science & Medicine*, vol. 52, no. 4, pp. 547–559, 2001.

[36] T. E. Seeman, B. Singer, C. W. Wilkinson, and B. McEwen, "Gender differences in age-related changes in HPA axis reactivity," *Psychoneuroendocrinology*, vol. 26, no. 3, pp. 225–240, 2001.

[37] Z. S. K. Lee, J. C. N. Chan, V. T. F. Yeung et al., "Plasma insulin, growth hormone, cortisol, and central obesity among young Chinese type 2 diabetic patients," *Diabetes Care*, vol. 22, no. 9, pp. 1450–1457, 1999.

[38] I. Chiodini, S. Di Lembo, V. Morelli et al., "Hypothalamic-pituitary-adrenal activity in type 2 diabetes mellitus: role of

autonomic imbalance," *Metabolism*, vol. 55, no. 8, pp. 1135–1140, 2006.

[39] H. Bruehl, M. Rueger, I. Dziobek et al., "Hypothalamic-pituitary-adrenal axis dysregulation and memory impairments in type 2 diabetes," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 7, pp. 2439–2445, 2007.

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Review Article

Specific EEG Changes Associated with Atrophy of Hippocampus in Subjects with Mild Cognitive Impairment and Alzheimer's Disease

D. V. Moretti, A. Prestia, C. Fracassi, G. Binetti, O. Zanetti, and G. B. Frisoni

IRCCS Centro S. Giovanni Di Dio Fatebenefratelli, 25125 Brescia, Italy

Correspondence should be addressed to D. V. Moretti, davide.moretti@afar.it

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We evaluated the association between hippocampal atrophy and increase of the EEG markers alpha3/alpha2 relative power ratio in mild cognitive impairment (MCI) and Alzheimer's disease patients. Seventy-nine subjects with MCI and 11 patients with AD underwent EEG recording and MRI scan. The MCI group was subdivided in three subgroups according to growing hippocampal atrophy. The groups were characterized by alpha3/alpha2 relative power ratio. In AD patients group mapped hippocampal regions were computed and related with alpha3/alpha2 power ratio. Results show that the increase of alpha3/alpha2 power ratio is correlated with atrophy of hippocampus both in MCI and in Alzheimer's disease patients. This finding confirms the possible diagnostic role of EEG markers as diagnostic and prognostic factors in patient with prodromal and declared Alzheimer's disease.

1. Introduction

Mild cognitive impairment (MCI) refers to the transitional state between the cognitive changes of normal aging and very early dementia [1]. Patients with MCI, who are at high risk of developing Alzheimer disease (AD; [2]), have smaller hippocampal volume than healthy elderly people [3, 4]. Medial temporal lobe (MTL) structures, in particular the hippocampus, show atrophy in the early stages of AD and are potential markers for detecting preclinical AD [5–7]. Moreover, a recent study has demonstrated that atrophy of the hippocampus on MRI in cognitively intact elderly people predicts dementia, in particular of Alzheimer type, during a 6-year followup [8].

Hippocampus is particularly important for memory formation, for attention [9] and for production of EEG rhythmic activity [10, 11]. Lesions of hippocampal synaptic plasticity block the memory-enhancing effects of direct hippocampal stimulation [12, 13]. Further, behavioral stress inter feres with synaptic plasticity in the hippocampal formation [14–16]. The associative memories involve the dorsal hippocampus, and a lesion of the area reduces the retrieval of associative tasks [17]. The hippocampal network system seems to be well suited to receive synaptic inputs from both the anterior and posterior thalamic nuclei [18–20], becoming suitable for an association with brain rhythms activity generation.

Recent works showed that in subjects with MCI is present, an increase of high alpha as compared to low alpha band occurs [21, 22]. As a working hypothesis, EEG markers alpha3/alpha2 power ratio could show modifications proportional to the hippocampal atrophy. In the present study the association between hippocampal atrophy and increase of alpha3/alpha2 relative power ratio was investigated in subjects with MCI.

Recent studies have demonstrated that the hippocampus is not a unitary structure from an anatomophysiological point of view [23]. The hippocampus, including strictly speaking subfields CA1–CA4 and the hippocampal formation, including also dentate gyrus, fimbria, subiculum, and parasubiculum, is a highly sophisticated structure. Stimuli coming from the entorhinal cortex are processed by the dentate gyrus, subfields CA4 and CA3, before being projected outside the medial temporal lobe via CA1 or subicular efferent projections. Moreover, in addition to the unsurprising right-left specialization for verbal and visuospatial material

[24], some degree of anterior-to-posterior specialization has been shown by fMRI studies [25].

As a consequence, it is conceivable that local structural changes take place in the hippocampus of patients with AD and that different hippocampal subregions are affected in AD Brickman et al. [26], and Shen et al. [27]. Local changes in hippocampal subregions could be detected through a radial atrophy mapping method able to assess group, based on high resolution MRI at 3 Tesla differences [23]. In this study, we tested the hypothesis that the increase of alpha3/alpha2 ratio is related with volumetric differences both in MCI patients and in mapped hippocampal regions in AD patients.

2. Materials and Methods

2.1. Subjects. For the present study, 79 subjects with MCI and 11 subjects with Alzheimer's disease (AD) were recruited from the memory Clinic of the Scientific Institute for Research and Care (*IRCCS*) of Alzheimer's and psychiatric diseases "Fatebenefratelli" in Brescia, Italy. All experimental protocols had been approved by the local ethics committee. Informed consent was obtained from all participants or their caregivers, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Diagnostic Criteria

2.2.1. MCI Patients. Patients were taken from a prospective project on the natural history of MCI. The project was aimed to study the natural history of nondemented persons with apparently primary cognitive deficits, that is, deficits not due to psychic (anxiety, depression) or physical (hypothyroidism, vit. B12 and folate deficiency, uncontrolled heart disease, and uncontrolled diabetes) conditions. Patients were rated with a series of standardized diagnostic and severity instruments, including the Mini-Mental State Examination (MMSE; [28]), the Clinical Dementia Rating Scale (CDRS; [29]), the Hachinski Ischemic Scale (HIS; [30]), and the Instrumental and Basic Activities of Daily Living (IADL, BADL, [31]). In addition, patients underwent diagnostic neuroimaging procedures (magnetic resonance imaging, MRI) and laboratory testing to rule out other causes of cognitive impairment. These inclusion and exclusion criteria for MCI were based on previous seminal studies [32–38]. Inclusion criteria of the study were all of the following: (i) complaint by the patient, or report by a relative or the general practitioner, of memory or other cognitive disturbances; (ii) Mini-Mental State Examination (MMSE) score of 24 to 27/30, or MMSE of 28 and higher plus low performance (score of 2–6 or higher) on the clock drawing test [39]; (iii) sparing of instrumental and basic activities of daily living or functional impairment steadily due to causes other than cognitive impairment, such as physical impairments, sensory loss, and gait or balance disturbances. Exclusion criteria were any one of the following: (i) patients aged 90 years and older; (ii) history of depression or juvenile-onset psychosis; (iii) history or neurological signs of major stroke; (iv) other psychiatric diseases, epilepsy, drug addiction, and alcohol dependence; (v) use of psychoactive drugs, including acetylcholinesterase inhibitors or other drugs enhancing brain cognitive functions; (vi) current or previous uncontrolled or complicated systemic diseases (including diabetes mellitus) or traumatic brain injuries. All patients underwent (i) semistructured interview with the patient and, whenever possible, with another informant (usually, the patient's spouse or a child of the patient) by a geriatrician or neurologist; (ii) physical and neurological examinations; (iii) performance-based tests of physical function, gait, and balance; (iv) neuropsychological battery assessing verbal and nonverbal memory, attention and executive functions (Trail Making Test B-A; Clock Drawing Test; [40]), abstract thinking (Raven matrices; [41]), frontal functions (Inverted Motor Learning; [42]), language (Phonological and Semantic fluency; Token test; [43]), and apraxia and visuoconstructional abilities (Rey figure copy; [44]); (v) assessment of depressive symptoms by means of the Center for Epidemiologic Studies Depression Scale (CES-D; [45]). Inclusion and exclusion criteria were homogeneous with previous works [46–48]. As the aim of our study was to evaluate the meaning of alpha3/alpha2 power ratio and its associations with structural changes of hippocampus as diagnostic marker of cognitive impairment, we were not interested in this study in the clinical subtype of MCI, that is, amnesic or nonamnesic, single or multiple domains.

2.2.2. AD Patients. The diagnosis of AD was made according to NINCDS-ADRDA criteria [49] and the Diagnostic and Statistical Manual of Mental Disorders IV [50]. Patients were rated with the same series of standardized diagnostic as MCI cohort.

2.3. EEG Recordings. All recordings were obtained in the morning with subjects resting comfortably. Vigilance was continuously monitored in order to avoid drowsiness.

The EEG activity was recorded continuously from 19 sites by using electrodes set in an elastic cap (Electro-Cap International, Inc.) and positioned according to the 10–20 International system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). The ground electrode was placed in front of Fz. The left and right mastoids served as reference for all electrodes. The recordings were used off-line to rereference the scalp recordings to the common average. Data were recorded with a band-pass filter of 0.3–70 Hz and digitized at a sampling rate of 250 Hz (BrainAmp, BrainProducts, Germany). Electrodes-skin impedance was set below 5 kΩ. Horizontal and vertical eye movements were detected by recording the electrooculogram (EOG). EOG activity was recorded with cup electrodes for the control of blinking and eye movements. A cup electrode placed 1 cm above supraorbital ridge registered the vertical EOG. It was referred to another electrode placed 2 cm below suborbital ridge of the right eye. The left and right horizontal EOG channels were collected from two electrodes at the left and the right lateral canthus. These electrodes were referred to an electrode placed at the glabella.

The recording lasted 5 minutes, with subjects with closed eyes. Longer recordings would have reduced the variability of the data, but they would also have increased the possibility

of slowing of EEG oscillations due to reduced vigilance and arousal. EEG data were then analyzed and fragmented off-line in consecutive epochs of 2 seconds, with a frequency resolution of 0.5 Hz. The average number of epochs analyzed was 140 ranging from 130 to 150. The EEG epochs with ocular, muscular, and other types of artifacts were discarded. Signals higher than 100 uV were discarded as artifact.

2.4. Analysis of Individual Frequency Bands. Frequency bands were determiner on an individuale basis, because of the variability of the brain rhythms with age and diseases. A digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, and no phase shift) computed the power density of EEG rhythms with a 0.5 Hz frequency resolution, ranging from 2 to 40 Hz. Two anchor frequencies were selected according to literature guidelines (47), which are the transition theta/alpha frequency (TF) and the individual alpha frequency (IAF) peak. As previously mentioned, the TF marks the transition frequency between theta and alpha bands, and it represents an estimate of the frequency at which theta and alpha spectra intersect. We computed the TF as the minimum power in the alpha frequency range since our EEG recordings were performed at rest. The IAF represents instead the frequency with the maximum power peak within the extended alpha range (5–14 Hz). The TF and IAF could be clearly identified in 99 MCI subjects whose EEG data were then statistically analyzed. Based on the TF and IAF, we estimated for each subject the frequency band range as follows: delta from TF-4 to TF-2, theta from TF-2 to TF, low alpha (alpha1 and alpha2) from TF to IAF, and high alpha band (or alpha3) from IAF to IAF + 2. Alpha1 and alpha2 band were computed for each subject as follows: alpha1 from TF to the middle point of the TF-IAF range and alpha2 from this middle point to IAF peak [46]. We found that the bandwidth in alpha1 and alpha2 bands was different among the groups. In no vascular damage and severe vascular damage groups, it was slightly narrower (1.48 and 1.53 Hz, resp.) than in mild and moderate vascular damage groups (1.7 and 1.87 Hz, resp.). We performed a statistical analysis to test if this difference was significant among groups in these frequency bands. It was not the case, since the analysis did not show a main group significant effect ($P = 0.06$). Finally, in the frequency bands so determined, we computed the relative power spectra for each subject. Relative power density for each frequency band was computed as the ratio between the absolute power and the mean power spectra from 2 to 40 Hz. The relative band power at each band was defined as the mean of the relative band power for each frequency bin within that band.

2.5. MRI Scans. MRI scans were acquired with a 1.0 Tesla Philips Gyroscan at the Neuroradiology Unit of the Città di Brescia hospital, Brescia. The following sequences were used to measure hippocampal volumes: a high-resolution gradient echo T1-weighted sagittal 3D sequence (TR = 20 ms, TE = 5 ms, flip angle = 30°, field of view = 220 mm, acquisition matrix = 256 × 256, and slice thickness = 1.3 mm) and a fluid-attenuated inversion recovery (FLAIR) sequence (TR = 5000 ms, TE = 100 ms, flip angle = 90°, field of view = 230 mm, acquisition matrix = 256 × 256, and slice thickness = 5 mm).

2.5.1. MCI Patients. Hippocampal and white matter hyperintensities (WMHs) volumes were obtained for each subject. The hippocampal boundaries were manually traced on each hemisphere by a single tracer with the software program DISPLAY (McGill University, Montreal, Canada) on contiguous 1.5 mm slices in the coronal plane. The starting point for hippocampus tracing was defined as the hippocampal head when it first appears below the amygdala, the alveus defining the superior and anterior border of the hippocampus. The fimbria was included in the hippocampal body, while the grey matter rostral to the fimbria was excluded. The hippocampal tail was traced until it was visible as an oval shape located caudally and medially to the trigone of the lateral ventricles [51, 52]. The intraclass correlation coefficients were 0.95. White matter hyperintensities (WMHs) were automatically segmented on the FLAIR sequences by using previously described algorithms [51, 52]. Briefly, the procedure includes (i) filtering of FLAIR images to exclude radiofrequency inhomogeneities, (ii) segmentation of brain tissue from cerebrospinal fluid, (iii) modelling of brain intensity histogram as a gaussian distribution, and (iv) classification of the voxels whose intensities were ≥3.5 SDs above the mean as WMHs [51, 52]. Total WMHs volume was computed by counting the number of voxels segmented as WMHs and multiplying by the voxel size (5 mm^3). To correct for individual differences in head size, hippocampal and WMHs volumes were normalized to the total intracranial volume (TIV), obtained by manually tracing with DISPLAY the entire intracranial cavity on 7 mm thick coronal slices of the T1-weighted images. Both manual and automated methods user here have advantages and disadvantages. Manual segmentation of the hippocampus is currently considered the gold standard technique for the measurement of such complex structures. The main disadvantages of manual tracing are that it is operator dependent and time consuming. Conversely, automated techniques are more reliable and less time consuming, but may be less accurate when dealing with structures without clearly identifiable borders. This, however, is not the case for WMHs which appear as hyperintense on FLAIR sequences.

Left and right hippocampal volumes were estimated and summed to obtain a total volume (individual) of both anatomical structures. Hippocampal total volume has been divided in tertiles obtaining three groups. In each group, hippocampal volume has been computed.

2.5.2. AD Patients: Radial Atrophy Mapping. In AD patients, the 3D parametric surface mesh models were created from the manual tracings of hippocampal boundaries [53, 54]. This procedure allows measurements to be made at corresponding surface locations in each subject, which are then compared statistically in 3D [53, 54]. To assess hippocampal morphology, a medial curve was automatically defined as the 3D curve traced out by the centroid of the hippocampal boundary in each image slice. The radial size of each hippocampus at each boundary point was assessed

Table 1: Mean values ± standard deviation of sociodemographic characteristics, MMSE scores, white matter hyperintensities, and hippocampal volume measurements in MCI cohort.

	MCI cohort	Group 1	Group 2	Group	*P* value (ANOVA)
Number of subjects (f/m)	79 (42/37)	27 (14/13)	27 (15/12)	25 (13/12)	
Age (years)	69.2 ± 2.3	66.8 ± 6.8	69.4 ± 8.7	71.5 ± 6.9	0.1
Education (years)	7.7 ± 0.8	8.3 ± 4.5	6.7 ± 3.1	8.2 ± 4.6	0.2
MMSE	27.1 ± 0.4	27.5 ± 1.5	27.4 ± 1.5	26.6 ± 1.8	0.1
Individual hippocampal volume (mm^3)	4889.8 ± 962.4	5809.6 ± 314.2	4969.4 ± 257.6	3890.1 ± 551.4	0.00001
White matter hyperintensities (mm^3)	3.8 ± 0.5	3.2 ± 2.8	4.2 ± 3.8	4.1 ± 3.6	0.7

by automatically measuring the radial 3D distance from the surface points to the medial curve defined for individual's hippocampal surface model.

2.6. Statistical Analysis and Data Management

2.6.1. MCI Patients. The analysis of variance (ANOVA) has been applied as statistical tool. Greenhouse-Geisser correction and Mauchly's sphericity test were applied to all ANOVAs. Preliminarily, the significant differences among groups in demographic variables, (age, education, and MMSE score) and morphostructural characteristics, (hippocampal and white matter hyperintensities, WMHs, and volume), were evaluated (Table 1). In order to avoid a confounding effect, subsequent ANOVAs were carried out using age, education, MMSE score, and WMHs as covariates. Duncan's test was used for post-hoc comparisons. For all statistical tests, the significance level was set at $P < 0.05$.

Two separate ANOVAs were performed. The first analysis was performed in order to verify the difference of hippocampal volume among groups. The second ANOVA was performed in order to check differences in alpha3/alpha2 relative power ratio in the three MCI subgroups ordered by decreasing tertile values of the hippocampal volume. In each ANOVA, group was the independent variable, the frequency ratios were the dependent variable.

2.6.2. AD Patients. In AD patients, the radial atrophy mapping was chosen because it is more suitable to study subregional volume of the hippocampus. Correlation maps between EEG rhythms and hippocampal surface were computed. The correlation analysis between EEG rhythms and hippocampal volume was performed only in 11 AD subjects; we otherwise compared hippocampal gray matter distribution maps between normal controls and AD patients in order to verify that the AD found correlations between EEG rhythms and hippocampal regions were present in areas where AD is more atrophic than normal subjects.

The correlation maps were generated on 3D models of the hippocampal formation where the dorsal and ventral surfaces can be appreciated. Zones with significant correlations were mapped onto the models based on an atlas where these are shown together with the corresponding MR sections ([55, 56]; Figure 1). The correlations and the associated *P* value maps were plotted onto a colour-coded model of the hippocampal surface. The statistical test for the correlations was computed using linear regression at each surface

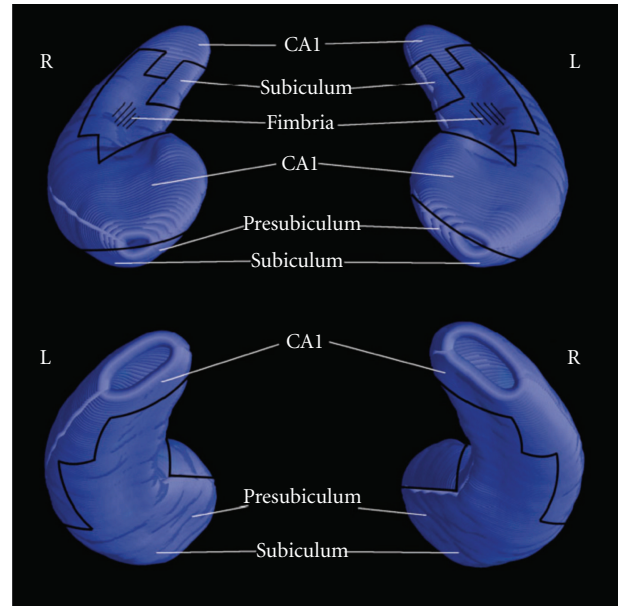

Figure 1: Cytoarchitectonic subregions mapped on blank MR-based models of the hippocampal formation of a healthy subject.

vertex on the hippocampus [54]. A surface point significance threshold of $P < 0.05$ was used to visualize the regional specificity of gray matter changes in the cortex. Set level correction for multiple comparisons was carried out by permutation testing at threshold of $P = 0.05$. Permutation tests are based on measuring the total area of the hippocampus with suprathreshold statistics, after setting the threshold at $P < 0.05$. To correct for multiple comparisons and assign an overall *P* value to each p map permutation, tests were used to determine how likely the observed level of significant atrophy (proportion of suprathreshold statistics, with the threshold set at $P < 0.05$) within each p map would occur by chance. The number of permutations N was chosen to be 100,000, to control the standard error SEp of omnibus probability *P*, which follows a binomial distribution B(N,p) with known standard error. When $N = 8,000$, the approximate margin of error (95% confidence interval) for p is around 5% of p. Both left and right hippocampal volumes were investigated in AD patients given the superior well-known left hemispheric involvement in declared dementia. The analysis on the AD subjects was conducted to verify the reliability of the alpha3/alpha2 ratio as factor associated with conversion of

Table 2: Relative alpha3/alpha2 relative power band ratios according to hippocampal volumes.

Hippocampal volume	Alpha3/alpha2 ratio (μv^2)	P value
Group1	1.04 ± 0.11	0.03
Group2	1.11 ± 0.15	
Group3	1.12 ± 0.14	

a subpopulation of MCI subjects in Alzheimer's disease. This results need further confirmation in a larger size population to strength the statistical power of the analysis. Of note, a larger population could be permitted to detect more precisely the volume ranges within the hippocampal subregions and their correlation with the EEG marker, ruling out other possible associations.

In the two groups of patients, MCI and AD patients, the MRI analysis method performed was different: volumetric analysis for MCI and radial atrophy mapping for AD patients. These different methods need different statistical approach in order to obtain more reliable results.

3. Results

3.1. MCI Patients. In this study, we were interested in morphofunctional (MRI-EEG) association and not in neuropsychological issues. MMSE values were provided as a general marker of the entity of the cognitive decline of patients.

Table 1 summarizes the ANOVA results of demographic variables, that is, age, education, MMSE score, and morphostructural characteristics, that is, hippocampal, and white matter hyperintensities volume in the whole MCI cohort as well as in the three subgroups in study. Significant statistical results were found in hippocampal volume (respectively, $F_{2,76} = 157.27$; $P < 0.00001$ and $F_{2,76} = 132.5$; $P < 0.00001$). Duncan's post-hoc test showed a significant increase ($P < 0.01$) in all comparisons. Table 2 shows the results of alpha3/alpha2 ratio in the groups based on the decrease of hippocampal volumes. ANOVA results revealed significant main effect group in alpha3/alpha2 ratio for hippocampal ($F_{2,76} = 3.38$; $P < 0.03$) decreasing volume.

3.2. AD Patients. Table 3 summarizes sociodemographic characteristics, MMSE scores, and alpha3/alpha2 power ratio in AD cohort. Figure 2 shows correlations between alpha3/alpha2 rhythms ratio and hippocampal volumes in AD patients. Negative significant associations are found between same areas of AD left hippocampus and alpha3/2 EEG rhythms. Correlations in right hippocampus resulted in being not significant at permutation testing ($P > 0.75$ *in both cases). There was no statistical difference considering the alpha2 or alpha3 spectral power alone.*

Table 3: Mean values ± standard deviation of sociodemographic characteristics, MMSE scores, and alpha3/alpha2 power ratio in AD cohort.

	AD
Number of subjects (f/m)	11 (6/5)
Age (years)	76.2 ± 2.3
Education (years)	4.6 ± 0.9
MMSE	21.3 ± 2.5
Alpha3/alpha2 ratio	1.5

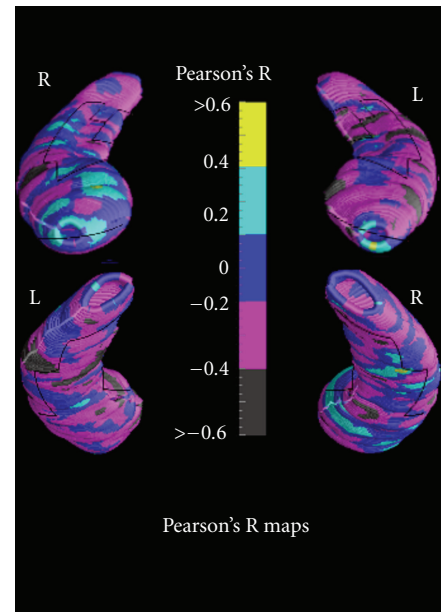

Figure 2: Correlation between alpha3/alpha2 power rhythm ratio and volumes of hippocampal subregions in AD patients.

4. Discussion

4.1. Preliminary Considerations. The findings of the present study permit to identify a reliable association between an EEG index (alpha3/alpha2 power ratio) and hippocampal atrophy. This EEG marker shows his reliability both in MCI and AD subjects, suggesting that it could identify some MCI subjects prone to conversion in AD. The principal limitations of the study are (1) the small size of the AD group; (2) the lack of a normal control group. These caveats need to be addressed by future studies performing a correlation analysis approach.

4.2. Alpha3/Alpha2 Ratio: Possible Relationship with Hippocampal Volume and Physiological Meaning in MCI and AD Patients. The increase of alpha3/alpha2 ratio is associated with the decrease of hippocampal volume, confirming previous results of our group showing that the increase of high alpha is related to hippocampal atrophy in MCI patients [21, 22]. The results show that in AD patients, increase of alpha3/alpha2 power ratio is correlated with the decrease of left hippocampal gray matter volumes. In particular, hippocampal areas involved in correlation are presubiculum, dorsal and ventral subiculum, CA2-3 sectors of the body, CA1 mesial, and lateral portion of the head. The prevalence of the modification of EEG rhythms in the left hemisphere in patients with AD was found also in a recent EEG coherence

study [57]. Indeed, in this study, pathologic changes of connectivity are significant on the frontotemporal region of the left hemisphere, but not on the right. Our findings confirm the asymmetry between left and right planum temporale previously shown in patients with AD [58]. A large body of literature has demonstrated the crucial role of the left hemisphere in semantic associative encoding [59] and of the left hippocampal-medial prefrontal pathways [60, 61].

The increase of high alpha synchronization has been found in internally-cued mechanisms of attention, associated with inhibitory top-down processes [62], acting as filter to irrelevant information. This filter activity could be carried out by hippocampus. Indeed, a recent work has demonstrated that the mossy fiber (MF) pathway of the hippocampus, connecting the dentate gyrus to the autoassociative CA3 network, is controlled by a feedforward circuit combining disynaptic inhibition with monosynaptic excitation. Analysis of the MF-associated circuit revealed that it could act as a highpass filter [63, 64].

The loss of inhibitory mechanism at hippocampal level impairs the filter function of hippocampus. The increase in cortico-subcortical inputs to hippocampal formation determines an increase of memory retrieval effort in long-term memory system and dysregulation of divided attention, in particular when multiple stimuli have to be processed [65–67] inducing behavioural dysfunction as well as subsequent memory deficits. The exchange of information between memory and attentive systems has been associated upper alpha band desynchronization [68, 69]. The synchronization of high alpha power has been demonstrated to be involved in top-down cognitive processes. This finding could suggest that there is an the attempt to focus attention on highly selective aspect to prevent interference of irrelevant stimuli (top-down process) in order to maintain a good memory performance [62]. Recently, we suggest that MCI subjects could fall in a "hyperattentive state" during the course of disease. Our results confirm this hypothesis, extending those findings to AD patients [70].

4.3. Hippocampal Formation and Alpha3/Alpha2 Ratio: Possible Network Interactions. A possible explanation should strongly consider that our results are obtained in an idling state. So, the discussion of the results has to address the default state of the brain. In this point of view, in a normal default state, large cell assemblies cooperate to keep an extensive network. This state is represented by the low alpha rhythm, typical of the EEG idling state. The increase of the alphae3/alpha2 power ration could suggest in MCI and AD patients the prevalence of smaller cell assemblies in the default state, due to synaptic disfunction or brain atrophy. Of note, seminal studies have demonstrated that large cell assemblies oscillates in low frequencies, whereas smaller cell assemblies develop higher frequencies [71].

The specific involvement of alpha rhythm could suggest that the hippocampal atrophy in AD is linked to functional changes in a broader network. Of note, the hypometabolism and atrophy of posterior cingulate/retrosplenial and medial temporal cortex pathway, strictly connected with both hippocampus and visual cortex, as well as with low alpha rhythm generation, are well demonstrated in AD [72]. So, the prevalence of high alpha could underlie the disruption of extensive synaptic connection deriving in the formation of smaller cell assemblies. The impairment of the network could explain memory and cognitive symptoms of AD beyond the hippocampal atrophy itself [70].

5. Conclusion

Our findings confirm the possible diagnostic role of EEG activity when integrated with morphostructural measures in patients with AD.

References

[1] R. C. Petersen and S. Negash, "Mild cognitive impairment: an overview," *CNS Spectrums*, vol. 13, no. 1, pp. 45–53, 2008.

[2] C. DeCarli, "Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment," *Lancet Neurology*, vol. 2, no. 1, pp. 15–21, 2003.

[3] C. R. Jack Jr., R. C. Petersen, Y. C. Xu et al., "Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease," *Neurology*, vol. 49, no. 3, pp. 786–794, 1997.

[4] A. T. Du, N. Schuff, D. Amend et al., "Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 71, no. 4, pp. 441–447, 2001.

[5] M. Bobinski, M. J. de Leon, A. Convit et al., "MRI of entorhinal cortex in mild Alzheimer's disease," *Lancet*, vol. 353, no. 9146, pp. 38–40, 1999.

[6] M. Golebiowski, M. Barcikowska, and A. Pfeffer, "Magnetic resonance imaging-based hippocampal volumetry in patients with dementia of the Alzheimer type," *Dementia and Geriatric Cognitive Disorders*, vol. 10, no. 4, pp. 284–288, 1999.

[7] M. P. Laakso, M. Lehtovirta, K. Partanen, P. J. Riekkinen, and H. Soininen, "Hippocampus in Alzheimer's disease: a 3-year follow-up MRI study," *Biological Psychiatry*, vol. 47, no. 6, pp. 557–561, 2000.

[8] T. den Heijer, M. I. Geerlings, F. E. Hoebeek, A. Hofman, P. J. Koudstaal, and M. M. Breteler, "Use of hippocampal and amygdalar volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly people," *Archives of General Psychiatry*, vol. 63, no. 1, pp. 57–62, 2006.

[9] L. Cahill, "Neurobiological mechanisms of emotionally influenced, long-term memory," *Progress in Brain Research*, vol. 126, pp. 29–37, 2000.

[10] L. Cahill and J. L. McGaugh, "Mechanisms of emotional arousal and lasting declarative memory," *Trends in Neurosciences*, vol. 21, no. 7, pp. 294–299, 1998.

[11] D. Paré and D. R. Collins, "Neuronal correlates of fear in the lateral amygdala: multiple extracellular recordings in conscious cats," *Journal of Neuroscience*, vol. 20, no. 7, pp. 2701–2710, 2000.

[12] D. Paré, D. R. Collins, and J. G. Pelletier, "Amygdala oscillations and the consolidation of emotional memories," *Trends in Cognitive Sciences*, vol. 6, no. 7, pp. 306–314, 2002.

[13] M. G. Packard, L. Cahill, and J. L. McGaugh, "Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 91, no. 18, pp. 8477–8481, 1994.

[14] Y. Ikegaya, H. Saito, and K. Abe, "Attenuated hippocampal long-term potentiation in basolateral amygdala-lesioned rats," *Brain Research*, vol. 656, no. 1, pp. 157–164, 1994.

[15] Y. Ikegaya, K. Abe, H. Saito, and N. Nishiyama, "Medial amygdala enhances synaptic transmission and synaptic plasticity in the dentate gyrus of rats in vivo," *Journal of Neurophysiology*, vol. 74, no. 5, pp. 2201–2203, 1995.

[16] I. Akirav and G. Richter-Levin, "Priming stimulation in the basolateral amygdala modulates synaptic plasticity in the rat dentate gyrus," *Neuroscience Letters*, vol. 270, no. 2, pp. 83–86, 1999.

[17] S. Frey, J. Bergado-Rosado, T. Seidenbecher, H. C. Pape, and J. U. Frey, "Reinforcement of early long-term potentiation (early-LTP) in dentate gyrus by stimulation of the basolateral amygdala: heterosynaptic induction mechanisms of late-LTP," *Journal of Neuroscience*, vol. 21, no. 10, pp. 3697–3703, 2001.

[18] M. Tsanov, N. Wright, S. D. Vann, J. T. Erichsen, J. P. Aggleton, and S. M. O'Mara, "Hippocampal inputs mediate theta-related plasticity in anterior thalamus," *Neuroscience*, vol. 187, pp. 52–62, 2011.

[19] J. P. Aggleton, S. M. O'Mara, S. D. Vann, N. F. Wright, M. Tsanov, and J. T. Erichsen, "Hippocampal-anterior thalamic pathways for memory: uncovering a network of direct and indirect actions," *European Journal of Neuroscience*, vol. 31, no. 12, pp. 2292–2307, 2010.

[20] H. Catenoix, M. Magnin, F. Mauguière, and P. Ryvlin, "Evoked potential study of hippocampal efferent projections in the human brain," *Clinical Neurophysiology*, vol. 122, no. 12, pp. 2488–2497, 2011.

[21] D. V. Moretti, M. Pievani, C. Fracassi et al., "Increase of theta/Gamma and Alpha3/Alpha2 ratio is associated with amygdalo-hippocampal complex atrophy," *Journal of Alzheimer's Disease*, vol. 17, no. 2, pp. 349–357, 2009.

[22] D. V. Moretti, C. Miniussi, G. B. Frisoni et al., "Hippocampal atrophy and EEG markers in subjects with mild cognitive impairment," *Clinical Neurophysiology*, vol. 118, no. 12, pp. 2716–2729, 2007.

[23] G. B. Frisoni, R. Ganzola, E. Canu et al., "Mapping local hippocampal changes in Alzheimer's disease and normal ageing with MRI at 3 Tesla," *Brain*, vol. 131, no. 12, pp. 3266–3276, 2008.

[24] A. C. Papanicolaou, P. G. Simos, E. M. Castillo, J. I. Breier, J. S. Katz, and A. A. Wright, "The hippocampus and memory of verbal and pictorial material," *Learning and Memory*, vol. 9, no. 3, pp. 99–104, 2002.

[25] B. A. Strange, P. C. Fletcher, R. N. Henson, K. J. Friston, and R. J. Dolan, "Segregating the functions of human hippocampus," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 7, pp. 4034–4039, 1999.

[26] A. M. Brickman, Y. Stern, and S. A. Small, "Hippocampal subregions differentially associate with standardized memory tests," *Hippocampus*, vol. 21, no. 9, pp. 923–928, 2011.

[27] K.-K. Shen, J. Fripp, F. Mériaudeau, G. Chételat, O. Salvado, and P. Bourgeat, "Detecting global and local hippocampal shape changes in Alzheimer's disease using statistical shape models," *NeuroImage*, vol. 59, no. 3, pp. 2155–2166, 2012.

[28] M. F. Folstein, S. E. Folstein, and P. R. McHugh, ""Mini mental state": a practical method for grading the cognitive state of patients for clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[29] C. P. Hughes, L. Berg, W. L. Danziger et al., "A new clinical rating scale for the staging of dementia," *British Journal of Psychiatry*, vol. 140, pp. 1225–1230, 1982.

[30] W. G. Rosen, R. D. Terry, and P. A. Fuld, "Pathological verification of ischemic score in differentiation of dementias," *Annals of Neurology*, vol. 7, no. 5, pp. 486–488, 1980.

[31] M. P. Lawton and E. M. Brody, "Assessment of older people: self-maintaining and instrumental activities of daily living," *Journal of Gerontologist*, vol. 9, no. 3, pp. 179–186, 1969.

[32] M. Albert, L. A. Smith, P. A. Scherr, J. O. Taylor, D. A. Evans, and H. H. Funkenstein, "Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease," *International Journal of Neuroscience*, vol. 57, no. 3-4, pp. 167–178, 1991.

[33] R. C. Petersen, R. Doody, A. Kurz et al., "Current concepts in mild cognitive impairment," *Archives of Neurology*, vol. 58, no. 12, pp. 1985–1992, 2001.

[34] R. C. Petersen, G. E. Smith, R. J. Ivnik et al., "Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals," *Journal of the American Medical Association*, vol. 273, no. 16, pp. 1274–1278, 1995.

[35] R. C. Petersen, G. E. Smith, S. C. Waring, R. J. Ivnik, E. Kokmen, and E. G. Tangelos, "Aging, memory, and mild cognitive impairment," *International Psychogeriatrics*, vol. 9, supplement 1, pp. 65–69, 1997.

[36] F. Portet, P. J. Ousset, P. J. Visser et al., "Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 77, no. 6, pp. 714–718, 2006.

[37] C. Geroldi, R. Rossi, C. Calvagna et al., "Medial temporal atrophy but not memory deficit predicts progression to dementia in patients with mild cognitive impairment," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 77, no. 11, pp. 1219–1222, 2006.

[38] B. Dubois, H. H. Feldman, C. Jacova et al., "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria," *Lancet Neurology*, vol. 6, no. 8, pp. 734–746, 2007.

[39] K. I. Shulman, "Clock-drawing: is it the ideal cognitive screening test?" *International Journal of Geriatric Psychiatry*, vol. 15, no. 6, pp. 548–561, 2000.

[40] P. Amodio, H. Wenin, F. del Piccolo et al., "Variability of Trail Making Test, Symbol Digit Test and Line Trait Test in normal people. A normative study taking into account age-dependent decline and sociobiological variables," *Aging: Clinical and Experimental Research*, vol. 14, no. 2, pp. 117–131, 2002.

[41] A. Basso, E. Capitani, and M. Laiacona, "Raven's coloured progressive matrices: normative values on 305 adult normal controls," *Functional Neurology*, vol. 2, no. 2, pp. 189–194, 1987.

[42] H. Spinnler and G. Tognoni, "Standardizzazione e taratura italiana di test neuropsicologici," *The Italian Journal of Neurological Sciences*, vol. 6, supplement 8, pp. 1–120, 1987.

[43] G. A. Carlesimo, C. Caltagirone, and G. Gainotti, "The mental deterioration battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioration Battery," *European Neurology*, vol. 36, no. 6, pp. 378–384, 1996.

[44] P. Caffarra, G. Vezzadini, F. Dieci, F. Zonato, and A. Venneri, "Rey-Osterrieth complex figure: normative values in an Italian population sample," *Neurological Sciences*, vol. 22, no. 6, pp. 443–447, 2002.

[45] L. S. Radloff, "The CES-D scale: a self-report depression scale for research in the general population," *Applied Psychological Measurement*, vol. 1, pp. 385–401, 1977.

[46] D. V. Moretti, C. Babiloni, G. Binetti et al., "Individual analysis of EEG frequency and band power in mild Alzheimer's disease," *Clinical Neurophysiology*, vol. 115, no. 2, pp. 299–308, 2004.

[47] W. Klimesch, "EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis," *Brain Research Reviews*, vol. 29, no. 2-3, pp. 169–195, 1999.

[48] R. Sperling, "Functional MRI studies of associative encoding in normal aging, mild cognitive impairment, and Alzheimer's disease," *Annals of the New York Academy of Sciences*, vol. 1097, pp. 146–155, 2007.

[49] G. McKhann, D. Drachman, M. Folstein et al., "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease," *Neurology*, vol. 34, no. 7, pp. 939–944, 1984.

[50] APA. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, APA, New York, NY, USA, IV edition, 1994.

[51] G. B. Frisoni, M. Pievani, C. Testa et al., "The topography of grey matter involvement in early and late onset Alzheimer's disease," *Brain*, vol. 130, no. 3, pp. 720–730, 2007.

[52] J. C. Pruessner, L. M. Li, W. Serles et al., "Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: minimizing the discrepancies between laboratories," *Cerebral Cortex*, vol. 10, no. 4, pp. 433–442, 2000.

[53] K. L. Narr, P. M. Thompson, P. Szeszko et al., "Regional specificity of hippocampal volume reductions in first-episode schizophrenia," *NeuroImage*, vol. 21, no. 4, pp. 1563–1575, 2004.

[54] P. M. Thompson, C. Schwartz, and A. W. Toga, "High-resolution random mesh algorithms for creating a probabilistic 3D surface atlas of the human brain," *NeuroImage*, vol. 3, no. 1, pp. 19–34, 1996.

[55] G. B. Frisoni, F. Sabattoli, A. D. Lee, R. A. Dutton, A. W. Toga, and P. M. Thompson, "In vivo neuropathology of the hippocampal formation in AD: a radial mapping MR-based study," *NeuroImage*, vol. 32, no. 1, pp. 104–110, 2006.

[56] H. M. Duvernoy, *The Human Hippocampus. Functional Anatomy, Vascularization and Serial Section with MRI*, Springer, Berlin, Germany, 3rd edition, 1998.

[57] D. V. Moretti, G. B. Frisoni, M. Pievani et al., "Cerebrovascular disease and hippocampal atrophy are differently linked to functional coupling of brain areas: an EEG coherence study in MCI subjects," *Journal of Alzheimer's Disease*, vol. 14, no. 3, pp. 285–299, 2008.

[58] P. M. Thompson, J. Moussai, S. Zohoori et al., "Cortical variability and asymmetry in normal aging and Alzheimer's disease," *Cerebral Cortex*, vol. 8, no. 6, pp. 492–509, 1998.

[59] E. Tulving, S. Kapur, F. I. Craik, M. Moscovitch, and S. Houle, "Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 91, no. 6, pp. 2016–2020, 1994.

[60] J. Apergis-Schoute, A. Pinto, and D. Paré, "Ultrastructural organization of medial prefrontal inputs to the rhinal cortices," *European Journal of Neuroscience*, vol. 24, no. 1, pp. 135–144, 2006.

[61] R. P. Vertes, "Interactions among the medial prefrontal cortex, hippocampus and midline thalamus in emotional and cognitive processing in the rat," *Neuroscience*, vol. 142, no. 1, pp. 1–20, 2006.

[62] W. Klimesch, P. Sauseng, and S. Hanslmayr, "EEG alpha oscillations: the inhibition-timing hypothesis," *Brain Research Reviews*, vol. 53, no. 1, pp. 63–88, 2007.

[63] O. C. Zalay and B. L. Bardakjian, "Simulated mossy fiber associated feedforward circuit functioning as a highpass filter," in *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pp. 4979–4982, 2006.

[64] S. M. Montgomery and G. Buzsáki, "Gamma oscillations dynamically couple hippocampal CA3 and CA1 regions during memory task performance," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 36, pp. 14495–14500, 2007.

[65] P. Johannsen, J. Jakobsen, P. Bruhn, and A. Gjedde, "Cortical responses to sustained and divided attention in Alzheimer's disease," *NeuroImage*, vol. 10, no. 3 I, pp. 269–281, 1999.

[66] A. Tales, J. Haworth, S. Nelson, R. J. Snowden, and G. Wilcock, "Abnormal visual search in mild cognitive impairment and Alzheimer's disease," *Neurocase*, vol. 11, no. 1, pp. 80–84, 2005.

[67] A. Tales, R. J. Snowden, J. Haworth, and G. Wilcock, "Abnormal spatial and non-spatial cueing effects in mild cognitive impairment and Alzheimer's disease," *Neurocase*, vol. 11, no. 1, pp. 85–92, 2005.

[68] P. Sauseng, W. Klimesch, W. Gruber, M. Doppelmayr, W. Stadler, and M. Schabus, "The interplay between theta and alpha oscillations in the human electroencephalogram reflects the transfer of information between memory systems," *Neuroscience Letters*, vol. 324, no. 2, pp. 121–124, 2002.

[69] P. Sauseng, W. Klimesch, M. Doppelmayr, S. Hanslmayr, M. Schabus, and W. R. Gruber, "Theta coupling in the human electroencephalogram during a working memory task," *Neuroscience Letters*, vol. 354, no. 2, pp. 123–126, 2004.

[70] D. V. Moretti, A. Prestia, C. Fracassi et al., "Volumetric differences in mapped hippocampal regions correlate with increase of high alpha rhythm in Alzheimer's disease," *International Journal of Alzheimer's Disease*, vol. 2011, article 208218, 2011.

[71] F. H. Lopes da Silva, J. P. Pijn, D. Velis, and P. C. Nijssen, "Alpha rhythms: noise, dynamics and models," *International Journal of Psychophysiology*, vol. 26, no. 1–3, pp. 237–249, 1997.

[72] G. B. Frisoni, A. Prestia, P. E. Rasser, M. Bonetti, and P. M. Thompson, "In vivo mapping of incremental cortical atrophy from incipient to overt Alzheimer's disease," *Journal of Neurology*, vol. 256, no. 6, pp. 916–924, 2009.

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Clinical Study

A Two-Study Comparison of Clinical and MRI Markers of Transition from Mild Cognitive Impairment to Alzheimer's Disease

D. P. Devanand,[1,2] Xinhua Liu,[3] Patrick J. Brown,[1] Edward D. Huey,[1,2] Yaakov Stern,[2] and Gregory H. Pelton[1]

[1] *Division of Geriatric Psychiatry, New York State Psychiatric Institute, College of Physicians and Surgeons, Columbia University, 1051 Riverside Drive, Unit 126, New York, NY 10032, USA*
[2] *Gertrude H. Sergievsky Center and Taub Institute for Research in Alzheimer's Disease and The Aging Brain, Department of Neurology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032, USA*
[3] *Department of Biostatistics, Columbia University School of Public Health, 722 West 168th Street, NY 10032, USA*

Correspondence should be addressed to D. P. Devanand, dpd3@columbia.edu

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A published predictor model in a single-site cohort study (questionable dementia, QD) that contained episodic verbal memory (SRT total recall), informant report of function (FAQ), and MRI measures was tested using logistic regression and ROC analyses with comparable measures in a second multisite cohort study (Alzheimer's Disease Neuroimaging Initiative, ADNI). There were 126 patients in QD and 282 patients in ADNI with MCI followed for 3 years. Within each sample, the differences in AUCs between the statistical models were very similar. Adding hippocampal and entorhinal cortex volumes to the model containing AVLT/SRT, FAQ, age and MMSE increased the area under the curve (AUC) in ADNI but not QD, with sensitivity increasing by 2% in ADNI and 2% in QD for a fixed specificity of 80%. Conversely, adding episodic verbal memory (SRT/AVLT) and FAQ to the model containing age, Mini Mental State Exam (MMSE), hippocampal and entorhinal cortex volumes increased the AUC in ADNI and QD, with sensitivity increasing by 17% in ADNI and 10% in QD for 80% specificity. The predictor models showed similar differences from each other in both studies, supporting independent validation. MRI hippocampal and entorhinal cortex volumes showed limited added predictive utility to memory and function measures.

1. Introduction

Mild cognitive impairment (MCI) often represents a transitional state between normal cognition and Alzheimer's disease (AD) [1, 2]. Accurate prediction of transition from MCI to AD aids in prognosis and targeting early treatment [3]. Episodic verbal memory impairment and informant report of functional deficits in complex social and cognitive tasks are features of incipient AD, and impairment in these domains is associated with transition from MCI to AD [4, 5].

Most biomarkers of MCI transition to AD are related to the underlying disease pathology of amyloid plaques and neurofibrillary tangles [6]. Hippocampal and entorhinal cortex atrophy on MRI scan of brain [7], parietotemporal hypometabolism on ^{18}FDG PET [8], increased amyloid uptake using PET [9], and decreased amyloid beta-42 (Aβ42) with increased tau/phospho-tau levels in the cerebrospinal fluid (CSF) [10, 11] each significantly predict transition from MCI to AD. The apolipoprotein E ε4 allele increases AD risk, but is not a strong biomarker of transition from MCI to AD [3].

In a meta-analysis, memory deficits appeared to be superior to MRI hippocampal atrophy in predicting transition to AD [12], but studies in the meta-analysis had highly variable subject inclusion/exclusion criteria and assessment methods. There has been a lack of direct head-to-head comparison of clinical and neuroimaging predictors of transition across different studies.

In our single-site study (Questionable Dementia or QD study) that evaluated and followed a broadly defined sample of patients with MCI, a published predictor model that included specific cognitive, functional, olfactory, and MRI measures strongly predicted transition to AD [3]. In the Alzheimer's Disease Neuroimaging Initiative (ADNI) study, cognitive and functional measures and several biomarkers are assessed in samples of MCI, AD, and healthy control subjects at baseline and serially during followup. In this paper, the first goal was to test the accuracy of a combination of predictor variables derived from the QD study to predict transition from MCI to AD in a completely independent ADNI sample. The validation of specific predictor combinations, rather than individual measures, has rarely been done in independent samples. This is essential before specific cut-points, and ranges for specific predictors in such models can be developed with confidence for eventual clinical application. The second goal was to evaluate the relative utility of clinical and MRI measures in predicting transition from MCI to AD.

2. Methods

Patients with MCI in the QD and ADNI studies were included, and patients with AD (ADNI) and healthy control subjects (QD and ADNI) were excluded. The 3-year followup samples were chosen because most transitions occur to AD within 3 years of clinical presentation [13].

2.1. QD Study. As previously reported, patients 41–85 years old who presented with subjective memory complaints for clinical evaluation to a Memory Disorders Clinic were eligible if they had a Folstein Mini-Mental State Exam (MMSE) score ≥22 out of 30, memory impairment defined as MMSE recall ≤2/3 objects at 5 minutes or a Selective Reminding Test (SRT) delayed recall score >1 SD below norms, and absence of a consensus diagnosis of dementia made by two experienced raters [3]. Patients could also be included if they had other cognitive and functional deficits. This study began before criteria for MCI were published [1, 2]. Baseline MCI subtype using the criterion of >1.5 SD below norms on cognitive tests was determined post hoc by using age, education, and sex-based regression norms derived from 83 healthy control subjects [4]. Using this approach, 73% of patients met the Peterson criteria for single or multidomain amnestic MCI, and this subsample was also compared to ADNI. The presence of specific neurological or major psychiatric disorders led to exclusion [3]. Patients were followed every 6 months for up to 9 years, and the two raters made a consensus diagnosis at each time point. The sample comprised 148 patients with MCI at baseline, and 126 patients were in the 3-year followup sample.

2.2. ADNI Study. Data were obtained from the ADNI study (http://adni.loni.ucla.edu/), a project launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and non-profit organizations as a $60 million, 5-year public-private partnership. The primary goal is to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

Participants 55–90 years old were enrolled if they had at least 6 years of education, spoke English or Spanish, agreed to longitudinal followup and neuroimaging tests, had single or multidomain MCI by the Petersen criteria with MMSE scores between 24 and 30, a memory complaint verified by informant, an abnormal memory score (1.5 SD below age-adjusted cutoff) on the Logical Memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale-Revised, and absence of a dementia diagnosis. All participants had a Geriatric Depression Scale score of <6 and a modified Hachinski score of ≤4. For a more detailed account of the inclusion/exclusion criteria, please see http://www.adni-info.org/. Raters at each site made consensus diagnoses at six-month intervals that included an evaluation of transition from MCI to AD, which was reviewed by a central committee. Data were obtained from ADNI on October 31, 2010. Of 394 individuals with MCI at baseline evaluation, 282 subjects completed 3 years of followup.

2.3. Comparable Baseline Measures Chosen for Analysis from QD and ADNI. In the QD study, the SRT total recall (12 items, 6 trials) was the strongest predictor among the five hypothesized neuropsychological predictors examined [3]. The SRT was not done in ADNI, but the comparable measure of total recall across 6 trials in the Auditory Verbal learning Test (AVLT) was not used for study inclusion criteria and was available. Informant report of the patient's functioning using the Pfeffer Functional Activities Questionnaire (FAQ) total score and MRI hippocampal and entorhinal cortex volumes was additional predictors in the final model in QD [3] that were also assessed in ADNI.

Both studies conducted MRI on 1.5T scanners: a single GE scanner in QD, and GE or Siemens or Philips scanners across 48 sites in ADNI. In QD, hippocampal volume was assessed by a semiautomated method with specific anatomical landmarks used to define hippocampal boundaries, and entorhinal cortex volume was computed from three slices centered at the level of the mammillary bodies [7]. In ADNI, MRI hippocampal and entorhinal cortex volumes were derived from postprocessed image analysis that used FreeSurfer (FS) version 4.3.0 by researchers at the University of California, San Francisco (UCSFFSX); the data are available at http://adni.loni.ucla.edu/. The volume derivation process is described at http://www.loni.ucla.edu/twiki/bin/view/ADNI/ADNIPostProc. For both studies, intracranial volume was a covariate in all analyses of hippocampal and entorhinal cortex volumes.

2.4. Statistical Analyses. Summary statistics were calculated to describe the sample characteristics in the ADNI and QD studies. For each study, Chi-square and t-tests were used

Table 1: Baseline sample characteristics of patients with MCI with three years of followup.

Variables	Alzheimer's Disease Neuroimaging Initiative (ADNI)				Questionable Dementia (QD) study			
	Total $N = 282$%	Nonconverter $N = 125$%	Converter $N = 157$%	Group difference Chi-square P value	Total ($N = 126$) %	Not converted ($N = 93$) %	Converted to AD ($N = 33$) %	Group difference Chi-square P value
Gender (% Male)	67.02	76.0	59.87	0.0063	26.19	48.39	39.39	0.3154
Race (%)								
Caucasian	92.20	92.00	92.36	0.8913	75.40	77.42	69.70	0.8452
Hispanic	2.84	2.40	3.18		16.67	15.05	21.21	
African American	2.48	2.40	2.55		5.56	5.38	6.06	
Other	2.48	3.20	1.91		2.40	2.15	3.03	
ApoE $\varepsilon 4$	56.03	40.00	68.35	<0.0001	27.27	25.27	33.33	0.5332
	Mean (SD)	Mean (SD)	Mean (SD)	t-test	Mean (SD)	Mean (SD)	Mean (SD)	t-test
Age (years)	74.59 (7.30)	74.63 (7.66)	74.56 (7.03)	0.9351	67.31 (9.72)	65.24 (9.69)	73.12 (7.21)	<0.0001
Education (years)	15.76 (2.88)	15.95 (2.81)	15.60 (2.94)	0.3074	15.18 (4.03)	15.58 (3.77)	14.06 (4.58)	0.0507
MMSE	27.08 (1.80)	27.62 (1.74)	26.66 (1.73)	<0.0001	27.52 (2.21)	28.02 (1.99)	26.12 (2.20)	<0.0001
AVLT/SRT	34.14 (10.90)	39.73 (12.16)	29.69 (7.16)	<0.0001	42.66 (9.49)	45.60 (8.26)	34.09 (7.50)	<0.0001
FAQ	2.84 (2.79)	1.61 (2.08)	3.82 (2.90)	<0.0001	1.69 (2.05)	1.28 (1.84)	2.73 (2.21)	0.0002
	$N = 274$	$N = 120$	$N = 154$	t-test	$N = 118$	$N = 89$	$N = 29$	t-test
Hippocampal volume	6.30 (1.10)	6.78 (1.01)	5.92 (1.02)	<0.0001	4.20 (0.73)	4.37 (0.62)	3.69 (0.74)	<0.0001
Entorhinal cortex volume	0.33 (0.08)	0.36 (0.07)	0.30 (0.07)	<0.0001	0.45 (0.10)	0.47 (0.09)	0.38 (0.09)	<0.0001
Intracranial volume	1580.79 (166.15)	1602.50 (152.48)	1563.69 (174.67)	0.0549	1306.60 (126.83)	1317.43 (128.55)	1273.71 (117.49)	0.0919

MMSE: Mini-Mental State Exam, AVLT: Auditory Verbal Learning Test (sum of 6 trials), SRT: Selective Reminding Task (sum of 6 trials), FAQ: Pfeffer's Functional Activities Questionnaire (10 items), SD: standard deviation, AD: Alzheimer's disease. Hippocampal, entorhinal, and intracranial volumes are in cubic centimeters. Entorhinal cortex volumes measured in cubic millimeters in ADNI were converted to cubic centimeters. Intracranial volume in ADNI covered all intracranial structures including the cerebellum, but intracranial volume in QD was restricted to supratentorial intracranial volume.

to detect differences in baseline categorical and continuous variables between MCI patients with and without transition to AD by three years of followup (there were few non-AD dementia cases in both studies). The QD and ADNI studies had different available followup duration times, and therefore survival analysis was not used for comparisons. For both datasets, specific sets of baseline predictors were examined in logistic regression models for the binary outcome of transition to AD within 3 years after baseline evaluation. With each model, sensitivity and specificity were calculated for all possible cut points on the predicted risk of transition to AD to construct receiver operating characteristic (ROC) curves. From the ROC curves, the area under the curve (AUC) was compared statistically between datasets and between nested models within each dataset.

3. Results

3.1. Demographic and Clinical Features of the Two Samples. Compared to the QD sample, the ADNI sample was older, had a greater proportion of males, had a higher proportion with the apoE $\varepsilon 4$ allele, and reported greater functional impairment (Table 1). The samples did not differ in years of educational attainment and MMSE scores.

3.2. Prediction of Transition from MCI to AD by 3-Year Followup. The majority of patients in ADNI (157/282 or 55.6%) and a minority of patients in QD (33/126 or 26.1%) converted to AD by 3-year followup; the disparity likely related to more stringent inclusion criteria for memory impairment in ADNI compared to QD. Based on logistic regression analyses, the combination of age and MMSE was a poor predictor in ADNI and showed low sensitivity at the fixed level of 90% specificity in QD (top of Table 2). Models that included age with MMSE and specific combinations of AVLT or SRT total recall, FAQ scores, hippocampal and entorhinal cortex volumes showed greater sensitivity, specificity, and predictive accuracy in the QD study compared to ADNI (Table 2).

3.3. Comparison of AUCs. Three predictor models were compared within and across studies with age and MMSE, which are common clinical indicators, contained in all models. Model 1 included AVLT/SRT and FAQ, Model 2 included hippocampal and entorhinal cortex volumes, and Model 3 included AVLT/SRT, FAQ, and hippocampal and entorhinal cortex volumes (Table 2). In each study, the increase in AUC for Model 1 compared to Model 2 was marginal (around 0.04 in both studies) and not statistically significant (bottom

Table 2: Predictive accuracy of specific combinations of predictor variables for classification of transition to Alzheimer's disease (AD) by 3 years of followup in two independent samples (ADNI and QD) of older adults with Mild Cognitive Impairment, and comparisons of three predictor models.

		ADNI			QD		
Model	Predictor variables	AUC (SE)	Sensitivity at specificity = 80% (90%)	Correct classification %	AUC (SE)	Sensitivity at specificity = 80% (90%)	Correct classification %
	Age	0.497	12.74 (5.73)	55.67	0.739	52.61 (29.85)	73.02
	MMSE	0.655	37.88 (19.20)	65.54	0.778	41.41 (26.79)	76.00
	Hippocampal vol.	0.725	48.05 (34.42)	64.60	0.753	62.07 (41.38)	80.51
	Entorhinal volume	0.718	50.65 (35.71)	67.16	0.773	67.86 (50.00)	80.34
	AVLT	0.756	49.47 (25.16)	44.33	0.849	71.63 (53.13)	80.00
	FAQ	0.738	49.05 (35.90)	44.33	0.708	45.46 (32.83)	75.42
	Age, MMSE	0.659	36.94 (18.79)	63.48	0.821	72.73 (39.39)	76.00
	Hippocampal and entorhinal volumes	0.744	55.84 (35.71)	68.98	0.824	67.86 (67.86)	88.03
	AVLT/SRT and FAQ	0.811	62.74 (42.68)	72.70	0.879	78.13 (59.38)	82.05
Model 1	Age, MMSE, AVLT/SRT and FAQ	0.828 (0.024)	73.25 (49.05)	73.40	0.921 (0.027)	90.63 (81.25)	87.07
Model 2	Age, MMSE, Hippocampal and entorhinal volumes	0.783 (0.028)	57.79 (40.26)	73.72	0.866 (0.046)	82.14 (71.43)	87.07
Model 3	Age, MMSE, AVLT/SRT, FAQ, Hippocampal and entorhinal volumes	0.865 (0.022)	75.33 (55.20)	77.01	0.940 (0.027)	92.59 (88.89)	89.72

Model comparisons	AUC difference	*P* value	AUC difference	*P* value
Model 1 versus Model 2	0.0396	0.2271	0.0428	0.3618
Model 1 versus Model 3	0.0428	0.0035**	0.0282	0.1979
Model 2 versus Model 3	0.0824	0.0001**	0.0710	0.0254*

A threshold of 0.5 was used on predicted risk derived from the logistic regression models. Area under the curve (AUC) was derived from receiver operating characteristic (ROC) analyses. $N = 282$ (157 converters) in ADNI and $N = 126$ (33 converters) in QD. The differences between models in AUCs are slightly different from the direct subtraction of AUCs between models because of missing data that ranged from 1% to 4% for the variables examined in ADNI and 1% to 5% for the variables examined in QD.
*$P < 0.05$, **$P < 0.01$.

of Table 2). The AUC increased consistently across the two studies when episodic verbal memory (AVLT/SRT) and function (FAQ) measures were added to the model containing the combination of age, MMSE, and hippocampal and entorhinal cortex volumes ($P < 0.0001$ in ADNI and $P = 0.0254$ in QD; Model 2 versus Model 3, bottom of Table 2 and Figure 1), with an appreciable increase in sensitivity for a fixed specificity of 80% and 90% in both ADNI (increases of 17% and 15%, resp.) and QD (increases of 10% and 17%, resp.; top of Table 2 and Figure 1). Conversely, adding hippocampal and entorhinal cortex volumes to AVLT/SRT, FAQ, age, and MMSE significantly increased the AUC in ADNI ($P = 0.0035$) but not in QD ($P = 0.20$) and led to a small increase in sensitivity for a fixed specificity of 80% and 90% in ADNI (increases of 2% and 6%, resp.) and QD (increases of 2% and 7%, respectively, top of Table 2).

In both samples, the differences in AUCs between the three statistical models examined were very similar (bottom of Table 2). Analyses of all combinations of predictors examined are in the supplemental Table 3. (see Supplementary Material available online at doi: 10.1155/2012/483469).

When the QD sample was restricted to patients with baseline amnestic MCI (32/90 transitioned to AD) using comparable criteria to ADNI inclusion criteria for amnestic MCI, the results were similar to the entire QD sample: 80.7% were correctly classified for Model 1, 85.5% for Model 2, and 84.2% for Model 3. AUCs were 0.877 for Model 1, 0.905 in Model 2, and 0.915 in Model 3 without significant differences in AUCs, partly because of reduced sample size.

4. Discussion

Within each sample, QD and ADNI, the differences in AUCs between predictor models were similar, suggesting robustness and generalizability across outpatient settings.

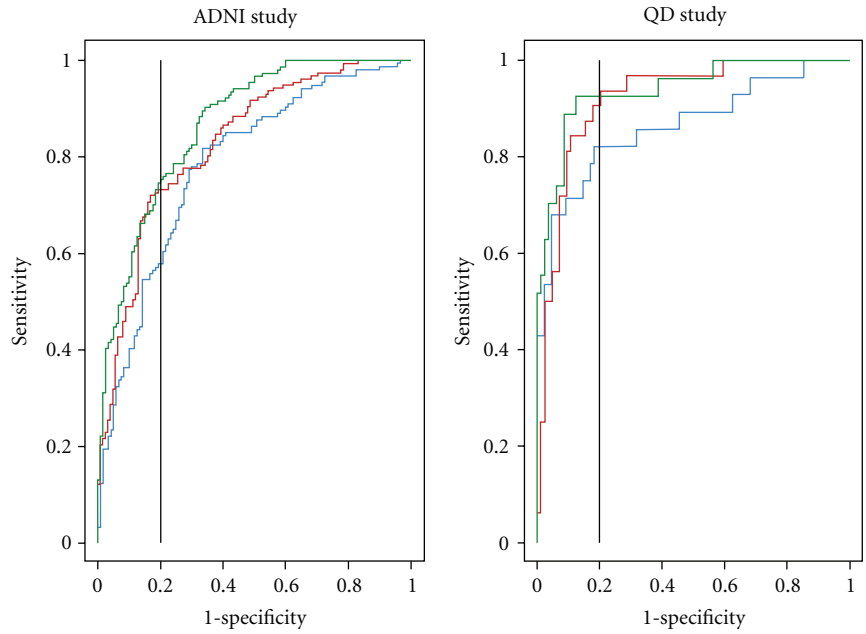

Figure 1: Comparison of receiver operating characteristic (ROC curves) for three statistical models in the ADNI and QD studies. Model 1 (red line) contained age, MMSE, AVLT/SRT and FAQ, Model 2 (blue line) contained age, MMSE, hippocampal and entorhinal cortex volumes, and Model 3 (green line) contained age, MMSE, AVLT/SRT, FAQ, hippocampal and entorhinal cortex volumes. The vertical lines at 80% specificity (0.2 on x-axis) indicate 20% false positives.

When advising patients and families about the likelihood of transition from MCI to AD, a predictor model with specificity over 80% is essential because a false positive rate of over 20% (specificity less than 80%) is clinically unacceptable [14, 15]. In the predictor model, adding hippocampal and entorhinal cortex atrophy to age, MMSE, and the episodic verbal memory and function measures increased sensitivity only to a small extent at fixed specificities of 80% and 90%. These findings suggest limited added utility for MRI hippocampal and entorhinal cortex volumes to clinical assessment of memory and function in predicting transition from MCI to AD. In contrast, adding measures of episodic verbal memory and function to the model that combined age, MMSE, and hippocampal and entorhinal cortex volumes appreciably increased sensitivity for fixed levels of 80% and 90% specificity in both samples. In both studies, the model that included AVLT/SRT, FAQ, and hippocampal and entorhinal cortex volumes with age and MMSE showed the strongest predictive accuracy.

For episodic verbal memory measures, numerical ranges and cutoffs for specific ages and education levels can inform the likelihood of transition to AD. Although delayed recall deficit is typical in AD, both immediate recall (incorporates learning) and delayed recall show comparable predictive accuracy for the transition from MCI to AD [4]. The use of a single episodic memory measure in the predictor models examined does not replace the need for a comprehensive neuropsychological evaluation for diagnostic purposes [4]. Informant reports of FAQ scores reflect instrumental, social, and cognitive functional impairments, but specific cutoffs for prediction of transition to AD are not established [5, 16]. International efforts to standardize MRI imaging parameters and methods of volumetric assessment [17], both of which have varied widely across studies, may lead to the development of specific cutoffs for hippocampal and entorhinal cortex atrophy that improve predictive accuracy.

The use of cognitive markers has some advantages over neuroimaging: objectivity in scoring, comparative economy in expense and time, and reliability. One argument is that episodic verbal memory should not be used as a marker because it is used for inclusion criteria and in the diagnostic process. However, evaluation of severity of episodic verbal memory deficit as a predictor in patients with amnestic MCI who have episodic verbal memory deficits is analogous to the established strategy of evaluating severity of depression as a predictor of clinical course and treatment response in major depression [18]. Further, using memory test scores in prediction creates a statistical handicap, rather than an advantage, by restricting the range in baseline memory test performance [12]. Of note, the AVLT memory measure examined as a predictor in this paper was not part of the study inclusion criteria in ADNI (WMS-R logical memory was used). The same rationale applies to the incorporation of the MMSE, which is widely used and clinically relevant, in predictor analyses even though it is part of the screening criteria for study inclusion.

Informant report of functional impairment using the FAQ was not part of the inclusion criteria in either QD or ADNI, and the definition of MCI by the original Petersen criteria requires the absence of significant functional

impairment [1, 2]. Therefore, the use of informant report of functional impairment is independent of the diagnostic criteria for MCI, and our findings indicate that this type of assessment is important in predicting transition to AD [3, 5].

Clinical and neurobiological markers have been incorporated recently into diagnostic classification systems. An international panel used the terms "prodromal dementia" and "predementia" to indicate that neurobiological markers may identify patients with incipient AD who cannot be diagnosed clinically [19]. The new NIA diagnostic criteria separate core clinical criteria from research criteria that employ neurobiological markers [20], partly because diagnostic and predictive accuracy for neurobiological markers has not been fully developed and validated. Our results emphasize the need for such validation.

There have been few comparisons of predictor models between studies. In a comparison of ADNI to a Finnish study, classification performance did not increase after the inclusion of 10 variables that included CSF measures, apolipoprotein E $\varepsilon 4$, MRI measures, age, and education [21]. The overall model was not strong, possibly because key cognitive and functional measures were excluded. Another study compared different samples of patients with MCI who had ^{18}FDG PET with generally positive results [22] but without cut-points for clinical application. Our report represents a novel independent validation of predictor models that included clinical, memory, functional, and MRI measures. The consistency in the differences between models in each study indicates that this two-study comparison is broader and more clinically relevant than prior validation attempts [21, 22].

From the ADNI database, several reports show moderate predictive accuracy for weighted scores within a global cognitive test [23] and moderately strong predictive accuracy for specific neuropsychological test scores [24], consistent with other studies [4]. The best possible fit from a high-dimensional pattern classification approach using ADNI MRI data [25] led to results similar to our report that used volumetric measures, but other MRI analytic strategies using ADNI data have led to lower predictive accuracy [26, 27]. Entorhinal cortex volume enhanced prediction in both ADNI and QD in our comparisons, supporting the evaluation of entorhinal cortex volume as a predictor [7].

There were some limitations to this paper. The two samples differed in sex and age distribution and cognitive test scores, significant episodic verbal memory deficits were required in ADNI compared to broader inclusion criteria in QD that may partly account for higher transition rates in ADNI, and different episodic verbal memory measures and different MRI volumetric assessment methods were compared. Nonetheless, within each sample for several combinations of predictors the differences in AUCs were similar. The high transition rate in ADNI suggests that some patients diagnosed with MCI by 3-year followup may convert in subsequent years, likely leading to a higher rate of false negatives in ADNI. This may partly explain the lower accuracy for predictor combinations in ADNI. In ADNI, the smaller number of patients at 3-year followup was partly related to some recently recruited patients not yet having had the opportunity to reach 3-year followup at the time of data analysis for this paper. This issue also precluded the use of survival analysis in this sample. In QD, we derived the strongest predictors from a set of a priori measures in a large neuropsychological test battery and examined comparable measures from the shorter ADNI neuropsychological assessment. While administering a comprehensive neuropsychological test battery is important for diagnostic purposes, our clinically relevant approach of examining individual measures facilitates comparison across studies and demonstrates the predictive strength of even a single episodic verbal memory test. Baseline MRI measures were examined because serial MRI measures were not available in QD. It remains unclear if serial imaging measures are superior to baseline imaging in predicting long-term outcome [28]. Serial imaging measures provide useful information about structural changes associated with disease progression, but they are expensive, not current clinical practice, and not useful in early converters. Cerebrovascular disease may contribute to cognitive decline in these patients [19, 20]. However, hyperintensities, lacunes, and infarcts could not be assessed systematically in QD because of the MRI sequences obtained (no FLAIR or comparable sequence) and therefore could not be compared with ADNI. Absent neuropathological validation, we considered examining CSF measures from ADNI (not done in QD) for in vivo validation of transition to AD, but CSF was not collected in approximately half the ADNI sample and neuropathological validation of CSF tau and Aβ abnormalities has not been established.

In QD, the pathophysiological measure [19] of olfactory identification deficits (not done in ADNI) strongly predicted transition to AD with limited overlap in prediction with the SRT and MRI measures [3, 29]. In ADNI, ^{18}FDG indices (not done in QD) significantly predicted transition to AD and were superior to the ADAS-cog [8], but the ADAS-cog is a global cognitive measure used primarily in clinical trials of AD patients and is not established as a strong predictor of transition from MCI to AD. PET amyloid imaging discriminates among AD, MCI, and controls [30] and correlates at autopsy with amyloid plaques [9]. However, approximately 10–30% of healthy controls show increased amyloid uptake [30] and whether these subjects have incipient AD needs confirmation in long-term followup studies. The sensitivity and specificity of CSF levels of Aβ42 and tau/phospho tau, and their ratio, for predicting MCI transition to AD in ADNI [31] and in a European multicenter study [32] ranged from 65% to 75%, which is slightly lower than that in other reports [10, 11]. For CSF markers, further refinement of assay technique and validation in long-term followup studies are needed to establish more definitive cut-points for individual and ratio measures that have varied to some extent across studies [10, 11, 32].

This report suggests that volumetric evaluation of medial temporal lobe atrophy adds only marginally to the information obtained by cognitive testing and assessment of episodic memory, and it cannot yet be recommended for wide clinical use to assess the risk of patients with MCI being diagnosed with AD during followup. In the clinic, visual inspection ratings are likely to lead to lower predictive accuracy than either the QD or ADNI volumetric assessments. Structural

neuroimaging with MRI remains useful to rule out specific causes of cognitive impairment, for example, stroke, tumor. A key conclusion from this report is that conducting neuropsychological evaluation is important, and interviewing family members or other informants about the patient's functioning may be at least as important as conducting an MRI scan. Several clinical and neurobiological markers, including cognitive test scores, functional ability, and MRI and ^{18}FDG PET measures, are influenced considerably by age and other demographic factors, and their utility needs to be evaluated in more heterogeneous samples. The comparative predictive utility of clinical and neurobiological markers needs further assessment across different populations as these measures improve in predictive accuracy.

Disclosure

Data used in the preparation of this paper included data obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu/). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. Complete listing of ADNI investigators is available at http://adni.loni.ucla.edu/.

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References

[1] R. C. Petersen, G. E. Smith, S. C. Waring, R. J. Ivnik, E. G. Tangalos, and E. Kokmen, "Mild cognitive impairment: clinical characterization and outcome," *Archives of Neurology*, vol. 56, no. 3, pp. 303–308, 1999.

[2] R. C. Petersen, G. E. Smith, S. C. Waring, R. J. Ivnik, E. G. Tangalos, and E. Kokmen, "Erratum: Mild cognitive impairment: clinical characterization and outcome," *Archives of Neurology*, vol. 56, no. 6, p. 760, 1999.

[3] D. P. Devanand, X. Liu, M. H. Tabert et al., "Combining early markers strongly predicts conversion from mild cognitive impairment to Alzheimer's disease," *Biological Psychiatry*, vol. 64, no. 10, pp. 871–879, 2008.

[4] M. H. Tabert, J. J. Manly, X. Liu et al., "Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment," *Archives of General Psychiatry*, vol. 63, no. 8, pp. 916–924, 2006.

[5] M. H. Tabert, S. M. Albert, L. Borukhova-Milov et al., "Functional deficits in patients with mild cognitive impairment: prediction of AD," *Neurology*, vol. 58, no. 5, pp. 758–764, 2002.

[6] C. R. Jack Jr., D. S. Knopman, W. J. Jagust et al., "Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade," *The Lancet Neurology*, vol. 9, no. 1, pp. 119–128, 2010.

[7] D. P. Devanand, G. Pradhaban, X. Liu et al., "Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease," *Neurology*, vol. 68, no. 11, pp. 828–836, 2007.

[8] S. M. Landau, D. Harvey, C. M. Madison et al., "Comparing predictors of conversion and decline in mild cognitive impairment," *Neurology*, vol. 75, no. 3, pp. 230–238, 2010.

[9] C. M. Clark, J. A. Schneider, B. J. Bedell et al., "Use of florbetapir-PET for imaging beta-amyloid pathology," *Journal of the American Medical Association*, vol. 305, no. 3, pp. 275–283, 2011.

[10] O. Hansson, H. Zetterberg, P. Buchhave, E. Londos, K. Blennow, and L. Minthon, "Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study," *The Lancet Neurology*, vol. 5, no. 3, pp. 228–234, 2006.

[11] P. J. Visser, F. Verhey, D. L. Knol et al., "Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study," *The Lancet Neurology*, vol. 8, no. 7, pp. 619–627, 2009.

[12] B. Schmand, H. M. Huizenga, and W. A. van Gool, "Meta-analysis of CSF and MRI biomarkers for detecting preclinical Alzheimer's disease," *Psychological Medicine*, vol. 40, no. 1, pp. 135–145, 2010.

[13] B. Winblad, K. Palmer, M. Kivipelto et al., "Mild cognitive impairment—beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment," *Journal of Internal Medicine*, vol. 256, no. 3, pp. 240–246, 2004.

[14] Consensus report of the Working Group, "Molecular and biochemicalmarkers of Alzheimer's disease," *Neurobiology of Aging*, vol. 19, no. 2, pp. 109–116, 1998, The Ronald and Nancy

Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group.

[15] Consensus report of the Working Group, "Molecular and Biochemical Markers of Alzheimer's Disease," *Neurobiology of Aging*, vol. 19, no. 3, p. 285, 1998, Erratum: The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group.

[16] P. J. Brown, D. P. Devanand, X. Liu, and E. Caccappolo, "Functional impairment in elderly patients with mild cognitive impairment and mild Alzheimer disease," *Archives of General Psychiatry*, vol. 68, no. 6, pp. 617–626, 2011.

[17] G. B. Frisoni, N. C. Fox, C. R. Jack Jr., P. Scheltens, and P. M. Thompson, "The clinical use of structural MRI in Alzheimer disease," *Nature Reviews Neurology*, vol. 6, no. 2, pp. 67–77, 2010.

[18] L. S. Schneider, J. C. Nelson, C. M. Clary et al., "An 8-week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression," *American Journal of Psychiatry*, vol. 160, no. 7, pp. 1277–1285, 2003.

[19] B. Dubois, H. H. Feldman, C. Jacova et al., "Revising the definition of Alzheimer's disease: a new lexicon," *The Lancet Neurology*, vol. 9, no. 11, pp. 1118–1127, 2010.

[20] M. S. Albert, S. T. DeKosky, D. Dickson et al., "The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimer's and Dementia*, vol. 7, no. 3, pp. 270–279, 2011.

[21] M. van Gils, J. Koikkalainen, J. Mattila, S. K. Herukka, J. Lötjönen, and H. Soininen, "Discovery and use of efficient biomarkers for objective disease state assessment in Alzheimer's disease," in *Proceedings of the IEEE Engineering in Medicine and Biology Society*, vol. 2010, pp. 2886–2889, September 2010.

[22] C. Haense, K. Herholz, W. J. Jagust, and W. D. Heiss, "Performance of FDG PET for detection of Alzheimer's disease in two independent multicentre samples (NEST-DD and ADNI)," *Dementia and Geriatric Cognitive Disorders*, vol. 28, no. 3, pp. 259–266, 2009.

[23] D. A. Llano, G. Laforet, and V. Devanarayan, "Derivation of a new ADAS-cog composite using tree-based multivariate analysis: prediction of conversion from mild cognitive impairment to alzheimer disease," *Alzheimer Disease and Associated Disorders*, vol. 25, no. 1, pp. 73–84, 2011.

[24] M. Ewers, C. Walsh, J. Q. Trojanowski, and North American Alzheimer's Disease Neuroimaging Initiative (ADNI), "Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance," *Neurobiology of Aging*. In press.

[25] C. Misra, Y. Fan, and C. Davatzikos, "Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: results from ADNI," *NeuroImage*, vol. 44, no. 4, pp. 1415–1422, 2009.

[26] R. Cuingnet, E. Gerardin, J. Tessieras et al., "Automatic classification of patients with Alzheimer's disease from structural MRI: a comparison of ten methods using the ADNI database," *NeuroImage*, vol. 56, no. 2, pp. 766–781, 2011.

[27] R. Wolz, R. A. Heckemann, P. Aljabar et al., "Measurement of hippocampal atrophy using 4D graph-cut segmentation: application to ADNI," *NeuroImage*, vol. 52, no. 1, pp. 109–118, 2010.

[28] E. A. Murphy, D. Holland, M. Donohue et al., "Six-month atrophy in MTL structures is associated with subsequent memory decline in elderly controls," *NeuroImage*, vol. 53, no. 4, pp. 1310–1317, 2010.

[29] M. H. Tabert, X. Liu, R. L. Doty et al., "A 10-item smell identification scale related to risk for Alzheimer's disease," *Annals of Neurology*, vol. 58, no. 1, pp. 155–160, 2005.

[30] M. A. Mintun, G. N. Larossa, Y. I. Sheline et al., "[11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease," *Neurology*, vol. 67, no. 3, pp. 446–452, 2006.

[31] G. De Meyer, F. Shapiro, H. Vanderstichele et al., "Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people," *Archives of Neurology*, vol. 67, no. 8, pp. 949–956, 2010.

[32] N. Mattsson, H. Zetterberg, O. Hansson et al., "CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment," *Journal of the American Medical Association*, vol. 302, no. 4, pp. 385–393, 2009.