REVIEW

Assessing the progression of mild cognitive impairment to Alzheimer's disease: current trends and future directions

Larry G Brooks[1] and David A Loewenstein[2,3]*

Abstract

With the advent of advances in biomarker detection and neuropsychological measurement, prospects have improved for identifying and tracking the progression of Alzheimer's disease (AD) from its earliest stages through dementia. While new diagnostic techniques have exciting implications for initiating treatment earlier in the disease process, much work remains to be done to optimize the contributions of the expanding range of tools at the disposal of researchers and clinicians. The present paper examines recent work in cerebrospinal fluid biomarkers, magnetic resonance imaging, positron emission tomography, neuropsychological measures, and functional assessment. The strengths and weaknesses of current methodologies are explored and discussed. It is concluded that AD from its mild cognitive impairment state through dementia represents a continuous process, and that progression over time can best be accomplished by interval-level variables. Biomarkers that are most sensitive to early AD may not be the most optimal for monitoring longitudinal change, and it is likely that multivariate models incorporating cognitive measures, functional variables and biomarker data will be the most fruitful avenues for future research.

Introduction

A hallmark feature of the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria for a

*Correspondence: dloewenstein@med.miami.edu
[2]Department of Psychiatry and Behavioral Sciences and Center on Aging, Miller School of Medicine, University of Miami, 1695 NW 9th Avenue, Suite 300, Miami, FL 33136, USA
Full list of author information is available at the end of the article

clinical diagnosis of probable Alzheimer's disease (AD), first established over 25 years ago, was the requirement of a dementia syndrome. The clinician then proceeded to systematically rule out and exclude other neurological and/or medical conditions that might have accounted for the observed cognitive decline. This set of criteria as well as the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition) criteria for a dementia syndrome and probable AD [1] were designed to be conservative so that a neurodegenerative condition could not be established unless cognitive function was sufficiently compromised to interfere with an individual's social and/or occupational function.

Since AD probably develops many years before cognitive symptoms are manifest [2] and cognitive deficits are evident before the appearance of a full-blown dementia syndrome, increasing attention has been focused on mild cognitive impairment (MCI) as an intermediary state between normal cognition and AD [3,4]. The generally accepted criteria for MCI are the presence of a memory or other cognitive complaint by an individual or other knowledgeable informant, objective deficits on standardized objective cognitive tests and the lack of a dementia syndrome characterized by intact general intellectual function and no significant deficits in social and/or occupational function. As disease-modifying agents are developed, the best hope for prevention or cure lies in treating the disorder in its earliest stages before the brain is severely compromised by multisystem degeneration [5].

Efforts at earlier detection of AD face significant challenges in improving assessment of the earliest cognitive and neuropathological changes associated with early AD, identifying those MCI cases that are most likely to progress over time, and gauging the progression of MCI to a clinical diagnosis of AD. This improvement requires assessment tools that are sensitive to subtle cognitive changes, as well as measures that are adequate in evaluating deterioration in cognitive abilities over time. Complicating efforts at early diagnosis are the fact that not all cases of MCI will progress to dementia, and

that not all cases of dementia will eventually be diagnosed with AD. This is particularly true in epidemiological studies, where the reversion of MCI to non-MCI has been as high as 40% [6] – as opposed to the progression ranging from 10 to 15% in specialty memory disorders clinics and other clinical settings [3,7].

The popular term regarding conversion from MCI to dementia of the AD type is probably a misnomer. If one has correctly identified underlying AD in a predementia phase, then progression to a clinical diagnosis of AD is merely dependent on the individual progressing to a particular threshold at which point there is sufficient cognitive and functional impairment to merit the diagnosis of a dementia syndrome (provided that the clinician can rule out other potential etiologies). In recent years, there has been increasing concern that AD is not being identified in its earlier stages because of a failure to emphasize the primary episodic memory deficit and abnormal biomarkers associated with the disorder, specifically volumetric magnetic resonance imaging (MRI), positron emission tomography (PET) neuroimaging, and cerebrospinal fluid (CSF) analysis of amyloid β or tau proteins [8]. Furthermore, the delineation between MCI and dementia that is critical to a diagnosis of AD may vary as a function of experience and/or idiosyncratic thresholds of an individual clinician in judging whether an individual's cognitive impairment is significantly interfering with social and/or occupational function [9].

What follows is an examination of different types of measures that are sensitive to early AD in the MCI state, and perhaps at an earlier stage, and are most effective for tracking progression to a dementia state over time.

Cognitive measures

Despite the excitement about recent advances in the identification of AD-related biomarkers, neuropsychological assessment remains a critical component of evaluation to ensure a cognitive correlate of biomarker abnormalities and to assist in detecting and tracking progression of early AD. Neuropsychological evaluation provides both standardized and objective assessment of the hallmark feature of MCI and AD: the disturbance of memory and/or other cognitive functions – in particular, episodic memory deficits as manifested by impaired delayed recall [10], faster rate of forgetting [11], and problems with learning new information [12]. Deficits in delayed recall and other memory functions have been found to be predictive of cognitive decline in community-dwelling older subjects [13] and of progression of MCI to dementia [14].

Deficits in early AD, however, are not only limited to memory. Although memory dysfunction is typically the most common manifestation of early AD, some cases first present with executive, language or visuospatial disturbances. It is widely accepted that memory impairment across multiple memory measures or a combination of deficits in memory and nonmemory measures have less reversion to normal and faster rates of progression to dementia than those with single amnestic or nonamnestic cognitive impairments [15]. This suggests that multiple cognitive impairments or severity of deficits in a single domain such as memory may be a proxy for the patient's stage of illness. As noted in the new proposed guidelines for MCI related to AD [16], serial cognitive assessments of an individual in the MCI stage of AD allows for the assessment of cognitive decline over time and enhances confidence in the progressive nature of the disorder and its underlying etiology. Techniques such as reliable change indices and consideration of practice effects are methods to measure meaningful change at an individual level, which can also be useful in analyzing the results of clinical trials [17].

In assessing the progression of mild cognitive impairment to AD, it is imperative that MCI is correctly diagnosed and that these underlying cognitive impairments accurately reflect the underlying AD pathology. Current challenges in the cognitive assessment of MCI include: test selection, the availability of normative databases, and the effect of different base rates of MCI and AD in different settings; establishing cut-off points for impairment; and developing measures more sensitive to early AD while having sufficient specificity to distinguish between etiologically different conditions.

Methodologically, the lack of uniformity in the selection of neuropsychological measures and the use of different normative databases often make it challenging to compare study results across settings and internationally. Further, differential base rates of true underlying cognitive impairment or AD pathology in older adults presenting to specialty memory disorder clinics compared with a general medical practice or in epidemiological settings may affect the diagnostic accuracy of neuropsychological tests. In general, a low prevalence or base rate of true cognitive impairment in a particular setting tends to reduce the positive predictive value or the probablility that a positive test represents true impairment while false negatives will remain low. In contrast, when the base rates of true cognitive impairment are high, the positive predictive value is high but there is an increased probability that a negative test will not reflect a true absence of impairment.

Another challenge in cognitive assessment is the issue of cognitive reserve [18], which allows persons with diseased brains to use compensatory mechanisms that may mask overt manifestations of disease. Possible solutions to the problem of diagnosing cognitive impairment in highly intelligent people is to apply appropriate norms for these subgroups, to develop more cognitively

challenging measures where compensation is more difficult or to employ test paradigms that allow within-subject comparisons of different aspects of memory (some of which are particularly vulnerable to early manifestations of AD).

Diagnostically, the lack of standardization in cut-off points employed to determine impairment also creates discrepancies in the literature, which affects the ability to compare studies examining progression to specific endpoints among different national and international research groups [19]. Many studies of amnestic mild cognitive impairment (aMCI) employ a 1.5 standard deviation cut-off point relative to age and educational norms on one or more memory measures, with the realization that as the number of tests increases, there is a tendency towards false positives [20]. Other studies recommend using multiple memory measures but require a cut-off point of 1.0 standard deviation below expected levels on at least two cognitive tests in the same cognitive domain [15]. In the current large ADNI-GO multisite neuroimaging study [21], provided that subjects meet clinical criteria for early MCI, educationally referenced scores on delayed paragraph recall at 0.5 to 1.0 standard deviation below expected levels are considered sufficient for inclusion as early aMCI. At the other extreme, an individual with objective memory impairment ≥3 standard deviations below expected levels may still be classified as MCI if the clinician does not judge there to be sufficient impairments in social and/or occupational function to meet criteria for dementia. Indeed, in the new proposed criteria for MCI related to AD a range of impairment of 1.0 to 1.5 standard deviations below expected levels on tests is typically expected on neuropsychological tests [16], but this is not a requirement as more emphasis is placed on clinical history and examination. MCI as it is currently conceptualized therefore represents a wide range of individuals with varying severity of cognitive impairment. It naturally follows that the rate of progression to dementia, and an eventual AD state, may largely reflect the degree of initial disease severity as measured by cognitive measures.

Specific patterns of cognitive impairments may not be specific to one disease entity. Disorders such as AD, diffuse Lewy body disease, cerebrovascular disorders and frontotemporal dementia are generally thought to have characteristic cognitive presentations in the early stages of disease but there can be considerable overlap in cognitive performance across disease entities. This overlap problem is particularly salient in the two most common forms of dementia – AD and vascular dementia – where meta-analytic studies have found a limited ability of cognitive tests to distinguish between groups [22]. In a study of autopsy-defined subjects with cerebrovascular disease and AD, a majority of AD subjects exhibited a cognitive profile characterized by memory impairment – but no reliable characteristic profile existed for cerebrovascular disease [23]. Another meta-analysis comparing AD with frontotemporal dementia showed significant differences between groups on multiple measures, but the considerable overlap between groups renders differential diagnosis in individual cases difficult [24]. Similarly, there is considerable heterogeneity among individuals that limits specificity in distinguishing between MCI of different etiologies [25].

Tracking progression from MCI to dementia and an eventual diagnosis of AD requires cognitive measures sensitive to change over time. Although measures such as the Alzheimer's Disease Assessment Scale (cognitive sub-scale) have been employed in a number of large-scale pharmacological studies of AD, there may be insufficient sensitivity to change in early-stage MCI. For example, in the GEM study, the annual rate of change on the Alzheimer's Disease Assessment Scale (cognitive sub-scale) for MCI patients was considerably less than the degree of change considered clinically significant in AD trials [26].

While there is currently a plethora of memory tests available, list-learning tests have the dual advantages of multiple learning trials and delayed recall. Dubois and colleagues contend that increased encoding specificity at acquisition and assessed failure to benefit from cuing at recall are superior to episodic memory tests using free recall alone in identifying early cases of AD [8]. Indeed, it has been previously shown that a primary deficit in profiting from encoding cues at baseline and follow-up was superior to free recall and other traditional measures in detecting cognitive impairment [27]. Deficits on the MCT, a test of controlled learning and cued semantic recall, were recently uniquely sensitive and related to the presence of [^{11}C]Pittsburgh compound B (PiB) on PET scans in community older people [27]. Our group has found that list-learning tests employing distractor tasks between acquisition trials and competing lists enhancing susceptibility to semantic interference both have excellent sensitivity for MCI and are predictive of progression from MCI to dementia [12,20]. The advantage of these aforementioned paradigms is that they target specific semantic memory processing deficits that may be specific to early AD. Comparison of the individual's performances on different aspects of the same test seems well-suited to dealing with issues of high cognitive reserve. Although promising, future research is needed to determine the specificity of such findings to AD and their utility in serial assessments over time.

Functional assessment in mild cognitive impairment

An important concept in MCI has been the notion that functional activities of daily living should be intact [3].

Although a discussion of all available functional assessment instruments is beyond the scope of this paper, research has increasingly shown that subjects with a formal diagnosis of MCI frequently have functional impairments. In aMCI patients, Instrumental Activities of Daily Living measures at baseline independently predicted progression to AD 1 year later [28]. Similarly, MCI subjects who progressed to AD 1 year later presented as more impaired on financial capacity at baseline and had greater decline than nonprogressors [29]. A 3-year longitudinal study of medical decision-making capacity showed that individuals with aMCI performed progressively worse in comprehending consent information as compared with their own baseline performance and with a control group [9].

Studies of the relationship between neuropsychological test performance and functional ability have linked Activities of Daily Living deficits and Instrumental Activities of Daily Living deficits to global cognitive impairment [30], executive function and attention [31], and task-specific neuropsychological deficits [32]. In most studies, however, neuropsychological measures have not explained the majority of the variability in functional measures, particularly in mildly impaired subjects. This lack of explanation consequently suggests there is something unique about informant-based observations of real-world behaviors or the subject's performance on performance-based tests that may not always be captured by neuropsychological tasks. A strength of informant report of cognitive deterioration is the ability to compare a subject's performance with premorbid functioning so that true decline can be measured. Although decline can be inferred by baseline neuropsychological testing, it cannot be proven in the absence of serial cognitive evaluation.

The Clinical Dementia Rating Scale (CDR) developed by John Morris was one of the first validated clinical instruments to identify individuals in a predementia state, and a CDR score of 0.5 became known to indicate the early stages of AD preceding dementia [33]. The CDR is included here as a functional assessment measure in that it combines objective cognitive testing with the clinical assessment of six different areas of daily function (memory, orientation, judgment, problem-solving, community affairs, and personal care) after an extensive interview with a knowledgeable informant. The CDR is therefore unique in relating cognitive deficits to real-world consequences in everyday life, and is a widely used tool for clinical assessment of disease with longstanding demonstrated utility in diagnosis [34] and prediction of disease progression [35]. In a number of studies, progression to dementia has been delineated by change from a global CDR of 0.5 (questionable dementia) to a global CDR of 1.0 (mild dementia) or higher [36,37]. The

CDR sum of boxes has been demonstrated as a particularly sensitive method of monitoring progression of cognitive impairment over time [38]. Change in CDR scores or change in CDR sum of boxes has been used as an outcome measure in studies assessing the utility of various techniques for predicting progression from MCI to AD, including CSF biomarkers [39], morphometry [39], functional MRI [40], amyloid burden [41], and 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-PET [42].

Taken together, this evidence shows there are functional impairments in the MCI stage of AD that progressively become worse until the clinician has decided the individual has reached the threshold at which they meet the criteria for dementia. Once this threshold is crossed, the person has not converted to AD but has merely progressed to a level of severity such that the cognitive deficits have a profound impact on the individual's life. Serial functional assessment is important, however, in that it is essential for tracking disease progression, developing optimal strategies for symptom management, and attempting to enhance quality of life.

Biomarkers

The recent criteria for MCI of Alzheimer's type set forth by the National Institute of Aging Alzheimer's Association workgroup propose that molecular biomarkers such as CSF Aβ-42, CSF tau/Aβ-42 ratio, p-tau/Aβ-42 ratio or amyloid load identified by imaging are most probably related to the underlying pathology of AD [16]. Topographic measures such as hypometabolism or hypoperfusion on PET or single-photon emission computed tomography or medial temporal lobe atrophy support the diagnosis of AD, and may be particularly useful in monitoring disease progression.

Cerebrospinal fluid proteins

CSF biomarkers have been shown to differentiate between healthy controls and AD patients [43], and have utility in predicting progression from aMCI to AD [44] and from MCI to AD [45]. The CSF Aβ-42/tau ratio differentiated patients with subjective cognitive complaints, with non-aMCI, and with aMCI from healthy controls [46], was predictive of progression from aMCI to AD [46], was predictive of progression from controls to MCI [47], predicted cognitive decline in cognitively normal older adults [48], and differentiated between AD and vascular dementia [49]. Low Aβ-42/Aβ-40 ratios predicted eventual development of MCI or AD at follow-up 3 to 7 years later among cognitively normal community volunteers [50]. A meta-analysis of CSF phosphorylated tau showed satisfactory clinical utility in diagnosing MCI and progression of MCI to dementia, but was less capable of differentiating AD from other types of dementia [51].

CSF biomarkers are additionally associated with a number of the cardinal features of AD. CSF proteins predict the rate of cognitive decline in AD [52], in mild AD [53], and in healthy older adults [54]. CSF biomarkers are related to hippocampal atrophy [55] and postmortem neuritic plaques [56]. The CSF Aβ-42/tau ratio also predicted the presence of postmortem neuritic plaques with a sensitivity of 91.6% and a specificity of 87.5% in a mixed population including AD, other dementia, and other neurologic disease [56]. In a more recent study, CSF amyloid was found in 90% of AD patients, in 72% of MCI patients, and in 36% (a 6.88 increased risk in apolipoprotein E4 carriers) of cognitively normal older people. Furthermore, 100% of subjects with MCI who progressed to AD and 94% of pathologically verified AD patients could be identified [57]. Despite impressive sensitivity, however, the specificity was limited; and given the predominance of AD patients in the sample, it is difficult to determine the ability of this biomarker to distinguish between etiologically distinct conditions.

Other studies have shown less promising results, such as the absence of a relationship between CSF proteins and disease progression [58]. CSF proteins were not associated with postmortem plaques and tangles in 50 AD patients [59]. A multisite study of CSF biomarkers demonstrated that although Aβ-42, p-tau, and total tau predicted progression from MCI to AD, a receiver-operating characteristic curve analysis was only modestly accurate at 0.78 for Aβ-42, 0.76 for p-tau, and 0.79 for total tau [60]. A meta-analysis found that CSF biomarkers were less sensitive than episodic memory scores in detecting preclinical AD [10]. Altogether, CSF biomarkers appear to have considerable promise in early detection of AD – but more work is required to optimize their contribution.

Neuroimaging

Given the prominence of the amyloid hypothesis of AD, the ability to detect β-amyloid accumulation *in vivo* in the brain has generated excitement about the possibility of earlier AD detection. PiB-PET imaging of amyloid deposition has been associated with cortical atrophy [61], glucose metabolism [62], CSF biomarkers [63], eventual development of AD in cognitively normal older adults [41], default mode network connectivity [64], CDR sum of boxes score [65], cognitive decline [61], and episodic memory [37]. Recent studies have shown that PiB may be useful in detecting preclinical AD [41,61] and in predicting the progression from MCI to AD [66]. PiB-PET imaging is also being studied to determine its usefulness in distinguishing diagnostic categories [67], and has shown the ability to distinguish between aMCI and non-aMCI [68].

Although PiB-PET imaging techniques are correlated to many of the key aspects and biomarkers of AD, there may be limitations to their usefulness. Most importantly, amyloid deposition has been found in a significant percentage of cognitively normal older subjects [69]. Further, a range of studies have failed to replicate associations between amyloid deposition and clinical measures [70], cognition [69], FDG-PET [71], and hippocampal atrophy in AD [69]. Cognitive reserve and the finding that amyloid appears well before cognitive symptoms may explain some of the discrepancies in the literature [27]. Also, PiB uptake appears to be nonspecific for AD, as it has been shown to be elevated in Parkinson's dementia [72] and in Lewy body disease [73].

In addition to measuring amyloid burden, FDG-PET imaging has been employed to study regional and global variations in cortical activity in AD progression. FDG-PET hypometabolism has been associated with amyloid burden [62], CSF biomarkers [74], maternal history of AD [75], apolipoprotein E4 status in healthy adults [76], verbal memory test decline [77], memory test performance [78], and perceived memory loss [79]. Regional variations in glucose metabolism have also correlated with progression from pre-MCI to MCI [77] and from aMCI to AD [78]. Diagnostically, FDG-PET increases statistical power over cognitive measures [67] and has superior diagnostic sensitivity (0.84) and specificity (0.74) to an initial clinical evaluation [80]. FDG-PET successfully identified different metabolic patterns in AD and cerebrovascular disease [81] and assisted in distinguishing between AD and frontotemporal dementia [82].

In addition to PET imaging, longitudinal volumetric neuroimaging with MRI has identified brain regions that tend to manifest neuronal loss early in the course of MCI. Research has demonstrated changes in medial temporal lobe structures in subjects with MCI [83] or in subjects with aMCI who progress to dementia [84]. Other brain regions implicated in disease progression include the anterior and posterior cingulate gyrus, precunus, and frontal lobes [84]. Recent work has also investigated the utility of functional MRI to predict progression of cognitive decline in MCI [40]. Research has shown that there is a prodromal period in AD in which there is stable decline, followed by more rapid cognitive and structural changes in the 2 to 3 years prior to the expression of clinical symptomatology [85]. Similarly, Carlson and colleagues showed that rates of ventricular volume expansion are greater in subjects who go on to develop MCI, and that the rate of expansion increases in the 2 to 3 years prior to clinical MCI diagnosis [86].

Taken together, CSF biomarkers, FDG-PET, and MRI studies have shown considerable promise in identifying early AD and monitoring the disease progression through the clinical stages to dementia. New techniques that

allow visualization of amyloid deposition offer an exciting possibility of detection of disease in its earliest possible stages but may not be as useful as cognitive measures, imaging techniques or other biomarkers for monitoring changes in the brain that occur between the MCI and dementia stages of AD. The use of these techniques also raises an important issue. Significant percentages of cognitively normal older people may have AD pathology but do not manifest cognitive symptoms during life [69], and many cases of MCI have non-AD pathology. Assessment tools with high specificity in early detection are needed to facilitate early intervention of AD. Despite the understandable excitement that biomarkers provide, it will be important to be appropriately cautious regarding the application of these new techniques to clinical care and practice until the techniques can be established as specific to AD [87].

Conclusion

While lauding a decade of efforts to delineate sub-classifications of AD, it is important to emphasize that AD remains a single disease entity throughout all its stages. Consequently, movement from stage to stage signifies disease progression on a continuum (which is not always linear), rather than a conversion from one entity to another. Nonetheless, efforts to differentiate disease stages have considerable utility, particularly in research, and it is imperative to establish greater uniformity in assessment, cut-off points, and diagnostic criteria to more meaningfully compare the results of national and international research efforts. The new proposed National Institute of Aging Alzheimer's Association guidelines for the diagnosis of AD recognize the need to identify preclinical AD as well as MCI due to AD [16]. These new criteria will undoubtedly stimulate the further research needed in the area.

Based on current evidence, we briefly summarize our views on how to best study the progression of deficits associated with the MCI stage of early AD as follows.

First, conversion to dementia has typically been used as a primary endpoint to judge treatment effects in AD although this may not be the optimal way to study progression in a disorder that falls on a continuum, particularly as attempts are made to treat the disorder in its earliest stages. Given their continuous nature, objective cognitive measures will probably be among the more useful measures for assessing AD progression and monitoring response to the earliest interventions.

Second, memory measures assessing learning over multiple trials with delayed recall are among the most powerful cognitive measures in early detection and monitoring of early AD, but nonmemory measures – particularly those tapping executive function, language and visual–spatial skills – should be employed in serial

assessment of MCI. In addition, ratings of cognitive and functional change – particularly those observed by skilled clinicians and knowledgeable informants over time – can provide critical information. Further development of newer paradigms that focus on encoding specificity, deficits in semantic memory processing, dysexecutive function, and the use of techniques such as reliable change analyses will be useful in detecting early impairment and gauging meaningful changes in performance over time.

Third, the presence of specific CSF biomarkers, the amyloid load in the brain, and specific patterns of brain hypometabolism or atrophy make it much more likely that cases of both early and later MCI represent early AD, which will be critical to the development of early clinical intervention studies. Further, serial assessment of these neuroimaging markers such as PET and MRI may have particular utility in assessing longitudinal change or response to intervention.

Finally, since each method provides unique information and variance, it is likely that a combination and statistical weighting of different biomarkers and neuropsychological tests across serial assessments will provide the most robust predictor at both the group and individual levels. For instance, combined FDG-PET and PiB-PET imaging has been shown capable of distinguishing between control, MCI, and AD subjects better than either technique in isolation [88]. Similarly, a recent study demonstrated that combined FDG-PET and episodic memory scores predicted progression from MCI to AD better than either measure alone [89].

Newly emerging technologies to study brain function have generated considerable enthusiasm. While sensitivity to early AD is critical, specificity to the neuropathology of the disorder and the ability to differentiate between different etiological conditions is critically important. Identifying the best combination of predictors of eventual clinical outcomes and the optimal means of utilizing these predictors are the most important challenges for future research.

Abbreviations

AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; CDR, Clinical Dementia Rating Scale; CSF, cerebrospinal fluid; FDG, 2-[^{18}F]-fluoro-2-deoxy-D-glucose; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography; PiB, [^{11}C]Pittsburgh compound B.

Competing interests

The authors declare that they have no competing interests.

Author details

^{1}Department of Rehabilitation Medicine, Miller School of Medicine – University of Miami, P.O. Box 016960 (C-206), Miami, FL 33101, USA. ^{2}Department of

Psychiatry and Behavioral Sciences and Center on Aging, Miller School of Medicine, University of Miami, 1695 NW 9th Avenue, Suite 300, Miami, FL 33136, USA. 3Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center, 4300 Alton Road, Miami Beach, FL 33140, USA.

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