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MCI SERIES

Heterogeneity in mild cognitive impairment: Differences in neuropsychological profile and associated white matter lesion pathology

LISA DELANO-WOOD,[1,3] MARK W. BONDI,[1,3] JOSHUA SACCO,[2] NORM ABELES,[2] AMY J. JAK,[1,3] DAVID J. LIBON,[4] AND ANDREA BOZOKI[5]

[1]Department of Psychiatry, School of Medicine, University of California–San Diego, La Jolla, California
[2]Deparment of Psychology, Michigan State University, East Lansing, Michigan
[3]Psychology Service, VA San Diego Healthcare System, La Jolla, California
[4]Department of Neurology, Drexel University, Philadelphia, Pennsylvania
[5]Department of Neurology, Michigan State University, East Lansing, Michigan

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Abstract

This study examined whether distinct neuropsychological profiles could be delineated in a sample with Mild Cognitive Impairment (MCI) and whether white matter lesion (WML) burden contributed to MCI group differences. A heterogeneous, clinical sample of 70 older adults diagnosed with MCI was assessed using cognitive scores, and WML was quantified using a semi-automated, volumetric approach on T_2-weighted fluid-attenuated inversion recovery (FLAIR) images. Using cluster and discriminant analyses, three distinct groups (Memory/Language, Executive/Processing Speed, and Pure Memory*)* were empirically derived based on cognitive scores. Results also showed a dose dependent relationship of WML burden to MCI subgroup, with the Executive/Processing Speed subgroup demonstrating significantly higher levels of WML pathology when compared to the other subgroups. In addition, there was a dissociation of lesion type by the two most impaired subgroups (Memory/Language and Executive/Processing Speed) such that the Memory/Language subgroup showed higher periventricular lesion (PVL) and lower deep white matter lesion (DWML) volumes, whereas the Executive/Processing Speed demonstrated higher DWML and lower PVL volumes. Results demonstrate that distinct MCI subgroups can be empirically derived and reliably differentiated from a heterogeneous MCI sample, and that these profiles differ according to WML burden. Overall, findings suggest different underlying pathologies within MCI and contribute to our understanding of MCI subtypes. (*JINS*, 2009, *15*, 906–914.)

Keywords: Mild cognitive impairment, MCI, Neuropsychology, WML, White matter lesion, White matter hyperintensity, Aging, Cognition

INTRODUCTION

Soon after Petersen introduced the concept of Mild Cognitive Impairment (MCI), a clinical construct thought to represent a transitional state between normal aging and dementia (Petersen et al., 1999; 2001), it became apparent that the original definition requiring a strict memory impairment was limiting and restrictive. Specifically, the criteria were criticized for their inability to adequately capture the range of variability often observed in patients with milder forms of cognitive impairment, and it was argued that MCI may not represent a separate and homogeneous clinical syndrome in terms of its neuropsychological profile (Ritchie & Touchon, 2000). In an attempt to better characterize possible subtypes of cognitive impairment and their possible differing etiologies and outcomes, Petersen et al. (Petersen, 2004a, 2004b) proposed three different MCI subtypes (Amnestic; Multiple-Domain; and Single Non-Memory Domain MCI), which were later redivided to include two major subgroups (amnestic and nonamnestic MCI), with further subdivisions within each (single- and multiple-domain). Although MCI is currently one of the most widely studied concepts in the dementia literature, many different and inconsistent definitions have been applied across studies and there is clearly a need for better characterization and clarification of the concept as

Correspondence and reprint requests to: Lisa Delano-Wood, Ph.D., VA San Diego Healthcare System, Building 13 – 151B, 3350 La Jolla Village Drive, San Diego, CA 92161. E-mail: ldelano@ucsd.edu

a whole (Davis & Rockwood, 2004; De Carli, 2003; Kavé & Heinik, 2004; Petersen & Morris, 2005). It is likely that ambiguity and definitional confusion may be related to inadequate characterization of patients who present with varying types of early, subtle cognitive impairment.

Given the current uncertainty inherent in the clinical concept of MCI, coupled with the critical importance of more accurately identifying and detecting prodromes of different dementia syndromes clinically, a major goal of this area of inquiry is to more clearly define MCI and to decipher whether the diagnosis primarily represents a risk factor for Alzheimer's disease (AD) specifically, or whether MCI is more accurately described as comprised of a heterogeneous group of individuals with different pathologies, neuropsychological profiles, and/or neurological markers (Bowler, 2002; Looi & Sachdev, 2000a; Rockwood et al., 2003). In regard to the latter, much attention has been focused on the contribution of white matter lesion (WML) pathology to cognitive, behavioral, and motor decline seen in dementia and, recently, in more subtle neuropsychological impairment (Garrett et al., 2004; Stephens et al., 2004). WMLs are defined as signal abnormalities within the white matter and are thought to be related primarily to ischemia (Fernando et al., 2006), increased fluid in the white matter, and gliosis (Fazekas, Schmidt, & Scheltens, 1998). Studies have demonstrated a link between WML pathology and cognitive impairment across the aging spectrum (Delano-Wood et al., 2008; Garrett et al., 2004; Gunning-Dixon & Raz, 2000; Inzitari, 2000), and important distinctions have been made between the two WML subtypes [deep white matter lesions (DWML) and periventricular lesions (PVL)], given that they appear to differ in their pathogenesis and perhaps clinical significance (Lazarus, Prettyman, & Cherryman, 2005; Simpson et al., 2007). However, the precise role of WML in age-related cognitive impairment and its possible role in conversion to MCI and dementia remains unclear. Moreover, despite a call for studies to investigate both types of WML (Bowler & Hachinski, 2003), few studies have made this differentiation, particularly in MCI.

As preventive and early intervention strategies become better established, much research is currently focused on the identification of meaningful dementia prodromes that may have differing etiologies and distinct underlying pathophysiological mechanisms. Although there is a need to define more accurately the transitional states between normal aging, AD, and other dementias, there is a relative dearth of studies attempting to empirically validate and verify the existence of the recently proposed MCI subtypes. The vast majority of MCI studies have investigated differences across MCI subgroups diagnosed clinically using Petersen's classification criteria (e.g., Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003; Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006; Storandt, Grant, Miller, & Morris, 2006; Zanetti et al., 2006). However, we are unaware of any published studies that have attempted to statistically derive subgroups from a heterogenous population diagnosed with MCI. Thus, because MCI likely represents a heterogeneous group of individuals with different pathologies and neuropsychological profiles (Bowler, 2002; Rockwood et al., 2003), the current study was designed to assess: (1) whether distinct groups could be empirically gleaned from a clinical population diagnosed with MCI, and (2) whether identified subgroups can be further differentiated based on WML burden. It was expected that MCI would not represent a homogeneous population and would instead be better characterized as a heterogeneous group based on neuropsychological scores. Specifically, per Petersen and Morris (2005), we hypothesized that the following two major groups would emerge from the data: (1) a subgroup demonstrating a neuropsychological profile consistent with amnestic MCI (specific cognitive deficits in memory), and (2) a subgroup with a cognitive profile consistent with the nonamnestic subtype of MCI (mild impairments in nonmemory domains such as executive functioning or processing speed). We further predicted that the nonamnestic group would demonstrate the highest level of WML pathology – particularly of DWML – given that this lesion type has been shown to be related to cognitive functions thought to be dependent on frontal-subcortical circuitry (e.g., executive functioning, processing speed, and attention/working memory; Delano-Wood et al., 2008). If groups were to reliably differ on neuropsychological test patterns, as well as on WML burden, such findings would speak to different underlying pathologies and contribute to improving our clinical characterization of the MCI construct.

METHOD

Participants

The clinical sample comprised 70 older adults who were consecutively recruited from the Michigan State University (MSU) Geriatric Neurology Clinic. A diagnosis of MCI was based on the following criteria suggested by Petersen and Morris (2005): (1) subjective patient memory complaints; (2) normal activities of daily living; (3) absence of dementia; (4) Mini-Mental State Exam (MMSE) score of 24 or greater; and (5) mild quantifiable cognitive impairment. Although no reliable cut-off for defining impairment in MCI has yet been defined, Busse et al. (2003, 2006) have shown that a more liberal cut-off (i.e., 1 *SD* below the mean) is optimal, because it offers higher sensitivity and predictive power than the traditional cut-off of 1.5 *SD*. As described elsewhere (Delano-Wood et al., 2008), given our aim to be broadly inclusive, we compromised by using a cutoff of 1.2 *SD* (after applying norms adjusted for age, education, and gender), signifying a level of performance worse than 88.5% of the population (indicative of mild to moderate impairment). All participants were categorized into four subgroups [single-domain amnestic MCI ($n = 12$); single domain nonamnestic MCI ($n = 12$); multiple-domain amnestic-MCI ($n = 28$); and multiple-domain nonamnestic-MCI (= 18)], based on impairment on one or more subtests across the entire neuropsychological battery described in detail later on.

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Participants were excluded from the study if there was evidence of current or past diagnosis of a neurologic or psychiatric disorder, stroke, known head injury with loss of consciousness, untreated hypothyroidism, Vitamin B12 (cobalamin) deficiency, metabolic derangement, or any significant visual or auditory impairment that precluded participation in neuropsychological testing. The final clinical sample consisted of 33 men (47%) and 37 women (53%) who ranged in age from 55 to 88 (mean age = 75 years; *SD* = 7.9). All participants provided written informed consent, and the procedures in the present study were approved by the Michigan State University Committee on Research Involving Human Subjects.

Materials and Procedures

Neuropsychological test battery

A comprehensive neuropsychological test battery was administered to each participant by a technician who was blind to the participant's medical status and diagnosis. Specifically, we employed the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Welsh, Butters, & Mohs, 1994), a reliable, well-standardized neuropsychological battery often used to detect impairment in mildly impaired populations (Chandler et al., 2005; Fillenbaum et al., 2008; Schmidtke & Hermeneit, 2007). Briefly, the CERAD contains the following subtests: verbal fluency ('animal' fluency), object naming (15 items), constructional praxis (figure copying), and learning and memory (three trials of a 10-word list learning, 10-min delayed free recall, and recognition). The CERAD battery was supplemented by the inclusion of additional neuropsychological tests to augment the assessment of processing speed and executive functioning (Trail Making Test, Parts A and B; Reitan & Wolfson, 1985 and Stroop Color-Word Test; Golden & Freshwater, 2002). All neuropsychological scores were standardized with a z-score transformation on the basis of the CERAD or other normative data of the neuropsychological tests (Welsh et al., 1994). Scores that reflected number of errors or response times were multiplied by –1, so that negative z scores consistently reflected poor performance. Finally, we employed the 15-item Geriatric Depression Scale (GDS; Yesavage et al., 1983), a brief measure widely used to assess depression in older adult samples.

MRI protocol and quantification of white matter lesions

Magnetic resonance imaging (MRI) was performed on a 1.5T Signa scanner (General Electric, Milwaukee, WI), and WML volumes were estimated from T_2-weighted axial fluid-attenuated inversion recovery (FLAIR) images (FOV = 20 × 20 cm; matrix = 256 × 256; flip angle = 90 degrees, TE = 142 ms, TR = 10000 ms, 5-mm slice thickness with no interslice gap). A semi-automated volumetric approach was employed, a methodology recently shown to be the most reliable approach for the analysis of WML when compared to other image types and traditional quantitative visual rating scales (Price, Schmalfuss, & Sistrom, 2005). WML volumes were obtained based on 17–21 axial images per subject using GE's Advantage Workstation software (version 4.2), and WML were measured according to the protocol established by Raz, Rodrigue, and Acker (2003). Briefly, the total volume of each region in cubic centimeters was calculated by multiplying the summed pixel cross-sectional area in square centimeters by slice thickness in centimeters, and WML volumes were normalized to the intracranial cavity (ICC) volume for each participant (Delano-Wood et al., 2008; Raz et al., 2003).

Statistical analyses

Using the methodology of Libon et al. (2007), composite scores were computed for memory (CERAD Word List Delayed Free Recall and Recognition; $r = .38$, $p = .01$), as well as executive functioning (Trails B and the Stroop Color-Word Test Interference score; $r = .69$, $p < .001$) prior to statistical analyses. Significant correlations between the tests that comprise each composite score supported this approach. Ward's minimum variance cluster analysis (Kaufman & Rousseau, 1990; Ward, 1963) was performed to identify patterns of impairment and assess for the presence of groups based on neuropsychological performance. This type of hierarchical agglomerative method takes into consideration all possible combinations of profiles, computes a distance measure (squared Euclidean distance) between profiles, and combines the pair with the smallest sum of squared difference to the first cluster. Profiles are continually combined, which minimizes the increase in within-group sum of squared variance. Ward's technique parcels the total sum of squares into within-group and between-group variability, thus yielding a measure of the percentage of variability accounted for by the clustering solution. For the cluster analysis, we used raw scores rather than demographically corrected scores to assess how participants cluster irrespective of their demographic status.

To determine whether cognitive scores could be combined to reliably predict group membership, and whether they accurately predicted the cluster groups (classification), discriminant function (DF) analysis was performed. DF analysis maximizes group differences by creating a weighted linear combination of the predictor variables (Kleinbaum, Kupper, & Muller, 1988), such that differences between groups are maximized using weights in the DF. The Wilk's lambda coefficient was computed to test the significance of the DF, and the partial Wilk's lambda was used as a measure of the contribution of individual neuropsychological variables to the DF. The partial Wilk's lambda of a given variable ranges between 1 (when all group means are equal) and 0 (when between groups variability largely outweighs within groups variability).

All raw neuropsychological scores were converted to z scores from grand means for the MCI group as a whole before being entered as variables for the cluster analysis

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[Memory composite (Mem), Executive Functioning composite (EF), Processing Speed (Speed), Visuospatial/Construction (VS), Confrontation Naming (Naming), and Verbal Fluency (Fluency)]. The number of clusters was set *a priori* to two to reflect the expected theoretical distinction between amnestic and nonamnestic MCI subtypes. A comparison was made between the cluster structures to identify best data fit, and no constraints were imposed on the numbers of participants in each cluster or the profiles of neuropsychological performance across groups. Thus, the data were allowed to empirically define the subgroups to address the question of whether the cognitive profiles exhibited by patients with MCI segregate into theoretically meaningful subsets. To assess whether group differences based on cognitive performance were statistically meaningful, multivariate analysis of covariance (MANCOVA) was conducted, controlling for age, education, and depressive symptomatology. Finally, analysis of covariance (ANCOVA) was performed to determine whether groups differed on WML load (adjusting for age, education, gender, and depression). Appropriate *post hoc* analyses were employed using Tukey's honestly significant difference (HSD). All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, 2004).

RESULTS

Cluster Analysis of Cognitive Scores

Results of the cluster analysis showed that the initial two-cluster solution produced widely unbalanced groups (Group 1: $n = 60$; Group 2: $n = 10$). Given that a large, dominant cluster typically indicates that too few clusters were requested (Hays, 1994), coupled with results from the dendogram, which indicated that Group 1 could be split into two distinct subgroups, an additional cluster analysis was performed with the number of clusters set to three, allowing for expression of greater heterogeneity in the sample. The resulting solution produced three groups (n sizes = 18, 18, and 34), and this solution was most meaningful given that it most optimally identified a set of subgroups that both minimized within-group variation and maximized between-group variation. The means and standard deviations for each of the three groups on the demographic, clinical, and cognitive variables of interest are presented in Table 1. For ease in interpreting group differences on the neuropsychological variables, it should be noted that the means and *SD*s of these variables reported in Table 1 are the original CERAD demographically-corrected standard scores and not the raw neuropsychological scores submitted to the cluster analysis.

Based on the group means observed in the cluster analysis (see Figure 1), the first group was labeled "Memory/Language," given poorer performance on tests comprising these cognitive domains (memory recall and recognition, fluency, and confrontation naming). Conversely, the second group (labeled "Executive/Processing Speed") demonstrated the opposite pattern of results, with poorer executive functioning, visuoconstruction, and processing speed than memory and language abilities. The third group exhibited mildly impaired memory and was thus labeled "Pure Memory." Figure 1 depicts the relative neuropsychological performance patterns of each of these three groups.

As shown in Table 1, the clusters significantly differed by age, $F(2, 69) = 4.19$, $p < .02$, education, $F(2, 69 = 6.21$, $p < .01$, and levels of depression, $F(2, 69) = 4.65$, $p < .02$. A MANCOVA was therefore performed to examine for cluster group differences on each of the raw neuropsychological test domains, adjusting for the effects of age, education, and depression. Results revealed that the groups differed on fluency ($F = 7.47$, $p = .001$, $\eta_p^2 = .19$), naming ($F = 7.47$, $p < .001$, $\eta_p^2 = .35$), executive functioning ($F = 37.04$, $p < .001$, $\eta_p^2 = .54$), processing speed ($F = 21.19$, $p < .001$, $\eta_p^2 = .39$), visuospatial processing ($F = 27.49$, $p < .001$, $\eta_p^2 = .46$), and memory ($F = 3.37$, $p = .04$, $\eta_p^2 = .10$).

Table 1. Demographic, cognitive, and clinical group means and standard deviations

	Clusters		
Variable	Executive/ Processing Speed	Memory/ Language	Pure Memory
Age	76.3 (7.2)	79.2 (5.8)	73.2 (7.8)
Gender	6M, 12W	9M, 9W	18M, 16W
Education (years)	12.2 (2.9)	11.5 (1.8)	14.9 (3.7)
Depression (GDS raw)	12.2 (6.3)	8.7 (8.2)	4.8 (4.4)
Trail Making A	–1.78 (.81)	–0.51 (.70)	–0.65 (.93)
Trail Making B	–2.33 (.77)	–0.31 (.94)	0.24 (.67)
Stroop Color-Word Test	–1.76 (.89)	–0.42 (.67)	–0.46 (.71)
Visuospatial/Construction	–1.18 (2.01)	–0.52 (.89)	–0.47 (1.10)
Category Fluency	–1.23 (.79)	–1.43 (.93)	–0.19 (.77)
Word List Free Recall	–0.39 (.74)	–1.37 (.86)	–1.24 (.75)
Word List Recognition	–0.22 (2.21)	–0.94 (2.72)	–0.85 (1.87)
Confrontation Naming	–0.15 (1.56)	–1.73 (1.00)	–0.36 (.83)

Note. All cognitive scores are represented as demographically corrected z scores.

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Discriminant Function Analysis of Neuropsychological Scores

A direct discriminant function (DF) analysis was performed using the six cognitive variables as predictors of membership in the three cluster groups. Because the DF analysis was performed between three groups, two DFs were generated and subject classification was based on a weighted combination of the scores along each function. The first DF accounted for 81% of the differences among the three groups, $F(2, 69) = 144.4$, Wilk's lambda = 0.085, $p < .001$. Individual discriminant scores correlated significantly ($p < .001$) with executive functioning, processing speed, and visuospatial/construction. The second DF explained the remaining variance (19%) and was also statistically significant, $F(2, 67) = 44.7$; Wilk's lambda = .476, $p < .001$. Individual discriminant scores of the second DF correlated significantly ($p < .001$) with tests of naming, fluency, and memory. ANOVA results showed a significant group effect of discriminant scores, $F(2, 69) = 144.0$, $p < .001$, and *post hoc* analysis revealed that each group differed significantly from each other (p values < .01). Using the full predictive model, the six variables correctly classified 18 Memory/Language subjects (100%), 18 Executive/Processing Speed subjects (100%), and 33 Pure Memory subjects (97.1%). The overall rate of correct classification was 98.6%, and all but one subject used to derive the DF was correctly classified.

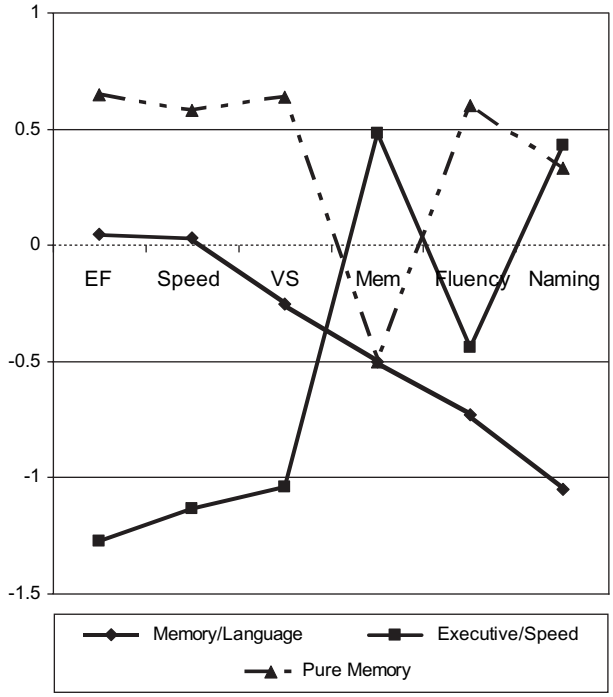

Fig. 1. Neuropsychological profile by cluster group. EF = Executive Functioning; VS = Visuospatial/Construction; Mem = Memory. All scores are standardized group means (not demographically corrected) and Mem and EF are represented as composite scores.

As shown in Figure 2, examination of the bi-territorial map of neuropsychological scores on the first and second DFs revealed three distinct clusters consistent with a unique neuropsychological pattern for each group. The stability of the classification procedure was submitted to a cross-validation run using leave-one-out classification in SPSS. Classification for the originally derived cases was 98.6% and fell minimally to 94.3% for the cross-validation cases. One Memory/Language participant was misclassified as Pure Memory and 3 Pure Memory were classified as Memory/Language. Overall, this pattern indicates a high degree of consistency in the classification scheme.

MCI Subgroup Differentiation by WML Burden

Figure 3 depicts group differences by total WML burden. Results of ANCOVA showed that the Executive/Processing Speed subgroup demonstrated significantly greater WML volume load than both the Memory/Language, $t(34) = -4.82$, $p < .001$, and Pure Memory subgroups, $t(50) = -9.13$, $p < .001$. The Memory/Language and Pure Memory subgroups did not differ significantly in terms of total lesion load, although there was evidence of a trend, $t(50) = 2.00$, $p = .051$.

Figure 4 shows that, in comparison to the other subgroups, the Pure Memory subgroup demonstrated significantly lower levels of both types of WML. Moreover, the Executive/Processing Speed subgroup showed significantly higher DWML burden in comparison to PVL, whereas the Memory/Language subgroup demonstrated significantly higher PVL *versus* DWML burden.

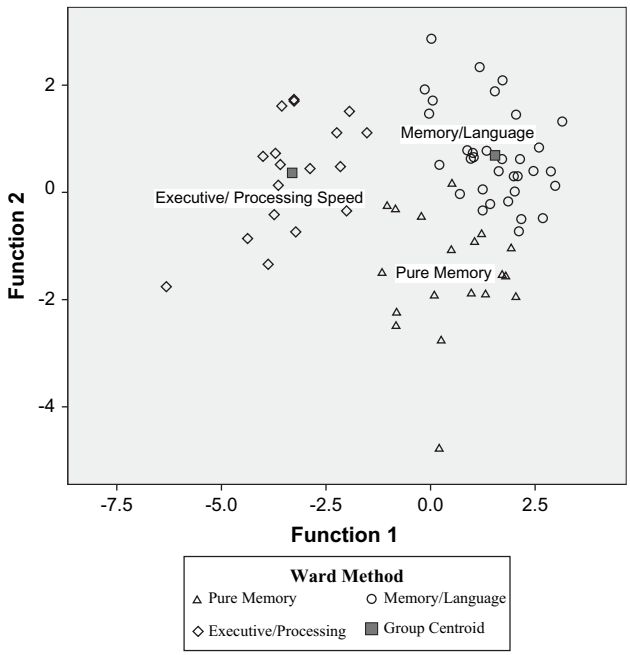

Fig. 2. Biterritorial map of the discriminant functions. Uncorrected raw scores were used in the discriminant function analysis.

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DISCUSSION

Cluster Analysis of Neuropsychological Scores and Description of MCI Subgroups

The first aim of the current study was to examine whether distinct groups with differing neuropsychological profiles could be delineated within a heterogeneous clinical sample of patients diagnosed with MCI. Results indicated that specific groups were found within the sample that generally conformed to expectations. Specifically, one group demonstrated deficits on tests of memory and language, with relatively intact executive functioning, processing speed, and visuospatial/construction skills. A second group demonstrated the opposite pattern of results, with primary deficits revealed on tests of executive functioning, processing speed, and visuospatial/construction skills in the context of preserved of memory and language abilities. Finally, a third group emerged with group means within normal limits on all neuropsychological domains with the exception of memory, which was mildly affected. The existence of an amnestic single-domain subgroup is consistent with the original conceptualization of MCI (Petersen et al., 1999) and is also one of the major MCI subtypes in Petersen's MCI classification scheme; other researchers have also found this subgroup to represent a sizable portion of their respective MCI samples (Bombois et al., 2007; Loewenstein et al., 2006; Storandt et al., 2006).

It appears that the first MCI subgroup (Executive/Processing Speed) is consistent with what would be expected in a population with vascular cognitive impairment (VCI) given deficits in executive functioning, processing speed, and visuoconstruction (Selnes & Vinters, 2006). Conversely, the Memory/Language subgroup appears to be consistent with what might be expected from a cortical, degenerative etiology such as AD, with prominent decline in episodic and semantic memory functions (Mickes et al., 2007; Powell et al., 2006; Salmon et al., 2002). Interestingly, this group demonstrated significantly poorer naming and fluency ability than the other groups, even after adjusting for education. Although episodic memory performance was also important in describing this group, our results highlight that semantic knowledge may also be affected early in the process of a dementing syndrome such as AD, a finding consistent with the results of some recent studies of early or prodromal AD, demonstrating that semantic memory exhibited the most severe deficits and decline in the two years preceding diagnosis (Mickes et al., 2007; Powell et al., 2006; Salmon et al., 2002). However, there is a vast literature suggesting that episodic memory impairment is greater than naming deficits in early AD (Bondi et al., 1994, 1999; Collie & Maruff, 2000; Rubin et al., 1998; Testa et al., 2004), and it is important to note that, given the cross-sectional nature of this study, individuals with differing etiologies presenting with a prominent naming deficit (e.g., frontotemporal dementia) may also be viable diagnostic possibilities. Finally, there were no differences in terms of overall severity between the most impaired groups (Memory/Language and Executive/Processing Speed). Thus, considerable differences existed between the types of deficits exhibited in these groups, although overall severity did not differ.

Given that some individuals with MCI do not convert to dementia, it is reasonable to posit that the identified third group may itself be heterogeneous, representative of individuals who present with isolated memory impairment for numerous reasons. First, although participants with severe depression were not included in the study, it may be that individuals in this group show isolated memory impairment secondary to subclinical depression or anxiety. This explanation is less tenable given their lower levels of depressive symptomatology when compared to the other subgroups. Second, because memory impairment is often affected early in the course of degenerative/cortical dementia syndromes, this group may be comprised of individuals who are in the very early stage of AD. Third, individuals in this group may simply have a relative weakness in memory ability compared to the normally distributed population (i.e., these individuals may fall on the low end of the normal curve on memory function).

It is reasonable to expect that memory performance may have more strongly differentiated our subgroups had we

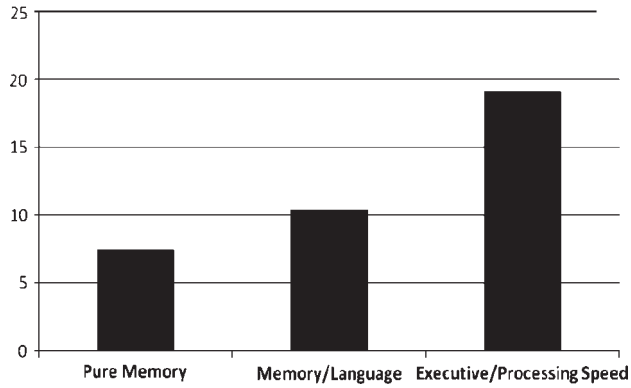

Fig. 3. Mean total white matter lesion (WML) volume (cc^3) by MCI subgroup.

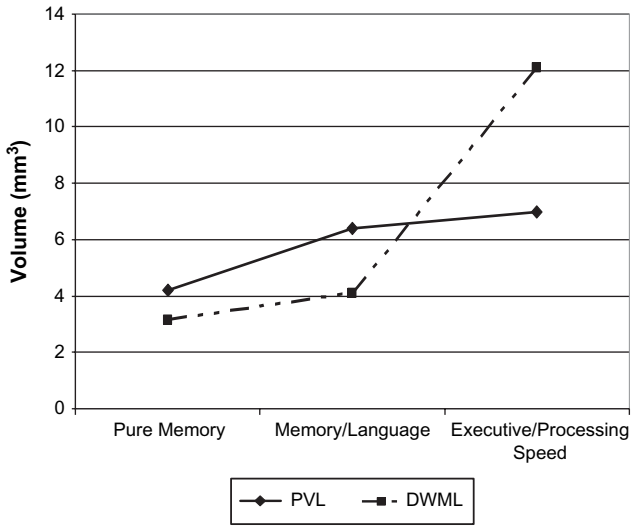

Fig. 4. MCI subgroup cluster differences by regional white matter lesion (WML) volume. PVL = periventricular lesions; DWML = deep white matter lesions.

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employed memory testing known to better discriminate between various clinical populations (e.g., the California Verbal Learning Test-II; Delis, Kramer, Kaplan, & Ober, 2000). It is thus possible that our memory testing was not appropriately sensitive and that we may have underestimated the severity of memory difficulty with our memory measure. Nevertheless, although this subgroup's memory performance was only mildly negatively affected, the discrepancy between performance on memory tasks and all other cognitive domains is somewhat striking, especially given the limited nature of our memory testing as part of this study. It is important to note that the cluster analysis used the subjects' raw neuropsychological test scores, and the Pure Memory group was the youngest and most highly educated of the three subgroups. However, the groups significantly differed from each other in this domain, even after adjusting for the effects of these variables and, when inspecting this subgroup's demographically corrected memory test scores, it is noteworthy that their performances are poorer than would appear from the cluster analysis *z*-score level. Finally, it may be that this third group also possesses more cognitive reserve. This is particularly apparent given their significantly younger age and higher level of education in comparison to the other groups. Indeed, in regard to the latter, studies have shown that higher levels of education may be a protective factor that may delay or prevent the development of dementia (Cabeza, Anderson, Locantore, & McIntosh, 2002; Mortimer, Snowdon, & Markesbery, 2003).

Regional WML Burden by MCI Subgroup

Each cluster subgroup was evaluated in terms of total WML volume to determine whether subgroup differences existed within the sample. Additionally, given that very few studies have analyzed WML types separately, this study also set out to examine the contribution of both PVL and DWML to neuropsychological functioning in MCI. As expected, the group demonstrating a nonamnestic cognitive profile evidenced significantly greater WML volume than the other subgroups. In addition, findings showed that, although the Memory/Language and Executive/Processing Speed groups differed considerably in terms of DWML (with the Executive/Processing Speed group evidencing significantly greater volume), the groups did not differ significantly in terms of PVL. Moreover, only DWML was associated with poorer cognitive functioning, predicting performance on tests of executive functioning, speed of processing, and visuospatial/constructional skills, but not tests of verbal memory or language. These results are consistent with Zanetti et al. (2006), who found that a dysexecutive syndrome characterized individuals with multiple-domain nonamnestic MCI; additionally, this subgroup in their sample demonstrated more vascular comorbidity (e.g., hypertension) and signs of vascular disease on neuroimaging. Interestingly, all patients who converted to dementia within three years progressed to either AD (55%) or vascular dementia (VaD) (45%), and all patients who were initially classified as amnestic MCI converted to AD, whereas all patients classified as multiple-domain nonamnestic MCI evolved to VaD. Bombois et al. (2007) showed that 92% of their MCI sample demonstrated WML on imaging and, similar to our results, WML was associated with executive dysfunction, but not memory or global cognitive function. However, in contrast to our results, subcortical WML did not differ between those with amnestic and nonamnestic MCI presentations. Results may differ for various reasons, including methodological differences in terms of sample selection, imaging technique employed, and WML quantification.

Interestingly, we also observed a dissociation between WML subtype and MCI subgroup. Specifically, the Memory/Language subgroup demonstrated higher levels of PVL *versus* DWML, whereas the Executive/Processing Speed subgroup exhibited the opposite lesion pattern (much higher level of DWML *vs.* PVL). Given that groups demonstrated similar levels of PVL, this lesion type was less important in differentiating the groups, and thus it may be that PVL is not reflective of pathological change in the brain and, instead, represents normal changes with age. Indeed, PVL are commonly observed in nondemented, healthy older adults (Shinkawa et al., 1995; Simpson et al., 2007), and some studies have suggested that WML located along the borders of the ventricles reflect primarily breakdown of the ependymal lining and are therefore more common and less indicative of pathology than DWML (Van Petten et al., 2004). Our results are consistent with other recent studies that have shown that PVL, but not DWML, may represent an age-related phenomenon (Lazarus et al., 2005; Prins et al., 2004).

In contrast to PVL, studies have suggested that DWML are related to underlying vascular risk and the presence of vascular disease (Fernando et al., 2006; Thomas et al., 2002). Given associations reported in the literature between DWML, microangiopathy, and hypoperfusion (Tomimoto et al., 2003), it may be that early manifestations of vascular cognitive impairment (VCI) associated with DWML lead to dysexecutive deficits in cognition, thought to be dependent on the integrity of frontal-subcortical circuits (Inzitari, 2000). DWML tend to predominate in the dorsolateral prefrontal cortex, and thus, concomitant cognitive deficits may be the result of small vessel disease disrupting frontal-subcortical pathways (Vataja et al., 2003). Taken together, our results lend further credence to the notion that DWML and PVL likely differentially impact clinical presentation, and they provide support for the need to analyze both WML subtypes separately. Additional research is needed to more clearly elucidate whether WML subtypes arise from dissociable pathogenic mechanisms.

To our knowledge, our study is among the first to employ cluster analysis to a heterogenous sample diagnosed with MCI, and the differential association of regional WML burden to MCI subgroup is a novel finding that may have important clinical ramifications. In addition, although our findings lend further support to the clinical subtyping schemes proposed by Petersen and Morris (2005), our findings also provide evidence for the ability to *empirically define* MCI subtypes and, importantly, our results underscore the potential to identify

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meaningful dementia prodromes that may have different etiologies and distinct underlying pathophysiological mechanisms. Nevertheless, it is important to note possible methodological limitations of the current study. First, although participants presented with a variety of cognitive concerns to a specialty neurology clinic, selection bias may have occurred, and thus, the generalizability of our findings may be somewhat limited. Along the same vein, the cross-sectional nature of this study makes it difficult to discern the accuracy of group membership, as well as whether and how groups convert to dementia. For example, there are multiple forms of progressive dementia, and thus, it is plausible that individuals in our sample may progress to forms other than AD and VaD. It will be important for these results to be replicated in an independent, larger, and more diverse cohort for the conclusions to be considered generalizable to the population at large. Moreover, the current study employed a volumetric methodology in the measurement of WML burden, and thus, little can be inferred regarding the extent and pattern of microstructural white matter changes in the pathology of MCI. Despite these limitations, these findings provide *prima facie* support for the existence of differing MCI subtypes within a generally heterogeneous sample, and they pave the way for additional studies to attempt to more clearly elucidate MCI subtypes and their potentially differing underlying etiologies and outcomes. An enhanced ability to clinically differentiate MCI subtypes will become increasingly more important, particularly, as preventive and early intervention strategies become better established. Ultimately, it is hoped that better characterization of specific MCI subtypes will be more useful to clinicians by helping provide a bridge between syndrome and etiology.

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REFERENCES

Bombois, S., Debette, S., Delbeuck, X., Bruandet, A., Lepoittevin, S., Delmaire, C., et al. (2007). Prevalence of subcortical vascular lesions and association with executive function in mild cognitive impairment subtypes. *Stroke*, *38*(90), 2595–2597.

Bondi, M., Monsch, A., Galasko, D., Butters, N., Salmon, D., & Delis, D. (1994). Preclinical cognitive markers of dementia of the Alzheimer type. *Neuropsychology*, *8*, 374–384.

Bondi, M.W., Salmon, D.P., Galasko, D., Thomas, R.G., & Thal, L.J. (1999). Neuropsychological function and apolipoprotein E genotype in the preclinical detection of Alzheimer's disease. *Psychology and Aging*, *14*(2), 295–303.

Bowler, J.V. (2002). The concept of vascular cognitive impairment. *Journal of the Neurological Sciences*, *203–204*, 11–15.

Bowler, J.V., & Hachinski, V. (2003). Vascular cognitive impairment – A new concept. In *Vascular cognitive impairment: Preventable dementia.* New York: Oxford University Press.

Busse, A., Bischkopf, J., Riedel-Heller, S.G., & Angermeyer, M.C. (2003). Subclassifications for mild cognitive impairment: Prevalence and predictive validity. *Psychological Medicine*, *33*, 1029–1038.

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

Cabeza, R., Anderson, N.D., Locantore, J.K., & McIntosh, A.R. (2002). Aging gracefully: Compensatory brain activity in high-performing older adults. *Neuroimage*, *17*(3), 1394–1402.

Chandler, M.J., Lacritz, L.H., Hynan, L.S., Barnard, H.D., Allen, G., Deschner, M., et al. (2005). A total score for the CERAD neuropsychological battery. *Neurology*, *65*(1), 102–106.

Collie, A., & Maruff, P. (2000). The neuropsychology of preclinical Alzheimer's disease and mild cognitive impairment. *Neuroscience and Biobehavioral Review*, *24*(3), 365–374.

Cummings, J.L. (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology*, *50*, 873–880.

Davis, H.S. & Rockwood, K. (2004). Conceptualization of mild cognitive impairment: A review. *International Journal of Geriatric Psychiatry*, *19*(4), 313–319.

Delano-Wood, L., Abeles, N., Sacco, J., Wierenga, C.E., Horne, N.R., & Bozoki, A. (2008). Regional white matter pathology in mild cognitive impairment: Differential influence of lesion type on neuropsychological functioning. *Stroke*, *39*, 794–800.

De Carli, C. (2003). Mild cognitive impairment: Prevalence, prognosis, aetiology, and treatment. *Lancet Neurology*, *2*(1), 15–21.

Delis, D., Kramer, J., Kaplan, E., & Ober, B. (2000). *CVLT-II: California Verbal Learning Test (2nd ed.), Adult version*. San Antonio, TX: The Psychological Corporation.

Fazekas, F., Schmidt, R., & Scheltens, P. (1998). Pathophysiologic mechanisms in the development of age-related white matter changes of the brain. *Dementia and Geriatric Cognitive Disorders*, *9*(Suppl 1), 2–5.

Fernando, M.S., Simpson, J.E., Matthews, F., Brayne, C., Lewis, C.E., Barber, R., et al. (2006). White matter lesions in an unselected cohort of the elderly: Molecular pathology suggests origin from chronic hypoperfusion injury. *Stroke*, *37*(6), 1391–1398.

Fillenbaum, G.G., van Belle, G., Morris, J.C., Mohs, R.C., Mirra, S.S., Davis, P.C., et al. (2008). Consortium to Establish a Registry for Alzheimer's Disease (CERAD): The first twenty years. *Alzheimer's & Dementia*, *4*, 96–109.

Garrett, K.D., Browndyke, J.N., Whelihan, W., Paul, R.H., DiCarlo, M., Moser, D.J., et al. (2004). The neuropsychological profile of vascular cognitive impairment – no dementia: Comparisons to patients at risk for cerebrovascular disease and vascular dementia. *Archives of Clinical Neuropsychology*, *19*(6), 745–757.

Golden, C.J., & Freshwater, S.M. (2002). *The Stroop Color and Word Test: A manual for clinical and experimental uses*. Chicago: Stoelting.

Gunning-Dixon, F.M., & Raz, N. (2000). The cognitive correlates of white matter abnormalities in normal aging: A quantitative review. *Neuropsychology*, *14*(2), 224–232.

Hays, W.L. (1994). *Statistics* (5th ed.). Fort Worth, TX: Harcourt Brace College Publishers.

Inzitari, D. (2000). Age-related white matter changes and cognitive impairment. *Annals of Neurology*, *47*, 141–143.

Kaufman, L., & Rousseau, P. (1990). *Finding groups in data.* New York: Wiley.

Kavé, G., & Heinik, J. (2004). Neuropsychological evaluation of mild cognitive impairment: Three case reports. *Clinical Neuropsychology*, *18*(3), 362–372.

Kleinbaum, D.G., Kupper, L.L., & Muller, K.E. (1988). *Applied regression analysis and other multivariable methods*. Boston: PWS-Kent Publishing.

Lazarus, R., Prettyman, R., & Cherryman, G. (2005). White matter lesions on magnetic resonance imaging and their relationship with vascular risk factors in memory clinic attenders. *International Journal of Geriatric Psychiatry*, *20*, 274–279.

Libon, D.J., Xie, S.X., Moore, P., Farmer, J., Antani, S., McCawley, G., et al. (2007). Patterns of neuropsychological impairment in frontotemporal dementia. *Neurology*, *68*(5), 369–375.

Looi, J.C.L., & Sachdev, P.S. (2000a). Diagnosis and management of vascular dementia. *Medicine Today*, *1*, 16–24.

Loewenstein, D.A., Acevedo, A., Agron, J., Issacson, R., Strauman, S., Crocco, E., et al. (2006). Cognitive profiles in Alzheimer's disease and in mild cognitive impairment of different etiologies. *Dementia and Geriatric Cognitive Disorders*, *21*(5–6), 309–315.

Mickes, L., Wixted, J.T., Fennema-Notestine, C., Galasko, D., Bondi, M.W., Thal, L.J., Salmon, D.P. (2007). Progressive impairment on neuropsychological tasks in a longitudinal study of preclinical Alzheimer's disease. *Neuropsychology*, *21*, 696–705.

Mortimer, J.A., Snowdon, D.A., & Markesbery, W.R. (2003). Head circumference, education and risk of dementia: Findings from the nun study. *Journal of Clinical and Experimental Neuropsychology*, *25*(5), 671–679.

Petersen, R.C. (2004a). MCI as a useful clinical concept. *Geriatric Times*, *5*(1), 1–3.

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

Petersen, R.C., Doody, R., Kurz, A., Mohs, R.C., Morris, J.C., Rabins, P.V., et al. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology*, *58*, 1985–1992.

Petersen, R.C., & Morris, J.D. (2005). Mild cognitive impairment as a clinical entity and treatment target. *Archives of Neurology*, *62*, 1160–1163.

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

Powell, M.R., Smith, G.E., Knopman, D.S., Parisi, J.E., Boeve, B.F., Petersen, R.C., & Ivnik, R.J. (2006). Cognitive measures predict pathologic Alzheimer disease. *Archives of Neurology*, *63*, 865–868.

Price, C., Schmalfuss, I., & Sistrom, C. (2005). Quantification of white matter alterations: A reliability analysis. Abstract presented at the International Neuropsychological Society.

Prins, N.D., van Dijk, E.J., den Heijer, T., Vermeer, S.E., Koudstaal, P.J., Oudkerk, M., et al. (2004). Cerebral white matter lesions and the risk of dementia. *Archives of Neurology*, *61*, 1531–1534.

Raz, N., Rodrigue, K.M., & Acker, E.M. (2003). Hypertension and the brain: Vulnerability of prefrontal regions and executive functions. *Behavioral Neuroscience*, *117*(6), 1169–1180.

Reitan, R.M., & Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery: Theory and interpretation.* Tucson, AZ: Neuropsychology Press.

Ritchie, K., & Touchon, J. (2000). Mild cognitive impairment: Conceptual basis and current nosological status. *Lancet*, *335*, 225–228.

Rockwood, K., Davis, H., & MacKnight, C., Vandorpe, R., Gauthier, S., Guzman, A., et al. (2003). The Consortium to Investigate Vascular Impairment of Cognition: Methods and first findings. *Canadian Journal of Neurological Science*, *30*, 237–243.

Rubin, E.H., Storandt, M., Miller, J.P., Kinscherf, D.A., Grant, E.A., Morris, J.C., & Berg, L. (1998). A prospective study of cognitive function and onset of dementia in cognitively healthy elders. *Archives of Neurology*, *55*(3), 395–401.

Salmon, D.P., Thomas, R.G., Pay, M.M., Booth, A., Hofstetter, C.R., Thal, L.J., & Katzman, R. (2002). Alzheimer's disease can be accurately diagnosed in very mildly impaired individuals. *Neurology*, *59*, 1022–1028.

Selnes, O.A., & Vinters, H.V. (2006). Vascular cognitive impairment. *Nature Clinical Practice Neurology*, *2*, 538–547.

Schmidtke, K., & Hermeneit, S. (2007). High rate of conversion of Alzheimer's disease in a cohort of amnestic MCI patients. *International Psychogeriatrics*, *116*, 1–14.

Shinkawa, A., Ueda, K., Kiyohara, Y., Kato, I., Sueishi, K., Tsuneyoshi, M., & Fujishima, M. (1995). Silent cerebral infarction in a community-based autopsy series in Japan. *Stroke*, *26*, 380–385.

Simpson, J.E., Ince, P.G., Higham, C.E., Gelsthorpe, C.H., Fernando, M.S., Matthews, F., et al. (2007). Microglial activation in white matter lesions and nonlesional white matter of ageing brains. *Neuropathology and Applied Neurobiology*, *33*(6), 670–683.

Stephens, S., Kenny, R.A., Rowan, E., Allan, L., Kalaria, R.N., Bradbury, M., & Ballard, C.G. (2004). Neuropsychological characteristics of mild vascular cognitive impairment and dementia after stroke. *International Journal of Geriatric Psychiatry*, *19*(11), 1053–1057.

Storandt, M., Grant, E.A., Miller, J.P., & Morris, J.C. (2006). Longitudinal course and neuropathologic outcomes in original *vs.* revised MCI and in pre-MCI. *Neurology*, *67*(3), 467–473.

Testa, J.A., Ivnik, R.J., Boeve, B., Petersen, R.C., Pankratz, V.S., Knopman, D., et al. (2004). Confrontation naming does not add incremental diagnostic utility in MCI and Alzheimer's disease. *Journal of the International Neuropsychological Society*, *10*(4), 504–512.

Thomas, A.J., O'Brien, J.T., Davis, S., Ballard, C., Barber, R., Kalaria, R.N., & Perry, R.H. (2002). Ischemic basis for deep white matter hyperintensities in major depression. A neuropathological study. *Archives of General Psychiatry*, *59*, 785–792.

Tomimoto, H., Ihara, M., Wakita, H., Ohtani, R., Lin, J.X., Akiguchi, I., et al. (2003). Chronic cerebral hypoperfusion induces white matter lesions and loss of oligodendroglia with DNA fragmentation in the rat. *Acta Neuropathology*, *106*(6), 527–534.

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: Review and meta-analysis. *Neuropsychologia*, *42*, 1394–1413.

Vataja, R., Pohjasvaara, T., Mantyla, R., Ylikoski, R., Leppavuori, A., Leskela, M., et al. (2003). MRI correlates of executive dysfunction in patients with ischaemic stroke. *European Journal of Neurology*, *10*(6), 625–631.

Ward, J.H. (1963). Hierarchical grouping to optimize an objective function. *Journal of the American Statistical Association*, *77*, 841–847.

Welsh, K., Butters, N., & Mohs, R.C. (1994). CERAD Part V: A normative study of the neuropsychological battery. *Neurology*, *44*, 609–614.

Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M.B., & Leirer, V.O. (1983). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatry Research*, *17*, 37–49.

Zanetti, M., Ballabio, C., Abbate, C., Cutaia, C., Vergani, C., & Bergamaschini, L. (2006). Mild cognitive impairment subtypes and vascular dementia in community-dwelling elderly people: A 3-year follow-up study. *Journal of the American Geriatric Society*, *54*(4), 580–586.