Title

The Patterns of Cognitive and Functional Impairment in Amnestic and Non-amnestic Mild Cognitive Impairment in Geriatric Depression

Journal

American Journal of Geriatric Psychiatry, 22(12)

ISSN

1064-7481

Authors

Reinlieb, Michelle
Ercoli, Linda M
Siddarth, Prabha
et al.

Publication Date

2014-12-01

DOI

10.1016/j.jagp.2013.10.010

Peer reviewed

HHS Public Access

Author manuscript

Am J Geriatr Psychiatry. Author manuscript; available in PMC 2016 February 12.

Published in final edited form as:

Am J Geriatr Psychiatry. 2014 December ; 22(12): 1487–1495. doi:10.1016/j.jagp.2013.10.010.

The Patterns of Cognitive and Functional Impairment in Amnestic and Non-amnestic Mild Cognitive Impairment in Geriatric Depression

Michelle Reinlieb, M.A., **Linda Ercoli, Ph.D.**, **Prabha Siddarth, Ph.D.**, **Natalie St. Cyr, M.A.**, and **Helen Lavretsky, M.D.**

Graduate Center, City University of New York (MR), New York, NY; and the UCLA Semel Institute for Neuroscience and Human Behavior (MR, LE, PS, NSC, HL), Los Angeles, CA

Abstract

Objectives—Depressed older adults are at risk for the development of mild cognitive impairment (MCI), but few studies have characterized MCI subtypes in geriatric depression. The objective of this study was to identify the clinical patterns of MCI in late-life depression.

Design—Baseline demographic, clinical, and neuropsychological test data collected as part of a randomized antidepressant trial for geriatric depression.

Setting—UCLA-based outpatient clinic.

Participants—One hundred thirty-eight older adults with major depression.

Measurements—A neuropsychological test battery and comprehensive evaluations of depression, apathy, quality of life, medical burden, and vascular risk factors.

Results—Seventy-one participants (51%) had MCI and 67 (49%) were cognitively normal. Of subjects with MCI, 14 (20%) had amnestic MCI and 57 (80%) had non-amnestic MCI. Overall, patients with MCI had greater depression severity, poorer quality of life, and worse performance on the Mini-Mental State Exam than patients without MCI. Patients with non-amnestic MCI had significantly greater depression severity than patients without MCI. Across all subjects, depression severity correlated with impaired performance in language and visuospatial functioning.

Conclusion—Our findings suggest that MCI is associated with greater severity of depression, poorer quality of life, and worse global cognitive function. Overall, subtypes of MCI in geriatric depression differ in the patterns of functional impairment, which may require different therapeutic approaches.

Keywords

Geriatric depression; mild cognitive impairment

Send correspondence and reprint requests to Helen Lavretsky, M.D., M.S., Department of Psychiatry and Biobehavioral Sciences and Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, 760 Westwood Plaza, C9-948A, Los Angeles, CA 90095. hlavretsky@mednet.ucla.edu.

The other authors have no disclosures to report.

Cognitive impairment frequently co-occurs with late-life depression (LLD).[1–7] Although some aspects of cognition may improve following successful antidepressant treatment, cognitive functioning may not return to baseline levels despite remission of mood-related symptoms.[8–10] Residual cognitive deficits among depressed older adults in remission may reflect underlying pathological aging-related neurodegenerative or vascular structural and functional brain changes that increase the risk for the development of mild cognitive impairment (MCI).

MCI has been used to characterize a transitional state between normal cognitive aging and dementia where the level of cognitive impairment minimally interferes with daily functioning.[11,12] Currently, MCI subtypes characterize memory (amnestic MCI [aMCI]) or non-memory-related (non-amnestic MCI [naMCI]) cognitive impairment, and whether single or multiple cognitive domains are impaired.[12–14] Although each MCI subtype may have multiple potential etiologies, aMCI has a high likelihood of progressing to Alzheimer disease (AD) and naMCI to a non-AD dementia.[13]

Depression is associated with an increased risk of developing MCI,[15] and patients with MCI and depression are at twice greater risk of developing AD than those without depression.[16] Furthermore, depression is the most common neuropsychiatric symptom in MCI[17,18] and approximately 50% of patients with LLD may have an MCI diagnosis.[19,20] One study found that depressed individuals with MCI at baseline were four times more likely to be classified as having MCI one year later than those without MCI, despite remission of depression.

Despite this link between depression and MCI, no consistent MCI criteria have been proposed for depressed older adults. In fact, MCI studies often exclude patients with major depressive disorder (MDD) even though formal MCI criteria do not exclude depressed older adults.[12,13] Characterizing MCI subtypes in geriatric depression may help develop a broader understanding of comorbid cognitive impairment and, furthermore, identify the subtype at higher risk for developing a particular type of dementia (e.g., vascular or AD). Characterizing MCI subtypes in geriatric depression may also help to develop targeted personalized treatment approaches based on cognitive and mood profiles.

The few studies that have characterized MCI subtypes in LLD have reported mixed findings. One study found that patients with aMCI and mild depression demonstrated worse performance in verbal memory and some aspects of executive functioning than patients with aMCI and no depression.[21] In a recent study, Johnson et al.[22] found that mildly depressed MCI patients exhibited greater deficits in immediate and delayed memory than non-depressed MCI patients. These studies excluded patients with MDD, however, who may be more cognitively vulnerable and at greater risk for MCI than those with mild depressive symptoms.

Studies that have characterized MCI subtypes in patients with MDD have only included patients in the remitted state. For instance, Bhalla et al.[23] found that older age predicted MCI diagnosis (aMCI or naMCI compared with cognitively normal; age did not predict MCI subtype) among remitted elderly depressed subjects. Another study[24] found that, among elderly patients with MDD in remission, later age of onset and ventricular atrophy were

associated with aMCI and vascular risk factor burden was associated with naMCI. Such studies can determine which depressed patients may be at risk for the development of MCI, and they have the advantage of assessing patients in a euthymic state without concern for potential state-related cognitive impairment. These studies cannot help to identify the MCI syndrome in patients in a current depressive episode, however.

It is important to characterize MCI subtypes among older adults in a current episode of major depression, as this may provide information about dementia risk. For instance, some studies suggest that certain subtypes of LLD may represent an early manifestation (i.e., a prodrome) of dementia.[25,26] In fact, studies have reported that 33%–60% of patients with AD at follow-up developed major depressive episodes at or after the onset of cognitive impairment,[27] or were depressed at the time of the baseline evaluation.[28] Such findings have led to the hypothesis that LLD, MCI, and dementia may represent a possible clinical continuum in a subset of individuals.[26] If this is the case, some patients may not demonstrate improvement in mood or cognitive symptoms prior to conversion to dementia. It is therefore important to understand how MCI subtypes manifest in acutely depressed patients so we can provide appropriate targeted interventions at this early stage.

The purpose of this study was to examine the clinical characteristics of MCI subtypes among older adults in a current major depressive episode using baseline data from a treatment trial of LLD. (It is important to note that our classification of MCI is psychometrically based and therefore deviates from the traditional Petersen MCI criteria [refer to the Methods section for additional details]). Based on the literature reviewed here, we hypothesized that MCI would be associated with older age, later age of depression onset, and greater cerebrovascular risk factor burden.

METHODS

One hundred ninety-seven adults aged 60 years and older with unipolar MDD participated in the randomized double-blind placebo-controlled trial of methylphenidate augmentation of citalopram. Of the 197 participants, 138 constituted this study as they had complete baseline neuropsychological data. Patients with complete neuropsychological data (N = 138) were younger (69.7 years, SD: 7.2) than those without complete data (N = 59; 72.6 years, SD: 8.9; $t_{(175)} = -2.11$, $p = 0.04$); no differences were detected on other clinical or demographic variable. As this report is limited to the analysis of baseline data, only recruitment methodology and baseline assessment results will be provided.

Participants were recruited through advertising in local newspapers and radio as well as referrals from UCLA-based clinics. Recruitment focused on participants with MDD (rather than those with cognitive impairment per se). Individuals who responded to the advertisement were screened by phone. Participants who signed informed consent underwent an initial diagnostic assessment including a physical, neurological, and neuropsychiatric examination, electrocardiogram, and laboratory testing to rule out other causes of mood or cognitive symptoms. Subjects were antidepressant-free for at least 2 weeks at baseline.

Subjects were evaluated using validated assessment instruments to establish current diagnosis and determine depression severity, level of psychosocial functioning, quality of life, and medical co-morbidity. Instruments included the Structured Clinical Interview for DSM-IV, Hamilton Depression Rating Scale-24 item (HDRS-24),[29] Geriatric Depression Scale,[30] and Clinical Global Impressions Scale[31] to establish diagnosis and measure depression severity. Measures of co-morbid psychiatric symptoms included the Hamilton Anxiety Rating Scale[32] and Apathy Evaluation Scale.[33] The Unified Parkinson Disease Rating Scale (UPDRS),[34] Cerebrovascular Risk Factor Prediction Chart (CVRF),[35] and Cumulative Illness Rating Scale-Geriatrics[36] assessed medical co-morbidity. Instruments used to assess quality of life, life satisfaction, and disability included the Medical Outcomes Study Short Form 36-Item Health Survey,[37] WHO Psychiatric Disability Schedule, and Quality of Life Enjoyment Scale.[38]

Participants completed a comprehensive neuropsychological test battery[39] to assess five cognitive domains: memory (California Verbal Learning Test-II [long delayed free recall], Rey-Osterrieth Complex Figure Test [30-minute delayed recall]), language (Boston Naming Test, FAS, Animal Naming Test]), attention and processing speed (Trail Making Test A, Stroop Color Trial [Golden Version]), executive functioning (Trail Making Test B, Stroop interference [Golden version]), and visuospatial functioning (WAIS-III Block Design, Rey-Osterrieth Complex Figure Test [copy]).

Inclusion criteria were as follows: 1) current episode of unipolar MDD according to DSM-IV criteria; 2) HDRS-24 score greater than or equal to 16; and 3) Mini-Mental State Exam (MMSE)[40] score greater than or equal to 26. Exclusion criteria were as follows: 1) history of any other psychiatric illness other than unipolar MDD or alcohol or substance abuse/dependence; 2) presence of psychotic symptoms; 3) severe or acute unstable medical illness; 4) acute suicidal or violent behavior or history of suicide attempt within the last year; or 5) presence of delirium, neurodegenerative dementia, Parkinson disease, or any other central nervous system diseases.

For data reduction purposes, cognitive measures were grouped into five composite domains based on clinical knowledge of test characteristics.[39] We transformed raw scores to z-scores for each test score of interest for each participant, and then averaged the z-scores. Z-scores were calculated from published normative data.[41–49] For variables in which good performance was represented by lower values (e.g., Trail Making Test), z-scores were reversed so that high z-scores represented good performance for all measures.

Petersen's MCI criteria[11] were used as a guide to classify MCI and determine subtype of MCI in affected patients. Subjects identified to have MCI were neither cognitively normal nor demented (dementia was an exclusion criteria), and they had preserved functional abilities. Subjects were screened for dementia via a review of an extensive history and mental status exam together with corroborating information about functional abilities from a knowledgeable family member. Clinically ambiguous cases were discussed and diagnosed at a consensus meeting.

Our classification method deviates from the Petersen criteria in that we do not have evidence of cognitive decline (i.e., repeat testing or structured assessment of self or collateral report of cognitive change). Furthermore, we used the 1 SD cutoff for MCI classification for exploratory purposes to gain a better understanding of the nature of MCI in LLD. Mild cognitive impairment was defined as any composite domain score 1 SD or more below norms; patients were classified as cognitively normal (no-MCI) if no domain score fell 1 SD or more below the normative sample. The 1 SD threshold has been found to yield high sensitivity for predicting dementia, balancing increased sensitivity with specificity.[14] Although this threshold seems somewhat liberal,[50] we emphasize that this is on a composite variable and not on a single test.

For subtyping MCI, participants were categorized into one of three mutually exclusive groups: aMCI, naMCI, or no-MCI.[11,12] Amnestic MCI was defined as a memory domain score 1 SD or more below age-corrected norms and naMCI as any non-memory domain score 1 SD or more below age-corrected norms. Single domain and multi-domain MCI groups were combined for analysis due to a relatively small sample size.

Statistical Analyses

Classification using 1 SD threshold—We first compared demographic and clinical variables between patients with and without MCI using χ^2 tests of independence and analysis of variance tests for dichotomous and continuous variables, respectively. To test for differences between the three groups (aMCI, naMCI, no-MCI), we also used the χ^2 test of independence and analysis of variance tests. We performed pairwise comparisons of least squares means for all significant omnibus F-tests. All post hoc analyses were corrected using the Tukey-Kramer adjustment. Significance tests were evaluated at the 5% level.

Classification using 1.5 SD threshold—To further explore the concept of MCI in LLD, we repeated the previous comparisons using a more conservative MCI definition. In these analyses, MCI was defined as any composite domain score of 1.5 SD or more below age-corrected norms and patients were classified as cognitively normal if none of their domain scores fell 1.5 SD or more below the normative sample. Using this approach, we were unable to conduct the three-subgroup comparisons (no-MCI, aMCI, naMCI) as a limited number of patients were classified as aMCI (N = 4).

RESULTS

Table 1 presents baseline demographic and clinical characteristics for the total sample and MCI subgroups. Table 2 presents mean baseline neuropsychological test performance. Overall, the average study participant was 69.7 (SD: 7.2) years old and completed about 4 years of college (M: 15.9; SD: 2.4). Approximately 54% of the sample was women, average baseline depression severity was 18.9 (SD: 3.1) on the HDRS-24, and the average baseline MMSE score was 28.8 (SD: 1.3).

Classification Using −1 SD Threshold

Prior to subtyping MCI, we examined the internal consistency between composite domains using Cronbach's α. All composite domains had good internal consistency reliability ranging from 0.80 to 0.90 (executive functioning, α = 0.80; processing speed, α = 0.85; memory, α = 0.84; visuospatial functioning, α = 0.90; language, α = 0.82). Of the 138 participants, 71 (51%) had MCI and 67 (49%) were cognitively normal. Of MCI subjects, 14 (20%) had aMCI and 57 (80%) had naMCI. Figure 1 displays the relative differences in baseline neuropsychological test performance between the three subgroups.

We first compared clinical and demographic characteristics between MCI (combining subtypes) and no-MCI groups. The MCI group had greater depression severity (HDRS-24: $F_{(1, 136)} = 7.37$, p = 0.008), poorer quality of life (QLSQ: $F_{(1, 136)} = 4.06$, p = 0.05), and worse global cognitive function (MMSE: $F_{(1, 136)} = 18.04$, p =<.0001) than the no-MCI group. No other comparisons were significant.

We next compared clinical and demographic characteristics across the three patient subgroups (aMCI, naMCI, no-MCI). We found differences in depression severity (HDRS: $F_{(2, 135)} = 3.73$, p = 0.03) and global cognitive functioning (MMSE: $F_{(2, 135)} = 9.76$, p = 0.01). No other comparisons were significant.

Post hoc comparisons revealed that the naMCI subgroup had significantly greater depression severity than the no-MCI subgroup ($t_{(122)} = -2.68$, p = 0.02); the difference between the aMCI and naMCI subgroups was not significant ($t_{(69)} = -0.37$, p = 0.93). Both aMCI ($t_{(79)} = -3.44$, p <0.01) and naMCI ($t_{(122)} = -3.63$, p <0.01) subgroups demonstrated significantly poorer performance on the MMSE than the no-MCI group.

Across all subjects (N = 138 for all comparisons), depression severity significantly correlated with impaired performance in language (Pearson's r = −0.21, p = 0.01) and visuospatial functioning (Pearson's r = −0.22, p = 0.01). The correlations with memory (Pearson's r = −0.10, p = 0.25), psychomotor speed (Pearson's r = −0.15, p = 0.09), and executive functioning (Pearson's r = −0.09, p = 0.30) were not significant.

Classification Using −1.5 SD Threshold

Due to a small number of aMCI subjects using this definition (N = 4), we could not perform a three-subgroup analysis, and instead all MCI subjects were combined in a single group. Using the 1.5 SD cutoff, 34 (25%) patients had MCI and 104 (75%) patients had no-MCI. The MCI group had lower levels of education ($F_{(1, 136)} = 7.99$, p = 0.01), greater depression severity (HDRS-24: $F_{(1, 136)} = 6.36$, p = 0.01), greater cerebrovascular risk factor burden (CVRF: $F_{(1, 136)} = 5.10$, p = 0.03), greater levels of psychomotor slowing (UPDRS: $F_{(1, 136)} = -4.27$, p = 0.04), and worse global cognitive function (MMSE: $F_{(1, 136)} = 7.16$, p = 0.01) than the no-MCI group. No other comparisons were significant.

DISCUSSION

The purpose of this study was to characterize the clinical characteristics of MCI subtypes in LLD. We found that depressed patients with MCI had greater depression severity, poorer

quality of life, and worse global cognitive functioning than depressed patients without MCI. When comparing MCI subtypes, patients with naMCI were significantly more depressed than patients without MCI. Finally, across all subjects, depression severity significantly correlated with impaired performance in language and visuospatial functioning.

Our first finding, that MCI in geriatric depression was associated with greater depression severity and poorer quality of life, adds new understanding to the literature about the clinical manifestations of LLD. In prior studies, Bhalla et al.[23] found that older age predicted MCI diagnosis. Another study[24] found that, among elderly patients with MDD in remission, later age of onset and ventricular atrophy were associated with aMCI and vascular risk factor burden was associated with naMCI. Finally, Schneider et al.[51] found that vascular burden was significantly correlated with deficits in attention and cognitive control among patients with LLD. No study, however, has found an association between MCI and depression severity or quality of life.

There are several methodological factors that could account for this discrepancy among findings. One possible explanation is that prior studies used a sample of depressed older adults in the remitted state rather than those in a current episode of MDD. Therefore, the profile of clinical characteristics across these groups is likely to differ despite the fact that cognitive impairment persists following successful treatment of depression. Another possibility is that patients in our study may have been less cognitively impaired than other samples due to a fairly conservative inclusion criteria of an MMSE score greater than or equal to 26. If this were the case, however, we might expect that a higher level of cognitive functioning would be associated with lesser severity of depression and better quality of life. On the other hand, these subjects may have had better insight into their impairment and related quality of life.

Our last finding was that depression severity was significantly associated with poor performance in visuospatial functioning and language and the correlations with memory, psychomotor speed, and executive functioning were not significant. The lack of association was surprising given that deficits in memory, psychomotor speed, and executive functioning are common in LLD.[1–3,6,7] This finding, however, is consistent with a study showing that current symptom severity only marginally affects cognition.[52] One possibility is that cognitive deficits represent a trait feature of geriatric depression and are secondary to structural brain changes, which may not be influenced by symptom severity.[52]

An important issue this study highlights is whether the traditional MCI definition should be applied to patients with MDD given that cognitive deficits are associated with LLD. MCI studies generally exclude those with MDD, making it difficult to determine whether the MCI construct is applicable to this patient population. Several studies have shown, however, that cognitive impairment in LLD persists following remission—suggesting that such deficits represent a trait rather than state characteristic of LLD that may be associated with increased risk for conversion to dementia. Future research should determine whether the clinical and cognitive profile of MCI in late-life major depression differs from that in non-depressed elderly and predicts the development of dementia in this population.

If the MCI construct does apply to LLD, the next question is whether the same diagnostic criteria should apply to depressed and non-depressed patients. We conducted secondary analyses to explore different classification methods in LLD. Using two different criteria sets (1.0 SD versus 1.5 SD), we had some overlap in findings (depression severity) but we also found several inconsistencies pointing to a greater influence of cerebrovascular factors on MCI in the 1.5 SD analyses. This highlights the need for consistent MCI criteria across studies. It also demonstrates that the threshold of impairment may provide additional information about the etiology of the cognitive deficits. Additional research is necessary to further explore the MCI construct in LLD and work toward validating criteria for use in this population.

Based on our findings, depressed older adults with MCI may require different treatment approaches than those without MCI based on divergent clinical profiles. For instance, a number of studies have shown that depressed older adults with cognitive impairment are less responsive to antidepressant treatment.[53–55] Given this relationship, one possible alternative may be treatments that target cerebrovascular risk factors. Alternative non-pharmacological therapies that target cognitive deficits have also been proposed for the treatment of LLD. Problem-solving therapy, for instance, has been effective in treating depressed older adults with cognitive impairment.[56,57] Meditation[58] and Tai Chi[59] may also be effective in this patient population. Future studies should examine whether MCI subtypes respond preferentially to different treatments based on their clinical or cognitive profiles. For example, problem-solving therapy may be most effective in naMCI patients with executive dysfunction, whereas patients with aMCI may demonstrate a stronger response to memory training interventions.

This study has several limitations. First, our sample was composed of predominantly Caucasian, college-educated, and relatively healthy older adults, which limited generalizability. Second, we did not have a non-depressed comparison group, limiting how much information we could gather about the characteristics of MCI in depressed versus non-depressed individuals. Third, for exploratory purposes, we used a fairly liberal definition of MCI, which runs the risk of over-identifying cases of MCI. Secondary analyses, however, explored the use of a stricter definition. Fourth, different published normative databases were used to calculate z-scores across the neuropsychological battery, which potentially impacted classification. Finally, our exclusion criteria was fairly conservative with respect to cognitive impairment as reflected in our mean MMSE score,[29] and these findings may not generalize to older adults with poorer cognitive functioning. This also led to a small percentage of MCI subjects relative to other reports in the literature, limiting our ability to classify patients into single- and multi-domain subgroups. Future studies could extend our work by comparing clinical profiles of these MCI subgroups in LLD.

A strength of this study was the use of participants in a depressed state at the time of assessment. Few other studies have addressed the validity of the MCI construct in LLD despite its seemingly high prevalence. This is important given the high comorbidity between depression and cognitive impairment and the elevated risk of dementia in older depressed adults. This cohort, however, is likely different from other MCI cohorts reported on in the literature (i.e., those in the remitted state or with minor or no depression), and it will be

important to compare baseline characteristics and outcomes of MCI samples with and without depression. It will also be important to examine the longitudinal cognitive course of depressed older adults with and without MCI to determine the risk for conversion to dementia in these subgroups and the impact of depression remission on MCI status. We are in the process of analyzing 4-month follow-up data from the parent study to examine these critical issues.

In conclusion, our findings contribute to the literature characterizing the clinical characteristics of MCI in LLD and suggest that MCI subtypes differ in their patterns of functional impairment. Older depressed adults with MCI may require different therapeutic approaches than those without MCI. Future research should focus on the development of targeted personalized treatments based on the cognitive and affective profile of MCI subtypes in this population. Alternative treatments that target cognitive deficits may be particularly effective as they may reduce the risk of cognitive decline and extend quality of life.

Acknowledgments

This work was supported by NIH grants MH077650 and MH086481 to Dr. Lavretsky. Dr. Lavretsky has received research funding from Forest Laboratories and consultant fees from Dey Pharmaceuticals and Eli Lilly Pharmaceuticals.

References

1. Salloway S, et al. MRI and neuropsychological differences in early-and late-life-onset geriatric depression. Neurology. 1996; 46(6):1567–1574. [PubMed: 8649550]
2. Kramer-Ginsberg E, et al. Neuropsychological functioning and MRI signal hyperintensities in geriatric depression. Am J Psychiatry. 1999; 156(3):438–444. [PubMed: 10080561]
3. Gallassi R, et al. Memory impairment in patients with late-onset major depression: the effect of antidepressant therapy. J Affect Disord. 2006; 91:243–250. [PubMed: 16499971]
4. Butters MA, et al. The nature and determinants of neuropsychological functioning in late-life depression. Arch Gen Psychiatry. 2004; 61:587–595. [PubMed: 15184238]
5. Lesser I, et al. Cognition and white matter hyperintensities in older depressed patients. Am J Psychiatry. 1996; 153(10):1280–1287. [PubMed: 8831435]
6. Nebes RD, et al. Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. Psychol Med. 2000; 30:679–691. [PubMed: 10883722]
7. Lockwood KA, Alexopoulos GS, van Gorp WG. Executive dysfunction in geriatric depression [see comment]. Am J Psychiatry. 2002; 159(7):1119–1126. [PubMed: 12091189]
8. Bhalla RK, et al. Persistence of neuropsychologic deficits in the remitted state of late-life depression. Am J Geriatr Psychiatry. 2006; 14:419–427. [PubMed: 16670246]
9. Butters MA, et al. Changes in cognitive functioning following treatment of late-life depression. Am J Psychiatry. 2000; 157:1949–1954. [PubMed: 11097959]
10. Doraiswamy PM, et al. Does antidepressant therapy improve cognition in elderly depressed patients? J Gerontol A Biol Sci Med Sci. 2003; 58(12):M1137–M1144. [PubMed: 14684712]
11. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004; 256:183–194. [PubMed: 15324362]
12. Winblad B, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004; 256(3): 240–246. [PubMed: 15324367]
13. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004; 256(3):183–194. [PubMed: 15324362]

14. Busse A, et al. Subclassifications for mild cognitive impairment: prevalence and predictive validity. Psychol Med. 2003; 33(6):1029–1038. [PubMed: 12946087]
15. Ravaglia G, et al. Prevalent depressive symptoms as a risk factor for conversion to mild cognitive impairment in an elderly italian cohort. Am J Geriatr Psychiatry. 2008; 16(10):834–843. [PubMed: 18827230]
16. Modrego PJ, Ferrandez J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. Arch Neurol. 2004; 61(8): 1290–1293. [PubMed: 15313849]
17. Lyketsos CG, et al. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA. 2002; 288(12):1475–1483. [PubMed: 12243634]
18. Barnes DE, et al. Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. Arch Gen Psychiatry. 2006; 63(3):273–279. [PubMed: 16520432]
19. Steffens DC. Separating mood disturbance from mild cognitive impairment in geriatric depression. Int Rev Psychiatry. 2008; 20(4):374–381. [PubMed: 18925486]
20. Lee JS, et al. Persistent mild cognitive impairment in geriatric depression. Int Psychogeriatr. 2007; 19(1):125–135. [PubMed: 16834811]
21. Hudon C, Belleville S, Gauthier S. The association between depressive and cognitive symptoms in amnestic mild cognitive impairment. Int Psychogeriatr. 2008; 20(4):710–723. [PubMed: 18397547]
22. Johnson JK, et al. Longitudinal change in neuropsychological performance using latent growth models: a study of mild cognitive impairment. Brain Imaging Behav. 2012
23. Bhalla RK, et al. Patterns of mild cognitive impairment after treatment of depression in the elderly. Am J Geriatr Psychiatry. 2009; 17(4):308–316. [PubMed: 19307859]
24. Yeh YC, et al. Subtypes of mild cognitive impairment among the elderly with major depressive disorder in remission. Am J Geriatr Psychiatry. 2011; 19(11):923–931. [PubMed: 22024616]
25. Steffens DC, et al. Perspectives on depression, mild cognitive impairment, and cognitive decline. Arch Gen Psychiatry. 2006; 63:130–138. [PubMed: 16461855]
26. Chen P, et al. The temporal relationship between depressive symptoms and Alzheimer's disease: a community-based prospective study. Arch Gen Psychiatry. 1999; 56:261–266. [PubMed: 10078504]
27. Zubenko GS, et al. A collaborative study of the emergence and clinical features of the major depressive syndrome of Alzheimer's disease. Am J Psychiatry. 2003; 160(5):857–866. [PubMed: 12727688]
28. Visser PJ, et al. Distinction between preclinical Alzheimer's disease and depression. J Am Geriatr Soc. 2000; 48(5):479–484. [PubMed: 10811539]
29. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23:56–62. [PubMed: 14399272]
30. Yesavage JA, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982; 17(1):37–49. [PubMed: 7183759]
31. Guy, W. Assessment Manual for Psychopharmacology. Rockville, MD: National Institute of Mental Health; 1976.
32. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959; 32(1):50–55. [PubMed: 13638508]
33. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res. 1991; 38(2):143–162. [PubMed: 1754629]
34. Fahn, S.; Elton, RL. U.p members: Unified Parkinsons Disease Rating Scale. In: Fahn, S., et al., editors. Recent Developments in Parkinsons Disease. Florham Park, NJ: Macmillan Healthcare Information; 1987.
35. Truelsen T, Lindenstrom E, Boysen G. Comparison of probability of stroke between the Copenhagen City Heart Study and the Framingham Study. Stroke. 1994; 25(4):802–807. [PubMed: 8160224]

36. Miller MD, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Res. 1992; 41:237–248. [PubMed: 1594710]
37. Ware JJ, Sherbourne CD. The MOS 36 short-form health survey I. Conceptual framework and item selection. Med Care. 1992; 30:473–483. [PubMed: 1593914]
38. Endicott J, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull. 1993; 29(2):321–326. [PubMed: 8290681]
39. Lezak, M.; Howieson, DB.; Loring, DW. Neuropsychological Assessment. 4th. New York: Oxford University Press; 2004.
40. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res. 1975; 12:189–198.
41. Selnes OA, et al. Normative data for a brief neurological screening battery. Percept Mot Skills. 1991; 73:539–550. [PubMed: 1766784]
42. Mitrushina M, Satz P. Repeated testing of normal elderly with the Boston Naming Test. Aging. 1995; 7(2):123–127. [PubMed: 7548262]
43. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol. 1999; 14(2):167–177. [PubMed: 14590600]
44. Van Gorp WG, et al. Normative data on the Boston Naming Test for a group of normal older adults. J Clin Exp Neuropsychol. 1986; 8(6):702–705. [PubMed: 3782449]
45. Wechsler, D. WAIS-III Administration and Scoring Manual. San Antonio, TX: The Psychological Corporation; 1997.
46. Van Gorp WG, Satz P, Mitrushina M. Neuropsychological processes associated with normal aging. Dev Neuropsychol. 1990; 6:279–290.
47. Golden, CJ. The Stroop Color and Word Test: A Manual for Clinical and Experimental Use. Wood Dale, IL: Stoelting; 1978.
48. Kolb, B.; Whishaw, I. Fundamentals of Human Neuropsychology. 2nd. New York: W.H. Freeman; 1985.
49. Spreen, O.; Strauss, E. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. New York: Oxford University Press; 1991.
50. Jak AJ, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. Am J Geriatr Psychiatry. 2009; 17(5):368–375. [PubMed: 19390294]
51. Schneider B, et al. Vascular burden and cognitive functioning in depressed older adults. Am J Geriatr Psychiatry. 2012; 20(8):673–681. [PubMed: 21857219]
52. Kohler S, et al. The pattern and course of cognitive impairment in late-life depression. Psychol Med. 2010; 40(4):591–602. [PubMed: 19656429]
53. Alexopoulos GS, et al. Executive dysfunction and the course of geriatric depression. Biol Psychiatry. 2005; 58:204–210. [PubMed: 16018984]
54. Sneed JR, et al. Response inhibition predicts poor antidepressant treatment response in very old depressed patients. Am J Geriatr Psychiatry. 2007; 15:553–563. [PubMed: 17586780]
55. Murphy GF, Alexopoulos GS. Attention network dysfunction and treatment of response of geriatric depression. J Clin Exp Neuropsychol. 2006; 28:96–100. [PubMed: 16448978]
56. Alexopoulos GS, et al. Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction: effect on disability. Arch Gen Psychiatry. 2011; 68(1):33–41. [PubMed: 21199963]
57. Kiosses DN, et al. A home-delivered intervention for depressed, cognitively impaired, disabled elders. Int J Geriatr Psychiatry. 2011; 26(3):256–262. [PubMed: 20665555]
58. Lavretsky H, et al. A pilot study of yogic meditation for family dementia caregivers with depressive symptoms: effects on mental health, cognition, and telomerase activity. Int J Geriatr Psychiatry. 2012
59. Lavretsky H, et al. Complementary use of tai chi augments escitalopram treatment of geriatric depression: a randomized controlled trial. Am J Geriatr Psychiatry. 2011; 19(10):839–850. [PubMed: 21358389]

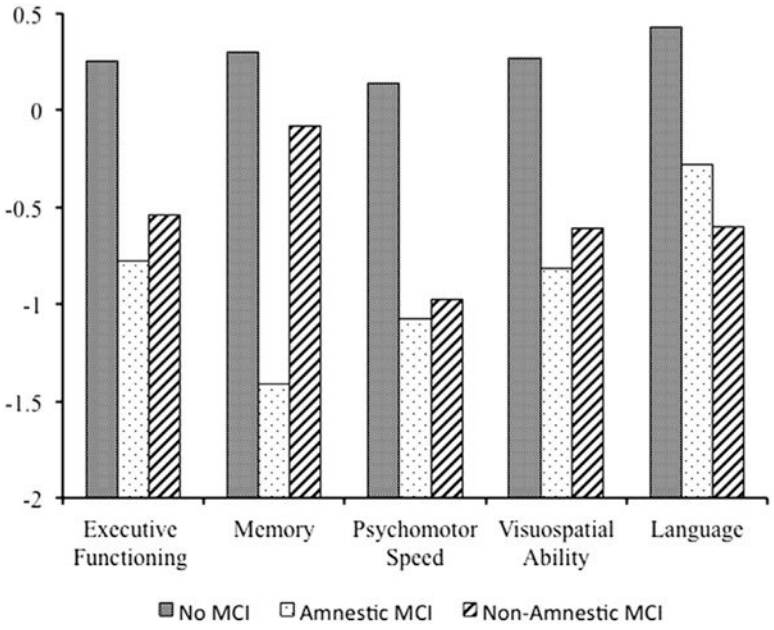

FIGURE 1.

Relative differences in baseline neuropsychological test performance (based on composite domain scores) between the no-MCI (N = 67), amnestic MCI (N = 14), and non-amnestic MCI (N = 57) subgroups.

TABLE 1

Baseline Demographic and Clinical Characteristics for the Total Sample and the MCI Subgroups

Variable	Total Sample (N = 138)	No MCI (N = 67)	MCI (N = 71)	Amnestic MCI (N = 14)	Non-amnestic MCI (N = 57)
Demographics					
Age, years	69.7 (7.2)	69.6 (7.1)	69.7 (7.4)	73.1 (8.4)	68.9 (6.9)
Women, %	54	52	56	60	53
Race, %					
Caucasian	75	84	66	79	63
African American	11	7	14	7	16
Asian	4	1	7	0	9
Hispanic	9	7	11	14	11
Age at depression onset, years	42.7 (23.8)	40.7 (23.3)	44.6 (24.2)	47.8 (27.6)	43.8 (23.5)
Education, years	15.9 (2.4)	16.2 (2.6)	15.5 (2.1)	14.9 (2.0)	15.7 (2.1)
Psychiatric Symptoms					
HDRS-24	18.9 (3.1)	18.2 (2.5)	19.6 (3.5)	19.3 (3.2)	19.7 (3.5)
HAM-A	9.1 (2.9)	8.7 (2.6)	9.4 (3.1)	9.1 (2.3)	9.5 (3.3)
AES	29.0 (11.1)	29.2 (11.2)	28.9 (11.0)	30.0 (11.0)	28.7 (11.1)
QLSQ	40.7 (7.2)	42.0 (6.4)	39.5 (7.7)	39.2 (9.6)	39.6 (7.2)
Comorbid Medical Symptoms					
CIRS-G	5.0 (3.9)	5.1 (3.9)	4.9 (4.0)	5.0 (4.2)	4.9 (4.0)
CVRF	11.0 (5.3)	11.1 (5.1)	10.9 (5.4)	12.5 (5.1)	10.5 (5.5)
UPDRS	4.4 (4.7)	4.0 (4.5)	4.9 (4.8)	5.8 (5.5)	4.7 (4.6)
Body mass index	28.9 (5.6)	26.9 (4.7)	26.8 (6.4)	23.9 (4.3)	27.6 (6.6)
SF-36	88.1 (20.6)	89.6 (18.9)	86.7 (22.2)	76.4 (29.4)	89.2 (19.6)

Notes: HDRS-24: Hamilton Depression Rating Scale-24 Item; HAM-A: Hamilton Anxiety Rating Scale; AES: Apathy Evaluation Scale; QLSQ: Quality of Life Seville Questionnaire; CIRS-G: Cumulative Illness Rating Scale-Geriatrics; CVRF: Cerebrovascular Risk Factor Burden; UPDRS: Unified Parkinson Disease Rating Scale; SF-36: Short-Form Health Survey, Physical Functioning Subscale.

Standard deviation in parentheses.

TABLE 2

Baseline Neuropsychological Test Performance for the Total Sample and the MCI Subgroups

Measure	Total Sample (N = 138)	No MCI (N = 67)	MCI (N = 71)	Amnestic MCI (N = 14)	Non-amnestic MCI (N = 57)
MMSE	28.8 (1.3)	29.2 (1.0)	28.3 (1.3)	28.0 (1.2)	28.4 (1.3)
Memory					
CVLT Long Delay	8.9 (3.4)	9.9 (3.0)	8.0 (3.6)	3.4 (1.5)	9.2 (2.9)
RCFT 30-Minute Delay	13.3 (6.2)	15.7 (5.5)	11.0 (6.0)	6.1 (3.6)	12.2 (5.9)
Language					
FAS	37.8 (11.1)	39.9 (11.3)	35.8 (10.6)	38.5 (12.0)	35.1 (10.2)
Animal Naming Test	20.4 (5.8)	22.8 (5.5)	18.2 (5.0)	17.5 (6.0)	18.4 (4.8)
Boston Naming Test	53.4 (6.5)	56.3 (3.6)	50.6 (7.4)	51.0 (.50)	50.5 (7.8)
Executive Functioning					
Stroop Color/Word	33.3 (9.6)	37.3 (9.6)	29.5 (8.1)	26.4 (7.9)	30.3 (8.1)
TMT-B	104.2 (77.4)	73.4 (22.9)	133.3 (97.3)	173.2 (154.2)	123.5 (76.3)
Psychomotor Speed					
TMT-A	41.0 (16.2)	33.3 (9.3)	48.2 (18.1)	53.6 (20.7)	46.9 (17.3)
Stroop Color	61.6 (13.2)	67.9 (11.9)	55.6 (11.6)	53.9 (12.0)	56.0 (11.5)
Visuospatial Functioning					
WAIS-III Block Design	32.8 (9.1)	36.3 (8.8)	29.5 (8.1)	25.2 (6.0)	30.5 (8.2)
RCFT Copy	30.0 (4.9)	32.5 (2.4)	27.7 (5.5)	26.3 (6.3)	28.0 (5.3)

Notes: MMSE: Mini-Mental State Exam; CVLT: California Verbal Learning Test, 2nd Edition Long Delay Free Recall; RCFT: Rey–Osterrieth Complex Figure Test; TMT: Trail Making Test, Part A and B.

Standard deviations in parentheses.