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SELECTIVITY OF EXECUTIVE FUNCTION DEFICITS IN MILD COGNITIVE IMPAIRMENT

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Abstract

Impairment in executive cognition (EC) is now recognized as relatively common among older persons with mild cognitive impairment (MCI), and may be predictive of the development of dementia. However, both MCI and executive functioning are broad and heterogeneous constructs. The present study sought to determine whether impairments in specific domains of EC are associated with specific subtypes of MCI. 124 MCI patients were divided into four subgroups (amnestic versus nonamnestic, and single- versus multiple-domain) based on their performance of widely-used neuropsychological screening tests. These patients and 68 normal elderly were administered 18 clinical and experimental tests of executive function. Principal components analysis suggested two highly reliable EC components, planning/problem-solving and working memory, and a less reliable third component, judgment. Planning/problem-solving and working memory, but not judgment, were impaired among the MCI patients. This was true even among those with Apure amnestic@ MCI, the least impaired group overall. Multiple-domain MCI patients had more severe impairments in planning/problem-solving and working memory than single-domain patients, leading to the supposition that they, not pure amnestic MCIs, are at highest risk of imminent dementia.

Keywords

executive function; mild cognitive impairment; dementia; principal components analysis; flexibility; working memory; planning

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The status of mild cognitive impairment (MCI) as an important clinical entity remains debated. Expert opinion ranges from it being early Alzheimer=s disease (AD) in virtually all cases (Morris et al., 2001) to it being a diagnostic nonentity (Milwain, 2000; Gauthier & Touchon, 2005; Whitehouse, 2007). Most opinions fall somewhere between these two extremes, and view MCI as a heterogeneous cognitive state that sometimes heralds the onset of progressive

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dementia (Chertkow et al., 2007). Much recent research has focused on determining the characteristics of patients with MCI that predict the progression to AD or another dementia.

It is now widely recognized that several subtypes of MCI can be identified, and the prognoses for them may differ (Lopez et al., 2003; Winblad et al., 2004). The most studied variety is pure amnestic MCI, an isolated and otherwise-unexplained memory impairment in an older person (Ganguli et al., 2004; Petersen, 2004). Although estimates vary, patients with this condition appear to "convert to" (i.e., develop) AD at a rate of 6% –15% per year (Daly et al., 2000; Fisk et al., 2003; Grundman et al., 1996). Patients with isolated impairments in other cognitive domains (e.g., language, spatial cognition) have also been identified, as have patients with mild impairments in multiple cognitive domains who remain functionally intact and don=t meet criteria for dementia. The prognoses for the various subtypes of MCI remain unknown (Chertkow et al., 2007).

The present study investigates the status of executive functioning in four subtypes of MCI. We conceptualize executive functions as Miyake et al. (2000) does: "general purpose control mechanisms that modulate the operation of various cognitive subprocesses and thereby regulate the dynamics of human cognition" (p.50). Although the identification and operation of these control processes has been the subject of much experimentation and discussion, a general model of executive cognition (EC) has yet to be validated or universally accepted (Burgess, 1997; Miyake et al., 2000). The present study is seen as a step toward that goal in that it attempts to identify, empirically, the latent structure underlying a large number of executive function tests.

There are many reasons to believe that decline in some aspects of EC is a strong risk factor for the imminent development of dementia. First, Baddeley and colleagues demonstrated 20 years ago that selective impairment of the central executive component of working memory is a prominent feature of Alzheimer's-type dementia (Baddeley et al., 1986, 1991). Second, onset of executive dysfunction typically follows onset of episodic memory impairment in AD, and precedes impairment of language or spatial cognition (Lafleche & Albert, 1995; Binetti et al., 1996; Bondi et al., 2002). Third, many of the cognitive tests that are most helpful for predicting which nondemented elderly will subsequently develop dementia have substantial executive control requirements (Bondi et al., 1994; Elias et al., 2000; Jacobs et al., 1995; Albert et al., 2001, 2007; Rapp & Reischies, 2005). Finally, even among patients with pure amnestic MCI, impairments in executive function can be found (Crowell et al., 2002; Griffith et al., 2003; Kramer et al., 2006; Royall et al., 2004). These observations have led to the hypothesis that only when executive functioning becomes impaired should an MCI patient be considered to have prodromal AD (Albert et al., 2001; Royall et al., 2002).

Not only is the development of executive impairment potentially predictive of the development of dementia, it also appears to be uniquely associated with functional impairment in the elderly. One study reported that just two executive function tasks (Wisconsin Card Sorting Test [WCST] and Trail Making Test [TMT] part B) accounted for more than 50% of the variance in functional abilities of normal elderly (Bell-McGinty et al., 2002). Among community-dwelling elders, executive function tests have predictive value above and beyond demographic and health variables, overall cognitive integrity (e.g., Mini-Mental State Exam [MMSE] score) and other specific cognitive functions (language, spatial skills, and memory) for both self-reported and empirically measured everyday functioning (Cahn-Weiner et al., 2000; Grigsby et al., 1998; Lewis & Miller, 2007; Royall et al., 1998, 2004). Thus, subtle changes in EC can have a major impact on the lives of elderly persons.

Questions remain as to 1) whether impairments in *specific* executive domains are associated with *specific* subtypes of MCI, and 2) whether these impairments have particular prognostic value. The present study addresses the first of these questions by studying normal elderly

subjects, patients with amnestic MCI (both single- and multiple-domain), and patients with nonamnestic MCI (both single- and multiple-domain) with an extensive set of clinical tests and experimental tasks of executive control. We selected 18 tests representing six conceptually distinct domains of EC: 1) spontaneous flexibility and generativity, 2) inhibition of prepotent responses, 3) planning and sequencing, 4) concept/rule learning and set shifting, 5) decision-making and judgment, and 6) working memory and resource-sharing. The cognitive test data were reduced using principal components analysis and the profile of each of the four MCI subgroups on the derived components was compared to each other and to normal elderly.

METHODS

Participants

One hundred, twenty-four persons with MCI and 68 cognitively normal older adults participated in this study. Most participants (81%) were recruited from the Johns Hopkins Alzheimer=s Disease Research Center (ADRC) and other research studies. They responded to direct-mail and posted announcements, newspaper ads, and solicitations of research volunteers at community lectures. A small number of subjects (19%) were referred from University clinics and physicians in the community from whom they sought evaluation of memory or other cognitive complaints. A health conditions checklist was used to gather information about major physical and psychological disorders. Volunteers were excluded from study participation if they had any history of psychosis, CNS disorder, or active systemic illness (e.g., cancer). Persons with histories of depression were not excluded, as depression is both very common in MCI and may be an important predictor of incident dementia (Jorm, 2001; Lyketsos et al., 2002; Mondrego & Ferrández, 2004; Visser, 2000) or a very early manifestation (Chen et al., 1999).

Every participant was required to have a family member or close friend available to be interviewed for a Clinical Dementia Rating (CDR) (Hughes et al., 1982). Only those with overall CDR scores of 0 or 0.5 were eligible. In addition, every participant was required to score in the normal range (i.e., at or above the 20th percentile for age and education) on the MMSE (Bravo & Hébert, 1997).

Each participant was administered the following screening tests to determine group assignment: Logical Memory subtest (story A) of Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987), a 30-item version of the Boston Naming Test (Goodglass & Kaplan, 1983; Brandt et al., 1989), word list generation (for the letters FAS and the semantic categories animals and vegetables) (Rascovsky et al., 2007; Salmon et al.,1999), and clock drawing to request (Rouleau et al., 1992). These specific tests were chosen for their brevity and their widespread use in the neuropsychological evaluation of geriatric cognitive disorders (Attix & Welsh-Bohmer, 2006). Tests of EC were not included in this screening/subtyping battery because they constitute the outcome variables of interest. In addition, the Activities of Daily Living – Prevention Instrument (ADL-PI) developed by the Alzheimer's Disease Cooperative Study (Galasko et al., 2006) was completed by each participant's "study partner" to supplement the CDR's assessment of functional capacity in everyday life.

MCI groups—Participants were diagnosed with MCI according to the Petersen (2004) criteria. Specifically, each participant or his/her study partner reported excessive decline in one or more cognitive domain and obtained an overall CDR score of 0.5, indicating questionable dementia. In addition, participants were required to perform at or below 1.5 standard deviations below the mean for age and education (i.e., 6.7th percentile), according to published norms, on one or more of the screening tests. Applying the criteria described in Figure 1 allowed the MCI sample to be divided into four groups: amnestic single domain (AS) (N=36); amnestic multiple

domain (AM) (N=45); nonamnestic single domain (NAS) (N=26), and nonamnestic multiple domain (NAM) (N=17).

Normal Control group—All participants in the normal control (NC) group were free of significant cognitive complaints. The absence of cognitive decline was confirmed by interview with the study partner; all normal control subjects obtained an overall CDR sore of 0. In addition, they all scored at or above 1.5 standard deviations below the mean for age and education on all four screening tests.

Procedures

Three clinical tests or experimental tasks were selected to evaluate each of the six EC domains proposed. Although our selection of tasks is based on previous literature, the very large number of executive tests and tasks available (Burgess et al., 1998; Miyake et al., 2000; Lezak et al., 2004) makes the ones selected somewhat arbitrary. It is also appreciated that our description of tasks as representative of particular domains is rationally based, rather than empirically based. However, this categorization was only preliminary, serving to guide test selection. An empirical categorization of tasks was achieved in the present study, using principal components analysis.

The tasks chosen to represent each domain are shown in Table 1. More detailed descriptions of the tasks, and the metrics derived from them, may be found in the on-line Appendix.

The Johns Hopkins University Institutional Review Board fully reviewed and approved the study protocol. All participants and their study partners gave written informed consent to participate.

Statistical Analysis

The baseline demographic and clinical characteristics of the five groups (four MCI and one normal control) were compared with one-way ANOVA, with planned comparisons between: 1) NC versus all MCI, 2) NC versus AS, 3) AS + AM versus NAS + NAM, and 4) AS + NAS versus AM + NAM. Given the large number of comparisons, α for both the omnibus ANOVAs and the planned comparisons was set to .01; this was viewed as a compromise between risking type-I and type-II statistical error. One-way ANOVAs were also performed on each of the 18 executive function measures

To derive composite scores summarizing executive test performance, an exploratory principal components analysis (PCA) of the 18 EC variables was performed. The number of components retained was determined by examination of the scree function and by factor analysis fitted by the maximum likelihood method and using the Akaike Information Criterion (AIC) (Akaike, 1974). Since the distributions of many of the EC variables were highly skewed, the 18 variables were first transformed to probit scores using the percentile method [in which the i^{th} sorted value is assigned the percentile z-score of (i/(n+1)) ×100, for each i=1, …, n] (Rosner & Glynn, 2007). These analyses were restricted to data from the MCI participants only, because large differences between the MCI and normal groups were found in descriptive analyses. The normal control group performed near test ceiling on several measures, producing clearly bimodal distributions for many of the tests. We restricted the PCA analysis to MCI subjects because our primary aim was to discover covariance among tests in MCI, rather than to identify scores that distinguish MCIs from controls. The derived components were subjected to orthogonal rotation using the varimax method and were standardized to have variance of 1 in order to maximize their interpretability. In light of our sample size and composition, we relied primarily on PCA rather than factor analysis to minimize reliance on model assumptions.

Component scores were computed for each participant using the principal components coefficients derived from analysis of the MCI subjects. Cronbach's alpha was used to estimate the reliabilities of the derived component scores. The mean component scores of the five groups were compared using analysis of covariance, with the same four planned comparisons described earlier. Given the total of 5 tests per component score (the omnibus comparison plus 4 planned comparisons), α was set to .01 (.05 divided by 5 = .01). In light of the descriptive nature of our study, this was seen as a reasonable compromise between risking type-I and type-II statistical errors.

RESULTS

Table 2 shows demographic and clinical characteristics for the five groups of participants. The groups were well matched for education, but they differed in age, with the NCs being slightly younger than the MCI groups (contrast = 3.55, t=3.11, df=187, p=.002). For reasons that are not clear, the sex distribution of the groups differed (χ^2 =17.43 df = 4, p=.002); men predominated among the amnestic MCIs, while women predominated among the cognitively normal subjects. As expected, the NC group also had a lower mean total score on the CDR sum-of-boxes score (contrast = 1.20, t=13.40, df=186, p<.001) and on the ADL-PI (contrast = 3.00, t=5.62, df=167, p<.001) than the MCI groups. They also had a higher mean MMSE score than the MCI groups (contrast = 1.11, t=7.08, df=187, p<.001). Also not surprisingly, the two single-domain groups (AS and NAS) were less impaired overall than the two multiple-domain groups (AM and NAM). This contrast was significant for the CDR sum-of-boxes (contrast = 0.37, t=2.69, df=186, p=.001), MMSE (contrast = 0.56, t=2.65, df=187, p=.009) and ADL-PI (contrast = 2.12, t=3.25, df=167, p=.002). Geriatric Depression Scale score was higher among MCIs than among normal elderly (contrast = 1.15, t=3.28, df=180, p=.001). None of the contrasts comparing amnestic to nonamnestic MCI patients (pooling over single- and multiple-domain subtypes) on demographic and clinical characteristics was significant.

Generally speaking, the groups were comparable in their medical histories (see Table 2). The only exception was in self-reported history of depressive disorder (χ^2= 22.30, df = 4, p<.001, Cramer's V = .349). Whereas 4.8% of the NC subjects and 2.9% of the AS patients described histories of depressive disorder, these figures rose to 11.8% in the NAM group, 15.4% in the NAS group, and 33.3% in the AM group.

Performance on the neuropsychological screening battery that was used to determine group assignment is shown in Figure 2. The groups differed in expected ways, with statistically significant differences among the 5 groups (p<.001) on all tasks. Effect sizes (η^2) ranged from .136 on word list generation to letter cues to .682 on delayed recall of the Logical Memory passages. These differences are to be expected, of course, as the groups were constituted based on subjects' performances on these tests.

PCA of the 18 executive function variables yielded six components with eigenvalues greater than 1.0, together accounting for 63% of the variance. However, inspection of the scree function and the factor analysis results suggested that models with three components fully accounted for the shared covariance among the measures. Thus, we opted for a three-component solution, which accounted for 44% of the variance.

Fifteen of the 18 tests loaded highly (≥.50) on one of the three rotated components. Tests from four of our six putative domains load highly on the first component (see Table 3), which may be a relatively general factor. We have labeled it "planning/problem-solving" to capture its contributions from tests requiring strategy formation and application as well as those requiring creativity and the production of novelty. Tests requiring multiple tracking, divided attention, and inhibitory control load significantly on component two, which is labeled here "working

memory." Finally, the Iowa Gambling Task and the Experimental Judgment Test load highly and specifically on the third component, which we are labeling "judgment."

Within the MCI group, Cronbach's alpha coefficients were 0.73, 0.72, and 0.34 for components one, two and three, respectively. For the entire sample, the reliabilities were 0.76, 0.76, and 0.22. Thus, the planning/problem-solving and working memory components had reasonably high internal consistency reliability. While the reliability of the judgment component was low, we choose to report it because of its clear interpretability. However, we recognize that ability to detect meaningful associations with the judgment factor are limited by the measure's low reliability.

The mean score on each of the executive function components for each group of participants is shown in Figure 3. A regression model, with age, sex, and MMSE scores as covariates, was computed on each of the three components. For component 1, there was a significant effect of group ($F=15.38$, $df=4,184$, $p<.0001$, adjusted $R^2=.451$). The results of the four planned contrasts appear in Table 4. The MCI patients, as a whole, performed less well than the normal control subjects. Even the AS group, the least impaired MCI subgroup overall, was severely impaired in planning/problem-solving compared to normal subjects. The difference between amnestic and nonamnestic MCI patients in this EC domain was not statistically significant, but the multiple-domain patients performed less well than single-domain patients.

For component 2, working memory, the five groups differed significantly ($F=10.61$, $df=4,184$, $p<.0001$), with the normal subjects again out-performing the MCI patients as a group. As in Component 1, the AS group differed from the normal group, and single-domain patients outperformed multiple-domain patients, but the amnestics did not outperform the nonamnestics.

For component 3, judgment, the five groups did not differ significantly ($F=1.42$, $df=4,184$, $p=.230$). Therefore, no planned comparisons were undertaken.

DISCUSSION

There are four major findings of this study. First, using a broad array of clinical tests and experimental tasks, we found moderate support for the existence of two highly reliable domains of executive functioning -- planning/problem-solving and working memory -- among elderly persons with MCI, and a less reliable third domain, judgment. Second, we found planning/problem-solving and working memory, but not judgment, to be selectively impaired in MCI compared to cognitively normal elderly. Third, even patients with "pure" amnestic MCI, the least impaired subgroup overall, displayed major impairments in these two executive domains. Finally, multiple-domain MCI patients (i.e., those with deficits in at least two domains [of episodic memory, language and spatial cognition]) have more significant planning/problem-solving and working memory deficits than single-domain patients.

Much of the previous research on the latent structure of executive cognition, including the elegant work of Miyake and colleagues on inhibitory control (Friedman & Miyake, 2004), used data from young normal subjects performing experimental paradigms. Few previous studies have used latent structure methods to determine the components of executive functions in the elderly. Fisk & Sharp (2004) studied normal subjects ranging from age 20–81 and found evidence for Miyake's three factors (updating, shifting, and inhibition), plus a fourth factor, access, which reflected efficiency in accessing long-term memory. Lamar et al. (2002) performed a PCA of data from a large collection of cognitive tests administered to 417 nondemented elderly in the Baltimore Longitudinal Study on Aging. Tests of executive functioning featured prominently in their battery. Two components of their four-component solution were interpreted as primarily executive. One, labeled "sustained attention and mental

tracking," had particularly high loadings for both parts A and B of the TMT. The other, "brief attention and mental manipulation," had high loadings on forward and backward digit span. Both these factors appear most highly related to the working memory component found in the present study. Rodríguez-Aranda & Sundet (2006) reported evidence for four executive factors (cognitive flexibility, speed of processing, word production, and loss of set) in their neurocognitive test data from 101 normal older adults. However, they included only four tests in their analysis, and multiple measures from each test, resulting in possibly spurious results.

Based on a principal components analysis of data from AD patients, Bondi et al. (2002) reported that the WCST and part B of the TMT loaded on a common executive factor. The WCST has characteristics in common with both the D-KEFS Sorting Test and the Brixton Test used in the present study, which loaded on planning/problem-solving and working memory, respectively. The TMT also loaded on working memory. Bondi and colleagues found that the Stroop Color-Word Test covaried with tests requiring rapid visual processing and visuomotor sequencing rather than executive cognition *per se.* It is not unreasonable to assume that the more advanced neuropathology of AD alters the relationship among cognitive mechanisms, thereby contributing to differences in the structure of executive control found by Bondi and colleagues and the present study.

Our principal components solution accounted for a modest 43% of the variance among measures. While this figure is somewhat lower than that obtained in some other studies (e.g., 86% in Lamar et al., 2002), we were intentionally conservative in our interpretation of the PCA results and our selection of a solution. Deciding the number of components to be retained in a PCA is a controversial issue, and several methods have been proposed. Perhaps the most commonly employed method, the Kaiser criterion, involves retaining all components with eigenvalues ≥ 1.0. We opted against this method as overly liberal (i.e., indicating a Astructure@ where the evidence is weak). There must be eigenvalues ≥ 1 in any correlation-based principal components analysis (given that the mean eigenvalue is always 1 in such analyses), even when all items are truly independent of each another. We also opted against a formal factor analysis to determine the number of components because of our modest sample size. In contrast, the scree criterion we employed estimates the number of systematic dimensions of shared covariation, and the AIC criterion does not rely on thresholds (as formal tests do) which may not be valid with small samples. Thus, we regarded the scree and AIC criteria as most suitable to determining the number of dimensions in this study. We find the convergence between them reassuring, and we believe our selection is appropriately reproducible while allowing for meaningful test structure to be detected.

While several previous investigations have reported impairments in executive cognition among MCI patients, most included very small samples and did not consider the heterogeneity of MCI (Winblad et al., 2004). Crowell et al. (2002) reported that 25 MCI patients -- defined using Petersen=s (2000) criteria but requiring that memory be below only −1 SD, and not further subtyped -- performed less well than 22 normal elderly on part B of the TMT, part B minus part A (the same metric used in the present study), and backward digit span. The MCI patients performed normally on tests of language, constructional praxis, and psychomotor speed. These authors concluded that executive dysfunction is frequently a second deficit in patients who present with "selective" memory impairment, and recommend that future studies sample a wider range of "both traditional and nontraditional executive measures." Kramer et al. (2006) identified 22 MCI patients with isolated memory impairments based on stringent CDR criteria (not a combination of clinical and psychometric criteria, as in the present study). They found that these patients performed more poorly than normal elderly on a modification of the TMT, the Stroop Test, and word-list generation (animal fluency). They concluded that exclusively amnestic MCI patients are probably extremely rare, and that concomitant executive dysfunction is common. They recommended comprehensive cognitive assessments for all MCI

patients, even when patients and families report only memory decline. Albert et al. (2007) found that scores on an executive functioning factor were lower at baseline in MCI patients who subsequently converted to dementia than in normal subjects or in MCI patients who declined but didn't convert. Rate of change in executive cognition over longitudinal assessments was greatest among those MCIs who subsequently converted.

A major finding of the present study is that the impairment of executive cognition in MCI is not global; only certain empirically-defined domains are affected. This is consistent with previous observations that some specific executive tests are performed normally and others are impaired in MCI. For example, Traykov et al. (2007) found their 20 MCI patients to be impaired on the Stroop Test and a modified WCST, but normal on the TMT, the Bells Test (a visual search task) and the WAIS Digit Symbol subtest. The authors conclude that response inhibition, switching, and cognitive flexibility are selectively impaired, while sustained and divided attention are intact. Zhang et al. (2007) reported that the TMT, Porteus Maze Test, and verbal fluency tests -- which they described as measures of planning -- were impaired among 32 MCI patients, whereas no-go accuracy, Stroop task performance, and negative priming -- described as measures of inhibition -- were not. In the present study, the Porteus Maze Test contributed to a planning/problem-solving factor, and the TMT and Stroop loaded together on a working memory factor, both of which were impaired among MCI patients. Differences in assignment of tasks to domains (done empirically in our study and conceptually in the Traykov and Zhang studies) may be a primary reason for the apparent discrepancies.

No previous study of EC in either normal or cognitively-impaired elderly has identified a specific factor related to judgment. Judgment, especially as it involves risk-taking and decision-making, appears to rely on neural circuitry (orbitofrontal cortex and its striatal, thalamic, and limbic connections) that is distinguishable from that supporting planning/problem-solving and working memory (primarily dorsolateral prefrontal cortex) (Rogers et al., 1998, 1999). Our finding that judgment is selectively spared in MCI may suggest that orbitofrontal cortex is largely unaffected in these patients, although the low reliability of our judgment component score dictates extreme caution in its interpretation.

Few previous studies of executive cognition in MCI have considered differences among MCI subtypes. In the present study, all four MCI subtypes, even the group with "pure" memory impairment, displayed deficits in planning/problem-solving and working memory, and multiple-domain patients were more severely impaired than single-domain patients. In contrast, neither the 10 amnestic nor the 28 "multiple cognitive deficits" MCI patients in the Cardiovascular Health Study were found to have impairments on a composite executive function measure (Lopez et al., 2006). The specifics of the sample characteristics and cognitive tests employed are likely responsible for the differences among studies.

The present study found differences in the lifetime prevalence of major depression among our groups, with the highest rate (33.3%) in the amnestic multiple-domain group. Other investigators have also found an association of depression with MCI (Jorm, 2000; Lopez et al., 2003), although differences in prevalence by MCI subtype has not, to our knowledge, been previously reported. There is a large and complex literature on neuropsychological deficits associated with late-life depression (Steffans et al., 2006), and several studies suggest that executive function deficits predominate (Lockwood et al., 2000; Butters et al., 2004). However, we do not believe the executive functioning deficits of our patients can be accounted for entirely by their histories of affective disorder, since our MCI group with the most severe executive impairment (NAM) had an only modestly elevated lifetime prevalence of depression (11.8%). Additional studies are clearly needed to resolve this issue.

Needless to say, the findings of the present study are not definitive and require replication. First, our MCI sample was recruited largely from other research studies and from memory disorder clinics rather than from population screening. Although this undoubtedly results in some selection bias, we suspect that our sample is quite comparable to most MCI samples described in the clinical literature. Second, the specific criteria we used for diagnosing MCI and classifying patients into subtypes may be questioned. Although our screening battery was composed of frequently-used, standardized neuropsychological tests, it was admittedly very brief, and "single-domain" deficits were identified by failure of single tests. In addition, we relied on the report of knowledgeable informants for the assessment of functional capacity rather than direct assessment of participants (as in Cahn-Weiner et al., 2000, 2002). However, we contend that our requirement of a cognitive test failure (score < 7^{th} percentile) in the setting of a normal MMSE score and the report of borderline functioning by a knowledgeable informant (i.e., CDR=0.5) conforms to the current standard for the diagnosis of MCI (Winblad et al., 2004). And although our MCI groups differed from each other and from the normal control group on both the CDR sum-of-boxes score and ADL-PI score, with a particularly high ADL-PI score in the NAM group, their functional deficits were not of sufficient magnitude to interfere significantly with daily life or to merit the diagnosis of dementia.

Among the other limitations of this study was that we did not allow MCI to be defined by a selective impairment in executive control. This was done to avoid conflating the independent and the dependent variables. However, it does complicate the meaning of "single-domain" (memory, language, or spatial cognition) MCI, as defined in this study. Another limitation of the study is its modest sample size for multivariate statistical approaches. Given the large number of executive function measures we employed (18), basing a principal components analysis on data from 124 subjects may result in a somewhat unstable structure. Because of this, we chose a relatively conservative approach to analysis.

A major implication of this study is that whether patients have impairment in memory or some other cognitive domain (language or spatial cognition) is less important in predicting their executive functioning (and, hence, their vulnerability to everyday functional impairment) than whether they are impaired in only one or more than one domain. It is our prediction that patients with multiple-domain MCI are at higher risk for the development of dementia, or to develop it sooner, than patients with pure amnestic MCI. This is supported by the findings of several recent studies (Alexopoulos et al., 2006; Rasquin et al., 2005; Tabert et al., 2006), but not all (Fischer et al., 2007; Yaffe et al., 2006). Continued follow-up of the participants in this study will allow us to test this prediction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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	Amnestic	Nonamnestic
Single Domain	*Only* WMS-R Logical Memory (delayed recall of Story A)	Boston Naming Test *or* Word List Generation (sum of letter and category trials) *or* Clock Drawing Test
Multiple Domains	WMS-R Logical Memory (delayed recall of Story A) *and* any one or more tests	*At least two of:* Boston Naming Test Word List Generation (sum of letter and category trials) Clock Drawing Test

Figure 1.
Operational criteria for four groups of participants with mild cognitive impairment. Subjects in each group performed at or below 1.5 SD below age-and education norms on the test(s) indicated.

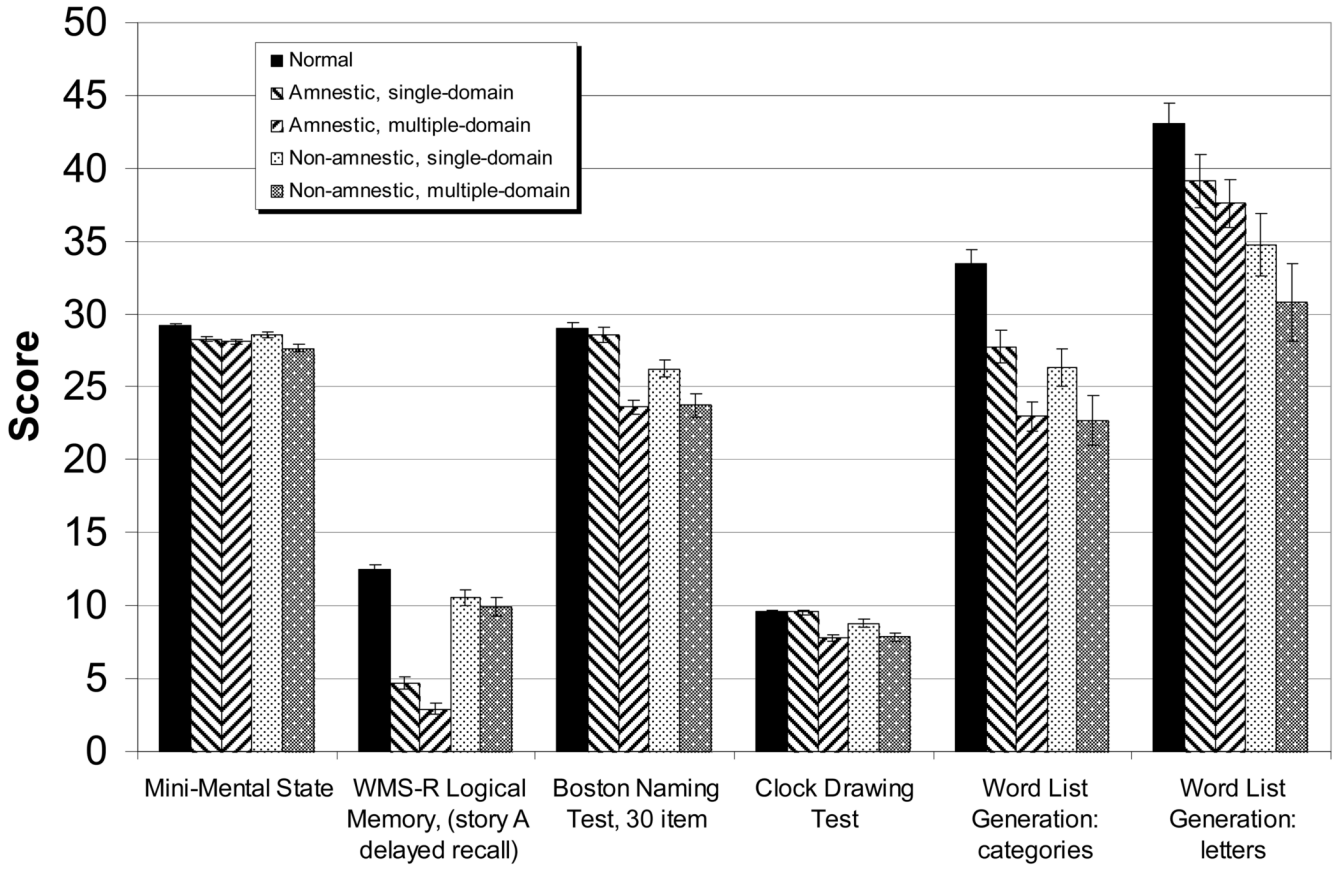

Figure 2.
Performance of five subject groups on neuropsychological screening battery. Age- and education-adjusted means ± standard errors. Note that although the data are drawn on one set of axes, the possible range of scores for the tests differ.

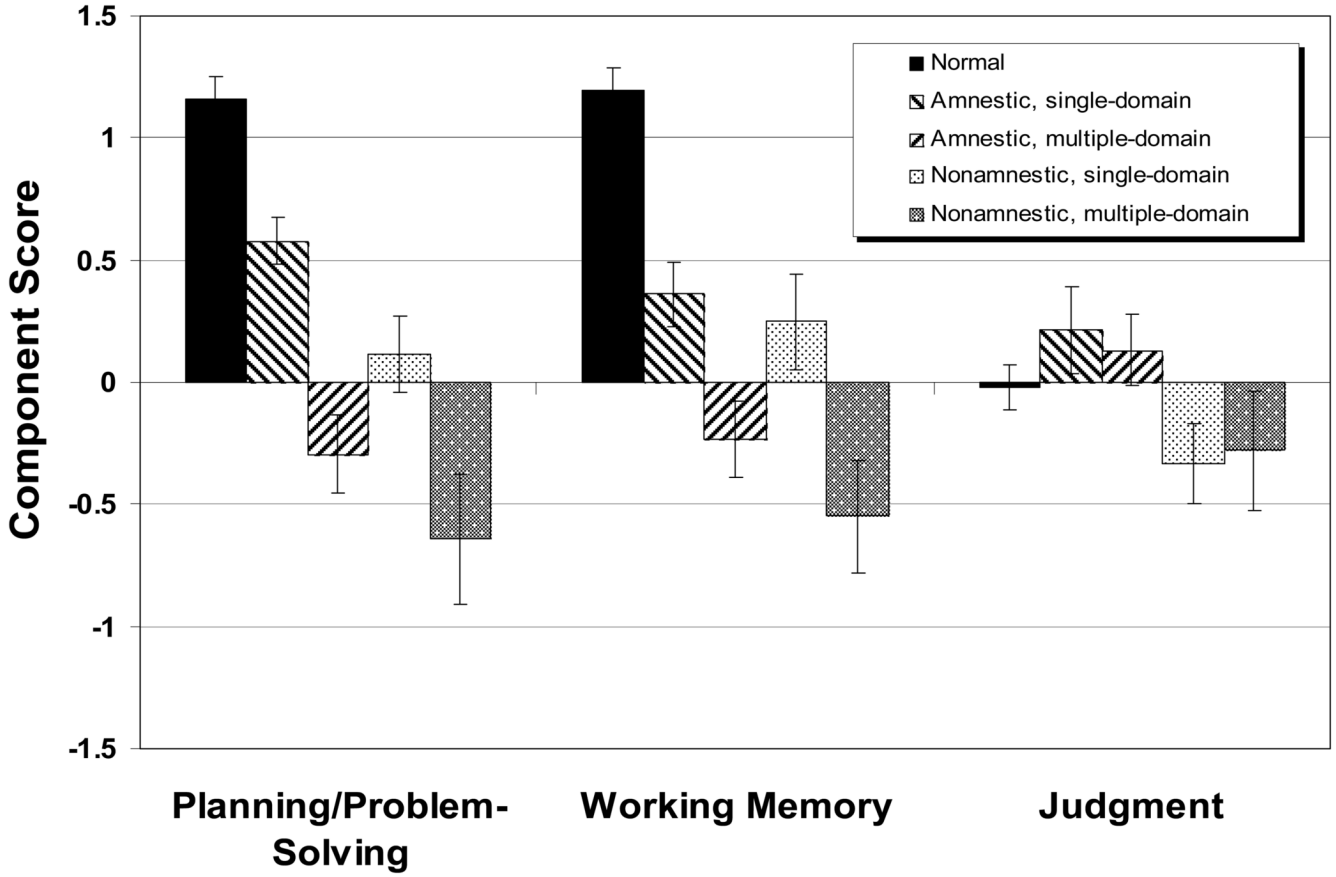

Figure 3.

Scores of normal control subjects and four groups of MCI participants on three executive functioning summary scores derived from principal components analysis. The component scores were derived from data of MCI subjects only. Means ± standard errors.

Table 1

Performance of five subject groups on 18 executive function tests (means and SDs), with effect sizes and *p*-values based on one-way ANOVA.

Proposed Domain	Test	Normal Control (CDR=0)	Amnestic MCI (CDR=.5)		Nonamnestic MCI (CDR=.5)		η^2	*p*
			Single Domain	Multiple Domain	Single Domain	Multiple Domain		
Spontaneous Flexibility and Generativity	Alternate Uses Test (raw score)	15.12 (5.65)	11.86 (5.34)	7.49 (5.83)	11.27 (4.90)	7.82 (5.60)	.244	<.001
	Random Number Generation (written trial RNG + oral trial RNG)	0.60 (0.09)	0.65 (0.24)	0.68 (0.21)	0.73 (0.31)	0.71 (0.25)	.052	.041
	Tinker Toy Test (raw score)	9.19 (1.80)	8.69 (1.98)	7.31 (2.47)	8.65 (1.79)	7.25 (1.88)	.139	<.001
Inhibition of Prepotent Responses	D-KEFS Stroop Test (inhibition trial scaled score)	10.70 (2.23)	10.26 (2.88)	9.73 (3.94	9.38 (3.44)	10.18 (3.01)	.024	.349
	Hayling Test (total scaled score)	5.22 (1.45)	4.67 (1.55)	3.89 (1.64)	4.50 (1.68)	3.71 (1.69)	.120	<.001
	Completions & Corrections Test total correct)	11.06 (1.26)	9.75 (1.95)	9.18 (2.34)	9.65 (1.81)	9.18 (2.04)	.164	<.001
Planning and Sequencing	Porteus Maze Test (test age)	15.60 (1.74)	15.07 (1.62)	12.92 (3.50)	13.83 (2.32)	11.00 (3.86)	.254	<.001
	D-KEFS Tower Test (total achievement scaled score)	11.81 (2.59)	10.17 (2.43)	9.00 (3.04)	9.77 (2.37)	8.53 (3.26)	.175	<.001
	Tic-Tac-Toe (total score)	−4.57 (2.44)	−4.69 (1.85)	−4.76 (2.59)	−5.08 (1.65)	−5.47 (1.70)	.014	.603
Concept/Rule Learning and Set Shifting	D-KEFS Sorting Test (confirmed sorts scaled score)	13.16 (1.85)	11.94 (2.51)	10.67 (2.73)	10.77 (2.41)	10.12 (2.64)	.201	<.001
	Brixton Test (scaled score)	5.26 (2.12)	4.64 (2.22)	3.80 (2.06)	4.73 (2.01)	2.76 (1.79)	.124	<.001
	Verbal Concept Attainment Test (raw score)	19.50 (2.47)	17.33 (3.14)	14.78 (4.03)	16.96 (3.28)	15.41 (3.20)	.263	<.001
Decision-Making and Judgment	Stanford Binet Absurdities Test (raw score)	29.47 (2.89)	29.31 (2.05)	25.93 (4.41)	27.08 (2.94)	23.88 (3.87)	.258	<.001
	Iowa Gambling Test (advantageous selections on block 1 minus block 5)	3.95 (6.45)	4.36 (6.85)	2.60 (5.52)	1.77 (6.53)	2.47 (6.38)	.022	.403
	Experimental Judgment Test (mean percent deviation)	7.75 (4.79)	10.25 (6.75)	10.61 (5.58)	6.68 (3.04)	7.50 (4.43)	.081	.004
Working Memory and Resource-Sharing	Trail Making Test (time on Part B minus time on Part A)	39.15 (20.57)	67.36 (14.31)	78.64 (63.71)	74.72 (43.21)	94.53 (50.02)	.173	<.001
	Brief Test of Attention (total correct)	15.31 (3.28)	14.31 (3.29)	12.53 (4.23)	14.12 (3.58)	10.71 (3.46)	.143	<.001
	TEA Telephone Search While Counting (dual task decrement score)	1.35 (1.81)	1.48 (1.83)	4.16 (5.36)	1.58 (2.34)	4.442 (5.48)	.130	<.001

Table 2

Demographic and clinical characteristics of study participants. Means (± SE), except as noted. For continuously distributed variables, effect sizes are eta-squared and p-values are based on one-way ANOVA. For frequency counts (sex) and percentages (prevalence of health conditions), effect sizes are Cramer's V and p-values are based on Pearson's chi-squared tests.

		Amnestic MCI (CDR=.5)		Nonamnestic MCI (CDR=.5)			
	Normal Control (CDR=0)	Single Domain	Multiple Domain	Single Domain	Multiple Domain	η^2 or V	*p*
N	68	36	45	26	17		
Age, years	72.41 (SD=7.25)	75.08 (SD=5.69)	78.33 (SD=7.66)	74.81 (SD=8.62)	75.59 (SD=7.69)	.087	.002
Education, highest grade completed	15.93 (SD=2.49)	15.92 (SD=2.17)	15.93 (SD=2.50)	15.42 (SD=2.73)	15.18 (SD=2.16)	.011	.714
Sex, male:female	27:41	26:10	28:17	14:12	4:13	.301	.002
Clinical Dementia Rating, sum of boxes	0.03 (0.01)	0.89 (0.09)	1.46 (0.12)	1.21 (0.15)	1.41 (0.18)	.528	<.001
Mini-Mental State Exam, score	29.26 (0.11)	28.33 (0.19)	28.11 (0.18)	28.54 (0.27)	27.65 (.27)	.208	<.001
Activities of Daily Living - Prevention Instrument, score	0.73 (0.18)	3.17 (0.60)	3.80 (0.63)	2.17 (0.58)	6.71 (1.80)	.195	<.001
Geriatric Depression Scale, score	1.24 (0.26)	2.12 (0.39)	2.76 (0.39)	1.96 (0.35)	2.74 (0.52)	.075	.007
Prevalence of Specific Health Conditions (percent of subjects):							
Hypertension	44.8	47.1	54.6	34.8	47.1	.119	.647
Hypercholesterolemia	38.8	40.0	33.3	55.6	46.7	.137	.587
Peripheral Vascular Disease	5.8	3.6	2.6	5.9	0	.098	.838
TIA	0	0	2.8	5.3	6.7	.174	.321
Seizure	0	0	2.7	0	0	.143	.541
Minor Head Injury	3.5	3.1	11.9	8.7	0	.174	.270
Cancer	8.5	6.3	7.1	0	0	.132	.572
Diabetes	13.1	6.3	16.3	16.0	5.9	.193	.608
Kidney Disease	1.6	0	2.4	0	0	.094	.817
Gastrointestinal Disease	18.0	11.1	13.5	33.3	26.7	.183	.296
Depression	4.8	2.9	33.3	15.4	11.8	.349	<.001
Anxiety	1.6	2.9	10.0	0	0	.205	.111

Table 3

Results of principal components analysis of executive function tasks (correlations between z-transformed test scores and components). Varimax rotated components. For clarity of presentation, only correlations ≥ 0.50 are shown.

Proposed Domain	Test	Component		
		1	2	3
		18% of variance Planning/Problem-Solving	17% of variance Working Memory	8% of variance Judgment
Spontaneous Flexibility and Generativity	Alternate Uses Test (raw score)	0.504		
	Random Number Generation (written trial RNG + oral trial RNG)	−0.594		
	Tinker Toy Test (raw score)	0.766		
Inhibition of Prepotent Responses	D-KEFS Stroop Test (inhibition trial scaled score)		0.655	
	Hayling Test (total scaled score)			
	Completions & Corrections Test (total correct)		0.639	
Planning and Sequencing	Porteus Maze Test (test age)	0.617		
	D-KEFS Tower Test (total achievement scaled score)	0.661		
	Tic-Tac-Toe (total score)			
Concept/Rule Learning and Set Shifting	D-KEFS Sorting Test (confirmed sorts scaled score)	0.507		
	Brixton Test (scaled score)		0.706	
	Verbal Concept Attainment Test (raw score)			
Decision-Making and Judgment	Stanford Binet Absurdities Test (raw score)	0.751		
	Iowa Gambling Test (advantageous selections on block 1 minus block 5)			0.655
	Experimental Judgment Test (mean percent deviation)			0.726
Working Memory and Resource-Sharing	Trail Making Test (time on Part B minus time on Part A)		−0.693	
	Brief Test of Attention (total correct)		0.662	
	TEA Telephone Search While Counting (dual task decrement score)		−0.548	

Table 4

Results of ANCOVA on three executive function components and significance level and effect sizes (ES), in SD units, for planned contrasts.

	Component 1: Planning/Problem-Solving	Component 2: Working Memory	Component 3: Judgment
Overall model, with age, sex, and MMSE as covariates	F(4,184)=15.38 p<.001 Adjusted R^2=.451	F(4,184)=10.61 p<.001 Adjusted R^2=.493	F(4,184)=1.42 p=.230 Adjusted R^2=.044
Contrasts:			
Normal v. all MCI	ES=.955, p<.001	ES=.816, p<.001	N/A
Normal v. Amnestic Single MCI	ES=.464, p=.009	ES=.486, p=.005	N/A
Amnestic v. Nonamnestic MCI	ES=.278, p=.079	ES=.276, p=.073	N/A
Single v. Multiple-Domain	ES=.550, p=.001	ES=.480, p=.002	N/A