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# Language performance in Alzheimer's disease and mild cognitive impairment: A comparative review

**Vanessa Taler and Natalie A. Phillips**

Department of Psychology/Centre for Research in Human Development, Concordia University, Montréal, Québec, Canada, and Bloomfield Centre for Research on Aging, Montréal, Québec, Canada

Mild cognitive impairment (MCI) manifests as memory impairment in the absence of dementia and progresses to Alzheimer's disease (AD) at a rate of around 15% per annum, versus 1–2% in the general population. It thus constitutes a primary target for investigation of early markers of AD. Language deficits occur early in AD, and performance on verbal tasks is an important diagnostic criterion for both AD and MCI. We review language performance in MCI, compare these findings to those seen in AD, and identify the primary issues in understanding language performance in MCI and selecting tasks with diagnostic and prognostic value.



## INTRODUCTION

Increased life expectancy worldwide has resulted in an increased number of individuals at risk of or suffering from Alzheimer's disease (AD), resulting in significant financial and emotional burden for sufferers and their families. Intense research interest has thus focused on identifying elderly individuals who will develop AD, both to commence pharmacological treatment as early as possible in the disease course and to allow psychological intervention and family and financial planning.

A considerable body of evidence suggests that a prodromal, or preclinical, phase of AD may occur years before diagnosis. At this stage, alterations can be detected at both the neuropathological and the cognitive level. Neuropathological changes are seen in the entorhinal cortex very early in the disease course. Marked neuronal loss (32%) in this region can be observed in very mild or questionable AD, as can neurofibrillary tangles and senile plaques in sufficient quantities for a diagnosis of AD (Gómez-Isla & Hyman, 2003). Increased tau phosphorylation, resulting in the formation of neurofibrillary tangles, is one of the earliest markers of AD and occurs prior to dementia onset (for a review, see Iqbal et al., 2005). Similarly, volumetric MRI studies have suggested that hippocampal atrophy is seen before dementia onset (Fox, Warrington, Stevens, & Rossor, 1996; Jack et al., 1999; Jack et al., 1997; Visser et al., 1999), and that this atrophy progresses subsequent to clinically identifiable dementia (Fox et al., 1996).

Individuals with preclinical AD also manifest alterations in various cognitive domains. Deficits are seen in episodic memory (Bäckman, Small, & Fratiglioni, 2001; Chen et al., 2001; Elias et al., 2000; Small, Herlitz, Fratiglioni, Almkvist, & Bäckman, 1997; Tierney et al., 1996), executive function (Albert, Moss, Tanzi, & Jones, 2001; Chen et al., 2001; Daly et al., 2000), perceptual speed (Albert et al., 2001, Fabrigoule et al., 1998; Fox, Warrington, Seiffer, Agnew, & Rossor, 1998), verbal ability (Convit et al., 2000; Grober & Kawas, 1997; Jacobs et al., 1995; Linn et al., 1995; Small et al., 1997), visuospatial skill (Albert et al., 2001; Chen et al., 2001; Fowler, Saling, Conway, Semple, & Louis, 2002; Howieson et al., 1997), and attention (Nielsen, Lolk, Andersen, Andersen, & Kragh-Sorenson, 1999; Rubin et al., 1998; Tierney et al., 1996). As is the focus of this review, deficits are also observed in the domain of language.

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Address correspondence to Natalie A. Phillips, Department of Psychology, Concordia University, 7141 Sherbrooke Street West, Montréal, Québec, Canada H4B 1R6 (E-mail: natalie.phillips@concordia.ca).


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A number of terms have been used to describe individuals who exhibit cognitive dysfunction in the absence of dementia. Kral (1962) proposed the term *benign senescent forgetfulness*. Other terms that have been proposed include *age-associated memory impairment* (AAMI; Crook et al., 1986) and *age-associated cognitive decline* (AACD; Levy, 1994). However, these terms are generally intended to denote individuals at the extremes of normal aging, rather than those in a preclinical stage of dementia. Some studies have found increased rates of conversion to dementia in these groups (Lane & Snowdon, 1989; Richards, Touchon, Ledesert, & Ritchie, 1999), while others have found similar rates in these individuals and in healthy elderly subjects (Hanninen et al., 1995). The term *cognitive impairment, no dementia* (CIND; Graham et al., 1997) connotes an underlying pathological state, although the underlying etiologies may be variable, resulting in a lack of specificity (Rivas-Vasquez, Mendez, Rey, & Carrazana, 2004).

A recently introduced term designed to capture the point on the spectrum of cognitive function between healthy aging and dementia is *mild cognitive impairment* (MCI). This term was first used by Flicker, Ferris, and Reisberg (1991) to describe individuals with a Global Deterioration Scale (GDS, Reisberg, Ferris, de Leon, & Crook, 1982) rating of 3. However, it was Petersen et al. (1999) who first set out formal criteria for a diagnosis of MCI. The criteria are as follows: (a) subjective complaint of memory loss, (b) objective impairment of ability, (c) preserved general cognitive function, (d) intact activities of daily living, (e) individual does not meet criteria for dementia. Individuals who meet these criteria (henceforth referred to as the "Petersen criteria") are at an increased risk for developing AD relative to the general population. In an extensive literature review utilizing these criteria, Petersen et al. (2001b) found an average annual conversion rate of 14%, compared to 1–2% in the general population. Other groups have found higher conversion rates: Geslani, Tierney, Herrmann, and Szalai (2005) report a conversion rate of 41% after one year and 64% after two years.

It should be noted that, although there is some overlap in the characteristics, constructs such as AAMI are not necessarily directly analogous with MCI. For example, Bartres-Faz et al. (2001) conducted a study examining performance on a range of cognitive functions, including language, by individuals meeting the diagnostic criteria for AAMI ($n=93$ of 104 individuals presenting with memory complaints) and MCI ($n=63$ of 104). They found that MCI individuals performed significantly worse than AAMI individuals on a number of tasks, including memory, phonetic fluency, and naming, and conclude that AAMI criteria, while selecting a population that is genetically distinct from healthy elderly adults, nonetheless do not delineate a population that is as impaired as those meeting the criteria for MCI. They suggest that AAMI may represent a point on the continuum of decline that is earlier than that represented by MCI. In a similar vein, Ritchie, Artero, and Touchon (2001) compared the constructs of AACD and MCI in a population-based study. MCI was estimated to have a prevalence of 3.2% and AACD 19.3%. It was found that MCI was a poor predictor of dementia over a 3-year period, manifesting temporal instability. AACD showed better stability and high predictive validity, despite the fact that it has been conceptualized as a benign impairment. Given these findings, comparisons between results obtained with MCI individuals and those diagnosed with similar syndromes should be undertaken with caution.

While it is generally accepted that MCI represents a risk factor for AD, there still exists controversy as to whether MCI individuals will always convert to AD—that is, whether MCI always represents prodromal AD. For example, Chertkow, Verret, Bergman, Wolfson, & McKelvey (2001, cited in Chertkow, 2002) found that 25% of their MCI subjects had not converted to AD even 10 years after the onset of memory problems. Patients at the Mayo Alzheimer's Disease Research Center converted at approximately 12% per year, and after 6 years, 80% had converted (Petersen & Morris, 2003). Morris et al. (2001), on the other hand, found conversion rates of 100% in the long term (9.5 years) in their group of cognitively impaired individuals, and claim that MCI always represents prodromal AD.

One possible explanation for these diverse findings may be the significant variability in criteria used to establish a diagnosis of MCI (Chertkow, 2002). Morris et al. (2001), who claim that MCI individuals will always convert to AD, use as a diagnostic criterion a rating of 0.5 on the Clinical Dementia Rating Scale (CDR, Hughes, Berg, Danziger, Coben, & Martin, 1982), which corresponds to "questionable AD." A second scale that has been used is the Global Deterioration Scale (GDS; Reisberg et al., 1982); a score of 3 has been suggested to represent MCI, where 1 is normal, 2 is normal with subjective complaint, and 3 through 7 denote increasing impairment (Kluger, Ferris, Golomb, Mittleman, & Reisberg, 1999). Other researchers assess MCI in terms of variance from age- and education-matched norms; for example, a cutoff score of 1.5 standard deviations below the

mean in memory tests may be applied. Others rely on the judgment of the clinician (for a discussion of the implementation of diagnostic criteria, see Petersen, 2004).

Recently, the Stockholm consensus group (Winblad et al., 2004) proposed the following revised criteria for MCI:

1. The person is neither normal nor demented.
2. There is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits.
3. Activities of daily living are preserved, and complex instrumental functions are either intact or minimally impaired.

Artero, Petersen, Touchon, and Ritchie (2006) evaluated these revised criteria and concluded that they predicted transition to dementia significantly better than did the original Peterson criteria, particularly when amnestic and nonamnestic MCI subgroups were combined (area under the curve, AUC=0.80; sensitivity: 95%; specificity: 66%). Thus, the inclusion of impairment in domains in addition to memory provides a better means to identify those individuals who will convert to dementia. However, the criteria cannot differentiate between the various dementias, such as AD, vascular dementia, and frontotemporal dementia.

A second consideration with respect to the diagnosis of MCI is that considerable heterogeneity is observed in this group. Petersen et al. (2001a) have pointed out that MCI may be divided into three subgroups, depending on the cognitive functions affected. In *amnestic MCI*, only memory is affected. In *multiple-domain MCI*, impairment is seen in multiple cognitive domains, but at a level insufficient to constitute dementia. Finally, a third subtype, termed *single nonmemory domain MCI*, presents as a specific impairment in a nonmemory domain. It should be noted that the "Petersen criteria" discussed above refer to the amnestic variant of MCI.

Heterogeneity is also seen in the etiology of the disorder (Petersen, 2003). It has been suggested that amnestic MCI is likely to evolve to AD, multiple-domain MCI to AD or vascular dementia, and single nonmemory domain MCI to another type of dementia, such as frontotemporal dementia, Lewy body dementia, primary progressive aphasia, or vascular dementia (Petersen, 2003). However, recent research (Fischer et al., 2007) suggests that MCI subtype is not a good predictor of evolution to one type of dementia or another.

The goal of identifying those MCI individuals who are most likely to convert to AD will probably best be met through implementation of a battery of tests designed to tap into a number of diverse indicators of AD, including a combination of genetic and cognitive markers, as well as findings from volumetric and functional neuroimaging, all of which have proven useful in early detection of AD (for a review, see Chong & Sahadevan, 2005). It is thus of great importance to specify the performance of MCI individuals across a variety of cognitive domains. Of particular interest are longitudinal studies of cognitive decline, where individual performance is correlated with eventual conversion.

It is well documented that AD patients often manifest deficits in language processing very early in the disease course. Deficits are seen in verbal fluency (for a review, see Henry, Crawford, & Phillips, 2004), naming (e.g., Bayles & Kaszniak, 1987, Bayles, Tomoeda, & Trosset, 1992, Bowles, Obler, & Albert, 1987; Fisher, Rourke, & Bieliauskas, 1999)—particularly of biological items (Fung et al., 2001; Whatmough et al., 2003)—semantic knowledge (Chertkow & Bub, 1990; Hodges, Salmon, & Butters, 1992a; Martin & Fedio, 1983), and discourse-level processing (for a review, see Caramelli, Mansur, & Nitrini, 1998). Syntactic and phonological abilities, on the other hand, are typically relatively preserved (Bayles, 1982; Bayles & Kaszniak, 1987; Irigaray, 1973; Kempler, Curtiss, & Jackson, 1987; Kertesz, 1994; Light & Burke, 1993; Patel & Satz, 1994; Schwartz, Marin, & Saffran, 1979; Whitaker, 1976).

Given that language impairment is frequent in AD and occurs early in the disease course, we believe that a review of the performance of MCI individuals in language tasks is timely and will contribute to the goal of identifying early markers of cognitive impairment in AD. While such tests cannot replace memory testing in these populations, they provide valuable additional information when making a clinical judgment of the status of an individual. There exists evidence (e.g., Alexopoulos, Grimmer, Perneczky, Domes, & Kurz, 2006; Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001; Sacuiu, Sjögren, Johansson, Gustafson, & Skoog, 2005) that MCI individuals with impairments in multiple domains, including language, are more likely to develop AD than are those with a pure memory impairment. Thus, understanding the nature of language impairment and possibly identifying sensitive measures of linguistic impairment constitute a vital tool in early detection of AD.

The current paper gives an overview of the findings in language performance in MCI published to

date. We review MCI individuals' performance on standardized neuropsychological tests, discuss findings in the experimental psycholinguistic literature, and compare these findings to those reported in the AD literature. We then offer suggestions for the features that should be present in a test of language performance that aims to identify prodromal AD.

Relevant references were identified through a Medline search using the following search terms: mild cognitive impairment; frontotemporal dementia, early diagnosis; alzheimer, early diagnosis; minimal alzheimer; very mild alzheimer, neuropsychology; questionable dementia; cognitive impairment no dementia, neuropsychology; age associated memory impairment, neuropsychology; age associated cognitive decline, neuropsychology; benign senescent forgetfulness. This was supplemented by a hand search of the reference lists of the articles identified in the Medline search.



## STANDARDIZED LANGUAGE TESTS

There are two aspects to consider when evaluating the utility of a standardized neuropsychological test in the assessment of MCI individuals. First, does the test distinguish accurately between normal aging, MCI, and AD? That is, does the test provide *diagnostic utility* with respect to MCI? Second, does the test distinguish between those individuals with MCI who will go on to develop AD and those who will not? In other words, does the test provide *prognostic utility*? A number of standardized language tests have been evaluated with respect to these criteria; the following section outlines the findings published in the literature to date.

### Semantic processing

Most epidemiological studies of MCI include some measure of semantic processing, typically verbal fluency or picture-naming measures. Below we describe the primary findings with respect to MCI performance on these tasks.

#### *Verbal fluency*

Verbal fluency tests are amongst the most widely used measures of cognitive functioning in dementia. These tasks assess an individual's ability to retrieve and produce words that conform to a given criterion within a specified time period. Letter (phonemic) fluency involves the generation of as many words as possible beginning with a given letter (in English, usually F, A, or S). Category fluency involves the generation of as many words as possible that fall into a given category (e.g., animals). Both category and letter fluency impose significant demands on executive processes; subjects must organize verbal retrieval and recall, initiate responses, and monitor prior responses, as well as inhibit inappropriate responses (Henry et al., 2004). However, the two tasks differ in terms of the search strategies required. Letter fluency relies on search strategies based on lexical representations, whereas category fluency requires a search for semantic extensions of a superordinate term, meaning that semantic associations within the lexicon must be intact in order for the task to be carried out successfully (Rohrer, Salmon, Wixted, & Paulsen, 1999).

Impairments in verbal fluency, and especially in category fluency, are well documented in AD. A recent meta-analysis of 153 studies with 15,990 AD participants examining semantic and letter fluency (Henry et al., 2004) found that, while AD individuals' performance on tests of both semantic and letter fluency was impaired relative to healthy elderly controls ($p < .001$ for both measures), the effect was much larger for semantic fluency ($r = .73$) than for letter fluency ($r = .55$). There was no significant correlation between dementia severity and the severity of the deficit in verbal fluency. Category, but not letter, fluency was correlated with verbal IQ ($p < .021$). Furthermore, performance on the Boston Naming Test (BNT), while strongly correlated with both fluency tasks, was more strongly correlated with category than with letter fluency ($r = .50$ and $r = .68$). The authors suggest that the specific deficit in category fluency is due to the degradation of the semantic knowledge required for category fluency tests, while letter fluency taps semantic memory to a lesser extent. A larger performance deficit was seen in the BNT than in the letter fluency test, whereas the deficit seen in the category fluency test was greater than that seen in the BNT. Thus, since retrieval demands are equivalent for the two fluency tasks, and the BNT also imposes demands on semantic knowledge, problems in effortful retrieval likely do not underlie the deficit in category fluency.

The diagnostic utility of category fluency for AD, even very early in the disease course, is also well established (e.g., Caccapolo-Van Vliet et al., 2003; Cerhan et al., 2002; Duff Canning, Leach, Stuss, Ngo, & Black, 2004; Lam, Ho, Lui, & Tam, 2006; Salmon et al., 2002); it yields a sensitivity of 100% and a specificity of 92.5% (Monsch et al., 1992), and performance on this task has been shown to decline with advancing AD (Perry,

Watson, & Hodges, 2000; Small & Bäckman, 1998). Given the diagnostic utility of fluency tasks, as well as the fact that deficits are seen very early in the disease course, a number of studies have undertaken to examine verbal fluency performance as a potential prognostic marker for AD and/or a diagnostic marker for MCI. These studies have taken the form of either longitudinal studies of individuals who are initially nondemented, or studies of individuals who have been diagnosed with cognitive impairment. Summary statistics for these studies are provided in Table 1, and the studies themselves are summarized in Appendix A.

Several prospective studies have found impairments in category fluency in healthy adults up to 9 years prior to the onset of dementia (Amieva et al., 2005; Auriacombe et al., 2006; Chen et al., 2001; Fabrigoule et al., 1998; Hodges, Erzinçlioğlu, & Patterson, 2006; Jorm, Masaki, Petrovitch, Webster Ross, & White, 2005; Masur, Sliwinski, Lipton, Blau, & Crystal, 1994; Nielsen et al., 1999; Small et al., 1997; Vogel, Gade, Stokholm, & Waldemar, 2005). Chen et al. (2001) found that verbal fluency scores declined more steeply in pre-AD individuals than in controls (those who remained nondemented for 10 years), particularly those with higher education levels. Letter fluency has also been found to be a reliable predictor of dementia onset in one study (Small et al., 1997), although other studies found that this was not the case (Chen et al., 2001; Goldman et al., 2001). Likewise, a number of studies examining category fluency in nondemented individuals with cognitive impairment have demonstrated lower performance on this task in those individuals who went on to develop dementia than in those who did not (Blackwell et al., 2004; Guarch, Marcos, Salamero, & Blesa, 2004; Hanninen et al., 1995; Ritchie et al., 2001). Finally, MCI individuals who have a memory impairment in addition to an impairment in one of four other cognitive domains (including naming and letter fluency) have been found in one study to have an 8 times higher risk of progressing to AD after a 2-year interval than those who manifested a memory deficit alone (Bozoki et al., 2001). Another study found that MCI individuals with impairments in multiple domains have over twice the risk of conversion after 3.5 years (Alexopoulos et al., 2006).

With respect to diagnostic utility, verbal fluency has been shown to discriminate accurately between MCI subjects and unimpaired control subjects (Bennett et al., 2002; Bschor, Kuhl, & Reischies, 2001; Dwolatzky et al., 2003; Geslani et al., 2005; Grundman et al., 2004; Petersen et al., 1999; Ribeiro, de Mendonça, & Guerreiro, 2006; Tabert et al., 2006). One issue that arises with respect to the various studies examining category fluency is whether the use of different semantic categories elicits comparable results. Cunje, Molloy, Standish, and Lewis (2007) tested verbal fluency performance in MCI individuals using four categories: animals, cities and towns, first names, and fruits and vegetables. No difference between categories was seen in 60-second scores, indicating that the different versions of the category fluency task allow for serial testing. The use of different versions can eliminate a learning bias, whereby participants show a false improvement in performance due to recollection of categories and practice between sessions. The 60-second category fluency scores showed good sensitivity and specificity for differences between healthy elderly and MCI individuals (area under the ROC curve = 0.87 for animals, 0.78 for cities and towns, 0.79 for fruits and vegetables, 0.83 for names, $p < .01$ in all cases). Murphy, Rich, and Troyer (2006) found that MCI-amnestic (MCI-A) and AD individuals produced fewer

**TABLE 1**
Summary statistics for the studies presented in Appendices A and B

| | *Test* | | |
|---|---|---|---|
| | *Category fluency* | *Letter fluency* | *Naming* |
| Studies reporting difference between NE and MCI/QD/preclinical dementia/miminal AD | 29 | 8 | 22 |
| Studies reporting no difference between NE and MCI/QD/preclinical dementia/minimal AD | 3 | 8 | 13 |
| Studies reporting difference between MCI/QD preclinical dementia/minimal AD and mild AD | 17 | 4 | 12 |
| Studies reporting no difference between MCI/QD and AD | 0 | 5 | 5 |
| Studies reporting predictive value for AD | 21 | 9 | 12 |
| Studies reporting no predictive value for AD | 6 | 7 | 12 |

*Note.* AD = Alzheimer's disease. NE = normal elderly. MCI = mild cognitive impairment. QD = questionable dementia.

items in semantic fluency than did healthy older adults, while letter fluency was relatively preserved in the MCI-A group. Control and MCI-A participants generated more items in category than letter fluency, while ADs exhibited the opposite pattern. In terms of clustering and switching, control and MCI-A participants performed similarly on letter fluency, while on semantic fluency, MCI-A participants' performance was intermediate between that of ADs and controls. Additionally, data from our lab indicate that deficits in switching in verbal fluency are equivalent in AD individuals and in MCIs who go on to develop AD, while MCIs who do not convert to AD exhibit performance similar to that of healthy elderly adults (Phillips, personal communication). Storandt, Grant, Miller, and Morris (2002) report that letter fluency scores decline faster with increasing impairment (defined by the CDR score).

Other studies have found that category fluency tasks are not sensitive to decline in MCI. Lambon Ralph, Patterson, Graham, Dawson, and Hodges (2003) found that MCI subjects showed only amnesia, and that impairments in language, including category fluency, did not manifest until AD set in. Although the mean number of items generated was lower in the MCI group than in the control group (36.97 vs. 44.26), this result did not reach significance. Karrasch, Sinervä, Grönholm, Rinne, and Laine (2005) found that verbal fluency measures distinguished between AD and control subjects, but did not distinguish between control and MCI subjects, nor between MCI and AD individuals. Again, control subjects scored higher on average than MCI individuals ($21.1 \pm 3.8$ vs. $18.9 \pm 5.9$) who scored higher than ADs ($18.9 \pm 5.9$ vs. $14.3 \pm 5.2$), but this effect did not reach significance.

One important point in reconciling these conflicting results is the question of diagnosis of MCI. If the MCI sample meets the criteria for amnestic MCI, as is the case in both the Lambon Ralph et al. (2003) and the Karrasch et al. (2005) studies, then impairment in a cognitive domain other than memory constitutes an exclusionary criterion. Thus, deficits in language tasks such as category fluency would not be expected. Lambon Ralph and colleagues (2003) note that their sample was biased towards patients with no focal deficits in other cognitive domains. These investigators found that deficits in semantic and linguistic domains emerged after the memory deficits that are the hallmark of MCI. This is consistent with the finding that MCI patients with deficits in cognitive domains other than memory are more likely to convert to AD (Alexopoulos et al., 2006; Bozoki et al., 2001; Sacuiu et al., 2005). Such patients are presumably more advanced in the disease course, neuropathology having spread from the entorhinal cortex to encroach on areas of the inferior and lateral temporal neocortex.

There exist a few studies examining more fine-grained aspects of verbal fluency tasks in MCI. Cooper, Lacritz, Weiner, Rosenberg, and Cullum (2004) examined the effects of practice in test–retest conditions with a category fluency task. It has been previously established (Cooper et al., 2001) that AD individuals' performance on an animal fluency task does not improve with practice, even at a very short test–retest interval. Cooper et al. (2004) demonstrated that, like AD individuals, MCI individuals do not benefit from practice. The authors suggest that the reliability of category fluency measures in AD and MCI, in combination with the lack of practice effect, means that this task may be a useful cognitive marker for pharmacological studies requiring short intervals between testing sessions. Forbes-McKay, Ellis, Shanks, and Venneri (2005) examined the individual items produced in a category fluency task by controls and minimal, mild, and moderate AD patients, and found that age of acquisition of items reliably differentiated between healthy adults and AD patients, although it was not sensitive to the severity of AD. Gómez and White (2006) report that measures other than number of items generated discriminate between healthy older adults and very mild AD patients—namely, clustering, switching, and size of cluster.

Östberg, Fernaeus, Hellström, Bogdanović, and Wahlund (2005) examined MCI individuals' performance on a verb fluency task, in which they were instructed to name as many things as possible that people do (as distinct from verbal fluency, described above, or verb generation, in which subjects are given nouns as stimuli and in response produce verbs). Verb fluency was found to be disproportionately impaired in MCI relative to noun and letter fluency; the authors suggest that this may be because verb referents are not taxonomic in the same way as noun referents, and verb fluency thus relies more on neocortical-hippocampal interaction, particularly the perirhinal cortex, which is affected by very early AD neuropathology.

In sum, deficits in verbal fluency have been demonstrated to be predictive of development of dementia and to be present in MCI in a number of studies (see Table 1). Greater impairments are seen in category fluency than in letter fluency in AD, and category fluency is more likely to be impaired in MCI and/or to constitute a predictive factor for dementia. This is presumably due to breakdown in

semantic representations, since impairments in letter fluency are much less likely to be present in MCI or early AD, suggesting that these deficits are not a result of executive or inhibitory dysfunction. Verb fluency appears to be more impaired than noun fluency, although this finding requires replication.

It is important to recall when interpreting these results that, while fluency measures may demonstrate impairment in preclinical AD, it does not follow that such an impairment is predictive only of AD. For example, similar deficits in fluency tasks have been reported in preclinical AD and preclinical vascular dementia (VaD; De Jager, Hogervorst, Combrinck, & Budge, 2003; Laukka, Jones, Small, Fratiglioni, & Bäckman, 2004). In contrast, Duff Canning et al. (2004) found that letter fluency distinguished VaD patients, but not AD patients, from normal controls, and Jones, Laukka, and Bäckman (2006) found that category but not letter fluency distinguished between preclinical AD and VaD individuals. Thus, category fluency may be more affected in AD and letter fluency in VaD, reflecting the semantic deficit seen in the former group. Verbal fluency is also equivalently impaired in frontotemporal dementia and AD (Pasquier, 1999), indicating the executive component in this task. Depression has been shown to affect letter but not semantic fluency, meaning that even mild depression may reduce or eliminate discrepancies between letter and category fluency in dementia (Ravdin, Katzen, Agrawal, & Relkin, 2003).

A second important consideration in interpreting findings relating to neuropsychological performance in prodromal AD is that considerable variability in performance is reported even in clinical cases of AD. For example, Fisher, Tierney, Rourke, and Szalai (2004) examined the performance of two subgroups of probable AD patients on letter and category fluency tasks. Participants were grouped into left-hemisphere AD (LAD) and right-hemisphere AD (RAD) subgroups on the basis of their performance on the Boston Naming Test and Copy tasks. It was found that LAD and RAD participants performed similarly on letter fluency, while LAD participants performed more poorly on category fluency and produced significantly more within-subclass clusters than did RAD participants. Similar results were found by Sherman and Massman (1999). Given the heterogeneity found amongst individuals diagnosed with probable AD, it is to be expected that not all preclinical AD individuals will manifest similar performances. Thus, while impaired performance on category fluency tasks may constitute a risk factor for conversion to dementia, it must be borne in mind that a subset of those individuals who go on to develop dementia will exhibit no impairment on semantic tasks.

### *Naming*

One well-documented symptom of Alzheimer's disease is word-finding difficulty (Bayles & Kaszniak, 1987; Bayles et al., 1992; Bowles et al., 1987; Fisher et al., 1999). Deficits in confrontation naming typically occur early in the disease course (Cummings & Benson, 1989; Huff, 1990). As such, naming tests are widely used in clinical practice as well as research settings.

One widely used naming test is the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), which comprises 60 items ranging from very frequent to very infrequent. This test predicts the rate of cognitive decline in AD (Carswell, 1999; Rasmusson, Carson, Brookmeyer, Kawas, & Brandt 1996) and distinguishes between subgroups of AD (J. K. Johnson, Head, Kim, Starr, & Cotman, 1999). In combination with the Block Design subtest of the Wechsler Intelligence Scale for Children–Revised (Wechsler, 1974), it has been demonstrated to be sensitive to asymmetric cognitive changes in early AD, where one hemisphere is affected more than the other (Delis et al., 1992; Fujimori et al., 1998; Jacobs et al., 1995; Massman et al., 1993). To facilitate testing of AD individuals, whose limited attention span renders the full 60-item version difficult to administer, Williams and colleagues developed two 30-item versions of the BNT (Williams, Mack, & Henderson, 1989). These researchers found that the two versions were equivalent, and that there was a significant correlation between each version and the full 60-item version, both in demented individuals and in healthy subjects. The same research group subsequently constructed four 15-item versions and validated them in demented and nondemented elderly individuals (Mack, Freed, Williams, & Henderson, 1992).

A number of studies have examined the diagnostic and prognostic utility of tests of naming performance in MCI and AD, including, but not limited to, the 15- and 60-item versions of the BNT. Summary statistics are provided in Table 1, and the findings are summarized in Appendix B. Differences have been found between healthy elderly controls and MCIs (Dwolatzky et al., 2003; Grundman et al., 2004; Petersen et al., 1999), between MCIs and ADs (Goldman et al., 2001; Petersen et al., 1999), and between incident AD and nondemented individuals up to two years prior to diagnosis (Blackwell et al., 2004; Nielsen et al.,

1999). Likewise, Bennett et al. (2002) found that MCIs had lower baseline scores and declined more than twice as rapidly as did healthy elderly controls on a composite score of semantic memory, including the BNT, and Storandt et al. (2002) reported more rapid rates of decline on the BNT as cognitive impairment progresses. Bozoki et al. (2001) found that the BNT discriminated best between individuals with memory impairment who converted to AD and those who did not, although this effect missed significance.

The Graded Naming Test (GNT, McKenna & Warrington, 1983) is a 30-item naming test with items that progressively decrease in familiarity. A number of studies have suggested that it is sensitive to semantic deficits in AD and MCI (e.g., Blackwell et al., 2004; Dudas, Clague, Thompson, Graham, & Hodges, 2005; Thompson, Graham, Patterson, Sahakian, & Hodges, 2002) and that it predicts incident dementia (De Jager & Budge, 2005). Of particular interest in the last study was the finding that deficits in naming of famous faces was highly predictive of conversion to AD in individuals with questionable AD (defined as complaints of declining episodic memory in the absence of dementia). In a similar vein, Semenza, Mondini, Borgo, Pasini, and Sgaramella (2003) demonstrated that tests of proper name retrieval, both to description and in naming faces, were more sensitive to very mild AD (comparable to MCI) than other, longer batteries such as the Mini-Mental State Examination (MMSE, Folstein, Folstein, & McHugh, 1975) and the Milan Overall Dementia Assessment (Brazzelli, Capitani, Della Sala, Spinnler, & Zuffi, 1994). This disproportionate deficit for person naming in very mild or questionable AD clearly requires further exploration.

However, several studies have reported that naming tests do not predict incident dementia (Albert et al., 2001; Chen et al., 2001; Devanand, Folz, Gorlyn, Moeller, & Stern, 1997; Fox et al., 1997; Fox et al., 1998; Newman, Warrington, Kennedy, & Rossor, 1994; Ritchie et al., 2001; Schmidtke & Hermeneit, 2007; Small, Fratiglioni, Viitanen, Winblad, & Bäckman, 2000), that differences are not seen until after diagnosis (Rubin et al., 1998), or that they are detectable at retest but not at baseline (Guarch et al., 2004). In addition, in a recent study the 15-item BNT did not distinguish between MCI, normal controls, and individuals diagnosed with major depressive disorder (Beinhoff, Hilbert, Bittner, Grön, & Riepe, 2005). These conflicting results may be due in part to the different tests used; shorter tests such as the 15-item BNT or the naming subtest of the MMSE were less likely to predict incident dementia or differentiate between subject groups (e.g., of 12 studies reporting no predictive or diagnostic value for the BNT, 6 report using a shortened version). Likewise, small sample sizes such as those used by Goldman et al. (2001) were less likely to yield significant differences between subject groups. Finally, it is possible that only a subset of preclinical AD patients exhibit a naming deficit. Hodges et al. (2006) report on the neuropsychological profile of 10 MCI patients followed over at least six years. They found that, while deficits in memory and category fluency occurred in most patients very early (in 7/10 patients at baseline and 8/10 at the end of the first year), naming deficits (assessed using the naming task from the Cambridge semantic test battery; Hodges & Patterson, 1995) were more variable and unstable.

Whatmough et al. (2003) capitalized upon the widely reported category effect in AD, whereby AD individuals perform better on naming artifacts than biological kinds (e.g., Daum, Riesch, Sartori, & Birbaumer, 1996; Fung et al., 2001; Silveri, Daniele, Giustolisi, & Gainotti, 1991). These authors tested 56 ADs and 16 MCIs, as well as 40 elderly controls, on a picture-naming task comprising 28 biological items (fruits, vegetables, or animals) and 28 artifacts (tools, clothing, or furniture). Patients were then stratified into five groups on the basis of their naming ability (the first three groups comprising both MCI and AD individuals, and the bottom two groups only ADs). Results revealed that the category effect favoring artifacts increased with worsening anomia. These findings highlight (a) the heterogeneity of semantic memory impairment in AD (given that ADs spanned five levels of naming impairment, and MCIs three); and (b) the relatively steeper decline in naming biological kinds than artifacts as semantic memory declines.

In sum, it appears that naming impairments do occur in preclinical AD, although the diagnostic and prognostic utility of these tests is limited. Testa et al. (2004) assessed the diagnostic utility of the BNT relative to other neuropsychological measures and found that, while impaired performance on the BNT is associated with increased risk of AD, it imparted no additional diagnostic utility once delayed recall impairments were included in the model.

### *Other standardized language tasks*

Although confrontation naming and verbal fluency are the most frequently used standardized language tasks, there also exist a few studies in which MCI individuals' performance on a broader range of standardized measures is reported. These studies are summarized in Appendix C and are discussed in more detail below.

*The Pyramids and Palm Trees Test (Howard & Patterson, 1992).* The Pyramids and Palm Trees Test (PPT) assesses semantic access via words or pictures. A few studies have reported MCI individuals' performance on the different versions of this task. Nestor, Fryer, Smielewski, and Hodges (2003) found that AD patients performed worse than MCIs on the picture version of the PPT, while MCIs did not differ from control participants. In contrast, Dudas et al. (2005) report diminished performance on the PPT (picture version) in MCI and AD.

*The Semantic Object Retrieval Test (Kraut et al., 2002).* The Semantic Object Retrieval Test (SORT) assesses semantic association by requiring participants to determine whether two objects are related through another (e.g., "desert" and "humps" are related through "camel"). Kraut et al. (2007) report data indicating that MCI individuals may be subdivided on the basis of SORT performance, and that performance on the SORT correlated with BNT performance; furthermore, in the semantically impaired group, SORT performance was associated with declines in performance on tests of frontal lobe function. The authors suggest that the SORT may provide valuable diagnostic and prognostic information, although that remains to be demonstrated.

*The ECO battery.* The Examen Cognitif par Ordinateur (ECO) battery used by Ritchie et al. (2001) includes a number of tests of language function, including verbal fluency and naming (discussed above), as well as reaction time (RT) for word and syntax comprehension. These authors found that RT (presented as a composite score of RT to syntax and to word comprehension) discriminated between normal subjects and those with preclinical dementia 2 years prior to diagnosis, independent of education effects.

*The ACT system.* Collie, Maruff, and Currie (2002) also examined RT for syntactic and semantic processing, as part of the Automated Cognitive Test system (ACT; Stollery, 1996). In the syntactic task, participants are shown sentences followed by exemplars and are required to verify whether the sentence are syntactically correct or not (e.g., A follows B, AB = incorrect; A is followed by B, AB = correct). In the semantic task, participants are provided with a semantic category and are asked to verify whether the word is an exemplar from the category or not (e.g., word = elm; category = tree). For the syntactic reasoning task, accuracy discriminated significantly between elderly controls and MCIs; however, RT did not, and neither accuracy nor RT discriminated between the two groups for the semantic test. Given that syntactic deficits are not typically reported in MCI or early-stage AD, this finding likely reflects deficits in domains other than syntax proper.

*Montreal Cognitive Assessment.* Our group has developed a short (10-minute) neuropsychological battery, the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), which assesses a number of cognitive functions, including animal naming, letter fluency, and sentence repetition. Both fluency and naming discriminated reliably between ADs, MCIs, and healthy elderly (item analyses available at http://www.mocatest.org/validation_study.html). Overall, the MoCA has 90% sensitivity and 100% specificity for MCI.

*Mindstreams battery.* Dwolatzky et al. (2003) report a new computerized cognitive assessment system (*Mindstreams*) designed to detect MCI in clinical practice. Verbal function is assessed using a naming test and a rhyming test, whereby participants are instructed to select the word that rhymes with the name of the picture presented. Both these measures were found to discriminate significantly between MCIs and healthy elderly subjects, as well as between MCIs and ADs. These two tests of verbal function were then compared with traditional verbal tests, including verbal fluency, BNT, and Wechsler Adult Intelligence Scale–Third Edition (WAIS-III) similarities, in terms of their capacity to discriminate between MCIs and healthy elderly. The best traditional verbal test was found to be the Controlled Oral Word Association–FS (COWA-FS; letter fluency), although this test did not discriminate as well as the two verbal tests included in the Mindstreams battery.

*DemTect.* DemTect (Kalbe et al., 2004) is a short test including five cognitive tasks, with a reported sensitivity of 80% for MCI and 100% for AD. The test includes a word fluency task (supermarket), and in the validation study it was found to be one of the two most sensitive tasks in terms of discrimination between controls, MCIs, and ADs.

*Vocabulary measures.* Bennett et al. (2002) used a number of tests of language including category fluency, the 15-item BNT, the extended range vocabulary test, and the National Adult Reading Test (NART; Nelson, 1982). These scores were then summarized to yield a measure of semantic memory, which was lower at baseline and declined

more rapidly for MCIs than for healthy control subjects. Lambon Ralph et al. (2003), on the other hand, found no difference between MCIs and healthy controls on the NART. It should be noted that the MCI group in the latter study was much smaller ($n=17$) than in the former ($n=211$), and that criteria for amnestic MCI were more strictly adhered to in the Lambon Ralph et al. (2003) study.

*Cookie Theft Picture.* Bschor et al. (2001) administered the Boston Cookie Theft Picture test from the Boston Diagnostic Aphasia Examination (BDAE; Goodglass & Kaplan, 1983). In this task, participants are shown a picture where a number of events are occurring in a familiar setting (a kitchen) and are asked to "report all that happens in the picture." It was found that this task could distinguish healthy controls and MCIs from ADs, but could not differentiate between controls and MCIs, nor between the AD subgroups (see Appendix C for details of measures).

*Complex Ideational Material.* In the Complex Ideational Material subtest of the BDAE (Goodglass & Kaplan, 1983), participants hear statements or short stories of increasing length and syntactic complexity and must then respond to questions about the material they have just heard. This test is considered to be a measure of executive function, but also relies on auditory comprehension. Bennett et al. (2002) created a summary measure of semantic memory on the basis of their participants' performance on this task as well as vocabulary scores, category fluency, and naming, and found that MCI individuals had a lower score at baseline and declined more rapidly than healthy control subjects.

*Other tests of semantic processing.* Lambon Ralph et al. (2003) included a number of additional tests of semantic processing in their study, including word–picture matching, picture sorting by feature, naming to verbal description, and semantic feature questions. MCI individuals could not be distinguished from normal control subjects on these measures; impairments began to appear at the point at which individuals developed mild dementia. Hodges and Patterson (1995) also included naming to verbal description, answering of semantic feature questions, and word–picture matching. They found that patients with minimal AD (MMSE > 23) showed deficits in the majority of these tests, suggesting that semantic memory is impaired very early in the disease course in many patients, although it was found that episodic memory was a more accurate marker of AD.

### Syntactic processing

While syntactic impairments are not typically seen in AD, certain studies have included measures of syntactic comprehension in MCI, typically the Token Test (De Renzi & Vignolo, 1962) or the Test for the Reception of Grammar (TROG; Bishop, 1989). Of all semantic and language tests, Lambon Ralph et al. (2003) found differences between MCI patients and control subjects only on the Token Test. This finding was taken to indicate impaired working memory or attentional-executive processing, rather than impaired syntactic processing, since MCI individuals showed no impairment on the TROG; impairments on this task only appeared once the individuals were at the DAT (mild dementia of the Alzheimer's type) stage. Hodges et al. (2006) also included the TROG as part of their battery and found no significant effects. De Jager et al. (2003) evaluated the sensitivity and specificity of a broad variety of neuropsychological tests for MCI, as well as AD and vascular cognitive impairment. These tests included the Token Test (shortened version; Lezak, 1995), which distinguished between MCI individuals and those suffering from cerebrovascular disease or AD. However, no difference was seen in the performance of control and MCI participants. Ribeiro et al. (2006), on the other hand, found significant impairments on a modified (Portuguese) version of the Token Test: A total of 33.7% of their MCI participants exhibited an impairment on this task (compared to only 30.2% on semantic fluency). In addition, as mentioned above, Collie et al. (2002) report deficits in MCI on a syntactic reasoning task.

In sum, the results of standardized language tests suggest that MCI individuals often manifest deficits in semantic processing, although this is not invariably the case. Episodic memory appears to be affected before other cognitive domains, although those individuals who manifest impairments in one or more cognitive domains in addition to memory are more likely to convert to AD (Alexopoulos et al., 2006; Bozoki et al., 2001; Sacuiu et al., 2005). As such, tools for detection of subtle deficits in the lexical-semantic domain are of particular interest, as these would allow greater prognostic sensitivity for AD. We now turn to an overview of the literature on MCI and language using nonstandardized measures.

## NONSTANDARDIZED LANGUAGE TESTS

While the majority of research on language function that has been conducted with MCI individuals

has focused on standardized tests of language function, there exists nonetheless a small body of literature reporting on various aspects of language performance in this group using other, nonstandardized, measures. These studies are discussed below, subdivided according to modality (receptive vs. expressive). Since MCI is a newly defined syndrome, such research is relatively scarce. We therefore include findings relating to minimal AD (typically defined as CDR of 0.5 and/or MMSE > 23), which mimics the deficits seen in MCI.

## Receptive language

Alterations in receptive language processing have been reported at a number of levels in MCI. We begin with a discussion of studies at the single-word level, then moving to sentence and finally discourse-level processing.

### *Single-word identification*

At the perceptual level, Massoud, Chertkow, Whitehead, Overbury, and Bergman (2002) demonstrated that word-reading threshold (WRT) is a potentially useful tool for discriminating MCI individuals who will progress to AD. These authors conducted a study with 13 AD participants, 13 MCI participants, and 12 healthy elderly controls, in which participants read aloud backward- and forward-masked words presented at increasingly long intervals. WRT was defined as the target duration at which 50% of words could be read, and a WRT threshold of 85 ms was found to successfully distinguish 10 of 13 ADs and 11 of 12 healthy elderly controls. This compares favorably with a previous study of letter identification threshold that allowed correct classification of only 59% of AD patients (Mendola, Cronin-Golumb, Corkin, & Growdon, 1995). Furthermore, while MCI individuals could not be distinguished from the other groups on the basis of this test, the 4 MCIs whose thresholds were above 85 ms had progressed to AD at two-year follow-up. This study indicates that impairments in single-word processing are of potential prognostic significance for MCI.

This issue was further investigated by Vandenbulcke, Peeters, Dupont, Van Hecke and Vandenberghe (2007). They report an functional magnetic resonance imaging (fMRI) study in which MCI individuals and healthy elderly controls performed a semantic-associative task with either words or pictures. It was found that activation in the lower bank of the posterior third of the left superior temporal sulcus (STS) indexed word-specific processing in elderly controls. MCI individuals, on the other hand, manifested a significant reduction in this activation. Participants also completed a word identification task similar to that used by Massoud et al. (2002), in which they were required to identify forward- and backward-masked pictures and words presented at increasing intervals (30–800 ms). Overall, the slope of time–accuracy function was steeper for controls than MCIs in the word but not the picture identification task, suggesting that controls are quicker to generate associations to the stimulus. Furthermore, there was a significant correlation between slope and fMRI response amplitude in the STS. The authors suggest that the STS may constitute the neural substrate for the deficit in word identification reported by Massoud et al. (2002) and postulate that dedifferentiation of the connections between orthographic word forms and their meaning may underlie the slowing in identification of written words in MCI.

### *Lexical-semantic processing*

While there exists plentiful evidence of semantic deficits in MCI, only a few studies examine lexical-semantic processing in MCI using nonstandardized tests. Puregger, Walla, Deecke, and Dal-Bianco (2003) report a magnetoencephalographic (MEG) study in which MCI subjects and healthy age-matched controls were asked to encode words either semantically (animate or inanimate) or non-semantically (presence or absence of letter "s") and then identify already-seen items. Behavioral measures showed no difference between the two groups, but differences were seen in the MEG signal while encoding was taking place: MCIs showed greater activation in the shallow (nonsemantic) encoding condition over left frontal and temporal sensors 250–450 ms following stimulus onset. No such effect was seen in control subjects. This finding was interpreted as reflecting additional neural activation required for shallow encoding, to compensate for neurodegeneration.

Similarly, Olichney et al. (2002) examined electrophysiological response in MCI individuals ($n = 14$) and healthy elderly controls ($n = 14$) to single words during a categorization task. Subjects were presented category statements (e.g., "a breakfast food") and then congruous items (e.g., "pancake") or length- and frequency-matched incongruous words. They found that MCI individuals manifested a delayed N400, a negative peak in the EEG waveform approximately 400 ms after stimulus onset, which is taken to reflect semantic integration processes. Furthermore, control subjects manifested a late positive component to new words, which was significantly diminished when a

word was repeated. This repetition effect was much weaker for MCI participants and was almost entirely accounted for by the 7 MCI subjects who did not subsequently convert to AD. That is, the absence of a repetition effect appears to predict subsequent conversion from MCI to AD. Taylor and Olichney (2007) report follow-up analyses of this cohort of MCI individuals. Converters manifested a delayed and spatially circumscribed N400 repetition effect at baseline, and this effect was absent altogether in the group averages after one year. Furthermore, the baseline P600 repetition effect accurately discriminated 11 of 13 MCI individuals who converted to AD over the next three years, suggesting that these effects may be clinically useful in prognosis of MCI.

Davie et al. (2004) report a study examining MCI individuals' sensitivity to expectancy violations. These researchers used a semantic priming paradigm, where subjects decided whether visually presented word pairs were related or not. Participants included healthy younger ($n=80$) and older ($n=22$) control subjects, as well as participants diagnosed with MCI ($n=10$). An expectancy bias was created by manipulating the proportion of category-related (apple–fruit) and coordinate-related pairs. When a high proportion (80%) of category pairs was presented, both control and MCI groups showed an expectancy bias, but MCI individuals showed a much greater cost for unexpected targets.

Taler and Jarema (2006) report a study in which groups of healthy elderly controls ($n=11$), MCI ($n=8$), and AD ($n=8$) individuals were asked to perform lexical decisions on nouns of differing categories: mass nouns such as *cheese*, count nouns such as *table*, and nouns that are mass/count ambiguous, such as *chicken*. Healthy older adults manifested faster response times to ambiguous nouns than to mass or count nouns, while neither MCI nor AD participants showed such an advantage for ambiguous nouns. This was interpreted as reflecting an impaired semantic network in these populations. These findings are consistent with previous research by the same authors (Taler & Jarema, 2004), in which MCI and AD individuals were asked to distinguish between mass and count readings of mass/count ambiguous items such as "chicken." In this study, participants were presented with pictures representing the mass and count readings of each noun and were asked to either "Point to the picture of chicken" or "Point to the picture of a chicken." While a minority of patients from both MCI and AD groups manifested control-like performance, most patients were impaired on this task. Furthermore, performance did not differ significantly across the two groups.

One important distinction in semantic processing is that between intentional and automatic processing: Word-naming and verbal fluency tasks require intentional processing, while tasks such as lexical decision and word identification tap more automatic processing. In AD, impairments are seen in both types of processing, and the order in which these impairments appear is not clear. Recent research indicates that MCI individuals' performance on intentional access tasks (picture naming and semantic probes) is impaired but performance on tasks tapping automatic access (lexical decision and semantic priming) is not (Duong, Whitehead, Hanratty, & Chertkow, 2006). Impairments were also seen in performance on Stroop tasks, and the authors suggest that impairments in lexical-semantic tasks may be attributable to deficits in inhibition during semantic search. The authors acknowledge that task difficulty may also play a role, although it appears that this factor cannot fully account for the findings. These findings are in contrast to those reported above, which suggest deficits in automatic as well as intentional processing. However, it is possible that the tasks used by Duong et al. (2006) did not tap a sufficiently subtle aspect of automatic lexical-semantic processing. For example, Taler and Jarema (2006) found that MCI and AD individuals did not show an advantage for lexical items with multiple related senses, the so-called "ambiguity advantage" (Rubinstein, Garfield, & Millikan, 1970), while older adults did. The priming task used by Duong et al. (2006) relied upon associative strength between prime and target and thus may not have been sensitive to subtle alterations in automatic lexical-semantic processing in MCI participants.

While most studies of single-word processing in AD and MCI have focused on nouns, Grossman and colleagues have conducted a number of studies examining verb processing in AD. These investigators have found different patterns in brain activation in AD patients versus healthy controls in processing of verbs of motion and cognition (Grossman et al., 2003a). In addition, they show impairment in identifying semantic relations among verbs (Grossman, Mickanin, Onishi, & Hughes, 1996). In combination with the finding that verb fluency is disproportionately impaired in MCI (Östberg et al., 2005), these findings indicate that further studies of deficits in verb processing may be fruitful in terms of characterizing the language impairment in prodromal AD.

In sum, while studies of lexical-semantic processing in MCI are scarce, they appear to hold promise for better characterization of the neuropsychological profile of MCI individuals. Qualitative alterations

are seen in a number of tasks, including single-word recognition, as well as in terms of priming and expectancy biases. Such alterations may be attributable to inhibition deficits, whereby MCI individuals have difficulty inhibiting information while performing semantic search; that is, the lexical-semantic impairments observed in MCI may be due to an interaction between executive function and language (Duong et al., 2006). Such a claim is consistent with the finding that MCI and preclinical AD individuals tend to exhibit greater impairments in category fluency, which comprises a substantial executive component, than on naming tasks, which place lesser demands on executive function.

### *Sentence and discourse level*

Croot, Hodges, and Patterson (1999) found effects of AD on sentence comprehension, even when patients were at the minimal stage of the disease, although these effects were variable across individuals. Chapman et al. (2002) assessed detail-level and gist-level discourse processing in MCI individuals ($n=20$), patients with mild AD (MMSE $\geq 16$; CDR $\leq 1$; $n=24$), and cognitively normal elderly control subjects ($n=25$). Participants were read a 578-word biographical narrative and were provided with a written copy of the text so that they could follow along. They were then given 5 minutes to review the written text, which was removed before they were asked questions probing detail- and gist-level processing. Participants were asked to summarize the text, provide the main idea in one sentence, and construct a lesson that could be learned from the story. Recognition and recall of specific details of the text were then tested. These authors found that AD and MCI individuals showed impairments in gist-level processing (summary, main idea, and lesson) relative to healthy elderly controls. A more detailed examination of individual participants' performance revealed that 13 of 20 MCI patients were in the impaired range in performance on gist-level tasks. Detail-level processing was also impaired in both groups and was relatively more impaired in AD than in MCI. The authors conclude that detail-level processing is impaired earlier in the disease course than is gist-level processing. Hudon et al. (2006) likewise examined memory for gist-level and detail information in MCI and AD. These researchers found an increase in false recognition of gist-level information in AD but not MCI. In recall, however, both MCI and AD participants exhibited deficits both for gist-level and detail information.

## Language production

Although limited research has been conducted on language production in MCI, the likelihood that alterations occur in spontaneous language production has been highlighted by a recent study indicating reductions in semantic skills and sophistication of vocabulary in Iris Murdoch's last novel, published a year before her diagnosis with AD (Garrard, Maloney, Hodges, & Patterson, 2005). Similarly, subtle language alterations were revealed in an analysis of the speeches given by Ronald Reagan in his reelection campaign for the US presidency, some 10 years prior to his diagnosis with AD (Venneri, Forbes-McKay, & Shanks, 2005). These cases suggest that spontaneous language may be among the skills altered very early in AD. In the present section, we report studies examining language production in both spoken and written modalities.

### *Production of definitions*

Hodges, Patterson, Graham, and Dawson (1996) examined the performance of control participants and minimal, mild, and moderate AD patients on naming and generation of definitions for a set of nouns and found that the quality of definition produced differed between groups. Specifically, all ADs produced definitions with less correct information that sometimes failed to convey the core concept. For the minimal and mild AD groups, this was correlated with inability to name the object.

### *Spontaneous speech*

AD individuals produce semantically impoverished discourse that is lacking in coherence, although the syntax is relatively preserved (Kemper et al., 1993). While studies of spontaneous speech in MCI are virtually nonexistent (although see Bschor et al., 2001, discussed above), some research has examined spontaneous language production in minimal AD, which is comparable to MCI.

Forbes, Venneri, and Shanks (2002) assessed the spontaneous speech of patients with minimal ($n=11$) and mild ($n=11$) AD, as well as age- and education-matched controls. These researchers used a simple and a complex picture description task and found that, while both tasks distinguished AD patients from controls, only the complex picture description task was able to differentiate between minimal AD patients and healthy control subjects. Significant differences were seen in measures of production of semantic paraphasias, word-finding

delays, error monitoring, and information conveyed. Forbes-McKay and Venneri (2005) recently conducted a study aiming to collect normative data for AD individuals in a picture-description task, as well as to determine whether normal cognitive decline can be differentiated from pathological alterations on the basis of spontaneous language production. In this study, 240 healthy participants aged between 18 and 90 years, as well as minimal ($n=10$), mild ($n=10$), and moderate ($n=10$) AD patients were asked to describe, both orally and in writing, two simple line drawings (the Cookie Theft Picture, Goodglass & Kaplan, 1983; and the Tripping Woman Picture, Semenza & Cipolotti, 1989) and two complex drawings (the Traffic Chaos Picture and the Bus Stop Picture, unpublished). It was found that measures of information content, pictorial themes, word-finding delays, and the response given to these delays discriminated best between healthy elderly individuals and AD patients, and the complex picture description task was sensitive even to early stages of AD. The pattern of errors seen in these studies points to a breakdown in lexical-semantic functioning in these individuals; no such breakdown was seen in healthy elderly subjects. These findings are thus consistent with the findings reported for other measures of semantic functioning, such as category fluency.

### *Writing*

It is well established that writing difficulties occur in AD, and in fact these difficulties were first reported by Alzheimer himself in describing his patient Augusta D. (Alzheimer, 1907; see Stelzmann, Schnitzlein, & Murtagh, 1995). At the linguistic level, AD individuals produce texts that are shorter than those produced by controls (Croisile, Carmoi, Adeleine, & Trillet, 1995; Croisile et al., 1996; Henderson, Buckwalter, Sobel, Freed, & Diz, 1992; Horner, Heyman, Dawson, & Rogers, 1988; Neils, Boller, Gerdeman, & Cole, 1989) and contain less relevant information (Croisile et al., 1995, 1996; Henderson et al., 1992; Kemper et al., 1993). Sentences are less syntactically complex than those produced by controls (Croisile et al., 1996; Kemper et al., 1993), although AD patients and control subjects produce a comparable number of grammatical errors (Croisile et al., 1996; Horner et al., 1988; Neils et al., 1989). That is, syntactic structures are simplified but coherent (Kemper et al., 1993). A high number of semantic substitutions or intrusions and misspellings are also seen (Croisile et al., 1996; Glosser & Kaplan, 1989; Henderson et al., 1992; Horner et al., 1988; Neils et al., 1989). In sum, it can be concluded that greater impairments are seen at the lexical-semantic than at the syntactic level (Croisile, 1999). Many AD patients do not show any impairment in spelling (Croisile, 1999; Luzzatti, Laiacona, & Agazzi, 2003). However, the most common pattern appears to be a surface dysgraphia, whereby writing of irregular or ambiguous words via an orthographic output lexicon is more impaired than writing of pronounceable words or nonwords through grapheme–phoneme correspondence rules (Croisile, 1999). Silveri, Corda, and di Nardo (2007) found that central orthographic (i.e., lexical-semantic) errors were more prevalent in the early stages of AD, and peripheral errors (e.g., omission of strokes) increased as the disease progressed. They suggest that dysgraphia in AD is the result of a reduction of general cognitive resources in AD, rather than disorders of specific subcomponents of spelling.

Despite these findings, systematic studies of writing performance as a diagnostic or prognostic marker for AD are scarce. One large-scale study that is of particular interest is the Nun Study conducted by Snowdon and colleagues. These researchers have demonstrated that text-level writing abilities in early adulthood are a strong predictor of subsequent onset of dementia (Snowdon et al., 1996) or mild cognitive impairments (Riley, Snowdon, Desrosiers, & Markesberry, 2005) decades later. These studies examined the relationship between autobiographies written by nuns two years prior to formally joining a congregation (average age=22 years) and their cognitive function several decades later (average age=80 years). The texts were measured in terms of idea density, defined as the average number of ideas expressed per 10 words, which corresponds to elementary propositions (verb, adjective, adverb, or prepositional phrase), and complex propositions (stating or inferring causal, temporal, or other relationships between ideas). Participants were then classified as having low idea density (bottom third) or high idea density. It was found that idea density correlated significantly with late-life cognitive function, as well as late-life scores on standardized measures of cognitive function, including the BNT and verbal fluency. Given these intriguing findings, it seems likely that writing ability constitutes an important potential diagnostic and prognostic tool for AD and MCI. However, it should be noted that this may reflect a discourse-level deficit rather than a deficit in writing per se, since narratives were not tested in the oral modality.

There also exist a few studies examining writing abilities in minimal AD. Werner, Rosenblum,

Bar-On, Heinik, and Korczyn (2006) report alterations in kinematic measures of handwriting, such as time taken to complete writing tasks and pressure on the writing surface, which discriminate between healthy elderly adults and MCI and mild AD individuals better than the MMSE. Forbes, Shanks, and Venneri (2004) had minimal (MMSE ≥ 25), mild (MMSE 19–24), and moderate (MMSE 12–18) AD individuals describe in writing two simple line drawings (the Cookie Theft Picture, Goodglass & Kaplan, 1983; and the Tripping Woman Picture, Semenza & Cipolotti, 1989) and two complex drawings (the Traffic Chaos Picture and the Bus Stop Picture, unpublished). Output was assessed according to syntactic complexity, number of paraphasias, information content, complexity (writing in cursive), and the proportion of words containing legible letters, stroke errors, or allographic errors (inappropriate mixing of upper and lower case). Consistent with previous literature, mild and moderate AD individuals produced written narratives with multiple error types (incoherent/indefinite phrases, semantic and graphemic paraphasias, and inability to abstract and describe all pictorial themes). Patients with minimal AD, however, were distinguishable from control subjects only on semantic measures: They manifested lower information content and capacity to abstract and describe pictorial themes. This is consistent with the claim that these individuals suffer from a central semantic impairment even in very early stages of the disease, as suggested by MCI patients' performance on semantic tasks discussed throughout the present paper.

## CONCLUSIONS

### Characterizing the language impairment in MCI

The findings reviewed here point toward the presence of linguistic deficits in MCI that parallel those found in AD. These include deficits in verbal fluency, especially category fluency, and in confrontation naming, as well as in a variety of other less studied language tasks including RT for language comprehension (Ritchie et al., 2001), accuracy in syntactic reasoning (Collie et al., 2002), and naming a rhyming word (Dwolatzky et al., 2003). Alterations in performance on a variety of other semantic tests have also been reported (e.g., in MCI: lexical decision, Taler & Jarema, 2006; semantic categorization, Olichney et al., 2002; semantic encoding, Puregger et al., 2003; semantic priming, Davie et al., 2004; in minimal AD: naming to verbal description and semantic feature questions, Hodges & Patterson, 1995). Alterations in productive and receptive discourse-level processing have also been reported in MCI and minimal AD (Chapman et al., 2002; Forbes et al., 2004; Forbes et al., 2002; Forbes-McKay & Venneri, 2005; Garrard et al., 2005; Hudon et al., 2006; Riley et al., 2005; Snowdon et al., 1996). However, these alterations appear earlier under more difficult conditions: A simple picture-description task, such as the Cookie Theft Picture, is less likely to reveal alterations in MCI or minimal AD (Bschor et al, 2001; Forbes-McKay & Venneri, 2005). Likewise, impairment in purer tests of syntax, such as the Token Test and the TROG, are less consistent: Lambon Ralph et al. (2003) and Ribeiro et al. (2006) report impaired performance on the former, whereas De Jager et al. (2003) do not, and Lambon Ralph et al.'s (2003) and Hodges et al.'s (2006) MCI participants manifested intact performance on the latter. In sum, it appears that linguistic impairments in MCI are most likely located at the semantic level, as is seen in the early stages of AD. Syntactic processing is typically reported to be more or less intact (although cf. Ribeiro et al., 2006).

Of particular interest are findings suggesting that timed tests are especially sensitive to the declines seen in MCI. Massoud et al. (2002) report that word-reading threshold may be useful in discriminating MCIs who will convert to AD; similarly, temporally precise methodologies, such as lexical decision (Taler & Jarema, 2006), event-related potentials (ERPs; Olichney et al., 2002), and MEG (Puregger et al., 2003), appear to distinguish well between MCI and healthy controls and even predict conversion to AD (Olichney et al., 2002). To a lesser extent, the reported deficits in category fluency tasks, which impose a time limit on responses, are also sensitive to MCI and predict conversion to AD, although it should be noted that studies that adhere strictly to the diagnostic criteria for amnestic MCI, which exclude individuals with deficits in domains other than memory (e.g., Karrasch et al., 2005; Lambon Ralph et al., 2003) are less likely to produce significant results. Furthermore, these tests have been reported to have diagnostic utility in large-scale epidemiological studies; their utility on an individual-by-individual basis is less clear.

One question that remains is the locus of the semantic deficit in MCI and AD. While much research has centered on degradation of semantic knowledge in these populations, recent research has suggested that these deficits may be due at least in part to deficits in executive functions that affect semantic search or categorization. For example,

Grossman et al. (2003b) examined rule-based and similarity-based categorization in AD and FTD and found deficits in rule-based but not similarity-based categorization in both AD and FTD. They argue that deficits in executive function underlie these declines in rule-based processing in AD. Duong et al. (2006) similarly conclude that semantic impairments in MCI may be due to inhibitory deficits affecting semantic search.

## Distinguishing prodromal AD from other dementias

One crucial issue is the distinction between prodromal phases of AD and other types of dementia. It has been suggested (Petersen, 2003) that MCI may evolve to AD, VaD, frontotemporal dementia (FTD), Lewy body dementia (LBD), or primary progressive aphasia (PPA). Any tool designed to detect prodromal AD must provide sufficient specificity in addition to sensitivity. When considering tools to detect early language impairments, care must be taken to exclude other dementias.

### *AD versus vascular dementia*

A number of studies indicate similar declines in semantic memory in AD and VaD (Bentham, Jones, & Hodges, 1997; De Jager et al., 2003; Laukka et al., 2004; Vuorinen, Laine, & Rinne, 2000). For example, Bentham et al. (1997) report that VaD and AD individuals perform similarly on category fluency, naming, picture sorting, and generation of definitions, showing impairment relative to healthy elderly adults, while neither group showed impairments relative to controls on word–picture matching. Vuorinen et al. (2000) found impairments in both groups on complex auditory comprehension and picture-naming tasks, but normal performance on oral reading and single-word repetition.

However, differences have been reported in language performance in VaD and AD. N. L. Graham et al. (2004) report more impaired semantic memory in VaD than AD on a variety of tasks: VaD patients exhibited impairments on category fluency, the Camel and Cactus test (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000), concrete and abstract word synonym test, and the GNT, while AD patients showed impairments only on category fluency and the GNT. VaD patients have also been found to perform better on tasks of confrontation naming than AD patients, and show better preserved lexical-semantic abilities, while declines in syntactic abilities are seen in VaD but not AD (Desmond, 2004; Pasquier, 1999).

While more errors are seen in naming tasks in AD than in VaD (Almkvist, 1994), the pattern of errors (visuoperceptual, semantic, or phonemic) has been reported to be similar in the two groups, although AD patients commit more superordinate errors than VaD patients (Lukatela, Malloy, Jenkins, & Cohen, 1998). More perseveration is seen in VaD than in AD (Desmond, 2004), and Traykov et al. (2002) report higher rates of perseverative errors in AD than in early-stage VaD in a semantic fluency task (using the categories of animals, fruits, vegetables).

Recently, it has been reported that language impairments may appear in the prodromal phase of VaD (Laukka et al., 2004; although cf. Jones et al., 2006). Likewise, a recent study (Sacuiu et al., 2005) had a large pool of nondemented elderly individuals complete a number of tasks, including a language task in which they were required to identify synonyms among five alternatives, as well as tasks assessing memory and visuospatial and executive function. Memory impairment in combination with impairment in any other domain best predicted incident dementia, prodromal AD was most related to impairments in memory and executive function, and the best predictor of VaD was impairment in language function according to informants, in combination with a global pattern of deficits. Frisoni, Galluzzi, Bresciani, Zanetti, and Geroldi (2002) report superior performance on category and letter fluency in amnestic MCI relative to MCI with subcortical vascular features, while both populations performed similarly on the Token Test. More recently, letter fluency has been found to be among the most accurate scales to distinguish between amnestic MCI and MCI with subcortical vascular features (Galluzzi, Sheu, Zanetti, & Frisoni, 2005). In contrast, Loewenstein et al. (2006) found similarly impaired performance in amnestic and vascular MCI on both letter and category fluency. Luis et al. (2004) likewise report similar performance in amnestic and vascular MCI on letter fluency, BNT, and Wechsler Adult Intelligence Scale–Revised (WAIS–R) Similarities and Vocabulary. These findings highlight both the need to exclude other syndromes such as VaD when considering the prognostic value of tests of language function and the difficulty in doing so.

### *AD versus frontotemporal dementia, semantic dementia, and primary progressive aphasia*

The term frontotemporal dementia (FTD) refers to a group of degenerative dementias affecting the frontal or temporal lobes. A variety of terms are

used to refer to different subtypes of FTD, including Pick's disease, dementia of the frontal type, frontal lobe dementia of the non-Alzheimer's type, frontotemporal lobar degeneration, semantic dementia (SD), progressive nonfluent aphasia, and primary progressive aphasia (PPA; Hutchinson & Mathias, 2007).

Of particular relevance with respect to language tests are dementias that specifically affect language function, including PPA and SD. There exist a few studies comparing language performance in these populations and examining the predictive value of neuropsychological tests in dementia diagnosis. Performance on language tasks has been found to be equivalent (Cosentino, Chute, Libon, Moore, & Grossman, 2006; Gregory, Orrell, Sahakian, & Hodges, 1997; Pachana, Boone, Miller, Cummings, & Berman, 1996) or lower (Diehl et al., 2005; Perry & Hodges, 2005) in FTD than in AD. Cosentino et al. (2006) had AD, behavioral FTD, and SD participants complete the PPT, the 15-item BNT, the COWA-FS and the verb similarity task (Price & Grossman, 2005), which is designed to resemble the PPT but utilizing verbs rather than nouns. No difference was seen between the three groups on any of these measures. Diehl et al. (2005) compared performance on the CERAD-NAB (Consortium to Establish a Registry for Alzheimer's Disease—Neuropsychological Assessment Battery) subtests by AD, FTD, and SD patients. Patients with FTD were more impaired than AD patients in animal fluency, and patients with SD were more impaired than both FTD and AD patients on animal fluency and the BNT. Perri et al. (2005) found equivalent BNT performance but lower phonological fluency performance in FTD than in AD. In a longitudinal study of semantic memory in SD, AD, progressive nonfluent aphasia (PNFA), frontal variant frontotemporal dementia (fvFTD), and posterior cortical atrophy (PCA), Rogers, Ivanoiu, Patterson, and Hodges (2006) report a performance pattern indicating amodal semantic impairment in SD and a similar but less impaired performance in AD. In PNFA, fvFTD, and PCA, semantic impairments were found, but appeared to be secondary to other factors.

In addition, language has been found to decline faster in PPA and in the behavioral variant of FTD than in AD (Blair, Marczinski, Davis-Faroque, & Kertesz, 2007), as assessed by the Western Aphasia Battery (WAB; Kertesz, 1982). Similarly, Kramer et al. (2003) found greater impairments on confrontation naming in SD than in AD or FTD patients but comparably diminished performance on animal fluency. B. T. Gold et al. (2005) report that individuals diagnosed with SD manifest impairments in naming but not picture recognition memory, while AD individuals show the opposite pattern.

Hodges et al. (1999) utilized a comprehensive set of semantic and language tests, in addition to tests tapping other aspects of cognitive function, in an attempt to distinguish early AD from the frontal lobe variant of FTD as well as SD (referred to as the temporal variant of FTD). Participants completed the National Adult Reading Test (NART, Nelson, 1982), letter fluency (FAS), the Pyramids and Palms test (PPT), and a semantic test battery comprising six subtests: category fluency for six main categories and two lower order categories (breeds of dog and types of boat); naming of line drawings; naming to verbal description; semantic feature questions (e.g., "What do we call the large African animal with a curved horn on its head?"); picture sorting; and word–picture matching. Participants also completed tests assessing auditory-verbal short-term memory, episodic memory, and visuospatial abilities. AD patients exhibited a predominant deficit in episodic memory, although declines were also seen in semantic memory (category fluency and naming to verbal descriptions) and visuospatial skills. SD participants exhibited profound deficits on all semantic tasks, as well as the NART (reflecting a disrupted ability to read irregular words). Finally, FTD (frontal variant) participants showed deficits in episodic memory and category fluency, similar to the AD group, but normal semantic memory.

Vandenberghe et al. (2005) report a study examining semantic priming in PPA, MCI, and probable AD. Participants named pictures that were preceded by a word that was the picture name, a semantically related noun, a semantically unrelated noun, or a pseudoword. While healthy controls and MCI and AD participants were faster to name the picture after a related than after an unrelated prime, the reverse pattern was obtained in PPA. The authors suggest that this "semantic interference effect" may distinguish between PPA and probable AD individuals. Similarly, Price and Grossman (2005) examined detection time for words following violations of thematic role assignment or transitivity in AD and FTD. Control participants took longer to detect items preceded by either type of violation, FTD patients were insensitive to both types of violation, and AD patients were slowed by thematic role but not transitivity violations. The authors interpret these findings in terms of a broader degradation of verb representations in FTD than in AD.

Hutchinson and Mathias (2007) recently conducted a meta-analysis of neuropsychological

deficits in AD and FTD, including a large number of language tests. The language tests that best discriminated between the two, with FTD individuals manifesting greater impairment than AD individuals, were the GNT, word–picture matching, WAB-spontaneous speech, WAB-comprehension, PPT-words, PPT-pictures, and picture-naming tasks (effect size >0.80 in all cases, small overlap, and high degree of accuracy in distinguishing the two groups, as measured by the 95% confidence interval).

These findings point the way to possible methods for distinguishing the different dementias at an early stage. A profound semantic deficit, in combination with relatively intact visuospatial abilities and episodic memory is a marker of SD; AD patients, in contrast, show impairments in episodic memory and milder semantic deficits. It should be noted, however, that not all studies have found differing performance in verbal episodic memory in AD and SD (e.g., Scahill, Hodges, & Graham, 2005). In addition, performance decrements in the NART have been reported in SD but not in AD (Hodges et al., 1999).

Of particular interest are recent studies examining semantic deficits at a more precise level than standardized semantic tasks such as category fluency. For example, Vandenberghe et al. (2005) posit the "semantic interference effect" as a potential distinguishing marker between PPA and AD, and Price and Grossman (2005) found differences in sensitivity to verb agreement violations in FTD and AD. Such fine-grained distinctions between differing dementias are likely to prove fruitful in early diagnosis.

Recently, de Mendonça, Ribeiro, Guerreiro, and Garcia (2004) proposed a set of criteria to identify frontotemporal MCI. These include symptoms of frontotemporal dysfunction, behavioral and affective symptoms, speech disturbance, and alteration in at least one test that reflects executive function. In addition, patients should have intact activities of daily living and a computed tomography (CT) or MRI scan that is either normal or shows frontotemporal atrophy. A total of 7 patients meeting these criteria were tested on a variety of neuropsychological tests, and the majority did not show impairment in naming (5/7) or language comprehension (4/7). These findings suggest that language tests likely differentiate between prodromal AD and FTD, although it should be noted that the criteria used by de Mendonça et al. (2004) target the behavioral (frontal) variant of FTD and probably exclude cases of prodromal SD and PPA, in which language/semantics are the primary systems affected.

### *Lewy Body Dementia (LBD)*

Lambon Ralph et al. (2001) report impairments in semantic memory in AD and LBD. However, differences were seen between the two groups: AD patients showed equivalent deficits across picture and word stimuli, while patients with LBD showed more severe deficits with picture stimuli. In addition, AD patients showed greater deficits in category than letter fluency, while LBD patients exhibited equivalent deficits across the two tasks. In the WAIS vocabulary subtest, similar performance has been reported in the two groups (Shimomura et al., 1998). Differentiation between these two syndromes is mainly based on the visuoperceptual difficulties seen in LBD relative to AD, in combination with the more impaired memory performance in AD, rather than on the basis of language tests.

## Heterogeneity in MCI and AD

Another issue that must be taken into account is the considerable variability that exists within AD and MCI populations. MCI is heterogeneous in terms of both clinical presentation and etiology. With respect to AD, while language impairments are often seen early in the disease course, this is not inevitably the case: Visuospatial and frontal variants of AD have also been described (Caine & Hodges, 2001; Cummings, 2000). No language or semantic test will have 100% sensitivity and specificity for AD; it is only in combination with a variety of genetic, cognitive, and neuroimaging markers that these methods can be useful.

## Diagnostic criteria for MCI

The Petersen criteria for MCI (Petersen et al., 1999) require that the patient manifest subjective memory complaints, preferably corroborated by an informant; impaired memory function (usually ≥1.5 *SD* below norms, adjusted for age and education); generally preserved other cognitive function; and intact activities of daily living. Specific psychometric tests are not provided; the diagnosis of MCI thus requires clinical judgment. Furthermore, it has been reported that a diagnosis of MCI is temporally unstable (Ritchie et al., 2001), and the pattern of cognitive dysfunction may be intrinsically fluctuating in early stages (Feldman & Jacova, 2005). One avenue to greater diagnostic accuracy may be serial administration of psychometric tests (Feldman & Jacova, 2005). In this case, creation of alternate forms of neuropsychological tests is an

important area for development. Given the varying criteria used to diagnose MCI, it is hardly surprising that conflicting results have been reported in the literature with respect to language performance in this population. Future research should focus on identifying diagnostic criteria for cognitive and etiological subtypes of MCI, allowing greater prognostic and diagnostic accuracy.

## Future directions

The challenge that remains is to develop a diagnostic tool that can detect the subtle declines in semantic abilities often seen in the very early stages of AD and that is sensitive enough to be useful on an individual-by-individual basis. While lexical-semantic processing is not affected in every case of AD, it is well established that this domain is typically affected early in the disease course, and it thus constitutes a primary target for detection and prognosis of MCI. On the basis of the research findings reviewed here, we suggest that the ideal tool for this purpose will focus on intentional lexical-semantic processing, utilizing a temporally precise methodology. Such a tool may prove useful in the accurate detection of individuals who are likely to develop AD in the future, thus providing the opportunity to commence pharmacological treatment, psychological intervention, and family and financial planning as early in the disease course as possible.

One methodology that provides such temporal precision is the event-related potential (ERP) methodology. For example, as discussed above, Olichney et al. (2002) and Taylor and Olichney (2007) report results indicating that ERP performance may be useful in discriminating those MCI individuals who will go on to develop AD. Likewise, ongoing work in our lab indicates alterations in ERP response to language stimuli in MCI relative to healthy elderly adults. Our results suggest reductions in lexical activation in MCI (Taler & Phillips, 2006), as well as impairments in activation of multiple semantic representations (Taler, Klepousniotou, & Phillips, 2007).

Another area that requires further investigation is the domain of discourse-level processing in MCI. There is a good deal of research indicating deficits in sentence-level language function in mild or minimal AD, both in production (Forbes et al., 2002; Forbes-McKay & Venneri, 2005; Kemper et al., 1993) and in comprehension (Chapman et al., 2002; Welland, Lubinski, & Higginbotham, 2002). Deficits in comprehension of prosody are also seen in AD and are correlated with severity of dementia (Taler, Baum, Saumier, & Chertkow, in press; Testa, Beatty, Gleason, Orbelo, & Ross, 2001). Such functions have yet to be thoroughly assessed in MCI, but deficits in sentence- or discourse-level processing seem likely, and preliminary research points to this conclusion (Chapman et al., 2002). As well as potential applications in terms of detection of prodromal AD, better characterization of these deficits in MCI will allow a more complete picture of the neuropsychological profile of these individuals. Discourse and prosody processing are fundamental aspects of human communication. As such, understanding how these functions are affected in MCI and AD paves the road for interventions with these individuals to improve communication with family and caregivers, which in turn holds promise for an improved quality of life both for patients and for their families.

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**APPENDIX A**

Published studies reporting category fluency performance in MCI and preclinical AD

| *Authors* | *Test used* | *Groups+sample sizes* | *Diagnostic criteria* | *Recruitment procedure* | *Significant effects* | *Effect sizes (Cohen's d)* |
|---|---|---|---|---|---|---|
| Adlam et al. (2006) | LF (F,A,S) & CF (animals, birds, fruit, items, tools, vehicles) | NE ($n$=30)<br>MCI ($n$=10)<br>mild AD ($n$=11) | MCI: Petersen criteria<br>AD: NINCDS-ADRDA criteria (McKhann et al., 1984 | Memory Clinic at Addenbrooke's Hospital, Cambridge | LF: NE=MCI > AD<br>CF: NE > MCI > AD | LF: MCI vs. AD: 1.14<br>CF, living: NE vs. MCI: 1.73; MCI vs. AD: 2.0;<br>CF, manmade: NE vs. MCI: 1.94; MCI vs. AD: 1.58 |
| Albert et al. (2001) | LF & CF | Baseline:<br>NE ($n$=42)<br>qAD ($n$=123)<br>3 year follow-up:<br>NE ($n$=32)<br>stable qAD ($n$=91)<br>qAD who converted to AD ($n$=23) | NE: CDR=0<br>qAD: CDR=0.5<br>AD: CDR=1 | Print media | CF: NE > converters<br>LF: NE > converters; qAD > converters | CF, NE vs. converters: 0.58<br>LF: NE vs. converters: 0.82; qAD vs. converters: 0.61 |
| Albert et al. (2007) | LF & CF | NE ($n$=33)<br>impaired at baseline, stable over 3 years ($n$=22)<br>NE/impaired at baseline and declined over 3 years ($n$=95)<br>NE/impaired at baseline and converted to dementia ($n$=47) | NE: CDR-SB=0<br>impaired: CDR-SB between 0.5 and 3 | Print media | No significant effects | |
| Amieva et al. (2005) | CF (colors, animals, fruits, cities) | Nondemented elderly ($n$=1,050), 215 went on to develop dementia | dementia: DSM-III-R<br>AD: NINCDS-ADRDA criteria | Randomly selected from electoral lists | Lower baseline up to 9 years previously and accelerated decline in pre-AD subjects | |
| Artero et al. (2003) | LF & CF (vegetables) | 128 individuals with cognitive difficulties | Cognitive difficulties ascertained using the Deterioration Cognitive Observée (DECO) screening instrument (Ritchie & Fuhrer, 1992) | Identified via a regional general practitioner network | Best predictive model for AD includes delayed auditory verbal recall+construction+CF (sensitivity=99%, specificity=73%) | |
| Auriacombe et al. (2006) | CF (colors, animals, fruits & cities) | Nondemented elderly ($n$=156), 52 of whom went on to develop AD | Dementia: DSM-III-R<br>AD: NINCDS-ADRDA criteria | Randomly selected from electoral lists | CF distinguishes AD up to five years prior to diagnosis; repetitions less reliable as a marker | CF: T5, 0.78; T8, 1.16; T10, 1.62; repetitions: T5, 0.38; T8, 0.63; T10, 1.28 |

(*Continued*)

**APPENDIX A**
(*Continued*)

| *Authors* | *Test used* | *Groups+sample sizes* | *Diagnostic criteria used* | *Recruitment procedure* | *Significant effects* | *Effect sizes (Cohen's d)* |
|---|---|---|---|---|---|---|
| Bäckman et al. (2002) | CF (items at grocery store) & LF (N,S) | Nondemented elderly ($n$=337), 61 of whom went on to develop dementia and 69 of whom went on to die | Dementia: DSM-III-R | All inhabitants of Kungsholmen, Sweden, aged ≥75 on October 1st, 1987 invited to participate | Nonconverters > converters on all measures | CF: 0.88<br>LF: 0.82 |
| Beinhoff et al. (2005) | CF (animals) | NE ($n$=57)<br>MCI ($n$=48)<br>AD ($n$=66)<br>MD ($n$=61) | MCI: Petersen criteria<br>AD: NINCDS-ADRDA criteria<br>MD: DSM-IV criteria. | Memory clinic | AD < MCI=MD < NE | NE vs. MCI: 1.04<br>MCI vs. AD: 1.02 |
| Bennett et al. (2002) | CF (part of summary measure of semantic memory) | NE ($n$=587);<br>MCI ($n$=211) | Cognitive impairment, but does not meet accepted criteria for dementia | Catholic clergy who agreed to participate | Semantic memory lower at baseline, declined more than twice as fast in MCIs | CF: 0.81 |
| Blackwell et al. (2004) | CF (animals, fruit, household items) | Subjective/objective memory loss ($n$=43), 11 of whom developed AD within 32 months | Normal performance on tests of language and visuospatial function, preserved ADL, CDR=0.5 | Memory clinic | Nonconverters > converters | 1.37 |
| Bozoki et al. (2001) | LF (C,F,L) | IMI ($n$=48) | Petersen criteria + neuropsychological evidence (diagnostic criteria and cognitive measures for clinical change based on those proposed for AAMI) | Michigan Alzheimer's Disease Research Center | Impairment in ≥2 cognitive tests+memory=higher risk of conversion to AD (at 4-year follow-up: memory impairment only: 24% conversion; memory impairment+1 or more cognitive domains: 77% conversion; memory impairment+2 or more cognitive domains: 100% conversion). | |
| Bschor et al. (2001) | LF (S) & CF (animals) | NE ($n$=40)<br>MCI ($n$=34)<br>mild AD ($n$=21)<br>moderate to severe AD ($n$=20) | ICD-10 criteria (Zaudig, 1992) | Memory clinic, Dept. of Gerontology, Freie Universität Berlin | NE > MCI > mild AD= mod/sev AD for both measures | CF: NE vs. MCI, 0.59, MCI vs. mild AD, 0.97<br>LF: NE vs. MCI, 0.84, MCI vs. mild AD, 0.50 |
| Caccapolo-Van Vliet et al. (2003) | LF (C,F,L) & CF (animals, food & clothing) | NE ($n$=230)<br>QD ($n$=155)<br>mild AD ($n$=244)<br>moderate AD ($n$=480)<br>severe AD ($n$=376)<br>very severe AD ($n$=247) | QD: cognitive impairment sufficient or close to sufficient for a diagnosis of dementia; no functional impairment<br>AD: NINCDS-ADRDA criteria | Memory Disorders Center/ recruited for a study of controls | LF: NE=QD; QD=mild AD; NE > mild AD > moderate AD > severe AD > very severe AD<br>CF: NE > QD > mild AD > moderate AD > severe AD > very severe AD | CF: NE vs. QD: 0.43; QD vs. mild AD: 0.49; mild AD vs. moderate AD: 0.79; moderate AD vs. severe AD: 0.71; severe AD vs. very severe AD: 1.04 |

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|---|---|---|---|---|---|---|
| Chen et al. (2000) | LF & CF | NE ($n$=483), who remained non-demented over 10-year follow-up<br>Converters to AD 1.5 years after testing ($n$=120) | NINCDS-ADRDA criteria | Randomly selected from voter registration lists | NE > incident AD for both LF and CF; however, neither was a better predictor of incident dementia than the MMSE | LF: 0.50<br>CF: 0.83 |
| Chen et al. (2001) | LF & CF | NE ($n$=551), 68 of whom went on to develop AD | NINCDS-ADRDA criteria | Randomly selected from voter registration lists | Decline in CF: nonconverters < converters decline in LF: nonconverters = converters | CF: 0.29 |
| Collie et al. (2002) | CF | Elderly adults ($n$=174), 23 of whom were impaired on 3 consecutive assessments | CERAD battery (Morris et al., 1988) | Recruited from an ongoing study on aging at an independent research institute in Melbourne, Australia | NE=MCI | |
| Cooper et al. (2004) | CF (animals) | NE ($n$=23)<br>MCI-A ($n$=23)<br>AD ($n$=23) | MCI-A: Petersen criteria | Clinic for Alzheimer's Disease and Related Disorders, University of Texas Southwestern Medical Center, Dallas | Only NE showed significant improvement across repeated administrations (24 to 96 hours apart) | |
| Croot et al. (1999) | CF (living, 4 categories & manmade, 4 categories) | NE ($n$=46)<br>minimal AD ($n$=16)<br>mild AD ($n$=16)<br>moderate AD ($n$=14) | NINCDS-ADRDA criteria<br>minimal: MMSE=24–30<br>mild: MMSE=18–23<br>moderate: MMSE=2–17 | Memory Clinic at Addenbrooke's Hospital, Cambridge | $p$-value not reported | |
| Cunje et al. (2007) | CF (animals, cities & towns, names, or fruits & vegetables) | NE ($n$=46)<br>MCI ($n$=45)<br>dementia ($n$=55) | Subjective memory loss with corroboration by a family member or friend, no deficits in ADL, no dementia | Five outpatient clinics in southern Ontario, and a local nursing home | No difference in sensitivity to MCI and dementia between the four versions; all discriminated between AD, MCI & NE participants; 60-second score more sensitive than 30-second score. | Animals, 0–30 s: 2.3, 31–60 s: 1.5, 0–60 s: 3.2<br>Cities & towns, 0–30 s: 1.9, 31–60 s: 1.5, 0–60 s: 2.7<br>Fruits & vegetables, 0–30 s: 1.5, 31–60 s: 1.3, 0–60 s: 2.5<br>Names, 0–30 s: 2.3, 31–60 s: 1.5, 0–60 s: 3.2 |
| Dartigues et al. (1997) | CF (colors, animals, fruits, cities) | Nondemented elderly ($n$=2,726), 59 of whom developed AD in 3-year follow-up | DSM-III-R criteria | Randomly chosen from electoral rolls in Gironde and Dordogne, France | CF was an independent and very good predictor of dementia/AD | |
| de Jager et al. (2003) | CF (fruits & vegetables) | NE ($n$=51)<br>MCI ($n$=29)<br>AD ($n$=60)<br>VCI ($n$=8)<br>VaD ($n$=4) | MCI: Petersen criteria<br>AD: NINCDS-ADRDA criteria<br>VCI: Hachinski criteria<br>VaD: NINCDDS/AIREN criteria (G. Gold et al. 1997) | Recruited from the Oxford Project To Investigate Memory and Ageing (OPTIMA) study | NE > MCI > AD<br>CVD (VaD+VCI) also exhibited deficits | NE vs. MCI: 0.74<br>MCI vs. AD: 1.48<br>NE vs. CVD: 1.32 |



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**APPENDIX A**
(*Continued*)

| *Authors* | *Test used* | *Groups+sample sizes* | *Diagnostic criteria used* | *Recruitment procedure* | *Significant effects* | *Effect sizes (Cohen's d)* |
|---|---|---|---|---|---|---|
| Devanand et al. (1997) | LF & CF | QD ($n$=62), 26 of whom went on to develop dementia | QD: cognitive impairment, fall between "normal" and "dementia" categories<br>Dementia: DSM-III<br>criteria AD: NINCDS-ADRDA criteria | Memory Disorders Clinic | Baseline performance on CF: nonconverters > converters; sensitivity=59.3%, specificity=55.6%; PPV=57.1%, NPV=57.7% | 0.64 |
| Devanand et al. (2006) | CF | MCI ($n$=23), 6 of whom went on to develop dementia | Age ≥ 40; impairment 6 months to 10 years; no dementia; MMSE ≥ 22; objective memory impairment OR subjective memory decline corroborated by informant; +ve score on at least one of the first eight items of the modified Blessed Functional Activity Scale (Blessed et al., 1968). | Memory Disorders Clinic | CF did not predict AD | |
| Dudas et al. (2005) | LF (FAS) & CF (living & manmade) | NE ($n$=29)<br>MCI ($n$=24)<br>AD ($n$=22) | Petersen criteria | Memory Clinic at Addenbrooke's Hospital, Cambridge | CF: NE > MCI > AD<br>LF: no significant effects | CF living: NE vs. MCI, 1.75; MCI vs. AD, 1.16<br>CF manmade: NE vs. MCI, 1.05; MCI vs. AD, 1.42 |
| Dwolatzky et al. (2003) | LF (F,A,S) & CF (animals) | NE ($n$=15)<br>MCI ($n$=20)<br>AD ($n$=19) | Petersen criteria | Memory clinics | NE > MCI on all tests; best discriminant was LF (F,S) | |
| Fabrigoule et al. (1998) | CF (colors, animals, fruits, cities) | nondemented elderly ($n$=1,159), 25 of whom developed dementia at 2 years (AD, n=16) | NINCDS-ADRDA criteria | Individuals randomly selected from electoral lists | Non-converters > Converters | 1.58 |

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|---|---|---|---|---|---|---|
| Fillenbaum et al. (2005) | CF (animals) | NE: $n=201$ (Seattle), $n=120$ (Hawaii)<br>CDR = 0.5: $n=33$ (Seattle), $n=65$ (Hawaii)<br>CDR = 1: $n=37$ (Seattle), $n=97$ (Hawaii)<br>CDR = 2: $n=33$ (Seattle), $n=55$ (Hawaii)<br>CDR = 3,4,5: $n=46$ (Seattle), $n=81$ (Hawaii) | CDR score | Seattle: King County telephone directories, Health Care Financing Administration (now CMS) Medicare recipient lists, Japanese-American organizational lists, and word of mouth<br>Hawaii: Japanese-American men born 1900–1919, living in Oahu in 1965, who had been on the World War II Selective Service Registration file | CDR 0 < CDR 0.5 in both populations | |
| Fleisher et al. (2007) | CF | 212 MCI-A individuals who progressed to AD within 36 months | Petersen criteria | Participants in a 36-month randomized drug trial | CF was not a measure in the model that was most predictive of progression to AD | |
| Forbes-McKay et al. (2005) | CF (animals and fruit) | NE ($n=40$)<br>minimal AD ($n=34$)<br>mild AD ($n=39$)<br>moderate AD ($n=23$) | AD: NINCDS-ADRDA criteria<br>minimal: MMSE 24–29<br>mild: MMSE 19–23<br>moderate: MMSE 13–18 | Outpatient diagnostic and management clinic in Aberdeen | AD > NE on number of words<br>Items were of higher frequency, shorter, more typical and had earlier AoA than controls' items | Number of words, NE vs. minimal AD: 1.78; minimal vs. mild: 0.96; mild vs. moderate: 0.29<br>AoA, NE vs. minimal: 1.80 |
| Galvin et al. (2005) | word fluency (type unspecified) | NE ($n=80$) who eventually came to autopsy | CDR score | Individuals enrolled in longitudinal studies of healthy aging and dementia | Baseline: dementia = no dementia<br>Final examination: no dementia > dementia | 1.02 |
| Galton et al. (2005) | CF (animals, fruit, household items) | QD ($n=31$), 11 of whom had converted to AD at 24.2 months<br>AD ($n=19$) | QD: subjective memory impairment, corroborated by an informant; normal ADL; MMSE ≥ 23; CDR = 0.5.<br>AD: NINCDS-ADRDA criteria | Memory Clinic at Addenbrooke's Hospital, Cambridge | nonconverters > converters > AD | nonconverters vs. converters: 1.11 |
| Geslani et al. (2005) | LF (P,R,W) & CF (animals) | MCI ($n=57$) | Petersen criteria + corroboration of memory deficit by physician | Referred by primary-care physicians | No comparison group | |
| Goldman et al. (2001) | LF (S,P) | NE ($n=9$) preclinical AD ($n=5$)<br>AD ($n=10$) | Clinically nondemented, but neuritic and diffuse plaques throughout the neocortex (autopsy findings) | Washington University's Alzheimer's disease Research Centre | No group differences | |

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**APPENDIX A**
(*Continued*)

| *Authors* | *Test used* | *Groups+sample sizes* | *Diagnostic criteria used* | *Recruitment procedure* | *Significant effects* | *Effect sizes (Cohen's d)* |
|---|---|---|---|---|---|---|
| Gómez & White (2006) | LF (S,P) & CF (animals) | NE ($n$=76)<br>very mild AD ($n$=77) | No dementia: CDR=0<br>AD: NINCDS-ADRDA criteria & DSM-III<br>very mild dementia: CDR=0.5 | Media appeals and presentations by researchers | CF: NE > AD in words generated, number of clusters, cluster size and number of switches<br>LF (P): NE > AD in words generated, number of clusters, cluster size and number of switches<br>LF (S): NE > AD in words generated and number of switches | CF: words generated, 1.17; number of clusters, 1.02; cluster size, 0.66; number of switches, 0.93<br>LF (P): words generated, 0.71; number of clusters, 0.52; cluster size, 0.52; number of switches, 0.60<br>LF (S): words generated, 0.61; number of switches, 0.55 |
| Griffith et al. (2006) | LF (C,F,L) & CF (animals, fruits/vegetables, clothing) | NE ($n$=49)<br>MCI ($n$=49) | Petersen criteria | Memory disorders clinic or recruited from community | LF: no effects<br>CF: NE > MCI; nonconverters > converters | CF: NE vs. MCI, 0.73; nonconverters vs. converters, 0.70 |
| Grundman et al. (2004) | CF | NE ($n$=107)<br>MCI ($n$=769) | Petersen criteria, CDR=0.5 | Advertising campaign targeting elderly subjects in cities with Alzheimer Disease Cooperative Study (ADCS) sites | NE > MCI | 0.87 |
| Guarch et al. (2004) | LF (P) | NE ($n$=34)<br>SML ($n$=43), 10 of whom went on to develop AD | Subjective memory loss; neuropsychological tests not used as inclusion/exclusion criteria. | Clinical psychology service at the Hospital Clinic i Provincial, Barcelona. | NE > SML<br>SML: basal=retest<br>basal: nonconverters=converters<br>retest: nonconverters > converters | NE vs. SML: 0.61<br>Nonconverters vs. converters, retest: 0.95 |
| Hanninen et al. (1995) | LF (P,A,S) & CF (animals) | AAMI ($n$=229)<br>At follow-up (3.6 years later on average), 104 AAMIs, 16 dementia cases, 13 mild decline cases and 17 normal memory | AAMI criteria (Crook et al., 1986) | Memory Research Unit of the Department of Neurology at the University of Kuopio in Eastern Finland | Best prediction of dementia used six measures, including both CF and LF.<br>At follow-up, NE > dementia on LF, all groups > dementia on CF. | LF: dementia vs. NE, 1.09; CF: dementia vs. NE, 1.91; dementia vs. AAMI, 1.49; dementia vs. mild decline, 1.64 |
| Hodges, Erzinclioglu, & Patterson (2006) | As Hodges & Patterson (1995) | NE ($n$=24)<br>MCI ($n$=10) | Grundman et al. (2004) criteria | Memory Clinic at Addenbrooke's Hospital, Cambridge | 7/10 MCIs showed deficits at baseline and 8/10 at the end of the first year | |

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| Hodges & Patterson (1995) | CF for six main categories [land animals, sea creatures, birds, household items, vehicles, musical instruments] and two subcategories [breeds of dog, types of boat] | NE ($n$=24)<br>minimal AD ($n$=17)<br>mild AD ($n$=52)<br>moderate AD ($n$=18) | NINCDS-ADRDA criteria | Memory Clinic at Addenbrooke's Hospital, Cambridge | NE > minimal > mild > moderate on all subtests | Living: NE vs. minimal AD, 2.0; minimal AD vs. mild AD, 0.7; mild AD vs. moderate AD, 1.37<br>Man-made: NE vs. minimal AD, 2.34; minimal AD vs. mild AD, 0.47; mild AD vs. moderate AD, 1.94 |
| Jacobs et al. (1995) | LF & CF | Nondemented elderly ($n$=443), 41 of whom had developed AD at follow-up (on average 2.05 years later) | NINCDS-ADRDA criteria | North Manhattan Aging Project, a community-based, epidemiologic study of dementia in northern Manhattan, NY. | No significant effects reported | |
| Jones et al. (2006) | LF (N,S) & CF (grocery store items) | NE ($n$=267)<br>preclinical AD ($n$=66)<br>preclinical VaD ($n$=20) | DSM-III-R and Hachinski Ischemic Scale (Hachinski et al., 1974). | All inhabitants of Kungsholmen, Sweden, aged ≥75 on October 1st, 1987 invited to participate | LF: preclinical AD = preclinical VaD<br>CF: preclinical AD < preclinical VaD | LF: AD vs. NE, 0.56<br>CF: AD vs. VaD, 0.52; AD vs. NE, 0.65 |
| Jorm et al. (2005) | CF (4-legged animals) | Japanese-American men aged 71–93 ($n$=1611), 52 of whom went on to develop dementia | DSM III-R | Recruited from population | Predicted incident dementia up to 3 years before onset but not 3–6 years before onset. | 0.65 |
| Kalbe et al. (2004) | CF (supermarket) | NE ($n$=145)<br>MCI ($n$=97)<br>AD ($n$=121) | NE: CDR=0<br>MCI: Petersen criteria<br>AD: NINCDS-ADRDA criteria; CDR=1 or 2 | Memory Clinic | NE > MCI > AD | NE <60 years vs. NE ≥60 years: 0.30<br>NE ≥60 years vs. MCI: 1.25<br>MCI vs. AD (MMSE≥21): 0.99<br>AD (MMSE≥21) vs. AD (MMSE<21): 0.61 |
| Karrasch et al. (2005) | CF | NE ($n$=15)<br>MCI ($n$=15)<br>AD ($n$=15) | Petersen criteria | Community sources | NE>AD, not MCI | |
| Lam et al. (2006) | CF (animals, fruit, vegetables) – 30-second and 60-second scores | NE ($n$=118)<br>QD ($n$=150)<br>mild AD ($n$=63) | NE: CDR=0<br>QD: CDR=0.5<br>mild AD: CDR=1 | Community social centres and residential hostels for the elderly in Hong Kong | NE > QD > mild AD for both 30-second and 60-second scores | 30-second: NE vs. QD, 1.07; QD vs. AD, 1.10<br>60-second: NE vs. QD, 1.11; QD vs. AD, 1.16 |

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**APPENDIX A**
(*Continued*)

| *Authors* | *Test used* | *Groups + sample sizes* | *Diagnostic criteria used* | *Recruitment procedure* | *Significant effects* | *Effect sizes (Cohen's d)* |
|---|---|---|---|---|---|---|
| Lambon Ralph et al. (2003) | As Hodges & Patterson (1995) | NE ($n$=48)<br>MCI ($n$=17)<br>mild AD ($n$=22)<br>moderate AD ($n$=8)<br>severe AD ($n$=8) | Subjective memory impairment, corroborated by a spouse/ family member; preservation of ADL; impairment on at least one test of memory; normal performance on tests of language, visuospatial and executive function; MMSE > 24. | Memory Clinic at Addenbrooke's Hospital, Cambridge | NE=MCI > AD (defined as >2 *SD* difference) | |
| Laukka et al. (2004) | LF (N,S) & CF (food items) | NE ($n$=149)<br>incident AD ($n$=43)<br>incident VaD ($n$=15) | DSM-III-R<br>Hachinski Ischemic Scale (Hachinski et al., 1974). | All inhabitants of Kungsholmen, Sweden, aged ≥75 on October 1st, 1987 invited to participate | NE > AD=VaD | CF: NE vs. AD, 0.85<br>LF: NE vs. AD, 0.76 |
| Lee et al. (2006) | CF (animals) | QD ($n$=72), 14 of whom progressed to AD in 3 years | CDR=0.5 | One public health center and 2 memory clinics in Korea | nonconverters=converters | |
| López et al. (2006) | CF (animals, birds, dogs) | NE ($n$=374)<br>MCI-A ($n$=10)<br>MCI-MD ($n$=28) | MCI-A: >1.5 *SD*s below controls in delayed recall + decline in cognitive functioning; MCI-MD: >1.5 *SD*s in at least one cognitive domain other than memory/ one abnormal test in ≥2 domains. | 5,201 noninstitutionalized individuals over 65; recruited from four communities using Part A Medicare list in 1988–1989; 687 African-Americans recruited in same manner in 1992–1993 | Animals: MCI-A and MCI-MD < NE<br>Birds and dogs: MCI-MD < NE | Animals, MCI-A vs. NE: 0.94; MCI-MD vs. NE: 0.84<br>Birds, MCI-MD vs. NE: 0.88<br>Dogs, MCI-MD vs. NE: 0.60 |
| Masur et al. (1994) | CF (fruits, animals, flowers and vegetables) | nondemented elderly ($n$=317), 64 of whom developed dementia in a follow-up of at least 4 years | Dementia: DSM-III<br>AD: NINCDS-ADRDA criteria | Recruited from community | Actuarial model including delayed recall, CF, the FOME (Fuld, 1981) and the WAIS Digit Symbol subtest (Wechsler, 1955) can identify subgroups with very low/very high chance of developing dementia. | |
| Meguro et al. (2004) | CF (4-legged animals) | NE ($n$=968)<br>CDR 0.5, AD ($n$=95)<br>CDR 0.5, UD ($n$=94)<br>CDR 0.5, ID ($n$=227)<br>CDR 0.5, others ($n$=37)<br>CDR 1 and 2 ($n$=80) | UD: only memory is impaired<br>ID: impairment in memory and ≤2 other cognitive domains<br>others: impairment in memory and ≥3 other cognitive domains<br>Dementia: DSM-III-R | All older residents in Tajiri were targeted | CDR 0 < CDR 0.5 < CDR < 1 and 2<br>CDR 0.5 (DAT) < other CDR 0.5 categories | CDR 0 vs. 0.5: 0.32<br>CDR 0.5 vs. 1&2: 1.20<br>CDR 0.5 (AD vs. UD): 0.77<br>CDR 0.5 (AD vs. ID): 0.67<br>CDR 0.5 (AD vs. others): 0.78 |

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| Mioshi et al. (2006) | CF (animals, fruit, household items) | NE ($n$=63)<br>MCI ($n$=36)<br>AD ($n$=67)<br>LBD ($n$=20)<br>FTD ($n$=55) | MCI: Grundman et al. (2004) criteria<br>AD: NINCDS-ADRDA criteria<br>LBD: McKeith et al. (2000)<br>FTD: Neary et al. (1998) | Memory Clinic, Early Onset Dementia Clinic and Drug Monitoring Clinic at Addenbrooke's Hospital, Cambridge | NE > MCI > dementia | NE vs. MCI, 0.9; MCI vs. dementia, 1.23 |
| Morris et al. (2001) | LF (S,P) | NE ($n$=177)<br>uAD ($n$=53)<br>iAD ($n$=69)<br>AD ($n$=105) | NE: CDR=0<br>MCI: CDR=0.5<br>iAD: CDR=0.5<br>AD: CDR=0.5; clinical criteria described in Morris, McKeel, Fulling, Torack & Berg, 1988a | Recruited through media | No group effects | |
| Murphy et al. (2006) | LF (F) & CF (animals) | NE ($n$=46)<br>MCI-A ($n$=33)<br>AD ($n$=33) | MCI-A: Petersen (2004) criteria<br>AD: NINCDS-ADRDA criteria | Physician referrals and newspaper advertisements | LF: NE > AD<br>CF: NE > MCI-A > AD | CF: NE vs. MCI-A, 0.49; NE vs. AD, 1.07; MCI-A vs. AD, 0.68 |
| Nielsen et al. (1999) | CF (animals) | Nondemented elderly ($n$=2,452), 102 of whom developed dementia in 2 years | NINCDS-ADRDA criteria | Randomly drawn from the population | NE > incident AD | 0.67 |
| Nordlund et al. (2005) | LF (F,A,S) | NE ($n$=35)<br>MCI ($n$=112) | Subjective and objective memory impairment > 6 months; positive outcome on stepwise comparative status analysis (STEP, Wallin et al., 1996), I-Flex (Royall et al., 1992), MMSE or CDR; MMSE ≥25; not more than 2 +ve outcomes on STEP | Memory clinic | NE=MCI | |
| Östberg et al. (2005) | LF (FAS), CF (animals) & verb fluency | SCI ($n$=40)<br>MCI ($n$=60)<br>AD ($n$=57) | MCI: Petersen criteria<br>AD: DSM-IV | Dept of Geriatrics, Huddinge University Hospital, due to cognitive complaints | Overall: SCI > MCI > AD<br>CF: SCI > MCI > AD<br>LF: SCI=MCI > AD<br>Verb fluency: SCI > MCI > AD | |
| Perry et al. (2000) | CF (animals, birds, water creatures, household items, vehicles, musical instruments) | NE ($n$=44)<br>minimal AD ($n$=13)<br>mild AD ($n$=14) | NINCDS-ADRDA criteria<br>minimal: MMSE=24–30<br>mild: MMSE=18–23 | Patients undergoing evaluation at the University of Cambridge Neurology unit | NE > minimal AD > mild AD | NE vs. minimal AD: 1.42; minimal AD vs. mild AD: 1.15 |
| Petersen et al. (1999) | LF | NE ($n$=234)<br>MCI ($n$=76)<br>mild AD ($n$=106) | MCI: memory complaint; normal ADL; normal general cognitive function; abnormal memory for age; not demented; CDR=0.5.<br>mild AD: CDR=0.5–1.0 | Community (subjects receiving general medical care at Mayo Clinic) and regional (evaluation of cognitive difficulties at Mayo Alzheimer's Disease Center) | NE > MCI=AD | NE vs. MCI: 5.86 |



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**APPENDIX A**
(*Continued*)

| *Authors* | *Test used* | *Groups+sample sizes* | *Diagnostic criteria used* | *Recruitment procedure* | *Significant effects* | *Effect sizes (Cohen's d)* |
|---|---|---|---|---|---|---|
| Ribeiro et al. (2006) | CF (food products) | NE ($n$=63)<br>MCI ($n$=116) | Subjective memory complaints; ≥1.5 SD below normal on delayed recall; preserved ADL; maintained professional, social and familial activities, score <3 on the first part of the Blessed Dementia Scale; preserved general cognitive function. | Dementia Outpatient Clinic, Hospital Santa Maria, and a Memory Clinic, Lisbon | NE > AACD<br>NE > AAMI | |
| Richards et al. (1999) | Combined score of LF (P) and CF (vegetables) | 111 individuals, classified as NE ($n$=74), AAMI ($n$=37), or AACD ($n$=39). | AAMI: memory impairment, no dementia<br>AACD: impairment in one domain: memory/learning, attention/ concentration, visuospatial reasoning, language, visuospatial function | Randomly recruited from 600 general medical practices in southern France | NE > AACD<br>NE > AAMI | AAMI: 0.61<br>AACD: 0.64 |
| Rubin et al. (1998) | LF (P,S) | NE ($n$=82), 10 of whom went on to develop AD, 6 iAD, and 11 uncertain dementia | CDR > 0 | Recruited from the community | No significant differences. | |
| Saxton et al. (2004) | LF (P,S) & CF (fruit) | Nondemented elderly ($n$=693), 72 of whom developed AD within 1.5–8 years (1.5–3.4 years: $n$=24; 3.5–5.0 years: $n$=20; 5.1–8.1 years: $n$=28) | NINCDS-ADRDA criteria | Selected from participants recruited from the community as part of the Cardiovascular Health Study. | CF significant predictor of AD up to 5 years prior to diagnosis. | |
| Schmidtke & Hermeneit (2007) | CF (animals) | MCI ($n$=88); 75 available for follow-up | Petersen criteria | Memory clinic | Nonconverters=converters, although $z$-score was low (–0.9) for entire MCI sample | |
| Small et al. (1997) | LF (N,S) & CF (food) | NE ($n$=179)<br>incident AD ($n$=26) | Dementia: DSM-IV criteria; type assessed by standardized criteria | All inhabitants of Kungsholmen, Sweden, aged ≥75 on October 1st, 1987 invited to participate | Baseline scores: NE > incident AD for both CF and LF | LF: 0.81<br>CF: 0.82 |
| Standish et al. (2007) | CF | NE ($n$=174)<br>MCI ($n$=166)<br>dementia ($n$=302) | Dementia: DSM-IV<br>AD: NINCDS-ADRDA criteria<br>MCI: Petersen criteria | Specialty geriatric clinics in southern Ontario | NE > MCI > dementia | |

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|---|---|---|---|---|---|---|
| Swainson et al. (2001) | LF (F,A,S) & CF (animals, fruits, household items) | NE ($n$=39)<br>QD ($n$=43)<br>mild AD ($n$=26)<br>MD ($n$=37) | QD: memory impairment but not meeting criteria for dementia/depression<br>AD: NINCDS-ADRDA criteria<br>MD: DSM-IV | Memory clinic, Addenbrooke's Hospital; Psychiatry Department, West Suffolk Hospital; Mental Health Services, Addenbrooke's NHS Trust | CF: QD+MD+NE > AD; MD+NE > QD; NE > MD<br>LF: QD+MD+NE > AD<br>No significant correlation between baseline performance and MMSE decline in QD individuals | |
| Tabert et al. (2006) | ANT (Goodglass & Kaplan, 1983)<br>LF (C,F,L) | NE ($n$=83)<br>MCI ($n$=148) | Age ≥40; cognitive impairment for 6 months–10 years; CDR 0–0.5.<br>For memory: MMSE, SRT, WAIS–R performance IQ.<br>If no formal cognitive deficit: subjective memory decline, positive score on 1 or more of the first 8 items of the modified Blessed Functional Activity Scale. | Memory disorders clinic; NE recruited by advertisement | NE > MCI<br>Nonconverters > converters | ANT: NE vs. MCI, 0.72; Nonconverters vs. converters, 0.59<br>LF: NE vs. MCI, 0.43; Nonconverters vs. converters, 0.72 |
| Tian et al. (2003) | LF | QD ($n$=195), 135 seen for followup at 24.5 months; 37 converted to dementia | Objective evidence of cognitive impairment but no dementia | Bristol Memory Disorders Clinic | Nonconverters > converters | 0.40 |
| Touchon & Ritchie (1999) | LF (P) & CF (vegetables) | NE ($n$=150)<br>359 initially nondemented individuals: 22 developed AD in third year | Dementia: DSM-III-R<br>AD: NINCDS-ADRDA criteria | General practitioner recruitment network | CF: NE > MCI 2 years prior to diagnosis, independent of education effects<br>LF: NE > MCI, but interacted significantly with education. | CF: 2.04<br>LF: 1.51 |
| Vogel et al. (2005) | CF (animals) | NE ($n$=58)<br>predementia AD ($n$=22)<br>mild AD ($n$=102) | AD: NINCDS-ADRDA criteria<br>predementia AD: Petersen criteria+subsequent progression to AD (10–30 months later) | Copenhagen University Hospital Memory Clinic | NE > predementia AD > AD | |
| Wang et al. (2006) | CF (4-legged animals) | NE ($n$=20)<br>MCI ($n$=58)<br>AD ($n$=20) | MCI: Petersen criteria<br>AD: NINCDS-ADRDA criteria | Neurological clinics | NE > MCI > AD | NE vs. MCI: 1.25<br>MCI vs. AD: 0.59 |

*Note.* Effect sizes are reported where possible. AAMI=age-associated memory impairment. AD=Alzheimer's disease. ADL=activities of daily living. ANT=Animal Naming Test. AoA=age of acquisition. CDR=Clinical Dementia Rating Scale. CF=category fluency. CVD=cerebrovascular disease. DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders—Third Edition, Revised. FOME = Fuld Object Memory Evaluation. iAD=incipient AD. ID=incipient dementia. IMI=isolated memory impairment. LBD=Lewy body dementia. LF=letter fluency. MCI=mild cognitive impairment. MCI-A=MCI-amnestic. MCI-MD=MCI-multiple domain. MD=major depressive disorder. MMSE=Mini Mental State Examination. NE=normal elderly. NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association. qAD=questionable Alzheimer's disease. QD=questionable dementia. SCI=subjective cognitive impairment. SML=subjective memory loss. SRT = Buscke Selective Reminding Tests. UD=uncertain dementia. VaD=vascular dementia. VCI=vascular cognitive impairment. WAIS-R=Wechsler Adult Intelligence Scale–Revised.

**APPENDIX B**

Published studies reporting naming performance in MCI and preclinical AD

| *Authors* | *Test used* | *Groups + sample sizes* | *Diagnostic criteria* | *Recruitment procedure* | *Significant effects* | *Effect sizes (Cohen's d)* |
|---|---|---|---|---|---|---|
| Adlam et al. (2006) | naming 64 line drawings | NE ($n$=30)<br>MCI ($n$=10)<br>mild AD ($n$=11) | MCI: Petersen criteria<br>AD: NINCDS-ADRDA criteria | Memory Clinic at Addenbrooke's Hospital, Cambridge | NE=MCI > AD | MCI vs. AD: 0.82 |
| Aggarwal et al. (2005) | BNT (20 items) | MCI ($n$=218), 82 of whom went on to develop AD | MCI: cognitive impairment but do not meet NINCDS-ADRDA criteria for dementia<br>AD: NINCDS-ADRDA criteria | Catholic clergy who agreed to participate | Reduced semantic memory (composite score of BNT, Extended Range Vocabulary, NART) predicted AD (relative risk=0.62); however, episodic memory impairment stronger predictor | |
| Albert et al. (2001) | BNT (15 items) | Baseline:<br>NE ($n$=42)<br>qAD ($n$=123)<br>3 year follow-up:<br>NE ($n$=32)<br>stable qAD ($n$=91)<br>qAD who converted to AD ($n$=23) | NE: CDR=0<br>qAD: CDR=0.5<br>AD: CDR=1 | Print media | No significant effects | |
| Albert et al. (2007) | BNT (15 items) | NE ($n$=33)<br>Individuals with memory impairment, stable over 3 years ($n$=22)<br>NE/impaired at baseline and declined over 3 years ($n$=95)<br>NE/impaired at baseline and converted to dementia ($n$=47) | NE: CDR-SB=0<br>memory impairment: CDR-SB between 0.5 and 3 | Print media | No significant effects | |
| Artero et al. (2003) | object naming | 128 individuals with cognitive difficulties | Cognitive difficulties ascertained using the Détérioration Cognitive Observée (DECO) screening instrument (Ritchie & Fuhrer, 1992) | Identified via a regional general practitioner network | Naming not included in best predictive model for AD. | |
| Beinhoff et al. (2005) | BNT (15 items) | NE ($n$=57)<br>MCI ($n$=48)<br>AD ($n$=66)<br>MD ($n$=61) | MCI: Petersen criteria<br>AD: NINCDS-ADRDA criteria<br>MD: DSM-IV criteria. | Memory clinic | NE=MD=MCI > AD | |
| Bennett et al. (2002) | BNT (15 items) | NE ($n$=587)<br>MCI ($n$=211) | Cognitive impairment, but does not meet accepted criteria for dementia | Catholic clergy who agreed to participate | Baseline: NE > MCI<br>MCIs declined >2 times as fast on semantic memory measures (including BNT) | 0.85 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Beversdorf et al. (2007) | BNT | NE ($n$=20)<br>MCI ($n$=26) | MCI: MMSE≥24, CDR=0.5 | Memory clinic | NE > MCI, but BNT was not the best predictor | 0.75 |
| Blackwell et al. (2004) | GNT, semantic battery test (naming line drawings) | Subjective/objective memory loss ($n$=43), 11 of whom developed AD within 32 months | Normal performance on tests of language and visuospatial function, preserved ADL, CDR=0.5 | Memory clinic | Nonconverters > converters on both measures | GNT: 1.65<br>Semantic Battery test: 1.08 |
| Bozoki et al. (2001) | BNT | IMI ($n$=48) | Petersen criteria+neuropsychological evidence (diagnostic criteria and cognitive measures for clinical change based on those proposed for AAMI) | Michigan Alzheimer's Disease Research Center | BNT discriminated best between converters and nonconverters, although not significant ($p$=.16); 42% of converters and 14% of nonconverters had abnormal results | |
| Bschor et al. (2001) | BNT | NE ($n$=40)<br>MCI ($n$=34)<br>mild DAT ($n$=21)<br>moderate to severe DAT ($n$=20) | ICD-10 criteria (Zaudig, 1992) | Memory Clinic at the Dept. of Gerontology, Freie Universität Berlin | NE > MCI > mild AD > moderate AD | NE vs. MCI: 1.29<br>MCI vs. mild AD: 1.17<br>mild AD vs. moderate AD: 1.19 |
| Busse et al. (2003) | Composite aphasia/apraxia score (naming objects, reading and obeying a sentence, writing a sentence, and performing a three-stage command) | nondemented elderly ($n$=1,045), 3% of whom met the criteria for MCI-A, 36% for MMSE≥26, 9% for AACD and 20% for AACD-m | MCI-A: Petersen criteria<br>AACD: Levy (1994) criteria<br>AACD-m: Levy criteria, but no requirement for subjective memory complaint<br>Dementia: DSM-IV | Random sampling from list provided by the local registry office in Leipzig | No group differences; language score not a significant predictor | |
| Caccapolo-Van Vliet et al. (2003) | BNT | NE ($n$=230)<br>QD ($n$=155)<br>mild AD ($n$=244)<br>moderate AD ($n$=480)<br>severe AD ($n$=376)<br>very severe AD ($n$=247) | QD: cognitive impairment sufficient or close to sufficient for a diagnosis of dementia; no functional impairment<br>AD: NINCDS-ADRDA criteria | Memory Disorders Center/recruited for a study of NE. | NE=QD=mild AD > moderate AD > severe AD > very severe AD | |
| Chen et al. (2000) | BNT (15 items) | NE ($n$=483)<br>Converters to AD 1.5 years after testing ($n$=120) | NINCDS-ADRDA criteria | Randomly selected from voter registration lists | NE > incident AD; however, not a better predictor of incident dementia than the MMSE | 0.65 |
| Chen et al. (2001) | BNT (15 items) | NE ($n$=551), 68 of who went on to develop AD | NINCDS-ADRDA criteria | Randomly selected from voter registration lists | Nonconverters=converters | |



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**APPENDIX B**
(*Continued*)

| *Authors* | *Test used* | *Groups+sample sizes* | *Diagnostic criteria* | *Recruitment procedure* | *Significant effects* | *Effect sizes (Cohen's d)* |
|---|---|---|---|---|---|---|
| Collie et al. (2002) | naming of 15 line drawings | Elderly adults ($n$=174), 23 of whom were impaired on 3 consecutive assessments | CERAD battery (Morris et al., 1988b) | Recruited from an ongoing study on aging at an independent research institute in Melbourne, Australia. | NE > MCI | 0.77 |
| Croot et al. (1999) | Naming (as Hodges & Patterson, 1995) | NE ($n$=46)<br>minimal AD ($n$=16)<br>mild AD ($n$=16)<br>moderate AD ($n$=14) | NINCDS-ADRDA criteria<br>minimal: MMSE=24–30<br>mild: MMSE=18–23<br>moderate: MMSE=2–17 | Memory Clinic at Addenbrooke's Hospital, Cambridge | $p$-value not reported | |
| De Jager & Budge (2005) | GNT | Baseline:<br>NE ($n$=117)<br>MCI ($n$=40)<br>3-year followup:<br>NE ($n$=85)<br>MCI ($n$=49) | MCI: >1.5 *SD* below control mean on memory testing | Talks/radio advertising in Oxfordshire for those who thought that their health, memory and thinking were good compared to their peers | Classification at 4 years was predicted by GNT | |
| De Jager et al. (2003) | BNT (30 items) | NE ($n$=51)<br>MCI ($n$=29)<br>AD ($n$=60)<br>VCI ($n$=8)<br>VaD ($n$=4) | MCI: Petersen criteria<br>AD: NINCDS-ADRDA criteria<br>VCI: Hachinski criteria<br>VaD: NINCDDS/AIREN criteria (G. Gold et al., 1997) | Oxford Project To Investigate Memory and Ageing (OPTIMA) study | NE > MCI > AD; CVD (VCI+VaD) also exhibited impairments | NE vs. MCI: 0.54<br>MCI vs. AD: 1.15<br>NE vs. CVD: 0.89 |
| Devanand et al. (1997) | BNT | QD ($n$=62), 26 of whom went on to develop dementia | QD: cognitive impairment, fall between "normal" and "dementia" categories<br>Dementia: DSM-III criteria<br>AD: NINCDS-ADRDA criteria | Memory Disorders Clinic | No significant effects | |
| Dudas et al. (2005) | Naming Test (Hodges et al., 1992b) and GNT | NE ($n$=29)<br>MCI ($n$=24)<br>AD ($n$=22) | Petersen criteria | Memory Clinic at Addenbrooke's Hospital, Cambridge | NE > MCI=AD | Naming:<br>NE vs. MCI, 1.42; MCI vs. AD, 0.64<br>GNT:<br>NE vs. MCI, 0.63; MCI vs. AD, 1.20 |
| Dwolatzky et al. (2003) | BNT | NE ($n$=15)<br>MCI ($n$=20)<br>AD ($n$=19) | Petersen criteria | Memory clinics | BNT discriminated between MCI and healthy elderly | |

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|---|---|---|---|---|---|---|
| Fillenbaum et al. (2005) | BNT (15 items) | NE: $n=201$ (Seattle), $n=120$ (Hawaii)<br>CDR = 0.5: $n=33$ (Seattle), $n=65$ (Hawaii)<br>CDR = 1: $n=37$ (Seattle), $n=97$ (Hawaii)<br>CDR = 2: $n=33$ (Seattle), $n=55$ (Hawaii)<br>CDR = 3,4,5: $n=46$ (Seattle), $n=81$ (Hawaii) | CDR score | Seattle: King County telephone directories, Health Care Financing Administration (now CMS) Medicare recipient lists, Japanese-American organizational lists, and word of mouth<br>Hawaii: Japanese-American men born 1900–1919, living in Oahu in 1965, who had been on the World War II Selective Service Registration file | CDR 0 < CDR 0.5 in both populations | |
| Fleisher et al. (2007) | BNT (10 items) | MCI-A who progressed to AD within 36 months ($n=212$) | Petersen criteria | Participants in a 36-month randomized drug trial | BNT was not a measure in the model that was most predictive of progression to AD | |
| Flicker et al. (1991) | object naming | NE ($n=32$)<br>Mildly impaired ($n=32$) | GDS rating of 3 | Selected from participants in aging studies at the Aging and Dementia Research Center, NYU Medical Center | NE > Mildly impaired | 0.79 |
| Galvin et al. (2005) | BNT | NE ($n=80$) who eventually came to autopsy | CDR score | Individuals enrolled in longitudinal studies of healthy aging and dementia | Baseline: dementia = no dementia<br>Final examination: no dementia > dementia | 1.32 |
| Galton et al. (2005) | PN (Cambridge Semantic Battery, Hodges & Patterson, 1995)<br>GNT | QD ($n=31$) 11 of whom had converted to AD at 24.2 months<br>AD ($n=19$) | AD: NINCDS-ADRDA criteria<br>QD: subjective memory impairment, corroborated by an informant; normal ADL; MMSE ≥ 23. CDR = 0.5. | Memory Clinic at Addenbrooke's Hospital, Cambridge | PN: AD < nonconverters<br>GNT: AD < converters < nonconverters | PN: Nonconverters vs. AD, 1.40<br>GNT: Nonconverters vs. converters, 2.18<br>Converters vs. AD, 0.76 |
| Geslani et al. (2005) | BNT (odd-even version) | MCIs ($n=161$) | Petersen criteria + corroboration of memory deficit by physician | Referred by primary-care physicians | Average score: 32.8 ± 9.44 (no comparison group) | |
| Goldman et al. (2001) | BNT | NE ($n=9$)<br>preclinical AD ($n=5$)<br>AD ($n=10$) | Clinically nondemented, but neuritic and diffuse plaques throughout the neocortex (autopsy findings) | Washington University's Alzheimer's disease Research Centre | NE = preclinical AD > very mild AD | Preclinical AD vs. very mild AD: 1.1 |

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**APPENDIX B**
(*Continued*)

| *Authors* | *Test used* | *Groups + sample sizes* | *Diagnostic criteria* | *Recruitment procedure* | *Significant effects* | *Effect sizes ( Cohen's d)* |
|---|---|---|---|---|---|---|
| Gómez & White (2006) | BNT | NE ($n$=76)<br>very mild AD ($n$=77) | NE: CDR = 0<br>very mild AD: NINCDS-ADRDA & DSM-III criteria; CDR = 0.5 | Media appeals and presentations by researchers | NE > very mild AD | 0.77 |
| Griffith et al. (2006) | BNT (15 items) | NE ($n$=49)<br>MCI ($n$=49) | Petersen criteria | Memory Disorders Clinic or recruited from community | NE = MCI | |
| Grundman et al. (2004) | BNT (15 items) | NE ($n$=107)<br>MCI ($n$=769) | Petersen criteria + CDR = 0.5 | Advertising campaign targeting elderly subjects in cities with Alzheimer Disease Cooperative Study (ADCS) sites | NE > MCI | 0.51 |
| Guarch et al. (2004) | BNT | NE ($n$=34)<br>SML ($n$=43), 10 of whom went on to develop AD | Subjective memory loss; neuropsychological tests not used as inclusion/exclusion criteria. | Clinical psychology service at the Hospital Clinic i Provincial, Barcelona. | NE > SML<br>SML: basal = retest<br>basal: nonconverters = converters<br>retest: nonconverters > converters | NE vs. SML: 0.89<br>Nonconverters vs. converters, retest: 1.56 |
| Hodges, Erzinçlioğlu, & Patterson (2006) | naming 64 line drawings | NE ($n$=24)<br>MCI-A ($n$=10) | Grundman et al. (2004) criteria | Memory Clinic at Addenbrooke's Hospital, Cambridge | NE = MCI-A even after 7 years of follow-up | |
| Hodges & Patterson (1995) | naming 64 line drawings | NE ($n$=24)<br>minimal AD ($n$=17)<br>mild AD ($n$=17), moderate AD ($n$=18) | NINCDS-ADRDA criteria | Memory Clinic at Addenbrooke's Hospital, Cambridge | NE > minimal = mild > moderate | |
| Hodges et al. (1996) | Naming of 48 line drawings | NE ($n$=10)<br>minimal AD ($n$=16)<br>mild AD ($n$=17)<br>moderate AD ($n$=18) | AD: NINCDS-ADRDA criteria<br>minimal: MMSE = 24–30<br>mild: MMSE = 18–23<br>moderate: MMSE = 2–17 | Memory Clinic at Addenbrooke's Hospital, Cambridge | NE > minimal = mild > moderate | |
| Hudon et al. (2006) | Dénomination orale d'images (Deloche & Hannequin, 1997) | NE ($n$=22)<br>MCI ($n$=14)<br>AD ($n$=14) | MCI: MCI-SD/MCI-MD, Petersen (2004) criteria | Memory clinics | NE = MCI > AD | NE vs. AD: 0.88<br>MCI vs. AD: 0.72 |

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|---|---|---|---|---|---|---|
| Jacobs et al. (1995) | BNT (15 items) | nondemented elderly ($n$=443), 41 of whom had developed AD at follow-up (on average 2.05 years later) | NINCDS-ADRDA criteria | North Manhattan Aging Project, a community-based, epidemiologic study of dementia in northern Manhattan, NY. | BNT significantly associated with increased risk of developing AD. | |
| Jacobson et al. (2002) | BNT | NE ($n$=20)<br>preclinical AD ($n$=20) | preclinical AD: either mild subjective memory complaints without functional impairment ($n$=9) or an abnormality in the participant's neurological examination ($n$=11). Did not meet NINCDS-ADRDA criteria for AD | Alzheimer's Disease Research Center at UCSD. | Best predictor was difference scores between naming (BNT) and visuoconstruction abilities (WAIS Block design), not raw BNT score; 10/20 preclinical AD individuals and 5/20 controls had asymmetric profiles | |
| Karrasch et al. (2005) | CERAD naming subtest | NE ($n$=15)<br>MCI ($n$=15)<br>AD ($n$=15) | Petersen criteria | Community sources | NE > AD, not MCI | |
| Lambon Ralph et al. (2003) | naming 64 line drawings | NE ($n$=48)<br>MCI ($n$=17)<br>mild AD ($n$=22)<br>moderate AD ($n$=8)<br>severe AD ($n$=8) | Subjective memory impairment, corroborated by a spouse/family member; preservation of ADL; impairment on at least one test of memory; normal performance on tests of language, visuospatial and executive function; MMSE >24. | Memory Clinic at Addenbrooke's Hospital, Cambridge | NE=MCI | |
| Lee et al. (2006) | BNT (15 items) | QD ($n$=72), 14 of whom progressed to AD in 3 years | CDR=0.5 | One public health center and 2 memory clinics in Korea | Nonconverters=converters | |
| López et al. (2006) | BNT | NE ($n$=374)<br>MCI-A ($n$=10)<br>MCI-MD ($n$=28) | MCI-A: >1.5 SDs below controls in delayed recall+decline in cognitive functioning; MCI-MD >1.5 SDs in at least one cognitive domain other than memory/one abnormal test in ≥2 domains. | 5201 noninstitutionalized individuals over 65; recruited from four communities using Part A Medicare list in 1988–1989; 687 African-Americans recruited in same manner in 1992–1993 | NE > MCI-A > MCI-MD | NE vs. MCI-A: 0.19<br>NE vs. MCI-MD: 1.40<br>MCI-MD vs. MCI-A: 0.92 |
| Mioshi et al. (2006) | PN (Cambridge Semantic Battery, Hodges & Patterson, 1995)<br>GNT | NE ($n$=63)<br>MCI ($n$=36)<br>AD ($n$=67)<br>DLB ($n$=20)<br>FTD ($n$=55) | MCI: Grundman et al. (2004) criteria<br>AD: NINCDS-ADRDA criteria<br>DLB: McKeith et al. (2000)<br>FTD: Neary et al. (1998) | Memory Clinic, Early Onset Dementia Clinic and Drug Monitoring Clinic at Addenbrooke's Hospital | NE > MCI > dementia | NE vs. MCI, 0.77; MCI vs. dementia, 0.77 |

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**APPENDIX B**
(*Continued*)

| *Authors* | *Test used* | *Groups+sample sizes* | *Diagnostic criteria* | *Recruitment procedure* | *Significant effects* | *Effect sizes ( Cohen's d )* |
|---|---|---|---|---|---|---|
| Morris et al. (2001) | BNT | NE ($n$=177)<br>uAD ($n$=53)<br>iAD ($n$=69)<br>AD ($n$=105) | NE: CDR=0<br>MCI: CDR=0.5<br>uAD: CDR=0.5<br>iAD: CDR=0.5<br>AD: CDR=0.5; clinical criteria described in Morris, McKeel, Fulling, Torack & Berg, 1988a | Recruited through the media | NE > uAD > iAD > AD | NE vs. iAD: 0.44<br>uAD vs. iAD: 0.25<br>iAD vs. AD: 0.24 |
| Nestor et al. (2003) | 64-item naming test (Bozeat et al., 2000) | Controls ($n$=15), MCIs ($n$=10); ADs ($n$=10) | MCI: insidious onset memory symptoms, objective memory impairment, no other significant deficits<br>AD: NINCDS-ADRDA criteria | Memory Clinic | MCI > AD | |
| Nielsen et al. (1999) | Naming subtest of CAMCOG | Nondemented elderly ($n$=2,452), 102 of whom developed dementia in 2 years | DSM-III-R criteria, NINCDS-ADRDA criteria | Randomly drawn from the population | Nondemented > incident demented | 0.83 |
| Nordlund et al. (2005) | BNT | NE ($n$=35)<br>MCI ($n$=109) | Subjective and objective memory impairment > 6 months; positive outcome on stepwise comparative status analysis (STEP, Wallin et al., 1996), I-Flex (Royall et al., 1992), MMSE or CDR; MMSE ≥25; not more than 2 +ve outcomes on STEP | Memory clinic | NE > MCIs | 0.60 |
| Petersen et al. (1999) | BNT | NE ($n$=234)<br>MCI ($n$=76)<br>mild AD ($n$=106) | MCI: memory complaint; normal ADL; normal general cognitive function; abnormal memory for age; not demented; CDR=0.5.<br>mild AD: CDR=0.5–1.0 | Community (subjects receiving general medical care at Mayo Clinic) AND regional (evaluation of cognitive difficulties at Mayo Alzheimer's Disease Center) | NE > MCI > AD | NE vs. MCI: 7.2<br>MCI vs. AD (CDR 0.5): 6.78 |
| Pyo et al. (2006) | ADAS-Cog Naming Objects and Fingers test | NE ($n$=843)<br>uncertain/MCI ($n$=135)<br>AD, CDR=0.5 ($n$=30)<br>AD, CDR=1 ($n$=125) | MCI: CDR=0.5, memory loss but no dementia | Media appeals | NE > MCI > AD (CDR 0.5) > AD (CDR 1) | NE vs. MCI: 1.04<br>MCI vs. AD (CDR 0.5): 0.09<br>AD (CDR 0.5 vs. 1): 0.23 |

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|---|---|---|---|---|---|---|
| Ribeiro et al. (2006) | Object naming test from the Battery of Lisbon for the Assessment of Dementia | NE ($n$=63)<br>MCI ($n$=116) | subjective memory complaints; ≥1.5 *SD* below normal on delayed recall; preserved activities of daily living; maintained professional, social and familial activities according to clinical judgment AND score <3 on the first part of the Blessed Dementia Scale; preserved general cognitive function. | Dementia Outpatient Clinic, Hospital Santa Maria, and a Memory Clinic, Lisbon | NE=MCI | |
| Richards et al. (1999) | Naming of 10 objects (ECO) | 111 individuals, classified as NE ($n$=74), AAMI ($n$=37), or AACD ($n$=39). | AAMI: memory impairment, no dementia<br>AACD: impairment in one domain: memory/learning, attention/ concentration, visuospatial reasoning, language, visuospatial function | Randomly recruited from 600 general medical practices in southern France | NE > AACD<br>NE=AAMI | NE vs. AACD: 0.79 |
| Rubin et al. (1998) | BNT | NE ($n$=82), 10 of whom went on to develop AD, 6 iAD, and 11 uncertain dementia | CDR > 0 | Recruited from the community | BNT discriminated between DAT/IDAT and NE, but only after diagnosis of dementia | |
| Saxton et al. (2004) | BNT | Nondemented elderly ($n$=693), 72 of whom developed AD within 1.5–8 years (1.5–3.4 years: $n$=24; 3.5–5.0 years: $n$=20; 5.1–8.1 years: $n$=28) | NINCDS-ADRDA criteria | Selected from participants recruited from the community as part of the Cardiovascular Health Study | Significant predictor of AD up to 3.5 years prior to diagnosis | |
| Schmidtke & Hermeneit (2007) | CERAD naming | MCI ($n$=88), 75 of whom were available for follow-up | Petersen criteria | Memory Clinic | Nonconverters=converters | |
| Small et al. (2000) | Naming subsection of Swedish MMSE | Nondemented elderly ($n$=569), 73 of whom went on to develop AD | DSM-III-R | Subjects participating in Kungsholmen project who were not demented at first follow-up (see Small et al., 1997) | Nonconverters=converters | |
| Swainson et al. (2001) | GNT<br>New semantic battery naming test | NE ($n$=39)<br>QD ($n$=43)<br>mild AD ($n$=26)<br>MD ($n$=37) | AD: NINCDS-ADRDA criteria<br>MD: DSM-IV<br>QD: memory impairment but not meeting criteria for dementia or depression | Memory clinic, Addenbrooke's Hospital; Psychiatry Department, West Suffolk Hospital; Mental Health Services, Addenbrooke's NHS Trust | AD < QD+MD+NE on both measures<br>QD < MD+NE on semantic naming<br>No significant correlation between baseline performance and MMSE decline in QD individuals | |

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**APPENDIX B**
(*Continued*)

| *Authors* | *Test used* | *Groups + sample sizes* | *Diagnostic criteria* | *Recruitment procedure* | *Significant effects* | *Effect sizes ( Cohen's d)* |
|---|---|---|---|---|---|---|
| Tabert et al. (2006) | BNT (15-item version) | NE ($n$=83)<br>MCI ($n$=148) | Age ≥40; cognitive impairment for 6 months-10 years; CDR 0–0.5.<br>For memory: MMSE, SRT, WAIS–R performance IQ.<br>If no formal cognitive deficit: subjective memory decline, positive score on 1 or more of the first 8 items of the modified Blessed Functional Activity Scale. | Memory disorders clinic; NE recruited by advertisement | NE > MCI<br>nonconverters > converters | NE vs. MCI: 0.43<br>Nonconverters vs. converters: 0.67 |
| Testa et al. (2004) | BNT | NE ($n$=409)<br>MCIs ($n$=67)<br>ADs ($n$=306) | consensus among behavioral neurologists, clinical neuropsychologists, nurses, and psychometrists; CDR & DRS | Community (subjects receiving general medical care at Mayo Clinic) AND Mayo Alzheimer's Disease Center) | Nondemented > incident AD, but no added diagnostic utility once delayed recall effects included in the model | |
| Thompson et al. (2002) | GNT<br>GFNT | NE ($n$=31)<br>qAD ($n$=28)<br>AD ($n$=31) | qAD: complaints of episodic memory impairment but no dementia<br>AD: NINCDS-ADRDA criteria | Memory Clinic at Addenbrooke's Hospital, Cambridge | GNT: NE=qAD > AD<br>GFNT: NE > qAD > AD<br>6 of 7 converters at 1–2 years showed impairment on GFNT; 17 of 21 nonconverters scored normally | |
| Touchon & Ritchie (1999) | object naming subtest of ECO | NE ($n$=150)<br>nondemented elderly ($n$=359), 22 of whom developed AD in 3rd year | dementia: DSM-III-R AD: NINCDS-ADRDA criteria | General practitioner recruitment network | Naming not a predictor of incident dementia 2 years prior to onset | |
| Vogel et al. (2005) | Naming of 30 colored line drawings of common objects in 6 categories | NE ($n$=58)<br>predementia AD ($n$=22)<br>mild AD ($n$=102) | AD: NINCDS-ADRDA criteria<br>predementia AD: Petersen criteria + subsequent progression to AD (10–30 months later) | Recruited from referrals to the Copenhagen University Hospital Memory Clinic | NE=predementia AD > AD | |

*Note.* Effect sizes are reported where possible. AACD=age-associated cognitive decline. AACD-m=age-associated cognitive decline—modified. AAMI=age-associated memory impairment. AD=Alzheimer's disease. BNT=Boston Naming Test. CAMCOG = Cambridge Cognitive Examination. CDR=Clinical Dementia Rating Scale. CERAD=Consortium to Establish a Registry for Alzheimer's Disease. CVD=cerebrovascular disease. ECO = Evaluation Cognitive par Ordinateur [Computerized Cognitive Evaluation]. FTD=frontotemporal dementia. GFNT=Graded Faces Test, naming component. GNT=Graded Naming Test. iAD=incipient AD. IMI=isolated memory impairment. LBD=Lewy body dementia. MCI=mild cognitive impairment. MCI-A=MCI-amnestic. MCI-MD=MCI-multiple domain. MCI-SD=MCI-single domain. MD=major depression. MMSE=Mini Mental State Examination. NE=normal elderly. NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders. PN=picture naming. qAD=questionable AD. QD=questionable dementia. SML=subjective memory loss. STEP = Stepwise Comparative Status Analysis. SRT = Buscke Selective Reminding Test. uAD=uncertain AD. VaD=vascular dementia. VCI=vascular cognitive impairment. WAIS-R=Wechsler Adult Intelligence Scale–Revised.

**APPENDIX C**

Published studies reporting performance of MCI and preclinical AD individuals on standardized tests other than verbal fluency or naming

| *Authors* | *Test used* | *Groups+sample sizes* | *Diagnostic criteria* | *Recruitment procedure* | *Significant effects* | *Effect sizes* |
|---|---|---|---|---|---|---|
| Adlam et al. (2006) | Word–picture matching; concrete & abstract word synonym test (Warrington et al., 1998) | NE ($n$=30)<br>MCI ($n$=10)<br>mild AD ($n$=11) | MCI: Petersen criteria AD: NINCDS-ADRDA criteria | Memory Clinic at Addenbrooke's Hospital, Cambridge | NE=MCI > AD on all tasks | MCI vs. AD: word–picture matching, 1.14<br>concrete word synonym test, 1.07<br>abstract word synonym test, 0.54 |
| Aggarwal et al. (2005) | ERVT (15 items; Ekstrom et al., 1976)<br>NART (20 items; Nelson, 1982) | MCI ($n$=218), 82 of whom developed AD | MCI: Cognitive impairment but do not meet NINCDS–ADRDA criteria for dementia<br>AD: NINCDS-ADRDA criteria | Catholic clergy who agreed to participate | Reduced semantic memory (composite score of BNT, Extended Range Vocabulary, NART) predicted AD (relative risk=0.62); however, episodic memory impairment stronger predictor | |
| Artero et al. (2003) | Word and syntax comprehension | 128 individuals with cognitive difficulties | Cognitive difficulties ascertained using the Deterioration Cognitive Observée (DECO) screening instrument (Ritchie & Fuhrer, 1992) | Identified via a regional general practitioner network | Word and syntax comprehension not included in best predictive model for AD | |
| Bennett et al. (2002) | Complex ideational material,<br>ERVT<br>NART | NE ($n$=587)<br>MCI ($n$=211) | Cognitive impairment, but does not meet accepted criteria for dementia | Catholic clergy who agreed to participate | Composite score of semantic memory: NE > MCI<br>Rate of decline: MCI > NE | ERVT: 0.46<br>NART: 0.42 |
| Blackwell et al. (2004) | NART | Subjective/ objective memory loss ($n$=43), 11 of whom developed AD within 32 months | normal performance on tests of language and visuospatial function, preserved activities of daily life, CDR=0.5 | Memory clinic | Nonconverters=converters | |
| Bschor et al. (2001) | Cookie Theft Picture | NE ($n$=40)<br>MCI ($n$=34)<br>mild AD ($n$=21)<br>moderate to severe AD ($n$=20) | ICD-10 criteria (Zaudig, 1992) | Memory clinic, Dept. of Gerontology, Freie Universität Berlin | NE/MCI > AD on "persons and objects", localizations, Actions and Sum of measures | |

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**APPENDIX C**
(*Continued*)

| *Authors* | *Test used* | *Groups + sample sizes* | *Diagnostic criteria* | *Recruitment procedure* | *Significant effects* | *Effect sizes* |
|---|---|---|---|---|---|---|
| Busse et al. (2003) | Composite aphasia/ apraxia score (naming objects, reading and obeying a sentence, writing a sentence, and performing a three-stage command) | nondemented elderly ($n$=1045), 3% of whom met the criteria for MCI-A, 36% for MMSE≥26, 9% for AACD and 20% for AACD-m | MCI-A: Petersen criteria<br>AACD: Levy (1994) criteria<br>AACD-m: Levy criteria, but no requirement for subjective memory complaint<br>dementia: DSM-IV | Random sampling from list provided by the local registry office in Leipzig | No group differences; language score not a significant predictor | |
| Caccapolo-Van Vliet et al. (2003) | BDAE–Repetition of phrases | NE ($n$=230)<br>QD ($n$=155)<br>mild AD ($n$=244)<br>moderate AD ($n$=480)<br>severe AD ($n$=376)<br>very severe AD ($n$=247) | QD: cognitive impairment sufficient or close to sufficient for a diagnosis of dementia; no functional impairment<br>AD: NINCDS-ADRDA criteria | Memory Disorders Center/recruited for a study of controls | NE=QD=mild AD=moderate AD > severe AD > very severe AD | |
| Collie et al. (2002) | Syntactic and semantic reasoning | Elderly adults ($n$=174), 23 of whom were impaired on 3 consecutive assessments | CERAD battery (Morris et al., 1988b) | Recruited from an ongoing study on aging at an independent research institute in Melbourne, Australia | Syntactic reasoning: % correct significant Semantic reasoning not significant | Syntactic reasoning: 0.14 |
| Croot et al. (1999) | TROG<br>Word–picture matching (Hodges & Patterson, 1995)<br>PPT | NE ($n$=46)<br>minimal AD ($n$=16)<br>mild AD ($n$=16)<br>moderate AD ($n$=14) | NINCDS-ADRDA criteria;<br>minimal: MMSE=24–30<br>mild: MMSE=18–23<br>moderate: MMSE=2–17 | Memory Clinic at Addenbrooke's Hospital, Cambridge | TROG, blocks correct: NE > minimal=mild > moderate<br>TROG, items correct: NE > mild > moderate, minimal=mild<br>syntactic misinterpretations accounted for more errors than expected by chance<br>other tasks: p-value not reported | |
| De Jager & Budge (2005) | synonyms test (Warrington et al., 1998) | Baseline:<br>NE ($n$=117)<br>MCI ($n$=40)<br>3-year followup:<br>NE ($n$=85)<br>MCI ($n$=49) | MCI: >1.5 *SD* below control mean on memory testing | Talks/radio advertising in Oxfordshire for those who thought that their health, memory and thinking were good compared to that of their peers | Classification at 4 years not predicted by synonyms test | |
| De Jager et al. (2003) | Token Test | NE ($n$=51)<br>MCI ($n$=29)<br>AD ($n$=60)<br>VCI ($n$=8)<br>VaD ($n$=4) | MCI: Petersen criteria AD: NINCDS-ADRDA criteria<br>VCI: Hachinski criteria<br>VaD: NINCDDS/AIREN criteria (G. Gold et al., 1997) | Participants were recruited from the Oxford Project To Investigate Memory and Ageing (OPTIMA) study | NE=MCI > AD<br>VaD also exhibited deficits | MCI vs. AD: 0.6<br>NE vs. CVD (VaD+VCI): 1.03 |

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|---|---|---|---|---|---|---|
| Devanand et al. (1997) | BDAE category naming | QD ($n$=62), 26 of whom went on to develop dementia | Dementia: DSM-III criteria<br>AD: NINCDS-ADRDA criteria<br>QD: cognitive impairment, fall between "normal" and "dementia" categories | Memory Disorders Clinic | Nonconverters=converters | |
| Dudas et al. (2005) | PPT (pictures) | NE ($n$=29)<br>MCI ($n$=24)<br>AD ($n$=22) | Petersen criteria | Memory Clinic at Addenbrooke's Hospital, Cambridge | NE > MCI=AD | NE vs. MCI: 0.80 |
| Dwolatzky et al. (2003) | Mindstreams battery (verbal tests: selecting name from 4 choices; selecting rhyming word from 4 choices) | NE ($n$=39)<br>MCI ($n$=29)<br>AD ($n$=30) | Petersen criteria | Memory clinics | NE > MCI > mild AD on both measures | Naming: NE vs. MCI, 0.79; MCI vs. AD, 0.98<br>Rhyming: NE vs. MCI, 1.20; MCI vs. AD, 0.54 |
| Flicker et al. (1991) | vocabulary, category retrieval, object function recall, object name recognition, object function recognition, object identification | NE ($n$=32)<br>Mildly impaired ($n$=32) | GDS rating of 3 | Selected from participants in aging studies at the Aging and Dementia Research Center, NYU Medical Center | NE > mildly impaired on vocabulary, category retrieval, object function recall, object name recognition | Vocabulary: 0.8<br>Category retrieval: 1.2<br>Object function: 0.54<br>Object name recognition: 0.74 |
| Griffith et al. (2006) | Token Test (short form) | NE ($n$=49)<br>MCI ($n$=49) | Petersen criteria | Memory Disorders Clinic or recruited from community | NE > MCI<br>converters=nonconverters | NE vs. MCI: 0.52 |
| Guarch et al. (2004) | WAIS Vocabulary | NE ($n$=34)<br>SML ($n$=43), 10 of whom went on to develop AD | Subjective memory loss; neuropsychological tests not used as inclusion/exclusion criteria. | Clinical psychology service at the Hospital Clinic i Provincial, Barcelona. | Nonconverters=converters | |
| Hodges & Patterson (1995) | Naming to verbal description, answering of semantic feature questions, word–picture matching, PPT | NE ($n$=24)<br>minimal AD ($n$=17)<br>mild AD ($n$=52)<br>moderate AD ($n$=18) | NINCDS-ADRDA criteria | Memory Clinic at Addenbrooke's Hospital, Cambridge | Naming to description: NE > minimal=mild > moderate<br>Semantic feature questions: NE > minimal=mild > moderate<br>Word-picture matching: NE=minimal=mild > moderate<br>PPT: NE > minimal=mild > moderate | |

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**APPENDIX C**
(*Continued*)

| *Authors* | *Test used* | *Groups+sample sizes* | *Diagnostic criteria* | *Recruitment procedure* | *Significant effects* | *Effect sizes* |
|---|---|---|---|---|---|---|
| Hodges et al. (1996) | Generation of verbal definitions in response to spoken name ($n$=12) | NE ($n$=10)<br>minimal AD ($n$=16)<br>mild AD ($n$=17)<br>moderate AD ($n$=18) | AD: NINCDS-ADRDA criteria<br>minimal: MMSE=24–30<br>mild: MMSE=18–23<br>moderate: MMSE=2–17 | Memory Clinic at Addenbrooke's Hospital, Cambridge | NE > minimal > mild > moderate<br>ADs: definitions had less correct information, sometimes failed to convey core concept; especially true in minimal and mild groups of items they failed to name | Core concept information:<br>NE vs. minimal AD, 1.14; minimal AD vs. mild AD, 0.76; mild AD vs. moderate AD, 1.33<br>Production of superordinate category:<br>NE vs. minimal AD, 1.14; minimal AD vs. mild AD, 0.98; mild AD vs. moderate AD, 0.62 |
| Jacobs et al. (1995) | 16 items from BDAE–Complex Ideational Material<br>BDAE–Repetition of Phrases (high frequency only) | nondemented elderly ($n$=443), 41 of whom had developed AD at 2 year follow-up | NINCDS-ADRDA criteria | North Manhattan Aging Project, a community-based, epidemiologic study of dementia in northern Manhattan, NY | No significant additional prognostic value from these tests | |
| Jorm et al. (2005) | Language subsection of CASI (Teng et al., 1994), comprising reading, writing & following a simple command | Japanese-American men aged 71–93 ($n$=1611), 52 of whom went on to develop dementia | DSM-III-R | Recruited from population | Predicted incident dementia up to 3 years before onset but not 3–6 years before onset | 0.24 |
| Lambon Ralph et al. (2003) | Word–picture matching; naming to verbal description; semantic feature questions; Token Test; TROG; reading of regular and exception words; NART | NE ($n$=48)<br>MCI ($n$=17)<br>mild AD ($n$=22)<br>moderate AD ($n$=8)<br>severe AD ($n$=8) | Subjective memory impairment, corroborated by a spouse/family member; preservation of ADL; impairment on at least one test of memory; normal performance on tests of language, visuospatial and executive function; MMSE >24 | Memory Clinic at Addenbrooke's Hospital, Cambridge | Token Test: NE > MCI<br>All other tests: NE=MCI | |

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|---|---|---|---|---|---|---|
| López et al. (2006) | AMNART | NE (*n*=374)<br>MCI-A (*n*=10)<br>MCI-MD (*n*=28) | MCI-A: >1.5 *SD*s below controls in delayed recall+decline in cognitive functioning; MCI-MD; >1.5 *SD*s in at least one cognitive domain other than memory/one abnormal test in ≥2 domains. | 5,201 noninstitutionalized individuals over 65; recruited from four communities using Part A Medicare list in 1988–1989; 687 African-Americans recruited in same manner in 1992–1993 | NE=MCI-A > MCI-MD | NE vs. MCI-MD: 0.95<br>MCI-MD vs. MCI-A: 1.80 |
| Marcos et al. (2006) | CAMCOG Language subtest<br>WAIS Vocabulary | PMCI (*n*=38)<br>SMCI (*n*=44) | MCI: Petersen criteria<br>AD: NINCDS-ADRDA criteria | Referred by neurologists or geriatric specialists | Vocabulary: PMCI=SMCI<br>Language: PMCI < SMCI<br>Sensitivity=79%.<br>Specificity=61% | Language: 1.09 |
| Masur et al. (1994) | WAIS Vocabulary (Wechsler, 1955) | Nondemented elderly (*n*=317), 64 of whom developed AD in a follow-up of at least 4 years | DSM-III, NINCDS-ADRDA criteria | Recruited from community | Not a significant predictor | |
| Meguro et al. (2004) | Language subsection of CASI (Teng et al., 1994), comprising reading, writing & following a simple command | NE (*n*=968)<br>CDR 0.5, AD (*n*=95)<br>CDR O.5, UD (*n*=94)<br>CDR 0.5, ID (*n*=227)<br>CDR 0.5, others (*n*=37)<br>CDR 1 and 2 (*n*=80) | UD: only memory is impaired<br>ID: impairment in memory and ≤2 other cognitive domains<br>Others: impairment in memory and ≥3 other cognitive domains<br>Dementia: DSM-III-R | All older residents in Tajiri were targeted | CDR 0 < CDR 0.5 < CDR < 1 and 2<br>CDR 0.5 (DAT) < UD and ID | CDR 0.5 (AD vs. UD): 0.72<br>CDR 0.5 (AD vs. ID):0.37 |
| Meyer et al. (2002) | MMSE | MCI (*n*=73), 35 of whom developed AD and 15 of whom developed VaD during an average of 3.88 years of follow-up | MMSE >1 *SD* below mean for age & education; memory complaints; no dementia | Volunteers enrolled in longitudinal studies of aging and dementia through Baylor College of Medicine | No group effects | |
| Nestor et al. (2003) | PPT (picture version) | NE (*n*=15)<br>MCI (*n*=10)<br>AD (*n*=10) | MCI: insidious onset memory symptoms, objective memory impairment, no other significant deficits<br>AD: NINCDS-ADRDA criteria | Memory clinic | MCI > AD | |

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**APPENDIX C**
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| *Authors* | *Test used* | *Groups + sample sizes* | *Diagnostic criteria* | *Recruitment procedure* | *Significant effects* | *Effect sizes* |
|---|---|---|---|---|---|---|
| Nordlund et al. (2005) | Token Test<br>ASLD repetition (Crosson, 1996) | Token Test:<br>NE ($n$=35)<br>MCI ($n$=110)<br>ASLD repetition:<br>NE ($n$=31)<br>MCI ($n$=86) | Subjective and objective memory impairment > 6 months; positive outcome on stepwise comparative status analysis (STEP, Wallin et al., 1996), I-Flex (Royall et al., 1992), MMSE or CDR; MMSE ≥25; not more than 2 +ve outcomes on STEP | Memory clinic | NE > MCI in both tests | Token Test: 0.73<br><br>ASLD: 0.75 |
| Pyo et al. (2006) | ADAS-Cog Language, Comprehension and Word-Finding Difficulty tasks | NE ($n$=843)<br>uncertain/MCI ($n$=135)<br>AD, CDR=0.5 ($n$=30)<br>AD, CDR=1 ($n$=125) | MCI: CDR=0.5, memory loss but no dementia | Media appeals | Language:<br>NE < MCI=AD (CDR 0.5) < AD (CDR 1)<br>Comprehension:<br>NE < MCI < AD (CDR 0.5)=AD (CDR 1)<br>Word-finding difficulty:<br>NE < MCI < AD (CDR 1) < AD (CDR 0.5) | Language:<br>NE vs. MCI, 0.73<br>AD (0.5) vs. AD (1), 0.08<br>Comprehension: NE vs. MCI, 0.53<br>MCI vs. AD 0.5, 0.53<br>Word finding difficulty:<br>NE vs. MCI, 0.47<br>MCI vs. AD (1), 0.24<br>AD (1) vs. AD (0.5), 0.12 |
| Ribeiro et al. (2006) | Modified version of Token Test from Battery of Lisbon for the Assessment of Dementia | NE ($n$=63)<br>MCI ($n$=116) | Subjective memory complaints; ≥1.5 *SD* below normal on delayed recall; preserved ADL; maintained professional, social and familial activities, score <3 on the first part of the Blessed Dementia Scale; preserved general cognitive function. | Dementia Outpatient Clinic, Hospital Santa Maria, and a Memory Clinic, Lisbon | 33.7% of MCI patients had an impairment in the Token Test (<1.5 *SD* below mean for age & education) | |
| Richards et al. (1999) | Eco word comprehension subtest (RT measures) | 111 individuals, classified as NE ($n$=74), AAMI ($n$=37), or AACD ($n$=39). | AAMI: memory impairment, no dementia<br>AACD: impairment in one domain: memory/learning, attention/ concentration, visuospatial reasoning, language, visuospatial function | Randomly recruited from 600 general medical practices in southern France | NE > AACD<br>NE > AAMI | AAMI: 0.57<br>AACD: 1.04 |

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|---|---|---|---|---|---|---|
| Sacuiu et al. (2005) | Synonym test (identify synonym amongst 5 alternatives) | nondemented elderly ($n$=313), 58 of whom went on to develop AD in 3 years | Dementia: DSM-II-R<br>AD: NINCDS-ADRDA criteria | All individuals born in 1901–1902 in Gothenburg, Sweden were invited to participate | Predicted all dementia and VaD, but not AD; Sensitivity=68%, specificity=48%, PPV=22.7, NPV=87.0 for all dementia | |
| Saxton et al. (2004) | WAIS–R Vocabulary | nondemented elderly ($n$=693), 72 of whom developed AD within 1.5–8 years (1.5–3.4 years: $n$=24; 3.5–5.0 years: $n$=20; 5.1–8.1 years: $n$=28) | NINCDS-ADRDA criteria | Selected from participants recruited from the community as part of the Cardiovascular Health Study | Nonconverters=converters | |
| Small et al. (2000) | Reading & writing subsections of Swedish MMSE | nondemented elderly ($n$=569), 73 of whom went on to develop AD | DSM-III-R | Subjects participating in Kungsholmen project who were not demented at first follow-up (see Small et al., 1997) | Nonconverters=converters | |
| Tabert et al. (2006) | BDAE repetition & comprehension | NE ($n$=83)<br>MCI ($n$=148) | Age ≥40, cognitive impairment for 6 months–10 years, CDR 0–0.5. For memory: MMSE, SRT, WAIS–R performance IQ. If no formal cognitive deficit: subjective memory decline, positive score on 1 or more of the first 8 items of the modified Blessed Functional Activity Scale. | Memory disorders clinic; NE recruited by advertisement | NE > MCI on both measures<br>Nonconverters = converters on both measures | Repetition: 0.27<br>Comprehension: 0.20 |
| Thompson et al. (2002) | NART | NE ($n$=31)<br>qAD ($n$=28)<br>AD ($n$=31) | AD: NINCDS-ADRDA criteria<br>qAD: complaints of episodic memory impairment but no dementia | Memory Clinic at Addenbrooke's Hospital, Cambridge | NE=qAD=AD | |
| Tian et al. (2003) | FAST (Enderby et al., 1987) | QD ($n$=195), 135 seen for followup at 24.5 months; 37 converted to dementia | Objective evidence of cognitive impairment but no dementia | Bristol Memory Disorders Clinic | Nonconverters=converters | |

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**APPENDIX C**
(*Continued*)

| *Authors* | *Test used* | *Groups + sample sizes* | *Diagnostic criteria* | *Recruitment procedure* | *Significant effects* | *Effect sizes* |
|---|---|---|---|---|---|---|
| Touchon & Ritchie (1999) | Mean RT on word and syntax comprehension; reading (from ECO) | NE ($n$=150)<br>nondemented elderly ($n$=359), 22 of whom developed AD in 3rd year | Dementia: DSM-III-R criteria<br>AD: NINCDS-ADRDA criteria | General practitioner recruitment network | Both word and syntax comprehension predicted incident dementia 2 years prior; interaction with education<br>Reading predicted dementia; no interaction with education | Word comprehension: 1.57<br>Syntax comprehension: 0.97<br>Reading: 1.9 |
| Vandenbulcke et al. (2007) | AAT (Graets et al., 1992); Verbal association test of the psycholinguistic assessment of language processing in aphasia; spontaneous speech | NE ($n$=13)<br>MCI ($n$=13) | CDR=0.5, memory decline, other cognitive domains and activities of daily living relatively preserved | Memory Clinic, University Hospital Gasthuisberg, Leuven | 1/13 impaired (>2 *SD* below NE mean) in AAT (naming subtest), semantic structure in spontaneous speech<br>1/13 impaired in AAT (auditory word-picture matching subtest) and semantic structure in spontaneous speech<br>1/13 impaired in AAT (visual word-picture matching subtest)<br>1/13 impaired in syntactic structure in spontaneous speech | |
| Wang et al. (2006) | Language subsection of CASI (Teng et al., 1994), comprising reading, writing & following a simple command | NE ($n$=20)<br>MCI ($n$=58)<br>AD ($n$=20) | MCI: Petersen criteria<br>AD: NINCDS-ADRDA criteria | Neurological clinics | NE > AD<br>MCI > AD<br>converters > nonconverters | MCI vs. AD: 0.48<br>Nonconverters vs. converters: 0.54 |

*Note.* Effect sizes are reported where possible. AACD = age-associated cognitive decline. AACD-M = age-associated cognitive decline-modified. AAT=Aachen Aphasie Test. AD=Alzheimer's disease. ADAS-Cog=Alzheimer Disease Assessment Scale–Cognitive subscale. AMNART=American version of National Reading Test. ASLD=Assessment of Subtle Language Disorders. BDAE=Boston Diagnostic Aphasia Examination. CAMCOG = Cambridge Cognitive Examination. CASI=Cognitive Abilities Screening Instrument. CERAD=Consortium to Establish a Registry for Alzheimer's Disease. ERVT=Extended Range Vocabulary Test. FAST=Frenchay Aphasia Screening Test. ICD-10 = International Statistical Classification of Diseases and Related Health Problems–10th Revision. MCI=mild cognitive impairment. MMSE=Mini Mental State Examination. NART=National Adult Reading Test. NE=normal elderly. NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders. NPV=negative predictive value. PMCI=progressive MCI. PPT=Pyramids and Palms test. PPV=positive predictive value. qAD=questionable AD. QD=questionable dementia. RT=reaction time. SMCI=stable MCI. SML=subjective memory loss. SRT = Buscke Selective Reminding Test. TROG=Test for the Reception of Grammar. VaD=vascular dementia. VCI=vascular cognitive impairment. WAIS=Wechsler Adult Intelligence Scale.