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CHARACTERIZING SEMANTIC MEMORY IN MILD COGNITIVE IMPAIRMENT

by

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CHARACTERIZING SEMANTIC MEMORY IN MILD COGNITIVE IMPAIRMENT

KELLI L. NETSON

PSYCHOLOGY

ABSTRACT

Episodic memory is clearly impaired in mild cognitive impairment (MCI), although recent studies have revealed deficits in other cognitive domains such as attention, executive function, and semantic memory. Studies of semantic memory in MCI have been limited by inconsistent use of diagnostic criteria and variability in the measures used. The purpose of this study was to examine semantic memory in a sample of individuals diagnosed with amnestic MCI using Mayo criteria. Performance of individuals with consensus-diagnosed MCI (n=12) was compared to that of normal controls (n=15) on a battery of semantic memory tasks. MANOVA results indicated that the MCI group had significant deficits relative to controls on measures of semantic fluency, verbal abstract reasoning, and confrontation naming, although they were not frankly impaired. Individuals with MCI also demonstrated less spontaneous use of semantic clustering as a recall strategy on a verbal learning task. The utility of diagnostic cutoff scores on these semantic memory measures was explored. Overall, results indicate that individuals with amnestic MCI demonstrate subtle deficits in multiple semantic memory functions, although these deficits are not so severe to indicate impairment. Furthermore, these deficits are consistent with other literature suggesting a strong executive component in this population. The clinical utility of semantic memory measures and implications for future research are discussed.

DEDICATION

This work is dedicated to the many people without whom I would not have survived the experience. As always, my parents and sisters provided invaluable support, love, encouragement, and patience. My Birmingham sisters made the experience bearable with their distractions, celebrations, and understanding. And finally, to the members of GCOTB, who helped me pick up the pieces and have a true appreciation for what it feels like to succeed.

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INTRODUCTION

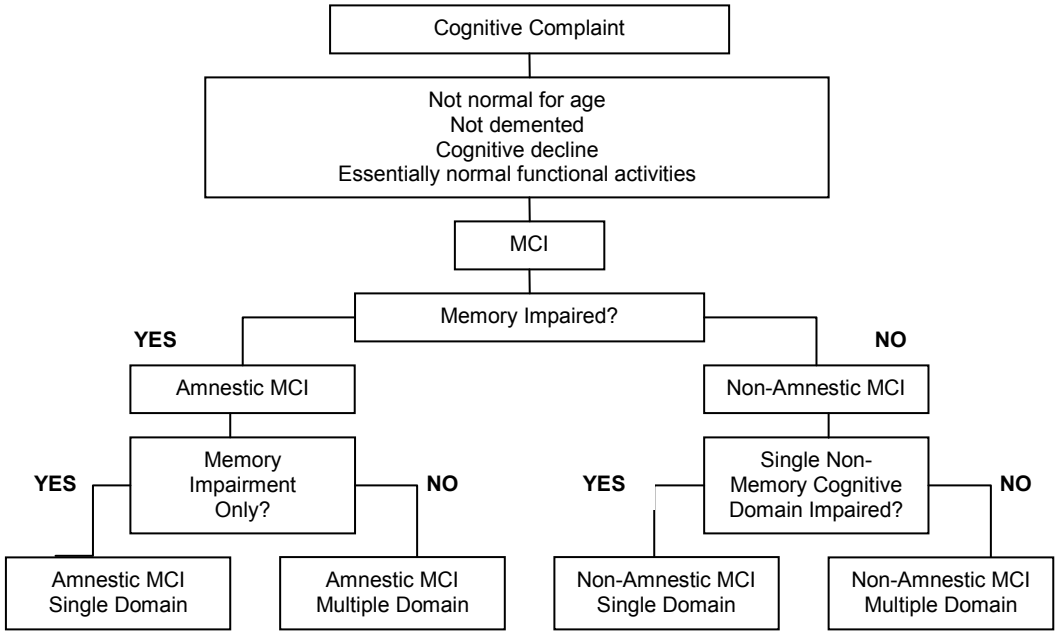
Neuropsychological studies of Alzheimer's disease (AD) and mild cognitive impairment (MCI) clearly identify episodic memory impairment as a hallmark symptom of both disorders (McKhann et al., 1984b; Petersen, 1995; Petersen et al., 1999a); however, episodic memory is certainly not the only cognitive domain that demonstrates decline (Hodges & Patterson, 1995; Perry & Hodges, 2000a; Perry, Watson, & Hodges, 2000; Vogel, Gade, Stokholm, & Waldemar, 2005). Semantic memory, which involves recognition of people, words, and items and the relationships between them (Tulving, 1987), has repeatedly shown decline in the later stages of AD (Hodges, Salmon, & Butters, 1992; Martin & Fedio, 1983). More recent findings suggest that semantic memory loss occurs much earlier in the course of AD, and possibly even prior to diagnosable dementia (Hodges & Patterson, 1995; Perry & Hodges, 2000a). However, to date, very few studies have been conducted examining semantic memory performance in individuals diagnosed with MCI using the Mayo criteria (Petersen, 1995, 2004; Petersen et al., 1999b). The proposed study will examine semantic memory in a prospectively diagnosed group of individuals with MCI with the goals of providing information about the specific semantic tasks that demonstrate impairment and better determining the extent of that impairment in MCI. Thus, the diagnostic entity of MCI will be reviewed, the construct of semantic memory will be defined, and the literature on semantic memory in AD will be reviewed to inform the aims and hypotheses of the present study and examine what is known about semantic memory in MCI.

Mild Cognitive Impairment

MCI is generally assumed to be a prodrome or precursor to diagnosable dementia, and in fact, as many as 50% of individuals with MCI will eventually progress to a diagnosis of AD (Bowen et al., 1997; Hanninen et al., 1997; Petersen et al., 1999a). Risk factors specifically for the development of MCI have not been examined and neuropathological diagnostic criteria for MCI do not currently exist (Markesbery et al., 2006). However, MCI has become a better-defined clinical entity with the introduction and more widespread use of diagnostic criteria used by the Mayo Clinic (Petersen, 1995, 2004; Petersen et al., 1999b). These diagnostic criteria define MCI as involving (1) subjective complaint of memory problems, (2) performance of at least 1.5 standard deviations below normal on neuropsychological measures of memory, (3) relatively normal performance in other cognitive domains, (4) normal activities of daily living (ADL), and (5) not meeting criteria for dementia as defined by the NINCDS-ADRDA (McKhann et al., 1984b). As these criteria have been used more frequently in clinical settings, the diagnostic system has evolved to account for various subtypes of MCI, including amnestic and non-amnestic MCI involving only memory impairment and normal memory with impairment in another cognitive domain, respectively (Petersen & Morris, 2005). There is some suggestion of even further differentiating subtypes based on probable etiology, classifying impairment as due to a degenerative, vascular, psychiatric, or medical process, with the most probable outcome of the degenerative type being AD (Petersen & Morris, 2005). Major depression may produce a diagnosis of MCI that is likely to resolve, highlighting the importance of taking a thorough history when diagnosing MCI and selecting groups for research. Petersen and Morris (2005) suggest

the following categorization as an indication of growing sophistication in the practice of diagnosing MCI.

Figure 1. Mild Cognitive Impairment Diagnostic Flowchart



Note: From "Mild Cognitive Impairment as a Clinical Entity and Treatment Target" by R.C. Petersen and J. Morris, 2005, Archives of Neurology, 63 (7), p. 1161. Copyright 2005 by the American Medical Association. Reprinted with permission.

Throughout the literature, memory problems that do not meet diagnostic criteria for dementia have been characterized a number of ways, including "pre-AD," (Vogel et al., 2005) "minimal AD," (Hodges & Patterson, 1995) and "possible AD," (Perry & Hodges, 2000a) with a variety of diagnostic criteria. Retrospective examination of these studies reveals diagnostic groups that represent a very heterogeneous sample of elderly individuals with early signs of memory impairment, but the classification of all of these samples as "MCI" is questionable. These groups are frequently examined to determine

the risk of converting from MCI to AD, which would represent a distinct "degenerative" subtype (Petersen & Morris, 2005).

Various studies have attempted to predict which individuals with MCI will progress to AD using biological and neuroimaging techniques. Presence of apolipoprotein ε4 allele (Petersen et al., 1995) and MRI evidence of volume loss in medial temporal lobe structures (Dickerson et al., 2004) are thought to contribute to a greater risk of conversion to AD and neuronal loss and atrophy in Layer II of the entorhinal cortex had been found post-mortem in the brains of those individuals who did convert to AD (Kordower et al., 2001). Postmortem examination of neural tissue for typical AD neuropathology has revealed that distinct neuropathology differentiates MCI from normal controls, specifically with increased β-amyloid plaque deposition in the neocortex and amygdala and increased neurofibrillary tangles in the entorhinal cortex, hippocampus, subiculum, and amygdala (Markesbery et al., 2006). Neuropathology was able to distinguish MCI from AD as well, with brains of early AD patients demonstrating more extensive plaque deposition and tangles in those structures affected by MCI, as well as more widespread neuropathological changes. Markesbery and colleagues (2006) concluded that neuropathologically speaking, MCI likely involves the same disease process as AD.

Semantic Memory

The processes that allow individuals to create and access memories have been widely studied. The construct of memory is vast and diverse, such that memory itself has been broken down into several component processes, among them, episodic and semantic

memory. Tulving (1987) first suggested the distinction between episodic memory, which includes time-specific events in an individual's own experience, and semantic memory. Semantic memory has been characterized as information that is generic and common across individuals within a society, generalizable to similar concepts, abstract and temporally non-specific, and acquired, to a large degree, early in life (Hodges, Patterson, Oxbury, & Funnell, 1992; Tulving, 1987, 1992). It is generally accepted that the cognitive architecture of semantic memory is a neural hierarchy that organizes abstract and general knowledge about the world; however there is considerable debate about the method or structure of this hierarchy, both conceptually and neuroanatomically. Various theories have proposed organization by category based on factual characteristics of the information (Warrington & Shallice, 1984), organization by the sensory modality through which the information was acquired (Noppeney & Price, 2002), and organization based on relevance of semantic details to the core "being" of the semantic fact in question (Sartori & Lombardi, 2004). While unique in their individual approaches, each of these theories provides a plausible organizational scheme for semantic memory, and it is likely that the ideal hierarchy employs strategies from each.

Psychometric Evaluation of Semantic Memory

Measuring semantic memory from a neuropsychological standpoint assumes that individuals possess a means of storing semantic knowledge, as well as the ability to access that information. Tasks used to test these abilities share a common requirement that an individual is able to recognize and identify a stimulus, be it visually or verbally presented, access the various areas of the semantic network that the stimulus is part of,

and then produce the necessary information in a manner that is useful to the task at hand. Neuropsychological tests of semantic memory include measures of confrontation naming, word/picture matching, verbally describing functional attributes of pictures, category fluency tasks, and category sorting tasks (Farah & Grossman, 2003; Hodges, Patterson et al., 1992). Confrontation naming requires an individual to recognize the physically descriptive, functional, and purpose-related attributes of the object to be named. In a fully functional semantic network, activation of these descriptive attributes should quickly promote access to semantic information regarding the object as well as lexical retrieval of the object's name. Similar to confrontation naming, verbal fluency requires rapid, time-limited production of target words in succession based on their relationship with each other. Phonemic fluency requires that each word begin with the same letter, while semantic or category fluency requires that each word is related to some superordinate category (i.e. animals, vegetables). Each of these tasks requires activation of the semantic network and a search strategy to compare and contrast various attributes before selecting and producing the appropriate word. Verbal fluency tasks also require executive control, first to strategize an appropriate search tactic, and secondly to maintain cognitive set and produce responses that are related to the exemplar in the correct manner by inhibiting inappropriate responses. Other tasks, such as the Pyramids and Palm Trees test (Howard & Patterson, 1992), examine both verbal and nonverbal semantic memory by requiring individuals to match pictures or words based upon semantic similarity. Examining both verbal and nonverbal stimuli is important as it aids in drawing a distinction between verbally- or linguistically-mediated difficulties in accessing the semantic network versus a central semantic processing deficit.

One weakness of neuropsychological examination of semantic memory is that it is often unable to reliably distinguish between deficits in accessing semantic networks versus degradation of the semantic networks themselves. However, some researchers (Henry, Crawford, & Phillips, 2004; Rohrer, Salmon, Wixted, & Paulsen, 1999) suggest that performance on phonemic versus semantic fluency tasks could aid in making this distinction. Phonemic fluency, requiring recruitment of concepts related by letter, and category fluency, requiring recruitment of concepts related to a superordinate exemplar, are thought to require similar executive demands for strategy, search, and retrieval (Henry & Crawford, 2004). Thus, differences in performance on the two tasks are thought to represent integrity of semantic knowledge stores and not retrieval processes, such that poor semantic fluency with intact phonemic fluency would indicate loss of semantic knowledge (Henry et al., 2004). However, there is some question as to whether retrieval strategies for phonemic and category-related tasks are actually equally taxing on executive processes. Another weakness of neuropsychological tests is that there are no "pure" semantic memory tasks; collateral cognitive, perceptual, and manual skills are required to access and produce responses to all current neuropsychological measures. Thus performance of "semantic memory" tasks may be affected by visual or auditory processing, attention, verbal ability, or other cognitive domains (Johnstone, Holland, & Larimore, 2000).

Neuroanatomy of Semantic Memory

One of the challenges of developing a theory of the neuroanatomic underpinnings of semantic memory has been that the tasks in question are thought to be uniquely

human, or are at least difficult to discern in an animal model (Hirono et al., 2001). Current knowledge about the neuroanatomy of semantic memory has been acquired largely from neuroimaging, behavioral, and lesion studies, and is generally correlational in nature. Most neuroanatomic studies have suggested that semantic memory in MCI and AD relies heavily on the integrity of the polar and inferolateral temporal cortex (Dudas, Clague, Thompson, Graham, & Hodges, 2005; Graham, LambonRalph, & Hodges, 1997, 1999). However, semantic memory impairment is perhaps most purely seen in semantic dementia (SD), a frontotemporal dementia characterized by a loss of conceptual knowledge, anomia, impaired comprehension, and fluent aphasia (Hodges, Patterson et al., 1992). Post-mortem studies of the brains of individuals with SD indicate that, regardless of the underlying etiology of the SD, neuronal loss is prevalent medially in the perirhinal cortex, more so on the left side, and additionally affected were the inferior temporal pole, anterior parahippocampal gyrus, and fusiform gyrus (Davies et al., 2005). Overall, the temporal pole is implicated in semantic memory functioning with relative consistency.

Evidence that the perirhinal cortex is implicated in semantic memory is consistent with the clinical presentation of individuals with MCI and AD, as some of the earliest neuropathological changes occur as neurofibrillary tangles become evident near the perirhinal cortex in the transentorhinal cortex of the medial temporal lobe (Braak & Braak, 1991). This type of neuropathology is seen in Braak's stages I and II, where the most superficial layer of the transentorhinal cortex is infiltrated with neurofibrillary tangles and neuropil threads, with only minimal involvement of the hippocampus proper (Braak & Braak, 1991). This level of neuropathology is associated with mild or

subclinical memory changes *not* associated with a diagnosis of dementia (Ball & Murdoch, 1997; Grober et al., 1999), which fits well with the construct of MCI. As AD pathology progresses, it spreads toward the inferolateral cortical areas, as well as toward the hippocampus and into deeper layers of the cortex (Braak & Braak, 1991). This, too, is consistent with patterns of cognitive decline in mid to later stages of AD, with more severe episodic memory impairment, greater semantic difficulty, and significant executive dysfunction (Lindeboom & Weinstein, 2004).

Radiological and functional neuroimaging techniques have also been used to examine neuroanatomic correlates of semantic memory *in vivo*. Damasio and colleagues (1996) used magnetic resonance imaging (MRI) and computed tomography (CT) images to examine confrontation naming ability in a sample of neurologically compromised individuals with focal lesions and found that on both an individual and group level, the location of the lesion was closely correlated with the category of naming impairment demonstrated. Specifically, impaired person-word retrieval was associated with focal lesions of the left temporal pole, while impaired animal-word retrieval correlated with lesions in the left infero-temporal lobe. Deficits in tool-word retrieval were associated with lesions in the posterolateral infero-temporal lobe at the parieto-occipital junction (Damasio et al., 1996). A review of PET and functional magnetic resonance imaging (fMRI) studies by Cabeza and Nyberg (2000) provides numerous findings of semantic memory activation in the left prefrontal and temporal cortical regions in healthy adults. Again, variations in structural activation occurred based on the category of information being assessed, such that animal knowledge was correlated with activation of occipital regions, while tool knowledge was associated with activation in the prefrontal cortex

(Cabeza & Nyberg, 2000). These structural variations lend support to an organizational scheme separating various categories within the brain; however, the precise structure of that organization, whether relying on the factual attributes of objects (Warrington & Shallice, 1984), or possibly the sensory modality through which the object knowledge was acquired (Noppeney & Price, 2002), remains unclear. Damasio (1996) suggests that various "category-specific" regions of the brain are "intermediary areas" that contain information about how to obtain or reconstruct a desired word form, and connect the cortical location of that information to the language center, allowing for the production of a response. Thus, semantic memory impairment based on damage to these areas would be a problem of accessing the information from a widely-distributed neural network, and would not necessarily indicate degradation of knowledge stores.

Semantic Memory in AD

Investigators have broadened the scope of research into the cognitive domains affected by AD, including executive function, attention, language ability, and semantic memory (Hodges & Patterson, 1995; Perry & Hodges, 2000a; Perry et al., 2000; Vogel et al., 2005). While episodic memory decline remains the hallmark trait of the disorder (Hodges & Patterson, 1995; Perry et al., 2000; Vogel et al., 2005), the importance of deficits in semantic memory has been highlighted and its relationship to everyday functioning has been explored (Aggarwal, Wilson, Beck, Bienias, & Bennett, 2005; Perry & Hodges, 2000b). There is considerable debate about whether the decline in semantic memory performance is a result of degradation of memory stores (Chertkow & Bub, 1990) or whether it results from an inability to access the information, most likely as a

result of some executive dysfunction (Nebes, Martin, & Horn, 1984; Ober & Shenaut, 1988).

Henry, Crawford, and Phillips conducted a meta-analysis of 153 studies examining verbal fluency in AD conducted between 1983 and 2002 (Henry et al., 2004). Studies were included in the meta-analysis if a measure of phonemic and/or semantic fluency was administered, if the study examined a patient group comprised solely of individuals diagnosed with AD, and if the study employed a control group. Findings from this meta-analysis suggest that individuals with AD demonstrate deficits on measures of both phonemic and semantic fluency, although the deficits in semantic fluency are more pronounced. Henry and colleagues suggest that the executive demands of both tasks are equivalent (Henry & Crawford, 2004; Henry et al., 2004), and therefore this indicates a degradation of the semantic memory stores instead of a deficient access strategy (Henry et al., 2004). However, other studies report improved performance after semantic priming (Chertkow, Bub, & Seidenberg, 1989; Giffard et al., 2002; Ober & Shenaut, 1988) and on tasks requiring less effortful retrieval (Nebes & Brady, 1988), thus supporting the notion that retrieval processes are impaired. Integrating these two notions, Henry and colleagues suggest that, while semantic memory decline likely results from degradation or disorganization of the semantic memory stores, increased demands on effortful retrieval may have an additive effect on performance deficits for semantic memory tasks (Henry et al., 2004).

Hodges and Patterson (1995) conducted a frequently cited study of semantic memory, examining 52 individuals with AD, stratified by MMSE scores into minimal (MMSE = 24-30), mild (MMSE = 18-23), and moderate (MMSE = 2-16) impairment

groups,. Participants in this study were administered a comprehensive neuropsychological battery, including an extensive semantic memory battery that has been used or adapted in several subsequent studies of semantic memory (Perry & Hodges, 2000a; Perry et al., 2000; Vogel et al., 2005). Individual measures were examined for their ability to differentiate patients from controls, as well as to distinguish between diagnostic levels in the patient group. Controls performed better than minimal, mild, and moderate AD groups on nearly all semantic memory measures. Only word-picture matching did not show significant impairment until the moderate stage of AD, and it is important to note that this task, where individuals were required to point to the named object from an array of eight pictures, may place more demands on visuospatial and word recognition than on semantic memory. Controls were distinguished from patients with minimal AD on measures of category fluency, picture naming, naming to description, semantic feature questions, and category matching, both verbal and non-verbal. There was no distinction between minimal and mild AD groups on any of the semantic memory measures administered, but the entire moderate AD group exhibited significant impairment (i.e. below 2 standard deviations) on nearly all semantic memory measures (Hodges & Patterson, 1995). Hodges and Patterson's (1995) cross-sectional study demonstrates that semantic memory deficits are present in the early stages of AD and likely worsen with disease progression. Even the minimal diagnostic group with performance above the diagnostic cutoff of MMSE = 24 exhibited some level of decline on nearly all the semantic memory measures. After attention and perceptual abilities were controlled for, semantic deficits were still seen across both verbal and non-verbal tasks, suggesting the existence of a central semantic processing deficit in the early stages of

AD. Semantic deficits varied between the minimal/mild groups and the moderate group, suggesting either later onset of semantic decline, or slower course of degeneration than that of episodic memory.

This lack of distinction between the minimal and mild AD groups strongly suggests that the "minimal AD" group is not completely consistent with MCI as defined by the Mayo criteria. Furthermore, the "minimal AD" group performed at the low end of the "normal" range on the MMSE with a mean score of 25.6 (range 24-30), and these participants showed deficits in two or more neuropsychological domains (Hodges & Patterson, 1995). In addition, even "minimal AD" suggests some functional impairment as a diagnostic criterion, while MCI requires relatively normal everyday functioning. It is, therefore, difficult to apply these results from Hodges and Patterson (1995) to a Mayo-diagnosed MCI sample.

Subsequent studies have attempted to chart the order and course of cognitive decline in AD (Perry & Hodges, 2000a; Perry et al., 2000), again comparing controls to patients with minimal and mild AD. Perry and colleagues found that measures of episodic memory were able to distinguish between controls and AD patients, but did not differentiate between the minimal and mild AD groups (Perry et al., 2000). However, category fluency and the Pyramids and Palm Trees test showed significant differences between controls and minimal AD, as well as between minimal and mild AD (e.g. controls > minimal > mild). In addition, the graded naming task distinguished between minimal and mild AD patients, but not between controls and the minimal AD group, suggesting that significant naming deficits may occur later in the disease course of AD than categorical deficits (Perry et al., 2000). The percentage of AD patients impaired in

each cognitive domain was largest for episodic memory, and proceeded in a step-down fashion for attention, semantic memory, visuoperceptual and spatial function, and short-term memory, indicating that attentional function or semantic memory is the most likely domain to decline following episodic memory impairment in early AD (Perry et al., 2000). The sample was highly variable with regard to the presence of attentional and semantic memory decline, thus no conclusions could be drawn regarding the domain most likely to decline following episodic memory.

Perry and Hodges conducted a longitudinal study of individuals diagnosed with "possible AD" to further investigate the course of decline within subjects (Perry & Hodges, 2000a). Participants were diagnosed with possible AD based on MMSE >24 and CDR=0.5, indicating impaired memory, but normal to mildly impaired everyday skills. While several of the individuals in this group would likely meet criteria for a diagnosis of MCI, there was some variability as to whether additional cognitive domains were impaired. Three components of the Hodges and Patterson (1995) semantic memory battery were included: 1) graded naming, 2) category fluency, and 3) Pyramids and Palm Trees. Participants with possible AD demonstrated baseline impairment on measures of episodic memory, but also demonstrated deficits on Graded Naming and category fluency measures (Perry & Hodges, 2000a). However, only one of twelve "possible AD" participants was impaired on a composite of semantic memory scores (i.e. greater than 2 standard deviations below normal). At one-year follow-up testing, "possible AD" participants demonstrated impairment on all three measures of semantic memory – graded naming, category fluency, and Pyramids and Palm Trees – with additional decline in executive function and attention. Similar to previous findings (Perry et al., 2000),

results were variable regarding whether attention or semantic memory showed initial decline, and 3 of the 12 "possible AD" participants demonstrated concomitant impairment in both domains (Perry & Hodges, 2000a). They suggest that their findings are in keeping with neuropathological evidence of neurofibrillary tangles and neuritic plaques that begin in the medial temporal lobe, and then spread to the temporal neocortex (Braak & Braak, 1991). Perry and Hodges (2000a) suggest that tests of selective attention and semantic memory are the most sensitive indicators that neuropathology has spread beyond the medial temporal lobe.

In general, the research on semantic memory in AD has demonstrated that episodic memory is the first neuropsychological domain to demonstrate impairment, but that it is quickly followed by deficits in semantic memory and/or attention (Hodges & Patterson, 1995; Perry & Hodges, 2000a; Perry et al., 2000). While semantic memory performance often distinguishes control subjects from those with mild forms of AD (Hodges & Patterson, 1995), such performance has been less sensitive in distinguishing pre-dementia groups from those with AD. Again, a major weakness that is relevant to the literature on semantic memory in MCI is that few of the studies examined employed Mayo diagnostic criteria to identify a group with clear-cut MCI. The majority of "pre-AD" or "minimal AD" groups examined demonstrate more impairment than would be found in an MCI group diagnosed with the Mayo criteria (Hodges & Patterson, 1995; Perry & Hodges, 2000a; Perry et al., 2000). Any comparisons to MCI at this point have attempted to "retro-fit" the criteria to the studies, resulting in findings that are not entirely applicable to the MCI diagnosis.

Semantic Memory in MCI

Studies explicitly examining semantic memory performance in MCI are few, and most use semantic memory as a contrast measure for episodic memory performance (i.e. no focus on semantic memory ability). Several studies have examined semantic memory in those at genetic risk for AD (Miller, Rogers, Siddarth, & Small, 2005), in variously diagnosed "pre-dementia" stages (Aggarwal et al., 2005; Hodges & Patterson, 1995; Perry & Hodges, 2000a; Perry et al., 2000), or only in those patients with MCI who eventually converted to AD (Vogel et al., 2005). In the Religious Orders Study (Aggarwal et al., 2005), individuals identified at baseline as having MCI demonstrated below-average performance on a composite of semantic memory tasks measuring naming, vocabulary, and reading; however their performance did not approach the level of "impairment," defined as more than 2 standard deviations below "normal" performance. It is notable that the Mayo criteria (Petersen, 1995, 2004; Petersen et al., 1999b) were not used to diagnose these participants, and the mean education of the group was over 17 years, significantly limiting this study's generalizability.

Dudas and colleagues investigated famous face recognition, famous person knowledge, and spatial memory in individuals with MCI as compared to those with AD and normal controls (Dudas et al., 2005). The study involved the development of the Face Place Test – a measure of famous face recognition and spatial memory requiring subjects to identify a famous faces and the famous face's spatial placement in an array of photos. Dudas and colleagues (2005) found that both the AD and MCI groups demonstrated significant impairment in famous person naming, item naming, and spatial memory, and that spatial memory was the only task that distinguished between the two patient groups,

demonstrating greater impairment in the AD group. These findings suggest that semantic memory abilities such as naming and item recognition, which are not thought to be dependent on the hippocampus, demonstrate impairment in MCI that is equivalent to the level of impairment in AD (Dudas et al., 2005). Conversely, hippocampus-dependent functions, such as spatial memory, tend to worsen progressively as the disease advances from MCI to AD. Consistent with these previous findings, Dudas and colleagues (2005) suggest that the neuroanatomic structures affected in MCI include the temporal pole, fusiform gyrus, and inferior temporal lobe; however, no neuroimaging or neuropathological correlations were performed to support this. This pattern of neuropsychological deficits and their progression is consistent with neuropathological changes associated with MCI and early AD, starting in the transentorhinal cortex and progressing medially toward the hippocampus as the disease progresses (Braak & Braak, 1991). One strength of this study is that it employed Mayo criteria (Petersen, 1995, 2004; Petersen et al., 1999b) in diagnosing MCI. However, the purpose of the study was to examine the utility of a new measure specific to the knowledge and recognition of famous persons, and thus several important areas of semantic memory, such as categorization and ability to identify functional attributes, remain unexamined in this diagnostic group.

Vogel and colleagues (2005) conducted the only study on a Mayo-diagnosed MCI sample to date that examined category fluency, naming, famous face identification and naming, and general information knowledge in patients with MCI as compared to patients with mild AD and to controls. Results indicated that the MCI group scored worse than controls on 4 of 5 measures: (1) category fluency, (2) identification of famous persons,

(3) naming famous persons, and (4) general information knowledge. The only normal performance for the MCI group was on confrontation naming. Conversely, the MCI patients scored significantly better than those with mild AD on all measures except general information knowledge, suggesting that the MCI group represents a distinct diagnostic state between cognitively normal and diagnosable dementia. While in this study MCI was diagnosed using Mayo criteria (Petersen, 1995, 2004; Petersen et al., 1999b), only those patients who eventually converted to AD were included. Given conversion estimates as high as 50% (Bowen et al., 1997; Collie & Maruff, 2000; Hanninen et al., 1997), this potentially excludes half of the clinical MCI population.

Summary

Research has demonstrated that semantic memory is an important component of the cognitive processes that contribute to everyday functioning (Aggarwal et al., 2005; Perry & Hodges, 2000b), such as the ability to recognize people and to determine the characteristics and appropriate uses of various objects (Tulving, 1987, 1992). Deficits in semantic memory have been consistently demonstrated in early stages of AD (Hodges & Patterson, 1995; Perry & Hodges, 2000a, 2000b) and in disease entities that are similar to MCI (Aggarwal et al., 2005; Hodges & Patterson, 1995; Perry & Hodges, 2000a, 2000b; Perry et al., 2000); however, few studies have explicitly examined semantic memory in a sample of individuals diagnosed with the widely-used Mayo diagnostic criteria. Prior behavioral and neuropsychological studies indicate a high likelihood of semantic memory decline in MCI (Vogel et al., 2005), and neuropathological data demonstrate disease involvement in the brain areas associated with semantic memory function (Damasio et

al., 1996; Davies, Graham, Xuereb, Williams, & Hodges, 2004; Davies et al., 2005; Hirono et al., 2001). Current gaps in the literature, including inconsistent application of diagnostic criteria and variability in the neuropsychological measures used, limit the ability of various centers to consistently replicate findings and present research that can be applied directly to a clinical population.

Specific Aims & Hypotheses

Aim 1: To examine the state of verbal semantic memory function in individuals diagnosed with MCI.

Hypothesis 1: Compared to normal controls, individuals with MCI will demonstrate deficits on measures of 1) category fluency, 2) naming to description, and 3) verbal abstract reasoning. No deficits will be evident on measures of 1) picture naming, 2) letter fluency, 3) vocabulary, or 4) general information knowledge.

Aim 2: To examine the relationship between episodic and semantic memory function in individuals with MCI.

Hypothesis 2: Individuals with MCI will demonstrate episodic memory impairment on the CVLT-II by definition; however, also anticipated is a) less use of semantic clustering during learning among individuals with MCI, b) a positive correlation between the semantic clustering learning score and the other measures in the semantic memory battery, and c) a positive association between semantic clustering and Delayed Free Recall scores, where more efficient semantic clustering results in better learning.

Aim 3: To determine whether semantic memory measures are useful in diagnosing MCI.

Hypothesis 3: Exploratory investigation of semantic memory measures will yield diagnostic cutoff scores that effectively differentiate individuals with MCI from normal controls.

METHODS

Participants

Participants were 27 individuals, 12 with amnestic MCI and 15 normal controls, who were enrolled in the UAB Alzheimer's Disease Research Center study. All participants were well characterized based upon neurological, neuropsychological, and radiological procedures. Diagnoses of amnestic MCI were made in the ADRC diagnostic consensus conference based on Mayo criteria (Petersen, 1995, 2004; Petersen et al., 1999a). Controls were also characterized during consensus conference as not meeting criteria for dementia or any other cognitive disorder based on neuropsychological and neurological examination. Participants were characterized during the ADRC Consensus Diagnostic Conference based on the clinical judgment of three neurologists and two clinical neuropsychologists with expertise in diagnosing dementia and MCI. Within the consensus conference, all relevant clinical, laboratory, neuroimaging, and neuropsychological findings were considered. Majority rule was used in cases of disagreement.

Inclusion/Exclusion Criteria

Inclusion and exclusion criteria for this study were in accordance with other studies from this Center (Griffith et al., 2006). Participants with amnestic MCI were recruited if they were an ADRC participant with a previous consensus diagnosis of amnestic MCI, or if they were undergoing a baseline assessment and were anticipated to

receive a consensus diagnosis of MCI (e.g. referred to the ADRC with a clinical diagnosis of MCI). Amnestic MCI diagnosis was assigned using Mayo criteria (Petersen et al., 2001), including, 1) subjective memory complaint by the patient and/or an informant; 2) objective memory impairment falling approximately 1.5 standard deviations or more below age and education equivalent control performance on a neuropsychological measure of memory; 3) relatively normal performance in other cognitive domains; 4) relatively normal activities of daily living; and 5) lack of dementia, as reflected by a failure to meet NINCDS-ADRDA criteria for dementia (McKhann et al., 1984a). Neuropsychologists on the ADRC consensus committee defined objective memory impairment using appropriate normative data in reference to a patient's age, education, and socioeconomic background. Normal controls were included if they were determined to have no memory or other cognitive impairment at consensus and did not meet criteria for MCI or dementia.

Exclusion criteria for the total sample included diagnosis of a potentially treatable form of dementia, another neurodegenerative disease, another chronic debilitating neurological illness (i.e. cerebral palsy), cancer (except skin cancer), severe pulmonary, renal, or liver disease, cardiac disease, autoimmune disease, alcoholism, or conditions expected to cause death within 1 year. Individuals suffering from untreated major depression (but not mild depression), any other severe psychiatric disorder, and/or severe behavioral problems were also excluded. Participants with MCI were not excluded for undergoing pharmacological treatment for memory loss; however, control participants were excluded if they were currently taking memory medications. Hachinski Ischemia Index scores were gathered on all participants (Hachinski et al., 1975). This index score

is derived from the number of vascular risk factors each participant has (i.e. hypertension, prior stroke), with a score greater than 4 indicating greater likelihood that cognitive problems are related to vascular changes as opposed to AD.

Procedures

As a part of their participation in the ADRC Clinical Core, participants completed neuropsychological testing using a battery of tests devised to detect cognitive impairment in older adults (Butters, Salmon, & Butters, 1994; Lezak, 1995; Pasquier, 1999). Specifically, the battery consisted of the Dementia Rating Scale (DRS;(Mattis, 1988), the CVLT-II (Delis, Kaplan, Kramer, & Ober, 2000), the Digit Symbol subtest of the WAIS-III (Wechsler, 1997), the Digit Span and Logical Memory I and II subtests of the WMS-R (Wechsler, 1989), a 30-item version of the Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 1983), measures of semantic word fluency (Spreen & Strauss, 1991), the Executive Clock Drawing Task (CLOX) (Royall, Cordes, & Polk, 1998), Trail Making Tests A and B from the Halstead-Reitan test battery (Reitan & Wolfson, 1993), the Purdue Pegboard (Tiffin & Asher, 1948), and the 10/36 spatial recall task from the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Rao & Society, 1990). The Geriatric Depression Scale was administered to assess self-reported depression symptoms (Yesavage, 1983). Some data from the ADRC testing battery were used in the present study. The CVLT-II and BNT were administered as part of the clinical battery used to diagnose MCI and thus, some group differences were anticipated due to diagnostic criteria. In addition to these measures, participants in the present study

completed a supplemental brief battery focused on measures of semantic memory, and were compensated for their time.

Phase I

Participants were identified by neuropsychological technicians as appropriate study referrals and recruited using fliers distributed during their annual ADRC research visit. Potential participants returned a portion of the flier providing contact information and giving permission for the PI to contact them regarding further participation. Those individuals completing the screening process and agreeing to participate completed a 2-3 hour semantic memory battery in-person at UAB and were compensated $30 cash. Informed consent was obtained in writing from all participants completing in-person assessments. Due to poor initial recruitment, study procedures were revised and a second phase of recruitment was undertaken.

Phase II

Similar to Phase I, potential participants were identified by neuropsychological technicians and support staff. Recruitment brochures were distributed during annual research assessment visits, as well as in 3 separate mailings to appropriate research referrals who met inclusion criteria and had completed an annual ADRC research assessment within the previous 3 months. Potential participants returned a postage-paid detachable postcard from the brochure providing contact information and permission for the PI to contact them with additional study information. Recruitment and data collection took place during separate telephone calls occurring at least 24 hours apart to ensure an

appropriate opportunity to decline participation. Telephone scripts were followed for both telephone calls (See Appendix A). Participants were verbally administered a battery of semantic memory tasks over the telephone. The evaluation took 45-55 minutes to complete and participants were compensated with a $20 gift card to their choice of two national discount stores. Telephone administration of verbal neuropsychological tasks has gained popularity and has been deemed a valid alternative to in-person assessment across multiple populations for tasks such as verbal fluency (Berns, Davis-Conway, & Jaeger, 2004; Crooks, Parsons, & Buckwalter, 2007; Lipton et al., 2003), verbal abstract reasoning (Crooks et al., 2007), vocabulary knowledge (Debling, Amelang, Hasselbach, & Sturmer, 2005; Taichman et al., 2005), and general fund of knowledge (Debling et al., 2005). Telephone assessment has demonstrated value in reaching participants for whom travel is difficult or prohibitive, and reducing participant burden, particularly in elderly populations (Crooks et al., 2007; Debling et al., 2005; Lipton et al., 2003). Informed consent was obtained verbally from all participants in Phase II of the study, and implied consent was assumed by virtue of the participant answering and continuing the assessment phone call in accordance with Institutional Review Board Procedures.

In both phases of the study, every attempt was made to have participants complete the semantic memory battery within 8 weeks of their ADRC battery date, although time between evaluations ranged from 9 days to over seven months with an average of 11.7 weeks between assessments. All semantic memory assessments were administered and scored by the principal investigator, who was blind to consensus diagnosis at the time of assessment.

Measures

Boston Naming Test

The BNT (Kaplan et al., 1983) examines confrontation naming of black-and-white line drawings. If the participant is unable to name the drawing spontaneously, a semantic cue is provided. If the participant is still unable to correctly name the drawing, a phonemic cue is provided. Participants were administered a 30-item version of the BNT (Morris et al., 2006) during the ADRC battery, and the score from that administration was used in analyses. Group differences on this measure may occur given its inclusion in the diagnostic battery; however, poor performance on this task is not required for a diagnosis of MCI.

California Verbal Learning Test, 2nd Edition

The CVLT-II (Delis et al., 2000) provides a measure of episodic memory through verbal learning, short-delay and long-delay recall, as well as delayed recognition. In addition, the CVLT-II provides indices of semantic clustering and learning strategies. The test involves presentation of a 16-item list presented 5 times, with immediate recall of items following each presentation. Short-delay free recall is examined following presentation of a distracter list. Following free-recall, semantic categories are provided and participants are asked to categorize items from the list. Free and semantically cued recalls are performed again after a 20-minute delay, and finally a Yes/No recognition trial is administered. Of significant interest in the present study was the semantic clustering score as a measure of the individual's ability to spontaneously employ semantic categorization as a recall strategy. Notably, CVLT-II recall performance is likely to be

impaired in the MCI group by definition; however, the semantic clustering score is not a part of the diagnostic criteria for MCI.

Category Fluency Tests

The category fluency tests will be similar to other semantic fluency measures (Hodges & Patterson, 1995; Spreen & Strauss, 1991) in which participants are given one minute to name as many exemplars of a provided category as possible. The categories assessed coincided with the semantic categories from the CVLT-II (Delis et al., 2000), including furniture, vehicles, vegetables, and animals. This measure also allowed for the examination of fluency for two superordinate categories (living and man-made objects), and the examination of spontaneous subordinate categorization (i.e. breeds of dog or types of boat). This test was included based on the finding that word production and word finding are two of the most sensitive measures of semantic memory in the elderly (Nilsson, 2003).

Controlled Oral Word Association Test

The COWA, a simple measure of verbal fluency (Benton & Hamsher, 1978), was administered, where participants were given a stimulus letter and asked to produce as many words as possible in one minute that begin with that letter. Instructions indicate that proper nouns and the same root word with a different suffix are not acceptable responses. Stimulus letters were C, F, and L. Performance on this measure provided was used as a comparison for semantic fluency to assess discrepancies that are thought to differentiate

deficits in executive function versus degradation of semantic networks (Henry & Crawford, 2004; Henry et al., 2004).

Naming to Description

The task of naming objects to description will be adapted from the task administered by Hodges and Patterson (1995). The initial task included one functional and one perceptual description for each of 64 common items taken from the widely used drawings by Snodgrass and Vanderwart (1980), which were divided into 8 categories: 1) domestic animals, 2) foreign animals, 3) birds, 4) fruit, 5) large household items, 6) small household items, 7) tools, and 8) vehicles (J.R. Hodges, personal communication, April 24, 2006; See Appendix B). The present study will use a 32-item set comprised of 4 items from each category. A functional description will be provided for 16 of the items and a perceptual description will be provided for the other 16 items, divided equally among the categories. The format for administration will be, "What do we call a . . .?" inserting the appropriate description.

WAIS-III Information

The Information subtest from the WAIS-III (Wechsler, 1997) examines general fund of knowledge, or what may be considered information stored in semantic memory.

WAIS-III Similarities

The Similarities subtest from the WAIS-III (Wechsler, 1997) is a test of verbal abstract reasoning and the ability to identify a superordinate semantic category

encompassing two stimulus words. This will be administered according to standardized testing procedures. Lezak (1983) suggests that the Similarities subtest is virtually independent of any memory factors, and thus scores should remain stable in the presence of memory impairment.

WAIS-III Vocabulary

The Vocabulary subtest from the WAIS-III (Wechsler, 1997) serves as an additional measure of general fund of knowledge as well as verbal reasoning and conceptualization. Standardized procedures were adapted for administration over the telephone. When administered in-person, participants are shown a stimulus card with the word to be defined printed on it. Over the telephone, the word was spelled aloud for the participant and they were permitted to write it down if they chose.

Analyses

Data analysis was completed using SPSS versions 11.5 and 16.0 (Chicago: SPSS, 2002, 2007). Group demographic variables were compared using independent samples t-tests and Chi-square analyses as appropriate. Proposed analyses for Hypothesis 1 initially involved Multivariate Analysis of Covariance (MANCOVA) using a measure of basic attention as a covariate. The DRS Attention scaled score was explored as such a measure; however, there were no significant group differences on DRS Attention ($p=.670$), and it was excluded from the analysis to preserve power. Hypothesis 2 was examined using Pearson correlations and stepwise regression. Exploratory analyses for Hypothesis 3 included Receiver Operating Characteristic (ROC) Curve analysis to determine

appropriate cutoff scores for various measures. A standard criterion of $p<.05$ was used for all primary analyses unless otherwise noted.

RESULTS

Fifty-three potential participants responded to recruitment literature and expressed interest in the study. After telephone screening, 8 participants were enrolled in Phase I. One individual withdrew for health reasons prior to consent and data collection. Of the 7 participants who completed the study, 1 was excluded due to a consensus diagnosis of non-amnestic MCI. In Phase II, 24 participants were enrolled and 23 completed the evaluation. Subsequently, 1 was excluded due to a consensus diagnosis of non-amnestic MCI and 1 control was excluded due to current use of memory medications.

In-Person vs. Telephone Assessment

Six participants (4 Control, 2 MCI) recruited in Phase I of the study completed in-person assessment. Twenty-one participants (11 Control, 10 MCI) completed telephone assessment in Phase II of the study. Demographic and neuropsychological performance was compared between the two groups. A conservative criterion of $p<.10$ was used to ensure that there were no group differences as a result of the methodology. There was a trend for participants tested in-person to be younger than those tested over the telephone ($p=.194$). Participants in the two phases of the study were found to be equivalent on education measures and performance on all semantic memory measures (see Table 1). Therefore, diagnostic groups from both phases of the study were combined for the remainder of analyses.

Table 1. In-Person vs. Telephone Assessment

Demographic/Testing Variables *Mean (SD)*	*Phase I (In Person) n=6*	*Phase II (Telephone) n=21*	*p value (<.10)*
Age	69.17 (8.38)	74.43 (8.55)	.194
Education	14.83 (2.23)	15.95 (3.25)	.439
Gender: n (%)			.326
Male	1 (16.7)	8 (38.1)	
Female	5 (83.3)	13 (61.9)	
Race: n (%)			.885
Caucasian	5 (83.3)	18 (85.7)	
African-American	1 (16.7)	3 (14.3)	
Phonemic Fluency Composite	34.00 (13.81)	38.62 (14.08)	.483
Category Fluency Composite	48.50 (5.43)	49.62 (9.93)	.795
Naming to Description Raw Score	20.83 (2.04)	20.29 (2.99)	.679
WAIS Vocabulary Raw Score	47.33 (9.42)	49.14 (10.00)	.696
WAIS Similarities Raw Score	23.33 (2.73)	22.76 (5.49)	.809
WAIS Information Raw Score	18.83 (3.49)	19.90 (4.55)	.600

Note: Significance level p<.10

Demographics

Diagnostic groups were compared on multiple demographic and medical variables using independent samples t-tests and Chi-square analyses. Results are presented in Table 2. As expected, the groups differed on CDR Sum of Boxes Score, a staging measure used to rate functional impairment due to dementia (Morris, 1993). The Sum of Boxes Score has been shown to be more sensitive than the Staging Score in individuals with mild

memory loss, such as that seen in MCI (Lynch et al., 2006). All participants in the control group received a CDR Sum=0, indicating no cognitive or functional impairment. Individuals with MCI ranged from CDR Sum=0.5 to CDR Sum=2.5. There was a trend for more participants with MCI to be receiving minimal assistance with some daily functions (i.e. cooking, driving, cleaning, managing medications) based on a brief telephone demographic interview (See Appendix C), although the level of assistance described was not suggestive of functional impairment based on a standard measure of Instrumental Activities of Daily Living (Lawton & Brody, 1969). There were no significant demographic or medical differences found between individuals with MCI and healthy controls.

Table 2. Demographic & Medical Information

Demographic Variable	*Control*	*MCI*	*p value*
Mean (SD)	*(n = 15)*	*(n = 12)*	
Age	72.20 (8.98)	74.58 (8.39)	.487
Gender: n (%)			.100
Male	7 (46.7)	2 (16.7)	
Female	8 (53.3)	10 (83.3)	
Race: n (%)			.396
Caucasian	12 (80.0)	11 (91.7)	
African-American	3 (20.0)	1 (8.3)	
Education	15.87 (3.00)	15.50 (3.23)	.763
Marital Status: n (%)			.555
Married	9 (60.0)	7 (58.3)	
Divorced	3 (20.0)	4 (33.3)	

Widowed	2 (13.3)	0 (0)	
Single	1 (6.7)	1 (8.3)	
Work Status: n (%)			.228
Retired	10 (66.7)	9 (75.0)	
Part-Time	2 (13.3)	3 (25.0)	
Full-Time	3 (20.0)	0 (0)	
Functional Performance: n (%)			.076
Independent	14 (93.3)	8 (66.7)	
Minimal Assistance	1 (6.7)	4 (33.3)	
CDR Sum of Boxes: n (%)			.000
=0	15 (100.0)	0 (0)	
=0.5	0 (0)	3 (25.0)	
=1.0	0 (0)	4 (33.3)	
=1.5	0 (0)	4 (33.3)	
=2.5	0 (0)	1 (8.3)	
Hachinski Index: n (%)			.522
=0	7 (46.7)	5 (41.7)	
=1	8 (53.3)	6 (50.0)	
=3	0 (0)	1 (8.3)	
Diabetes Diagnosis: n (%)	1 (6.7)	2 (16.7)	.411
Hypertension Diagnosis: n (%)	7 (46.7)	7 (58.3)	.547
Memory Medications: n (%)			.159
0	14 (93.3)	8 (66.7)	
2	0 (0)	2 (16.7)	
Previous Rx, None Currently	1 (6.7)	2 (16.7)	
Days Since ADRC Evaluation	87.53 (56.33)	85.92 (48.21)	.938

Note: Significance level $p<.05$

Hypothesis 1

The first hypothesis was that individuals with MCI would have poorer performance on measures of semantic fluency, Naming to Description, and verbal abstract reasoning, with no group differences on phonemic fluency, general vocabulary knowledge, confrontation naming, or general fund of knowledge. Participants in both diagnostic groups performed well on all measures administered when compared to normative samples, scoring in the average to high average range for vocabulary knowledge, verbal abstract reasoning, general fund of knowledge, and confrontation naming. MANOVA revealed a significant omnibus test, $F(7, 19)=4.35$, $p=.005$, for diagnostic group with an observed power of .945. Results for individual measures are presented in Table 3.

Table 3. Neuropsychological Performance of MCI vs. Normal Control

Semantic Memory Measure *Mean (SD)*	*Possible Range*	*Achieved Range*	*Control (n = 15)*	*MCI (n = 12)*	*p value*
Phonemic Fluency Composite		15-63	37.13 (13.29)	38.17 (15.18)	.852
Semantic Fluency Composite		29-72	52.67 (9.05)	45.25 (7.45)	.031
Boston Naming Test	0-30	16-30	28.00 (1.13)	24.83 (4.30)	.011
Naming to Description Raw Score	0-32	15-25	21.07 (2.71)	19.58 (2.75)	.172
Similarities Raw Score	0-33	9-32	24.93 (4.10)	20.33 (4.91)	.014
Vocabulary Raw Score	0-66	19-63	48.60 (7.70)	48.92 (12.17)	.935
Information Raw Score	0-28	8-28	20.33 (3.89)	18.83 (4.80)	.378

**Note:* Significance level p<.05

Post-hoc univariate comparisons revealed poorer performance in the MCI group on tasks of semantic fluency (effect size η=.173), and verbal abstract reasoning (effect size η=.220), but no differences on vocabulary knowledge and general fund of knowledge. These findings were consistent with the hypothesis. Hypothesized differences on the Naming to Description task were not observed. There was an unanticipated significant group difference in confrontation naming performance (effect size η=.232). Because this finding was unanticipated, correlations between the Boston Naming Test and other measures in the semantic memory battery were explored, with results presented in Table 4. The BNT was highly correlated with WAIS Information, Vocabulary, and Similarities, as well as semantic fluency and all recall trials from the CVLT-II.

Table 4. Boston Naming Test Correlations

Pearson Correlations	*Boston Naming Test 30-Item Form*	*p value*
Phonemic Fluency Composite	.260	.191
Semantic Fluency Composite	.363	.063
Naming to Description Raw Score	.318	.106
Similarities Raw Score	.725	.000
Vocabulary Raw Score	.631	.000
CVLT-II Trial 1-5 Total	.508	.007
CVLT-II Short-Delay Free Recall	.483	.011
CVLT-II Short-Delay Cued Recall	.381	.050
CVLT-II Long-Delay Free Recall	.454	.017
CVLT-II Long-Delay Cued Recall	.449	.019

Note: Significance level p<.05

Semantic fluency

Follow-up analyses were performed on the group differences in semantic fluency performance. First, there was a trend for more individuals with MCI (n=8) than controls (n=5) whose average semantic fluency was worse than their average phonemic fluency, $\chi^2(1)=2.97$, $p=.085$. There was no difference between groups in the ratio of average semantic to phonemic fluency performance (p=.218). The semantic fluency composite score was examined to determine whether specific components of the composite score revealed greater differences than others. Four categories (animals, vegetables, furniture, and vehicles) were combined to produce the composite score. Univariate analysis was performed for each category, plus subscores for living and manmade objects. Results are presented in Table 5. Only fluency for Animals and Living Things yielded a significant group difference.

Table 5. Semantic Fluency Performance

Fluency Category *Mean (SD)*	*Control* *(n = 15)*	*MCI* *(n = 12)*	*p* *value*
Animals	16.47 (3.91)	12.83 (2.52)	.010
Vegetables	12.13 (2.85)	11.17 (2.95)	.397
Living Things	28.60 (5.93)	24.00 (4.05)	.031
Furniture	12.93 (3.73)	11.00 (2.52)	.138
Vehicles	11.13 (3.20)	10.25 (3.25)	.486
Manmade Items	24.07 (5.35)	21.25 (4.75)	.166
Living-Manmade Discrepancy	4.53 (6.75)	2.75 (4.73)	.446
Living > Manmade: n (%)	11 (73)	8 (67)	.706

**Note:* Significance level p<.05

Hypothesis 2

The second hypothesis suggested that individuals with MCI would use semantic clustering as a memory strategy less often than controls. This hypothesis was supported, with lower semantic clustering scores (p=.000) among individuals with MCI (Mean=.02, SD=.24) than among controls (Mean=1.11, SD=.86). Also consistent with the hypothesis, the use of semantic clustering was correlated with free recall after a delay (r=.576, p=.002). However, linear regression analysis examining the predictive power of semantic clustering and short-delay memory on long-delay memory revealed that Short Delay Free Recall was a significant predictor of Long Delay Free Recall, $F(1, 25)=211.28$, p=.000, but Semantic Clustering was removed from the stepwise model as it did not account for a significant amount of additional variance, R^2 *change*=.003, p=.386.

The hypothesis that the Semantic Clustering score from the CVLT-II would be correlated with other measures in the semantic memory battery was not supported, and no significant correlations were noted (See Table 6). However, the Semantic Clustering score was negatively correlated with change scores between free recall and cued recall for both short-delay (r=-.446, p=.020) and long-delay (r=-.421, p=.029) trials. This indicates that individuals who spontaneously used semantic clustering as a learning strategy gained less benefit when cues were provided by the examiner. There was a significant group difference (p=.001) in the short-delay change score following the first provision of category cues, with the MCI group producing more additional items (Mean=2.83, SD=2.16) following the cue than the control group (Mean=.47, SD=1.12). There was a trend for a significant group difference in the same direction for long-delay change score (p=.072).

Table 6. Semantic Clustering Correlations

Pearson Correlations	*Semantic Clustering Raw Score*	*p value*
CVLT-II Trial 1-5 Total	.418	.030
CVLT-II Short-Delay Free Recall	.559	.002
CVLT-II Short-Delay Cued Recall	.495	.009
CVLT-II Long-Delay Free Recall	.576	.002
CVLT-II Long-Delay Cued Recall	.443	.021
Phonemic Fluency Composite	-.089	.659
Semantic Fluency Composite	.309	.117
Boston Naming Test	.285	.149
Naming to Description Raw Score	.083	.681
Similarities Raw Score	.270	.173
Vocabulary Raw Score	-.111	.582

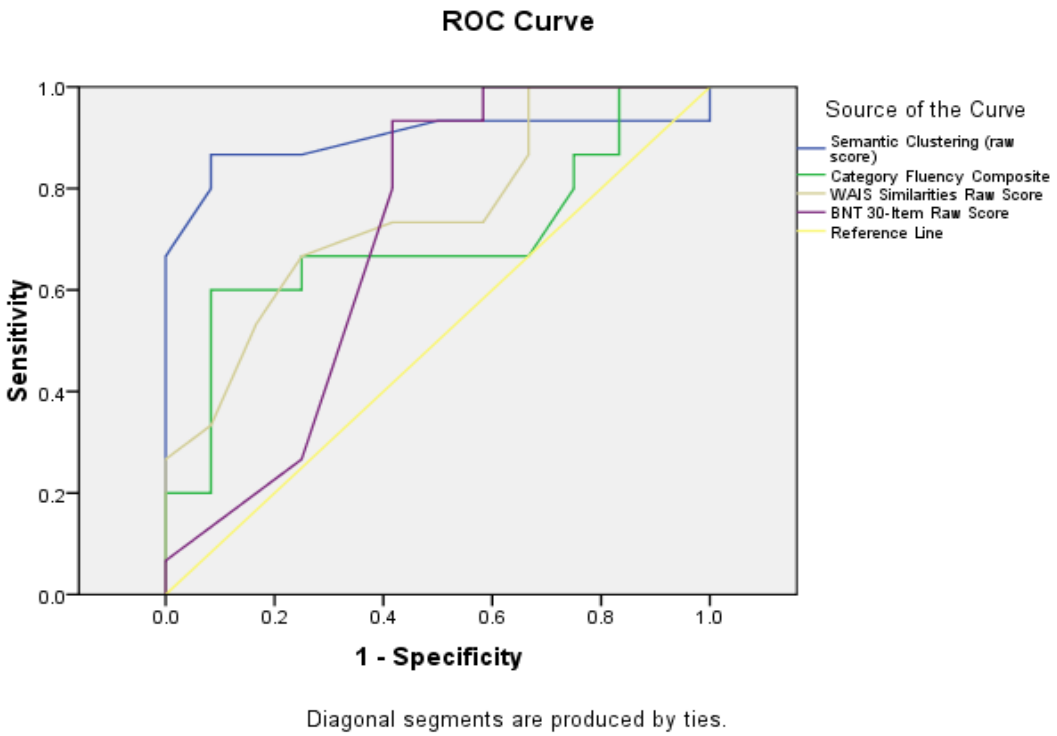
Note: Significance level p<.05

Hypothesis 3

Hypothesis 3 suggested the development of cutoff scores on various measures that would classify participants correctly as MCI or control. Receiver Operating Characteristic (ROC) curve analysis was used to determine these cutoff scores based on measures that were significantly different between the diagnostic groups. Results indicate that CVLT-II Semantic Clustering score produced a significant area under the curve of .897 (p=.000), which is considered a "good" classification measure (Metz, 1978); See Figure 2). The Similarities raw score produced an area of .750 (p=.094) and BNT raw score gave an area of .703 (p=.111). These measures are considered "fair." The Category

Fluency Composite score produced an area of .694 (p=.105) and is considered a "poor" measure of classification. Cutoff scores yielding acceptable sensitivity and specificity were examined for the Semantic Clustering score. A semantic clustering score of -0.15 yielded 93% sensitivity and 80% specificity.

Figure 2. ROC Curve Classifying MCI



Note: Semantic clustering curve is "good," while Similarities and BNT are considered "fair." Category Fluency is a "poor" classification measure.

Level of impairment

As proposed, the number of individuals in each diagnostic group with various levels of impairment was examined. Very subtle impairment was defined as performing 1

SD below normative data when available, or the control group mean. Subtle impairment was 1.5 SD below the mean, and significant impairment was 2 SD below the mean. The MCI group had significantly more individuals than controls with clear impairment on the Boston Naming Test and subtle impairment on the CVLT-II Semantic Clustering score. Results from these analyses are presented in Table 7.

Table 7. Level of Impairment on Semantic Memory Measures

Semantic Memory Measure	*Control (n = 15)*	*MCI (n = 12)*	*p value*
Phonemic Fluency	Very Subtle = 2 Subtle = 4 Impaired = 0	Very Subtle = 2 Subtle = 0 Impaired = 3	.072
Semantic Fluency	Very Subtle = 1 Subtle = 2 Impaired = 0	Very Subtle = 1 Subtle = 0 Impaired = 2	.246
Boston Naming Test	Very Subtle = 0 Subtle = 0 Impaired = 1	Very Subtle = 0 Subtle = 2 Impaired = 5	.013
Naming to Description	Very Subtle = 1 Subtle = 0 Impaired = 1	Very Subtle = 0 Subtle = 2 Impaired = 1	.329
Vocabulary	Very Subtle = 2 Subtle = 1 Impaired = 0	Very Subtle = 0 Subtle = 1 Impaired = 1	.410
Similarities	Very Subtle = 2 Subtle = 2	Very Subtle = 1 Subtle = 0	.073

	Impaired = 0	Impaired = 4	
Information	Very Subtle = 0	Very Subtle = 0	.692
	Subtle = 1	Subtle = 2	
	Impaired = 1	Impaired = 1	
Semantic Clustering†	Very Subtle = 1	Very Subtle = 6	.011
	Subtle = 0	Subtle = 0	
	Impaired = 0	Impaired = 0	

Note: Significance level $p<.05$
†As compared to normative data

DISCUSSION

The goal of this study was to characterize semantic memory functioning in a group of individuals with prospectively consensus-diagnosed MCI based on Mayo diagnostic criteria (Petersen, 1995, 2004; Petersen et al., 1999b). In general, this sample of individuals with MCI did not demonstrate any frank impairment (i.e. >1.5 SD below the mean) on the semantic memory tasks when compared to normal controls, consistent with the diagnostic criteria of MCI. However, subtle deficits in performance on several measures in the semantic memory battery were evident. Hypotheses that individuals with MCI would demonstrate subtle deficits relative to controls were supported, with group differences on several semantic memory measures and learning strategy. Use of these measures to develop diagnostic cutoff scores was explored and discussed below.

Semantic Fluency

It was hypothesized that the MCI group would demonstrate poorer performance on measures of semantic fluency, verbal abstract reasoning, and naming to description with no deficits on general vocabulary knowledge, general fund of knowledge, or confrontation naming. Results provided partial support for this hypothesis. The MCI group demonstrated poorer semantic fluency than the control group. This is consistent with other studies that have found subtle semantic fluency deficits in MCI patients relative to controls. Vogel and colleagues (2005) examined semantic memory with a Danish neuropsychological battery that included Animal Fluency. Their findings

indicated that Animal Fluency performance was able to effectively distinguish individuals with MCI from controls as well as from those with mild AD. An additional study found clinically significant declines in both the phonemic and semantic fluency of individuals with MCI based on D-KEFS performance relative to controls, although individuals with MCI performed in the low average to average range based on normative data (Nutter-Upham et al., 2008). This suggests that fluency deficits may exist in MCI, although likely not to an extent producing impairment.

Semantic vs. Phonemic Fluency

A discrepancy between semantic and phonemic fluency has commonly helped distinguish between cortical or subcortical dementia, with poorer semantic fluency suggesting the presence of a cortical dementia such as AD (Farah & Grossman, 2003). In the present study, individuals with MCI were more likely to have poorer semantic than phonemic fluency performance. There were also more individuals in the MCI group whose semantic fluency performance fell in the impaired range. However, the majority of those in the MCI group with impaired semantic fluency demonstrated impaired phonemic fluency as well.

There is debate about whether semantic fluency deficits are a result of degraded semantic memory networks or executive dysfunction that in turn affects the strategic accessing of this information (Chertkow et al., 1989; Giffard et al., 2002; Henry & Crawford, 2004; Henry et al., 2004; Ober & Shenaut, 1988). A recent investigation (Duong, Whitehead, Hanratty, & Chertkow, 2006) of multiple tasks of semantic memory and executive functioning suggested that deficits in MCI are related to poor inhibition

during intentional search procedures, with eventual progression to degraded semantic networks in later stages of AD. Comparisons between groups with AD and SD provide further support for poor executive control and explicit retrieval, with eventual degradation of the semantic networks in AD (Rogers & Friedman, 2008). The failure to find a discrepancy between semantic and phonemic fluency in the present sample suggests that the deficits may be driven by executive processes involved in the strategy and search procedures necessary to complete the tasks (Duong et al., 2006; Henry et al., 2004; Rogers & Friedman, 2008).

While executive tasks were not explicitly measured in the current study, they have clearly become an important avenue for investigation as a mediator of semantic fluency in individuals with MCI and AD. Future studies of semantic fluency in MCI should certainly include explicit executive function measures to help tease apart the mechanism of decline in verbal fluency. The utility of the semantic/phonemic discrepancy in a sample of individuals with MCI is not immediately clear in the present study. There is a possibility that individuals with MCI who demonstrate poor semantic fluency are on a diagnostic trajectory toward AD; however, this must be investigated in a longitudinal design.

Living vs. Manmade Discrepancy

A discrepancy between the features relied upon to generate lists of living things and those used to list manmade objects has been suggested (Warrington & Shallice, 1984), with the implication that living things rely on perceptual cues and manmade objects rely on functional cues to trigger the semantic network. This distinction has been

supported in recent investigations of various semantic fluency procedures (Ventura, Morais, Brito-Mendes, & Kolinsky, 2005; Ventura, Morais, & Kolinsky, 2005). Further investigations of semantic fluency decline have revealed variable results with regard to a disparity in living versus manmade items, with the majority of studies finding that patients with AD do not differ from controls based on production of living or manmade category exemplars (Cronin-Golomb, Keane, Kokodis, Corkin, & Growdon, 1992; Ventura, Morais, & Kolinsky, 2005). This discrepancy was not borne out in the current sample of individuals with MCI, suggesting relatively equivalent performance in fluency for both living and non-living items. This study was not designed, however, to examine the types of features participants were using to produce their fluency lists. This would be an interesting area to investigate by examining the fluency lists for feature similarities. This would involve the development of rating criteria to group items together based on perceptual (i.e. fruits that are the same color) or functional (i.e. tools that cut wood) features.

Verbal Abstract Reasoning

The MCI group demonstrated average performance on a task requiring verbal abstract reasoning and the identification of a superordinate category for two similar items based on normative data. However, when compared with the control group who had a similarly high level of education, the MCI group showed evidence of subtle deficits in their ability to identify a superordinate category for word pairs with an abstract relationship as level of difficulty increased. The impact of a high level of education in this sample cannot be ignored. The Similarities subtest of the WAIS-III is highly related

to the Vocabulary and Information subtests, which are, in-turn, often used as a proxy for level of education or overall intellectual functioning (Corral, Rodriguez, Amenedo, Sanchez, & Diaz, 2006). The ability to fully investigate the relationship of education and a diagnosis of MCI on verbal abstraction ability was limited by the high level of education in this sample. Recruitment of a more representative sample, and perhaps even over-sampling of individuals with lower education would be useful in determining whether this level of subtle impairment occurs in less well educated MCI patients. If the performance of this task relies on exposure to multiple concepts and the presence of many and diverse semantic connections that would be acquired in the course of a more thorough education, then level of education would logically impact performance significantly. If, however, deficits on this task in the early stages of dementia are related to executive control and the selection of appropriate responses (Giovannetti et al., 2001), then performance may be less impacted by education.

The Similarities subtest requires several skills for successful completion. One study using the Similarities subtest to differentiate between AD and vascular dementia patients examined the quality of errors made when a zero-point response was given (Giovannetti et al., 2001). Findings indicated that individuals with AD were more likely to provide an answer that was appropriate to the question or "in-set," but that was not a central feature of the semantic relationship between the two items. Further analysis and comparison with other measures in the battery indicated that this was driven by executive processes and the inability to select an appropriate response from many possible options in the individuals with AD. The subtle differences seen in the current sample of individuals with MCI may represent the early stages of that executive dysfunction,

although longitudinal follow-up would be needed in order to make that determination. In the aforementioned study (Giovannetti et al., 2001), responses to the Similarities test were analyzed for their content and error types were broken down into multiple categories. Unfortunately, the current sample size does not support a similar analysis; however, replication of these procedures in a larger sample of individuals with MCI may yield informative results and better explain the source of these subtle deficits.

Given the clearly established involvement of executive function in the performance of the Similarities subtest, it is often included in batteries designed to examine executive deficits. One such study found that individuals with very mild AD exhibited variable levels of performance, but very little frank impairment (Stokholm, Vogel, Gade, & Waldemar, 2006). Others have suggested that impairment was not evident on this task until patients progressed from very mild to mild AD (Baudic et al., 2006). However, poor performance on Similarities along with deficits in general vocabulary knowledge, have been shown to predict conversion to AD within 2 years in a sample of elderly individuals with memory complaint (Guarch, Marcos, Salamero, & Blesa, 2004). Indeed, comparing the current MCI sample's performance strictly to normative data demonstrates no impairment at a group level. However, there are clearly some mild deficits when compared with a similar, highly educated control group.

Confrontation Naming

Group differences on confrontation naming were not anticipated, given prior findings of minimal impairment on this task until more moderate to severe stages of dementia (Perry et al., 2000; Testa et al., 2004). However, the MCI group was found to

have lower mean performance, as well as significantly more individuals who were classified as "impaired" relative to normal controls. When correlating BNT performance with other measures in the semantic memory battery, strong positive relationships were found with a number of other measures, including verbal abstract reasoning, vocabulary knowledge, general fund of knowledge, and episodic memory. Recent research has suggested that lexical retrieval deficits play a significant role in performance on episodic memory tasks, particularly in an MCI sample (Jefferson et al., 2006), and that finding would certainly have a significant impact on the current study's measures, as they are all verbal tasks. Another assessment battery (Semantic Object Retrieval Task – SORT) looking specifically at semantic memory in MCI revealed deficits in approximately one-third of their MCI sample (Kraut et al., 2007). Additionally, all of the semantic memory measures were significantly correlated with the BNT . Impaired performance on the SORT and the BNT was correlated with tests of frontal lobe function, again suggesting an executive component to the deficits seen in MCI.

A very recent investigation of metabolic activity and its association with semantic memory functions in individuals with MCI and dementia revealed a positive correlation between confrontation naming performance and levels of NAA and Choline in the left frontal pole (Rami et al., 2008), with the implication that reduced levels of these metabolites represent axonal loss or membrane dysfunction and are present in neurodegenerative diseases such as AD. This finding is certainly consistent with structural studies that implicate the temporal pole and entorhinal cortex in semantic memory (Dudas et al., 2005; Graham et al., 1997, 1999). However, other semantic memory measures in their battery (i.e. semantic fluency) were not associated with

metabolism in the temporal pole, but instead in the left prefrontal cortex, again raising the question of the role of executive function in the performance of semantic memory tasks.

Naming to Description

The Naming to Description task was expected to produce group differences based on findings by Hodges and Patterson (1995) that this task distinguishes between individuals with very mild AD and controls; however, participants with MCI and controls were equivalent on nearly all components of this task, including living versus man-made items, as well as perceptual versus functional clues. This finding was surprising, given indications that individuals with AD often demonstrate a split in their ability to identify living and man-made items (Hodges & Patterson, 1995; Hodges, Patterson, Graham, & Dawson, 1996). Similar to verbal fluency measures, a functional clue is more useful in describing a manmade item, while a perceptual clue is more informative when describing a living thing, even in healthy adult populations (Marques, 2005). However, this differentiation did not appear in either group in this study. Several possible explanations exist.

First, this test was developed for administration to British participants and therefore some subtle cultural and linguistic differences are present in the text of the descriptions (e.g. a fruit with a "stone" inside instead of a "pit"). In addition, some of the descriptions were vague so as to produce more than one plausible answer. However, only the answer intended by the authors was scored as correct. This seemed to be a problem more commonly in the fruit category. Examples include, "A fruit, grown on trees in this country, usually eaten raw," where the intended answer is "pear." One can easily and

quickly produce multiple appropriate responses for this vague description, but only "pear" was counted as correct. There were also some clues that appeared to mix functional and perceptual attributes, when the intention was for a "pure" functional or perceptual description. For example, "The four-legged animal of varying sizes, with a furry coat and a tail that barks" may be perceived as mixing a perception (four legs, furry tail) and a function (barking). Finally, several of the participants in this highly educated group took issue with some of the technical aspects of the descriptions and questioned their factual basis (e.g. camels can't actually survive without water; penguins aren't necessarily "small" birds).

An additional factor is the selection of test items administered. The PI randomly selected four items from each of eight categories, and then selected the perceptual cue for two of the items in a category and the functional cue for the two remaining items. Items were removed from the measure if they could not be easily edited (e.g. change one or two words) for an American audience. As mentioned previously, some items remained culturally specific after editing. Given that the Naming to Description test has not been normed in an American sample, these findings must be interpreted with caution. However, the measure's use in this study was supported by previous research on semantic memory in AD performed by the test's authors (Hodges & Patterson, 1995; Hodges, Patterson et al., 1992; Hodges, Salmon, & Butters, 1990; Hodges, Salmon et al., 1992). Future use of the measure may yield diagnostic group differences similar to Dr. Hodges' findings, although more careful editing and investigation of the psychometric properties in this population is recommended.

Semantic Clustering

It was hypothesized that individuals with MCI would have lower semantic clustering scores than controls, indicating failure to spontaneously use semantic clustering as a learning strategy. It was also anticipated that the semantic clustering score would correlate with other measures in the semantic memory battery and have a strong predictive relationship with verbal learning. Again, there was partial support for the hypothesis. The Semantic Clustering score is derived by counting the number of times two words from the same category are recalled in succession on all free recall trials (Delis et al., 2000). The score is adjusted for chance and standardized, such that a positive raw score indicates use of the strategy above and beyond chance-level, and a negative score indicating semantic clustering at less-than-chance. This group of individuals with MCI did not spontaneously use semantic clustering as a memory strategy for verbal learning to the same degree as did the normal controls. Instead, the MCI group tended to rely on a less efficient serial clustering strategy. This has also been shown in prior studies examining learning strategy in MCI (Ribeiro, Guerreiro, & De Mendonca, 2007). Several possibilities exist to explain this finding. Group differences on verbal abstract reasoning suggest difficulty in the MCI group in articulating an appropriate superordinate category for similar items. The identification of a superordinate category during the CVLT-II would be even more difficult given the presentation of words from four competing categories in mixed order without specific task instructions to place words into a category. However, it is more likely that, while the ability to identify a simple semantic category remains intact, the executive processes required to spontaneously implement semantic categorization as a learning strategy are impaired.

Ribeiro and colleagues (2007) found that individuals with MCI were able to benefit from semantic cues and improve their cued recall to the same degree as controls. They calculated indicies for semantic clustering at short-delay and long-delay in addition to the overall semantic clustering score that has been used in the present study, and found that semantic clustering improved at long delay for both the control and MCI groups, presumably as a result of being provided with the cues during the Short Delay Cued Recall trial. In the current sample, there was a negative relationship between semantic clustering and cued recall change scores (i.e. additional words recalled as a result of cueing) for both short-delay and long-delay. Given that individuals with high semantic clustering scores had already implemented the strategy that was being encouraged by providing category cues, this is a logical finding. The MCI group had greater improvement following the initial presentation of category cues than the control group. The difference in improvement between the MCI and control groups as a result of those category cues may reflect a ceiling effect for the control group. In effect, their free recall was already adequate and thus they produced relatively similar lists after cueing. It should be noted that even with the significant improvement in recall after cueing, the MCI group remained impaired in their memory performance at all trials (Short Delay Free, Short Delay Cued, Long Delay Free, and Long Delay Cued), consistent with the use of the CVLT in meeting the diagnostic criteria for MCI.

A component of the second hypothesis was that the Semantic Clustering score would independently predict Long Delay Free Recall. It was anticipated that even participants who did not use semantic clustering on Trials 1-5 and Short Delay Free Recall would gain benefit from the introduction of categories during the initial cueing

and would make use of semantic clustering spontaneously during Long Delay Free Recall. This hypothesis was not supported. Although the semantic clustering and Long Delay Free Recall scores have a strong relationship, the predictive power of semantic clustering was eclipsed by the Short Delay Free Recall scores, suggesting that initial learning better explained delayed recall, regardless of learning strategy.

It was anticipated that the Semantic Clustering score would be correlated with the other measures in the semantic memory battery, with the potential for the development of a semantic memory "factor." There was no support for this hypothesis, with no correlations approaching significance. It is possible that the Semantic Clustering score is more representative of executive processes, such as recognizing the implicit structure of a task and spontaneously implementing an effective strategy. In fact, the semantic load of this task is relatively small. There are only four possible categories, and the relationships between the list items and those categories is very concrete, unlike other tasks in the semantic memory battery (i.e. Similarities) where more abstract reasoning and understanding of multiple relationships is required. The hypothesis that semantic clustering and executive functions are highly related has been suggested elsewhere (Ribeiro et al., 2007), and warrants further exploration in this population.

Cutoff Scores

One goal of the study was to determine whether measures from the semantic memory battery would be able to effectively differentiate between individuals with MCI and normal controls using cutoff scores. Clearly, no single instrument will provide as complete a diagnostic picture as a clinical diagnosis made by an interdisciplinary team,

and it is important to note that semantic memory impairment is not a diagnostic feature of amnestic MCI. However, examining the measures on which the groups differed to see how well the measures were able to differentiate diagnostic groups proved an interesting exercise. The clinical relevance of establishing diagnostic cutoff scores in this sample is in the brief and accurate identification of individuals at-risk for more severe memory decline. In addition, the ability to effectively administer accurate measures over the telephone would certainly broaden the sample that could easily be assessed and referred for more extensive evaluation and treatment. However, none of the measures administered over the telephone proved to be effective at classifying individuals with MCI and controls with adequate accuracy. The Semantic Clustering score from the CVLT-II proved the only "good" indicator of diagnostic classification, suggesting that a raw score less than -.15 identifies MCI with 93% sensitivity and 80% specificity.

It should be noted, however, that the semantic clustering score is derived from and highly correlated with recall scores (See Table 6) from the CVLT-II, which is a primary measure of episodic memory used in diagnosing MCI. Therefore, it is not surprising that the semantic clustering score is more valuable in classifying participants than other measures that were not available to the diagnostic consensus committee. In summary, the exploratory analysis of the diagnostic utility of the semantic memory battery did not yield particularly useful results. Perhaps more important would be the use of semantic memory measures in predicting conversion from MCI to AD in a longitudinal follow-up.

Medical Factors

A surprising finding of the current investigation was a non-significant difference in the number of individuals currently taking medications targeted at memory problems. Only two people with MCI were currently taking any memory-related medications, and two had previously discontinued medications. Perhaps this should not be surprising given the recent debate about whether cholinesterase inhibitors are effective in treating MCI or preventing conversion to AD (Aisen, 2008; Raschetti, Albanese, Vanacore, & Maggini, 2007; Winblad et al., 2008). One control had been prescribed the medication by a family doctor based on subjective memory complaint, but noticed no improvement and discontinued the medication several years prior to the present evaluation. One individual in the control group who was excluded from analyses suggested that he had been told the medications were unnecessary, but was so fearful of developing AD based on family history that he took them prophylactically. This raises several important issues that, unfortunately, are beyond the scope of this study with regard to prescribing practices and the efficacy of cholinesterase inhibitors as prophylactic treatment. From a methodological standpoint, these medications may be masking more severe deficits in the MCI sample, and the inclusion of individuals taking the medications introduces unwanted heterogeneity. However, given the small sample size and the unclear benefits of these medications in MCI, individuals were not excluded from the MCI group based on medication usage.

Limitations

Telephone Assessment

The primary limitation was a change in the procedures of data collection from an in-person assessment to telephone assessment mid-way through the study. While the success of data collection over the phone supports the utility of this procedure in limited settings (Crooks et al., 2007; Debling et al., 2005; Lipton et al., 2003), in-person assessment remains ideal. Several barriers to an adequate assessment environment include an increased possibility of distraction due to family members, pets, call waiting, and the doorbell. In addition, participants are not visually observed during the assessment and could have access to alternative sources of information, such as the internet or a dictionary, thus invalidating their personal responses. However, these issues did not appear to play a significant role in the present study given the lack of performance differences when the two methodologies were compared. The primary issue with telephone assessment in this sample was hearing difficulty on the part of participants and the need for significant repetition of stimulus material. Fortunately, the measures in use did not limit the number of repetitions provided to the examinee and did not appear to invalidate any responses; however, it was a frustrating limitation that would not have occurred with as much frequency during in-person assessment. The examiner did not have difficulty hearing or understanding responses from the participants.

Although performing telephone assessments limited the data collected to only verbal tasks, it provided a significant benefit in participant acquisition. Recruitment increased in volume and turnaround time once the assessment procedure was changed. Although no formal data were collected, anecdotal reports suggest that participants were

more willing to participate in the telephone assessment due to its briefer length and the lack of a return visit to UAB, which often involves difficult traffic, complicated directions, and parking at a significant distance from the appointment site. Many potential participants of this demographic group do not drive, or prefer not to drive in large cities. The ability to complete the assessment without arranging transportation or individually dealing with the hassle appeared to be attractive to many of the participants. While many individuals noted that they disliked talking on the telephone in general, none felt that they would be unable to complete the evaluation. Although telephone assessment placed limitations on the type and amount of data that was collected, it appeared to broaden the sample of participants willing and able to participate and reduce participant burden significantly.

Demographics

The sample of participants in the current study was not necessarily representative of the demographics of the general population. The most prominent difference in demographics was the high level of education in the sample as a whole. The control group and MCI group in this study were highly educated, with over half of the entire sample achieving at least a high school education. While this is similar to some other studies of semantic memory in MCI (Aggarwal et al., 2005), it does limit the generalizability of these findings. Given the developmental nature and early acquisition of semantic memory (Hodges, Patterson et al., 1992; Tulving, 1987, 1992), the possible impact of amount and quality of education must be considered. High levels of education may have contributed to the strong performance of both groups (average to high average

range) on tests of verbal abstract reasoning, as well as vocabulary knowledge and general fund of knowledge. Vocabulary knowledge and general fund of knowledge, which are often used as proxy measures for level of educational attainment and overall intellectual functioning (Corral et al., 2006), did not exhibit any group differences, suggesting relative preservation in the MCI group of general intellect. However, the emergence of deficits in the MCI group on verbal abstract reasoning, category fluency, and confrontation naming, despite above-average education, suggests a certain robustness to these findings. If these deficits are present, even in a highly-educated group with presumably multiple and diverse semantic connections, there is likely a very real process of decline in this set of cognitive skills. However, greater recruitment of individuals with average and even lower levels of education will be critical to understanding the relationship of education to semantic memory functioning in the MCI population, and whether or not subtle decline is detectable in individuals with lower levels of education.

A second demographic factor in this sample was racial differences. It was initially anticipated that approximately 20% of the sample would be African-American based on the ADRC participant base as a whole. In the final sample, only 13% were African-American, and only one participant with MCI was African-American. Racial disparities in the diagnosis of MCI and rates of conversion to AD have been explored previously, suggesting that there is a higher rate of diagnosis of dementia in African-Americans (Green et al., 2002; Gurland et al., 1999; Tang et al., 2001), but lower rates of conversion from MCI to AD (Griffith et al., 2006). Based on the limited number of African-Americans in the current sample, it is impossible to draw any conclusions about possible racial and ethnic differences in semantic memory functioning in MCI. Again, recruitment

of a larger sample would permit an investigation of any racial differences in semantic memory performance. Further investigation into the cultural relevance and possible test bias of the semantic memory battery would also be possible with a larger sample and greater numbers of African-American participants.

No Follow-up

While this study employed a cross-sectional design to characterize semantic memory functioning in a sample of individuals with MCI, the utility of these findings is limited with regard to their power to predict progression to AD. However, given the participants' involvement in the ADRC, longitudinal follow-up will eventually be available and data on conversion to AD can then be collected. Furthermore, the absence of a comparison group of individuals with AD limits any specific conclusions about progressing impairment on these semantic memory tasks following the conversion to AD. While these are clear limitations to the design of this study, the current cross-sectional findings provide a foundation from which to explore these issues with longitudinal follow-up and a larger diagnostic scope of participants.

Future Directions

Based on the finding of subtle deficits in semantic memory functioning in this sample of individuals with MCI, future investigations should focus on longitudinal follow-up with this sample to determine whether performance on any of the semantic memory measures is able to predict conversion to dementia within a particular timeframe. It may very well be that individuals with MCI who exhibit semantic memory deficits may

be further along on the trajectory to AD. It may also be possible that individuals exhibiting semantic memory deficits may have a subtype of MCI that is more likely to convert to AD. Regardless, longitudinal characterization of these semantic memory deficits would be ideal.

While the assessment of verbally-mediated semantic memory functions yields significant findings, a more complete investigation of other semantic memory tasks, including non-verbal performance, may provide additional information about the mechanisms of impairment. Examining visual tasks such as picture matching or picture sorting may provide a dissociation and help clarify whether semantic memory deficit in MCI are related to linguistically-mediated processes or whether they point toward a more central semantic processing deficit.

Finally, gathering functional neuroimaging data during these semantic tasks may further inform as to the mechanisms that underlie semantic memory deficits. Correlational studies suggest that semantic memory function in MCI and AD depends on the integrity of the polar and inferolateral temporal cortex (Dudas et al., 2005; Graham et al., 1997, 1999). Prior functional imaging in healthy adults has revealed activation in the left prefrontal and temporal cortical regions during semantic memory tasks (Cabeza & Nyberg, 2000). However, investigating a dissociation between activation in the temporal areas versus frontal and prefrontal activation may aid in determining whether deficits in MCI are a product of degraded semantic networks, or of executive dysfunction in MCI that later progresses to degraded networks in the more advanced stages of AD (Duong et al., 2006; Rogers & Friedman, 2008).

CONCLUSIONS

The purpose of this study was to investigate verbal semantic memory functioning in a group of individuals diagnosed with MCI. In addition to deficits in episodic memory, individuals with MCI demonstrated subtle deficits on various semantic memory tasks when compared with the healthy control group. Specifically, individuals with MCI had poorer semantic fluency, verbal abstract reasoning, confrontation naming, and spontaneous use of semantic clustering as a learning strategy. While these deficits were present as compared to the control group, impairment was not noted based on normative samples. This suggests that semantic memory deficits at this early stage of memory impairment are subtle. However, the specific semantic memory deficits that are present in this MCI sample have been previously shown to progress in later stages of dementia and eventually have a significant impact on functional status (Aggarwal et al., 2005; Hodges & Patterson, 1995; Perry & Hodges, 2000a, 2000b). Therefore, these semantic deficits may provide an avenue for early identification of individuals at risk for progression to dementia. Given that executive dysfunction has been frequently implicated in deficits of category fluency, verbal abstract reasoning, and implementation of learning strategies, further investigating the relationship of executive function to semantic memory measures will be imperative.

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APPENDIX A

TELEPHONE SCRIPT

Telephone Script #1 – Information and recruitment

Hello. This is Kelli Netson from UAB. I received a return postcard from you indicating that you would like more information about the TASK study. Is this a good time to talk with you about the study?

The purpose of the TASK study is to examine different types of memory abilities that may change with memory problems like Mild Cognitive Impairment and Alzheimer's Disease. I am looking at skills like trivia skills and word knowledge to examine these types of memories, and these skills can be assessed over the telephone.

If you would be interested in participating, we would need to schedule a time to spend 30-45 minutes on the telephone. During that time, we will go over some general questions about your health and day-to-day functioning, and then I will ask you several questions and have you complete some tasks that involve semantic memory. It will be important for us to schedule that phone call at a time where you will be able to focus and not have any interruptions. After we have finished the study phone call, you will receive a $20 gift card in the mail within 2-3 weeks to thank you for your help with the study. Does that sound like something you might be interested in participating in?

IF "NO": I appreciate your interest in the study. Thank you for your time.

IF "YES": There is some important information for you to know before we schedule this appointment. First, this is strictly for research, and I will not be providing you with any sort of diagnosis or feedback on your performance. Second, because this will be done over the telephone, there is no paperwork for you to sign to give your consent. By answering the phone during our scheduled study phone call, you are agreeing to participate with the understanding that you can stop at any time during the course of the study. If you decide you no longer wish to participate, your ability to receive care at UAB and participate in other ADRC studies will not be affected in any way. Do you have any questions about participating in the TASK study? Would you like to schedule a time for a study telephone appointment?

I will call you at _____ on _____, 2008. Will that be a good time to spend 30-45 minutes on the phone without being interrupted?

If you have any questions before your study phone call, feel free to contact me at the number or email address printed on your study brochure. Thank you for your interest in the TASK study. I will talk to you again soon.

Telephone Script #2 – Study call

Hello. This is Kelli Netson from UAB. I was calling about your TASK study appointment. We will need 30-45 minutes to talk on the phone and finish all of the questions. Is this still a good time for that appointment? I just want to remind you that your participation in this phone call is strictly voluntary. You are free to stop at any time. Do you have any questions before we get started? Do you need any time to get rid of any distractions like TV or cell phones that might interrupt us?

First, I'd like to go over some general questions about your background and your general health.

Demographic Questionnaire

1) Verbal Fluency

Now, I'm going to give you a letter of the alphabet. You will have 1 minute to give me as many words as you can think of that begin with that letter. There are 2 rules. First, don't give me any names of people or places. That means, if the letter was "T," you could say toy, talk, and take, but you couldn't say "Tom" because that's someone's name, and you couldn't say "Texas," because that's the name of a place. The second rule is that you can't give me the same word with different endings. You could say "talk" but you could not *also* say "talks, talked, talking." Do you have any questions?

Your first letter is "C." Begin.

Time for 60 seconds.

Repeat for letters F & L.

Now we're going to do something a little bit different. This time I'm going to give you a category and I want you to give me as many words as you can think of that belong in that category. The words can begin with any letter. Do you have any questions?

Your first category is "Animals." Begin.

Time for 60 seconds.

Repeat for Vegetables, Vehicles, and Furniture.

2) Naming to Description

Now I'd like for you to listen to some characteristics of different things and tell me what I'm describing.

3) WAIS Information, Similarities, Vocabulary

Administered as described in WAIS-III Manual.

That completes the study evaluation. Thank you so much for your help with this study. Do you have any questions about anything we did?

To thank you for your help, you'll be receiving a gift card in the mail in the next couple of weeks. What is the best address to use when mailing the gift card to you?

Once again, thank you so much for your help.

APPENDIX B

HODGES NAMING TO DESCRIPTION TASK

ITEM #	DEFINITION	ITEM	F/P
1	A farmyard bird that pecks at grain, lays eggs and can be eaten.	CHICKEN	F
2	A large household container with handles and a lid.	TRASH CAN	P
3	A domestic animal that can jump and catches mice.	CAT	F
4	A small, coloured object with a row of teeth along one side.	COMB	P
5	A bad-tempered animal that is ridden in the desert, and can survive without water.	CAMEL	F
6	A small fruit with shiny red or black skin and a stone inside.	CHERRY	P
7	The sharp implement used with both hands for chopping trees or wood.	AXE	F
8	The large metal vehicle with wheels, and many seats on one or two decks.	BUS	P
9	A large bird with a sharp hooked beak sharp claws and a large wingspan.	EAGLE	P
10	A heavy wooden container for liquids that can be rolled along the ground.	BARREL	F
11	The large, four-legged animal with hooves, a mane and a tail.	HORSE	P
12	A handheld item with a handle, used for smoothing hair or sweeping up dirt.	BRUSH	F
13	A large animal with strong hind legs and a pouch for carrying its young.	KANGAROO	P
14	A native fruit, that grows on trees that can either be eaten raw or cooked in pies.	APPLE	F
15	The lightweight tool with a wooden handle and soft bristles.	PAINTBRUSH	P
16	The vehicle that carries passengers in the air.	AIRPLANE	F
17	A nocturnal bird, said to be wise, which lives in barns and catches and eats small animals.	OWL	F
18	A small square kitchen item with a lever on the side and two slots in the top.	TOASTER	P
19	The garden pest that climbs trees and stores nuts.	SQUIRREL	F
20	A square object with 3 metal prongs, attached to a wire.	PLUG	P

21	A dangerous meat-eating wild animal that lives in India and climbs trees.	TIGER	F
22	A small red fruit with speckled skin and a green leafy stalk.	STRAWBERRY	P
23	The sharp, flexible tool used by carpenters for cutting wood.	SAW	F
24	The wooden vehicle with runners and a seat, that can be pulled by dogs.	SLED	P
25	A small upright black and white bird with small wings and short legs.	PENGUIN	P
26	A piece of furniture, for sitting or standing on.	STOOL	F
27	The four-legged animal of varying sizes, with a furry coat and a tail, that barks.	DOG	P
28	A fragile vessel held in the hand and used for drinking.	GLASS	F
29	A large four-legged animal with a thick leathery skin and a horn on its nose.	RHINOCEROS	P
30	A fruit, grown on trees in this country, usually eaten raw.	PEAR	F
31	The lightweight tool with a handle and a thin metal shaft with a flattened end.	SCREWDRIVER	P
32	The fast and dangerous vehicle that can be ridden or raced.	MOTORCYCLE	F

Note: Used with written permission from J.R. Hodges (personal communication, April 24, 2006).

APPENDIX C

DEMOGRAPHIC FORM

KNOWING/TASK Study Demographic Information

DOB: _____ Age: ____ Gender: M F Education: _____

Race: C AA A H O Marital: M D S W Handedness: R L A

Medications:

Medical Problems:

Falls?

ADLs?

Working?

Social Activities?

APPENDIX D

IRB APPROVAL FORM

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines. The Assurance became effective on November 24, 2003 and expires on October 26, 2010. The Assurance number is FWA00005960.

Principal Investigator:	NETSON, KELLI L
Co-Investigator(s):	
Protocol Number:	**X080401003**
Protocol Title:	*TASK Study: Telephone Assessment of Semantic Knowledge in Individuals with Mild Cognitive Impairment*

The IRB reviewed and approved the above named project on 4/25/08. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 4-25-08

Date IRB Approval Issued: 4/25/08

Marilyn Doss

Marilyn Doss, M.A.
Vice Chair of the Institutional Review
Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

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