2012

Analysis of verbal fluency in amnestic and non-amnestic mild cognitive impairment

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ANALYSIS OF VERBAL FLUENCY IN AMNESTIC AND NON-AMNESTIC MILD COGNITIVE IMPAIRMENT

A Thesis

Presented To

Eastern Washington University

Cheney, Washington

In Partial Fulfillment of the Requirements

for the Degree

Master of Science

By

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Spring 2012

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MASTER'S THESIS

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Abstract

Background: Mild Cognitive Impairment (MCI) is defined as significant memory impairment that lies somewhere on the spectrum between normal, healthy aging and dementia. Tests of verbal fluency are simple and efficient tools that have shown to be sensitive enough to discriminate between healthy aging and early cognitive decline. The purpose of this study was to investigate letter and category verbal fluency abilities in two subtypes of MCI: amnestic and non-amnestic, and two domains of amnestic MCI: single and multiple.

Methods: Participants were 25 persons with single domain amnestic MCI, 49 with multiple domain amnestic MCI, 16 with non-amnestic MCI, and 90 cognitively healthy older adults. Participants were asked to generate as many words as possible belonging to a category "animal" or beginning with a specific letter "f". Verbal fluency performance on the letter and category fluency subtests were analyzed across 30-second intervals and according to the clustering and switching scoring paradigm developed by Troyer et al., 1998.

Results: Single domain amnestic MCI was found to be the least impaired of our MCI groups, performing comparably to the control group on each dependent measure across both fluency tasks. The Multiple domain amnestic MCI group showed equal impairment in word and switch generation on both fluency tasks while the non-amnestic MCI group performed more poorly, in terms of word and switch production, on the letter fluency task compared to the category fluency task.

Conclusions: Our findings demonstrate that verbal fluency performance is sensitive enough to discriminate between MCI groups. Results from the study also lend evidence to the understanding of the functional brain areas that are compromised at the MCI stage of impairment.

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1. Introduction

1.1 Importance of studying MCI and Verbal Fluency

Advances in medicine and an improving standard of living have increased the average life expectancy worldwide. This increase has resulted in a larger share of the global population living over the age 65. As age is the prime contributing factor to dementia, the number of people at risk for developing Alzheimer's disease (AD) and other types of age-related cognitive decline will grow dramatically in the coming years. By 2050, estimates show that 20.7 percent of people living in the U.S. will be over the age 65 (Sattler & Ryan, 2009), compared to 13 percent in 2010 (U.S. Census Bureau, 2012), resulting in approximately 88.5 million elder Americans (U.S. Census Bureau, 2011). Currently, 5.4 million Americans have symptoms that meet diagnostic criteria for probable AD. Within the general U.S. population, 1 in 7 people between the ages 65 and 84, and 1 in 2 people over the age 85, are living with Alzheimer's-type dementia (Alzheimer's Association, 2012). With these estimates in mind, it is anticipated that by 2050 between 11 and 16 million people will meet criteria for Alzheimer's-type dementia in the U.S. alone.

In light of these projections, intensive research has focused on identifying risk factors for developing AD and other types of dementia (e.g., frontotemporal, vascular, Lewy body) with the aim of developing and/or innovating assessment techniques for early detection. Artero, Petersen, Touchon, and Ritchie (2006) discovered that individuals present symptoms of dementia 3 to 5 years before they meet criteria for diagnosis. Older adults who are experiencing cognitive deficits that do not meet clinical criteria for dementia and who's level of impairment is greater than that considered to be "healthy

aging" are classified as having Mild Cognitive Impairment (MCI; Petersen, 1999). Estimates show that between 12 to 41% of individuals with MCI convert to AD after one year, which is significantly high compared to 1 to 2% of the general population displaying no cognitive deficits (Petersen et al., 2001; Geslani, Tierney, Hermann, & Szalai, 2005). Furthermore, 64% of people with MCI have been found to convert to AD within two years (Geslani et al., 2005), and 80% within six years (Petersen & Morris, 2003). It has also been suggested that 100% of individuals with MCI will convert to dementia within 10 years (Morris et al., 2001).

Clearly, the presentation of MCI is considered to be a significant risk factor for future development of dementia. Because MCI exists as a recognizable risk, it is of heightened importance that individuals with MCI be identified so treatment and intervention may begin early. Early diagnosis of MCI has many benefits to individuals and their families. One such benefit is related to symptomatic treatment of MCI through medication. While no medication has been shown to slow or stop progression of symptoms, medications like acetylcholinesterase inhibitors (e.g., Cognex, Aricept) have shown the greatest efficacy when administered early in the course of cognitive decline (Gauthier et al., 2002). Furthermore, early detection, diagnosis, and care management of individuals with MCI has been found to reduce outpatient costs by nearly 30 percent (Alzheimer's Association International Conference on Alzheimer's Disease, 2010).

Commonly, dementia is associated with problems in memory ability. Yet, deficits often affect non-memory abilities as well. Changes in cognitive domains that typically manifest signs of dementia include: executive function, language ability, perceptual speed, attention, and visuospatial skills (Taler & Philips, 2008). Of these, deficits in

language ability (e.g., verbal fluency, word comprehension) appear to occur early in the course of dementia (Henry, Crawford, & Phillips 2004). Verbal fluency ability, of note, has been observed to be impaired in individuals' years before they meet criteria for the diagnosis of dementia or MCI (Backman, Jones, Berger, Laukka, & Small 2005).

Tests of verbal fluency require individuals to produce words within a fixed time. Typically, these words either start with a certain letter or belong to a given category. Verbal fluency tasks are simple and efficient clinical tools to detect cognitive decline (Radonovic et al., 2009). Furthermore, verbal fluency tasks have been found to discriminate between those with normal cognitive function and individuals in the early stages of cognitive decline (Clark et al., 2009). While a single test evaluating language processing cannot replace memory testing for AD, which is often considered the 'gold standard' in defining dementia processes (Lezak, Howieson, Loring, Hannay, & Fischer, 2004), it does provide important information for making clinical judgments as to the status and stage of possible impairment (Taler & Phillips, 2008).

The purpose of the present study is to identify differences in verbal fluency performance between individuals with MCI compared to cognitively healthy older adults. Relationships between components of verbal fluency ability and neuropsychological factors thought to be important to verbal fluency ability (i.e., language ability and executive functioning; Taler & Phillips, 2008) will also be investigated.

1.2 MCI Diagnostic Criteria

Individuals with MCI show alterations in cognitive domains that are more severe than can be accounted for by normal aging alone. The term MCI was first introduced by researchers to capture the point on the spectrum of cognitive function between healthy

normal aging and dementia (Flicker, Ferris, & Reisberg, 1991). Cognitive domains subject to possible alterations include: episodic memory, executive functioning, perceptual speed, visuospatial skill, and language ability (Taler & Philips, 2008; Albert, Moss, Tanzi, & Jones, 2001).

Given the range of cognitive domains impacted by MCI, the presentation of MCI can vary between individuals. Specifically, as research has advanced it has become clear that clinical subtypes of MCI exist (Petersen et al., 2001). For example, an individual may experience isolated memory impairment, memory deficits coupled with other non-memory impairments, or present with no memory difficulties but have deficit(s) in other cognitive domains (e.g., word finding ability, attention, speeded processing). Individuals that present with memory impairment fall within the amnestic MCI subtype while individuals that do not present with changes in memory are diagnosed as having non-amnestic MCI.

As shown in Figure 1, amnestic and non-amnestic MCI can be further categorized as either having a single cognitive deficit (single domain) or multiple deficits (multiple domain; Petersen et al., 2001). For example, an individual who *only* has deficits in memory ability would be classified as having single domain amnestic MCI. A patient with difficulties in memory who has additional objective impairment in non-memory cognitive areas (e.g., visuospatial skills, executive functioning) would be classified as having multiple domain amnestic MCI. If difficulties in non-memory cognitive domains exist in the *absence* of memory complaints, the patient would be classified as having non-amnestic MCI. Naturally, it follows then that if an individual has one or multiple (two or

more) impacted cognitive areas the individual is diagnosed with having either single or multiple domain non-amnestic MCI, respectively (Petersen, 2003).

The first diagnostic measure used to classify individuals with MCI was introduced by Flicker and colleagues (1991). They defined MCI as a score of 3 out of 7 points on the Global Deterioration Scale (GDS; Reisberg, Ferris, de Leon, & Crook, 1982). Specific deficits at this stage include a noticeable decrease in job performance, word or name finding difficulties, and difficulty retaining visual information (Reisberg et al., 1982). The Clinical Dementia Rating Scale (CDR; Hughes, Berg, Danziger, Coben, & Martin, 1982) is another scale-oriented classification scheme used to identify MCI. On the CDR, a rating of 0.5 equates to "questionable Alzheimer's Dementia."

Although rating scales often serve as adequate measures in assessing the level of cognitive impairment, criteria that captures the multifaceted nature of MCI and utilizes clinical judgment is favored due to its diagnostic sensitivity. Petersen and colleagues at the Mayo Alzheimer's Disease Research Center developed the first set of formal criteria for diagnosing MCI (1999). Petersen and colleagues' diagnostic scheme includes: (a) subjective complaints of memory loss, (b) objective impairment of memory ability, (c) lack of dementia criteria being met, (d) intact activities of daily living, and (e) preserved general cognitive function. These criteria have since been expanded in order to capture qualities common to both memory and non-memory cognitive impairment. Specifically, Petersen (2004) proposed a method to generate clinical judgments that differentiate between subtypes and domains of MCI. Figure 2 outlines the proposed scheme by Petersen in an algorithmic manner. The new diagnostic scheme is analogous but not identical to the old criteria. Specifically, the largest change concerns point (a) and (b)

listed above, (i.e., rather than being memory specific, the new criteria has been generalized to include any cognitive impairment).

Based on the diagnostic scheme, once a decline in function has been identified that does not meet explicit criteria for dementia, the next step is to determine which precise cognitive areas are compromised. As outlined in Figure 2, if significant memory impairment exists (generally considered to be 1.5 standard deviations below age equivalents) the individual is described as having amnestic MCI. In the case that no memory impairment is observed but other cognitive domains are compromised, individuals are described as having non-amnestic MCI. From here, the diagnosis is specified to include single or multiple domains contingent upon the existence of additional cognitive deficits.

Recently a working group was assembled by the National Institute on Aging and the Alzheimer's Association to revise the diagnostic criteria specifically for MCI due to Alzheimer's type dementia (Albert et al., 2011). The core clinical criteria is made up of the following: (a) cognitive concern as a result of change in cognition as reported by the impaired individual, an informant, or clinician, (b) objective evidence of impairment in one or more cognitive areas, typically including memory impairment, (c) preserved functional ability, (d) does not meet criteria for dementia, (e) other types of brain diseases that could lead to cognitive decline have been ruled out, and (f) evidence of progressive decline (Albert et al., 2011).

Reported incidence rates of MCI subtypes and domains vary widely (Luck, Luppa, Briel, Riedel-Heller, 2010). Among those reported, few studies used published criteria to identify MCI. In a recent study, Roberts and colleagues (2012) estimated the

incidence of MCI subtypes using diagnostic criteria developed by Petersen (2004). Of the 1,450 participants who were neurologically normal at the beginning of testing, 296 developed MCI. The overall incidence rate of MCI was 63.5 per 1,000 person-years. They also found that the rate was higher for men than woman. Conversely, the opposite is generally found within AD populations (see Henry et al., 2004). Robert and colleagues also found that individuals who did develop MCI met criteria for amnestic MCI approximately three times more than non-amnestic MCI (2012).

1.3 Progression of MCI to dementia

The heterogeneity seen in the diagnosis of MCI is also seen in the progression of the disorder. When degenerative etiology is assumed, it is suggested that different MCI subtypes/domains evolve into different types of dementia (Petersen, 2004). Furthermore, when MCI subtypes/domains are taken into consideration, the type of dementia that an individual will likely develop is predicted more accurately (Arterro et al., 2006). Thus, differences between the subtypes and domains of MCI exist as important tools for predicting the future development of dementia.

Amnestic MCI is often considered the pre-clinical stage of AD (Winblad et al., 2004). Therefore, as outlined in Figure 3, single-domain amnestic MCI is suggested to develop into AD (Petersen, 2003). Multiple-domain amnestic MCI is more complicated because it spans both memory and non-memory domains. Multiple-domain amnestic MCI is suggested to manifest into either AD or vascular dementia (Petersen, 2003). Because non-amnestic MCI pertains to impairment in cognitive domains other than memory, there is a higher likelihood that individuals characterized as having non-amnestic MCI will progress to a non-Alzheimer's type dementia. Petersen suggests that

depending on the location of ischemia and the cognitive areas it impacts, non-amnestic MCI likely evolves into either frontotemporal, Lewy body, or vascular dementia (2003).

Acknowledging that MCI has multiple etiologies which likely progress into specific types of dementia makes identifying MCI subtypes and domains an important endeavor because their use may lead to an earlier and more accurate prospective diagnosis of dementia. Thus, identifying assessments that are sensitive enough to detect differences between subtypes and domains of MCI is a task worth exploring. If differences exist between non-amnestic and amnestic MCI on tests of verbal fluency, these tasks may be a valuable resource to clinicians based on the quickness and ease of administration and scoring.

1.4 Tests of Verbal Fluency

Verbal fluency tests are the most widely used measures of language processing, and in a broader sense, cognitive functioning in dementia (Taler & Phillips, 2008). Verbal fluency tasks are commonly used in clinical assessments due to their validity, simple administration, and adequacy as follow-up measures for cognitive performance (Henry et al., 2004). Clearly, verbal fluency assessments deserve more attention in the MCI literature considering the close link between MCI and dementia.

As noted in brevity above, verbal fluency assessments evaluate an individual's ability to retrieve and generate words that fit within a given category (e.g., "name as many animals as you can think of") or begin with a certain letter (e.g., "tell me all of the words you can think of that begin with the letter R") within a specific time period (e.g., 60 or 90 seconds). Letter fluency, also referred to as phonemic fluency, involves the rapid generation of as many words that begin with a specific first letter as possible (e.g.,

F, A, S). Individuals are also advised to avoid repetitions, words that do not start with the specified letter, names of people, names of places, numbers, and word that are similar but have different endings (e.g., say, saying, says). Category fluency, also referred to as semantic fluency, requires an individual to produce as many words as they can that fall within a given category (e.g., animals, parts of the body). Individuals are advised to avoid repetitions and words that do not belong to the specified category.

Letter and category fluency tasks differ in the respective search strategies required to recall and produce words. Letter fluency tasks rely on lexical (i.e., word) representation strategies (Rohrer, Salmon, Wixted, & Paulson, 1999). Specifically, letter fluency requires an individual to select and retrieve information based on the spelling of words and their fund of word knowledge. Category fluency, on the other hand, requires a search through conceptual knowledge stores for semantic extensions derived from a target word (Taler & Phillips, 2008). For example, if the category "animals" was given and an individual said "horse," they may also say "pig, cow, and sheep" in succession due to the close semantic associations with farm animals. Chertkow and Bub (1990) also suggest that adequate performance on the semantic fluency task requires involvement from both search processes (a frontal lobe function) and semantic memory stores (a temporal lobe function). If semantic associations are not intact, the category fluency task may be more difficult or impossible (Rohrer et al., 1999).

Along with the application of search strategies, organization strategies are also necessary for optimal fluency performance. According to Troyer, Moscovitch, Winocur, Leach, and Freeman (1998), two strategies used for optimal fluency performance are clustering and switching. A cluster is defined as a group of semantically (e.g., animals

that are pets) or phonemically (e.g., words that rhyme) related words (Troyer, Moscovitch, & Winoccur, 1997). An example of this strategy would be if an individual said the word "fantasy" and followed it by the words “fan, fanatical, and fantastic”. All of these words grouped together would be considered a cluster of words starting with letters f, a, and n. Switching refers to the shift from one cluster of words that has been exhausted to the start of another cluster of words (Troyer et al., 1997). Or simply, a shift is defined as the point of change from one cluster to a new cluster of words. While clustering relies heavily on verbal memory of words, word sounds, and word storage (Murphy, Rich, & Troyer, 2006), switching relies on strategic search processes and cognitive flexibility (Troyer et al., 1997). Because clustering and switching depend on different cognitive processes they are often investigated to supply additional information about cognitive ability when the volume of words produced alone does not generate enough information about how the individual approached the task and the underlying brain areas that may be impaired.

1.5 Neuroanatomy of Verbal Fluency

Frontal and temporal lobes are highly involved in verbal fluency processes (Jones, Laukka, & Backman, 2006). Letter and category fluency both rely heavily on frontal lobe functioning (Lezak et al., 2004) including executive processes, requiring individuals to organize retrieval, initiate verbal responses, monitor responses previously recalled, and inhibit responses that do not fit within the criterion (Henry et al., 2004). Both measures also access semantic memory stores in fluency performance, a function of the temporal lobe, although the letter fluency task appears to tap this ability to a lesser extent than the category fluency task (Lezak et al., 2004).

Functional brain imaging studies have shown that in neurologically normal adults letter fluency performance is associated with activation in the frontal lobes, more notably within the dorsolateral prefrontal cortex, inferior frontal gyrus, and the premotor cortex compared to baseline resting states (Cuenod et al., 1995; Mummery, Patterson, Hodges, & Wise, 1996; Birn et al., 2010). Where phonemic fluency performance utilizes more frontal lobe activation, semantic fluency draws more on the temporal lobe, particularly the left temporal lobe (Mummery et al., 1996). Areas of enhanced activation during category fluency include the anteromedial and posterior regions of the temporal cortex. Anterior regions of the frontal lobe are also found to be activated during this task (Gourovitch et al., 2000; Birn et al., 2010; Mummery et al., 1996).

In line with functional imagining studies, letter fluency ability is thought to be primarily involved with frontal lobe functioning, while category fluency relies more heavily on temporal lobe functioning (Troyer, Moscovitch, Winocur, Alexander, Stuss, 1998; Martin, Wiggs, Lalonde, Mack., 1994). Lesion studies support the involvement of these brain areas in fluency ability (Jones et al., 2006). For example, frontal-lobe lesion patients have been found to have impaired performance on letter fluency compared to controls (Owen, Downes, Sahakian, Polkey, & Robbins, 1990), whereas temporal-lobe atrophy patients exhibit mild impairment on letter fluency and significant impairment on category fluency tasks (Hodges, Patterson, Oxbury, & Funnell, 1992).

Voxel-based lesion symptom mapping (VLSM), a statistical technique used to analyze the relationship between lesion data and behavioral measures (Bates et al., 2003), provides further support for the theory that letter fluency is primarily mediated by the frontal lobe and category fluency by the temporal lobe. Using VLSM, Baldo, Schwartz,

Wilkins, and Dronkers (2006) found that a group of stroke patients who suffered from left-hemisphere lesions experienced poorer letter fluency performance when lesions were found in the anterior brain regions, including the frontal cortex, while poorer category fluency was associated with lesions in more posterior regions, including the temporal cortex.

To examine what areas of the brain are utilized during efficient clustering and switching Troyer and colleagues (1998) studied patterns of performance in individuals with frontal and temporal lobe lesions. Individuals with frontal lobe lesions demonstrated a marked decrease in switching on both letter and category fluency when compared to controls. However, they managed to produce normal cluster sizes on letter and category verbal fluency tasks. Based on this finding, the authors suggest that switching ability is related to frontal lobe processes such as strategic search ability and cognitive flexibility. Clustering, on the other hand, was shown to be impaired on category fluency (but not letter fluency) in temporal lobe lesion participants. Furthermore, these participants were unimpaired on switching on letter fluency but showed deficits compared to controls on category fluency switches. Based on their results, Troyer et al. suggests that semantic-fluency clustering depends on "access to and the integrity of semantic stores" whereas phonemic-fluency clustering may depend more on "fund of word knowledge and the ability to identify phonemic characteristics of words" (p. 503, 1998). The various cognitive processes involved in the clustering between phonemic and category fluency may account for the lack of deficits in clustering ability on phonemic fluency with individuals with temporal lobe lesions.

Recognizing the different areas of the brain that are employed during a verbal fluency task is important when investigating neurological disorders which, in our case, are age-related neurodegenerative disorders such as MCI and dementia. The remaining introductory sections are dedicated to exploring the neuropathology that exists in MCI and the dementia types they are predicted to evolve into. The changes in brain structure in MCI and dementia serve as the basis for understanding verbal fluency performance and developing our hypotheses when direct observation of verbal fluency performance is lacking.

1.6 AD and Verbal Fluency Ability

AD is characterized by protein fragment beta-amyloid (plaques) and twisted protein tau segments (tangles) as well as nerve cell damage and death in the brain (Alzheimer's Association, 2012). Brain areas compromised in AD are predominantly located in the medial-temporal lobe and temporal-parietal association areas (Braak, & Braak, 1991). Other areas of the brain also become affected by the disease such as the frontal cortex (Braak, & Braak, 1991). Because the temporal lobes are impacted to the greatest degree by AD, individuals with AD are predicted to have a lower performance on category fluency than letter fluency tasks. In a meta-analysis, 153 studies examining category and letter fluency performance in AD were investigated (Henry et al., 2004). As predicted, the meta-analysis found that individuals with AD had more impairment on category fluency than letter fluency. The review also revealed that individuals with AD were impaired on both category and letter fluency relative to healthy older adults. The authors argued that the greater deficit in category fluency is due to degradation of the semantic knowledge stores required for category fluency tests (Henry et al., 2004).

Since plaques and tangles accumulate in the temporal lobes and frontal cortex, it is predicted that individuals with AD would exhibit smaller cluster sizes and fewer switches on letter and category fluency, with these deficits evident on category fluency tasks to a greater extent. Research suggests that individuals with AD do in fact produce overall smaller cluster sizes and switch less compared to healthy older adult controls on both fluency tasks while a differential impairment on category verses letter fluency exists (Murphy et al., 2006). Furthermore, both participants with AD and controls showed greater clustering on category fluency than letter fluency but switched more on letter fluency than category fluency (Murphy et al., 2006). To summarize, individuals with AD had greater difficulty creating clusters; especially clusters on category fluency tests. This is consistent with evidence that supports semantic clustering being related to temporal lobe functioning (Troyer et al, 1998), as individuals with AD generally have neurological damage in this area.

1.7 Amnestic MCI and Verbal Fluency Ability

Based on the theory that amnestic MCI is the preclinical stage of AD (Winblad et al., 2004), it is expected that participants with amnestic MCI will show similar trends in performance on verbal fluency tasks as individuals with AD. However, several research groups have reported that verbal fluency impairment in amnestic MCI is selective (Taler & Phillips, 2008). For example, Murphy and colleagues (2006) found that individuals with amnestic MCI, while being impaired on category fluency, were relatively unimpaired in generating words that begin with a given letter. Adlam, Bozeat, Arnold, Watson, and Hodges (2006) reported similar results. Specifically, they found that category fluency was impaired in amnestic MCI, while letter fluency was not.

Furthermore, several studies have found impairments in category fluency, not letter fluency, in adults up to nine years before the onset of AD (Amieva et al., 2005; Hodges, Erzinçlioğlu, & Patterson, 2006).

Contrary to the selective category fluency impairment results stated above, Nutter-Upham and colleagues (2008) found that both phonemic and semantic fluency were statistically reduced in amnestic MCI compared to cognitively intact older adults. This finding suggests that both the temporal and frontal lobes are compromised at the amnestic MCI stage, impacting quality of semantic stores, lexical representations, and effortful retrieval (Nutter-Upham et al., 2008).

Regarding the extensive literature reviewed, switching and clustering performance in amnestic MCI was only found to be explored by Murphy and colleagues (2006). They found that both amnestic MCI and normal controls produced greater average cluster sizes on semantic compared to phonemic fluency tasks. Furthermore, the amnestic MCI groups cluster sizes were comparable to the control group on both fluency tasks. In regard to total switches, both groups switched more on phonemic fluency than semantic. Switching ability was similar on both fluency tasks between the control and amnestic MCI groups. To summarize, according to Murphy et al.'s results, clustering and switching abilities do not appear to be compromised at the MCI stage of impairment.

Of those author's who examined differences in verbal fluency ability between neurologically normal older adults and those with amnestic MCI, only one research group (Brandt & Manning, 2009) examined differences between the single and multiple domains. They found that individuals with single domain amnestic MCI were equally impaired on category fluency and letter fluency. Furthermore, participants with single

domain amnestic MCI were the least impaired of the following groups: single domain amnestic MCI, multiple domain amnestic MCI, non-amnestic MCI, and AD, and performed comparably to controls. While, compared to controls, the multiple domain amnestic MCI group showed deficits in both fluency tasks, they demonstrated an unequal impairment on the verbal fluency tasks. Specifically, they performed worse on category compared to letter fluency. Results from this study suggest that single domain amnestic MCI performance parallels Nutter-Upham and colleagues' (2008) results while multiple domain amnestic MCI performance is more consistent with the results reported by Adlam et al. (2006) and Murphy et al. (2006). These findings may reflect the importance of separating MCI into single and multiple domains. To this author's knowledge, no research has been conducted on clustering and switching ability in single domain amnestic MCI compared to multiple domain amnestic MCI.

1.8 Other Dementia Verbal Fluency Ability

Since non-amnestic MCI is predicted to progress into one of three types of dementia (i.e., frontotemporal, Lewy Body, or vascular), it is of interest to understand verbal fluency performances and the brain areas affected by each of these disorders. This information may aid in predicting how individuals with non-amnestic MCI will perform on verbal fluency measures.

Frontotemporal Dementia (FTD) is characterized by prominent atrophy of frontal and temporal lobe structures (Broe et al., 2003). Based on the distribution of neuropathology of FTD, it is suggested that participants would demonstrate impairment in both letter (frontal lobe function) and category (temporal lobe function) fluency. A recent study has shown that individuals with FTD do, in fact, show similar impairment in

letter and category fluency (Rascovsky, Salmon, Hanse, Thal, & Galasko, 2007). Individuals with FTD also show worse overall fluency ability than individuals with AD (Rascovesky et al., 2007).

Lewy-body dementia (LBD) is neuropathologically characterized by inclusions, or Lewy bodies, found throughout the cortex (O'Brien, 2009). Since inclusions are widespread throughout the cortex, it is predicted that individuals with LBD would experience difficulty on both letter and category fluency tasks. Findings on tests of verbal fluency show a similar performance pattern to those with FTD. Specifically, equivalent deficits were found across both fluency tasks (Shimomura et al., 1998). Performance on these tasks suggests that Lewy bodies are present in both the frontal and temporal lobe structures, impacting semantic networks, lexical representations, and search and retrieval processes.

Vascular dementia (VaD) is a heterogeneous collection of impairments resulting from cerebrovascular disease (Jones et al., 2006). The first structural/neurological changes are typically found in the frontal-striatal circuitry (Roman & Royall, 1999). Given the pathological change in the frontal lobe area, individuals with VaD are expected to be more impaired in letter fluency. In line with this hypothesis, several studies have found greater letter fluency impairment in clinical VaD compared to AD (e.g., Lafosse, 1997; Carew, Lamar, Cloud, Grossman, & Lisbon, 1997). Yet, both letter and category fluency measures in individuals with VaD are found to be significantly impaired compared to controls without any markers of dementia (Almkvis, 1994; Fahlander, Wahlin, Almkvist, & Backman, 2002).

Clustering and switching abilities of individuals with FTD, LBD, and VaD has not been widely studied. Of the literature reviewed, only one study (Jones et al., 2006) could be found that investigated clustering and switching ability in individuals with FTD and LBD. When analyzed together, the authors did not find any significant group differences between clustering and switching on the letter fluency task. Both FTD and LBD did, however, show significantly lower cluster size and number of switches compared to healthy older adults, with the exception of LBD on category cluster size which was similar to healthy older adults.

1.9 Non-amnestic MCI Verbal Fluency Ability

Despite evidence suggesting that amnestic and non-amnestic MCI have different clinical outcomes, verbal fluency performance of individuals with non-amnestic MCI has largely been ignored. Following a thorough review of the literature, only one study could be found that has examined verbal fluency performance in non-amnestic MCI (Brandt & Manning, 2009). Brandt and Manning found that non-amnestic MCI performance on both category and letter fluency was below that of healthy older adults. Additionally, non-amnestic MCI participants were not more impaired in category than letter fluency, or vice-versa. Of interest, the fluency patterns seen in individuals with non-amnestic MCI are similar to those observed in study outcomes of verbal fluency ability in individuals with LBD, VaD, and FTD. More specifically, non-amnestic MCI performance was poorer on both category and letter fluency but neither fluency subtest showed more impairment than the other. Examination of clustering and switching on verbal fluency tasks was not included in Brandt and Manning's study nor any study to this author's knowledge.

1.10 Current Research

While studies of verbal fluency performance concerning individuals with amnestic MCI show conflicting results, research concerning non-amnestic MCI has, for the most part, been neglected. Research suggests that when single and multiple domains are taken into account it can lead to more accurate predictions of the etiology of impairment (Anterro et al., 2006). However, only one research group has explored single and multiple domain amnestic MCI verbal fluency performance. Given the possibility that MCI develops into different types of dementia (Petersen, 2003), understanding how verbal fluency performance differs between MCI subtypes and domains may aid in early detection, accurate diagnosis and treatment of these disorders. The aim of the present study is to determine patterns of verbal fluency performance in single and multiple amnestic MCI and non-amnestic MCI compared to neurologically normal older adults.

To examine verbal fluency ability, letter and category fluency total responses, number of switches, and mean cluster sizes will be measured across two 30 second intervals for the following groups: single domain amnestic MCI, multiple domain amnestic MCI, non-amnestic MCI, and healthy older adult controls. Cognitive domains that are typically associated with verbal fluency (i.e., language, executive functioning) will also be examined to determine if they exist as cognitive correlates with word production, clustering, or switching for letter and category fluency.

As stated above, conflicting performance outcomes exist within the literature on amnestic MCI verbal fluency ability. Specifically, Murphy et al. (2006) and Adlam et al. (2006) found that amnestic MCI participants performed more poorly on category fluency than letter fluency, whereas Nutter-Upham et al.'s (2008) results suggest that amnestic

MCI has nearly equivalent deficits in both letter and category fluency. Since amnestic MCI will be analyzed as two separate groups (single domain and multiple domain) in the current study, results are expected to be similar to Brandt and Manning's (2009). Specifically, single domain amnestic MCI and multiple domain amnestic MCI is expected to perform more poorly on category versus letter fluency. Based on Murphy et al.'s results, clustering and switching abilities of the amnestic MCI groups is expected to be similar to controls on both fluency tasks.

In accordance with Brandt and Manning's (2009) findings and FTD, LBD, and VaD verbal fluency literature, non-amnestic MCI is expected to produce fewer words than controls on both category and letter fluency. It is also expected that they will show equivalent deficits on letter and category tests. Based on the clustering and switching performance of FTD and VaD participants, it is predicted that the non-amnestic MCI participants will have an equivalent level of deficit on switching and clustering for both of the fluency tasks.

2 Methods

2.1 Participants

Participants were 25 persons with single domain amnestic MCI (14 female, 11 male), 49 with multiple domain amnestic MCI (26 female, 23 male), 16 with non-amnestic MCI (10 female, 6 male), and 90 cognitively healthy older adults (61 female, 29 male), see Table 1. Each MCI participant was closely matched with a healthy older adult participant in terms of age, gender, and education. All participants were age 50 years or older and able to provide informed consent. Participants were tested voluntarily as part of two larger studies investigating the relationship between cognition and everyday

functional abilities of healthy older adults and individuals with MCI or AD at Washington State University (see Schmitter-Edgecombe, Woo, & Greeley, 2009; Schmitter-Edgecombe, Parsey, & Cook, 2011). Both studies were reviewed and approved by the Washington State University Institutional Review Board. Eastern Washington University reviewed and approved the analyses of the verbal fluency data from the larger subset of data for the purpose of the present study.

Participants were recruited through advertisements, community health and wellness fairs, physician referrals, referrals from local agencies working primarily with older adults, and from past studies in the Aging and Dementia laboratory at Washington State University. Initial screening of potential participants was conducted over the phone. Screening included a medical and cognitive interview to exclude participants who were significantly cognitively impaired or met exclusion criteria. Exclusion criteria included history of significant head trauma, current or recent (past year) psychoactive substance abuse, history of cerebrovascular accidents, and known medical, neurological, or psychiatric causes of cognitive dysfunction (e.g., epilepsy, schizophrenia).

Participants who met initial screening criteria completed a 3 hour battery of standardized and experimental neuropsychological tests including measures of memory, attention, executive functioning, language abilities, speeded processing, visuospatial skills, and general intellectual ability. Each participant appointed a knowledgeable informant (e.g., spouse, adult child) who was contacted to supply subjective information on functional and cognitive ability and completed the CDR, which was administered by an examiner who had completed CDR certification. Individual participant medical information was also reviewed when available. All participants were given a report

reviewing their performance on the neuropsychological tests as compensation for their time.

Inclusion criteria for participants in the amnestic MCI group followed the criteria outlined by Petersen and colleagues (2004) and Albert and colleagues (2011). Reference to the individual's medical, education, and socioeconomic background was also made before carefully determining whether the individual met criteria for MCI. Individuals classified as amnestic MCI met each of the following criteria: (a) subjective memory impairment with support from a knowledgeable informant as obtained from the CDR and knowledgeable informant interview, (b) objective memory impairment confirmed by a score falling 1.5 standard deviations below the mean of age and education matched peers on list learning, immediate recall, or delayed recall on the Rey Auditory Verbal Learning Test (RAVLT; Lezak et al., 2004) or the Memory Assessment Scales (MAS; Williams, 1991) depending on the study sample; (c) nonfulfillment of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM–IV) criteria for dementia (American Psychiatric Association, 2000) (d) preserved general cognitive functions as confirmed by a 27 or above on the Telephone Interview for Cognitive Status (TICS; Brandt & Folstein, 2003) (e) no significant impact of the memory deficit on the participant's daily activities, as confirmed by a total CDR score lower than 1.0; and (d) absence of severe depression as confirmed by a score below or equal to 10 on the 15 item Geriatric Depression Scale (GDS; Yesavage et al., 1983) or 18 on the 30 item GDS.

Participants who met criteria for amnestic MCI were further divided into either a single or multiple domain amnestic MCI group. Those classified as single domain amnestic MCI met all of the above criteria and had no performances on a non-memory

measure 1.5 standard deviations below the mean of age and education matched peers. Those classified as multiple domain amnestic MCI had at least one performance on a non-memory measure that was 1.5 standard deviations below the mean of age and education matched peers. On an individual basis, participants who scored slightly higher than 1.5 standard deviations below the mean compared to their matched peers (e.g., SD = - 1.3) were considered if supporting collateral information was supplied (e.g. informant report) that strongly suggested they fell within the multiple versus single domain group.

Similar criteria were used for classifying non-amnestic MCI as was for amnestic MCI with the exception of objective memory impairment. Rather, participants in the non-amnestic MCI group performed at least 1.5 standard deviations below the mean on one or more non-memory measure of attention/speeded processing, language, or executive function. Non-amnestic MCI participants were not further classified into either single (N = 10) or multiple domain (N = 6) MCI for the analysis due to small sample size.

Participants classified as cognitively healthy older adults met the following criteria: (a) no self or informant reported history of cognitive changes; (b) performance within or above the average range on neuropsychological measures and a CDR of 0; (c) score on the TICS within normal limits; and (d) a score below or equal to 10 on the 15 item GDS or 17 on the 30 item GDS.

2.2 Materials and Procedure

All participants were administered the Delis Kaplin Executive Functioning System (D-KEFS) Verbal Fluency subtest (Delis, Kaplan, & Kramer, 2001). D-KEFS verbal fluency was administered along with a battery of neuropsychological measures (e.g., Trails, CLOX I & II, D-KEFS Design Fluency). All neuropsychological measures were

administered on an individual bases according to standardized instructions and were collected across two days of testing. D-KEFS Verbal Fluency subtest was administered on Day 1 of testing in both studies.

The letter fluency subtest, which is a component of the D-KEFS verbal fluency subtest, required that participants name as many words as possible starting with the letter F, A, and S for a total of 60 seconds each. Participants were instructed to refrain from providing names of persons, places, and numbers, as well as words with different suffixes (e.g., run, runs, running). Participants were also administered a category fluency subtest which required them to name as many animals as possible. Participants were asked to stop the task after a total of 60 seconds.

2.3 Scoring

Three scores were obtained for the letter (F, A, and S) and category (animal) verbal fluency subtests: total responses, average cluster size, and total switches. Scores were calculated for two time intervals: 1-30 seconds and 31-60 seconds, referred to as Time 1 and Time 2, respectively. Total responses were scored by tallying all of the words recited excluding set-loss errors (e.g., names of people, places) and repetitions. Clustering and switching scores were coded in consonance with the scoring method derived by Troyer and colleagues (1997). According to their criteria, a cluster on letter fluency is defined as a group of words generated in sequence that began with the same first letters (e.g., sea, seashell, seahorse), words that differ by vowel sound (e.g., sat, sit, seat), homonyms (e.g., ant, aunt), or words that rhyme (e.g., splint, sprint). Homonyms were scored when a participant explicitly stated the spelling of the word (i.e., “ant: a-n-t and aunt: a-u-n-t”) or stated that they meant the alternative spelling of the word (i.e., “ant

and the other aunt"). Animal clusters were defined as a group of words generated in sequence that belonged to a pre-defined semantic category (for a list of semantic categories see Troyer, 2000) such as pets (e.g., cat, dog) or African animals (e.g., lion, tiger, antelope). Minimal modifications to the Troyer (2000) scoring categories were made to include items specific to the Pacific Northwest region.

Cluster size was scored as the total number of words that fit within a given cluster starting with the second word. Therefore, if a cluster included the words "ostrich, raven, owl, robin" they would be defined as a bird cluster of three (see Figure 4). Furthermore, a cluster of the word "panda" would be counted as a cluster of zero. In accordance with Troyer et al.'s scoring criteria set-loss errors and repetitions were included in cluster totals because they are "thought to provide information about the underlying cognitive processes regardless of whether or not they were included in the total number of words generated" (p. 140, 1997). To obtain the average cluster size, total cluster sizes were summed and divided by the total number of clusters made for each 30 second interval. Letter fluency F, A, and S tests were combined to create one overall phonemic average cluster score for each 30 second interval.

Switching was scored as the point of transition from one cluster that had been exhausted to another cluster, including clusters with a score of zero. Like total responses and mean clusters, switches were calculated for Time 1 and Time 2 and letter fluency tests F, A, and S were combined to provide one total switching score. An example of how clustering and switching is scored on the letter and category fluency task is represented in Figure 4.

All protocols were first scored by this author followed by a second scoring conducted by an independent rater to limit scoring errors. If incongruent scores were obtained, both raters discussed the disparity and came to a consensus based on Troyer and colleagues scoring scheme.

2.4 Analysis

Independent samples *t*-tests were used to compare the MCI and control groups on demographic variables, including age, education, and gender, to determine if significant differences existed that might impact the analyses. Only the *t*-test comparing the mean level of education of single domain amnesic MCI and multiple domain amnestic MCI was found to be significant ($t(118) = 1.96$), $p = .05$). The mean level of education of the single domain amnestic MCI group was significantly higher ($M = 16.54$, $SD = 2.86$) than the multiple domain amnestic MCI group ($M = 15.13$, $SD = 3.04$). Education was, therefore, used as a covariate in subsequent analyses.

Figure 1: Example of how to score switches and clusters on the letter and category verbal fluency tasks

Prior to running analyses, frequencies were investigated for each set of letter and category fluency scores that were obtained. These included: total responses, mean cluster size, and total number of switches for each fluency subtest. Participants who performed three standard deviations above or below the mean performance for a given measure were removed from all fluency analyses within the specific fluency subtest. For example, if a participant performed 3 or more standard deviations above the mean on total letter responses they were removed from all letter fluency analyses but remained in the category fluency analyses if none of their performances were above or below 3 standard deviations on any category fluency task.

The dependent measures (i.e., total responses, average cluster size, number of switches in both letter and category fluency) were analyzed using a four (i.e., single domain amnestic MCI, multiple domain amnestic MCI, non-amnestic MCI, and neurologically healthy older adults) by two (i.e., 0-30 seconds and 31-60 seconds) mixed model analysis of covariance (ANCOVA) with repeated measures on the second factor; education was included as a covariate in the models. In those instances where the covariate was not found to be significant, the analysis was repeated without including the covariate of education [i.e., a four by two mixed model analysis of variance (ANOVA) was performed]. Pairwise comparisons were computed using Tukey's HSD post-hoc when appropriate. Significance level was set at .05 for the ANCOVA or ANOVA and post-hoc tests. Eta-squared was used as a measure of effect size. Paired samples *t* tests were also calculated on the dependent measures for each participant group. This analysis was completed to determine if differences existed between participant groups' 0-30 second response, cluster, or switch total scores and their 31-60 second scores. Finally, I examined correlations among and between the fluency tasks and select neuropsychological variables that research suggests plays a role in verbal fluency performance (Taler & Phillips, 2008): language ability (i.e., Boston Naming Task, BNT; Ivnik, Malec, Smith, Tangalos, & Petersen, 1996) and executive functioning ability (Trails B; Goodglass, Kaplan, & Barresi, 2001). Pearson correlations were used with a significance level set at $p < .05$.

3 Results

3.1 Letter Fluency

Six participants (1 amnestic MCI single domain, 3 amnestic MCI multiple domain, 1 non-amnestic MCI, 1 control) performed 3 standard deviations above or below the mean on one or more of the dependence measures. These participants were removed from all letter fluency analyses as outliers.

3.1.1 Total Responses

To compare the total response performance of the MCI groups and control participants, a four by two mixed model ANOVA on total letter fluency responses was performed. A significant main effect for time, $F(1, 170) = 305.43$, $MSE = 13.98$, $p < .001$, $\eta^2 = .64$ revealed that more responses were generated at Time 1 ($M = 22.13$) then at Time 2 ($M = 13.45$). The main effect of group, $F(1, 170) = 3.78$, $MSE = 13.98$, $p = .01$, $\eta^2 = .06$, indicated that non-amnestic MCI ($M = 15.43$) made the fewest responses over the time frame allotted, followed by amnestic MCI multiple domain ($M = 16.30$), and amnestic MCI single domain ($M = 18.06$). As expected, the control group made the greatest number of responses on the letter fluency subtest, $M = 21.35$. These main effects were modified by a significant two-way interaction $F(3, 170) = 3.78$, $MSE = 13.98$, $p = .01$, $\eta^2 = .06$.

Breakdown of the interaction revealed that at Time 1 the control group ($M = 26.53$) produced significantly more responses than the multiple domain amnestic MCI ($M = 21.07$) and non-amnestic MCI ($M = 18.13$), ps $< .001$ groups. The control group did not significantly differ from the single domain amnestic MCI ($M = 22.79$), $p > .05$. No differences were observed between single domain amnestic MCI, multiple domain

amnestic MCI, and non-amnestic MCI groups. At Time 2 the control group (M = 16.17) significantly differed in total responses from the multiple domain amnestic MCI group (M = 11.54), $p < .001$, only. There were no differences in total responses between the control and either the single domain amnestic MCI (M = 13.33) or non-amnestic MCI (M = 12.73) groups. Furthermore, no group differences were observed between the single domain amnestic MCI, multiple domain amnestic MCI, and non-amnestic MCI groups.

Paired-samples t tests were calculated to compare all participant groups' total word responses on letter fluency at Time 1 to their Time 2 total responses. A significant decrease in word production was found from Time 1 to Time 2 for each of the groups: single domain amnestic MCI group, $t(23) = 8.56$, $p < .001$; multiple domain amnestic MCI group, $t(45) = 13.22$, $p < .001$; non-amnestic MCI group, $t(14) = 3.14$, $p = .007$; control group, $t(88) = 18.77$, $p < .001$.

3.1.2 Mean Cluster Size

A mixed model ANCOVA was conducted by controlling for the education of the participants, with the effect of group (amnestic MCI single domain vs. amnestic MCI multiple domain vs. non-amnestic MCI, vs. control) and time interval (Time 1 vs. Time 2) on letter mean cluster size. The amount of participants' education co-varied with the mean cluster size, $F(1, 169) = 5.83$, $MSE = .12$, $p = .02$, $\eta^2 = .03$. However, education was not significantly related to time, $F(1, 169) = 2.95$, $MSE = .26$, $p > .05$, $\eta^2 = .02$. The main effect for time, while not reaching the $p < .05$ level, was approaching significance, $F(1, 169) = 3.67$, $MSE = .09$, $p = .06$, $\eta^2 = .02$. The main effect for group was not significant, $F = 2.27$. Furthermore, the time by group interaction was not found to be significant, $F = .89$.

Paired-samples *t* tests indicated that no differences in size of cluster was observed between Time 1 and Time 2 for any of the groups: single domain amnestic MCI group, $t(23) = .41$, $p > .05$; multiple domain amnestic MCI group, $t(45) = -.54$, $p > .05$; non-amnestic MCI group, $t(14) = 1.34$, $p > .05$; control group, $t(88) = .55$, $p > .05$. This lack of significance indicates that participants' cluster size did not notably change over time despite total responses significantly decreasing across the 60 second task.

3.1.3 Total Switches

To assess participants' performance on total number of switches produced on the letter fluency task a group (single domain amnestic MCI vs. multiple domain amnestic MCI, vs. non-amnestic MCI, vs. control) by time interval (Time 1 vs. Time 2) mixed modal ANOVA was performed. Results of this ANOVA revealed a significant main effect for time, $F(1, 170) = 6.50$, $MSE = 36.34$, $p < .001$, $\eta^2 = .10$. Post hoc tests indicated that more switches were made at Time 1 ($M = 14.03$) then at Time 2 ($M = 10.70$). The main effect of group, $F(1, 170) = 6.97$, $MSE = 35.02$, $p < .001$, $\eta^2 = .11$, revealed that non-amnestic MCI ($M = 10.17$) made the fewest number of switches over the time frame allotted, followed by multiple domain amnestic MCI ($M = 12.03$), and single domain amnestic MCI ($M = 12.75$). The control group made the greatest number of switches on letter fluency ($M = 14.49$). These main effects were modified by a significant two-way interaction $F(3, 170) = 3.04$, $MSE = 9.90$, $p = .03$ $\eta^2 = .05$.

Breakdown of the interaction revealed that at Time 1 the control group ($M = 16.82$) switched more than the multiple domain amnestic MCI group ($M = 13.83$), $p = .01$, and the non-amnestic MCI group ($M = 10.67$, $p < .001$), but did not significantly differ from the single domain amnestic MCI group ($M = 14.79$, $p > .05$). No differences

were observed between single domain amnestic MCI, multiple domain amnestic MCI, and non-amnestic MCI groups. At Time 2 the control group (M = 12.17) did not significantly differ in total switches from any group; however, the control group was trending toward a significant difference with the multiple domain amnestic MCI group (M = 10.24), p = .06. There were no differences in total switches between the control or multiple domain amnestic MCI groups and either the single domain amnestic MCI (M = 14.79) or non-amnestic MCI (M = 9.67) groups. Furthermore, no group differences were observed between the single domain amnestic MCI and non-amnestic MCI groups.

Paired-samples t tests were calculated to compare participant groups' total switches on letter fluency at Time 1 to their Time 2 total switches. Control group total switches at Time 1 was 16.82 (SD = 5.71) and the total for Time 2 was 12.17 (SD = 3.79). A significant decrease from Time 1 to Time 2 was found, $t(88) = 9.15$, $p < .001$ for the control group. A significant decrease was also found from Time 1 (M = 14.79, SD = 4.11) and Time 2 (M = 10.71, SD = 4.16) for the single domain amnestic MCI group, $t(23) = 4.67$, $p < .001$, and Time 1 (M = 13.82, SD = 5.48) and Time 2 (M = 10.24, SD = 4.98) for the amnestic MCI multiple domain group, $t(45) = 5.85$, $p < .001$. While the control and amnestic MCI groups showed a significant decrease in switches over the 60 second letter fluency task, the non-amnestic MCI group's Time 1 (M = 10.67, SD = 4.17) total switches did not significantly differ from their total switches at Time 2 (M = 9.67, SD = 3.98), $t(14) = 1.22$, $p > .05$.

3.2 Category Fluency

Three participants (1 single domain amnestic MCI, and 2 control) performed 3 standard deviations above or below the mean performance on 1 or more dependent

variable and were selectively removed from all category fluency analyses as outliers. Furthermore, 1 control participant did not complete the category fluency task, thus, data for this participant was not entered into the category fluency analyses.

3.2.1 Total Responses

A group (multiple domain amnestic MCI vs. single domain amnestic MCI vs. non-amnestic MCI vs. controls) by time interval (Time 1 vs. Time 2) mixed model ANVOA conducted using total responses on category fluency revealed a main effect for group , $F(3, 173) = 6.63$, $MSE = 14.12$, $p < .001$, $\eta^2 = .10$. Post hoc tests indicated that only the multiple domain amnestic MCI group ($M = 8.61$) made significantly fewer responses than the control group ($M = 10.69$), $p < .001$. There were no differences in total responses on category fluency between the single domain amnestic MCI ($M = 9.67$) and non-amnestic MCI ($M = 9.50$) groups compared to either the control or amnestic MCI multiple domain groups. A main effect for time interval $F(1, 173) = 372.22$, $MSE = 6.36$, $p < .001$, $\eta^2 = .68$, revealed that participants made more responses at Time 1 ($M = 12.79$) than Time 2 ($M = 6.45$). A group by time interaction was not significance, $F= 1.63$.

Paired-samples *t* tests were calculated to compare participant groups' total word responses on category fluency at Time 1 to their Time 2 total responses. A significant decrease in word production was found from Time 1 to Time 2 for each of the groups: single domain amnestic MCI group, $t(23) = 10.62$, $p < .001$; multiple domain amnestic MCI group, $t(48) = 11.76$, $p < .001$; non-amnestic MCI group, $t(15) = 8.17$, $p < .000$; control group, $t(87) = 16.29$, $p < .001$.

3.2.2 Mean Cluster Size

To exam differences in average cluster size performance on category fluency a four by two mixed modal ANOVA was calculated to examine the effects of group (amnestic MCI single domain vs. amnestic MCI multiple domain vs. non-amnestic MCI vs. control) and time interval (Time 1 vs. Time2) on category mean cluster size. While the group by time interval interaction (F = 1.98) and the main effect for group (F = .90) were not significant, the main effect for time was found to be significant, $F(1, 173)$ = 5.94, MSE = 0.55, p = .02, η^2 = .03. The main effect for time revealed that participants' average cluster size decreased as the task progressed; at Time 1 the average cluster size was M = 1.27, while at Time 2 it was M = 1.03.

Paired-samples t tests were calculated to compare participant groups' mean cluster size on category fluency at Time 1 to their Time 2 mean cluster size. The control group's mean cluster size at Time 1 was 1.18 (SD = .60) and the total for Time 2 was 1.14 (SD = .82). A significant decrease was not found from Time 1 to Time 2, $t(87)$ = .35, p > .05 for the control group. Single domain amnestic MCI group average cluster size for Time was 1.51 (SD = .87) and the mean for Time 2 was .90 (SD = .68). A significant decrease was found from Time 1 to Time 2, ($t(23)$ = 2.54, p = .02) for single domain amnestic MCI. However, a significant decrease of average cluster size was not found between Time 1 (M = 1.07, SD = .51) and Time 2 (M = 1.0, SD = .87) for the multiple domain amnestic MCI group, ($t(48)$ = .52, p > .05), or the non-amnestic MCI group's average cluster size on Time 1 (M = 1.31, SD= .83) compared to time 2 (M = 1.09, SD = .90), $t(15)$ = .82, p < .05.

3.2.3 Total Switches

A group by time interval mixed model ANVOA conducted using total switches on category fluency revealed a main effect for group , $F(3, 173) = 2.84$, $MSE = 4.62$, $p = .04$, $\eta^2 = .05$. Post hoc tests indicated that only the multiple domain amnestic MCI group ($M = 4.53$) made significantly fewer switches than the control group ($M = 5.23$), $p = .05$. There were no differences in total switches on cluster fluency between the single domain amnestic MCI ($M = 4.79$) and non-amnestic MCI ($M = 4.47$) groups compared to either the control or multiple domain amnestic MCI groups. A main effect for time interval $F(1, 173) = 87.39$, $MSE = 2.51$, $p < .001$, $\eta^2 = .34$, revealed that participants' made more switches at Time 1 ($M = 5.72$) than Time 2 ($M = 3.79$). A group by time interaction lacked significance, $F = .72$.

Paired-samples *t* tests were calculated to compare participant groups' total number of switches on category fluency at Time 1 to their Time 2 responses total. A significant decrease in switching ability was found from Time 1 to Time 2 for each of the groups: single domain amnestic MCI group, $t(23) = 3.27$, $p = .003$; multiple domain amnestic MCI group, $t(48) = 6.71$, $p < .001$; non-amnestic MCI group, $t(15) = 3.50$, $p = .003$; control group, $t(87) = 9.36$, $p < .001$.

3.3 Correlations among fluency tasks

Correlations were computed to examine the relationship among fluency task scores (i.e., total responses, mean cluster size, total switches) between and within letter and category fluency subtests. Total phonemic switches was positively correlated with total responses on letter fluency for the single domain amnestic MCI ($r = .85$, $p < .001$), multiple domain amnestic MCI ($r = .87$, $p < .001$), non-amnestic MCI ($r = .93$, $p < .001$), and control groups ($r = 80$, $p < .001$). This suggests that the more responses participants'

produced on letter fluency, the more switches they made. A similar pattern was observed in regard to the relationship between total responses and total switches on category fluency (single domain amnestic MCI, $r = .73$, $p < .001$; multiple domain amnestic MCI, $r = .71$, $p < .001$; non-amnestic MCI, $r = .52$, $p = .04$; control, $r = .72$, $p < .001$).

Average cluster size on letter fluency was also correlated with phonemic total responses for single domain amnestic MCI ($r = .51$, $p = .01$), multiple domain amnestic MCI ($r = .54$, $p < .001$), non-amnestic MCI ($r = .61$, $p = .02$), and control ($r = .29$, $p = .006$) groups. When comparing average cluster size to total responses on the category fluency task, significant correlations were observed for the multiple domain amnestic MCI ($r = .45$, $p = .001$) and control ($r = .42$, $p = .003$) groups. Significant correlations were not found for the single domain amnestic MCI ($r = .24$) or non-amnestic MCI ($r = .31$) groups.

The relationship between total switches and average cluster sizes were also evaluated. For letter fluency, only the control group's total switches were significantly correlated with the average size of the clusters they produced ($r = -.27$, $p = .01$). This suggests that when larger cluster sizes were produced fewer switches were generated, and vice-versa. The average cluster size on the letter fluency task did not correlate with switching ability for the single ($r = .00$) and multiple domain amnestic MCI groups ($r = .21$), or the non-amnestic MCI group ($r = .28$). Total number of switches was significantly correlated on category fluency with mean cluster size scores for non-amnestic MCI ($r = -.59$, $p = .02$), and control ($r = -.23$, $p = .03$) groups. The amnestic MCI multiple and single domain groups' switching ability did not correlate with their average cluster size on the category fluency task ($r = -.14$ and $r = -.40$, respectively).

To make comparisons across fluency tasks all outliers (9 total) were removed prior to running correlation analyses. Average responses on the letter fluency tasks ("F"+"A"+"S" divided by 3) was correlated with total responses on category fluency ("animals") for the amnestic MCI single domain (r = .42, p = .04), amnestic MCI multiple domain (r = .33, p = .03), and control (r = .21, p = .05) groups. Of note, while no relationship between total responses on letter and category fluency was observed for the non-amnestic MCI (r = .24) group, the correlation was similar to that of the control group, suggesting that the low sample size the of non-amnestic MCI group impacted the correlations power. Average switches made on letter fluency ("F"+"A"+"S" divided by 3) was examined with relation to total switches on category fluency ("animals"). Control (r = .24, p = .03) and non-amnestic MCI domain (r = -.51, p = .05) correlation analyses were found to be significant, while the single (r = .26) and multiple domain (r = -.15) amnestic MCI groups' were not No significant correlations were observed in relation to mean cluster size between letter and category fluency for any of the groups' performances (single domain amnestic MCI, r = -.02; multiple domain amnestic MCI, r = -.06; non-amnestic MCI, r = -.05; control, r = .01).

3.1 Correlations with neuropsychological variables

Correlations were computed to examine the relationship between fluency task scores (i.e., total responses, mean cluster size, total switches) and select neuropsychological variables related to verbal fluency performance including language ability (BNT) and executive functioning (Trails B). As shown in Table 3, BNT total correct score was not found to be significantly correlated with groups' letter fluency total response score (single domain amnestic MCI r = -.09, multiple domain amnestic MCI r =

.18; non-amnestic MCI r = .17, control r = .16), total switches (single domain amnestic MCI r = .17, multiple domain amnestic MCI r = .27; non-amnestic MCI r = -.14; control r = .40), or average cluster size (single domain amnestic MCI r = -.32, multiple domain amnestic MCI r = -.07; non-amnestic MCI r = .29, control r = .12).

BNT was, however, significantly correlated with single domain amnestic MCI (r = .49, p = .02), multiple domain amnestic MCI (r = .51, p < .001), and control (r = .34, p = .001) groups' total responses on category fluency. BNT was not correlated with the non-amnestic MCI group's (r = .24, p > .05) total semantic fluency responses. Similarly, BNT was correlated with the single domain amnestic MCI (r = .50, p < .001), multiple domain amnestic MCI (r = .53, p = .009), and control (r = .39, p < .001) groups' total number of switches on category fluency, but not with the non-amnestic MCI group's total switches (r = .16, p > .05). BNT was not correlated with any of the groups' average cluster size on category fluency (single domain amnestic MCI r = -.20, multiple domain amnestic MCI r = .08; non-amnestic MCI r = -.16, control r = -.02).

Time on Trails B was significantly correlated with total responses on letter fluency for the non-amnestic MCI (r = -.55, p = .04) and control (r = -.22, p = .04) groups. This relationship suggests that the more time spent on the Trails B task was related to fewer words produced on the letter fluency task, and the less time spent on the Trails B task was related to more responses on the letter fluency task. Significant correlations were not found between Trails B scores and letter total responses for single domain amnestic MCI (r = -.27) or multiple domain amnestic MCI (r = -.01) groups. A significant correlation emerged between Trails B and total switches on letter fluency for non-amnestic MCI (r = .56, p = .04) and control groups (r = -.25, p = .02). Significant

correlations were not found between Trails B scores and letter switches for the amnestic MCI single domain (r = -.05) or amnestic MCI multiple domain (r = .08) groups. No significant correlations were found between Trails B scores and average cluster sizes on letter fluency for any of the groups (rs = -.35 to .15).

Time on Trails B was significantly correlated with total responses on category fluency for the non-amnestic MCI (r = -.60, p = .02) and control (r = -.28, p = .008) groups. Significant correlations were not found between Trails B scores and category total responses for amnestic MCI single domain (r = -.38, p = .08) or amnestic MCI multiple domain (r = -.27, p = .07) groups, although both trended toward significance. Trails B was significantly correlated with total switches on category fluency for the single domain amnestic MCI (r = -.46, p = .03), multiple domain amnestic MCI (r = -.39, p = .006), and control (r = -.33, p = .002) groups. For non-amnestic MCI, Trails B did not correlate with category total switches (r = -.25, p > .05). No significant correlations were found between Trails B scores and average cluster sizes on category fluency for any of the groups, rs = -.19 to .12.

4 Discussion

Tests of verbal fluency are simple and efficient tools that have shown to be sensitive enough to discriminate between healthy aging and early cognitive decline (Taler & Phillips, 2008). The purpose of this study was to investigate verbal fluency abilities in two subtypes of MCI (amnestic and non-amnestic) and two domains of amnestic MCI (single and multiple). Verbal fluency performance on the letter and category fluency subtests were analyzed across two 30-second intervals. It was found that verbal fluency performance is sensitive enough to discriminate between amnestic MCI single and

multiple domains and between multiple domain amnestic MCI, non-amnestic MCI, and control participants on total words generated and switching ability for both letter and category fluency tasks. Similar to Murphy and colleagues' (2006) findings, participant groups in our study did not differ on average cluster size on either fluency task.

The study findings indicate that the control group produced more responses and switched more frequently on the letter fluency task than the multiple domain amnestic MCI and non-amnestic MCI groups during the first 30 second interval (see Table 2 and Figures 5 and 6 in Appendix A). During the final 30 seconds of the letter fluency task the control group was only found to produce significantly more words, and trended toward significantly more switches, than the multiple domain amnestic MCI group. Similar to Brandt and Manning's (2009) findings, the single domain amnestic MCI group's performance did not significantly differ from the control group on letter fluency responses or switching production. It is possible that the neurological changes present in individuals with single domain amnestic MCI was not widespread enough to be detected on the letter fluency task. Specifically, during this prodromal stage of AD the frontal lobe, needed to successfully complete this task, may be relatively uncompromised in individuals with single domain amnestic MCI. These areas likely become compromised as plaques, tangles, or infarcts spread leading to the impairment on the letter fluency task that is commonly seen in individuals with AD (please see Henry et al., 2004).

On the letter fluency task, the single and multiple domain amnestic MCI groups, as well as the control group, generated significantly more words and made more switches on the first 30 seconds than the second 30 seconds (refer to Figures 5 & 6). Previous research has noted this pattern in word production on letter fluency tasks (e.g., Fernaues

& Almkvist, 1998), leading to suggestions of differing attentional processes at work. While the non-amnestic MCI group produced more words on the first 30 seconds than the last 30 seconds, the total number of switches produced did not notably decrease across the time interval. These findings may suggest that while the amnestic MCI and control groups' initial fluency ability began similarly, with a semi-automatic and rapid retrieval of words accompanied by adequate flexibility in moving from one subcategory to another, their word and switching production diminished considerably as time progressed. Non-amnestic MCI participants, on the other hand, did not begin the task with the same rapid retrieval of words and flexibility to switch between subcategories. In addition, the non-amnestic MCI group did not have the same dramatic decrease in switching ability that was observed by the other participant groups. Since switching ability and participant performance on the letter fluency task are considered to be related to frontal lobe functioning (Troyer et al., 1998), it is suggested that the non-amnestic MCI group's ability to initiate search processes through lexical memory and/or cognitive flexibility (allowing them to effectively switch between subcategories) is impaired to a greater extent than the other MCI groups.

In comparing the participants' performance between the fluency tasks, each participant group was found to generate more responses, switched to a greater extent, and made larger cluster sizes on the category fluency task relative to the letter fluency task (as seen in Figures 7 & 8). This finding is well supported in the literature (i.e., Nutter-Upham et al., 2008; Henry et al., 2004) with the exception of switching, which has been found to be greater on phonemic fluency measures (Murphy et al., 2006). On the category fluency task, each groups' word and switch generation significantly decreased during final 30

seconds of the task. Although each MCI group made fewer responses and switched less than the control group, the single domain amnestic MCI and non-amnestic MCI groups' performance did not differ significantly from controls. Multiple domain amnestic MCI, in contrast, generated significantly fewer words and switched less between semantic subcategories on the category fluency task.

The category fluency task performance of the multiple domain amnestic MCI group is similar to that found in the longitudinal study conducted by Raoux and colleagues (2008) which followed individuals in a predementia stage up to the onset of dementia of the Alzheimer's type. Specifically, participants at two and five years before the diagnosis of dementia generated less words and had a significantly lower switching index on the category (animal) fluency task compared to cognitively healthy older adults. Furthermore, switching and word production was found to be measurably diminished at each visit. The predementia group's mean cluster size was not significantly different from normal controls at any time, including the visit where the diagnosis of dementia was made. This finding supports the present study and lack of significant results for any of the MCI groups' average cluster sizes. Murphy et al. (2008) also found clustering ability to be preserved in category (and letter) fluency tasks in their amnestic MCI group.

Based on our results, the participants with multiple domain amnestic MCI showed performance deficits in switching and word generation on both fluency tasks compared to controls. In contrast to Brandt and Manning's (2009) findings, more impairment on category than letter fluency was not observed for the multiple domain amnestic MCI group. In our case, participants in the multiple domain amnestic MCI groups showed nearly equivalent deficits on each of the fluency tasks compared to control participants.

Nutter-Upham and colleagues' (2008) found that individual's with amnestic MCI, relative to neurologically normal older adults, had a poorer performance on both semantic and phonemic fluency tasks. Our verbal fluency performance results, augmented by Raoux et al.'s (2008) results (which found that predementia participants have impairment on switching ability but not clustering on semantic fluency) and Nutter-Upham's findings (which showed that amnestic MCI participants' had equivalent deficits on switching and word production on both fluency tasks) suggest that individuals with multiple domain amnestic MCI are experiencing changes in executive ability.

Further support for the hypothesis that multiple domain amnestic MCI participants are experiencing impairment in executive ability is given by Troyer et al.'s (1998) frontal and temporal lobe lesion study. Results from that study indicate that participant's with frontal lobe lesions produced fewer words and switched less than controls and participants with temporal lobe lesions. Individuals with temporal lobe lesions were unimpaired on clustering and switching on the letter fluency task but were impaired on clustering and switching on the category fluency task. Individuals with multiple domain amnestic MCI performed more similarly to the group with frontal lobe lesions than those with temporal lobe lesions.

Unlike the amnestic MCI and control groups, our non-amnestic MCI participants demonstrated a distinct impairment on the letter fluency task compared to the category fluency task in terms of word and switch generation. This does not support our hypothesis that non-amnestic MCI participant's would have a nearly equal amount of impairment on both fluency tasks. As switching on category fluency is suggested to be mediated by frontal and anterior-temporal regions needed to access semantic memory

stores (Troyer et al., 1998), it is hypothesized that temporal regions are preserved at this stage of impairment in non-amnestic MCI individuals. The temporal regions may, however, become compromised as neurodegeneration progresses, as deficits related to this area are evidenced in the verbal fluency literature of Lewy Body dementia, vascular dementia, and frontotemporal dementia patients (i.e., Rascovsky et al., 2007; Shimomura et al., 1998; Almkvis, 1994; Fahlander et al., 2002). As the current study was limited in the number of non-amnestic MCI participants, further research should be conducted to determine if the pattern of fluency performance observed in our study accurately represents this population.

To further understand how our participant groups approached the verbal fluency task, relationship between responses, switches, and clusters were examined. Results suggest that switching was associated with word generation; the more words a participant generated, the more switches they made. However, past research has suggested that word generation can be influenced by other variables, such as average cluster size. For example, individuals with Alzheimer's disease are found to have reduced cluster sizes, which negatively impact their total word generation (Troyer, et al., 1998). In our study, it may appear that using word generation alone is enough to understand how participants are performing based on the relatively consistent nature of switching and word generation being impaired together or unimpaired together. While this may largely be the case for the current study, it is still of interest to determine whether clustering *or* switching ability is impacting the overall word generation. Furthermore, understanding why one (i.e., clustering or switching) is impaired without the other (i.e., word generation) may yield additional information as to how a participant is performing on the task. In the present

study, for example, on the second time interval of the letter fluency task multiple domain amnestic MCI participants' word generation was found to be impaired compared to the control group while their switching ability was not. This may suggest that while word generation was limited, they were still able to search for phonemically unrelated words resulting in a switch between subcategories.

Clustering and switching production do not seem to be as dependent on one another as each of them, independently, is to word generation. That being said, the control group's switching production had a positive relationship with average cluster size on both fluency tasks; the performance of participants with non-amnestic MCI on switching was only correlated with cluster size for category fluency, not letter fluency. These findings suggest that, for the non-amnestic MCI and control group, switching production decreased with larger cluster sizes, and vice-versa.

The present study suggests that tasks that place considerable demands on effortful search and retrieval processes will result in performance deficits for individuals with multiple domain amnestic MCI and non-amnestic MCI. Presumably, these deficits are due to decrements in frontal lobe functioning. Past research has documented relationships between participant's verbal fluency ability and frontal lobe abilities (Troyer et al., 2008). Participant performance on the Trails B assessment was used as a measure of frontal-executive functioning. In the present study, for the non-amnestic MCI group, letter fluency total responses and switches were negatively related to time on Trails B. These findings suggest that the more time a participant spent on the Trails task the less words and switches they made on the letter fluency task. A similar pattern was seen for the non-amnestic MCI group for word generation on the category fluency task.

The relationship between these tasks further supports the hypothesis that non-amnestic MCI is experiencing impairments in frontal lobe functioning. For both of the amnestic MCI groups, the total number of switches on the category fluency task was negatively related to time on Trails B. This suggests that the longer individuals with amnestic MCI took to complete Trails B, the fewer number of switches they provided. These results also suggest that the amnestic MCI groups' executive abilities are tapped to a greater extent when switching on the category fluency than the letter fluency task based on the positive correlation between Trails B and switching on category fluency and the lack of a correlation with switching on letter fluency.

Tests known to represent verbal knowledge have shown to be related to verbal fluency measures (i.e., Nutter-Upham et al., 2008). In the present study, total items correctly identified on the BNT was found to be positively related to total words and switches on the category fluency task for each of the groups, except non-amenstic MCI. Like category fluency, the BNT is thought to tap into semantic memory (LaBarge, Balota, Storandt, & Smith, 1992). Of interest, the non-amnestic MCI group's word and switch generation did not correlate with BNT as the amnestic MCI groups' did. Furthermore, the non-amnestic group's performance on the BNT was not found to be impaired compared to the control group.

Unlike the non-amnestic MCI group, the multiple domain amnestic MCI group did show a significantly reduced score on the BNT compared to the control group. This, along with the correlation between the BNT and category fluency scores may be related to a reduced ability to retrieve information from intact semantic stores, a depletion of semantic stores, a combination of the two, or an unknown impairment. This relationship

is, however, in contrast with the lack of impairment on clustering ability on the category fluency task, a task that is thought to rely heavily on access to, and the integrity of, semantic memory stores (Troyer et al., 2008). Perhaps the correlation between BNT and category fluency is more sensitive at picking up slight decrements in the capacity of semantic stores and/or ability to retrieve information from them. It is also plausible that significant impairment may be necessary in order for clustering scores on category fluency to be notably lower than neurologically healthy older adults, as are commonly seen with individuals with AD (for a review, please see Henry et al., 2004). Future research should focus on identifying the stage of impairment where difficulties forming clusters on category fluency tasks become apparent. Additional studies should be conducted to determine whether access to semantic stores, the integrity of the semantic stores themselves, or a combination therein, is impacted at the prodromal stage of impairment.

Prior to concluding, limitations to the present study are considered. One limitation of the present study is the low sample size of the non-amnestic MCI group. Additionally, due to the lack of participants, we were unable to divide the non-amnestic MCI group into single and multiple domain groups, an endeavor that may be of interest to researchers in the future. Another important limitation is the homogeneity of participants in regard to level of education and ethnicity. Specifically, our study sample was composed largely of well-educated, Caucasian individuals, which limits our ability to generalize the results and conclusions to other populations with MCI. The neuropsychological correlates that were used in this study were also limited by the battery of tests that were given to participants. Future studies may be interested in

exploring how performance on verbal fluency measures is related to other tests that task the frontal lobe and language ability. Future research may also be interested in tasks that are not as structured as the ones implemented here such as the Behavioral Assessment of the Dysexecutive Syndrome (BADS; Wilson, Alderman, Burgess, Emslie, & Evans, 2003). Finally, the data used to complete this study was derived from two separate studies collected by the same laboratory at Washington State University. It is possible that differences in study administration and testing battery could have impacted the present results, although no systematic errors were evident.

Like Raoux and colleagues (1998), future studies should utilize a longitudinal approach when researching verbal fluency ability in individuals at the MCI stage of impairment as they progress toward dementia, especially those with non-amnestic MCI as the study of this type of MCI has largely been neglected. These studies may further our understanding on how individuals who are cognitively impaired approach verbal fluency tasks as neurodegeneration progresses along with the underlying brain mechanisms that enact this change.

In summary, results from the present study suggest that individual's with single and multiple domain amnestic MCI can be differentiated from each other as well as from individuals with non-amnestic MCI based on performance on the verbal fluency task. Future studies may be interested in exploring the sensitivity and selectively of this measure as a clinical tool for diagnosing individuals with MCI as the current study findings suggest that verbal fluency tasks have the potential to aid to classifying MCI when accompanied with memory testing. Implications of accurate classification include early intervention and healthcare cost reduction.

The study findings also lend information to understanding the cognitive and neurological areas impacted at the MCI stage of degeneration. In particular, multiple domain amnestic MCI is suggested to be experiencing diminished frontal lobe functioning and temporal lobe deficits. Although, it is likely that temporal lobe impairments are present to a lesser extent, this hypothesis is founded on the lack of clustering deficits on the category fluency task. Based on the non-amnestic MCI group's performance, individuals who meet criteria are likely experiencing prominent frontal lobe impairment. Finally, while single domain amnestic MCI may be experiencing significant impairment in memory ability, their semantic stores and frontal executive functioning appear to be unimpaired at this stage of cognitive decline.

The current study suggests that when testing individual suspected of meeting criteria of MCI, scoring verbal fluency performance according to the cluster and switch criteria put for by Troyer and colleagues (1997) may be unnecessary. Specifically, based on the results of the study it appears that each time total switches generated by an MCI group significantly differed from controls their total responses did as well. Furthermore, average cluster size did not significantly differ from control participants' for any of the MCI groups. Therefore, it is suggested that simply calculating total responses for each of the fluency tasks is sufficient in accurately delineated the control group's performance on the verbal fluency task from the MCI groups'. Implications of reducing the scoring criteria to total correct responses include reduced scoring time per test and ease of scoring. Furthermore, training of individual scorers would also be considerably limited.

Finally, we stress the importance of dividing the amnestic MCI group into respective cognitive domain participant groups in future studies of verbal fluency due to

the significant performance divergence found between the single and multiple amnestic MCI domains. These differences may also explain the variance in performance outcomes of studies that kept amnestic MCI as a single entity.

References

Adlam, A. R., Bozeat, S., Arnold, R., Watson, P., & Hodges, J. R. (2006). Semantic knowledge in mild cognitive impairment and mild Alzheimer's disease. *Cortex, 42*, 675-684.

Albert, M. S., Moss, M. B., Tanzi, R., & Jones, K. (2001). Preclinical prediction of Alzheimer's disease using neuropsychological tests. *Journal of the International Neuropsychological Society, 7,* 631-639.

Almkvist, O. (1994). Neuropsychological deficits in vascular dementia in relation to Alzheimer's disease: Reviewing evidence for functional similarity or divergence. *Dementia, 5,* 203-209

Alzheimer's Association. (2012). Alzheimer's disease facts and figures. *Alzheimer's and Dementia: The Journal of the Alzheimer's Association, 8,* 131–168.

Alzheimer's Association International Conference on Alzheimer's Disease. (2010, July 14). Retrieved from: http://www.alz.org/icad/2010_release_early_071410_1230pm.asp

Amieva, H., Jacqmin-Gadda, H., Orgogozo, J.-M., Le Carret, N., Helmer, C., Letenneur L.,..Dartigues J.F. (2005). The 9 year cognitive decline before dementia of the Alzheimer type: A prospective population-based study. *Brain, 128,* 1093-1101.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*. Washington, DC: American Psychiatric Press, Inc.

Artero, S., Petersen, R. C., Touchon, J., & Ritchie, K. (2006). Revised criteria for mild cognitive impairment: Validation within a longitudinal population study.

Dementia and Geriatric Cognitive Disorders, 22, 465–470.

Bäckman, L., Jones, S., Berger, A. K., Laukka, E. J., & Small, B. J. (2005) Cognitive impairment in preclinical Alzheimer's disease: A meta-analysis. *Neuropsychology, 19*, 520-531

Baldo, J. V., Schwartz, S., Wilkins, D., Dronkers, N. F. (2006). Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *Journal of International Nueropsychological Society, 12*, 896-900.

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T. & Dronkers, N. F. (2003). Voxel-based lesion-symptom mapping. *Nature Neuroscience, 6,* 448-450.

Birn, R. M., Kenworthy, L., Case, L., Caravella, R., Jones, T. B., Bandettini, P. A., Martin, A. (2010). Neural systems supporting lexical search guided by letter and semantic category cues: A self-paced overt response fMRI study of verbal fluency. *Neuroimage, 49,* 1099-1107.

Braak, H., & Braak, E. (1991) Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica, 82,* 239-259.

Brandt, J. & Folstein, M. (2003). *Telephone Interview for Cognitive Status.* Lutz, FL: Psychological Assessment Resources, Inc.

Brandt, J., & Manning, K. J. (2009). Patterns of word-list generation in mild cognitive impairment and Alzheimer's disease. *The Clinical Neuropsychologist, 23,* 870-879.

Broe, M., Hodges, J. R., Schofield, E., Shepherd, C. E., Kril, J. J., & Halliday, G. M. (2003). Staging disease severity in pathologically confirmed cases of

frontotemporal dementia. *Neurology, 60,* 1005-1011.

Carew, T. G., Lamar, M., Cloud, B. S., Grossman, M., & Lisbon, D. J. (1997). Impairment in category fluency in ischemic vascular dementia. *Neuropsychology, 11*, 400-412.

Chertkow, H., & Bub, D. (1990). Semantic memory loss in Alzheimer-type dementia. In M. F. Schwartz (Ed.), *Modular deficits in Alzheimer-type dementia.* (pp. 207-244). Cambridge, MA US: The MIT Press.

Clark, L. J., Gatz, M., Zheng, L., Chen, Y. L., McCleary, C., & Mack, W.J. (2009). Longitudinal verbal fluency in normal aging, preclinical, and prevalent Alzheimer's disease. *American Journal of Alzheimer's Disease & Other Dementias, 24*, 461-468.

Cuenod, C. A., Bookheimer, S. Y., Hertz-Pannier, L., Zeffiro, T. A., Theodore, W. H., Le Bihan, D. (1995). Functional MRI during word generation, using conventional equipment: A potential tool for language localization in the clinical environment. *Neurology, 45*, 1821-1827.

Delis, D. C., Kaplan, E., & Kramer, J. H. *(*2001*).* Delis-Kaplan Executive Function System (D-KEFS). San Antonio, TX*:* The Psychological Corporation.

Fahlander, K., Wahlin, A., Almkvist, O., & Bäckman, L. (2002). Cognitive functioning in Alzheimer's disease and vascular dementia: further evidence for similar patterns of deficits. *Journal of Clinical Experimental Neuropsychology, 24*, 733-734.

Flicker, C., Ferris, S. H., & Reisberg, B. (1991). Mild cognitive impairment in the elderly: Predictors of dementia. *Neurology, 41*, 1006-1009.

Gauthier, S., Feldman, H., Hecker, J., Vellas, B., Ames, D., Subbiah, P.,…Emir, B. (2002). Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. *International Psychogeriatrics, 14*, 389-404.

Gourovitch, M. L., Kirkby, B.S., Goldberg, T. E., Weinberger, D. R., Gold, J. M., Esposito, G.,…Berman, K. F. (2000). A comparison of rCBF patterns during letter and semantic fluency. *Neuropsychology, 15,* 353-360.

Geslani, D. M., Tierney, M. C., Herrmann, N., & Szalai, J. P. (2005). Mild cognitive impairment: An operational definition and its conversion rate to Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 19*, 383-389.

Henry, J. D., Crawford, J. R., & Phillips, L. H. (2004). Verbal fluency performance in dementia of the Alzheimer's type: A meta-analysis. *Neuropsychologia, 42,* 1212-1222.

Hodges, J. R., Erzinçlioğlu, S., & Patterson, K. (2006). Evolution of cognitive deficits and conversion to dementia in patients with mild cognitive impairment: A very-long-term follow-up study. *Dementia Geriatric Cognitive Disorders, 21*, 380-391.

Hodges, J. R., Patterson, K., Oxbury, S., & Funnell, E. (1992). Semantic dementia: Progressive fluent aphasia with temporal lobe atrophy. *Brain 115,* 1783–806.

Hughes, C. P., Berg, L., Danzinger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *British Journal of Psychiatry, 140*, 566-572.

Ivnik, R. J., Malec, J. F., Smith, G. E., Tangalos, E. G., & Petersen, R. C. (1996). Neuropsychological testing norms above age 55: COWAT, BNT, MAE TOKEN, WRAT-R Reading, AMNART, Stroop, TMT, and JLO. *The Clinical*

Neuropsychologist, 10, 262-278.

Jones, S., Laukka, E. J., & Bäckman, L. (2006). Differential verbal fluency deficits in the preclinical stages of Alzheimer's disease and vascular dementia. *Cortex, 42*, 347-355.

LaBarge, E., Balota, D. A., Storandt, M., & Smith, D. S. (1992). An analysis of confrontation naming errors in senile dementia of the Alzheimer's type. *Neuropsychology, 6*, 77-95.

Lafosse, J. M., Reed, B. R., Mungas, D., Sterling, S. B., Wahbeh, H., & Jagust, W. J. (1997). Fluency and memory differences between ischemic vascular dementia and Alzheimer's disease. *Neuropsychology, 11,* 514-522.

Lezak, M. D., Howieson, D. B, Loring, D. W., Hannay, H. J., & Fischer, J. S. (2004). *Neuropsychological Assessment* (4th ed.). New York: Oxford University Press.

Luck, T., Luppa, M., Briel, S., & Riedal-Heller, S. G. (2010). Incidence of mild cognitive impairment: A systematic review. *Dementia and Geriatric Cognitive Disorders 29, 164-175.*

Martin, A., Wiggs, C. L., Lalonde, F., & Mack, C. (1994). Word retrieval to letter and semantic cues: A double dissociation in normal subjects using interference tasks. *Neuropsychologia, 32*, 1487-1494.

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., & Rubin, E. H. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. *Archives of Neurology, 58,* 397–405.

Mummery, C. J., Patterson, K., Hodges, J. R., & Wise, R. J. (1996). Nonlinear regression in parametric activation studies. *Neuroimage, 4*, 60-66.

Murphy, K. J., Rich, J. B., & Troyer, A. K. (2006). Verbal fluency patterns in amnestic mild cognitive impairment are characteristic of Alzheimer's type dementia. *Journal of the International Neuropsychological Society, 12*, 570-574.

Nutter-Upham, K. E, Saykin, A. J., Rabin, L. A., Roth, R. M., Wishart, H. A., Pare, N.,… Flashman, L. A. (2008). Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. *Archives of Clinical Neuropsychology, 23*, 229-241.

O'Brien, J. (2009). Dementia with Lewy bodies and Parkinson's disease dementia: Are they the same entity? *International Psychogeriatrics, 21*, 212-224.

Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia, 28*, 1021-1034.

Petersen, R. C. (2003). *Mild cognitive impairment: Aging to Alzheimer's disease*. New York: Oxford University Press.

Petersen, R. C. (2004). Challenges of epidemiological studies of mild cognitive impairment. *Alzheimer Disease and Associated Disorders, 18*, 1-2.

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

Petersen, R. C., & Morris, J. C. (2003). Clinical features. In R. C. Petersen (Ed.), *Mild cognitive impairment: Aging to Alzheimer's disease* (pp. 15-39). New York, NY US: Oxford University Press.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E.

(1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology, 56,* 303-308

Radanovic, M., Diniz, B. S., Mirandez, R. M., Novaretti, T. M., Flacks, M. K., Yassuda, M. S.,…Forlenza, O. V. (2009). Verbal fluency in the detection of mild cognitive impairment and Alzheimer's disease among Brazilian Portuguese speakers: The influence of education. *International Psychogeriatrics, 21*, 1081-1087.

Rascovsky, K., Salmon, D. P., Hansen, L. A., Thal, L. J., & Galasko, D. (2007). Disparate letter and semantic category fluency deficits in autopsy-confirmed Frontotemporal dementia and Alzheimer's disease. *Neuropsychology, 21*, 20-30.

Reisberg, B., Ferris, S. H., de Leon, M. J., & Crook, T. (1982). The global deterioration scale for assessment of primary degenerative dementia. *The American Journal of Psychiatry, 139*, 1136-1139.

Raoux, N., Amieva, H., Le Goff, M., Auriacombe, S., Carcaillon, L., Letenneur, L.,… Dartigues, J. F. (2008). Clustering and switching processes in semantic verbal fluency in the course of Alzheimer's disease subjects: Results from the PAQUID longitudinal study. *Cortex, 44*, 1188-1196

Roberts, R. O., Geda, Y. E., Knopman, D. S., Cha, R. H., Pankratz, V. S., Boeve, B. F.,… Petersen, R. C. (2012). The incidence of MCI differs by subtype and is higher in men: The Mayo clinic study of aging. *Neurology, 78,* 342-351.

Rohrer, D., Salmon, D. P., Wixted, J. T., & Paulsen, J. S. (1999). The disparate effects of Alzheimer's disease and Huntington's disease on semantic memory. *Neuropsychology, 13*, 381-388.

Román, G. C., & Royall, D. R. (1999). Executive control function: A rational basis for

the diagnosis of vascular dementia. *Alzheimer Disease and Associated Disorders, 13,* 569-580.

Sattler, J. & Ryan, J. (2009). *Assessment with the WAIS-IV*. La Mesa, CA: Jerome M. Sattler Publisher Inc.

Schmitter-Edgecombe, M., Parsey, C., & Cook, D. (2011). Cognitive correlates of functional performance in older adults: Comparison of self-report, direct observation and performance-based measures. *Journal of the International Neuropsychological Society, 17,* 853-864.

Schmitter-Edgecombe, M., Woo, E., & Greeley, D. (2009). Characterizing multiple memory deficits and their relation to everyday functioning in individuals with mild cognitive impairment. *Neuropsychology, 23,* 168-177.

Shimomura, T., Mori, E., Yamashita, H., Imamura, T., Hirono, N., Hashimoto, M.,… Hanihara, T. (1998). Cognitive loss in dementia with Lewy bodies and Alzheimer disease. *Archives of Neurology, 55,* 1547-1552.

Taler, V., & Phillips, N. A. (2008). Language performance in Alzheimer's disease and mild cognitive impairment: A comparative review. *Journal of Clinical and Experimental Neuropsychology, 30,* 501-556.

Troyer, A. K. (2000). Normative data for clustering and switching on verbal fluency tasks. *Journal of Clinical and Experimental Neuropsychology, 22,* 370-378.

Troyer, A. K., Moscovitch, M., & Winocur, G. (1997). Clustering and switching as two components of verbal fluency: Evidence from younger and older healthy adults. *Neuropsychology, 11,* 138-146.

Troyer, A. K., Moscovitch, M., Winocur, G., Alexander, M. P., & Stuss, D. (1998).

Clustering and switching on verbal fluency: The effects of focal frontal- and temporal-lobe lesions. *Neuropsychologia, 36,* 499-504.

Troyer, A. K., Moscovitch, M., Winocur, G., Leach, L., & Freedman, M. (1998). Clustering and switching on verbal fluency tests in Alzheimer's and Parkinson's disease. *Journal of International Neuropsychological Society, 4,* 137–143.

U.S. Census Bureau. (2011). *Profile for America: Facts for features.* Retrieved April 3, 2012, from http://www.census.gov/newsroom/releases/archives/facts_for_features_special_editions/cb11-ff08.html.

U.S. Census Bureau. (2012). *State & county quick facts.* Retrieved April 3, 2012, from http://quickfacts.census.gov.

Wechsler, D. (1997). *Wechsler adult intelligence test-third edition*. New York, NY: The Psychological Corporation.

Williams, J. M. (1991). *Memory Assessment Scales professional manual*. Odessa: Psychological Assessment Resources, Inc.

Wilson, B. A., Alderman, N., Burgess, P. A., Emslie, H., & Evans, J. J. (2003). Behavioral Assessment of the Dysexecutive System (BADS). *Journal of Occupational Psychology, Employment and Disability, 2,* 33-37.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O.,… Petersen, R. C. (2004). Mild Cognitive Impairment--beyond controversies, towards a consensus: Report of the international working group on mild cognitive impairment *Journal of Internal Medicine, 256,* 240-246.

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

Appendix A:Tables and Figures

Table 1: Table of demographic and test variables

	Amnestic MCI Single Domain (n = 25)		Amnestic MCI Multiple Domain (n = 49)		Non-Amnestic MCI (n = 16)		Control (n = 90)		*p*	Group Differences
Variable or test	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Demographics										
Age (years)	73.26	10.63	71.54	8.88	71.00	11.47	71.35	9.38	.82	
Education (years)	16.54	2.86	15.13	3.04	15.56	2.92	15.74	2.70	.23	
Gender (F, M)	14, 11	-	26, 23	-	10, 6	-	61, 29	-	.46	
CDR	0.50	-	0.50	-	0.50	-	0.00	-	-	
TICS^	33.88	2.90	30.00	8.21	32.75	3.07	34.30	4.38	< .001	aMCIs>aMCIm* contro>aMCIm***
Neuropsychological Correlates										
BNT total correct	56.12	4.19	52.21	8.31	54.13	3.22	56.73	2.57	< .001	aMCIs>aMCIm* control>aMCIm***
Trails B (seconds)^	102.00	48.36	139.82	63.92	109.20	35.19	81.88	27.37	< .001	aMCIs>aMCIm** control>aMCIm***

Note: Unless otherwise indicated, mean scores are raw scores. Norm sources for the cognitive tests are in parentheses following the test. MCI = Mild Cognitive Impairment; aMCIs = amnestic MCI single domain; aMCIm = amnestic MCI multiple domain; F = female; M = male; CDR = Clinical Dementia Rating Scale (Hughes et al., 1982) TICS = Telephone Interview of Cognitive Status (Brandt & Folstein, 2003); BNT = Boston Naming Test (Ivnik, Malec, Smith, Tangalos, & Petersen, 1996); Trails B; (Delis & Kaplin, 2001)
^ Data available for 184 of 188 participants
* $p < .05$, ** $p \leq .01$, $p \leq .001$***

Table 2: Performance on verbal fluency tasks by group

	Single Domain Amnestic MCI		Multiple Domain Amnestic MCI		Non-Amnestic MCI		Control	
Variable	Time 1	Time 2	Time 1	Time 2	Time 1	Time 2	Time 1	Time 2
Letter Fluency (F + A + S)								
Total Responses	22.79 (5.50)	13.33 (5.47)	21.07 (7.63)	11.54 (6.51)	18.13 (5.67)	12.73 (7.59)	26.52 (6.58)	16.17 (5.76)
Mean Cluster Size	.44 (.22)	.41 (.31)	.36 (.26)	.39 (.35)	.53 (.30)	.37 (30)	.51 (.32)	.49 (.38)
Total Switches	14.79 (4.11)	10.71 (4.16)	13.83 (5.48)	10.24 (4.99)	10.67 (4.17)	9.67 (3.98)	16.82 (5.72)	12.17 (3.79)
Category Fluency (Animal)								
Total Responses	13.33 (4.02)	6.00 (2.48)	11.42 (3.39)	5.80 (2.81)	12.38 (2.33)	6.63 (2.87)	14.02 (3.36)	7.36 (3.23)
Mean Cluster Size	1.51 (.87)	.90 (.68)	1.07 (.51)	1.00 (.87)	1.31 (.83)	1.09 (.90)	1.17 (.60)	1.13 (82)
Total Switches	5.58 (2.19)	4.00 (1.64)	5.55 (2.13)	3.51 (1.60)	5.38 (1.86)	3.56 (1.63)	5.95 (2.12)	3.87 (1.67)

Note: Mean scores are raw scores, standard deviations are in parentheses; Time 1 = 0-30 seconds; Time 2 = 31-60 seconds

Table 3: Table of neuropsychological tests and dependent variable correlations by verbal fluency

LETTER FLUENCY

	Amnestic MCI Single Domain			Amnestic MCI Multiple Domain			Non-Amnestic MCI			Control		
Variable	Total Words	Mean Cluster	Total Switch	Total Words	Mean Cluster	Total Switch	Total Words	Mean Cluster	Total Switch	Total Words	Mean Cluster	Total Switch
BNT	-.09	0.17	-.32	.18	0.27	-.07	.17	-.14	.29	.16	.40	.12
Trails B	-.27	-.35	-.05	-.01	.01	.08	-.55*	-.26	-.56*	-.22*	.15	-.25*

CATEGORY FLUENCY

Variable	Total Words	Mean Cluster	Total Switch	Total Words	Mean Cluster	Total Switch	Total Words	Mean Cluster	Total Switch	Total Words	Mean Cluster	Total Switch
BNT	.49**	-.20	.50***	.51**	.08	.53**	.24	-.16	.16	.34***	-.02	.39***
Trails B	-.38	.12	-.46*	-.27	-.01	-.39**	-.60*	-.19	-.25	-.28**	.04	-.33**

Note: Scores are correlation values represented by *r;* C.S. = Cluster Size; BNT = Boston Naming Test (Ivnik, Malec, Smith, Tangalos, & Petersen, 1996); Trails B; (Goodglass, Kaplan, & Barresi, 2001)

*$p < .05$, **$p < .01$, *** $p \leq .001$

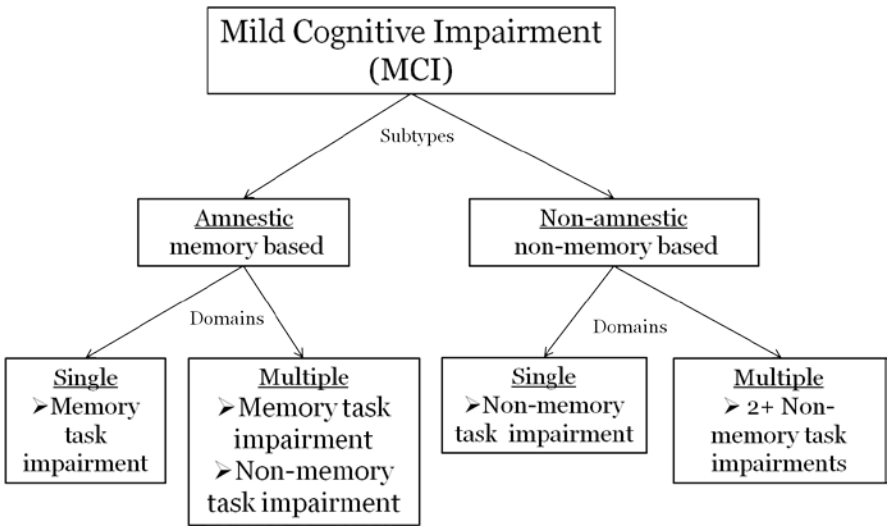


Figure 2: Breakdown of MCI into subtypes and domains

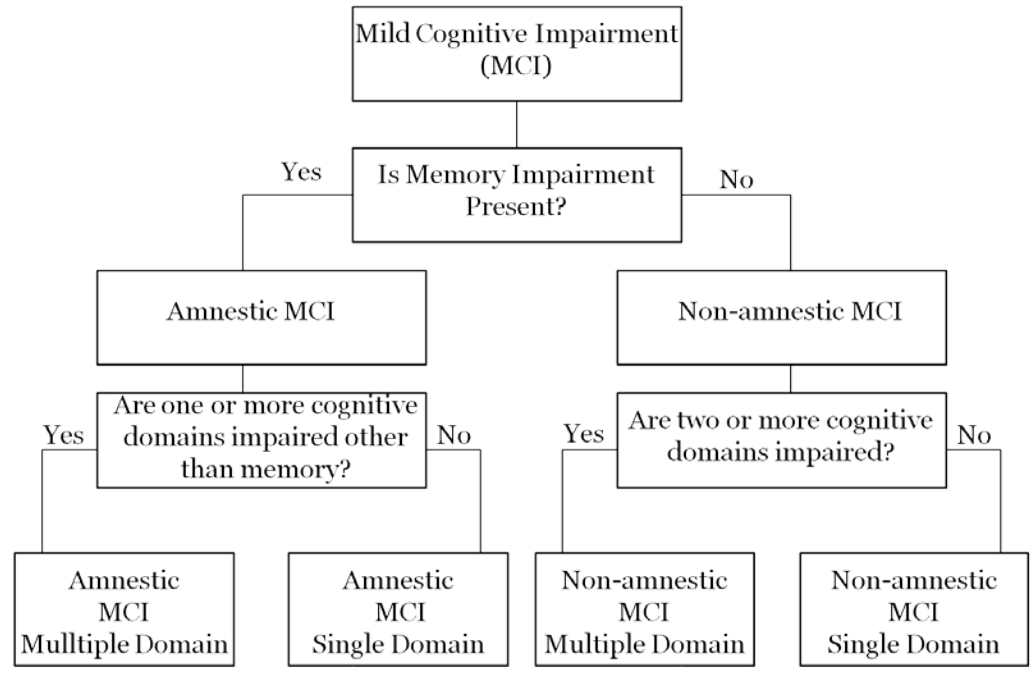


Figure 3: MCI diagnostic flowchart

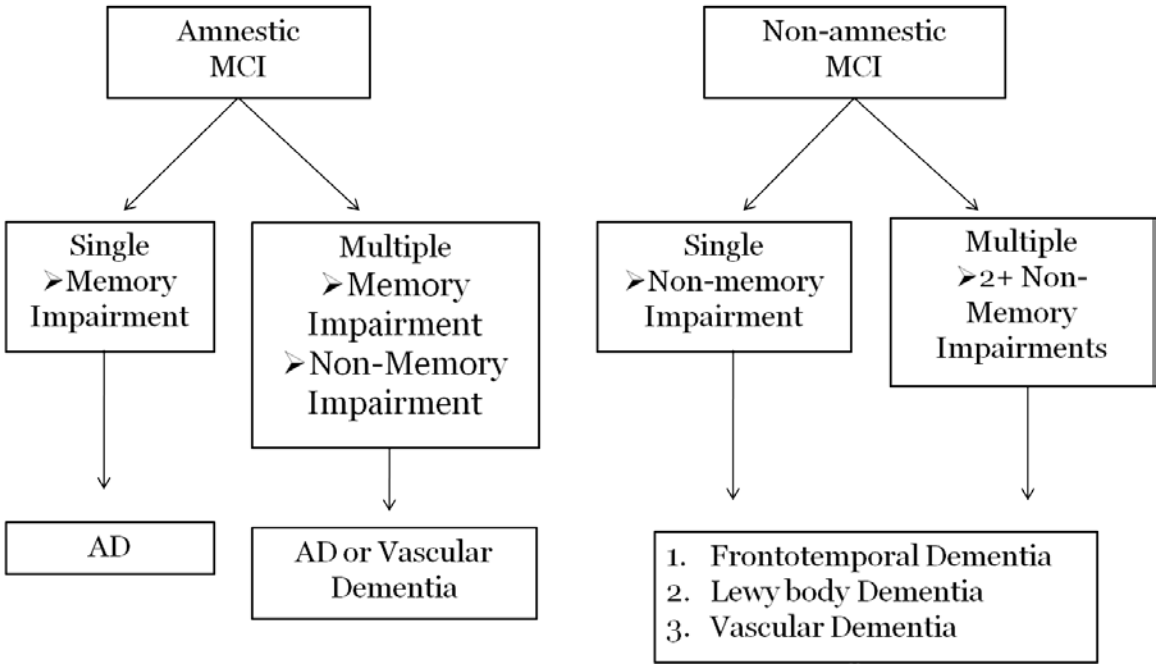


Figure 4: Conversion of MCI subtypes and domains to dementia types

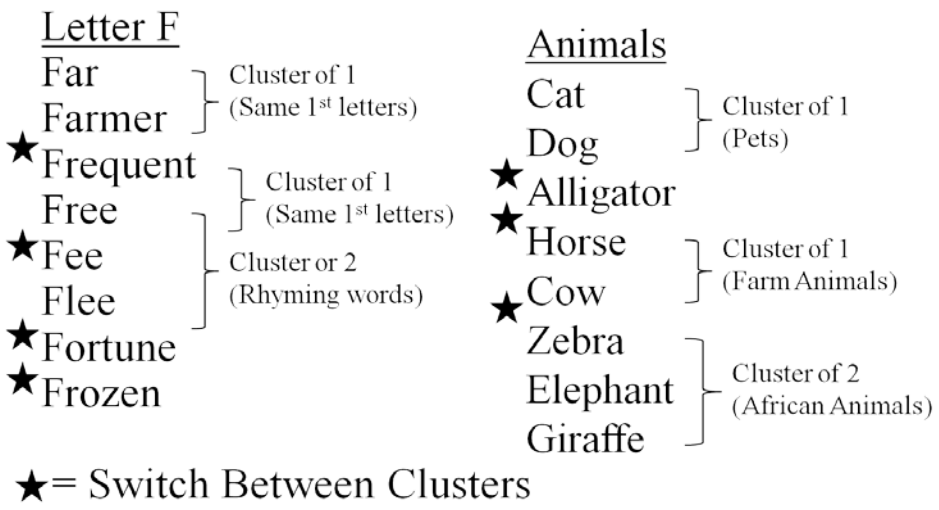


Figure 4: Example of how to score clusters and switches on the verbal fluency tasks

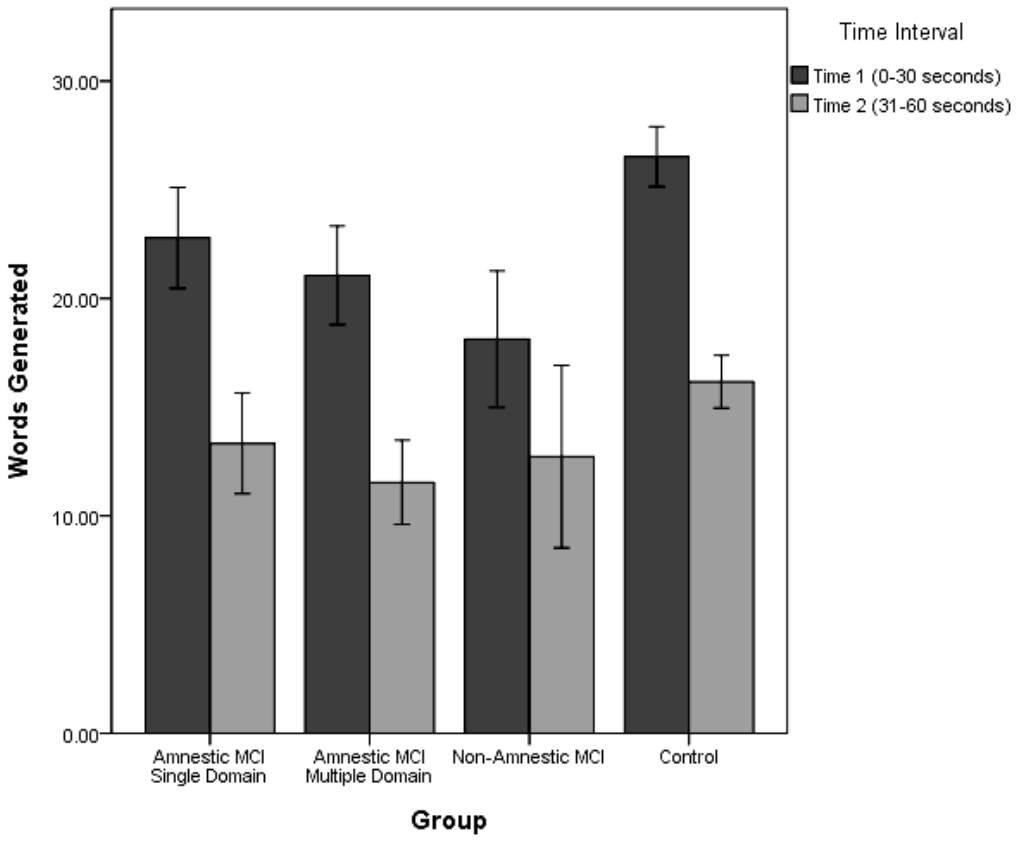


Figure 5: Bar graph of total words generated on the letter fluency task at each time interval by group. Error bars represent 95% confidence interval.

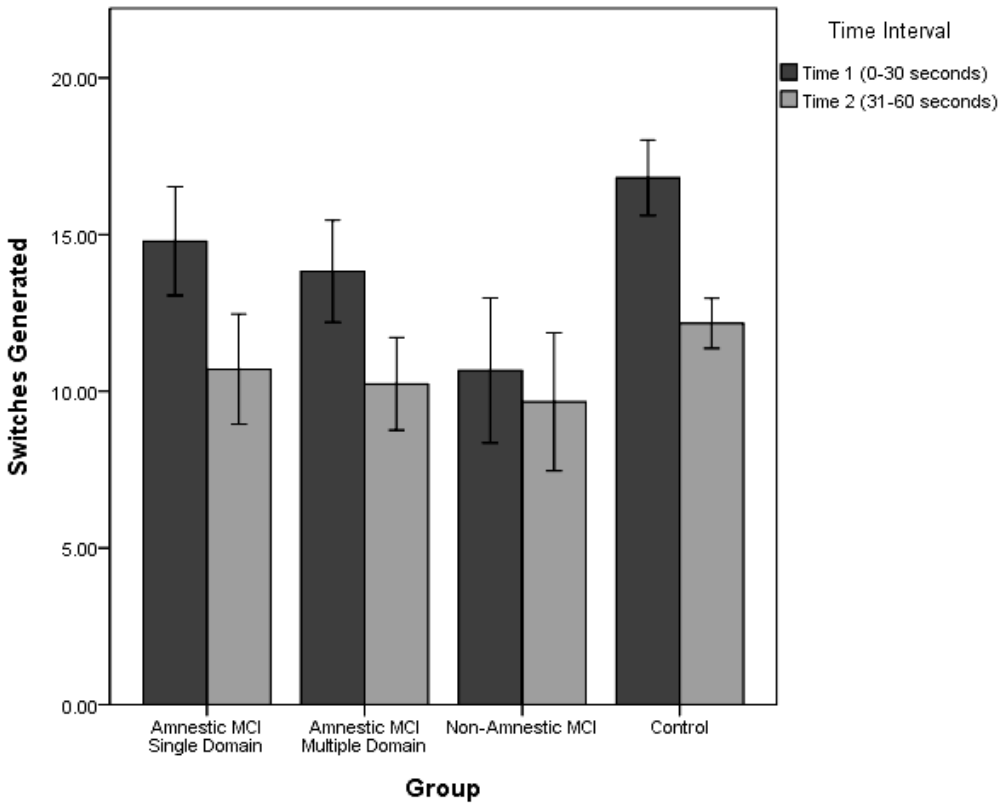


Figure 6: Bar graph of total switches generated on the letter fluency task at each time interval by group. Error bars represent 95% confidence interval.

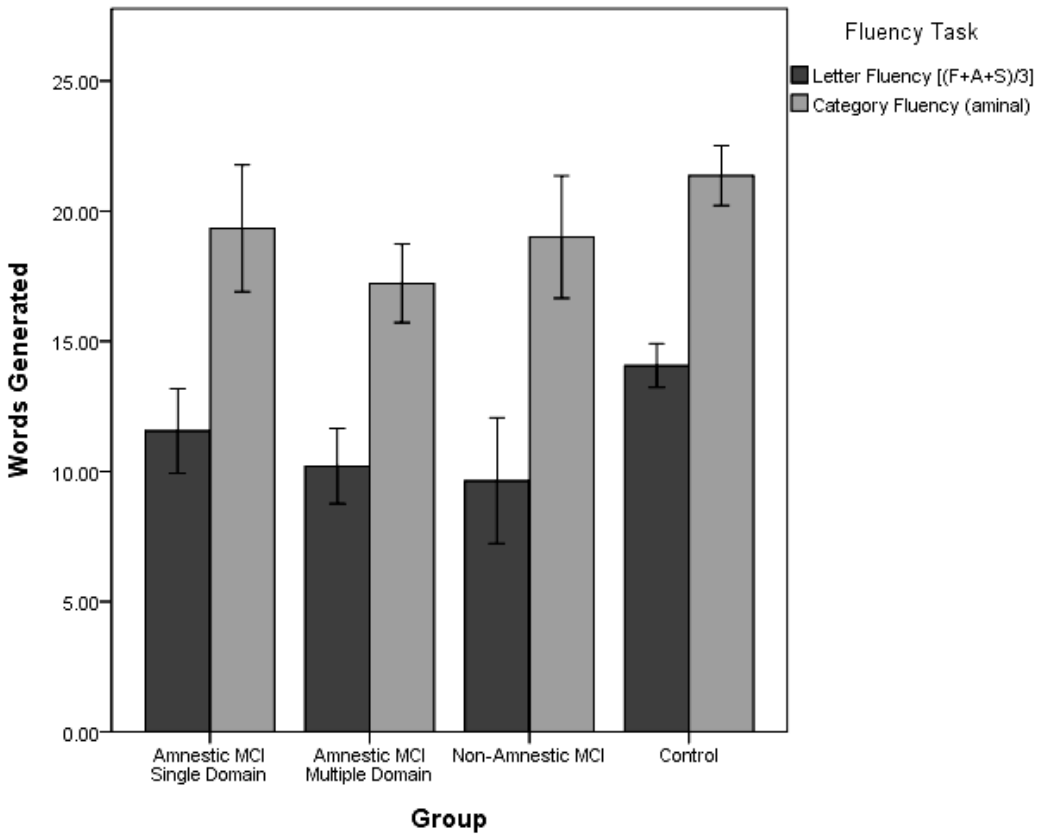
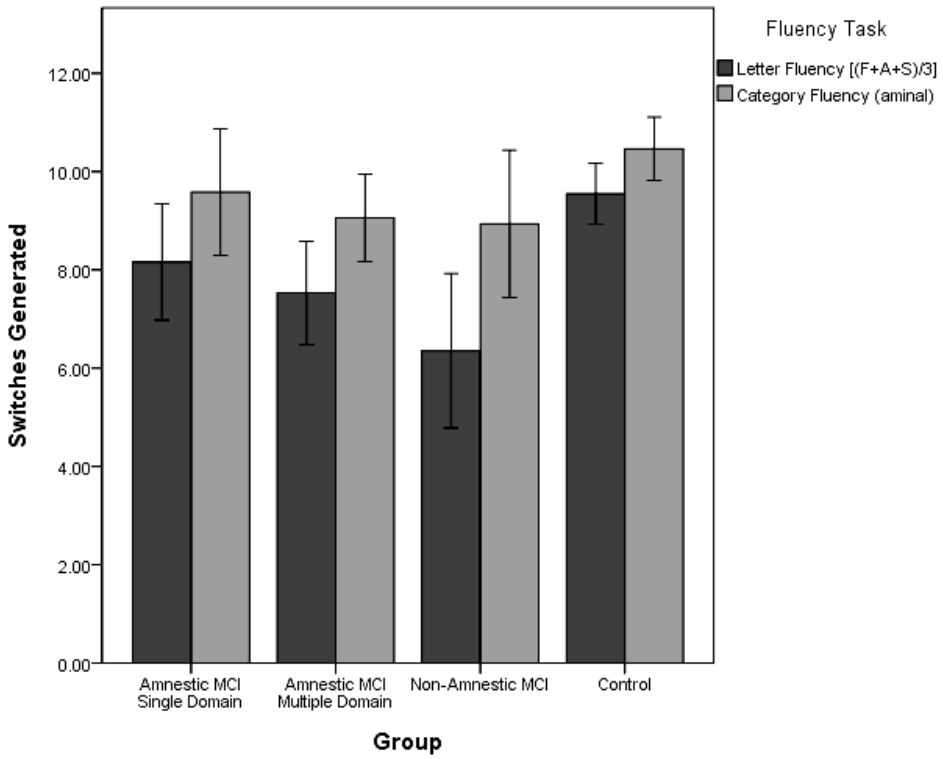


Figure 7: Bar graph of total words generated by group on each fluency task. Error bars represent 95% confidence interval.


Fluency Task
Letter Fluency [(F+A+S)/3]
Category Fluency (aminal)
Switches Generated
12.00
10.00
8.00
6.00
4.00
2.00
0.00
Amnestic MCI Single Domain
Amnestic MCI Multiple Domain
Non-Amnestic MCI
Control
Group

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