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The Semantic Memory Imaging In Late Life Pilot Study

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by

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CHAPTER 1: INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia (Kalaria et al., 2008) and is a worldwide health concern. It has been projected that by the year 2050, over 100 million people worldwide will be diagnosed with AD (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007), including between 11 and 16 million in the United States alone (Thies & Bleiler, 2011). Currently, there are no effective treatments for reversing AD pathology or slowing the progression of the condition for individuals who have received a diagnosis of AD. However, several promising strategies have been identified that may delay or even prevent the onset of AD (Daviglus et al., 2010). Various lifestyle factors, such as a Mediterranean-style diet (Gu, Nieves, Stern, Luchsinger, & Scarmeas, 2010) and participation in physical activity (Rolland, Abellan van Kan, & Vellas, 2008; Sofi et al., 2011), social activity (Fratiglioni, Paillard-Borg, & Winblad, 2004; Saczynski et al., 2006), and cognitively stimulating activity (Wilson et al., 2002; Wilson, Scherr, Schneider, Tang, & Bennett, 2007), have been associated with a decreased risk for developing AD. It has been estimated that half of all AD cases can be attributed to modifiable risk factors (Barnes & Yaffe, 2011). Additionally, AD-related neuropathology accumulates for decades prior to the onset of cognitive symptoms (Ghebremedhin, Schultz, Braak, & Braak, 1998; Kok et al., 2009). Thus, implementation of an intervention well before the onset of observable symptoms, such as episodic memory loss, could provide the greatest opportunity to slow or minimize damage due to the disease, particularly if these interventions are targeted toward persons with the greatest AD-risk.

Risk Factors and Biomarkers for AD

In order to identify those individuals who are at the highest likelihood of developing the disease, considerable research efforts have been directed toward identifying specific risk factors

and biomarkers of AD. Two well-established susceptibility risk factors for late-onset (age 65 years and older), non-sporadic AD are a history of dementia in a first-degree relative (Fratiglioni, Ahlbom, Viitanen, & Winblad, 1993) and inheritance of at least one Apolipoprotein E (APOE) ε4 allele (Bertram & Tanzi, 2008; Corder et al., 1993; Saunders et al., 1993). It is important to note that these risk factors are not deterministic for developing the disease. In addition to these genetic risk factors, a number of biological markers have demonstrated effectiveness in predicting conversion from mild cognitive impairment (MCI) to AD (Clark et al., 2008). These methods include analyses of cerebrospinal fluid indices of isoprostane (Brys et al., 2009; de Leon et al., 2006; de Leon et al., 2007), total tau and phosphorylated tau (Buerger, Teipel, et al., 2002; Buerger, Zinkowski, et al., 2002; Hampel, Buerger, et al., 2004), and amyloid-β (Aβ)$_{42}$ (Blennow & Hampel, 2003; Brys et al., 2009; Hampel, Teipel, et al., 2004; Hansson et al., 2006). Additionally, several neuroimaging methods have also been demonstrated to be effective predictors of conversion from MCI to AD, including structural magnetic resonance imaging (sMRI) of hippocampal volume (de Leon, George, Stylopoulos, Smith, & Miller, 1989; Jack et al., 1999; Wolf et al., 2003), hippocampal rate of atrophy (Henneman et al., 2009; Morra et al., 2009; Stoub, Rogalski, Leurgans, Bennett, & Detoledo-Morrell, 2008), and entorhinal cortex volume (Cardenas et al., 2003; Devanand et al., 2007; Juottonen, Lehtovirta, Helisalmi, Riekkinen, & Soininen, 1998; Stoub et al., 2008), electroencephalography (Buscema, Grossi, Capriotti, Babiloni, & Rossini, 2010; Jelic et al., 2000), and positron emission tomography of regional glucose metabolism (Chetelat et al., 2003; Chetelat et al., 2005) and amyloid imaging using the ^{11}C Pittsburgh Compound B (Rowe et al., 2007; Wolk & Klunk, 2009; Wolk et al., 2009). Unfortunately, most of the existing imaging techniques that show promise for early detection of AD are expensive, not widely available, time-consuming, and/or highly invasive.

Functional magnetic resonance imaging (fMRI) is a possible alternative to these approaches that has a number of advantages and relatively few disadvantages for early AD detection.

fMRI as a Biomarker for AD

Amongst the various neuroimaging biomarker methods, fMRI presents several advantages. It has the benefit of being minimally invasive, widely available, and potentially less labor intensive compared to other approaches. Given that it can serve as a "cognitive stress test," fMRI has the potential to reveal possible abnormalities in brain function during cognitive performance and may be more sensitive to earlier disease-related changes that cannot be seen with purely structural techniques. Indeed, fMRI has proven to be effective as a tool for detecting patterns of activation that may serve as a biomarker of subsequent cognitive decline in healthy older adults. For example, AD risk factors such as a first-degree family history of dementia and the presence of the APOE ε4 allele have been associated with altered fMRI activation in cognitively intact older adults (Bondi, Houston, Eyler, & Brown, 2005; Han et al., 2007; Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Antuono, et al., 2009; Woodard et al., 2009). fMRI studies have also suggested that these risk factors may impact brain functioning throughout the lifespan (Filippini et al., 2009; Trachtenberg, Filippini, & Mackay, 2010; Trivedi et al., 2008; Trivedi et al., 2006; Xu et al., 2009), decades prior to the onset of memory decline or other observable AD symptoms. Furthermore, in longitudinal studies, fMRI has been used to successfully predict conversion from MCI to AD (Miller et al., 2008; Petrella, Prince, Wang, Hellegers, & Doraiswamy, 2007; Vannini, Almkvist, Dierks, Lehmann, & Wahlund, 2007) and to predict future cognitive decline in healthy older adults (Bookheimer et al., 2000; Lind et al., 2006; O'Brien et al., 2010; Persson et al., 2006; Woodard et al., 2010). Thus, fMRI has

considerable promise as a method for assisting in determining who may be at the greatest risk for AD.

fMRI Task Design: Episodic versus Semantic Memory

A crucial decision when designing fMRI experiments is the choice of task to be used in the scanner. Typically, most tasks fall into two broad categories: episodic memory (e.g., discriminating between previously learned and novel stimuli) and semantic (recall of general facts and knowledge about the world that are not contextually specific). Because episodic memory deficits are among the earliest symptoms of AD, a considerable body of research has employed episodic memory tasks during task-activated fMRI. However, the use of episodic memory techniques with older adults presents challenges. First, episodic memory impairment is typically observed not only in association with symptom onset of MCI or AD (Bondi & Kaszniak, 1991; Irle, Kaiser, & Naumann-Stoll, 1990; Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994; Petersen et al., 1999; Petersen et al., 2001), but declines in episodic memory performance are also observed in normal aging (Nilsson, 2003). Further, episodic tasks may also be inherently more difficult and less engaging than semantic tasks, and intergroup and interindividual differences in task performance may confound interpretation of the functional imaging results. Finally, in persons with AD or MCI, the presence of episodic memory decline may signal the presence of irreversible brain damage, limiting the effectiveness of episodic memory tasks for preclinical identification of early AD.

The use of semantic memory tasks during fMRI may provide a practical alternative to the use of episodic tasks. Semantic memory tasks involve immediate, context-independent familiarity with previously learned information, and these tasks are typically easier, more interesting and engaging, and less frustrating for older participants to complete than episodic

memory tasks. Difficult tasks can result in greater between-subject variability in task performance, which can confound interpretation of fMRI data (Sugarman et al., 2012). Unlike episodic memory skills, semantic memory abilities remain relatively intact across the lifespan (Nilsson, 2003) but are commonly affected in individuals with AD (Hodges, Salmon, & Butters, 1990, 1992; Nebes, 1989). In a recent longitudinal study (Hantke et al., 2013), a semantic memory task was compared to an episodic memory task in a sample of cognitively intact older adults who underwent neuropsychological testing at baseline and 18-month follow-up. Baseline fMRI activation from the semantic memory task provided superior prediction compared to the episodic memory task in determining which individuals were at the highest risk for cognitive decline during the 18-month interval. Thus, analysis of fMRI activation pattern and magnitude during semantic memory processing has a number of advantages compared to episodic memory for discriminating between healthy aging and disease-related changes and risk.

Semantic Memory and AD

Several studies have indicated that individuals with AD may possess deficits in semantic memory systems that extend beyond normal aging processes (Hodges et al., 1990; Hodges, Salmon, et al., 1992; Nebes, 1989). For example, compared to cognitively intact controls, individuals with AD are often impaired on measures of object naming, verbal fluency, knowledge regarding the functions of specific items, ability to sort items into categories, and ability to correct semantic errors in sentences (Nebes, 1989). One study reported that deficits on neuropsychological measures traditionally associated with semantic memory may only be present in a subset of individuals with AD, especially in mild AD (Hodges & Patterson, 1995). In this study (Hodges & Patterson, 1995), a sample of individuals diagnosed with mild AD completed seven semantic knowledge tasks, including verbal fluency, object naming, and sorting

pictures. On average, individuals in the sample obtained scores in the impaired range (as determined by a *z*-score $\leq$ -2) on only 4.1 out of the 7 tasks, and about one-third of the sample had impaired scores on two or fewer tasks. In contrast, 100% of this sample obtained impaired scores on measures of delayed episodic recall. However, a sample of individuals with moderate AD obtained impaired scores on 6.7 out of the 7 semantic memory tasks (Hodges & Patterson, 1995). Thus, in mild AD, deficits on neuropsychological measures traditionally associated with semantic memory are less frequently observed than the universal deficits in episodic memory, which are a hallmark of the condition. As the disease progresses, deficits in semantic memory are present for almost all individuals with the condition. It is possible that other approaches to assessing the integrity of semantic knowledge structures may be more sensitive to early changes associated with loss of these structures associated with AD than the measures used in this study. Indeed, several other studies have identified semantic knowledge deficits in early AD using different approaches.

Several studies have suggested that the breakdown of semantic knowledge structures may occur in a hierarchical manner (Hodges, Salmon, et al., 1992; Martin & Fedio, 1983; Salmon, Butters, & Chan, 1999). In individuals with mild AD, impairment may be most evident with regard to highly specific, subordinate semantic information. In contrast, knowledge for superordinate, category-level information is intact. For example, one study (Tröster, Salmon, McCullough, & Butters, 1989) observed that during a category fluency task (naming items that are in a supermarket), patients with AD had a propensity to name category-level items (e.g., "fruit", "meat") rather than specific items (e.g., "bananas", "bacon"). Other studies (Hodges & Patterson, 1995; Hodges, Salmon, et al., 1992) found that patients with AD were not impaired in their ability to sort objects into broad categories (e.g., man-made vs. living), but were impaired

relative to controls in their ability to sort the objects into more specific categories (e.g., land animals vs. sea animals). These findings indicate that patients with AD may have reduced access to lower-level semantic information, whereas more generalized higher-level knowledge is less likely to be affected early in the disease course.

Impairment in semantic memory might be evident prior to a diagnosis of AD. One study (Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Zhang, et al., 2009) found that individuals with MCI perform equivalently to cognitively intact controls on a task where they had to identify whether a given name was that of a famous individual. However, the individuals with MCI were able to name significantly fewer facts regarding these individuals, reflecting the loss of highly specific, subordinate semantic information in this patient group. Another study (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006) observed that individuals with MCI were impaired on measures of verbal category fluency and on tasks requiring knowledge of object functions. These studies indicate that semantic deficits may be present early in the course of AD. The changes in brain function that may precede and eventually lead to these semantic knowledge specificity deficits in MCI and early AD may be detectable in otherwise cognitively healthy persons using task-activated fMRI.

Neuroimaging of Semantic Memory

A large body of research has examined the neural networks associated with semantic memory retrieval in healthy adults. A review of 120 of these studies (Binder, Desai, Graves, & Conant, 2009) used activation likelihood estimate techniques to identify that the semantic memory network is composed of seven distinct left-lateralized brain regions: posterior inferior parietal lobe, middle temporal gyrus, fusiform and parahippocampal gyri, dorsomedial prefrontal cortex, inferior frontal gyrus, ventromedial prefrontal cortex, and posterior cingulate cortex.

Thus, a variety of cortical regions in temporal, parietal, and frontal lobes appear to participate in semantic memory retrieval. In addition, the hippocampus and surrounding areas including parahippocampal gyrus are associated not only with semantic memory processes, but they are also critical neural structures that support episodic memory consolidation and retrieval (Tulving & Markowitsch, 1998). Some of the regions that participate in the semantic memory network, including the inferior parietal lobe and middle temporal gyrus, are not modality-specific, i.e., they are active during semantic knowledge retrieval regardless of the nature of the sensory or motor requirements of the task (Binder & Desai, 2011). Thus, these regions may contain representations of semantic concepts that are independent of the modality of experience or the specific type of semantic information. In particular, the anterior temporal lobe appears to process memories linked to social knowledge and specific biographical information (Olson, McCoy, Klobusicky, & Ross, 2013), and atrophy specifically in this region has been associated with semantic memory loss (Chan et al., 2001). For example, one study (Devlin et al., 2002) had participants perform a lexical word identification task during PET with words from four categories: fruits, animals, tools, and vehicles. Compared to a letter identification task, they found that bilateral temporal lobe regions displayed significant activity regardless of the word category. There were no significant differences between word categories after correcting for multiple comparisons.

The anterior temporal lobe has been specifically associated with biographical semantic knowledge. The anterior temporal lobe demonstrates recruitment in response to famous and familiar faces, and anterior temporal lobe lesions can cause an inability to form new associations between people and objects. Social knowledge tasks such as making moral judgments or interpreting social gestures also recruit the anterior temporal lobe (Olson et al., 2013).

Specifically, the left anterior temporal lobe has been implicated in processing the semantic aspects of objects and people, whereas the right anterior temporal lobe is more associated with processing perceptual characteristics (Campanella, Fabbro, & Urgesi, 2013). A review of functional neuroimaging studies in healthy participants (Gainotti, 2013) also indicated strong laterality effects during fame recognition. Specifically, retrieval of semantic information associated with famous faces and voices appears to be predominantly lateralized to the right temporal lobe. In contrast, the left temporal lobe was more active during recognition of famous compared to unfamiliar names.

Further evidence for the important role of the anterior temporal lobes during semantic memory retrieval has been demonstrated through studies involving patients with semantic dementia. One study (Snowden, Thompson, & Neary, 2012) found that in a sample of patients with semantic dementia, right-lateralized anterior temporal lobe atrophy was associated with impairment during visual semantic tasks, including famous face recognition. Conversely, left-lateralized anterior temporal lobe atrophy was associated with verbal impairment, including famous name recognition. A review of studies of patients with semantic dementia (Gainotti, 2007) observed consistent patterns of impairment associated with lateralized anterior temporal lobe atrophy. Right-lateralized atrophy is associated with impaired recognition of faces and feelings of familiarity and information associated with the person, whereas left-lateralized atrophy is more associated with identity recognition and retrieval of famous names.

Some studies have observed that the regions associated with the semantic memory network have considerable overlap with the "default mode network" (Binder & Desai, 2011; Binder et al., 2009; Buckner, Andrews-Hanna, & Schacter, 2008; Whitfield-Gabrieli et al., 2011). The default mode network refers to the network of brain activity that occurs during

passive, resting states and is typically deactivated with external stimulation in cognitively healthy individuals (Binder et al., 1999). The regions associated with the default mode network include the posterior cingulate, inferior parietal lobe, anterior temporal lobe, parahippocampal gyrus, and medial prefrontal cortex. Like the semantic memory network, default mode network activity is typically left-lateralized, although the extent of lateralization is not as pronounced as the semantic memory network (Binder et al., 2009).

Neuroimaging of Semantic Memory and AD

AD is prominently associated with atrophy primarily in the medial temporal lobes, including hippocampus and entorhinal cortex, early in the disease course, although global atrophy is seen in more advanced cases (Zakzanis, Graham, & Campbell, 2003). Resting-state PET studies have observed that hypometabolism in patients with AD compared to cognitively intact controls is most commonly observed in the hippocampus, posterior cingulate, inferior parietal lobule, and lateral temporal lobe (Mosconi et al., 2008). Thus, given that many of these regions are also involved during semantic memory retrieval (Binder et al., 2009), the presence of semantic memory impairment in a large number of patients with AD is not surprising.

One study (Hodges & Patterson, 1995) observed that patients with mild AD are not consistently impaired in semantic memory abilities, in contrast to the universal impairment in episodic memory in this population. The authors speculated that parahippocampal and entorhinal cortex atrophy were not sufficient to cause semantic memory impairment, and that this impairment only occurs when atrophy has spread to the temporal neocortex, including middle temporal gyrus. They based their rationale on studies of patients with semantic dementia who had the most pronounced atrophy in the temporal lobes (Hodges, Patterson, Oxbury, & Funnell, 1992). This postulation is supported by results from their sample of individuals with moderate

AD, who all obtained impaired scores on relatively gross neuropsychological measures traditionally associated with semantic memory (Hodges & Patterson, 1995). Presumably, individuals with moderate AD had a greater extent of temporal lobe atrophy compared to the sample with mild AD. Further research has indicated that anterior temporal cortex atrophy might be a defining component of semantic dementia, whereas atrophy in AD occurs throughout the temporal cortex but not always in anterior regions (Chan et al., 2001). Thus, semantic memory impairment in individuals with AD may be mediated by the extent of temporal lobe atrophy. Although anterior temporal lobe atrophy is not always present early in the disease course, fMRI may be valuable for detecting possible functional abnormalities in anterior temporal lobe or other interconnected regions that may precede observable structural changes (Xu et al., 2009).

There have been a limited number of neuroimaging studies examining the semantic memory network in individuals with AD. One study (Grossman et al., 2003) compared patients with AD to cognitively intact controls while making pleasantness judgments for animals and implements during fMRI. Results revealed that the patients with AD displayed significantly lower activity than controls in posterolateral temporal and inferior parietal cortex. In contrast, the patients with AD had significantly greater activity in left inferior temporal cortex compared to controls. These results indicated that the patients with AD might compensate for neurological dysfunction at the temporo-parietal junction through recruitment of alternative regions such as inferior temporal cortex. Further, these results provide further evidence for temporal dysfunction that likely underlies semantic memory impairment in AD.

There have also been a number of studies implicating abnormalities in the default mode network in individuals with AD (Greicius, Srivastava, Reiss, & Menon, 2004; Koch et al., 2012) and in individuals at-risk for AD (Filippini et al., 2009; Westlye, Lundervold, Rootwelt,

Lundervold, & Westlye, 2011). Asymptomatic carriers of the APOE ε4 allele typically display increased default mode network activity compared to non-carriers (Filippini et al., 2009; Westlye et al., 2011). However, *reduced* task-related deactivation in several regions that include the posterior cingulate and hippocampus has been observed in individuals with AD (Greicius et al., 2004; Koch et al., 2012; Petrella et al., 2007) and MCI (Petrella et al., 2007). Reduced default mode activity may also be prognostic of conversion from MCI to AD (Petrella et al., 2007). Further, several regions associated with the default mode network are also often sites of amyloid-beta plaque accumulation during the early stages of AD (Buckner et al., 2005). One group postulated that increased used of default mode resources across the lifespan might increase susceptibility for late-life AD neuropathology (Buckner et al., 2005).

As described previously, the regions associated with the default mode network have considerable overlap with the semantic memory network. Many of the regions associated with the default mode network also show significant AD-related atrophy, hypometabolism on FDG-PET, and accumulation of amyloid-containing plaques (Buckner et al., 2005). Thus, given the association between the semantic memory network and AD-related neuropathology, functional neuroimaging during semantic memory tasks has considerable potential as a valuable methodology for studying risk for AD.

Semantic Memory Imaging with Famous Name Discrimination

Previous studies from our research group (Douville et al., 2005; Hantke et al., 2013; Leveroni et al., 2000; Nielson et al., 2006; Nielson et al., 2010; Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Antuono, et al., 2009; Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Zhang, et al., 2009; Smith, Nielson, Woodard, Seidenberg, Durgerian, et al., 2011; Smith, Nielson, Woodard, Seidenberg, Verber, et al., 2011; Sugarman et al., 2012; Woodard et al.,

2009; Woodard et al., 2007; Woodard et al., 2010; Woodard et al., 2012b) have studied aspects of fMRI semantic memory activation using a paradigm known as the famous name discrimination task (FNDT). The FNDT requires participants to determine whether visually presented names are those of well-known public personalities or are non-famous names. Completion of this task requires the ability to access semantic memory stores to properly recognize famous names and to correctly reject non-famous names. Further, this task can be used to probe memories of different ages by presenting names of famous individuals who attained their fame during different time epochs. In cognitively intact older adults, we compared the recognition of recent (achieved fame within approximately the last 10 years) and remote (achieved fame approximately 40-50 years ago but are not typically know by younger adults) famous names. A third category, enduring names, consisted of persons who first achieved fame approximately 40-50 years ago and are still well-known today by older and younger adults alike. We observed a temporal gradient in hippocampal (Douville et al., 2005) and neocortical (Woodard et al., 2007) regions, with greater activation being observed in these regions during recent relative to remote famous name recognition. Overall, the brain regions involved in fame recognition (relative to the rejection of non-famous names) include bilateral hippocampus and parahippocampal gyri, right caudate nucleus, and several cortical regions, including cingulate cortex, bilateral frontal lobes, left middle temporal gyrus, and right fusiform gyrus, and the precuneus (Douville et al., 2005; Woodard et al., 2007). This pattern of task-activated recruitment is consistent with other neuroimaging findings using semantic memory tasks (Binder et al., 2009).

The FNDT requires little effort and can be completed with high accuracy (>87% correct identification of famous names) even by individuals with MCI (Woodard et al., 2009).

Moreover, this task may be sensitive to detection of individuals at-risk for cognitive decline and/or AD. Cognitively intact older adults who are carriers of one or more APOE ε4 alleles typically display greater activation than non-carriers (Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Antuono, et al., 2009; Smith, Nielson, Woodard, Seidenberg, Durgerian, et al., 2011; Woodard et al., 2009; Woodard et al., 2010) for famous names compared to non-famous names.

Increased activity in asymptomatic APOE ε4 carriers has been observed during other task-activated fMRI studies as well (Trachtenberg et al., 2010). Neuroimaging differences between APOE ε4 and non-carriers may reflect early pathology associated with AD in the absence of clinical symptoms. This preclinical pathology may include structural and metabolic changes in regions including the hippocampus and temporal lobe (Twamley, Ropacki, & Bondi, 2006). Individuals undergoing these early changes may engage in cognitive "scaffolding". That is, they recruit additional regions to compensate for declining integrity in neural resources (Park & Reuter-Lorenz, 2009).

In a longitudinal study, we demonstrated that increased baseline FNDT activation was protective against subsequent cognitive decline after 18 months (Woodard et al., 2010). In this study, cognitively intact elders who exhibited greater activity in hippocampal and cortical regions during famous name recognition (relative to non-famous name identification) were at reduced risk for developing symptoms of cognitive decline 18 months later. Optimal discrimination between cognitively stable and declining individuals was identified using a logistic regression model containing hippocampal and cortical fMRI activity as well as whether participants were carriers of the APOE ε4 allele. The task-activated fMRI information was superior to demographic information alone or baseline structural measurement of hippocampal volume for predicting subsequent decline.

To be performed successfully, the FNDT only requires a general familiarity with fame (or absence of fame) for a given individual, and does not require higher-order semantic knowledge beyond familiarity. However, within the semantic memory network, it has been argued that highly specific attribute knowledge associated with semantic targets may be the most susceptible to late-life semantic memory loss, while more general, categorical information is likely to remain relatively unimpaired until later stages of MCI or AD (Giffard et al., 2001; Hodges, Salmon, et al., 1992; Tröster et al., 1989; Warrington, 1975). This postulation suggests the presence of a hierarchical model of semantic memory loss associated with AD, involving a less specific superordinate (e.g., categorical information) component and a highly specific subordinate component (e.g., specific facts) attributable to knowledge of public figures, events, or concepts (Chertkow & Bub, 1990). During a post-fMRI scan questionnaire task, we observed that MCI patients are able to name fewer specific attributes about famous individuals even though they were able to complete the FNDT with accuracy comparable to that of cognitively intact controls (Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Zhang, et al., 2009). Thus, within the person identity network, the hierarchy of semantic information may be characterized by multiple levels that are differentially vulnerable to AD-related neuropathology. Simple recognition of famous names (superordinate) may be less affected in the early phases of memory loss, while attributional information (subordinate) may be more sensitive to early cognitive decline or risk for dementia.

Development of Semantic Knowledge Tasks Requiring Deeper Processing

Previous work from our group (Holcomb, 2013; Loacano et al., 2011) has investigated the use of two new tasks that resemble the FNDT in presentation style but require deeper semantic processing to complete: the Categories task and the Attributes task. Like the FNDT,

participants are presented with names and are required to make a two-alternative forced-choice decision. Target famous names are presented along with either two broad occupational categories (e.g., Movies, Music, Politics, etc.) or bodies of work that could be attributed to the target name (e.g., album titles, movies, television shows, life events). The participant is asked to identify the Category or Attribute that is most associated with the target name for the Categories and Attributes tasks, respectively. Based on a hierarchical model of semantic knowledge, recognition of attributes associated with an individual requires greater specificity than categorical knowledge, which in turn requires greater semantic processing than simple familiarity with the famous names. In our initial pilot study (Loacano et al., 2011), cognitively intact older adults (age 65-83 years) were able to perform these tasks with greater than 85% accuracy for both recent and remote famous names. Reaction times were longer for the Attributes task than for the Categories task, reflecting the greater depth of semantic processing required to complete the task.

Subsequent research (Holcolmb, 2013) examined whether behavioral performance on the three famous name tasks (FNDT, Categories, and Attributes) could discriminate between healthy older adults with and without a family history of AD. A sample of 80 cognitively intact older adults (50% of whom had a parental family history of AD) aged 65 years and older completed these three tasks that included 60 famous names: 20 recent (individuals who gained fame in 1995 or later, e.g., Angelina Jolie), 20 enduring (gained fame between 1960 and 1970 and are still well-known today, e.g., Paul McCartney), and 20 remote famous names (individuals who gained fame between 1960 and 1970 but who are less recognizable by younger adults, e.g., Imogene Coca). No significant differences in accuracy or reaction time were observed between individuals with and without a family history of AD. Across the three tasks, overall accuracy was greater than 90% for every category of stimuli with the exception of recent names on the FNDT

and Attributes tasks, where accuracy was 88% and 84%, respectively. In the current study, we used a total of 45 famous names, including 15 from each of the three time epochs (recent, remote, and enduring). We selected a subset of the 60 famous names from the previous study (Holcolmb, 2013) that had the highest accuracy. We expected a recognition accuracy of over 90% across all tasks It is important that all participants perform the tasks at a near-ceiling level because between-subject variability in task performance could confound the interpretation of fMRI results.

These two semantic knowledge tasks require deeper semantic processing than the FNDT to complete successfully. To date, no fMRI study has examined brain activity during these tasks. Given that behavioral evidence of semantic memory loss typically occurs in hierarchical fashion with the earliest deficits observed for more specific information, these two novel tasks were expected to yield superior information at the neural level regarding risk for AD compared to the FNDT. Further, because these tasks require deeper processing and longer reaction times, they were expected to elicit an overall broader network of brain activity compared to the FNDT.

Hypotheses

Aim 1. To identify specific regions of fMRI activity associated with retrieval of general and specific semantic knowledge pertaining to famous individuals. In this study, cognitively intact older adults completed three semantic knowledge tasks: FNDT, Categories, and Attributes. All three tasks were presented on separate imaging runs. We included novel control conditions for the Categories and Attributes task to permit contrasts of famous compared to non-famous names. For the Categories task, the control task involved the presentation of non-famous names, during which the participants were asked to make a gender decision (Male vs. Female) based on the target name. The control condition for the Attributes task also involved the presentation of a

different set of target non-famous names, and we asked participants to choose the most likely country of origin of the name from two alternatives. We hypothesized that tasks requiring recognition of lower-level semantic knowledge properties (i.e., the Categories and Attributes tasks) would recruit a broader, richer semantic memory network than the FNDT, with the broadest network for the task requiring the greatest specificity of knowledge (i.e., the Attributes task). Specifically, we anticipated that these tasks would recruit more regions than the FNDT that are part of the semantic memory network (Binder et al., 2009), including left anterior temporal lobe, posterior cingulate, dorsomedial and ventromedial prefrontal cortex, and parahippocampal gyri. Additionally, we hypothesized that the more specific tasks would recruit a less left-lateralized pattern of activity, with more activity in the right hemisphere due to the higher task demands.

Aim 2. To determine whether a temporal gradient in activation pattern and magnitude is obtained with the Categories and Attributes semantic knowledge tasks in cognitively healthy older adults. This study goal was designed to extend our understanding of the brain's neural response associated with retrieval of semantic knowledge that differs in conceptual level (general versus specific) and in memory age (recent versus remote). We have observed that several regions display a temporally graded pattern of activation during the recognition of famous names from different eras, with greater activation being observed in both hippocampal and neocortical regions during recent famous name recognition relative to remote famous name recognition (Douville et al., 2005; Woodard et al., 2007). In the current investigation, we aimed to illustrate the roles of subcortical and cortical structures with regard to semantic knowledge tasks of varying specificity and age. We examined this phenomenon by including famous names from three categories – recent, enduring, and remote famous names. The latter category was designed

to capture knowledge that was acquired several decades ago but has not been contaminated by recent updating. We hypothesized that consistent with our previous research, semantic knowledge associated with Recent famous names would elicit greater fMRI BOLD response compared to Remote and Enduring names in medial temporal and neocortical regions. Given the anticipated larger network of brain activity for the Categories and Attributes tasks compared to the FNDT, we hypothesized an interaction between task and time epoch. That is, we expected to observe more regions demonstrating a significant temporal gradient effect for the two novel tasks.

Aim 3. To determine whether differences in brain activation during semantic knowledge tasks are observed between individuals with and without risk factors for AD. Consistent with our previous findings (Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Antuono, et al., 2009; Woodard et al., 2009), we anticipated that carriers of the APOE ε4 allele would display a greater magnitude and extent of activation during the FNDT (contrasting famous vs. non-famous names) than non-carriers. Given that the Categories and Attributes tasks would presumably place greater demands on the semantic knowledge network than does the FNDT, it is possible that additional recruitment of several brain regions in older individuals with risk factors may be accentuated. Because specific details about famous persons may be the most susceptible to loss in the early stages of cognitive decline, we hypothesized that the greatest between-group differences in brain activation pattern and magnitude would be observed for the Attributes task, as it requires the most specific semantic information to complete. Specifically, we anticipated that individuals with risk factors would compensate for early neural dysfunction by recruiting additional dorsomedial prefrontal cortex, ventromedial prefrontal cortex, ipsilateral (left) anterior temporal lobe, and contralateral (right) temporal lobe.

CHAPTER 2: METHOD

Participants

Our participants consisted of 16 cognitively intact older (65-89 years) adults, recruited via community advertisements in the Detroit metropolitan area and through the Healthy Black Elders Participant Recruitment Pool at the Wayne State University Institute of Gerontology. We recruited participants with and without a self-reported history of AD in a biological parent (eight individuals in each group). To separate our participants into groups with or without a clear family history, we excluded individuals who did not have a parental history of AD, but had other affected first- or second-degree relatives (i.e., biological siblings, grandparents, aunts, or uncles). Fliers were posted on public community bulletin boards, senior centers, and churches, and interested participants were asked to contact the phone number on the flier for additional information about the study or to enroll.

Criteria for inclusion in the study required that participants were in good self-reported physical and psychological health, cognitively intact, strongly right-handed, and native English speakers. To be classified as cognitively intact, participants must have scored above 26 on the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975). Eligible participants were required to score not lower than 1.5 standard deviations below their respective age-appropriate means on indexes from the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958) based on a sample of healthy older adults collected in the Milwaukee, WI area, and they had to obtain a raw score greater than 121 on the Mattis Dementia Rating Scale-2 (DRS-2; Jurica, Leitten, & Mattis, 2001; Mattis, 1976, 1988). Handedness was determined by the Edinburgh Handedness Inventory (Oldfield, 1971), and left-handed or ambidextrous (Laterality Quotient < 40) individuals was an exclusion criterion, due to the higher frequency of reversed brain

laterality in these individuals (no consented participants were excluded due to this criteria). Additional exclusion criteria included the presence of significant neurological illnesses or conditions, and psychological disturbance meeting DSM-IV Axis I conditions (including substance abuse), a score above 10 on the Geriatric Depression Scale (GDS; Yesavage, Brink, Rose, & Adey, 1986; Yesavage et al., 1983), any impairments in activities of daily living as determined by the Lawton and Brody Self-Maintaining and Instrumental Activities of Daily Living Scale (LADL; Lawton & Brody, 1969), or contraindications for MRI scanning: pregnancy, weight inappropriate for height (severe enough that they will be unable to fit in the scanner), the presence of ferrous objects or implants in the body (MRI-safe implants were identified using http://www.mrisafety.com), or a history of claustrophobia. Medical conditions resulting in exclusion included untreated hypertension (blood pressure > 140/90 mm Hg), cardiac disease, endocrine disorders (including Type I and Type II diabetes and thyroid problems), renal disease, glaucoma, macular degeneration, and chronic obstructive pulmonary disease. These conditions would be likely to affect fMRI imaging results, cognitive functioning, and/or the participants' ability to engage in the study.

We consented a total of 23 individuals for this study, although only 16 individuals completed the MRI scan and were included in the final sample. One individual was excluded because he had a heart stent that was not deemed to be safe at our MRI field strength. Another two individuals reported claustrophobia while in the MRI scanning room and did not complete the second day of testing. Three individuals obtained scores that were greater than 1.5 SDs below age- and gender-corrected norms on the RAVLT for Total Learning and Delayed Recall. Two of these individuals also met the additional exclusion criterion of a score below 27 on the MMSE.

Finally, one individual was excluded from the sample for obtaining a score below 27 on the MMSE and reporting symptoms of depression greater than 10 items on the GDS.

Measures

fMRI Tasks

All participants in the final sample completed three semantic knowledge tasks while in the MRI scanner: the FNDT, Categories, and Attributes tasks. We presented the tasks in the same order for all participants so that participants experienced the three tasks in increasing order of semantic specificity. For all tasks, each stimulus was presented for 3500 ms, with 500-ms intervals between stimuli for an overall rate of one name every four seconds. One-fourth of all trials were randomly interspersed crosshair fixation trials to introduce "jitter" into the fMRI time series. Participants were instructed to not respond during these fixation trials. We created the programs and displayed all stimuli using E-Prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA). All tasks were two-alternative forced choice design and responses were made via button press with their right index or middle finger. Participants completed eight practice trials outside of the scanner for each of the three tasks to ensure basic familiarity. Each task was composed of a total of 120 trials (90 names plus 30 fixation trials). Each task was preceded by 12 seconds with a fixation cross present and include an additional 12 seconds at the end of the scan. Thus, the total time for each task was 8 minutes and 24 seconds. We provided participants with a response pad for their right hand.

During the FNDT (Douville et al., 2005), participants viewed a total of 90 names, including 45 names of famous individuals and 45 non-famous names randomly selected from a local telephone book. Within the 45 famous names, there were 15 recent, 15 enduring, and 15 remotely famous individuals. The participant's task was to indicate whether each presented name

is famous (by pressing the left button with their right index finger) or non-famous (by pressing the right button with their right middle finger). The famous names included individuals who achieved fame over a time period ranging from the 1960s to the 2000s. Thus, we were able to examine brain activity associated with semantic memories of various ages. These same 45 famous names were used in all three tasks, allowing for analyses comparing memories of different ages for all tasks.

For the Categories task (Holcomb, 2013; Loacano et al., 2011), we presented each of the 45 famous names from the previous task in the center of the screen, along with a choice of two occupational categories (e.g., Movies or Politics) beneath the target name on the left and right sides of the screen. We instructed participants to identify the occupational category affiliated with the target famous name by pressing the button corresponding to the side of the desired selection. As a comparison condition for this task, we included 45 non-famous names with a choice of gender categories (i.e., Male or Female). Each given name was unambiguous regarding the gender (e.g., names like Dana or Sam were not included), and no common first names were in the target surnames (e.g., names like Peterson or Daniels were not included). Behavioral pilot data from our lab indicated that this control task could be performed at greater than 90% accuracy and with comparable reaction times to category identification trials for famous names. Thus, a similar level of cognitive processing appears to occur between the experimental and control tasks, and fMRI comparison between the two tasks should theoretically isolate the semantic memory retrieval component.

For the Attributes task (Holcomb, 2013; Loacano et al., 2011), we presented each of the 45 famous names in the center of the screen with two possible specific bodies of work or life events that could be attributable to the target name (e.g., Elton John: Goodbye Yellow Brick

Road or I Can't Get No Satisfaction) on the left and right at the bottom of the screen. The attributes represented life events, movies, television shows, songs, album titles, etc. We instructed participants to choose the attribute most associated with the famous individual by pressing the button corresponding to the side of the desired selection. As a control condition, participants were presented with non-famous names from different cultures (e.g., Jean-Pierre Bernard, Hiromi Fujita) and were instructed to select from two choices the most likely country of origin for the name. Accuracy for this task was greater than 90% in pilot data from our lab, with comparable reaction times to attribute identification trials for famous names. Thus, this control condition appears to require a similar amount of cognitive processing compared to the experimental condition.

Imaging Parameters

For the three famous name tasks, whole-brain, event-related fMRI was conducted on a Siemens (Washington, D.C.) MAGNETOM Verio 3.0 Tesla scanner with a 12-channel head coil. Echoplanar images were collected with an echoplanar pulse sequence (TE = 25 ms, TR = 2000 ms, flip angle = 90 degrees, field of view = 224 mm, matrix size = 64). Thirty-three contiguous axial 4-mm-thick slices were collected during each TR to provide entire coverage of the brain. Voxel size was 3.5 mm x 3.5 mm x 4.0 mm in the x, y, and z planes, respectively. A total of 252 TR measurements were collected for each task.

Additional Pulse Sequences

In addition to the three functional tasks, we conducted nine additional pulse sequences to obtain additional data including resting state fMRI and sMRI data. These sequences included: 1) a "localizer" pulse sequence to determine image planes for coronal and sagittal images (0:13); 2) a test fMRI sequence (0:26); 3) gradient echo (GRE) imaging to estimate the field map (1:02); 4)

T1-weighted imaging using a magnetization-prepared rapid gradient echo (MPRAGE) pulse sequence (4:20); 5) "resting-state" fMRI to observe the BOLD signal while not actively engaged in a task (6:46); 6) T2-weighted structural imaging (4:43); 7) pulsed arterial spin labeling (PASL) to observe the vasculature of the brain (4:28); 8) T2-weighted imaging with fluid attenuated inversion recovery (FLAIR) to nullify the effects of fluids (2:26); and 9) susceptibility-weighted imaging to get an estimate of iron deposition and microbleeds in the brain (5:05).

The localizer pulse sequence consisted of three structural slices oriented in the sagittal, transversal (horizontal), and coronal planes. Voxel size was 1.1 mm x 1.0 mm x 7.0 mm in the x, y, and z planes, respectively, with TR = 8.6 ms, TE = 4 ms, and flip angle = 20 degrees. The test fMRI sequence included the same parameters as the three semantic memory tasks with the exception that only 10 TR measures were recorded rather than the full sequence of 252 TRs. GRE imaging included a dual-echo pulse sequence (TR = 468 ms, TE 1 = 4.92 ms, TE 2 = 7.38 ms) with voxel size 3.5 mm isotropic. Thirty-six contiguous slices with flip angle = 60 degrees and field of view = 224 mm were collected for each individual. The T1-weighted MPRAGE structural sequence included 112 contiguous slices with voxel size 0.6 mm x 0.6 mm x 1.3 mm (flip angle = 9 degrees, field of view = 248 mm, TR = 1680 ms, TE = 4.77 ms). The resting state scan used the same imaging parameters as the semantic memory fMRI sequences, except only recording 200 TR measurements (6 minutes 40 seconds). We instructed participants to stay still and awake and behave normally during the resting state scan, thinking about whatever comes to mind. We did not display any sort of visual stimuli during this scan. The T2-weighted structural scan recorded 176 contiguous slices with voxel size of 1.0 mm isotropic (TR = 3200 ms, TE = 354 ms, field of view = 250 mm). The PASL scan collected 26 contiguous slices with voxel size

4.0 mm isotropic (TR = 2830.2 ms, TE = 11 ms, field of view = 256 mm, flip angle = 90 degrees), with a total of 91 measurements. The T2 FLAIR sequence collected 46 contiguous slices with voxel size of 1.0 mm x 1.0 mm x 3.0 mm in the x, y, and z planes, respectively (TR = 9000 ms, TE = 128 ms, flip angle = 150 degrees, field of view = 256 mm). Last, the susceptibility-weighted imaging included 72 contiguous slices with voxel size 0.8 mm x 0.7 mm x 1.2 mm in the x, y, and z planes, respectively (TR = 28 ms, TE = 20 ms, flip angle = 15 degrees, field of view = 230 mm).

Neuropsychological Tests

We assessed participant cognitive functioning through a battery of neuropsychological testing to determine cognitive inclusion criteria and obtain data for further analyses. We adapted the battery from the Alzheimer's Disease Centers' Uniform Data Set (Weintraub et al., 2009). In addition to the MMSE, DRS-2, and RAVLT, which were used to determine cognitive inclusion criteria, we administered Controlled Oral Word Association Test (Ruff, Light, Parker, & Levin, 1996), Category Fluency Test (Gladsjo et al., 1999), Trail Making Test Parts A and B (Reitan, 1958), Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), the Digit-Symbol Coding subtest from the Wechsler Adult Intelligence Scale-III (Wechsler, 1997), and the Digit Span and Logical Memory I and II (first story only) subtests from the Wechsler Memory Scale-Revised (Wechsler, 1987). This battery contains an assessment of dementia severity, attention, processing speed, executive functioning, memory, and language (Weintraub et al., 2009). We administered all tests on a separate day prior to collecting MRI data.

The MMSE (Folstein et al., 1975) is a standardized 30-point cognitive screening measure for dementia intended for use with adults aged 60 years and older. The measure is composed of items including orientation, following of a three-step command, following a written command,

serial mental subtraction, repetition of phrases, generating a sentence in writing, copying a simple drawing, and recalling three words after a delay. Cognitively intact individuals typically perform near ceiling levels on this measure. For example, in the Alzheimer's Disease Centers' Uniform Data Set, a sample of 3257 cognitively normal older adult participants obtained a mean score of 29.0 out of 30 on the measure, with 75% of the sample scoring at 28 or above (Weintraub et al., 2009). One-week test-retest reliability in a sample of patients with probable AD was r = .94 (Thal, Grundman, & Golden, 1986). One-month test-retest reliability in cognitively intact older adults has been reported as r = .38 (J. C. Morris et al., 1989). However, this low reliability might be due to the truncated distribution of scores in cognitively intact individuals due to ceiling effects.

The DRS-2 (Jurica et al., 2001) is a brief measure of cognitive functioning in five cognitive domains with a maximum score of 144. The test is administered and scored in an identical manner as the original DRS (Mattis, 1988). Scores from this measure are grouped into five domains: Attention (contains items related to auditory working memory and visual scanning/processing), Initiation/Perseveration (including verbal and motor fluency tasks), Construction (visuo-motor reproductions of designs), Conceptualization (abstract verbal reasoning), and Memory (including brief episodic memory measures and orientation to time, day, year, location, and current political figures). This measure requires 20 to 35 minutes to administer. Split-half reliability is reported at .90 and one-week test-retest reliability is .97 (Jurica et al., 2001). Cognitively intact older adults typically perform at near-ceiling levels on this measure. One study (Schmidt et al., 1994) found that cognitively intact older adults between the ages of 50 and 80 obtained a mean score of 141.2 out of 144, with 80% scoring at 135 or

higher. A cut score of 122 or lower can be used to distinguish between cognitively intact older adults and individuals with AD (Coblentz et al., 1973).

Basic attention and working memory skills were assessed using the Digit Span subtest on the Wechsler Memory Scales-Revised (Wechsler, 1987). In this test, the examiner first reads a sequence of numbers and the participant is require to repeat the numbers back in the same order. The sequence begins with two trials with three numbers each. The sequences extend by one number every two trials and continue until the participant reaches nine digits or makes an error on consecutive trials of the same sequence length. Next, the process is repeated with the exception that the participant's task is to repeat the numbers in the opposite order of that read by the experimenter. This portion of the subtest is known as "Digits Backward". Number sequences for Digits Backward begin with two numbers and reach a maximum span of eight numbers. We calculated the total score as the total number of correctly recalled sequences.

We evaluated processing speed using the WAIS-III Digit Symbol Coding subtest and Trail Making Test, Part A. In WAIS-III Digit Symbol Coding (Wechsler, 1997), participants are presented with a key at the top of the page with the numbers 1-9 in boxes and a corresponding symbol for each number. Lower on the page, the participants have a series of boxes with numbers presented without the corresponding symbol. Participants are given 120 seconds to fill out as many boxes as they can, in order, with the appropriate symbols. The total score is calculated as the total number of correctly filled boxes. Trail Making Test, Part A (Reitan, 1958) is a measure of psychomotor processing speed and visual scanning abilities. Participants must draw lines connecting the numbers 1 through 25 in order as quickly as possible. The numbers are presented scattered throughout a single page. The participant's score is the total completion time

for the measure. Alternate-form reliability for scores from this measure ranges from r = .76 to .81 (Wagner, Helmreich, Dahmen, Lieb, & Tadic, 2011).

We assessed executive functioning using Trail Making Test, Part B (Reitan, 1958), a measure of psychomotor processing speed, visual scanning, and cognitive set shifting. This measure is similar in presentation to Trail Making Test, Part A, except the participant is presented with the numbers 1 through 13 and the letters A through L. Participants are required to switch back and forth between the letters and numbers (i.e., 1, A, 2, B, etc.) as they complete the measure. Alternate-form reliability for scores from this measure ranges from r = .86 to .89 (Wagner et al., 2011).

The RAVLT (Rey, 1958) is a measure of verbal episodic learning and memory. The test requires participants to attempt to learn a list of 15 semantically unrelated words across five learning trials. Following the presentation of a second list as a distractor trial, the participant is then required to immediately recall as many words as possible from the list (Immediate Recall). After a 20-minute delay period, the participant is required to recall the words again (Delayed Recall). A 50-item yes/no recognition measure of words from the list is presented after the delayed free recall trial. Internal consistency between Cronbach's alpha values of .79 and .82 for all RAVLT index scores has been reported (Magalhaes, Magalhaes, Noblitt, & Lewis, 2012). For the current study, we used norms collected from our research group with a sample of community-dwelling older adults in the Milwaukee, WI area. Individuals who scored greater than 1.5 SD below age and gender-corrected mean scores on Total Learning (sum of recall scores across the five learning trials) and/or on the Delayed Recall trial were excluded from the final sample. As described previously, three participants fell below these cutoff scores and were excluded from our final sample.

We evaluated contextual episodic memory using the first story from the Logical Memory I and II subtests on the Wechsler Memory Scales-Revised (Wechsler, 1987). In this test, the experimenter reads the participant a short story and the participant is required to immediately recall as many details from the story as possible. Following a 20-minute delay, the participant is again required to recall as many details from the story as they can. The raw score is calculated as the number of correctly recalled details from the story (out of a maximum of 25 details).

We evaluated language functioning using the Boston Naming Test, Category Fluency test, and Controlled Oral Word Association Test. In the Boston Naming Test (Kaplan et al., 1983), participants are asked to name 60 individually presented line drawings of objects that decrease in their frequency of occurrence. For example, an earlier test item is "harmonica" and a later item is "abacus." The test is intended to identify difficulties with object naming (anomia) and semantic memory retrieval. The total score is calculated as the total number of items correctly named spontaneously or with a semantic cue (provided only in cases of a clear perceptual error by the participant). One study (Dikmen, Heaton, Grant, & Temkin, 1999) observed a test-retest reliability of $r = .92$ for the Boston Naming Test total score, with a median test-retest interval of 11 months in healthy adults. The Category Fluency test and Controlled Oral Word Association Test (Benton & des Hamsher, 1976) were administered as further measures of semantic memory retrieval, as well as verbal fluency. Participants were asked to list as many items from a category as they can during a one-minute span, including animals (Category Fluency) and words beginning with the letter C, F, and L (Controlled Oral Word Association Test). Scores from the Controlled Oral Word Association Test have been reported to demonstrate a 11-month test-retest reliability of $r = .72$ (Dikmen et al., 1999).

Additional Measures

We administered the GDS as a brief screening measure of symptoms of depression. The GDS is composed of 30 yes/no items assessing for symptoms of depression over the previous week. A cut score of greater than 10 items endorsed depressive direction used to discriminate between depressed and non-depressed older adults with 84% sensitivity and 95% specificity (Yesavage et al., 1983). As described previously, only one participant in our study endorsed greater than 10 items on this measure and was excluded from the final sample.

The Edinburgh Handedness Inventory (Oldfield, 1971) was used as a self-report of participant handedness. In this measure, participants rate their hand preferences for 10 common actions including writing, sweeping, and opening a jar. For each action, if the participant has a strong hand preference and cannot envision using the other hand to perform this task, they place two checkmarks for their hand preference for that action. If they only have a slight hand preference, they place one checkmark for that action. If participants do not have a hand preference for a given action they can place a checkmark for both the left and right hands. The "Laterality Quotient" is calculated as the difference between the total checkmarks for the right and left hands divided by the total number of check marks, multiplied by 100. Values greater than 40 represents strong right-handedness.

The Stanford Brief Activities Scale (Taylor-Piliae et al., 2007; Taylor-Piliae et al., 2006) was completed by all participants and used to assess current physical activity. This measure is a two-item self-report measure designed to classify participants as having high or low amounts of physical activity. Survey items pertain to physical activity performed over the previous year. Participants who reported two or fewer instances of low intensity physical activity (e.g., going for walks, doing chores, or playing golf) per week were assigned to the low physical activity

group. Participants who reported moderate (e.g., brisk walking for 15 minutes; performing moderately difficult chores for 45 minutes) to heavy (e.g., jogging for 30 minutes; moderately difficult chores for 60 minutes) physical activity at least three times a week were classified as having high physical activity. Previous research indicated an interaction between physical activity and APOE ε4 carrier status such that APOE ε4 carriers who are low in physical activity are at increased risk for developing cognitive decline (Woodard et al., 2012b). Further, physical activity has been demonstrated to influence the BOLD signal during fMRI of semantic memory (Smith, Nielson, Woodard, Seidenberg, Durgerian, et al., 2011). We gathered this information to potentially enhance the interpretation of our fMRI results.

The LADL (Lawton & Brody, 1969) is a self-report measure assessing for participant proficiency in independently completing activities of daily living across eight domains, including using a telephone and performing basic housework. To meet inclusion criteria, all participants must have reported no impairment in these activities of daily living and must have obtained an overall score of 5 on the measure. Impairment in independent activities of daily living would be potentially indicative of cognitive decline, which is why this measure is included in our participant criteria.

Procedure

A research assistant performed brief telephone screening when potential participants inquired about the study. This brief screening ensured that participants had no significant self-reported physical or psychological difficulties, had not been diagnosed with dementia or MCI, are right-handed, have no ferrous implants in their body, had no history of claustrophobia, were native English speakers, and met all medical inclusion criteria. All information collected during this screening was anonymous and confidential, and the written phone script on which the

research assistant recorded participant responses was shredded immediately after the calls. Although we did not keep official information regarding interested callers who did not end up participating in the study, an estimated 30 individuals called and did not meet our criteria. The primary reasons for not being able to participate included having implants that were not compatible for MRI, reported history of neurological illness, and not having a clear parental history of AD. This final exclusion criteria was relevant because we completed data collection for individuals without a parental history while still recruiting for individuals with a parental history.

Participants who met these basic inclusion criteria and agreed to participate were scheduled for the first study visit at our lab. This session consisted of written informed consent, the collection of demographic information and medical background, and neuropsychological testing. Participants who continued to meet all cognitive and demographic inclusion and exclusion criteria were invited to return for the second session, during which they completed sMRI and fMRI scanning and were provided with materials for genotype testing. The first session lasted approximately two hours, and the second session required approximately two and a half hours at the Wayne State University MR Research Facility at Harper University Hospital Neuroimaging Center. We compensated participants at a rate of $15 per hour, rounded up to the nearest hour, plus the costs of parking.

The first session included the completion of a written demographic and health history questionnaire and a battery of neuropsychological testing to assess cognitive abilities and determine inclusion criteria. The questionnaire included information pertaining to age, ethnicity, years of education, patterns of alcohol and drug use, lifestyle behaviors including physical activity patterns, and a medical and psychiatric history in which the participant simply indicated

the presence or absence of a history or neurological, cardiovascular, or psychiatric illnesses or disorders. We also gathered information regarding current prescription and non-prescription medications and the potential presence of any metallic bodily implants. We then conducted a structured interview for a parental history of dementia, defined as a having a biological parent with a formal diagnosis of AD prior to death or a reported history of AD-like symptoms without a diagnosis. We also conducted all neuropsychological testing during this session and administered the GDS, Edinburgh Handedness Inventory, LADL, and Stanford Brief Activities Scale. Participants also completed an MRI Safety Form detailing their previous experiences with MRI scans and ensuring that there are no contraindications for scanning such as pregnancy or the presence of any ferrous metallic implants.

The second and final session consisted of sMRI and fMRI at the Wayne State University Magnetic Resonance Research Facility at Harper University Hospital Neuroimaging Center in Detroit, MI. This appointment lasted a total of approximately two and a half hours. Although we collected all pulse sequences described in the Imaging Parameters section, the primary sequences of interest for the current study were the three fMRI tasks: FNDT, Categories, and Attributes tasks. Participants completed practice versions of these three tasks on a laptop computer prior to entering the MRI scanner to ensure proper comprehension of test instructions. Participants also completed the MRI Safety Form (same form that they also completed at the first session) that was reviewed by a technician to ensure that there are no contraindications for entering the MRI scanner.

At the end of this second session, we provided participants with a DNA Genotek Oragene (DNA Genotek Inc., Kanata, ON) tube in order to collect a saliva sample for APOE genotype information. We gave participants this tube labeled with their participant number along with a

pre-paid mailing envelope. We instructed them to complete this at-home procedure immediately after waking, and before doing anything else (i.e. brush teeth, floss, drink water, eat, etc.). If possible, they should have been the only one touching the sample to prevent contamination. Participant placed the sealed vial in the pre-paid mailer (no other participant identifying information was placed on the mailer or vial besides the participant ID number on the vial) and was sent to the Woodard Lab at 5057 Woodward Ave, Detroit, MI. We sent the samples to the Center for Applied Genomics Technology at the Mott Center at Wayne State University for APOE genotype analysis based on the base pairs of rs429358 and rs7412.

Data Analyses

Neuropsychological Test Data

We calculated the raw scores from all neuropsychological measures using standard scoring procedures. We also calculated demographically-corrected scaled scores (Mean = 10, SD = 3) for Mayo's Older American Normative Studies (MOANS) (Lucas et al., 1998) for White participants and the Mayo's Older African American Normative Studies (MOAANS) (Rilling et al., 2005) for Black participants. We compared performance between individuals with and without risk factors for AD (i.e., APOE ε4 carriers and non-carriers) using independent samples *t*-tests.

Task Performance Data

We analyzed behavioral data for the fMRI tasks using E-Prime 2.0. For each trial, we obtained accuracy and reaction time data. Reaction times were removed from incorrect trials and trials shorter than 200 ms. These trials were also excluded from fMRI analyses. We excluded trials in which an individual did not make a response from fMRI analyses and accuracy calculations (i.e., they were not counted as correct or incorrect trials). Each trial had a maximum

reaction time of 4000 ms due to the intertrial interval. For each task, we analyzed the potential presence of a temporal gradient by comparing behavioral performance (accuracy and mean reaction time) between recent, remote, and enduring famous names using repeated measures ANOVAs. We also compared performance between APOE ε4 allele carriers and non-carriers using independent samples *t*-tests for overall accuracy and reaction time data for each task and using 3 (time epoch) by 2 (group) mixed design ANOVAs.

We hypothesized that performance between low- and high-risk participants will differ for FNDT, Categories, and Attributes Tasks, with high risk participants demonstrating longer reaction times and/or lower accuracy on these tasks. We expected the magnitude of this difference to increase across tasks, with FNDT showing the smallest difference, Categories showing an intermediate difference, and Attributes showing the largest difference, as this task requires the greatest specificity of semantic knowledge processing. In addition, the time epoch of the stimulus was expected to contribute to the presence of a temporal gradient, such that high-risk participants would exhibit longer reaction times and/or lower accuracy for Recent and Enduring stimuli than for Remote stimuli compared to low-risk participants. Because Recent and Enduring stimuli are presumably at least somewhat dependent on intact hippocampal functioning, and because high-risk participants may be experiencing early hippocampal dysfunction, we expected the high-risk participants to perform more poorly than the low-risk participants on these two task categories. Even though previous research using these tasks did not find significant differences in behavioral performance between adults with and without a family history of AD (Holcomb, 2013), we hypothesized that the proposed performance differences would be observed between carriers and non-carriers of APOE ε4 allele. Previous research has indicated that the APOE ε4 allele is more robust than family history as a predictor

of cognitive decline (Woodard et al., 2010) and incidence of AD (Huang, Qiu, von Strauss, Winblad, & Fratiglioni, 2004; Raber, Huang, & Ashford, 2004). Thus, we expected this risk factor to be more sensitive to detecting these subtle differences in behavioral performance.

Imaging Analyses

fMRI

We conducted fMRI processing and analysis using the Statistical Parametric Mapping package (SPM8; Wellcome Department of Cognitive Neurology, London, UK) for Matrix Laboratory (MATLAB) version R2009a (The MathWorks, Natick, MA). We preprocessed images using a five-step approach: 1) slice timing correction to account for different acquisition times between the 33 slices for each TR, 2) realignment of all images for each participant to reduce artifacts due to head movement during scans, 3) within-subject coregistration between functional and structural data, 4) spatial normalization into standard stereotaxic space, and 5) smoothing to suppress noise and effects due to residual differences in functional and gyral anatomy during group analysis.

For each participant, we performed slice timing correction on the 33 slices for all scans, in ascending order (i.e., the most ventral slice was the first correction for each scan). We created a mean resliced image of all 252 scans for each functional run. After slice timing correction, all scans were realigned to the mean image for each participant with a 2nd Degree B-Spline interpolation. Prior to the estimation of realignment parameters, each scan was smoothed with a Gaussian smoothing kernel with full width at half maximum (FWHM) of 5 mm. We then performed a coregistration procedure to ensure that the neuroanatomy was consistent between the functional and structural scans. All functional data were warped using a 3rd Degree B-Spline Interpolation to match the subject's T1-weighted structural scan. Following coregistration, we

subjected each scan to an affine and non-linear spatial normalization to match the SPM8 fMRI brain template in Montreal Neurological Institute (MNI) standard space (Collins, Neelin, Peters, & Evans, 1994). Finally, we smoothed all images with an 8 mm by 8 mm by 8 mm Gaussian smoothing kernel. We created SPM models for each participant containing each trial type: Enduring, Remote, and Recent Famous names, Unfamiliar names, incorrect trials for all four categories (where applicable), and Fixation trials.

Our proposed functional contrasts included: 1) famous name recognition compared to non-famous name rejection (FNDT), 2) famous name categorization compared to non-famous name gender categorization (Categories Task), and 3) famous name attributes compared to non-famous name country-of-origin identification (Attributes Task). For each contrast, data were analyzed separately and compared between APOE ε4 carriers and non-carriers, and we hypothesized that APOE ε4 carriers would display a greater spatial extent of activation than non-carriers, consistent with our previous work. We anticipated that the magnitude of this difference would be directly related to task specificity, with the greatest differences in activation pattern and magnitude being seen for the Attributes Task.

Further, for each task we compared responses across time epochs to demonstrate the presence of a temporal gradient in the regional recruitment of semantic memories of varying specificity. We hypothesized that greater hippocampal and neocortical activity would be observed for Recent compared to Enduring and Remote stimuli for all tasks (Woodard et al., 2007). Further, we hypothesized that Enduring names would have a more cortical representation compared to Remote names, which would be more represented in hippocampal regions. Thus, for each of the three tasks, we conducted four planned famous names comparisons to evaluate the temporal gradient: 1) Recent compared to Enduring, 2) Recent compared to Remote, 3) Enduring

compared to Remote, and 4) Remote compared to Enduring. We also expected that the magnitude of the temporal gradient would be amplified in tasks with deeper semantic specificity (i.e., the Categories and Attributes tasks) and in APOE ε4 carriers.

We performed data analysis for all fMRI contrasts using the preprocessed images in a two-step process. First, a contrast map was generated for each individual across all voxels. These maps were generated for all correct trials for the task conditions (e.g., famous compared to non-famous names) in the contrast, including fixation trials and incorrect trials as additional model parameters. For the group-level analysis, we combined the contrast maps into a one-sample *t*-test across all participants, generating whole-brain *t*-map results. We used an alpha level of $p < .001$ with minimum cluster size of 25 voxels to identify regions with significant activity in the contrast, superimposed on a reference MRI atlas. For temporal gradient results, we used a more liberal cluster threshold of 10 voxels in order to identify significant regions. We localized peak sites on the *t*-map for each cluster of activation in MNI coordinates. We then converted these coordinates into Talairach space (Talairach & Tournoux, 1988) using the MATLAB command "icbm_spm2tal.m" (Lancaster et al., 2007). We used Talairach Client v2.4.2 (Research Imaging Center, University of Texas Health Science Center San Antonio) to determine the specific structural location and Brodmann area (Brodmann, 1906) for all significant clusters of activity.

Each of the planned functional contrasts described above was compared across groups (APOE ε4 carriers and non-carriers) to determine whether participants in either group recruited distinct regions to a significantly greater extent than the other group. SPM models were set up as independent samples *t*-tests to compare the activation maps between groups, with the resulting *t*-maps only showing voxels demonstrating significant effects at an alpha level of $p < .01$, with a minimum cluster size of 10 voxels. We chose to use this liberal threshold due to the small sample

size. For each comparison, the model was run twice to illustrate regions selectively utilized in each group. We repeated the same procedures described above for regional identification and localization.

We conducted paired samples *t*-tests to compare activity between tasks, including pairwise comparisons for: 1) FNDT compared to Categories, 2) Categories compared to FNDT, 3) FNDT compared to Attributes, 4) Attributes compared to FNDT, 5) Categories compared to Attributes, and 6) Attributes compared to Categories. The resulting *t*-maps included voxels displaying significantly more activity for one task compared to another at an alpha level of $p < .005$ with minimum cluster size 10 voxels. We conducted this procedure with the sample as a whole and within each group (APOE ε4 carriers and non-carriers) separately. The analyses were then repeated separate for each of the three time epochs (Enduring, Remote, and Recent) to determine whether differences between tasks might be specific to a particular time epoch.

ROI Analyses

We conducted further analyses examining the hemodynamic response function (HRF) in selected regions with common activity across the three tasks. We constructed regions of interest (ROIs) consisting of voxels with significant activity for the Famous compared to Unfamiliar contrast across all three tasks using the Marseille Boîte À Région d'Intérêt (MarsBaR) toolbox for SPM8 (Brett, Anton, Valabregue, & Poline, 2002). We used the finite impulse response (FIR) event time course option to plot the estimate HRF following famous and unfamiliar names for all three tasks at the rate of the TR. That is, we plotted the signal at 0, 2, 4, 6, 8, 10, 12, and 14 seconds for each participant. One-way ANOVAs compared the mean signal for each task at each time point. Additionally, we analyzed the HRF across the three time epochs to determine if the signal demonstrated temporally graded patterns of recruitment in any or all of the three tasks.

Finally, we analyzed additional ROIs in regions that appeared to display specific activity for each task. These analyses attempted to determine if HRF could reveal specific regions of semantic memory retrieval for each task.

sMRI

We also conducted basic structural imaging analyses using the T1-weighted scans to determine how well sMRI indices can discriminate between APOE ε4 carriers and non-carriers, using fMRI of the Brain (FMRIB) Software Library (FSL, FMRIB Analysis Group, Oxford, UK). We performed sMRI analyses using two procedures: 1) FMRIB's Automated Segmentation Algorithm (FAST) and 2) FMRIB's Integrated Registration and Segmentation Tool (FIRST).

FAST (Zhang, Brady, & Smith, 2001) separates the brain into three tissue types (grey matter, white matter, and cerebrospinal fluid) and creates a separate image for each tissue type. We performed voxelwise volumetric analyses on the resulting images for each participant to generate a whole-brain volume (in mm^3) for each of the three tissue types. We logged each of the values both as a raw volume and as a percentage of the total intracranial volume by dividing each volume by the sum of the three volumes.

FIRST (Patenaude, Smith, Kennedy, & Jenkinson, 2011) transforms all structural images to a standardized template brain and then performs estimated segmentations using an automated algorithm for the following brain structures: thalamus, caudate, putamen, pallidum, brainstem/4^{th} ventricle, hippocampus, amygdala, and nucleus accumbens. It provides separate segmentations for the left and right structures for every region except for the brainstem. We performed voxelwise volumetric analyses (in mm^3) on the resulting images for every structure for each participant.

We compared the resulting volumes from FAST and FIRST to determine how well these volumes can distinguish between our two groups (APOE ε4 carriers and non-carriers), using independent samples *t*-tests.

CHAPTER 3: RESULTS

The Results section will first describe all findings regarding the sample as a whole, followed by between-group analyses comparing APOE ε4 carriers and non-carriers.

Participant Demographics

Full participant demographics are displayed in Table 1. The average age in the sample of 16 participants was 70.4 years (*SD* = 5.3 years). Eight individuals had a self-reported parental history of AD. The average education in the sample was about college graduate level (Mean = 15.5 years, *SD* = 2.2 years). The sample consisted of eight black older adults and eight white participants. No individuals in the sample reported any impairment in activities of daily living. No participants reported clinically significant symptoms of depression on the GDS (Mean = 1.2, *SD* = 1.1, Range = 0-3). All participants were strongly right-handed, according to the EHI Laterality Quotient (Mean = 84.1, *SD* = 20.3, Range = 44-100). Twelve participants (75%) engaged in a high level of self-reported physical activity, according to the SBAS.

	Mean	SD	Range
Age	70.4	5.3	65-84
Education	15.5	2.2	12-18
Sex	12 Female, 4 Male		
Ethnicity	8 White, 8 Black		
ADL Rating	5.0	0.0	5-5
Subjective Memory Impairment	4 out of 16 reporting impairment		
Objective Memory Impairment	0 reporting impairment		
GDS	1.2	1.1	0-3
Handedness (EHI)	84.1	20.3	44-100
Physical Activity (SBAS)	12 High PA, 4 Low PA		

Table 1. Participant demographics. ADL = Activities of Daily Living, GDS = Geriatric Depression Scale, EHI = Edinburgh Handedness Inventory, SBAS = Stanford Brief Activities Scale.

Neuropsychological Test Data

Overall participant neuropsychological test performance is displayed in Table 2. All participants were classified within the normal range of functioning. MMSE scores ranged from 27 to 30, and DRS-2 scores ranged from 134-144. DRS-2 scaled scores, based on Mayo's Older American Normative Studies (MOANS) (Lucas et al., 1998) for White participants and the Mayo's Older African American Normative Studies (MOAANS) (Rilling et al., 2005) for Black participants ranged from 10-15, indicating that the entire sample performed in the Average to Above Average ranges. The mean DRS-2 Scaled Score did not significantly differ between White (Mean = 12.6) and Black (Mean = 13.2) participants ($t(14) = 0.73$, $p = .479$, Cohen's $d = 0.37$). All participants performed above the RAVLT cutoff level of 1.5 SDs below age and gender-corrected normative means.

	Mean	SD	Range
DRS-2 Total	140.1	2.7	134-144
SS	12.9	1.7	10-15
DRS-2 Attention	36.3	0.7	35-37
SS	12.2	1.2	10-14
DRS-2 I/P	36.5	1.5	31-37
SS	11.2	1.7	6-13
DRS-2 Construction	5.9	0.3	5-6
SS	10.7	1.4	7-12
DRS-2 Conceptualization	37.2	1.5	35-39
SS	11.8	1.9	8-15
DRS-2 Memory	24.2	1.0	23-25
SS	11.7	1.6	9-13
MMSE	28.9	1.0	27-30
RAVLT Trials 1-5	47.8	8.1	34-63
RAVLT List B	5.5	1.3	3-8
RAVLT IR	8.4	2.3	6-13
RAVLT DR	9.4	2.3	6-13
RAVLT Recognition Hits	13.8	1.4	11-15
RAVLT Recognition False Positives	1.8	2.4	0-8
RAVLT Gained Access	11.4	2.6	8-17
RAVLT Lost Access	6.8	2.9	1-12
WMS-R Logical Memory IA	13.1	2.0	10-16
WMS-R Logical Memory IIA	11.2	2.3	8-15
WMS-R Digit Span Forward	8.2	1.4	5-10
WMS-R Digit Span Backward	6.3	2.2	3-10
WMS-R Digit Span Total	14.4	3.2	9-20
COWAT (Sum of C, F, and L)	41.7	6.6	30-57
Animal Fluency	20.8	4.3	11-30
Trail Making Test Part A	36.6	12.3	24-64
Trail Making Test Part B	85.9	31.5	39-150
WAIS-III Digit Symbol Coding	60.8	13.8	39-89
Boston Naming Test	55.0	3.9	45-60

Table 2. Results of neuropsychological testing for the entire sample. Results are displayed as raw scores with the exception of demographically corrected scaled scores (SS) on the DRS-2. DRS-2 = Dementia Rating Scale-2, MMSE = Mini-Mental State Exam, RAVLT = Rey Auditory Verbal Learning Test, WMS-R = Wechsler Memory Scale-Revised, COWAT = Controlled Oral Word Association Test, WAIS-III = Wechsler Adult Intelligence Scale-III.

Behavioral Performance

Overall Task Performance

Table 3 displays mean performance for famous and unfamiliar names across the FNDT, Categories, and Attributes tasks. As shown, mean accuracy exceeded 93% for the famous and unfamiliar names on the FNDT and Categories. Accuracy was somewhat lower for the Attributes task, at 87.3% for the famous names and 88.3% for unfamiliar names. For famous names within each task, the repeated measures ANOVA indicated a main effect of task ($F(2,14) = 5.06$, $p = .022$, $\eta^2_p = .42$). Paired-samples *t*-tests indicated significant differences between Attributes and Categories ($t(15) = 2.82$, $p = .013$) and Attributes and FNDT ($t(15) = 2.87$, $p = .012$), but not between FNDT and Categories ($t(15) = 0.21$, $p = .839$). In contrast, there was not a significant main effect of task for unfamiliar names ($F(2,14) = 2.61$, $p = .109$, $\eta^2_p = .27$).

As expected, mean reaction time increased in proportion to the increased semantic specificity across the three tasks. For famous names, the FNDT had the shortest reaction times and Attributes had the longest reaction times, with the Categories task in the middle ($F(2,14) = 288.16$, $p < .001$, $\eta^2_p = .98$). Paired-samples *t*-tests revealed significant differences ($ps < .001$) between each of the three tasks. The unfamiliar names followed a similar pattern with increasingly long reaction times across the FNDT, Categories, and Attributes tasks ($F(2,14) = 58.84$, $p < .001$, $\eta^2_p = .89$). As with the famous names, paired-samples *t*-tests revealed significant differences ($ps < .001$) for unfamiliar names between each of the three tasks. The unfamiliar names had significantly longer reaction times than famous names for the FNDT ($t(15) = 5.08$, $p < .001$). There was not a significant difference in reaction time between famous and unfamiliar names on the Categories ($t(15) = 0.57$, $p = .578$) and Attributes ($t(15) = 1.48$, $p = .160$) tasks.

		Mean	SD
FNDT			
Famous	RT (ms)	1091	292
	Acc	94.2%	9.6%
Non-Famous	RT (ms)	1372	436
	Acc	93.2%	14.4%
Categories			
Famous	RT (ms)	1729	304
	Acc	94.7%	5.2%
Non-Famous	RT (ms)	1758	320
	Acc	95.6%	4.4%
Attributes			
Famous	RT (ms)	2080	336
	Acc	87.3%	13.2%
Non-Famous	RT (ms)	2010	256
	Acc	88.3%	16.8%

Table 3. Mean behavioral performance for the three fMRI tasks across the entire sample. FNDT = Famous Name Discrimination Task, RT = reaction time.

Temporal Gradient Results

Figure 1 displays the behavioral results for the famous names from FNDT, Categories, and Attributes tasks separated by time epoch. Consistent with previous research (Holcomb, 2013), we observed a temporal gradient in accuracy and reaction time for each of the three tasks. For each task, we observed the highest accuracy for Enduring famous names, followed by Remote and Recent names, respectively. Likewise, we observed the shortest reaction times for the Enduring famous names, followed by the Remote and Recent names, respectively. One-way repeated-measures ANOVAs for reaction times revealed a main effect of Epoch for all three tasks (ps < .009, η^2_ps > .49). For the FNDT, paired samples comparisons revealed that Recent names had significantly longer reaction times than the other two epochs (ps < .001). Remote and Enduring names did not differ significantly ($t(15) = 0.78$, $p = .449$). For Categories, a similar pattern emerged, with Recent reaction times significantly longer than the other two epochs (ps <

.005) and no significant difference between Enduring and Remote famous names ($t(15) = 0.44$, $p = .665$). For Attributes, Enduring names had significantly shorter reaction times than both Remote and Recent names ($ps < .001$), and Recent and Remote famous names did not differ significantly ($t(15) = 0.89$, $p = .387$)

For accuracy, the main effect of epoch was significant on the FNDT ($F(2,14) = 4.95$, $p = .024$, $\eta^2_p = .41$). Further inspection revealed that Recent Names had significantly lower accuracy than Enduring ($t(15) = 2.48$, $p = .026$) or Remote names ($t(15) = 3.22$, $p = .006$). The Enduring and Remote names did not differ significantly ($t(15) = 0.97$, $p = .347$). The main effect of epoch was not significant for Categories ($F(2,14) = 2.05$, $p = .166$, $\eta^2_p = .23$) or for Attributes ($F(2,14) = 2.89$, $p = .089$, $\eta^2_p = .29$).

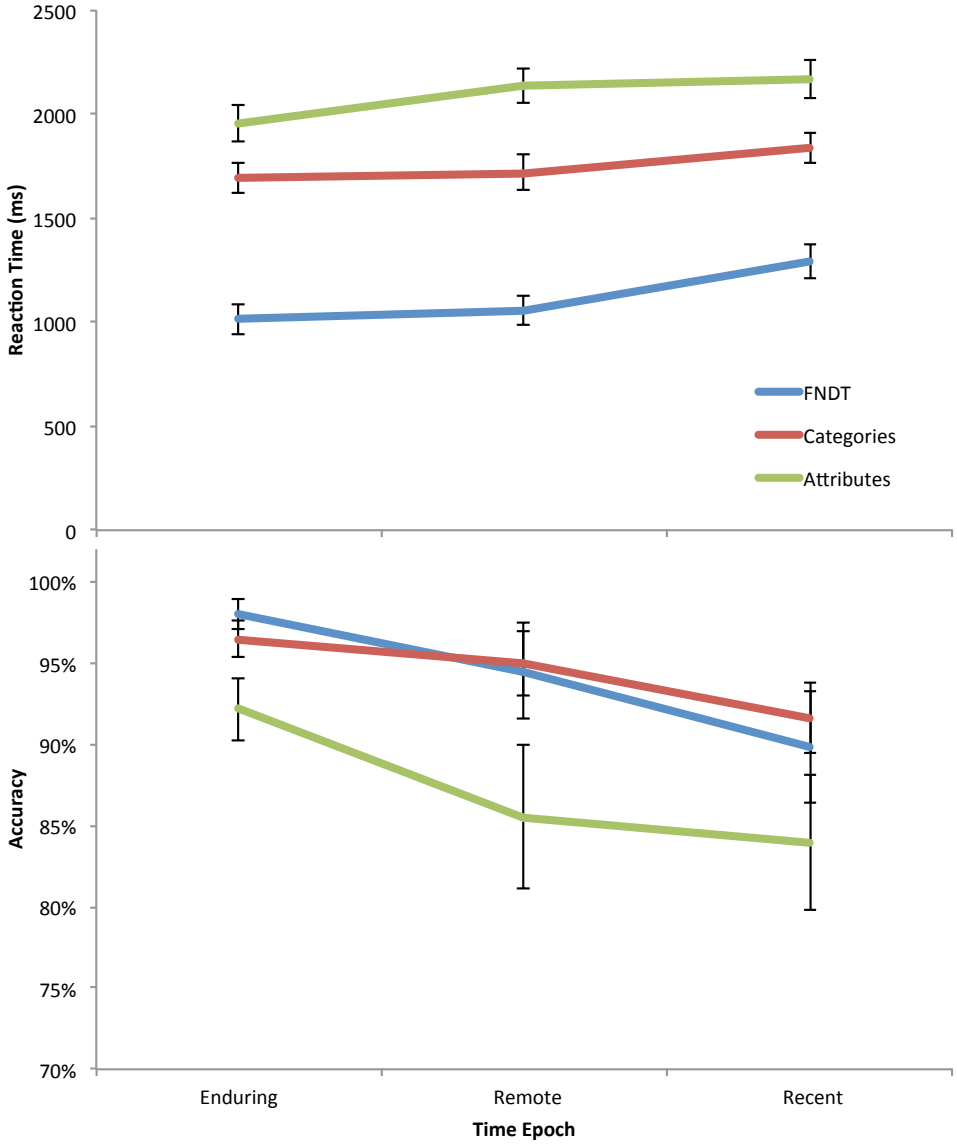


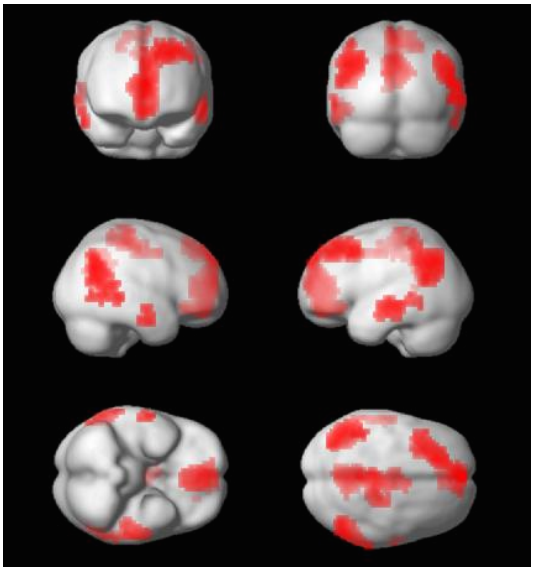
Figure 1. Behavioral performance on the three fMRI tasks, separated by time epoch. Error bars represent the standard error of the mean.

fMRI Results

Overall Results

Figure 2 displays the results for the famous compared to unfamiliar name contrast for the FNDT superimposed upon a standard space template brain provided by SPM, along with a list of locations for significant clusters of activity. Overall results were generally consistent with previous findings using this task (Douville et al., 2005; Woodard et al., 2007). Six separate

clusters of significant activity were detected. These regions include bilateral clusters of activity in medial temporal lobe and inferior parietal lobe (including supramarginal and angular gyri) as well as a cluster composed of the precuneus and posterior cingulate. A large left-lateralized cluster was also detected in medial prefrontal cortex including inferior frontal gyrus. These regions have all been implicated with semantic memory retrieval (Binder et al., 2009).

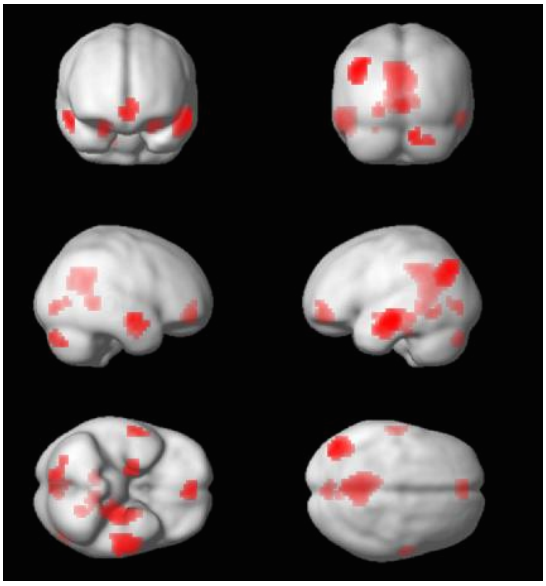


	Talairach Coordinates				
Region	X	Y	Z	k	t_{max}
Left Middle Temporal Gyrus	-41	-70	31	319	9.06
Left Superior Temporal Gyrus	-54	-59	14	*	5.59
Left Supramarginal Gyrus	-44	-45	48	*	4.72
Medial Frontal Gyrus	1	48	0	689	8.98
Medial Frontal Gyrus	-2	53	22	*	7.41
Medial Frontal Gyrus	-2	39	-5	*	7.21
Precuneus	-2	-50	30	623	7.74
Posterior Cingulate Cortex	10	-37	53	*	6.39
Posterior Cingulate Cortex	0	-36	49	*	6.31
Left Middle Temporal Gyrus	-54	-20	-8	134	7.61
Left Middle Temporal Gyrus	-57	-36	-6	*	4.18
Left Middle Temporal Gyrus	-57	-47	-7	*	4.15
Right Inferior Temporal Gyrus	56	-54	-2	225	6.26
Right Middle Temporal Gyrus	63	-37	0	*	6.25
Right Angular Gyrus	39	-64	33	*	6.18
Right Inferior Temporal Gyrus	57	-7	-15	27	5.56
Right Inferior Temporal Gyrus	60	-14	-5	*	4.33

Figure 2. Regions of significant activity for the famous compared to unfamiliar name contrast for the FNDT. Locations are shown for significant foci of activity. k = cluster size in voxels. * = focus belongs to the same cluster as the row above, foci separated by a minimum of 8 mm.

Figure 3 displays the results for the famous compared to unfamiliar name contrast for the Categories task. Significant activity was detected in nine separate clusters. Several of these regions were consistent with the FNDT, including precuneus, posterior cingulate, bilateral middle temporal gyrus, and left angular gyrus. Notably, there was a relative absence of prefrontal cortex activity compared to the FNDT. However, activity was detected in several additional areas, including bilateral parahippocampal gyri and the cerebellum. Additionally, we detected activity in the occipital lobe, in the lingual gyrus. This activity might represent the additional visual processing for the famous names (i.e., reading the two category names) compared to the

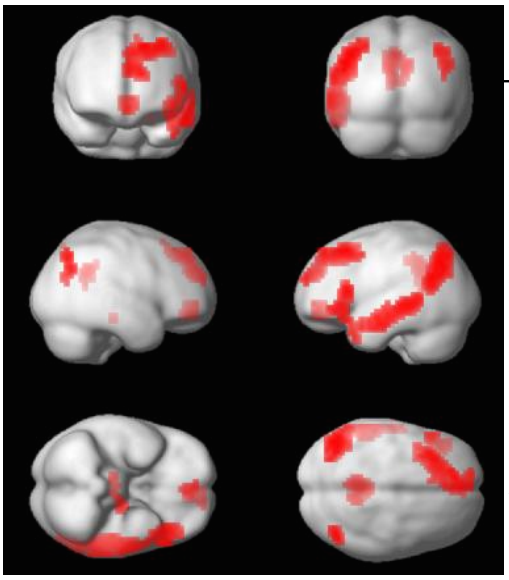
unfamiliar names (which were just "Male" and "Female"). The spatial extent of the clusters of activation was notably less than that seen for the FNDT.



	Talairach Coordinates				
Region	X	Y	Z	k	t_{max}
Left Middle Temporal Gyrus	-51	-17	-11	126	10.59
Left Parahippocampal Gyrus	-25	-16	-18	104	9.28
Left Parahippocampal Gyrus	-18	-31	-8	*	6.92
Precuneus	-9	-48	30	402	9.00
Posterior Cingulate	-5	-56	22	*	8.41
Posterior Cingulate	-9	-44	-2	*	7.68
Right Parahippocampal Gyrus	21	-6	-16	29	7.97
Anterior Cingulate	-2	47	3	46	7.18
Left Angular Gyrus	-39	-70	28	97	6.20
Right Middle Temporal Gyrus	53	-4	-15	31	6.10
Right Superior Temporal Gyrus	50	4	-14	*	5.99
Right Lingual Gyrus	1	-80	-5	30	5.32
Right Lingual Gyrus	4	-71	3	*	3.95
Right Cerebellum	11	-77	-33	31	5.16
Right Cerebellum	18	-70	-36	*	4.79
Right Cerebellum	27	-70	-36	*	4.22

Figure 3. Regions of significant activity for the famous compared to unfamiliar name contrast for the Categories Task.

Figure 4 displays the results for the famous compared to unfamiliar name contrast for the Attributes task, which yielded seven separate clusters of activity. These clusters include several regions consistent with the other two tasks, including bilateral middle temporal gyrus, left angular gyrus, precuneus, and posterior cingulate. Additional regions consistent with the FNDT include left medial inferior and middle frontal gyrus and right angular gyrus. Regions consistent with the Categories task include left parahippocampal gyrus and anterior cingulate. A notable finding is that the activity in left temporal lobe extended to anterior temporal cortex to a greater extent than the other two tasks.

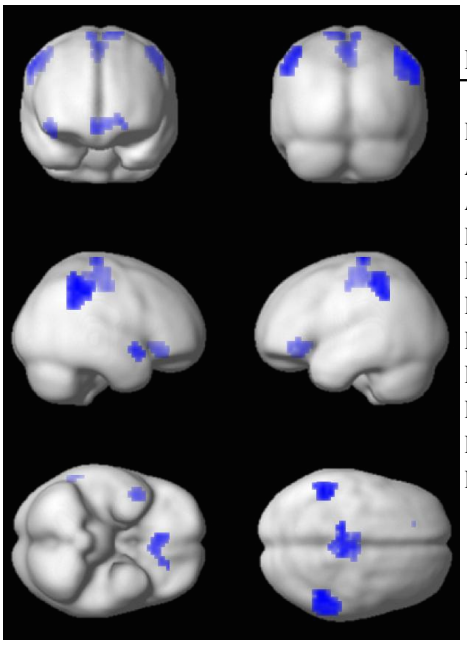


Region	Talairach Coordinates X	Y	Z	k	t_{max}
Left Inferior Frontal Gyrus	-51	17	14	366	9.74
Left Middle Temporal Gyrus	-51	-6	-17	*	7.25
Left Inferior Frontal Gyrus	-41	29	-3	*	6.30
Posterior Cingulate	-9	-50	23	171	8.91
Precuneus	9	-50	27	*	7.01
Posterior Cingulate	-3	-45	38	*	6.85
Left Middle Frontal Gyrus	-28	16	50	297	8.43
Left Middle Frontal Gyrus	-22	20	47	*	7.83
Left Superior Frontal Gyrus	-13	24	48	*	6.21
Left Angular Gyrus	-41	-66	32	231	7.35
Left Angular Gyrus	-41	-60	25	*	6.87
Anterior Cingulate	1	47	3	46	6.26
Right Angular Gyrus	39	-66	27	52	5.65
Left Parahippocampal Gyrus	-15	-17	-14	38	5.22

Figure 4. Regions of significant activity for the famous compared to unfamiliar name contrast for the Attributes Task.

We constructed paired-samples designs between each possible pair of tasks to determine activity specific to each task for the respective famous to unfamiliar name contrasts. We used a more liberal voxel cluster threshold of 10 voxels in order to increase our ability to detect activity, with an alpha level of $p < .005$, uncorrected for multiple comparisons.

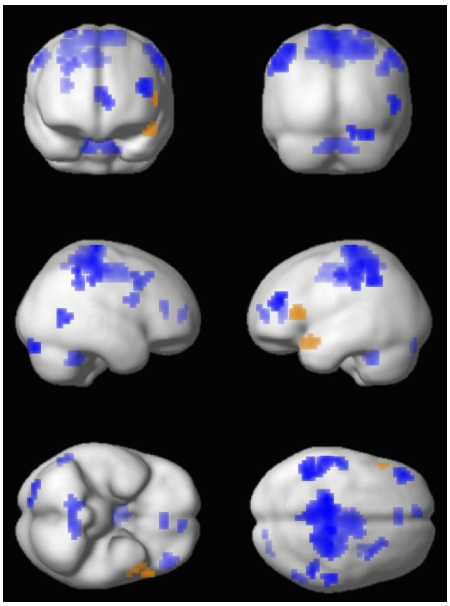
The comparison between FNDT and the Categories task is displayed in Figure 5. As shown, we detected significantly greater activity for FNDT compared to Categories in posterior and anterior cingulate, precuneus, right posterior inferior parietal lobe (including supramarginal and angular gyri), and the right insula. No significant clusters were detected for Categories compared to FNDT.



Region	Talairach Coordinates X	Y	Z	k	t_{max}
FNDT compared to Categories					
Left Supramarginal Gyrus	-48	-49	44	41	5.38
Anterior Cingulate	1	26	-6	35	4.24
Anterior Cingulate	-18	34	2	*	3.28
Right Insula	40	5	-4	14	4.22
Right Supramarginal Gyrus	46	-49	45	91	4.15
Right Supramarginal Gyrus	52	-39	43	*	3.85
Right Supramarginal Gyrus	39	-53	52	*	3.76
Precuneus	-13	-34	67	11	4.06
Precuneus	-3	-33	50	80	3.85
Posterior Cingulate	0	-26	47	*	3.81
Precuneus	7	-34	64	*	3.74

Figure 5. Regions of significantly greater activity for the FNDT compared to Categories task. No significant clusters (with minimum cluster size of $k = 10$) were detected for the Categories compared to FNDT contrast.

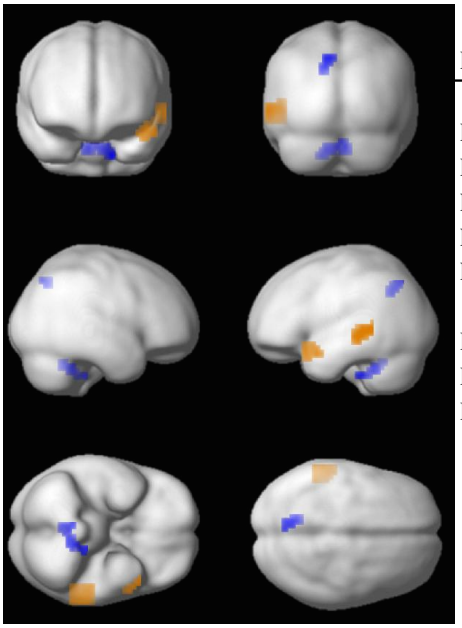
The comparison between FNDT and the Attributes task is displayed in Figure 6. Two significant clusters emerged for the Attributes compared to FNDT contrast, including the left anterior temporal lobe and inferior frontal gyrus. We observed significant activity for the FNDT compared to Attributes contrast in 12 clusters comprising several regions, including precuneus, bilateral inferior parietal lobe, left prefrontal cortex, anterior cingulate, and cerebellum.



Region	Talairach Coordinates X	Y	Z	k	t_{max}
FNDT compared to Attributes					
Precuneus	17	-39	49	614	6.44
Precuneus	10	-37	53	*	6.01
Precuneus	-9	-40	60	*	5.50
Left Supramarginal Gyrus	-42	-52	47	92	5.19
Left Supramarginal Gyrus	-48	-51	36	*	4.76
Left Inferior Parietal Lobule	-54	-25	42	*	4.30
Anterior Cingulate	-5	32	20	21	4.50
Anterior Cingulate	-8	30	12	*	3.90
Right Middle Frontal Gyrus	26	4	39	18	4.30
Right Middle Frontal Gyrus	34	1	46	*	3.35
Right Superior Frontal Gyrus	21	14	44	*	3.23
Right Cerebellum	14	-85	-23	15	4.27
Right Cerebellum	31	-78	-26	*	3.77
Anterior Cingulate	26	3	25	13	4.24
Left Dorsolateral Prefrontal Cortex	-41	36	23	26	4.11
Medial Cerebellum	-4	-44	-31	51	3.85
Medial Cerebellum	9	-44	-34	*	3.74
Right Supramarginal Gyrus	52	-28	44	13	3.71
Right Supramarginal Gyrus	56	-37	36	*	3.05
Left Frontopolar Cortex	-8	50	14	10	3.68
Left Dorsomedial Prefrontal Cortex	-5	53	22	*	3.17
Right Supramarginal Gyrus	43	-49	38	19	3.53
Right Supramarginal Gyrus	46	-49	45	*	3.42
Right Middle Temporal Gyrus	50	-61	1	12	3.42
Attributes compared to FNDT					
Left Inferior Frontal Gyrus	-51	17	14	11	4.60
Left Anterior Temporal Lobe	-47	9	-12	10	4.16

Figure 6. Regions of significantly greater activity between the FNDT and Attributes tasks. Significant clusters for FNDT compared to Attributes are shown in blue, and significant clusters for Attributes compared to FNDT are displayed in orange.

Finally, the comparison between the Categories and Attributes task is displayed in Figure 7. Two significant clusters containing three recruitment foci emerged for the Attributes compared to Categories contrast, including in left medial temporal lobe, left anterior temporal lobe, and inferior frontal gyrus. The anterior temporal and inferior frontal foci lie in very similar locations compared to the foci for the Attributes compared to FNDT contrast, as shown in Figure 5. We detected two significant clusters for the Categories compared to Attributes contrast, in the precuneus and cerebellum.



Region	Talairach Coordinates X	Y	Z	k	t_{max}
Categories compared to Attributes					
Precuneus	-13	-64	32	20	3.72
Precuneus	-9	-71	39	*	3.26
Medial Cerebellum	-8	-44	-34	33	3.71
Medial Cerebellum	5	-44	-30	*	3.48
Medial Cerebellum	-14	-33	-37	*	3.34
Attributes compared to Categories					
Left Middle Temporal Gyrus	-57	-34	-2	72	4.45
Left Inferior Frontal Gyrus	-41	17	-15	17	4.04
Left Anterior Temporal Lobe	-47	10	-15	*	3.59

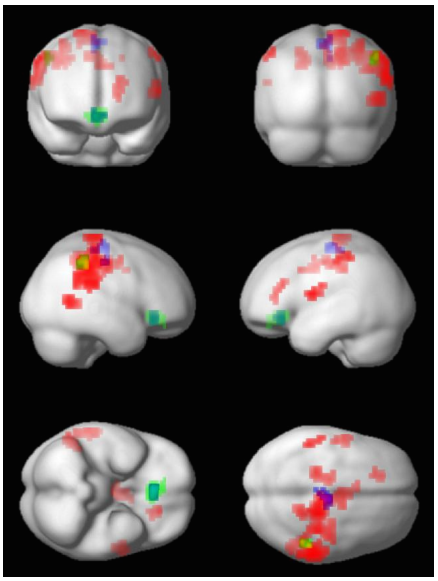
Figure 7. Regions of significantly greater activity for the Attributes compared to Categories task. Significant clusters for Categories compared to Attributes are shown in blue, and significant clusters for Attributes compared to Categories are displayed in orange.

Cross-task Comparisons Split by Epoch

We conducted an additional set of analyses comparing the three tasks while holding time epoch constant, allowing for cross-task analyses for the Enduring, Remote, and Recent names separately. Each time epoch was contrasted against the respective unfamiliar name control task. These analyses were intended to potentially identify regions that were selectively utilized by each task during each time epoch. We used a same liberal voxel cluster threshold of 10 voxels in order to increase our ability to detect activity, with an alpha level of $p < .005$, uncorrected for multiple comparisons. Thus, some of the clusters in the following analyses might represent Type I Errors.

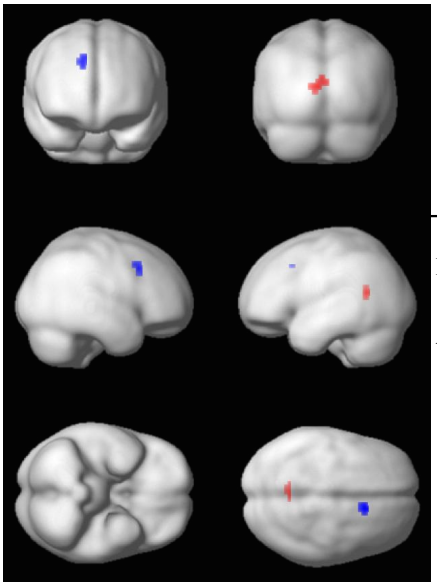
Figures 8 and 9 display the comparisons between FNDT and Categories, split by time epoch. For the FNDT relative to Categories contrast, there was considerably greater activity for Recent names, including in posterior cingulate, precuneus, and bilateral inferior parietal lobule (Figure 8). In contrast, only two clusters of increased activity were observed for both Remote (in

anterior cingulate and right supramarginal gyrus) and Enduring names (in posterior cingulate and anterior cingulate). As shown in Figure 9, only two small clusters (10 voxels each) showed significantly greater activity for Categories compared to FNDT. One cluster was in posterior cingulate for Recent names, and the other cluster was in anterior cingulate for Enduring names.



	Talairach Coordinates				
Region	X	Y	Z	k	t_{max}
Recent (red)					
Posterior Cingulate	4	-27	36	305	7.22
Precuneus	17	-48	38	*	4.88
Precuneus	30	-32	47	*	4.57
Right Angular Gyrus	47	-51	6	29	6.94
Right Supramarginal Gyrus	56	-40	28	120	5.08
Right Supramarginal Gyrus	56	-38	39	*	5.07
Right Supramarginal Gyrus	52	-30	26	*	4.69
Anterior Cingulate	-22	22	29	18	4.89
Precuneus	-22	-36	46	46	4.11
Precuneus	-18	-35	38	*	3.88
Precuneus	-18	-22	43	*	3.35
Right Supramarginal Gyrus	39	-44	31	13	4.05
Left Precentral Gyrus	-54	-6	15	23	3.88
Left Precentral Gyrus	-54	-13	22	*	3.15
Left Supramarginal Gyrus	-48	-42	48	10	3.31
Left Supramarginal Gyrus	-54	-32	42	*	3.07
Remote (green)					
Anterior Cingulate	1	25	-2	47	5.37
Right Supramarginal Gyrus	46	-41	43	12	3.89
Enduring (blue)					
Posterior Cingulate	4	-25	43	22	3.59
Posterior Cingulate	0	-24	58	*	3.35
Posterior Cingulate	0	-29	54	*	3.10
Anterior Cingulate	1	26	-6	14	3.29

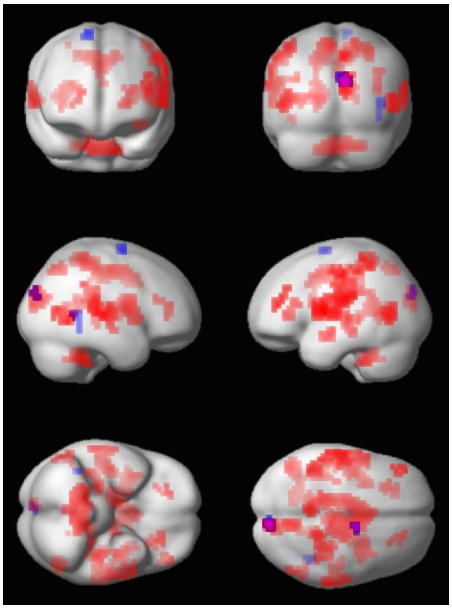
Figure 8. Regions of significantly greater activity for the FNDT compared to Categories task, split by the time epoch for famous names.



Region	Talairach Coordinates X	Y	Z	k	t_{max}
Recent (red)					
Posterior Cingulate	-9	-55	8	10	3.31
Enduring (blue)					
Anterior Cingulate	11	12	40	10	4.05

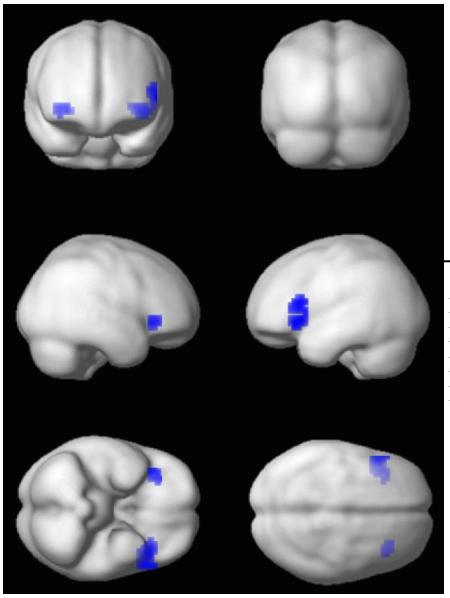
Figure 9. Regions of significantly greater activity for the Categories task compared to FNDT, split by the time epoch for famous names. No significant clusters with minimum of $k = 10$ voxels were identified for Remote famous names.

Figures 10 and 11 display the results for the comparisons between FNDT and Attributes. As with the comparison with Categories, FNDT displayed greater activity for Recent names across several regions bilaterally, including anterior cingulate, posterior cingulate, insula, cerebellum, and middle temporal gyrus. In contrast, activity was more balanced for the other time epochs, with no significant clusters for Remote and only three clusters for Enduring in right cuneus, parahippocampal gyrus, and medial frontal gyrus. As shown in Figure 11, significantly greater activity for Attributes was observed only for Enduring names, with activity bilaterally in inferior frontal gyrus, close to the anterior temporal lobe.



Region	Talairach Coordinates X	Y	Z	k	t_{max}
Recent (red)					
Anterior Cingulate	0	-1	38	449	5.41
Anterior Cingulate	-5	-9	38	*	5.21
Posterior Cingulate	4	-28	40	*	5.09
Right Superior Temporal Gyrus	60	-29	12	93	5.37
Right Insula	37	-19	5	*	4.25
Right Superior Temporal Gyrus	60	-20	12	*	3.82
Left Middle Temporal Gyrus	-41	-61	3	161	5.06
Posterior Cingulate	-15	-49	16	*	4.83
Posterior Cingulate	-18	-61	4	*	4.29
Right Thalamus	24	-29	11	63	5.03
Right Insula	37	-36	21	*	4.27
Right Insula	37	-43	17	*	3.27
Left Transverse Temporal Gyrus	-54	-15	7	297	4.91
Left Insula	-28	1	13	*	4.74
Left Precentral Gyrus	-54	-2	12	*	4.54
Right Cuneus	8	-82	13	56	4.87
Right Caudate	21	1	17	133	4.73
Right Insula	30	-3	14	*	4.67
Right Thalamus	11	-12	9	*	4.50
Right Cerebellum	11	-42	-30	125	4.40
Right Cerebellum	22	-41	-34	*	4.25
Medial Cerebellum	-4	-44	-31	*	3.95
Enduring (blue)					
Right Cuneus	4	-86	23	15	4.04
Right Parahippocampal Gyrus	37	-45	2	10	3.90
Right Fusiform Gyrus	37	-44	-8	*	3.18
Right Medial Frontal Gyrus	10	-11	63	10	3.81

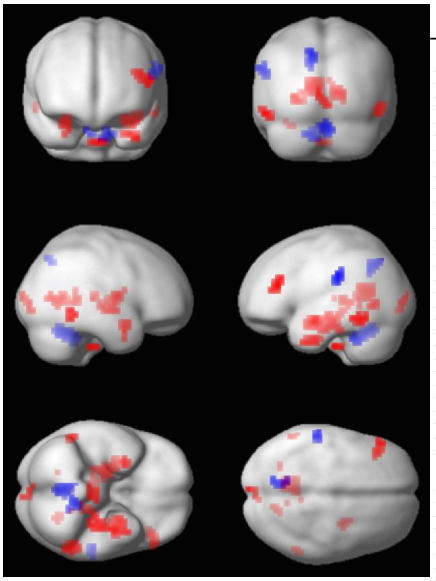
Figure 10. Regions of significantly greater activity for FNDT compared to the Attributes task, split by the time epoch for famous names. Note that due to the large number of activation foci for Recent names, only clusters greater than $k = 50$ voxels are displayed in the table. No significant clusters with minimum of $k = 10$ voxels were identified for Remote famous names.



Region	Talairach Coordinates X	Y	Z	k	t_{max}
Enduring (blue)					
Left Insula	-38	19	0	35	4.47
Right Inferior Frontal Gyrus	34	25	2	26	4.28
Left Inferior Frontal Gyrus	-51	17	14	34	4.24
Left Inferior Frontal Gyrus	-47	15	3	*	3.08

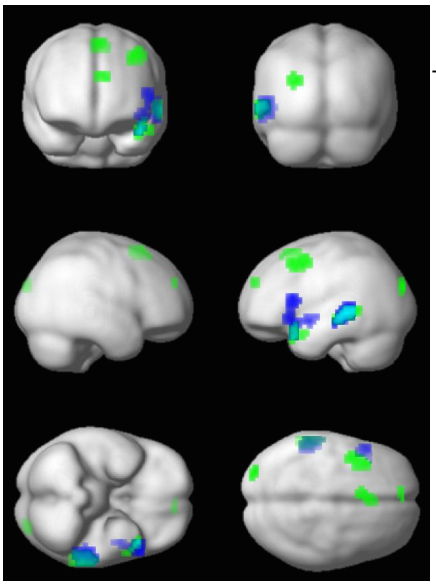
Figure 11. Regions of significantly greater activity for the Attributes task compared to FNDT, split by the time epoch for famous names. No significant clusters with minimum of $k = 10$ voxels were identified for Recent or Remote famous names.

Figures 12 and 13 display the comparisons between the Categories and Attributes tasks. Several regions of significant activity for Categories compared to Attributes for Recent names, including in bilateral middle temporal gyri, parahippocampal gyri, and right thalamus. No significant clusters were detected for Remote names. Four clusters were detected for Enduring names, in cerebellum, left supramarginal gyrus, and precuneus. For the Attributes compared to Categories contrasts (Figure 13), no significant activity was observed for Recent names. However, significant activity was observed for both Remote and Enduring names in left middle temporal gyrus, anterior temporal lobe, and inferior frontal gyrus. Additionally, significant clusters were detected for Remote names in middle frontal gyrus, medial prefrontal cortex, and middle occipital gyrus.



	Talairach Coordinates				
Region	X	Y	Z	k	t_{max}
Recent (red)					
Right Thalamus	24	-8	-1	58	5.21
Right Thalamus	24	-8	13	*	4.22
Right Thalamus	14	-15	8	*	3.24
Left Parahippocampal Gyrus	-28	0	-12	171	4.94
Posterior Cingulate	-9	-55	8	*	4.45
Left Middle Temporal Gyrus	-38	-7	-13	*	4.19
Left Inferior Temporal Gyrus	-34	-2	-31	20	4.24
Left Parahippocampal Gyrus	-27	-2	-27	*	3.45
Right Lingual Gyrus	17	-61	1	49	3.70
Right Lingual Gyrus	8	-58	4	*	3.67
Right Parahippocampal Gyrus	14	-41	6	*	3.66
Left Middle Frontal Gyrus	-38	22	29	21	3.70
Left Middle Frontal Gyrus	-47	30	22	*	3.56
Right Thalamus	8	-28	7	20	3.54
Right Thalamus	21	-25	11	*	3.25
Enduring (blue)					
Left Cerebellum	-12	-42	-30	17	4.52
Medial Cerebellum	1	-51	-28	40	4.26
Left Supramarginal Gyrus	-54	-30	24	16	4.18
Precuneus	-13	-64	32	19	3.85

Figure 12. Regions of significantly greater activity for Categories compared to the Attributes task, split by the time epoch for famous names. Note that due to the large number of activation foci for Recent names, only clusters greater than $k = 20$ voxels are displayed in the table. No significant clusters with minimum of $k = 10$ voxels were identified for Remote famous names.



Region	Talairach Coordinates X	Y	Z	k	t_{max}
Remote (green)					
Left Middle Frontal Gyrus	-35	11	46	53	6.45
Left Middle Frontal Gyrus	-41	-2	48	*	3.71
Left Medial Prefrontal Cortex	-9	48	32	12	4.60
Left Superior Frontal Gyrus	-10	10	61	28	4.60
Left Middle Temporal Gyrus	-57	-37	-2	52	4.37
Left Middle Temporal Gyrus	-60	-27	-8	*	3.36
Left Anterior Temporal Lobe	-40	17	-18	20	4.07
Left Inferior Frontal Gyrus	-41	13	-11	*	3.64
Left Anterior Temporal Lobe	-51	7	-16	*	3.39
Left Middle Occipital Gyrus	-28	-89	19	13	3.80
Enduring (blue)					
Left Middle Temporal Gyrus	-47	-34	-5	88	7.01
Left Middle Temporal Gyrus	-51	-41	1	*	5.49
Left Middle Temporal Gyrus	-56	-23	-11	*	4.16
Left Inferior Frontal Gyrus	-47	14	14	61	4.54
Left Inferior Frontal Gyrus	-43	19	0	*	4.14
Left Anterior Temporal Lobe	-41	-1	-5	*	3.71

Figure 13. Regions of significantly greater activity for the Attributes task compared to Categories, split by the time epoch for famous names. No significant clusters with minimum of *k* = 10 voxels were identified for Recent famous names.

Aim 1 Summary

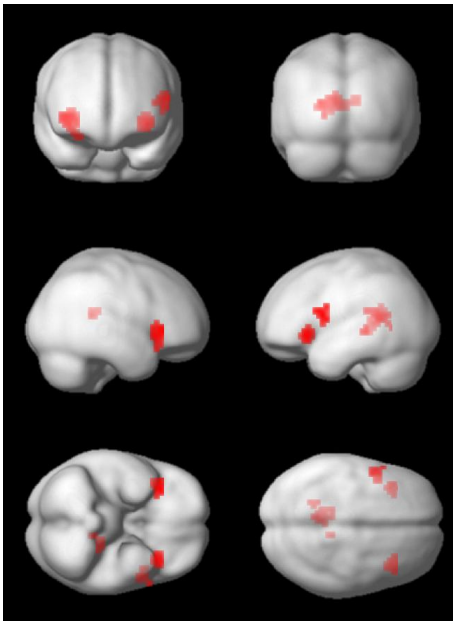
We hypothesized that the task requiring deeper processing of semantic knowledge would recruit a broader semantic network including an overall greater number of regions than the FNDT. However results indicated that the FNDT generated greater activity than the other two tasks in most regions, although there was evidence of selective recruitment specific to tasks. In particular, the Attributes task generated significantly more activity than the other two tasks in left anterior temporal lobe and left inferior frontal gyrus. The Attributes task also demonstrated the strongest left-lateralized recruitment.

Temporal Gradient Results

As described in the Methods section, we conducted analyses for the four *a priori* contrasts of interest for the temporal gradient analyses that we thought might demonstrate significant activity based on previous research and theory, including 1) Recent compared to Enduring, 2) Recent compared to Remote, 3) Enduring compared to Remote, and 4) Remote

compared to Enduring contrasts. We used a voxel cluster threshold of 10 voxels and an alpha level of $p < .001$, uncorrected for multiple comparisons.

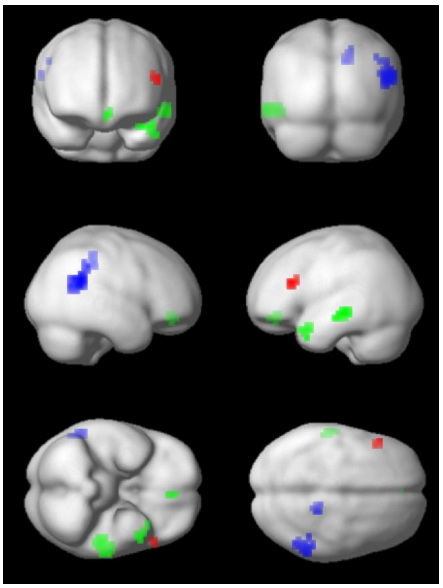
Figure 14 displays the temporal gradient results for the FNDT. We only detected significant activity for the Recent compared to Enduring contrast. Specifically, we detected four clusters with greater activity for Recent names, including posterior cingulate and left inferior frontal gyrus. Interestingly, we detected activity bilaterally in insular cortex for this contrast.



	Talairach Coordinates				
	X	Y	Z	k	t_{max}
Recent > Enduring					
Posterior Cingulate	-12	-46	12	100	7.26
Posterior Cingulate	8	-38	13	*	5.44
Left Parahippocampal Gyrus	-21	-34	-1	*	4.37
Left Insula	-31	21	0	27	5.68
Right Insula	37	15	5	51	5.35
Right Insula	34	20	9	*	4.97
Right Inferior Frontal Gyrus	24	19	-10	*	4.29
Left Precentral Gyrus	-51	1	13	21	4.74
Left Insula	-41	4	17	*	4.43
Left Inferior Frontal Gyrus	-54	10	21	*	3.93

Figure 14. Temporally graded functional activity for famous names on the FNDT. No significant clusters (with minimum cluster size of $k = 10$) were detected for the Recent compared to Remote, Enduring compared to Remote, or Remote compared to Enduring contrasts.

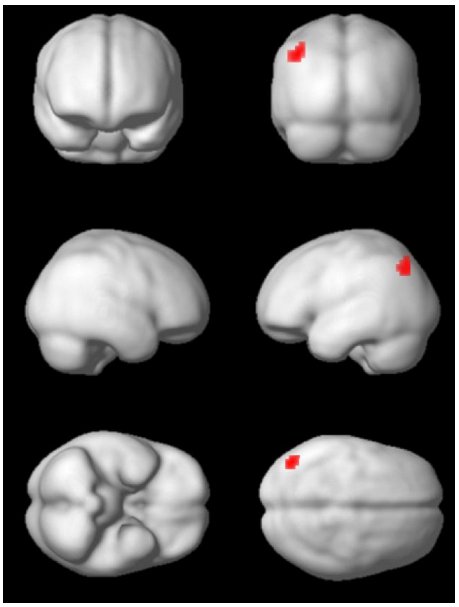
Figure 15 displays the temporal gradient results for the Categories task. The Recent compared to Enduring contrast yielded one significant cluster in left dorsolateral prefrontal cortex. We detected three significant clusters for the Recent compared to Remote contrast, including clusters in left medial and anterior temporal lobe and left inferior frontal gyrus. The Enduring compared to Remote contrast yielded two significant clusters in right supramarginal gyrus, angular gyrus, and posterior cingulate cortex. The reverse contrast (Remote compared to Enduring) did not yield any significant clusters.



	Talairach Coordinates				
	X	Y	Z	k	t_{max}
Recent>Enduring (red)					
Left Dorsolateral Prefrontal Cortex	-51	19	25	13	4.27
Recent>Remote (green)					
Left Superior Temporal Gyrus	-47	-27	-8	41	5.64
Left Middle Temporal Gyrus	-56	-23	-8	*	4.91
Left Middle Temporal Gyrus	-54	-17	-11	*	4.35
Left Anterior Temporal Lobe	-40	10	-19	14	5.42
Left Inferior Temporal Gyrus	-47	-8	-28	*	4.77
Left Inferior Frontal Gyrus	-30	17	-18	*	4.08
Anterior Cingulate	-4	39	-5	10	4.60
Enduring>Remote (blue)					
Right Angular gyrus	49	-59	20	52	6.70
Right Supramarginal Gyrus	47	-44	35	*	4.15
Right Supramarginal Gyrus	39	-48	38	*	3.92
Posterior Cingulate	13	-41	35	17	5.16
Precuneus	17	-39	46	*	4.41

Figure 15. Temporally graded functional activity for famous names on the Categories task. No significant clusters (with minimum cluster size of k = 10) were detected for the Remote compared to Enduring contrast.

Figure 16 displays the temporal gradient results for the Attributes task. One significant cluster was detected for the Recent compared to Enduring name contrast in left angular gyrus. No significant clusters were detected for the other three contrasts.



	Talairach Coordinates				
	X	Y	Z	k	t_{max}
Recent>Enduring					
Left Angular gyrus	-41	-77	34	17	5.59

Figure 16. Temporally graded functional activity for famous names on the Attributes task. No significant clusters (with minimum cluster size of k = 10) were detected for the Recent compared to Remote, Enduring compared to Remote, or Remote compared to Enduring contrasts.

Aim 2 Summary

We hypothesized that we would observe a greater number of regions demonstrating a temporal gradient for tasks requiring more specific semantic knowledge recruitment. Results from the FNDT were consistent with previous research, indicating the greatest activity for Recent names in several regions. The Categories task displayed a similar pattern with greater recruitment for Recent names in several regions. Additionally, we observed greater recruitment for Enduring compared to Remote names for Categories in precuneus and right prefrontal regions, consistent with hypotheses. Contrary to hypotheses, we only observed one small cluster displaying greater activity for Recent compared to Enduring names for the Attributes task. Thus, we did not observe a greater amount of temporally graded activity for the task requiring the most specific semantic knowledge retrieval.

ROI Analyses

We further analyzed activity in specific regions of interest (ROIs) to compare the hemodynamic response function (HRF) for famous and unfamiliar names between tasks. The HRF is a proxy of blood flow to any particular region following each stimulus type. We generated ROIs based on activity common to all three tasks for the famous to unfamiliar contrasts displayed in Figures 2-4. This method generated three ROIs: left middle temporal gyrus, left angular gyrus, and posterior cingulate. All three of these regions have been heavily implicated in the retrieval of semantic memories (Binder et al., 2009).

Results from the left middle temporal gyrus are displayed in Figure 17. The HRF for famous names demonstrated significant differences between the three tasks. In particular, the Attributes task had a significantly lower inhibitory signal at two seconds and a significantly higher positive signal at 6, 8, and 10 seconds, with a peak around six seconds. A similar trend

was observed for unfamiliar names with regard to the Attributes task, although the difference was only statistically significant at 10 seconds post-stimulus onset. Additionally, a one-way ANOVA for sum of the signals at 6, 8, and 10 seconds was marginally significant ($F(2, 14) = 3.42$, $p = .062$, $\eta^2_p = .33$), with the largest activity for the Attributes task. The Categories task demonstrated a negative HRF in this region for unfamiliar names while the FNDT was not significantly different from zero at any time point. The difference in HRF between famous and unfamiliar names on the FNDT was not significant at any time point, which contrasts with the results from this region in previous research with this task (Woodard et al., 2007).

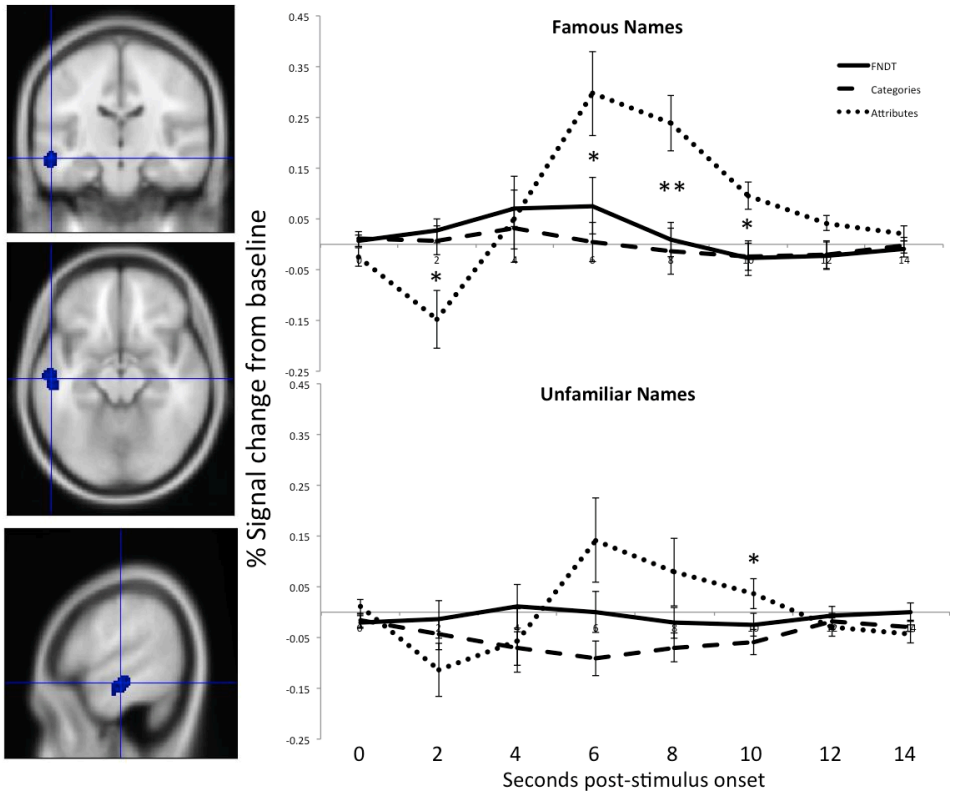


Figure 17. Analysis of the hemodynamic response function in the left medial temporal lobe averaged across correct responses for famous and unfamiliar names for all three tasks. *$p < .05$, **$p < .01$ for one-way repeated measures ANOVAs at each time point. Error bars represent the standard error of the mean.

Figure 18 displays the results for posterior cingulate cortex. Visual inspection of the line graphs indicates a similar pattern to the left middle temporal gyrus, with a higher signal for the

Attributes task for famous names and a peak around six seconds post-stimulus onset. However, no statistically significant findings between tasks were observed at any time point. Additionally, a one-way ANOVA for the sum of the signals at 6, 8, and 10 seconds did not demonstrate a significant main effect of task ($F(2, 14) = 0.78$, $p = .478$, $\eta^2_p = .10$). For unfamiliar names, both the FNDT and Categories task demonstrated a negative HRF, indicating that this region was inhibited during those trials. In contrast, the HRF was relatively consistent at zero for unfamiliar names for the Attributes task. A comparison of the famous and unfamiliar names on the FNDT revealed a significantly higher signal for famous names at two, four, and six seconds post-stimulus onset, consistent with previous findings from this task (Woodard et al., 2007).

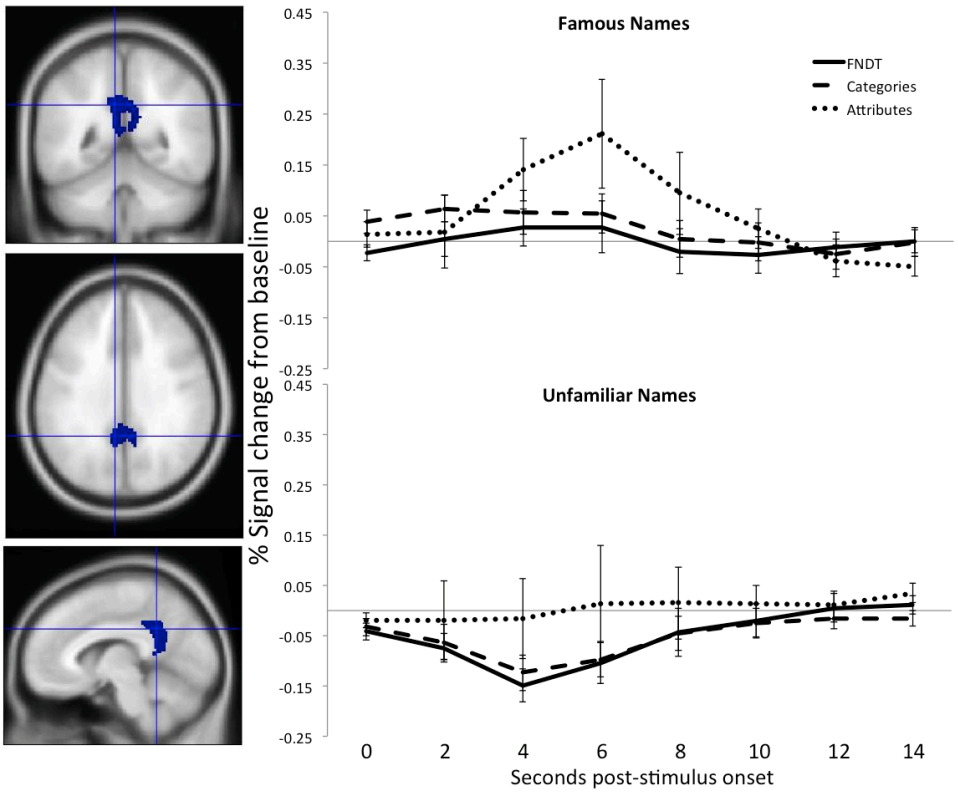


Figure 18. Analysis of the hemodynamic response function in posterior cingulate cortex averaged across correct responses for famous and unfamiliar names for all three tasks. One-way repeated measures ANOVAs did not reveal significant effects of task at any time point. Error bars represent the standard error of the mean.

Figure 19 displays the results for the left angular gyrus. As with the left middle temporal gyrus (Figure 17), the HRF is much more pronounced in the Attributes task compared to the FNDT and Categories tasks. For famous names, the HRF was significantly lower at two seconds and higher at 6, 8, and 10 seconds post-stimulus onset, with a peak around six seconds. The Attributes HRF also demonstrated a significantly higher HRF for unfamiliar names at 6, 8, and 10 seconds. The FNDT and Categories demonstrated a negative HRF for unfamiliar names, consistent with the posterior cingulate cortex.

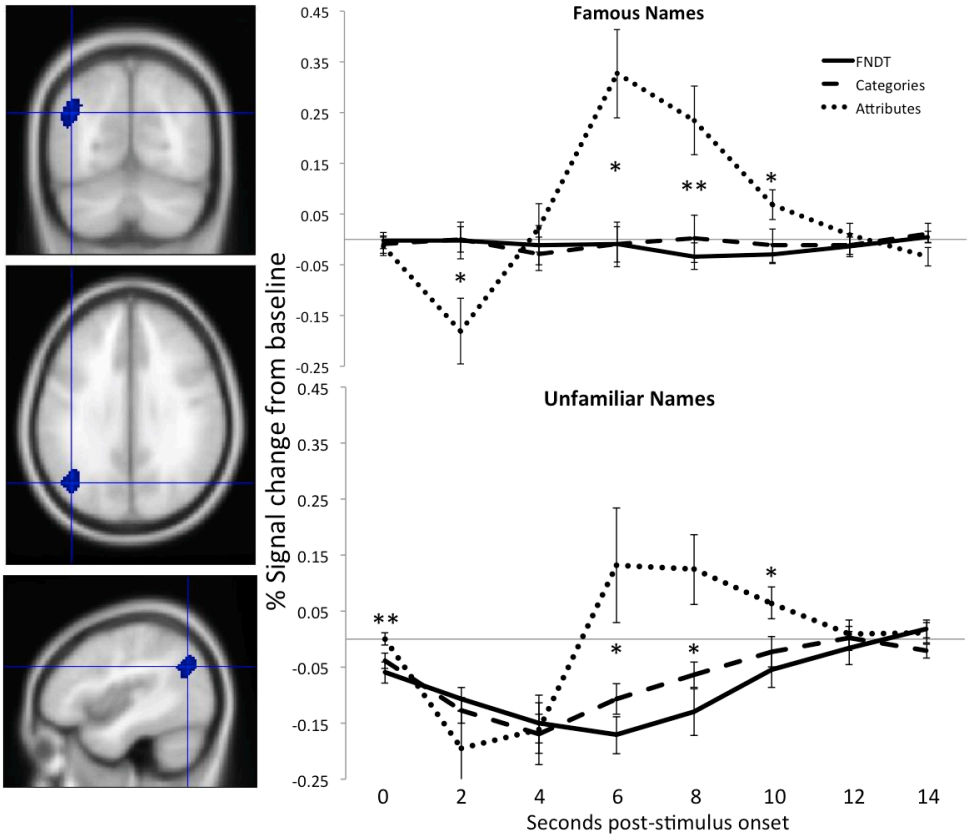


Figure 19. Analysis of the hemodynamic response function in the left angular gyrus averaged across correct responses for famous and unfamiliar names for all three tasks. *$p < .05$, **$p < .01$ for one-way repeated measures ANOVAs at each time point. Error bars represent the standard error of the mean.

We also analyzed activity in left anterior temporal lobe, due to this region's association with specific biographical knowledge (Olson et al., 2013) and the selective recruitment of this region during the Attributes task compared to the other tasks (see Figures 6 and 7). This ROI was

created by selecting significant voxels for the famous compared to unfamiliar name contrast for the Attributes task that were not significant for either the FNDT or Categories famous compared to unfamiliar contrast. Results from the HRF analysis are displayed in Figure 20. As shown, the Attributes task demonstrated a significantly lower signal at two seconds and a significantly higher peak at six seconds for famous names. Further, a one-way ANOVA comparing the sum of the signals at 6, 8, and 10 seconds had a significant main effect of task ($F(2, 14) = 3.86$, $p = .046$, $\eta^2_p = .36$), with the largest HRF for the Attributes task. A similar trend was observed for unfamiliar names, although the differences were not significant at any time point or for the sum of the signals at 6, 8, and 10 seconds ($F(2, 14) = 1.26$, $p = .315$, $\eta^2_p = .15$). The average signal was not significantly different from zero for famous or unfamiliar names for both the FNDT and Categories tasks. These results complement Figures 6 and 7 in demonstrating that this region is selectively responsive to the Attributes task.

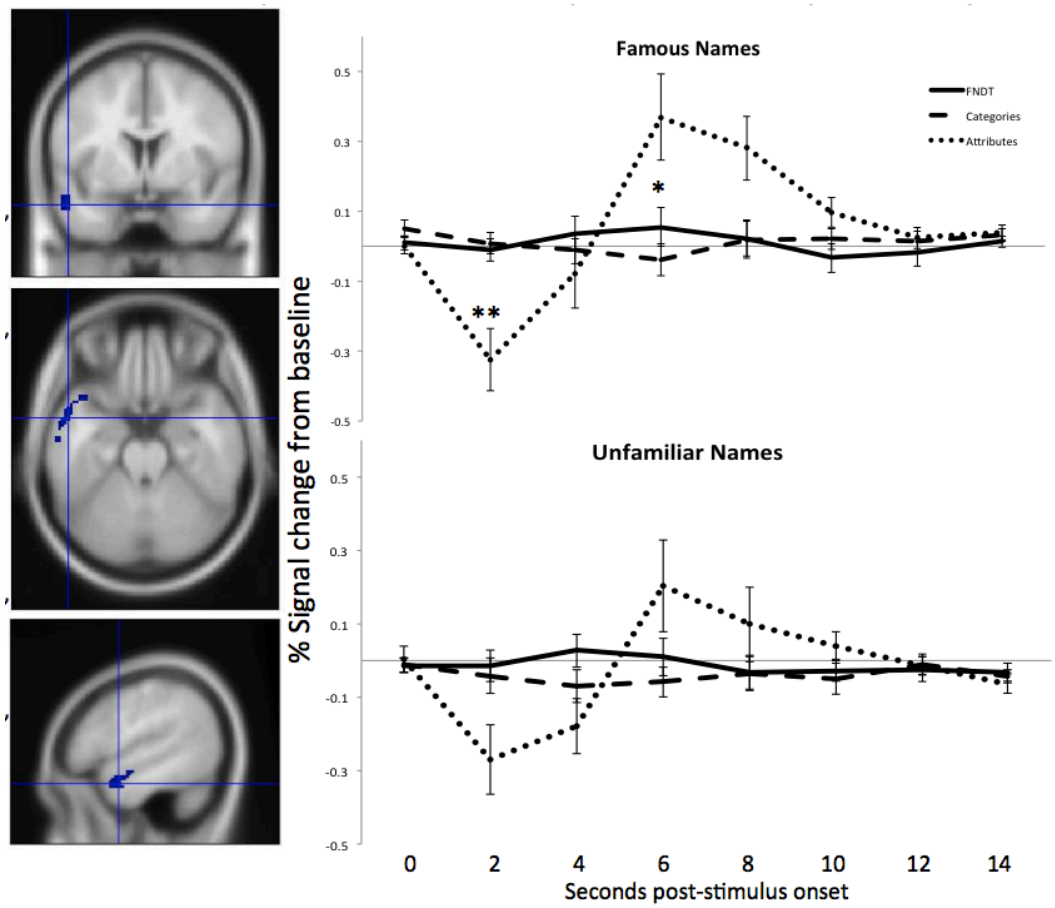


Figure 20. Analysis of the hemodynamic response function in the left anterior temporal lobe averaged across correct responses for famous and unfamiliar names for all three tasks. *$p < .05$, **$p < .01$ for one-way repeated measures ANOVAs at each time point. Error bars represent the standard error of the mean.

Next, we analyzed the HRF in left inferior frontal gyrus, as this region also appeared to demonstrate greater activity for Attributes compared to the other two tasks (Figures 4, 6, 11, and 13). This ROI was generated from the cluster in Figure 6 demonstrating significantly greater activity for Attributes compared to FNDT. Figure 21 displays the mean HRF at each time point for famous and unfamiliar names. As shown, the Attributes tasks demonstrated a much larger and more pronounced response than the other two tasks. The peak at six seconds post-stimulus onset represents a 0.55% signal increase from baseline, and is significantly larger than the other two tasks. Further, for unfamiliar names the HRF was significantly lower for Attributes at two seconds and significantly greater at six and eight seconds.

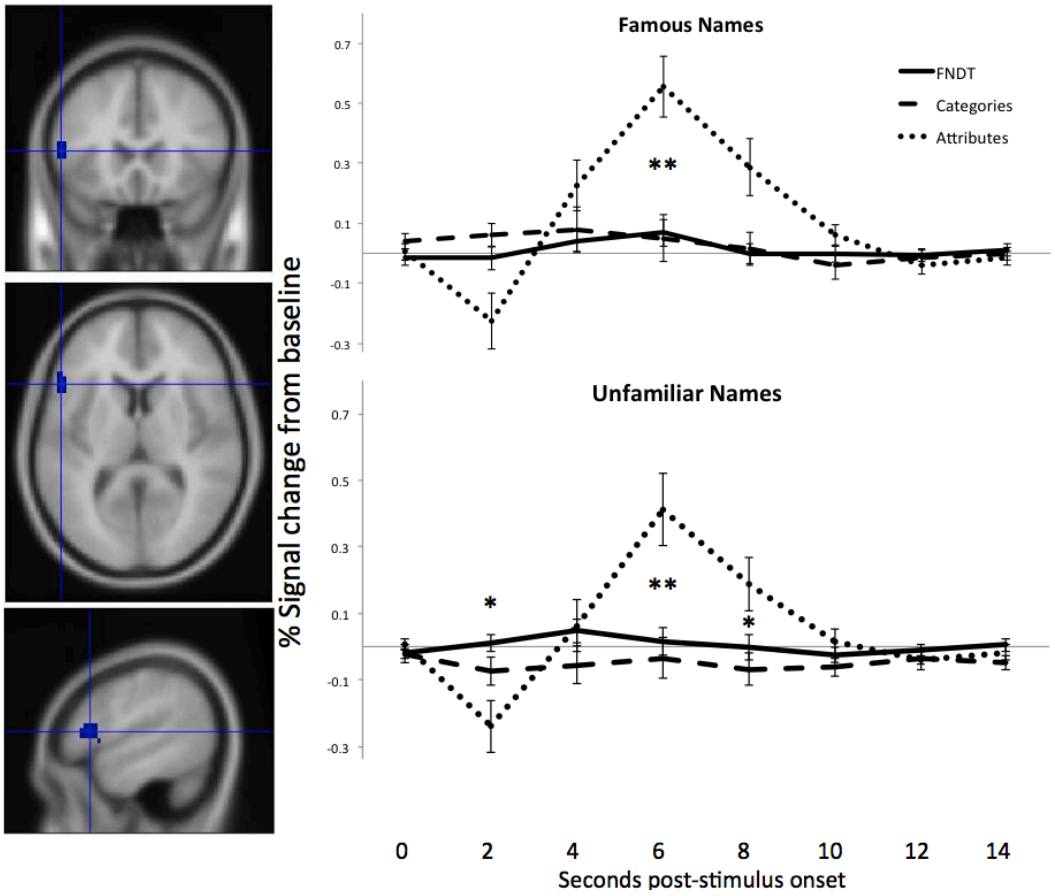


Figure 21. Analysis of the hemodynamic response function in the left inferior frontal gyrus averaged across correct responses for famous and unfamiliar names for all three tasks. *$p < .05$, **$p < .01$ for one-way repeated measures ANOVAs at each time point. Error bars represent the standard error of the mean.

Figures 17-21 identified regions demonstrating significantly larger activity for Attributes compared to the other tasks. Next, we attempted to identify regions that demonstrated specific responses for FNDT and Categories. First, we analyzed activity in left parahippocampal gyrus because this region appeared to demonstrate a strong response to the Categories task, as shown in Figures 3 and 12. The ROI was generated from the cluster identified in the famous compared to unfamiliar name contrast for the Categories task in Figure 3. However, analysis of the HRF (Figure 22) resembled the pattern from the other four ROIs, with the largest signal for the Attributes task for both famous and unfamiliar names. The signal was significantly larger for

Attributes at 6, 8, and 10 seconds for both name categories. Thus, this analysis failed to identify a region that was selectively responsive to the Categories task.

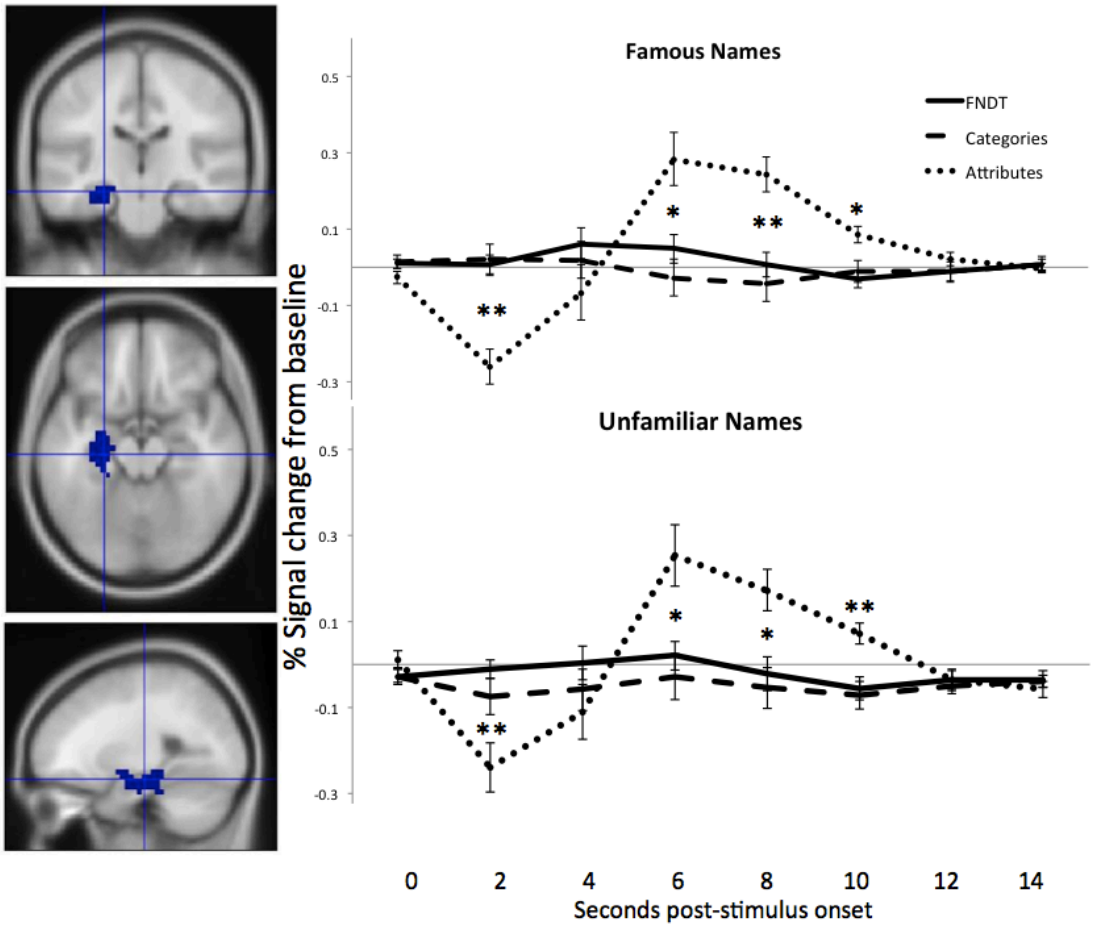


Figure 22. Analysis of the hemodynamic response function in left parahippocampal gyrus averaged across correct responses for famous and unfamiliar names for all three tasks. *$p < .05$, **$p < .01$ for one-way repeated measures ANOVAs at each time point. Error bars represent the standard error of the mean.

Additionally, we attempted to identify a region that might demonstrate a specific response to FNDT and not the other two tasks. We identified the anterior cingulate as a candidate region based on the significant activity during the famous compared to unfamiliar name contrast (Figure 2) and the significantly greater activity than the Attributes task in this region (Figure 6). We generated an ROI based on the anterior cingulate cluster from Figure 6 and analyzed the HRF, anticipating that the signal might be significantly larger for the FNDT than the other two

tasks. However, as shown in Figure 23, we did not observe a larger signal for the FNDT for famous or unfamiliar names in this region. Rather, the mean HRF was very similar across all three tasks and of a small magnitude. One-way ANOVAs revealed significant differences for famous names at 8 seconds and unfamiliar names at 10 seconds, although these could represent false positives due to the large number of comparisons. Notably, we did not observe a large magnitude HRF for the Attributes task in this region, indicating that the large signal observed in other regions may truly be associated with semantic processing rather than the high demands of the task.

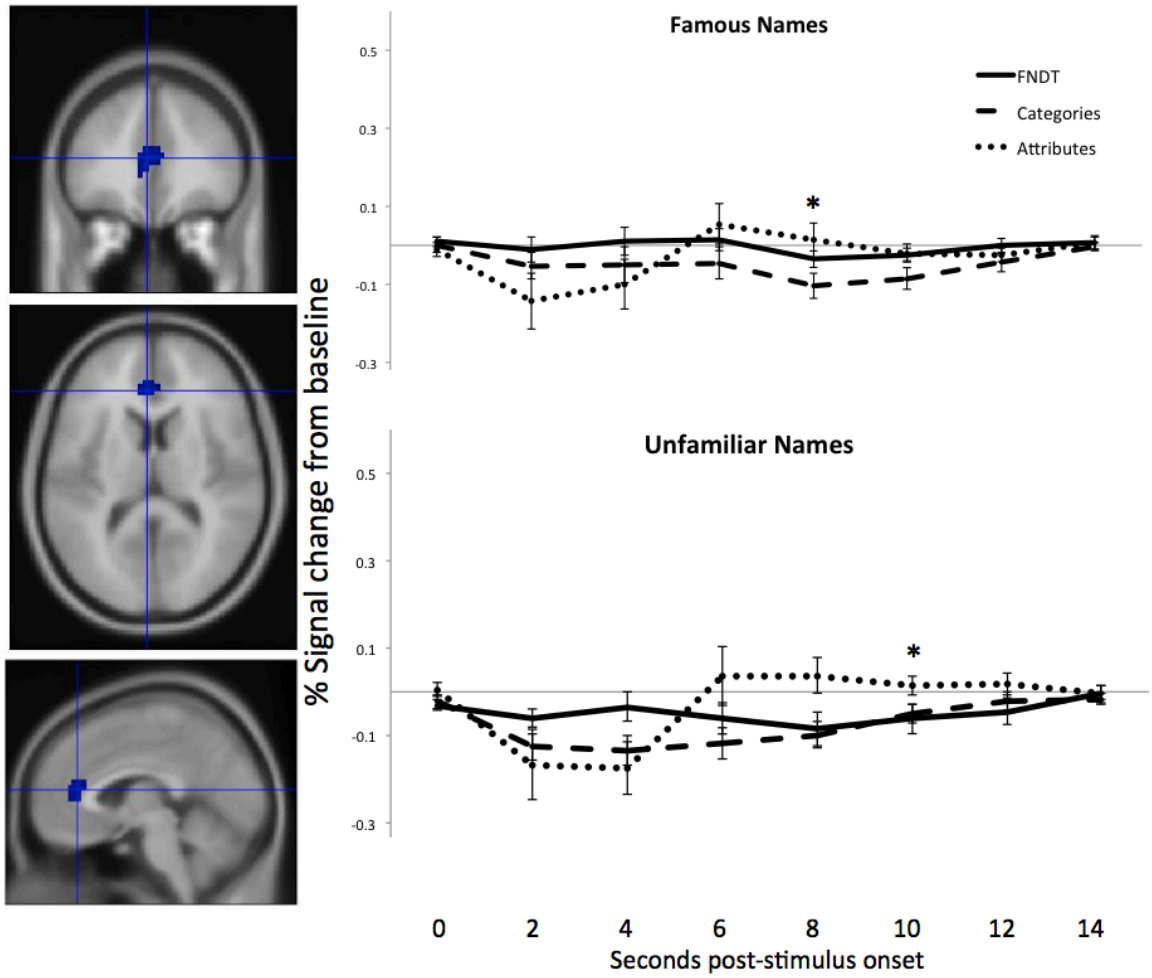


Figure 23. Analysis of the hemodynamic response function in anterior cingulate cortex averaged across correct responses for famous and unfamiliar names for all three tasks. *$p < .05$ for one-way repeated measures ANOVAs at each time point. Error bars represent the standard error of the mean.

Finally, we analyzed the three ROIs with common activity across the three tasks (left middle temporal gyrus, left angular gyrus, and posterior cingulate) split by time epoch to determine if there was a temporally graded pattern of HRFs in these regions (Figures 24-26). Previous research (Woodard et al., 2007) found greater activity in posterior cingulate and left middle temporal gyrus for Recent compared to Remote famous names. However, we did not observe a similar pattern of temporally graded responses for any of the three tasks in any region. The only significant finding between 4 and 10 seconds was for Categories in the posterior cingulate, where the results of a One-way ANOVA were significant at eight seconds post-stimulus onset, with the greatest activity for Recent names.

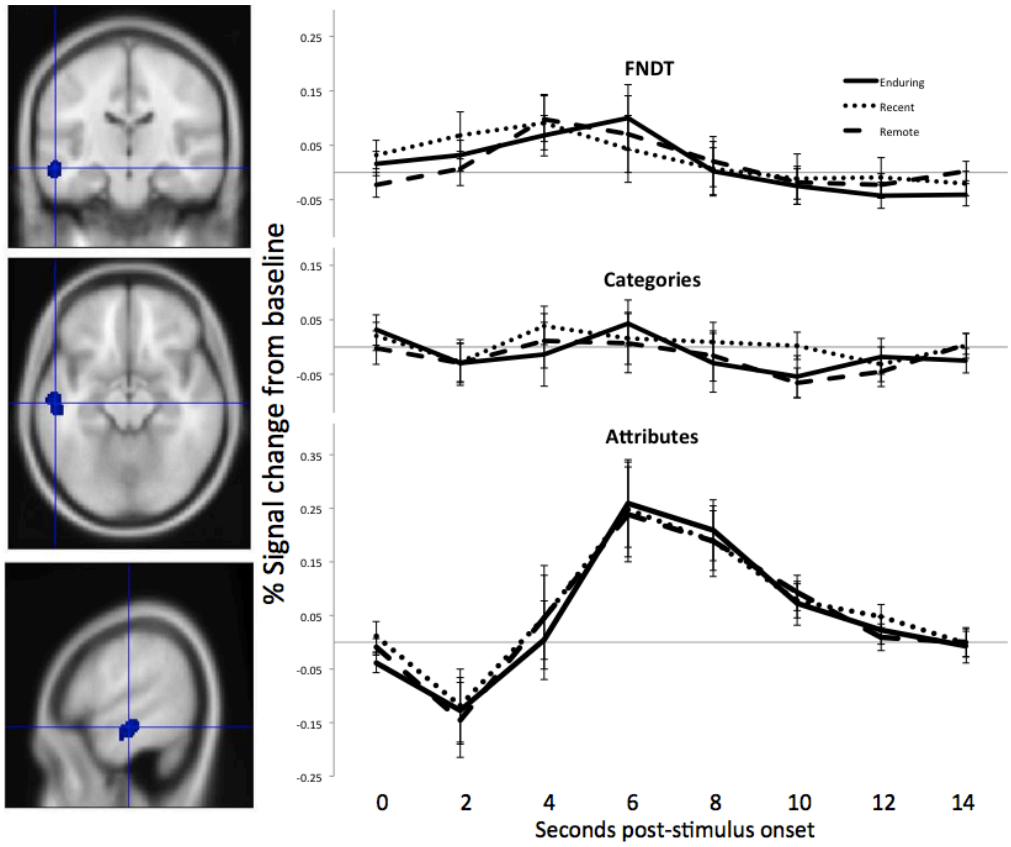


Figure 24. Analysis of the hemodynamic response function in the left middle temporal gyrus averaged across correct responses for the three famous name time epochs for all three tasks. *p < .05, **p < .01 for one-way repeated measures ANOVAs at each time point. Error bars represent the standard error of the mean.

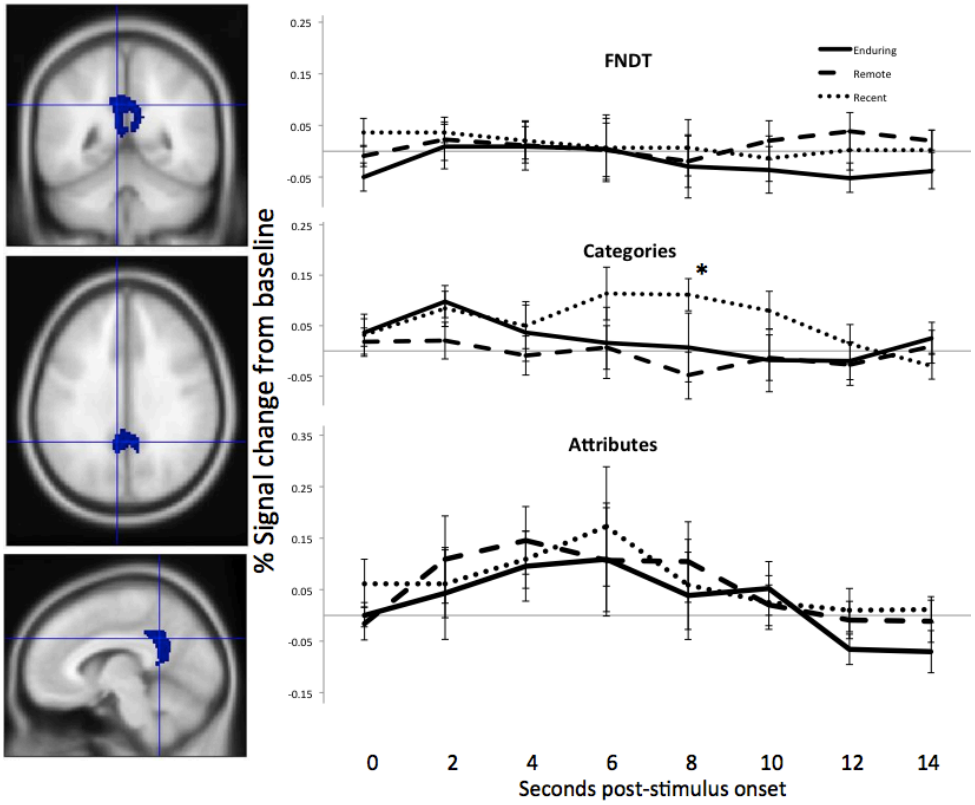


Figure 25. Analysis of the hemodynamic response function in the posterior cingulate averaged across correct responses for the three famous name time epochs for all three tasks. *$p < .05$ for one-way repeated measures ANOVAs at each time point. Error bars represent the standard error of the mean.

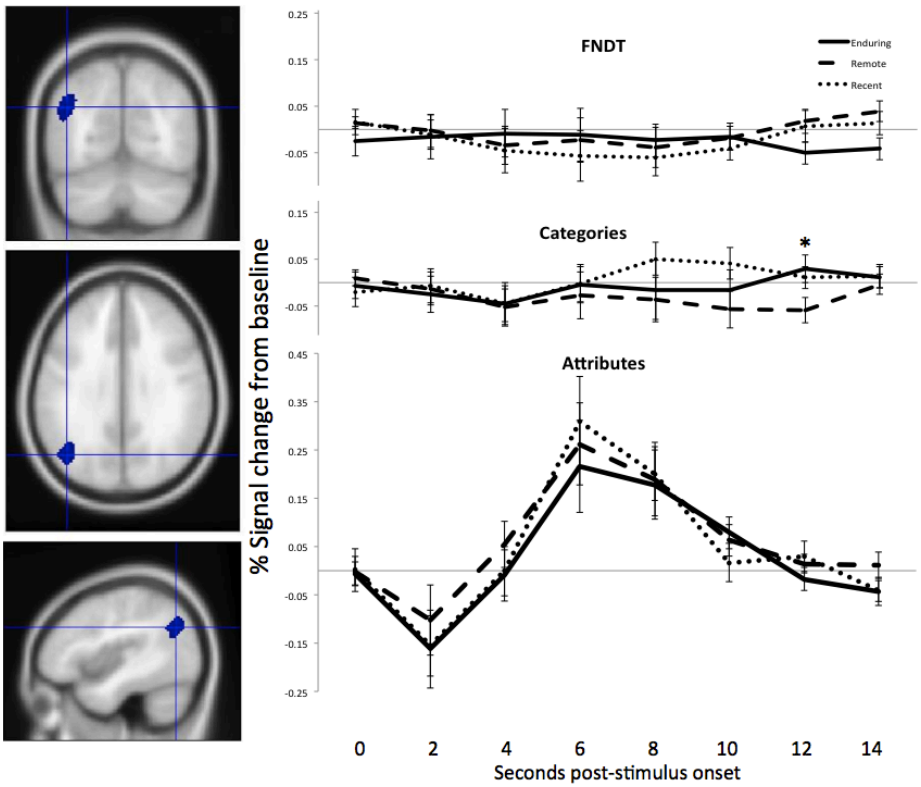


Figure 26. Analysis of the hemodynamic response function in left angular gyrus averaged across correct responses for the three famous name time epochs for all three tasks. *$p < .05$ for one-way repeated measures ANOVAs at each time point. Error bars represent the standard error of the mean.

Findings Regarding AD Risk

Demographics and Neuropsychological Testing

Genotyping analysis revealed that 5 out of the 16 participants were carriers of the APOE ε4 allele. Four participants had an ε3/ε4 genotype and one participant had a ε2/ε4 genotype. For the remaining participants, six had an ε3/ε3 genotype, three were ε2/ε3, and one participant was ε2/ε2. The final participant returned a sample that we were unfortunately unable to properly analyze or determine genotype. Thus, we had genotype information for 15 participants in our sample. Demographics and neuropsychological test performance are displayed in Tables 4 and 5, respectively, split into APOE ε4 positive ($n = 5$) and negative ($n = 10$) participants.

	APOE ε4 Positive (n = 5)			APOE ε4 Negative (n = 10)					
	Mean	SD	Range	Mean	SD	Range	t (or χ^2)	p	Cohen's d
Age	67.2	1.5	65-69	72.0	6.1	65-84	**2.34**	**.040**	**1.05**
Education	15.8	2.3	13-18	15.5	2.4	12-18	0.24	.818	0.12
Sex	3 Female, 2 Male			8 Female, 2 Male			0.68	.409	
Ethnicity	1 White, 4 Black			7 White, 3 Black			*3.35*	*.067*	
ADL Rating	5.0	0.0	5-5	5.0	0.0	5-5	--		
Subjective Memory Impairment	1/5 Reporting Complaints			2/10 Reporting Complaints			0.00	1.000	
Objective Memory Impairment	0 Reporting Complaints			0 Reporting Complaints			--		
Family History Status	4/5 Family History Positive			3/10 Family History Positive			*3.35*	*.067*	
GDS	1.2	1.3	0-3	1.2	1.1	0-3	0.00	1.000	0.00
Handedness (EHI)	83.4	24.9	44-100	82.8	19.5	54-100	0.05	.964	0.03
Physical Activity (SBAS)	5 High PA, 0 Low PA			6 High PA, 4 Low PA			2.73	.099	

Table 4. Participant demographics, split by APOE ε4 status. ADL = Activities of Daily Living, GDS = Geriatric Depression Scale, EHI = Edinburgh Handedness Inventory, SBAS = Stanford Brief Activities Scale.

As shown in Table 4, the APOE ε4 positive participants were slightly younger than APOE ε4 negative participants. A nonsignificant trend with a higher proportion of APOE ε4 positive participants were being Black and having a parental history of AD was observed. APOE ε4 positive participants also had a nonsignificant trend toward a higher level of physical activity. The two groups did not differ significantly in education, sex, depressive symptoms, or handedness.

	APOE ε4 Positive (n = 5)			APOE ε4 Negative (n = 10)					
	Mean	SD	Range	Mean	SD	Range	t (or χ^2)	p	Cohen's d
DRS-2 Total	140.2	2.3	137-143	140.3	3.0	134-144	0.07	.944	0.04
SS	13.2	2.2	10-15	12.8	1.6	10-15	0.36	.727	0.22
DRS-2 Attention	35.8	0.4	35-36	36.6	0.7	35-37	**2.68**	**.020**	**1.30**
SS	11.4	0.9	10-12	12.7	1.2	10-14	**2.40**	**.037**	**1.21**
DRS-2 I/P	36.8	0.4	36-37	36.3	1.9	31-37	0.79	.444	0.36
SS	11.2	1.3	9-12	11.1	2.0	6-13	0.12	.909	0.06
DRS-2 Construction	6.0	0.0	6-6	5.9	0.3	5-6	1.00	.343	0.47
SS	11.6	0.9	10-12	10.3	1.5	7-12	*2.10*	*.057*	*1.00*
DRS-2 Conceptualization	36.6	1.7	35-39	37.5	1.4	35-39	1.03	.338	0.59
SS	11.8	2.8	8-15	11.7	1.6	10-14	0.07	.943	0.05
DRS-2 Memory	25.0	0.0	25-25	24.0	0.9	23-25	**3.35**	**.008**	**1.59**
SS	13.0	0.0	13-13	11.2	1.6	9-13	**3.52**	**.007**	**1.67**
MMSE	29.0	1.0	28-30	28.9	1.0	27-30	0.18	.859	0.10
RAVLT Trials 1-5	49.8	10.9	34-63	47.2	7.2	38-60	0.48	.648	0.31
RAVLT List B	5.2	0.4	5-6	5.7	1.6	3-8	0.94	.369	0.42
RAVLT IR	8.8	2.4	6-12	8.4	2.5	6-13	0.30	.769	0.16
RAVLT DR	10.4	1.9	8-13	9.2	2.3	6-12	1.05	.320	0.54
RAVLT Recognition Hits	14.0	1.0	13-15	13.5	1.6	11-15	0.73	.481	0.35
RAVLT Recognition False Positives	2.2	2.6	0-5	1.0	1.2	0-3	0.98	.372	0.71
RAVLT Gained Access	10.4	1.7	9-13	11.7	3.0	8-17	1.08	.301	0.51
RAVLT Lost Access	6.2	2.3	4-10	7.3	3.3	1-12	0.76	.464	0.37
WMS-R Logical Memory IA	13.2	1.6	12-15	13.3	2.1	10-16	0.10	.922	0.05
WMS-R Logical Memory IIA	11.2	2.2	9-14	11.5	2.4	9-15	0.24	.812	0.13
WMS-R Digit Span Forward	8.2	1.3	7-10	8.3	1.6	5-10	0.13	.899	0.07
WMS-R Digit Span Backward	4.8	1.3	3-6	7.2	2.1	4-10	**2.68**	**.020**	1.28
WMS-R Digit Span Total	13.0	1.6	11-15	15.5	3.5	9-20	*1.89*	*.081*	*0.87*
COWAT (Sum of C, F, and L)	44.0	2.5	41-47	41.6	7.3	30-57	0.93	.370	0.42
Animal Fluency	20.4	4.1	17-27	20.8	4.8	11-30	0.17	.870	0.09
Trail Making Test Part A	39.4	12.7	27-54	34.5	12.9	24-64	0.70	.502	0.38
Trail Making Test Part B	89.2	37.9	51-150	78.5	24.1	39-117	0.58	.587	0.37
WAIS-III Digit Symbol Coding	55.0	10.0	42-65	63.2	15.6	39-89	1.17	.273	0.60
Boston Naming Test	53.8	5.0	45-57	56.1	3.1	52-60	0.94	.387	0.61

Table 5. Results of neuropsychological testing, split by APOE ε4 status. Results are displayed as raw scores with the exception of demographically corrected scaled scores (SS) on the DRS-2. DRS-2 = Dementia Rating Scale-2, MMSE = Mini-Mental State Exam, RAVLT = Rey Auditory Verbal Learning Test, WMS-R = Wechsler Memory Scale-Revised, COWAT = Controlled Oral Word Association Test, WAIS-III = Wechsler Adult Intelligence Scale-III.

Table 5 shows the results of neuropsychological testing split by group. DRS-2 scaled scores were derived from Mayo's Older American Normative Studies (MOANS) (Lucas et al., 1998) for White participants and the Mayo's Older African American Normative Studies (MOAANS) (Rilling et al., 2005) for Black participants. As shown, there were no significant differences between groups in the DRS-2 Total raw or scaled score. The APOE ε4 positive group had slightly lower DRS-2 Attention raw and scaled scores, although all participants performed at or above the Average level and no participant scored lower than 35 out of 37 on this subscale. The APOE ε4 positive group had a slightly higher Construction scaled score, although the raw scores did not differ significantly. This discrepancy might have been due to ethnic differences

between the groups, as a raw score of six out of six for white participants corresponded to a scaled score of 10 for White participants (Lucas et al., 1998) and a score of 12 for Black participants (Rilling et al., 2005). The APOE ε4 positive group had significantly higher raw and scaled scores on the Memory subscale, although no participant scored below the Average range or obtained a raw score lower than 23 out of 25. There were no significant differences between groups on the MMSE, RAVLT, COWAT, Animal Fluency, Boston Naming Test, WAIS-III Digit Symbol Coding, or WMS-R Logical Memory. The APOE ε4 positive scored lower on WMS-R Digit Span, which appeared to be due to a significantly lower score on the Digits Backward component of this subtest.

Behavioral Performance

Figure 27 displays the overall behavioral results for the three fMRI tasks, separated by famous and unfamiliar names. The two groups did not differ significantly in mean reaction time or accuracy for famous or unfamiliar names on any task (*p*s > .25). However, this lack of significant findings may be in part due to the restricted sample size. Inspection of the figure demonstrates a trend in the hypothesized direction of longer reaction times and lower accuracy for APOE ε4 positive participants. The accuracy differences appear to be largest for unfamiliar names on the FNDT and for both famous and unfamiliar names on Attributes.

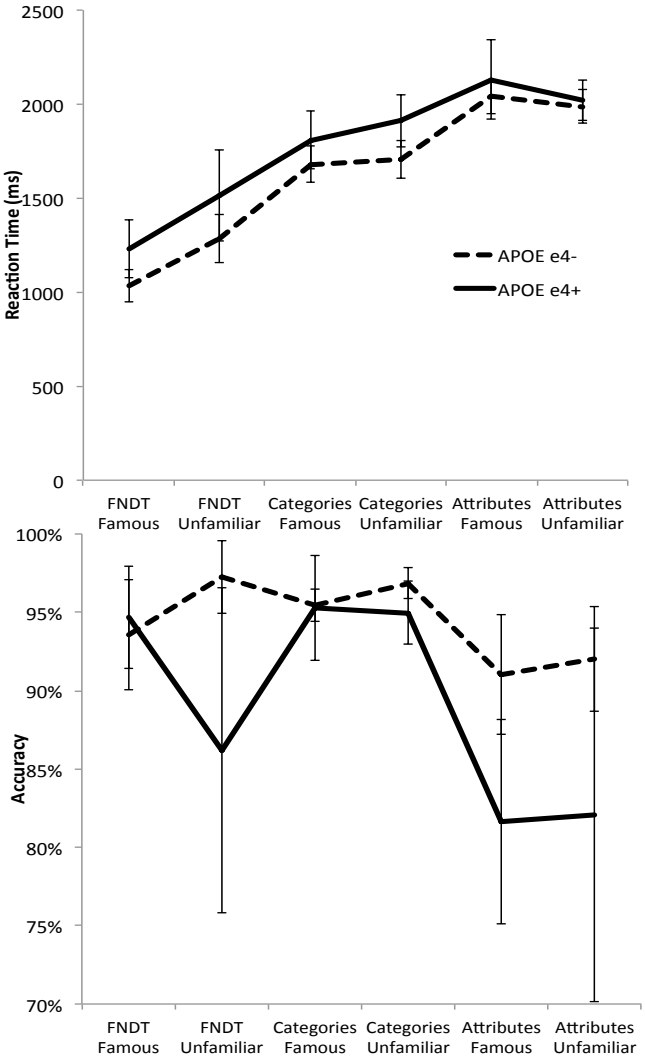


Figure 27. Behavioral performance on the three fMRI tasks, split by APOE ε4 status and famous and unfamiliar names. APOE ε4 positive participants are solid lines, APOE ε4 negative are dotted lines. There were no significant differences between groups for any of the 12 measurements (*p*s > .25). Error bars represent the standard error of the mean.

Figure 28 displays the behavioral results for famous names, separated by APOE ε4 status and time epoch. APOE ε4 positive participants had a non-significantly trend toward longer reaction times for each time epoch on each task. The two groups had comparable accuracies on the FNDT and Categories task. APOE ε4 positive participants had lower accuracies across all three time epochs on the Attributes task, although it was significantly lower for only Enduring

names ($t(13) = 3.10$, $p = .009$). As shown by the error bars, there was substantial variance within the APOE ε4 group on Remote and Recent names for the Attributes task.

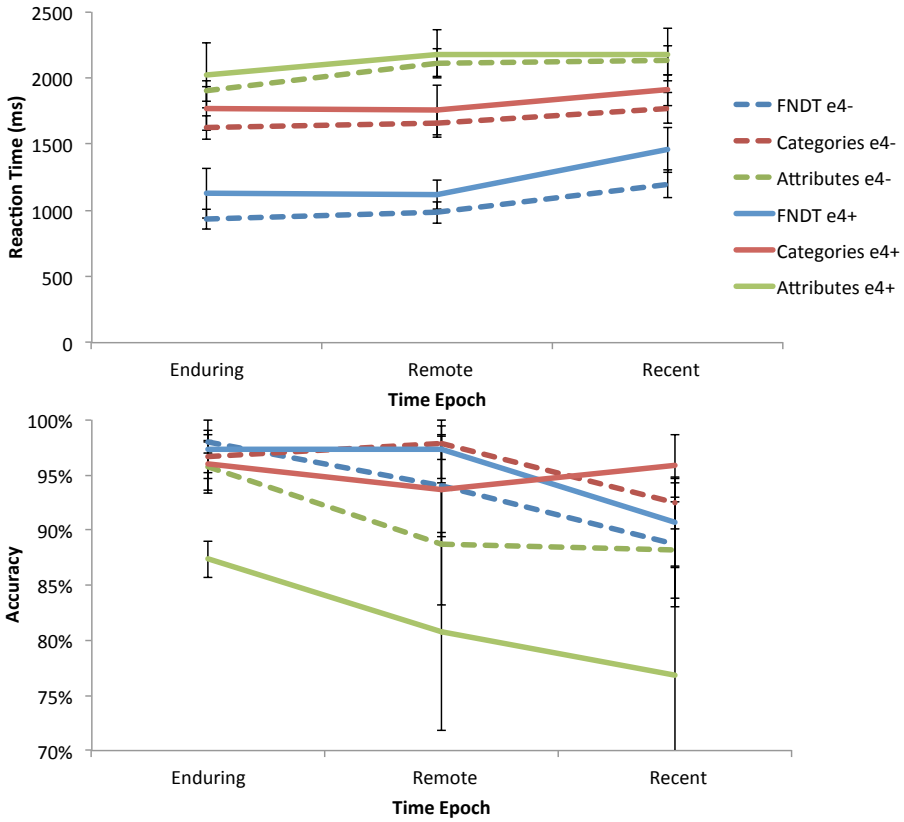
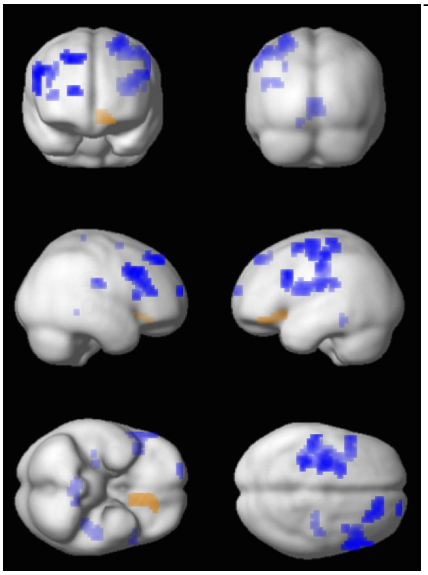


Figure 28. Behavioral performance on the three fMRI tasks, split by APOE ε4 status and time epoch. APOE ε4 positive participants are solid lines, APOE ε4 negative are dotted lines. The only significant difference between APOE ε4 positive and negative participants was on Accuracy for Enduring names for the Attributes task ($p = .009$). Error bars represent the standard error of the mean.

fMRI Results

Figures 29-31 display the results of the famous compared to unfamiliar contrasts for each of the three fMRI tasks, split by APOE ε4 carrier status. For each task, regions with significantly greater activity in each group are displayed. Due to the restricted sample size in each group, we employed a very liberal statistical threshold of $p < .01$, uncorrected for multiple comparisons, with a minimum cluster size of 10 voxels. Thus, there is an elevated risk for false positive clusters in these analyses, and results should be interpreted with caution.

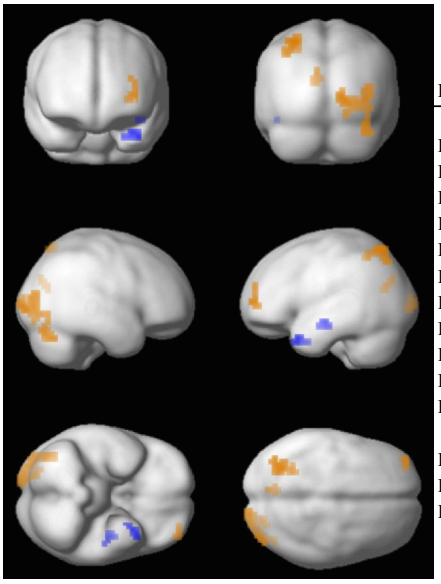
As shown in Figure 29, for the FNDT we found one cluster with greater activity for APOE ε4 positive participants, in anterior cingulate. However, we found several clusters with significantly greater activity for APOE ε4 negative participants in bilateral prefrontal cortex and insular cortex and the insula. We also observed significantly greater activity in left premotor cortex, which could potentially represent this region's proximity to cingulate cortex or a false positive finding.



	Talairach Coordinates				
Region	X	Y	Z	k	t_{max}
APOE ε4+ > ε4- (orange)					
Anterior Cingulate	-12	16	-3	37	5.17
Anterior Cingulate	-15	35	-5	*	3.53
APOE ε4- > ε4+ (blue)					
Right Dorsolateral Prefrontal Cortex	52	8	37	72	5.70
Right Dorsolateral Prefrontal Cortex	50	17	37	*	4.61
Right Dorsolateral Prefrontal Cortex	52	22	27	*	4.25
Right Premotor Cortex	21	29	52	32	5.45
Right Superior Frontal Gyrus	13	33	49	*	4.38
Left Premotor Cortex	-26	-17	62	113	5.42
Left Premotor Cortex	-22	-3	56	*	3.88
Left Supramarginal Gyrus	-42	-29	50	*	3.60
Left Insula	-31	-3	20	152	5.02
Left Insula	-41	-23	25	*	3.84
Left Dorsolateral Prefrontal Cortex	-38	10	24	*	3.46
Left Premotor Cortex	-28	-22	36	24	4.80
Medial Cerebellum	-2	-44	-2	44	3.93
Medial Cerebellum	-15	-39	-16	*	2.86
Left Supramarginal Gyrus	-29	-37	60	28	3.58
Right Insula	30	-24	26	15	3.54
Right Insula	24	-23	22	*	3.48
Right Insula	39	-21	23	*	3.01
Right Inferior Frontal Gyrus	37	14	15	11	3.49
Right Dorsolateral Prefrontal Cortex	14	56	22	12	3.09

Figure 29. Regions of significantly greater activity between APOE ε4 positive and negative participants for famous compared to unfamiliar names on the FNDT. Significant clusters for APOE ε4 positive compared to negative participants are shown in orange, and significant clusters for APOE ε4 negative compared to positive participants are shown in blue.

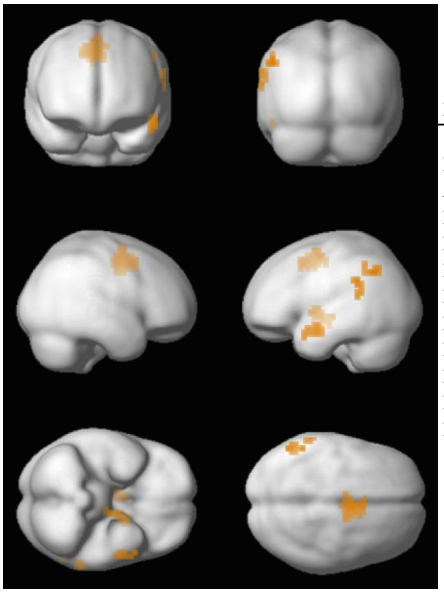
Figure 30 displays results for the famous compared to unfamiliar name contrast on the Categories task. Significant regions with greater activity for APOE ε4 positive participants were clustered in the occipital lobe, cerebellum, left superior parietal lobe, and a small region in left prefrontal cortex. APOE ε4 negative participants displayed significant activity in left middle temporal gyrus and left anterior temporal lobe.



Region	Talairach Coordinates X	Y	Z	k	t_{max}
APOE ε4+ > ε4- (orange)					
Right Inferior Occipital Gyrus	21	-93	-6	68	3.54
Right Cerebellum	37	-69	-25	*	3.08
Right Lingual Gyrus	14	-97	-3	*	3.07
Left Superior Parietal Lobule	-29	-72	49	35	3.26
Left Superior Parietal Lobule	-29	-59	47	*	3.01
Left Superior Parietal Lobule	-35	-75	38	*	2.61
Left Superior Frontal Gyrus	-34	54	14	13	3.22
Left Superior Frontal Gyrus	-34	49	25	*	2.49
Left Cuneus	-9	-76	20	10	2.54
Left Cuneus	-9	-72	14	*	2.49
Right Lingual Gyrus	21	-80	-8	10	2.49
APOE ε4- > ε4+ (blue)					
Left Anterior Temporal Lobe	-30	11	-26	11	3.52
Left Middle Temporal Gyrus	-38	-13	-10	10	3.15
Left Middle Temporal Gyrus	-43	-17	-14	*	2.91

Figure 30. Regions of significantly greater activity between APOE ε4 positive and negative participants for famous compared to unfamiliar names on Categories. Significant clusters for APOE ε4 positive compared to negative participants are shown in orange, and significant clusters for APOE ε4 negative compared to positive participants are shown in blue.

Figure 31 displays results for the Attributes task. We detected significantly greater activity for APOE ε4 positive participants in several left-lateralized regions, including anterior temporal lobe, middle temporal gyrus, angular gyrus, and supramarginal gyrus. Additionally, there was a significant cluster in cingulate cortex near the precentral gyrus and a cluster in the thalamus, close to parahippocampal gyrus. We did not detect any regions with significantly greater activity for APOE ε4 negative participants.



Region	Talairach Coordinates X	Y	Z	k	t_{max}
APOE ε4+ > ε4- (orange)					
Right Premotor Cortex	4	-5	49	99	4.06
Anterior Cingulate	1	2	45	*	3.99
Posterior Cingulate	11	-11	45	*	3.80
Left Thalamus	-15	-1	-2	25	3.52
Left Thalamus	-12	-18	-3	*	2.93
Left Angular Gyrus	-52	-60	33	13	3.41
Left Supramarginal Gyrus	-52	-50	41	*	2.72
Left Middle Termporal Gyrus	-51	-3	-17	19	3.32
Left Anterior Temporal Lobe	-48	10	-16	*	2.80
Left Supramarginal Gyrus	-61	-43	27	10	3.24
Left Superior Temporal Gyrus	-61	-42	16	*	2.92

Figure 31. Regions of significantly greater activity between APOE ε4 positive and negative participants for famous compared to unfamiliar names on Attributes. Significant clusters for APOE ε4 positive compared to negative participants are shown in orange. No significant clusters were detected with greater activity for APOE ε4 negative participants at a threshold of $p < .01$ uncorrected and minimum cluster size of $k = 10$ voxels.

sMRI Results

The previous analyses indicated that we were able to discriminate between APOE ε4 carrier status using behavioral data from the semantic memory tasks and fMRI data. However, determining the incremental utility of these advanced methods could assist in demonstrating their practicality. Thus, we conducted a set of analyses attempting to determine how well sMRI indices could distinguish between APOE ε4 positive and negative participants. We performed automated segmentation algorithms on each participant's T1-weighted structural scans to estimate these structural indices, as described in the Method. FMRIB's Automated Segmentation Algorithm (FAST) separates the brain into three tissue types (grey matter, white matter, and cerebrospinal fluid) and creates a separate image for each tissue type. FMRIB's Integrated Registration and Segmentation Tool (FIRST) transforms all structural images to a standardized template brain and then performs estimated segmentations using an automated algorithm for the

following brain structures: thalamus, caudate, putamen, pallidum, brainstem/4th ventricle, hippocampus, amygdala, and nucleus accumbens.

Table 6 displays the results from these analyses. As shown, there were no significant differences between groups (all *p*s > .1). There were medium effect sizes for a smaller proportion of white matter and a greater proportion of cerebrospinal fluid for APOE ε4 positive participants. Within the grey matter structures, the only structures with medium or large effect sizes had larger volumes for ε4 positive participants, which is the reverse of the hypothesized direction for these effects. These slightly larger structures do not appear to be attributable to the slightly younger age in the APOE ε4 positive group, as age was not significantly correlated with any of the structures with Cohen's *d* > 0.5 (*r*s between -.08 and .28, *p*s > .29).

	APOE ε4 Positive (*n* = 5)		APOE ε4 Negative (*n* = 10)				
	Mean	SEM	Mean	SEM	*t*	*p*	Cohen's *d*
Tissue (% of tICV)							
Grey Matter	38.4%	0.4%	39.2%	0.7%	0.94	.366	0.43
White Matter	39.3%	0.7%	40.1%	0.3%	1.05	.334	0.69
Cerebrospinal Fluid	22.3%	0.5%	20.7%	0.8%	1.64	.126	0.76
Structure (in mm^3)							
Left Thalamus	7221	178	6823	149	1.71	.119	0.89
Right Thalamus	6904	208	6595	168	1.15	.278	0.60
Left Caudate	3150	79	3150	114	0.00	.997	0.00
Right Caudate	3187	86	3278	110	0.65	.526	0.31
Left Putamen	4528	195	4222	192	1.12	.288	0.56
Right Putamen	4614	191	4401	138	0.90	.392	0.49
Left Pallidum	1830	58	1725	78	1.09	.298	0.51
Right Pallidum	1708	52	1714	91	0.06	.951	0.03
Left Hippocampus	3269	165	3315	118	0.23	.824	0.13
Right Hippocampus	3395	194	3257	155	0.56	.591	0.29
Left Amygdala	1150	53	1129	52	0.28	.787	0.14
Right Amygdala	1159	82	1103	99	0.44	.670	0.21
Left Nucleus Accumbens	373	52	358	46	0.23	.824	0.12
Right Nucleus Accumbens	242	25	269	47	0.52	.614	0.23
Brainstem/4th Ventricle*	20468	675	20417	873	0.05	.964	0.03

Table 6. Results of automated segmentation analyses, split by APOE ε4 status. tICV = Total Intracranial Volume. *Brainstem volume could not be calculated for three participants (two APOE ε4 positive, one negative) due to a restricted field of view of the structural scan that did not include the bottom of the brain.

Aim 3 Summary

We hypothesized that APOE ε4 carriers would demonstrate compensatory recruitment during the three fMRI tasks, potentially reflecting subtle neurological dysfunction in the absence

of observable impairment. Results revealed that indeed, APOE ε4 carriers demonstrated greater activity in some regions, with a greater number of regions for the tasks requiring a greater specificity of semantic knowledge retrieval. In particular, APOE ε4 carriers exhibited greater activity in left anterior frontal lobe during the Attributes task. However, APOE ε4 non-carriers exhibited several regions with significantly greater activity for the FNDT and Categories, including left anterior frontal lobe for Categories. Further, all results from these analyses need to be interpreted with caution due to the small group sizes and liberal statistical threshold.

CHAPTER 4: DISCUSSION

These findings represent the results of a pilot study that is the first direct neurobiological analysis of person-related semantic knowledge at hierarchically different specificity levels in older adults. Our three tasks represent a continuum of semantic knowledge from superordinate to subordinate details. Specifically, successful completion of the FNDT requires only simple identification of a famous individual, perhaps based on an unrestricted search of knowledge using categorical, attributional, and/or other types of cues. In contrast, the Categories task explicitly restricts participants' search strategy to identification of a broad characteristic associated with the individual (occupation), and the Attributes task explicitly focuses the participants' search strategy on identification of specific details (bodies or work or life events). Successful completion of the Categories and Attributes tasks presumably requires more cognitive processing compared to the FNDT, as suggested by the increasingly long mean reaction times and lower accuracy. However, all three tasks were relatively easy and could be completed with a high level of accuracy (>87%) by an ethnically diverse sample of community-dwelling, cognitively intact older adults. This study also introduced novel control tasks using unfamiliar names for the Categories and Attributes tasks that involved making similar types of judgments but did not require specific recall of biographical information associated with famous individuals. These control tasks had comparable reaction times and accuracies compared to their respective famous name tasks, despite the fact that they were largely surface processing types of cognitive tasks. Thus, our interpretation of the famous compared to unfamiliar name contrasts for all three tasks is the isolation of the semantic knowledge retrieval associated with person identification. This Discussion section will include an analysis of the overall findings from the three tasks across the sample as a whole, followed by an analysis of the relative utility of

neuropsychological testing, fMRI, and sMRI to distinguish between participants with differential risk for AD.

Entire Sample Results

The famous compared to unfamiliar name contrast for the FNDT yielded activity in regions consistent with previous research on the task and regions that are generally considered to be part of the semantic memory network: middle temporal gyrus, angular gyrus, posterior cingulate, supramarginal gyrus, precuneus, prefrontal cortex, and inferior frontal gyrus. The Categories and Attributes yielded activity in several overlapping regions, including left middle temporal gyrus, angular gyrus, posterior cingulate, and precuneus. Regions of activity were left-lateralized for all tasks, which is consistent with the verbal (rather than visual) nature of these semantic retrieval tasks (Gainotti, 2013).

We did observe several important differences between the tasks. In particular, the Categories task yielded very little frontal recruitment, with only one significant cluster in anterior cingulate. Notably, this task generated significant activity in bilateral parahippocampal gyri, which was not observed for the FNDT. Functional abnormalities and atrophy in this region have been implicated with risk for AD (Devanand et al., 2007), and the ability to study this region could represent a possible advantage of the Categories task relative to the FNDT. However, there was not a statistically significantly greater amount of activity in this region compared to the FNDT, perhaps because of low study power. Further, the HRF signals for both famous and unfamiliar names were essentially indistinguishable for all five ROIs between the FNDT and Categories task. The regions associated with semantic retrieval appeared to be inhibited during the control tasks.

The contrast map between the famous compared to unfamiliar names for FNDT and Categories was inconsistent with our hypotheses. We anticipated that the Categories would generate a broader semantic retrieval map including additional regions (such as contralateral temporal lobe, hippocampus, and/or prefrontal cortex) compared to the FNDT due to the additional cognitive processing and retrieval of more specific semantic information. In contrast, we observed *reduced* activity for the Categories task compared to FNDT in several regions including posterior and anterior cingulate, precuneus, right posterior inferior parietal lobe, and the right insula. In particular, this difference was greatest for Recent names. Further, no regions had significantly greater activity for Categories compared to FNDT on the famous compared to unfamiliar name contrast, even with the liberal statistical threshold of $p < .005$, uncorrected for multiple comparisons. When we split the analyses by epoch, we detected only two small clusters, in posterior cingulate for Recent names and anterior cingulate for Enduring names. This finding is surprising because the behavioral results indicated longer reaction times for Categories, suggesting a higher level of cognitive processing necessary to complete the task. When older adults are presented with difficult tasks, they typically engage in cognitive "scaffolding" by recruiting additional neural regions in order to successfully complete the task (Park & Reuter-Lorenz, 2009).

One potential reason for the reduced activity for Categories compared to FNDT is related to the task design. Specifically, it could be that the active semantic memory search process is a key component of the neural activity for the FNDT. That is, the task requires participants to determine whether a given name is present in their semantic memory, and may elicit an unconstrained probe for memories associated with the individual. In contrast, the design of the Categories task gives participants a name and essentially reveals to them that the person is

famous, eliminating the necessity of the search for name recognition. Further, participants may be restricted in their search toward just a broad detail about the person, as the Categories task elicits a more controlled semantic memory probe than the FNDT. As an example, we will use a fictional stimulus of "Frank Sinatra" with the choices of "Music" and "Politics." Matching the name to "Music" restricts the semantic search to only one feature of his life, and does not require remembering specific songs, associations with other individuals, other career accomplishments, or aspects of his personal life, each of which may be potential cues for his person identity. For the FNDT, perhaps some of this additional information may be used by individuals during an unconstrained search of their semantic memory storage, and the categorical information is implicitly retrieved, along with other types of information, during completion of the FNDT. Thus, the restriction of the semantic search cue during the Categories task could account for the decreased activity for this task relative to the FNDT.

Additionally, activity might have been partially suppressed during the Categories task due to lack of novelty of the task and the stimuli. That is, participants had been exposed to the task design and the same famous names for the first time during the FNDT. Thus, the names may have been already primed by the FNDT, facilitating successful completion of the Categories task and reducing the need for the individual to conduct an extensive search of their semantic memory to retrieve the name. This previous practice on the FNDT may have resulted in the lack of significant clusters for the Categories compared to FNDT contrast.

One previous fMRI study did compare retrieval of information associated with famous individuals at differing levels of semantic specificity and may serve as a precedent for our findings. This study (Turk, Rosenblum, Gazzaniga, & Macrae, 2005) had participants complete identity and occupation tasks associated with famous faces. For the identity task, participants had

to choose between two names for pictures of famous individuals. For the occupations task, participants decided whether a given famous face was an actor or a singer, similar to our Categories task. The contrast between the tasks revealed significantly greater activity for the identity task in regions including bilateral fusiform cortex and right inferior frontal gyrus, despite longer mean reaction times for the occupations task. The increased activity for the identity compared to occupations task is similar to the increased activity we found for the FNDT compared to Categories. However, there are some important distinctions between the studies. In particular, the identity task is substantially different than the FNDT. In the identity task, participants had to identify an individuals name, which could be argued to be a more specific semantic detail that an occupation because the occupational distinction only requires simple familiarity with the face. Thus, the significant activity for identity compared to occupation may reflect deeper semantic retrieval. In contrast, the FNDT gives participants the famous name for each task and only requires participants to determine whether they recognize the name. The level of familiarity necessary to complete the FNDT is shallower than Categories. Thus, despite the apparent similarity of the findings between this previous study (Turk et al., 2005) and the current work, the comparability appears to be limited.

In contrast to the Categories task, the results from the Attributes task generally supported our hypotheses. The famous compared to unfamiliar name contrast yielded significant activity in similar regions to the FNDT, including left temporal lobe, bilateral angular gyrus, inferior frontal gyrus, posterior cingulate, and precuneus. Notably, temporal activity appeared to be more left-lateralized for Attributes, with consistent activity throughout left middle temporal gyrus and a lack of significant activity in right temporal lobe. This strong left lateralization is consistent with the retrieval of specific verbal (rather than visual) semantic information associated with famous

names (Gainotti, 2013). Importantly, activity in left temporal lobe extended to the anterior temporal lobe to a greater extent than the other two tasks. In particular, the Enduring and Remote names appeared to drive this difference compared to the other two tasks. Left anterior temporal lobe has important associations with specific biographical information, social knowledge (Olson et al., 2013), and semantic information associated with famous individuals (Campanella et al., 2013). Atrophy in this region is specifically associated with semantic memory loss (Chan et al., 2001). Importantly, we observed significantly greater activity and a larger HRF in this region compared to both FNDT and Categories.

The enhanced ability to study activity and possible abnormalities in the anterior temporal lobe is one of the most important findings from this study, as it allows for a more robust analysis of the semantic memory network that may yield valuable information pertaining to AD risk. Further, given that semantic memory loss typically occurs in a hierarchical manner (Giffard et al., 2001; Hodges, Salmon, et al., 1992; Tröster et al., 1989; Warrington, 1975), analysis of neural regions involved with this type of subordinate information may elucidate early neurobiological evidence of pathological processes. The Attributes task also yielded a larger HRF than the other two tasks in left angular gyrus and medial temporal lobe, regions which demonstrated overlapping activity with the other two tasks, supporting our hypothesis that the processing of more specific semantic knowledge should stimulate a greater brain response.

Additionally, the Attributes task generated significantly greater activity and a larger HRF than the other two tasks in left inferior frontal gyrus, another region heavily implicated with semantic memory retrieval (Binder et al., 2009). Specifically, this region appears to be most active when deciding between two competing alternatives in semantic memory, rather than participating in semantic memory retrieval specifically (Moss et al., 2005; Thompson-Schill,

D'Esposito, Aguirre, & Farah, 1997). As such, this region has been referred to as the "semantic executive system" (Poldrack et al., 1999). Thus, the Attributes task may have generated specific activity in this region because successful completion of the task requires deciding between two specific semantic details, such as bodies of work or life events. Although the other two tasks also required making decisions based on semantic information, the deeper semantic processing likely resulted in greater utilization of this semantic executive system. Likewise, the unfamiliar name control task generated the largest HRF for the Attributes task in this region, perhaps because the task required deciding between two countries, which represents a more specific semantic decision than Categories (choice of male vs. female) or FNDT (choice of famous vs. unfamiliar).

The larger HRF signals for the Attributes task could have been related to the additional cognitive processing rather than deeper semantic retrieval. This task had longer reaction times and lower accuracy than the other two tasks. Left parahippocampal gyrus, a region that appeared to demonstrate activity for Categories and not Attributes, had a similar pattern in which the famous name HRF for Attributes was significantly higher than the other two tasks. This finding indicated that the larger HRF might not be due to specific semantic retrieval but rather to higher cognitive demands. We were unable to find regions that demonstrated selectively larger HRFs for Categories and FNDT in a similar manner. Notably, there are some limitations to this interpretation. The anterior cingulate exhibited comparable HRFs across all three tasks, indicating that the cognitive processing did not universally generate a larger HRF for the Attributes task across the brain. Additionally, Categories and FNDT exhibited comparable HRFs across all ROIs that we analyzed, despite the longer mean reaction times for the Categories task. If the additional cognitive processing was indeed responsible for the larger HRF in the Attributes task, then we should have also observed a larger HRF for Categories compared to FNDT. Thus,

the large HRF signals generated during the Attributes task likely represent the greater depth of semantic retrieval compared to the other two tasks, rather than simply longer cognitive processing and/or greater task difficulty.

One surprising result from the comparisons between tasks is that the FNDT demonstrated greater activity than Attributes in several regions including precuneus, bilateral supramarginal gyri, cerebellum, anterior cingulate, and prefrontal cortex. In particular, these differences were most pronounced for Recent famous names. Similarly, Categories also had several significant clusters of activation compared to Attributes for Recent names. One potential reason for the reduced activity in the Attributes task is similar to the argument made earlier for the reduced activity during the Categories task relative to the FNDT. The participants are not required to determine whether the given name is famous, eliminating the need for a broad semantic search of famous individuals. Rather, in this highly constrained semantic memory probe, the search is more confined to very specific details about an individual. Completing this search engages several regions that are consistent with semantic memory retrieval, but not perhaps to the same extent as the FNDT. In other words, perhaps only the specific cue provided engages the semantic search system rather than multiple cues that may be generated automatically during the FNDT. In contrast, there are strong foci of recruitment for Attributes in left anterior temporal lobe, consistent with the retrieval of the specific biographical information (Olson et al., 2013), and left inferior frontal gyrus, consistent with making a semantic decision (Moss et al., 2005). Additionally, activity might have been suppressed on the Attributes task due to the lack of novelty for the famous name stimuli and the previous practice during the FNDT and Categories tasks.

This study also analyzed patterns of temporally graded neural recruitment in response to memories of different ages through the three famous name time epochs. For the FNDT, we observed greater recruitment for Recent compared to Enduring names in several regions, including posterior cingulate, left parahippocampal gyrus, and bilateral insula and inferior frontal gyri. This increased cortical and parahippocampal recruitment for Recent names is consistent with previous research with this task (Douville et al., 2005; Woodard et al., 2007). The increased activity in the insula is a novel finding with this task, although previous research has indicated that this region may be particularly involved in the processing of salient events (Menon & Uddin, 2010). Names with more recent exposure could potentially be more salient for participants, resulting in the increased recruitment. Additionally, the insula is functionally connected to other regions implicated with semantic memory retrieval, including posterior cingulate and angular gyrus (Menon & Uddin, 2010), and functional activity between these regions could be positively correlated.

We also observed evidence for temporally graded activity with our two novel tasks. Specifically, we observed activity for the Recent compared to Enduring name contrast in left dorsolateral prefrontal cortex for Categories and in the right angular gyrus for Attributes. Further, we observed three regions with increased activity for the Recent compared to Remote contrast in the Categories task, including in left medial and anterior temporal lobe and anterior cingulate cortex. This increased activity for Recent names compared to other time epochs is consistent with our hypotheses.

We did not observe any differences between Enduring and Remote names for the FNDT and the Attributes task. We hypothesized that we might see greater neocortical recruitment for Enduring names due to the increased consolidation of the memory associated with more frequent

updating, and conversely we expected to observe more hippocampal activity for the Remote names due to reduced hippocampal involvement associated with infrequent updating. We did observe significant activity for the Enduring compared to Remote name contrast in the Categories task supporting this hypothesis. Specifically, we observed activity in two separate right-lateralized clusters composed of angular and supramarginal gyri, precuneus, and posterior cingulate. This increased activity in cortical regions is consistent with theory in that Enduring names might have a more permanent representation in neocortex compared to Remote names, which might have a less consolidated memory representation located predominantly in the medial temporal lobes (Squire & Alvarez, 1995). However, we did not observe any significant clusters for the Remote compared to Enduring contrast for any of the three tasks. ROI analyses were unable to detect significant differences in the HRF for any of the three tasks at any time point, with the exception of one time point in the posterior cingulate for the Categories task.

The relative lack of temporally graded findings for the Attributes task (just one small cluster of 17 voxels for the Recent compared to Enduring contrast in left angular gyrus) was unexpected due to the overall larger signal for famous names that we observed in the HRF analyses. We anticipated that with the larger signal, we would be able to elucidate a larger magnitude of differences between the time epochs. It is unclear why we did not observe these anticipated effects. However, one speculation is that responding to the task required simultaneous stimulation not only of a name, but also multiple potential attributes, which could have resulted in widespread recruitment of memories encompassing many time periods. If this widespread recruitment were indeed the case, it would be more difficult to distinguish between memories of different ages with neural recruitment patterns. An alternative explanation could be that the general feelings of familiarity associated with famous individual during the FNDT and

Categories could simultaneously activate several memories about the individual, most of which are from the same time period. In contrast, completing the Attributes task could only activate highly specific memories that are less associated with a specific time period, in turn dampening the effects of a temporal gradient on neural recruitment.

Risk Differentiation Results

One-third of our sample with decipherable genotypes tested positive for the APOE ε4 allele, which is consistent with previous samples of older adults that specifically recruited for 50% to have a family history of AD (Woodard et al., 2010). We had group sizes of 5 APOE ε4 and 10 APOE ε4 negative participants, representing a very restricted sample for detecting differences between groups. Nonetheless, we conducted our between-groups analyses as planned in order to determine which methods could best distinguish between the two groups. One unexpected result is that the APOE ε4 positive group was significantly younger than the APOE ε4 negative group, which could potentially confound the interpretation of the findings.

Neuropsychological test data were mostly ineffective in distinguishing between groups. Although some differences emerged on subscales of the DRS-2, all participants performed at close to ceiling levels on this measure and all participant Total Scores fell in the Average to Above Average range. One notable finding is that APOE ε4 positive participants performed significantly worse on WMS-R Digit Span Backward, but not Forward. The Backward portion of this working memory task requires manipulation of the rehearsed information and engages central executive systems. Disruption in executive resources is the predominant impairment in working memory abilities for patients with mild AD (R. G. Morris & Baddeley, 1988), and this selectively lower performance for APOE ε4 positive participants could potentially represent early executive dysfunction. On tasks of semantic memory, the two groups performed

comparably on COWAT and Animal Fluency. The APOE ε4 positive group had a medium effect size (d = 0.61) in the direction of lower performance on the Boston Naming Test, an object-naming test of semantic memory and language skills. However, this slightly lower performance could have been due to ethnic differences between the groups, as previous research has indicated that this measure might be culturally biased (Pedraza et al., 2009).

A comparison of the behavioral performance during the three fMRI tasks was mostly consistent with expectations, although the restricted sample size limited our ability to detect statistically significant differences between groups. The APOE ε4 positive group had non-significantly longer reaction times on every task and time epoch, potentially representing an additional amount of cognitive expenditure in order to successfully complete the task. With regard to accuracy, the APOE ε4 positive group demonstrated a non-significant trend toward lower accuracies on unfamiliar names for the FNDT and both famous and unfamiliar names for the Attributes task, although there was a large variance within the group for all three stimulus types. Separating the data by time epoch revealed that the APOE ε4 positive group had significantly lower accuracy for Enduring names on Attributes. This lower accuracy on Attributes is consistent with our hypotheses, because successful completion of this task requires retrieval of specific semantic information, which might be the most susceptible to loss early in the disease process. Although the two groups were generally comparable on neuropsychological testing, we observed this difference on a semantic memory task requiring deep processing of information associated with famous individuals.

Comparison between groups on the fMRI contrasts revealed several differences in activity between groups on the famous compared to unfamiliar contrasts for each task. We hypothesized that the APOE ε4 positive group would demonstrate significantly greater activity

for each task, representing compensatory recruitment for subtle neural dysfunction. Further, the amount of compensatory recruitment should increase consistent with the specificity of semantic knowledge retrieval. Examination of regions with significantly great activity for the APOE ε4 positive group across the three tasks is mostly consistent with these hypotheses. For the FNDT, we observed just one significant cluster in anterior cingulate. For Categories, we observed five clusters including in left superior parietal lobule, cerebellum, and superior frontal gyrus. For Attributes, we observed greater activity in several left-lateralized regions, including the crucial region in left anterior temporal lobe. The greater activity in this region indicates that this task might be sensitive to subtle disruption that could indicate the preliminary phase of semantic memory impairment.

However, some additional findings from these analyses confound interpretation of these results. In order to detect significant differences between groups, we had to use a liberal statistical threshold of $p < .01$ uncorrected with minimum cluster size of 10 voxels, which results in a large risk for Type I errors. Some of the activity likely represents false positives, especially in regions that do not make theoretical sense for finding differences between groups, such as premotor cortex and the occipital lobe. We also observed significantly greater activity for APOE ε4 negative participants on the FNDT, which contradicts our hypotheses and previous research using this task (Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Antuono, et al., 2009). During the Categories task, we observed significantly greater activity for APOE ε4 negative participants in left anterior temporal lobe, the same region where we observed the greater activity APOE ε4 positive participants in the Attributes task. Inspection of individual participant contrast maps reveals no clear outliers that might have driven this contradictory finding. However, the amount of regions with greater activity for APOE ε4 negative participants declined in accordance

with the increasing specificity of the tasks, and we did not find any significant regions on the Attributes task. Thus, our findings are consistent with a superior ability to discriminate between the two groups with the most specific task. The number of regions with greater activity for APOE ε4 positive participants increased in proportion to semantic specificity requirements of the task. These significant findings between groups were detected in the absence of significant group differences in the sMRI analyses. This finding highlights the advantage of fMRI for studying the functional integrity of brain tissue, which can be sensitive to subtle dysfunction in the absence of observable atrophy (Xu et al., 2009).

Limitations and Future Directions

The largest limitation of this study is the small sample size. Because of this limitation, we used a liberal threshold for detecting significant clusters of activity of $p < .001$ uncorrected for single-group single-task analyses, $p < .005$ for between-task, and $p < .01$ between-group analyses, whereas a family-wise error correction with an alpha level of $p < .05$ would have been preferable. Thus, it is possible that some of the results from our study represent false positives. Conversely, it is likely that several of the null findings (including the scarcity of significant clusters in the paired-samples comparisons between tasks) represent Type II errors, and more significant differences might emerge with a larger sample size.

The overarching goal of this pilot study is to apply for grants to the National Science Foundation and/or the National Institutes of Health, which would allow for a larger sample size and superior statistical analyses to reduce the likelihood of both Type I and Type II errors. Additionally, a larger sample size would also allow for the analysis of the contribution of additional variables to the fMRI signal such as physical activity. For example, a previous study (Smith, Nielson, Woodard, Seidenberg, Durgerian, et al., 2011) observed an interaction between

physical activity and APOE ε4 carrier status on the FNDT such that physically active APOE ε4 carriers demonstrated the largest amount of fMRI activity. An 18-month longitudinal follow-up (Woodard et al., 2012a) revealed that low physical activity was a risk factor for cognitive decline, but only amongst APOE ε4 carriers. A larger sample size could be useful for further examining the relationship between physical activity and the BOLD signal and the interaction between physical activity and the APOE ε4 allele, including whether similar findings are present during Categories and Attributes. A larger sample size could also analyze the relationship between other variables and the fMRI signal, including neuropsychological testing and the combined effects of parental history and the APOE ε4 allele. At present, our limited sample size does not have sufficient power to analyze these variables.

Finally, a longitudinal follow-up could assist in determining the prognostic utility of these tasks in assisting with prediction of cognitive decline in older adults. One overarching goal of this line of research is to determine whether fMRI of semantic memory could be implemented in clinical settings as an early biomarker of AD. A previous study from our research group demonstrated that functional activity from the FNDT can predict future cognitive decline over an 18-month follow-up interval (Woodard et al., 2010). Further, a five-year follow-up (Rao et al., 2015) demonstrated that patterns of functional activity change over time consistent with changes in cognition. APOE ε4 carriers experienced a subtle decline in cognition and corresponding decreases in the BOLD signal. APOE ε4 non-carriers exhibited stable cognitive functioning, but an increase in the BOLD signal, presumably as compensatory scaffolding to preserve cognitive performance. Our current findings indicate that these three tasks can discriminate between APOE ε4 carriers and non-carriers. In particular, Attributes demonstrated a larger signal for APOE ε4 carriers in important semantic memory regions that have been associated with cognitive decline.

A longitudinal follow-up would be able to determine whether Attributes and Categories can provide superior and/or supplementary information regarding future cognitive decline relative to the FNDT. The prognostic utility of these fMRI tasks could be compared to other predictors such as sMRI, resting state fMRI, and neuropsychological testing.

Conclusion

The current study analyzed three fMRI tasks requiring cognitively intact older adults to retrieve varying levels of semantic knowledge specificity associated with famous names. Relative to their respective unfamiliar name control tasks, each task recruited regions consistent with the semantic memory network. Contrary to hypotheses, tasks with greater semantic specificity did not yield activity in an overall greater number of regions than the FNDT. The Categories task, which may have constrained semantic knowledge retrieval to one domain of an individual's life, generated lesser activity than the FNDT in inferior parietal lobule, precuneus, insula, and anterior cingulate. The Attributes task, which required participants to retrieve highly specific semantic information, yielded the most left-lateralized recruitment, including significantly greater activity than the other two tasks in left anterior temporal lobe and left inferior frontal gyrus. These two regions are highly implicated with social knowledge and semantic decision-making, respectively. The ability to study activity and possible abnormalities in these important regions represents a potential advantage of this task for studying the semantic memory network. Examination across time epochs revealed that the FNDT and Categories tasks generated the greatest activity for Recent famous names, consistent with previous research. In contrast, the Attributes task yielded very few regions demonstrating temporally graded activity.

Comparisons between APOE ε4 carriers and non-carriers revealed subtle non-significant differences in behavioral performance between groups indicating that the tasks might have been

more difficult for APOE ε4 carriers. fMRI comparisons between groups revealed that the two groups generated different patterns of activity across the three tasks. The number of regions in which APOE ε4 carriers generated significantly more activity increased in proportion to the semantic knowledge specificity of the task, including significantly greater activity in left anterior temporal lobe during the Attributes task. This additional activity might represent compensatory recruitment to support cognitive performance in the presence of prodromal neurological changes. No significant differences between groups were observed based on sMRI analysis. Future analyses may further examine the relative abilities of these three tasks to discriminate between individuals with and without risk factors for AD and to predict future cognitive changes.

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ABSTRACT

THE SEMANTIC MEMORY IMAGING IN LATE LIFE PILOT STUDY

by

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Introduction: Several functional magnetic resonance imaging (fMRI) studies have analyzed the famous name discrimination task (FNDT), an uncontrolled semantic memory probe requiring discrimination between famous and unfamiliar individuals. Completion of this simple task recruits a semantic memory network that has shown utility in determining risk for Alzheimer's disease (AD). Specific semantic memory probes using biographical information associated with famous individuals may build on previous findings and yield superior information regarding risk for AD.

Method: Sixteen cognitively intact elders completed the FNDT and two novel tasks during fMRI: Categories (matching famous individuals to occupational categories) and Attributes (matching famous individuals to specific bodies of work or life events). Five participants were carriers of the Apolipoprotein E (APOE) ε4 allele.

Results: Relative to their respective control tasks, participants recruited brain regions for all three tasks consistent with previous research, including left temporal lobe, left angular gyrus, precuneus, posterior cingulate, and anterior cingulate. The FNDT generated significantly more activity than the other tasks in anterior cingulate and several posterior regions. Categories had

significantly lesser activity than other tasks in inferior parietal lobe, precuneus, and posterior cingulate. Attributes, the most specific semantic probe, demonstrated the strongest left lateralization with significantly greater activity in left inferior frontal gyrus and anterior temporal lobe. APOE ε4 carriers had regions with greater activity across all three tasks, with the greatest number of regions for Attributes, including in left anterior temporal lobe.

Discussion: This pilot study identified neural correlates of different levels of semantic processing. The FNDT, an unconstrained semantic knowledge probe, demonstrated greater activity across most regions. The Attributes task, a specific semantic probe, had focused left-lateralized activity, including anterior temporal lobe and inferior frontal gyrus. APOE ε4 carriers demonstrated significantly greater activity in left anterior temporal lobe during Attributes only, demonstrating this task's potential utility for determination of AD risk.

AUTOBIOGRAPHICAL STATEMENT

Michael A. Sugarman is a doctoral candidate in clinical psychology at Wayne State University, specializing in clinical neuropsychology. He has completed clinical practica in neuropsychology at the John D. Dingell Veterans' Affairs Medical Center and the Rehabilitation Institute of Michigan. Additionally, he has conducted outpatient assessments and individual, group, and family psychotherapy at the Wayne State University Psychology Clinic. He has taught at both the undergraduate and graduate levels. In September 2015, he began his predoctoral internship in clinical neuropsychology at the Edith Nourse Rogers VA Hospital in Bedford, MA.

Mr. Sugarman is a co-author of one book chapter and 12 peer-reviewed journal articles, including seven as first author. His areas of expertise include functional magnetic resonance imaging as a preclinical biomarker for Alzheimer's disease, neuropsychological testing, and meta-analyses of pharmaceutical effectiveness. He has presented his research findings at conferences including International Neuropsychological Society, American Academy of Clinical Neuropsychology, and the American Psychological Association. He also serves as a consultant for the Research and Editing Consulting Program, a grammar and statistical consulting service for foreign authors attempting to publish in English-language journals, and has served as an ad-hoc peer reviewer for seven different journals.